SEPTEMBER 2007 VOLUME 61 NUMBER 3

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NEUROSURGERY

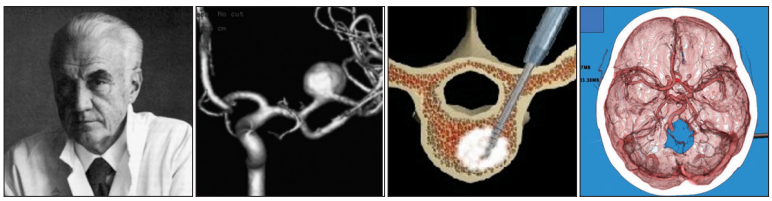
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ANNUAL MEETING ISSUE
(26th Annual Meeting of the Japan Society of Neurological Surgeons)

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Editor's Choices



433 460 531 564

Neuroform Stent-assisted Coil Embolization of Wide-neck Intracranial Aneurysms: Strategies in Stent Deployment and Midterm Follow-up

The authors evaluated the midterm results of stent-assisted coil embolization in the treatment of wide-necked intracranial aneurysms and assessed the efficacy of various strategies in stent deployment. The study was carried out in 42 patients with 46 wide-necked cerebral aneurysms enrolled in a prospective single-center registry of patients treated with a flexible self-expanding Neuroform stent. Angiographic and clinical follow-up was available in 31 patients with 33 aneurysms, ranging from 3 to 24 months. The study examined rates of aneurysm occlusion, neck remnants, residual aneurysms, and recanalization, as well as patient clinical outcome. The results of the study indicate that Neuroform stent-assisted coil-embolization is a safe and effective technique in the treatment of wide-necked cerebral aneurysms. However, the long-term durability and patient tolerance of this approach is yet unclear. **[p. 460]**

Segmental Polymethylmethacrylate-augmented Pedicle Screw Fixation in Patients with Bone Softening Caused by Osteoporosis and Metastatic Tumor Involvement: A Clinical Evaluation

Patients with spinal instability caused by degenerative conditions, fractures, and metastatic disease often require stabilization with screw/rod implants. Individuals with bone softening due to osteoporosis and cancer have an increased likelihood of hardware failure, often due to screw loosening and pull-out. In this study, the authors report on the use of a novel device used to cement screws into the spines of 23 such patients. In this device, the tap threads serve a dual purpose in preventing the backflow of cement toward neural elements while allowing for a custom form for subsequent screw placement. Solid instrumentation, without hardware failure, was achieved with a low complication profile in all 23 patients included in this study. **[p. 531]**

Comparison of Open Discectomy with Microendoscopic Discectomy in Lumbar Disc Herniations: Results of a Randomized Controlled Trial

This paper reports the results of a prospective controlled randomized study to compare the intraoperative, postoperative, and outcome differences between patients with lumbar disk herniations treated with open discectomy versus microendoscopic discectomy (MED). In total, 40 patients with herniated lumbar discs and sciatica unresponsive to conservative therapy were included in this study. The study found very few differences between the two techniques in terms of final outcome. However, patients treated with MED recovered faster and returned to work earlier than those treated with the open discectomy technique. **[p. 545]**

Craniotomy and Clipping of Intracranial Aneurysms in a Stereoscopic Virtual Reality Environment

Neurosurgical training for microsurgical clipping of intracranial aneurysms has become more difficult since the advent of endovascular coiling techniques. This paper reports a new and innovative method for planning and training for aneurysm surgery in a virtual reality environment. Patient-specific Digital Imaging and Communications in Medicine data of CT angiograms and skulls were transferred into the workstation (Dextroscope, Volume Interactions Pte Ltd, Singapore, Singapore). The authors successfully devised a way to add an aneurysm clip database into the patient dataset. Three dimensional volume renderings were followed by data co-registration and fusions. A number of snapshots were used to illustrate expected virtual head positioning and craniotomy to simulate microscopic visualization. Clip selection could be carried out with reference to the angle of application. The exposure and degree of aneurysm obliteration from different angles of approaches are evident. The future role of this method in neurosurgical training is encouraging. **[p. 564]**

VEGF Gene-transferred Bone Marrow Stromal Cells Engineered with an HSV-1 Vector Can Improve Neurological Deficits and Reduce Infarction Volume in Rat Brain Ischemia

The present study evaluates the hypothesis that intracerebral transplantation of VEGF gene-transferred bone marrow stromal cells (MSCs) could provide a greater therapeutic effect than intracerebral transplantation of native (non-gene-transformed) MSCs in a rat model of transient middle cerebral artery occlusion (MCAO). The results of the study showed that animals receiving the gene-transferred MSCs demonstrated significant functional recovery compared with control animals. Fourteen days after the insult, there was a significantly lower infarct volume without aggravating cerebral edema in the experimental group compared to controls. In addition, the transplanted VEGF gene-modified MSCs strongly expressed VEGF protein for at least 14 days. This suggests that VEGF gene-transferred MSCs may provide a more potent autologous cell transplantation therapy for stroke than using native MSCs alone. **[p. 586]**

Collagen Scaffolds Populated with Human Marrow Stromal Cells Reduce Lesion Volume and Improve Functional Outcome after Traumatic Brain Injury

Despite encouraging reports of significantly improved functional outcome after transplantation of human marrow stromal cells (hMSCs) in rat models of TBI, lesion volume from extensive parenchyma loss remains largely unchanged. The authors have conducted a study to examine new ways to deliver hMSCs to the injured brain and thus maximize therapeutic benefit by using collagen scaffolds implanted with hMSCs. The experimental animals were compared to control animals with respect to sensorimotor function and spatial learning, and the brain tissue was processed for histopathology analysis. The results of the study demonstrated that the scaffolds populated by hMSCs improved spatial learning and sensorimotor function, reduced lesion volume, and fostered the migration of hMSCs into the lesion boundary zone after TBI in the rat model. This suggests that this method may be a new way to reconstruct the injured brain and improve neurological function after TBI. **[p. 596]**

Charles Y. Liu, M.D., Ph.D., *Contributor*

Neurosurgery Online
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Featured on the Web

Chained Lightning, Part II: Neurosurgical Principles, Radiosurgical Technology, and the Manipulation of Energy Beam Delivery

The fundamental principle of radiosurgery is the focusing of energy within a contained target with minimal injury to surrounding structures. Various methodologies for improved radiation beam generation and beam delivery have been developed to optimize conformal therapy. This article, the second in a three part series reviewing the history of radiosurgery, examines the development of stereotactic principles and their application to radiation treatment as a methodology for containing energy within a target. The evolution of stereotactic radiosurgical instruments are evaluated as well as various devices designed to manipulate beam delivery for conformal therapy. Different radiosurgical modalities are also compared with regards to issues of mechanics, geometry, dosimetry, and economics. **[p. 433]**

Effects of Tobacco Dose and Length of Exposure on Delayed Neurological Deterioration and Overall Clinical Outcome after Aneurysmal Subarachnoid Hemorrhage

The association between smoking and intracranial aneurysms is now well recognized. However, the relationship between tobacco use and outcome after aneurysmal subarachnoid hemorrhage (SAH) is less well understood and published results are contradictory. This retrospective study examines the influence of tobacco exposure/dose on delayed neurological deterioration and clinical outcome in 320 patients with SAH. The results found that tobacco use was associated with delayed neurological deterioration, particularly in patients that were long-term or current smokers. However, no tobacco use variable was associated with clinical outcome. Despite this, this study does suggest that the timing and duration of tobacco use may be more important than the actual dose of tobacco in predicting the occurrence of delayed neurological deterioration, and that the distribution of various patterns of tobacco use within a dataset may influence the overall results of a given study. **[p. 475]**

De Novo vs. Transformed Atypical and Anaplastic Meningiomas: Comparison of Clinical Course, Cytogenetics, and Outcome

The clinical course of patients with atypical or anaplastic meningiomas can be quite heterogeneous. To gain insight on the factors that influence this behavior, data from 36 patients with atypical or anaplastic meningiomas were examined retrospectively. This study compared the differences in clinical behavior, cytogenetics, cytokinetics, receptor status, and outcome between de novo malignant meningiomas and those that progressed to malignancy from benign tumors. The study found significant differences in hormone receptors, proliferative indices, cytogenetic findings, and survival between these subtypes. The authors conclude that different subtypes of atypical and anaplastic meningiomas may exist. However, further studies are necessary to confirm this. **[p. 495]**

Minimally Invasive Lumbar Discectomy in Obese Patients

Spinal surgery in obese patients is associated with an increased risk of complications. Minimally invasive surgery has the advantage of smaller incisions and thus, theoretically, a smaller risk of infection. This study retrospectively examines the outcome and complication rates in a series of 32 patients with body mass index (BMI) greater than or equal to 30 who underwent minimally invasive lumbar microdiscectomy. The method of study included chart review, followed by telephone interview if important information was missing from the chart. The study found that almost all patients had a favorable outcome, with all but one reporting that they would undergo the intervention again. The overall complication rate was 12.5%. A trend toward lower infection rates was also noted. This approach may be the preferable approach for lumbar herniated disks in the obese patient population. **[p. 539]**

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Are We "Ishmael"?

"Call me Ishmael"

Herman Melville, ***Moby-Dick***

In the stream of history, neurosurgery does not exist in a vacuum. It exists as a miniature component of the global macrocosm of medicine, arguably as one of its crown jewels.

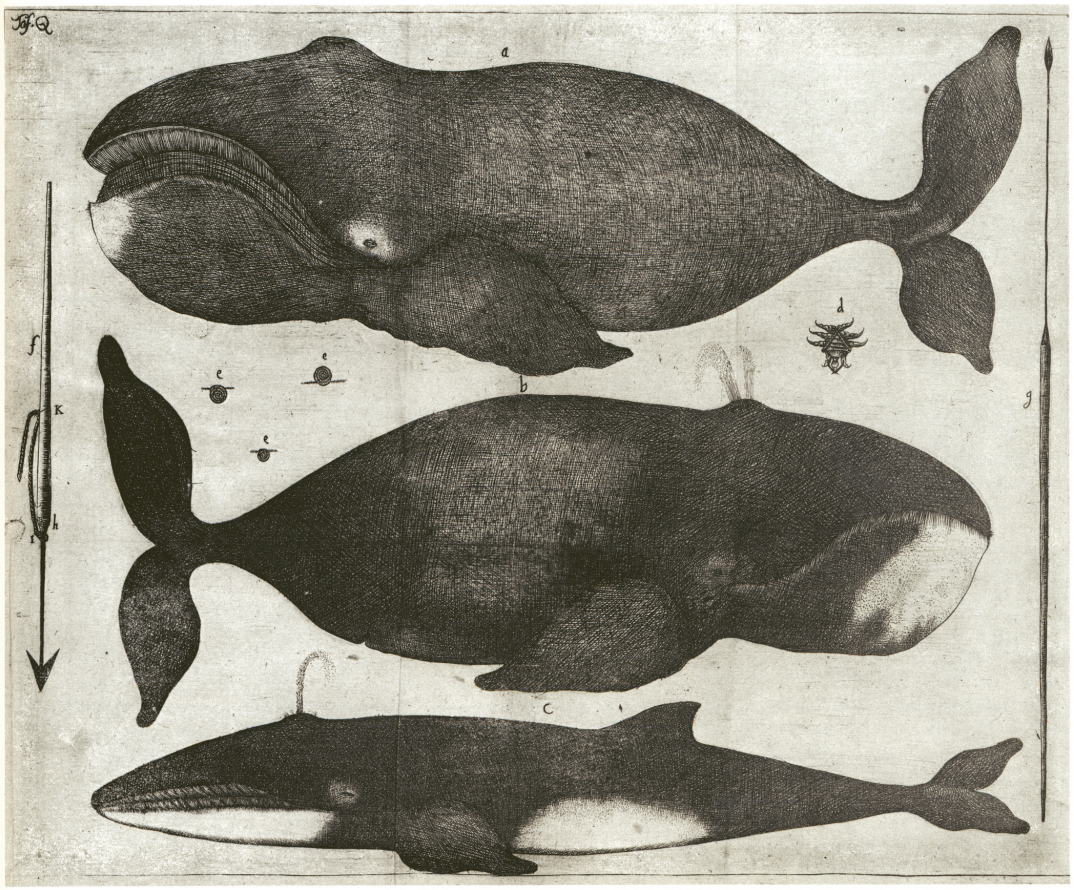
Medicine is sustained and driven forward by a number of principle forces:

1) National economic vitalities
2) Popular attitudes and demands
3) Energizing global intellectual, affectual, and economic buoyancies
4) Parallel progress in transferable technical and biological areas
5) Crises and situations, real and perceived

Neurosurgery is at the edge of what is a fragile process - at once a societal luxury, a manifestation of robust sophistication and economic well being, while simultaneously being vulnerable to the vicissitudes of those economic and public attitudes which are the basis of its own vitality and existence. Its relevance to the everyday lives of most of the world's population is remote. Because of the relatively small number of practitioners in parallel with a low incidence of appropriate treatable diseases, the influence of those who would be spokesmen at regional or national levels is muted and hardly substantial in the forces of influence. Neurosurgery was the final elegant surgical specialty to evolve in the development of modern medical practice and the first to suffer in difficult economic times or when individuals collectively hold the value of medical care and its practitioners in less esteem, asserting right over privilege.



Cachalot Fishery, *detail (colored aquatint, 1834) by Ambroise Louis Garneray. Courtesy of the New Bedford Whaling Museum.*



Bowheads, a finback, sea snails, sea louse, harpoon, and lance, *(engraving, 1675) by Friderich Martens.*

During these times, on virtually every continent, the previously socially elevated status of neurosurgery and its practitioners is losing ground and, in some respects, losing the strength of presence that it had enjoyed in the first century of its modern emergence. This begs the question: Are we, in neurosurgery, a medical counterpart to the Biblical outcast Ishmael (Genesis 16:12) or Melville's remote observer in the unfolding drama - an individual without influence in the dramatic plot or passion of the moment? I suspect that many colleagues that have been in situations which have evolved in the past decade would emphatically agree.

The situation is often exacerbated internally as hospital and university administrators more frequently interfere in legitimate academic process and fail to support progressive academic enterprise, while focusing purely on economics, expediency, or satisfaction of the pursuit of personal chronyism. This is a prevailing occurrence that has initiated pessimism and disheartenment in young academicians, a group who historically have provided principal progress in our field.

However, the situation under global scrutiny is hardly monolithic. Importantly, neurosurgery's buoyancy is sustained by a remarkable vitality and emerging clinically applicable innovations in the field of imaging, genomics, molecular and cellular biology, biotechnology and nanotechnology—areas that have created a wave of practical realization of current clinical benefit as well as expectations for remarkable advances in the near future that will revolutionize the role and character of neurosurgery and its capabilities for dealing with currently stale and seemingly insurmountable challenges.

In many ways, neurosurgeons are medical counterparts to astronauts, achieving in many cases what once was considered unthinkable and existing under continuous critical scrutiny regarding the overall societal value of cost versus spectacular enterprise. Our activities, like those of astronauts, have served global society well, with multiple secondary ramifications of our development affecting the practice of medicine globally—for instance, endoscopy, navigation, and minimally invasive techniques. Applications in emerging sciences will, through our employment in neurosurgery, effect changes in many other disciplines.

Currently, no field of surgery or medicine can look to these advances with the anticipation or expectation of our next generation, a reality that should be energizing and highly restorative to the optimism of all of us.

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CHAINED LIGHTNING, PART II: NEUROSURGICAL PRINCIPLES, RADIOSURGICAL TECHNOLOGY, AND THE MANIPULATION OF ENERGY BEAM DELIVERY

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THE FUNDAMENTAL PRINCIPLE in the radiosurgical treatment of neurological conditions is the delivery of energy to a lesion with minimal injury to surrounding structures. The development of radiosurgical techniques from Leksell's original design has focused on the refinement of various methodologies to achieve energy containment within a target. This article is the second in a series reviewing the evolution of radiosurgical instruments with respect to issues of energy beam generation and delivery for improved conformal therapy.

Continuing with concepts introduced in an earlier article, this article examines specific aspects of beam delivery and the emergence of stereotactic radiosurgery as a measure for focusing energy beams within a target volume. The application of stereotactic principles and devices to gamma ray and linear accelerator-based energy sources provides the methodology by which energy beams are generated and targeted precisely in a focal lesion. Advanced technological systems are reviewed, including fixed beams, dynamic radiosurgery, multileaf collimation, beam shaping, and robotics as various approaches for manipulating beam delivery. Radiosurgical instruments are also compared with regard to mechanics, geometry, and dosimetry. Finally, new radiosurgical designs currently on the horizon are introduced. In exploring the complex history of radiosurgery, it is evident that the discovery and rediscovery of ideas invariably leads to the development of innovative technology for the next generation.

KEY WORDS: Medical technology, Minimally invasive surgery, Radiation oncology, Radiation physics, Radiosurgery, Radiotherapy, Stereotactic neurosurgery

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Throughout its evolution, radiosurgery has been guided by the fundamental principle that energy is focused within a targeted lesion while minimizing injury to surrounding tissue (52). As previously discussed, the primary means for energy containment can be achieved through the exploitation of properties of beam generation or the manipulation of beam delivery (42). Initial approaches in radiosurgery focused on beam generation and the creation of particle beams as a technique for applying their unique properties for effective energy containment. Bragg peak characteristics and high linear energy transfer radiation for charged particle beams were used to concentrate and contain doses of radiation in targeted lesions while minimizing energy deposition to surrounding structures.

The concept of energy containment within a target volume is of particular concern to neurosurgery. Because of the close proximity of critical structures in the brain, reducing radiation to overlying and surrounding tissues is essential. Accordingly, a Swedish neurosurgeon, Lars Leksell (*Fig. 1*) (55–57), made the first technological advances toward improving radiosurgical beam delivery. The application of stereotactic principles with isocentric targeting afforded the potential for delivering concentrated radiation precisely to a target with a sharp dose falloff to surrounding tissue. This enterprise, termed stereotactic radiosurgery by Leksell, led to a blossoming in the use of radiation for treating central nervous system diseases. Radiosurgery today is still based on Leksell's original principles.

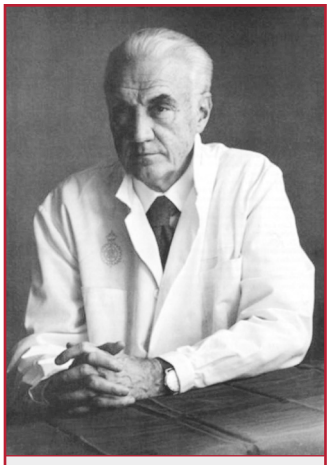


FIGURE 1. *Photograph of Lars Leksell, Swedish neurosurgeon, and pioneer of stereotactic radiosurgery.*

However, the incorporation of modern technology such as computed tomographic (CT) and magnetic resonance imaging (MRI), computers, and robotics have equipped radiosurgery for the next generation.

This article, the second in a series examining the evolution of radiosurgery, specifically explores the development of stereotactic radiosurgery as a means of affecting beam delivery. The application of stereotactic principles and head frames as a method for precision lesion localization is reviewed. Gamma ray and linear accelerator (LINAC)-based sources for beam origination are evaluated. Fixed-beam systems, dynamic radiosurgery, beam shaping, and robotic beam delivery are examined as strategies for energy containment. In addition, issues for consideration and further development with respect to mechanical and geometric limitations, dosimetric comparisons, and economic factors are presented.

Lesion Localization

Stereotactic Principles

In radiosurgery, aligning the energy beam with the target requires the ability to precisely localize a lesion in three-dimensional space. Stereotaxy developed as a method for using a reference frame from which Cartesian coordinates could be derived to describe an intracranial target in space. The first use of stereotaxy began as early as 1908 when the neurosurgeon Sir Victor A.H. Horsley and the engineer Robert H. Clarke described a technique for placing electrodes in the dentate nucleus of animals (43). Applying these principles, Horsley and Clarke were able to map structures in the monkey brain based on coordinates relative to skull landmarks.

Spiegel et al. (89) first used stereotactic devices in humans with the design of the stereoencephalotome in 1947. This device consisted of a ring that encircled the patient's head, which was aligned and affixed to the patient through the external auditory canals and with orbital tabs. Using pneumoencephalography, Spiegel and Wycis (86–88) were able to localize intracerebral landmarks and guide treatment of movement disorders, chronic pain, psychiatric conditions, and epilepsy. This work was paralleled by Leksell (55–57), who advanced stereotactic practice by using skull pin fixation for rigid frame immobilization and improved localizing precision. Leksell used this device to develop focused beam radiation therapy for the treatment of movement disorders. Subsequently, a number of centers began investigating stereotaxy as a method for performing ablative procedures for a number of neurological disorders (18).

The advent of CT imaging further advanced the clinical application of stereotaxis. Axial CT imaging allowed for both diagnostic identification of lesions and facilitated the precise calculation of their anteroposterior and lateral coordinates. Accurate measurement of vertical coordinates was made possible by the development of the Brown-Roberts-Wells frame and the N-shaped rod localizer (13, 14, 40). The localizer consists of a total of nine fiducial rods: three sets of three rods (two vertical, one diagonal) arranged in an N-shaped configuration. Computer software was designed to analyze an axial CT image transecting a single plane through all nine rods. By referencing distances between the diagonal and vertical rods, differences in angulation could be accounted for to determine exact vertical coordinates (18). Using anteroposterior, lateral, and vertical dimensions, any intracranial point could then be localized by x, y, and z coordinates relative to the base frame. These same mathematical concepts were applied to the use of stereotactic frames and magnetic resonance imaging.

Stereotactic Frame-based and Frameless Localization

The primary requirement for precision stereotactic treatment is a method by which any arbitrary point or volume within the head or body can be identified with confidence and then accessed for treatment. The initial solution to this task is the classical stereotactic method using a head frame, imaging localization such as ventriculography or angiography, and a stereotactic atlas. Over the years, various neurosurgeons and engineers have designed particular stereotactic frame systems adapted for specific methodological and workflow approaches. The advent of planar imaging technique such as CT and MRI have allowed stereotactic surgeons to dispose of the old indirect means of imaging with atlas localization for a more direct image-guided approach.

Within the context of modern image-guided stereotaxy, the function of stereotactic head frames are: 1) head immobilization, 2) referencing a CT or MRI scan to a stereotactic coordinate system, and 3) providing the stereotactic coordinates by which the radiation beam can be aligned and targeted (58). The recent development of staged or fractionated stereotactic radiosurgery introduces the capability for repeated frame application.

Head frame devices are categorized as either minimally invasive or noninvasive systems. Minimally invasive systems are conventional head fixation devices, which use penetrating cranial pins for rigid immobilization. Current systems consist of either an MRI or CT-compatible base ring that is affixed to the cranium by four pins that pierce the scalp and the outer table of the cranium. MRI-compatible base rings are used for same-session imaging for both diagnostic and treatment planning. Conversely, CT-compatible base rings allow for image fusion of a treatment session CT with a pretreatment MRI scan, on which a plan has been dictated in advance of treatment. Fusing CT base ring imaging with a preoperative MRI scan facilitates the efficiency of both treatment planning and execution. Once imaging with the affixed base ring is obtained, a fiducial local-

izer box is attached to the ring and is used to transform coordinates from the reference CT or MRI scan to a stereotactic coordinate system established by the base frame. Once the stereotactic coordinates of the target are identified, the base ring can be attached to the treatment unit for rigid immobilization and alignment of the radiation beam with the target.

Noninvasive systems use a mask that has been specifically molded to the external contour of the patient's face. Development of vacuum-formed and thermoplastic masks has facilitated ease of fitting, application, and increased patient comfort while maintaining a high degree of accuracy and positioning reproducibility (*Fig. 2*) (92, 94, 97). Modification with an upper jaw ("bite block") or ear canal fixation device can further improve positioning reproducibility (e.g., Gill-Thomas-Cosman frame) (25, 33, 38).

These conventional, noninvasive mask systems suffer in comparison with frame-based systems from the standpoint of overall accuracy of interfraction repositioning error and intrafraction motion. As a result, these systems are generally not used for high-precision single-fraction treatments such as those for functional indications. In addition, margins may need to be increased to reliably dose the treatment volume.

To circumvent these limitations of conventional stereotactic frames and mask devices, advanced image-guided techniques have been developed that turn the entirety of the radiation vault into a stereotactic apparatus. These image-guided approaches, when coupled with a radiation treatment system, are termed image-guided radiotherapy/radiosurgery. Techniques include stereoscopic fluoroscopy, which uses orthogonal x-ray machines to perform real-time imaging of the patient, which is then corroborated with a reconstructed reference CT scan (51). Millimeter deviations in the digitally reconstructed x-rays are translated into a corresponding change in the position of the target. The treatment beam can then be adjusted to re-aim the beam toward the target's "new" coordinates.

Another technique uses an optical tracking system in which room-mounted infrared video cameras sense the position and orientation of the mask, thereby making appropriate micrometer adjustments of the patient headrest or couch to realign the patient with the beam (66). Some LINAC-based radiosurgical units use a hybrid system of stereoscopic fluoroscopy in conjunction with an infrared camera system. More recently, devices have been equipped with an on-board cone-beam CT imaging system. Several newly developed LINAC-based radiosurgical systems use a cone-beam CT system in which a kilovolt x-ray source and flat-panel detector are mounted on a LINAC gantry unit. With gantry rotation, three-dimensional volumetric CT images are generated, which are crosscalibrated with the treatment delivery system.

By using image guidance in concert with robotic patient couch positioning, accuracy rivaling conventional pin-fixed stereotactic localization can be obtained. Phantom testing has demonstrated positioning errors of less than 1.0 mm using a frameless image-guided LINAC unit (100). Although the use of many of these advanced frameless imaging technologies provides submillimetric positioning accuracy, stabilization of the target during frameless radiation delivery remains a primary distinction from conventional fixed-frame systems.

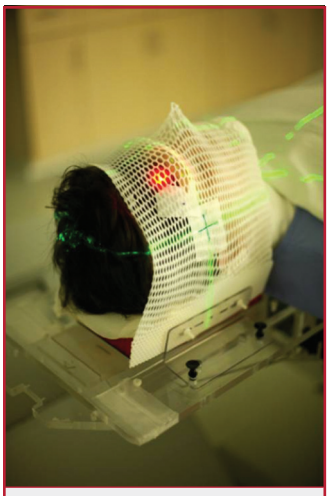


FIGURE 2. *A thermoplastic mask is used for stereotactic radiosurgery.*

Beam Generation

Gamma Knife Radiosurgery

The original gamma knife radiosurgery unit designed by Leksell consisted of directing multiple 200-kV x-ray beams at a stereotactically defined target. Modern gamma knife units use up to 201 radially convergent ^{60}Co sources set in a hemispheric shell (*Fig. 3, A–C*) (59). The ^{60}Co sources emit photon energy by undergoing radioactive decay to ^{60}Ni. The half-life of ^{60}Co is 5.27 years. In the process of decay, ^{60}Co emits one electron with an energy of up to 315 keV and then two gamma rays with energies of 1.17 and 1.33 MeV. Each source provides a radiation beam that is individually collimated and set precisely to aim at a single focal point at the isocenter of the hemisphere.

In the modern era, gamma knife radiosurgery is performed with a stereotactic frame rigidly affixed to the patient's head. MRI or CT scans are performed with a fiducial localizer for target localization. Treatment planning is then performed using computer software that references the target to the base frame and allows for the creation of a dose plan constructed from either single or multiple isocenters. Multiple isocenters are used to optimize conformation of dose to irregularly shaped or large target volumes. For each target point or "shot," the head frame is rigidly affixed to the system helmet by a pair of trunnions. The trunnions are manually or automatically set according to the defined x, y, and z coordinates for the given "shot."

LINAC-based Radiosurgery

LINACs use electromagnetic waves to accelerate electrons through a tube. The basic LINAC design consists of an electron gun, which injects electrons into an evacuated copper tube, and a microwave generator, which creates sinusoidal fields that confer energy to the electrons. The electrons gain energy and accelerate through and exit the tube, striking a target and producing x-rays. Typical x-rays generated by modern LINACs differ from gamma rays produced by isotope decay in that x-rays are produced over a range of energies, although these energies tend to be higher (4–6 MeV) than those of ^{60}Co. Such higher energies allow a greater proportion of energy deposition to deeper structures.

The first LINAC for clinical radiotherapy was instituted at the Hammersmith Hospital in London in 1952 (93). The first

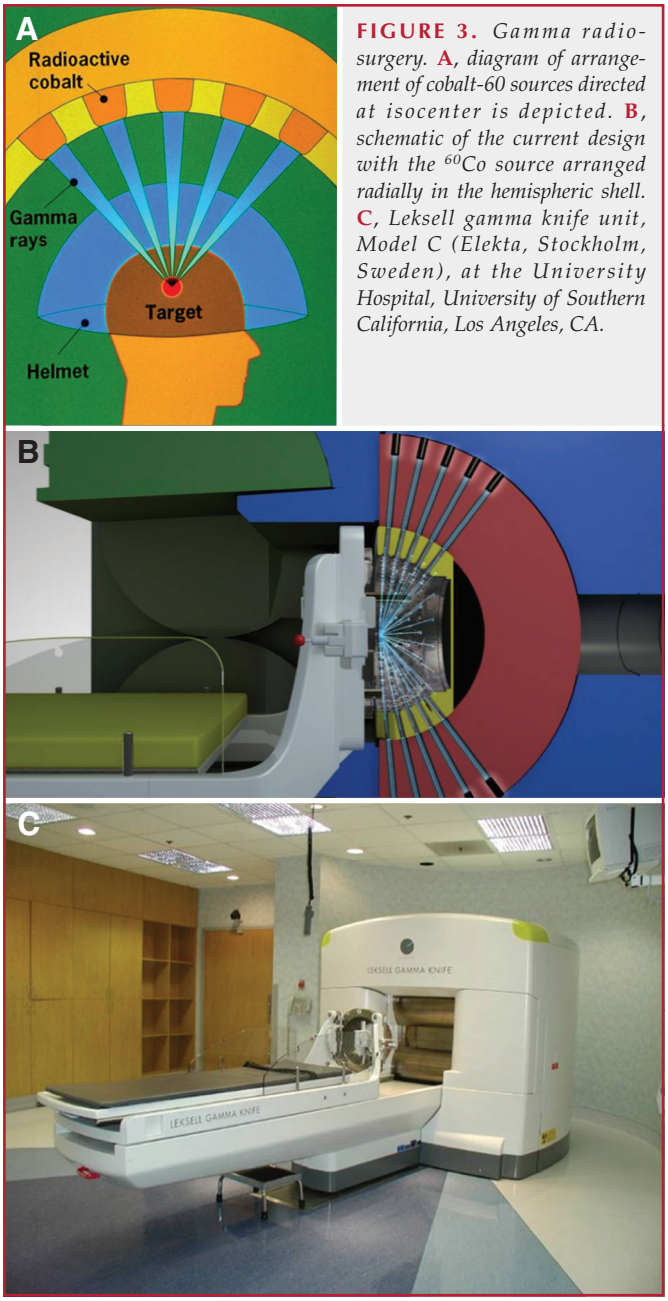


FIGURE 3. *Gamma radiosurgery.* **A**, *diagram of arrangement of cobalt-60 sources directed at isocenter is depicted.* **B**, *schematic of the current design with the* ^{60}Co *source arranged radially in the hemispheric shell.* **C**, *Leksell gamma knife unit, Model C (Elekta, Stockholm, Sweden), at the University Hospital, University of Southern California, Los Angeles, CA.*

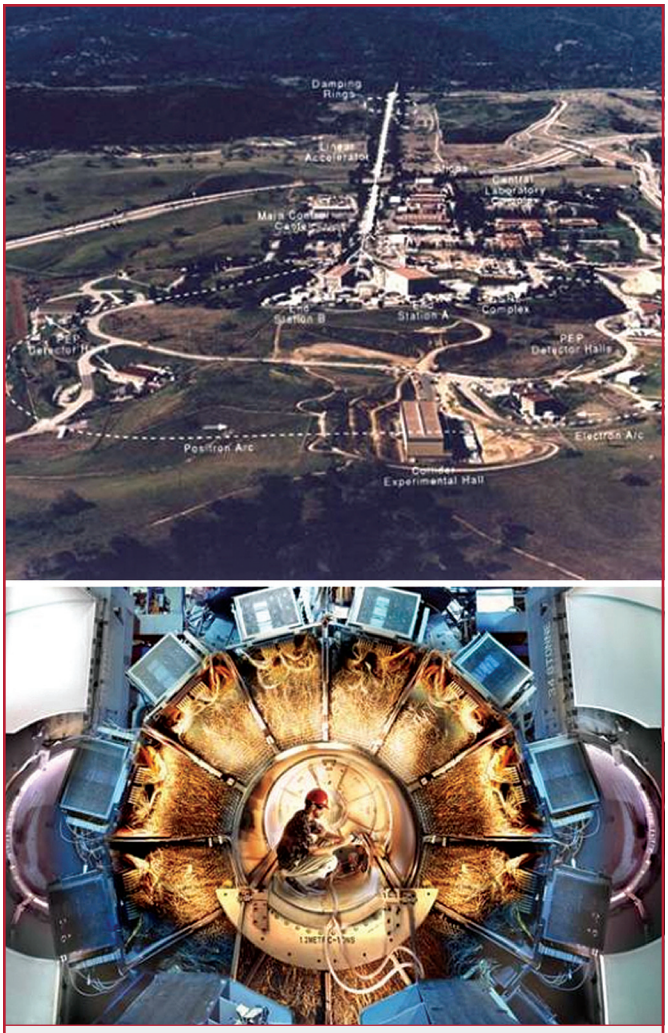


FIGURE 4. **A**, *photograph of the Stanford LINAC research facility.* **B**, *photograph of a technician making adjustments from within the Stanford LINAC. The Stanford LINAC, first established in 1962 at Stanford University, is an electron accelerator designed for high-energy physics research.*

clinical LINAC in the United States was installed at Stanford University in 1954 (*Fig. 4*) (93). The basic LINAC design has been adapted for clinical use in hospitals with rotating isocentric gantries and position-adjustable couches to facilitate treatment and patient comfort.

The adaptation of radiotherapy LINACs for stereotactic radiosurgery was first described in 1984 by Betti and Derechinsky (6, 7). Since then, several subsequent modifications have been, and continue to be, developed (19–21, 31, 39, 62, 73). Like gamma knife radiosurgery, LINAC-based radiosurgery consists of a collimated radiation beam focused on a stereotactically identified target. Unlike the gamma knife unit, a LINAC has only one source of radiation. Therefore, multiple static beams or arcs that converge on the target volume must be used. This is accomplished by using a gantry that rotates over the head of the patient thereby producing an arc of radiation with the isocentric target at its focus (*Fig. 5, A–C*). During treatment, the patient couch can then be angled in the horizontal plane to produce another arc of radiation. With simultaneous gantry and couch movement, multiple noncoplanar intersecting arcs can be created ("dynamic radiosurgery") (72, 73). The intersecting arcs produce a concentrated dose at the isocenter with a sharp dose falloff to surrounding tissue.

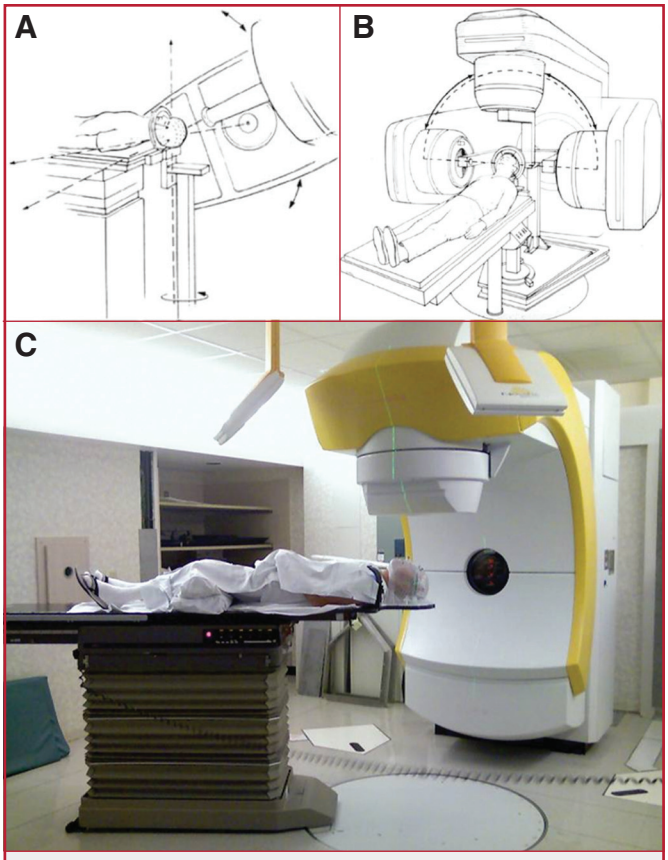


FIGURE 5. *LINAC-based radiosurgery.* **A**, *illustration showing the alignment of the target at the stereotactic isocenter.* **B**, *illustration showing the gantry arc rotation around the isocenter.* **C**, *setup of the Novalis Shaped Beam Surgery unit (BrainLAB, Heimstetten, Germany), a dedicated LINAC-based radiosurgery system.*

A set of circular secondary collimators of varying aperture can be used together with the built-in LINAC rectangular collimator to conform the beam to a number of projected isocenter sizes. Like gamma radiosurgery, multiple isocenter treatment with varying arc weighting can be performed for improved dose conformity to nonspherical and irregularly shaped lesions. Unlike the gamma unit, LINAC-based radiosurgery requires rotation of the gantry and couch for each noncoplanar arc, but with modern high-dose rate systems, multiisocentric treatment times now are comparable to gamma radiosurgery sessions.

Robotic Radiosurgery

Gamma radiosurgery is a frame-based system and is, therefore, subject to inherent limitations of frame-helmet geometry. The use of a frame with cranial pin fixation also makes fractionation of radiation of primarily intracranial pathology somewhat cumbersome. In addition, the use of frame-based stereotactic localization is impractical for extracranial disease. To overcome these obstacles, several frameless radiosurgery systems have been developed. One modality, pioneered by John Adler at Stanford University, combines industrial robotics with near real-time image guidance to introduce frameless robotic stereotactic radiosurgery (2, 51).

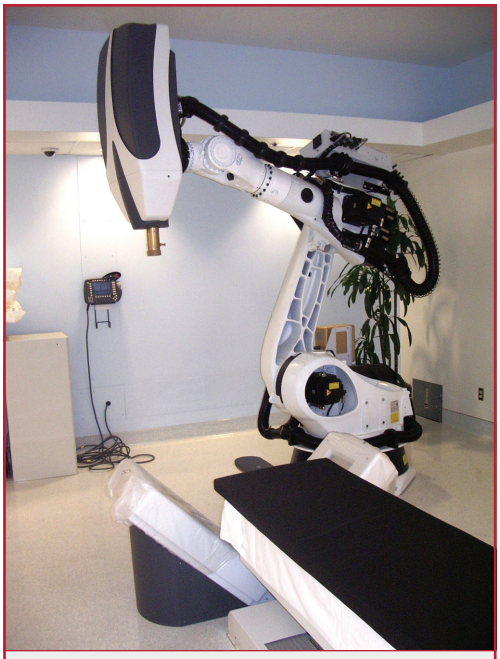


FIGURE 6. *Photograph of the Cyberknife unit (Accuray, Sunnyvale, CA) at the Norris Cancer Hospital, University of Southern California, Los Angeles, CA.*

Robotic radiosurgery consists of a lightweight (130 kg) 6-MV LINAC mounted on a robotic arm capable of aiming along six different axes (*Fig. 6*). The live image guidance is directed by two orthogonally placed x-ray sources pointed at amorphous silicon detectors that track patient movement. Digital x-rays of external cranial or spinal landmarks are imaged in real-time and compared with reference images reconstructed from a pretreatment CT scan (17, 41, 51). Computer processing measures the extent of movement of the target relative to the reference images (up to 10 mm in any direction) and relays the new coordinates of the target to the robotic arm/LINAC. Therefore, any patient movement is identified by the system and is translated into a change in position of the target. The robotic arm is then appropriately adjusted to re-aim the beam toward the new target position.

Gamma knife and LINAC-based radiosurgery systems rely on isocentric targeting and multiple converging beams to concentrate dose within the target volume. Robotic radiosurgery, however, because of its mobile LINAC, is capable of positioning along more than 100 arbitrary set points in space, each with multiple approach angles. This capability allows for multiple degrees of freedom in treatment planning and does not restrict robotic radiosurgery to only isocentric delivery (51). The robotic arm is only restricted in

aiming from beneath the treatment couch (i.e., posteroanterior in a supine patient) (102). Because radiation beams are not confined to isocentric geometry, they can be placed in complex overlapping patterns to conform to irregular tumor shapes. In addition, there is no arbitrary limitation in the size of the lesion that can be treated. Like gamma knife and LINAC-based radiosurgery, dose weighting and beam collimation (range, 5–60 mm) can be modulated to appropriately match the target size.

Energy Containment: Beam Delivery

Fixed-beam Delivery

Gamma Radiosurgery. To optimize energy containment within the target volume, stereotactic radiosurgery designs have been outfitted with various technical devices for beam shaping and delivery. Since its original design, gamma knife radiosurgery has primarily been a fixed-beam delivery unit (99). The gamma knife unit positions up to 201 ^{60}Co sources arranged on a hemispheric shell with each source aimed precisely at a single isocenter. The sources are arranged in a pattern that spans 30 degrees in the sagittal plane and 360 degrees in the transverse plane. The sources are primarily collimated by a fixed collimator, which is subsequently docked with an exchangeable "helmet" that consists of 201 collimators appropriately set to align with each source. Helmets with varying collimator apertures can be docked to define an approximately spherical dose distribution at an isocenter of 4, 8, 14, or 18 mm. In addition, each source in the helmet can be plugged with tungsten blocks to "turn off" certain beams, thereby altering the "shape" of the dose distribution to shield critical structures (30, 103).

Further conformality of the dose distribution is performed by the construction of multiple isocenters to create a planned treatment volume that appropriately matches an irregularly shaped target volume. "Sphere-packing" is the formation of a number of spherical isocenters of varying beam weighting, collimator sizes, and stereotactic coordinates such that the final dose distribution conforms to the target while minimizing radiation to surrounding tissue. In theory, a virtually limitless number of small isocenters can be "stacked" in a complex three-dimensional plan to achieve optimal conformality with the only restriction being the duration of treatment time.

To facilitate the sequential dosing of multiple small isocenters, current gamma knife units feature an automatic positioning system (APS) (48, 50). The APS device is characterized by computer-driven repositioning of the patient's head by precise robotic motors built into the system unit (*Fig. 7, A* and *B*). For a given multishot plan, the motors automatically reposition the head for each successive shot without the need for staff members being present in the radiation area. Studies have demonstrated that despite the increased number of moving parts, there is no loss of focusing precision resulting from progressive mechanical tolerances (84). Because the procedure for head positioning is directed by computer-driven motors, the potential element of human error in treatment planning and execution is eliminated (34).

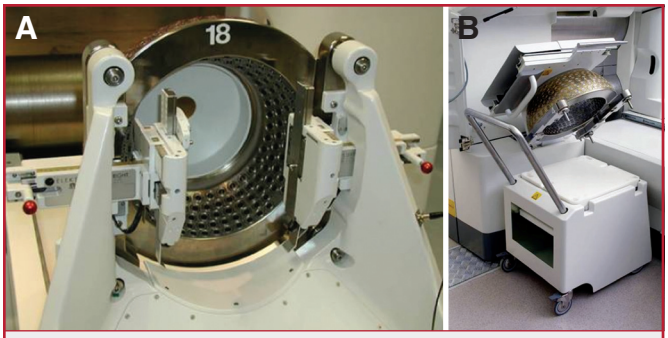


FIGURE 7. *Gamma radiosurgery fixed-beam delivery system.* **A**, *the collimator helmet is docked to the APS unit.* **B**, *manual exchange of various aperture collimators is performed.*



FIGURE 8. *LINAC-based radiosurgery tertiary collimators.*

LINAC-based Radiosurgery

LINAC-based radiosurgery consists of either a conventional radiotherapy LINAC that has been modified for radiosurgery use or a LINAC designed specifically for radiosurgery. Both units create a rectangular beam shape through primary or secondary collimators built into the head of the machine. When a conventional radiotherapy LINAC is adapted for radiosurgery, additional collimators are outfitted to the beam head and necessitate appropriate quality assurance testing before use. For the treatment of smaller intracranial lesions, further collimation is achieved with a variety of tertiary collimators with ranges of aperture sizes to create sharp penumbras on the order of 2 to 4 mm. Circular collimators are designed and machined to create spherical dose distributions (*Fig. 8*).

The combination of gantry and couch rotation results in a variety of different techniques for beam delivery (39, 44, 62, 73). With multiple arc delivery, a large number of beam entry points spanning a large area of the patient's head results in a concentrated dose in the target area with minimized dose to normal tissue. LINAC units retrofitted with a pedestal-mounted stereotactic system restrict full gantry rotation around the treatment

couch, whereas couch-mounted systems and modern dedicated radiosurgical units allow for 360 degrees of arc delivery.

Optimizing arc parameters such as number of arcs, angular increment between arcs, beam weighting, and arc angles can be customized for each treatment to minimize the radiation that passes through sensitive structures. Multiple isocenters can also be constructed to conform to a nonspherical target volume. The addition of multiple isocenters with varying beam weighting may increase duration of the treatment session as a result of the manual switching out of different collimators; however, with modern high-dose rate LINAC-based radiosurgical units, treatment time for each isocenter can be performed in less than 10 minutes, comparing well with gamma knife treatment times.

Dynamic Beam Shaping

Micro Multileaf Collimators. The concept of beam shaping beyond conventional rectangular or circular apertures began in early radiotherapy. Simple beam modifiers, known as "wedges" or "compensators," were custom cut from lead alloy blocks for each specific treatment plan and patient (10, 36, 46, 61, 76). These modifiers function to selectively attenuate portions of the beam, taking into account the "beam's eye view" from multiple different static beam positions, thereby ensuring homogeneous dose distribution throughout the target. The laborious process of machining a large number of blocks for each patient, and manually switching the compensators with adequate test verification, however, made treatment delivery time-consuming and impractical.

Beam shaping in radiosurgery began with simple constructs using four independent rectangular jaws that were modulated across the beam to conform to the beam's eye view projection of the target (35, 53). The advent of multileaf collimation, first developed in Japan in the 1960s, represented a significant technological advancement in beam shaping and delivery (91). By manipulating multiple computer-driven tungsten leaves that can be moved against each other across the beam head, a variety of field openings are created to conform to the spatial organization of the target in the beam's eye view. Treatment planning can be performed with specified leaf configurations for each individual static field position (three-dimensional conformal therapy) (15, 26, 37, 90). Alternatively, the intensity of incoming beams can be dynamically modulated by constantly shifting the leaves as the gantry rotates through a series of segmented static fields (intensity modulated radiotherapy [IMRT]) (8, 9, 45a). With IMRT, the beam intensity is appropriately increased or decreased to shape the beam to irregular concave surfaces or to shield critical structures.

Conventional multileaf collimators were designed with leaf widths unsuitable for treating smaller intracranial lesions. Development of the first micro multileaf collimator for radiosurgery was based on the basic leaf architecture of the standard Varian MLC (Varian Medical Systems, Palo Alto, CA) (22, 85). The current micro multileaf collimator design consists of 26 pairs of tungsten leaves, which move perpendicularly to the beam's central axis (*Fig. 9*). The leaves are of varying widths with the central leaves being 3 mm to allow for fine adjustments for smaller targets. The intermediate and outer leaves are 4.5 and 5.5 mm, respectively. Each microleaf is driven by a 10 mm diameter motor that also provides positional feedback by relaying the number of rotations of the motor shaft for each leaf. Micro multileaf collimation allows for dynamic modulation of the beam to produce conformal field shapes throughout a single arc, introducing the advantages of three-dimensional conformal radiotherapy techniques to stereotactic radiosurgery (5, 54).



FIGURE 9. *Micro multileaf collimation.* Courtesy of, *BrainLAB, Heimstetten, Germany.*

Lesion Targeting

Dose Planning

Part of effective targeting and conformal beam delivery rests on the facility by which the radiosurgical team is able to create an optimized dose plan that matches the three-dimensional contour of the target volume. Advances in computers and planning software have significantly improved the efficiency and user interface of radiosurgical planning systems. These developments include faster, more powerful computer workstations, high-resolution MRI and CT scans, and Ethernet connections for immediate transfer of the diagnostic images to the planning system.

Creating a treatment plan for gamma knife radiosurgery requires a complex set of operations orchestrated by the radiosurgical team and planning software capable of performing the necessary calculations to execute the desired treatment. Once the target lesions are identified on the diagnostic images, three-dimensional dose matrices are constructed around each target. The matrices function to calculate the dose delivered to the target within each matrix as well as the relative contribution of any additional beams passing through the matrix en route to other lesions. Forward dose planning is performed by the radiosurgical team for each matrix by creating spherical isodose distributions within each target volume. The appropriate stereotactic coordinates and collimator size are selected for each individual shot. The tailoring of dose distributions to match the size and shape of the target volume is achieved through a method of trial and error. The prescribed dose to the specific isodose line and the weighting of each isocenter relative to each other is determined by the physicist and radiation oncologist. Finally, the treatment exposure time for each shot is calculated based on the prescribed dose and beam weighting while also accounting for cobalt source decay.

Modern planning software provides a useful feature in which the isodose planning takes place directly on the diagnos-

tic reference images. By incorporating the diagnostic images in the planning process, the surgeon and physicist can visualize the shape of the lesion, thereby outlining the contour of the target as well as surrounding critical areas. The software then reconstructs three-dimensional volumes based on these outlined structures, allowing for quick assessment of their spatial relationship (e.g., pituitary tumor versus optic nerve). Isocenters or "shots" can then be placed within the outlined target volume with immediate verification of target volume coverage as well as potential overlap of isodose curves to surrounding tissue.

Standard gamma knife planning software uses iterative or "forward" optimization of multiple isocenters, collimator sizes, and beam weighting to create a conformal dose plan. An alternative radiosurgical planning method was adopted from planning systems generated for conventional IMRT (27). The development of IMRT introduced a major innovation in radiation dose planning known as inverse treatment planning. This method was initially conceptually devised in the late 1960s and 1970s. At that time, however, clinical application of these techniques was impractical because of the lack of computer processing power necessary to develop treatment plans as well as the lack of standardized software and hardware tools.

Inverse planning represents a significant departure from classic radiosurgical methods that are forward-planned. The typical workflow pattern of forward planning involves the human-guided placement of radiation dose by manual arrangement of shots, beams, or arcs followed by examination of the dose distribution and recursive alterations of the plan to arrive at a final treatment plan. Inverse planning involves operator contouring of target structures as well as at-risk structures followed by assignment of dose constraints by the operator for these structures. A number of computer algorithms are then used to create a dose plan that attempts to fall within the operator-defined constraints. Computer processing then yields the appropriate beam arc, angle, weighting, and collimator leaf settings to achieve the prescribed parameters. Inverse planning has since become a primary planning modality for a number of current LINAC-based and frameless radiosurgical treatment platforms.

Issues for Consideration

Stereotactic radiosurgery is minimally invasive surgery in its most state-of-the-art form. It has become an essential component of the neurosurgical armamentarium and has widespread clinical applications (3, 4, 47, 65, 69, 70, 74, 75, 78, 83, 106). Gamma knife radiosurgery, LINAC-based radiosurgery, and robotic radiosurgery present a variety of options for the neurosurgeon to use for directing focused radiation. Each of these current modalities, however, presents unique issues with regard to their mechanics and geometry, dosimetry, and economic feasibility (*Table 1*).

Mechanics, Geometry, and Kinematics

Gamma knife radiosurgery achieves isocenter targeting by positioning the stereotactically defined target at the exact isocenter of the fixed ^{60}Co beams. Proper execution, therefore, depends on the ability to approximate the lesion within the center of the hemispheric collimator helmet. This methodology poses several practical issues unique to gamma radiosurgery. Patients with peripheral cranial lesions may not be able to be situated in the frame such that these lesions can be positioned near the isocenter of the helmet. As a consequence, superficial convexity or lower brainstem and posterior fossa lesions may extend beyond the geometric reach of the convergent beams. These constraints also limit the treatment of extracranial lesions. Additionally, with a larger patient head size, even more centrally located lesions may incur helmet-frame collisions and, thereby, prove difficult or impossible to treat.

LINAC-based radiosurgery functions by sweeping a gantry in a continuous arc over the stereotactic isocenter. Because the gantry creates a relatively large radial arc, there are no limitations regarding frame-gantry geometry as seen with the frame-helmet in gamma knife radiosurgery. Therefore, LINAC-based radiosurgery can accommodate lesions at the anatomic periphery, even in patients with larger cranial volumes. This frame-

TABLE 1. Issues unique to current modalities with regard to their mechanics, dosimetry, and economic feasibility.

	Gamma knife radiosurgery	Linear accelerator-based radiosurgery	Robotic radiosurgery
Radiation source	Cobalt-60	4 to 20-MV linear accelerator	Portable 6-MV linear accelerator
Beam delivery	201 isocentric fixed beams	Arc delivery, isocentric, dynamic	Robotic arm, nonisocentric
Immobilization	Frame-based	Frame-based and frameless capability	Frameless
Tracking/positioning	Fixed frame	Varies by manufacturer: stereoscopic fluoroscopy, infrared optical tracking, cone-beam computed tomography	Near real-time imaging with stereoscopic fluoroscopy
Fractionation capability	Not capable	Yes	Yes
Extracranial targets	Not capable	Yes	Yes
Cost of implementation	Approximately $3 million	Less than $2 million	Approximately $4 million

gantry setup also permits LINAC-based radiosurgery treatment to extend beyond cranial lesions to treat the spine and body as well (79, 80, 101).

LINAC-based radiosurgery, however, poses its own particular mechanical considerations. Conventional LINACs retrofitted with a floor-mounted stereotactic system preclude rotation of the gantry 360 degrees around the patient, thereby restricting beam delivery from beneath the couch (64). For supine patients with posteriorly located lesions, entrance beams must pass through a significant portion of normal tissue before converging on the isocenter. Current dedicated linear accelerator radiosurgical units, however, are designed to allow for complete 360-degree gantry rotation.

In the early development of LINAC-based radiosurgery, there was concern for a potential decrease in focusing precision as a result of the increased moving parts and a progressive loss of mechanical tolerances (98). With gamma knife radiosurgery, the patient is docked to the machine and the convergent beams are fixed in position. Even in APS mode, once the computerized motors align the appropriate stereotactic coordinates, the frame is locked in place for the duration of that shot. Conventional LINAC-based radiosurgery, however, relies on the intersection of three movable mechanical axes: gantry, couch, and collimator. Misalignment between the gantry and couch, irregularities in the bearings in which the gantry and couch rotate, and gravitational distortions resulting in gantry "sag" can contribute to uncertainty in beam accuracy (62).

Today, however, improved technology for current gantry and couch systems has significantly corrected for this potential loss in focusing precision. Current widespread implementation of dedicated stereotactic radiosurgery and radiotherapy units, which have been configured for high precision and stability in gantry, collimator, and table rotations, are demonstrating treatment accuracy that is comparable to gamma knife radiosurgery technology. Examination of a dedicated stereotactic radiosurgery LINAC shows variations in isocenter position with table, gantry, and collimator rotation to be less than 0.5 mm (23). Compounded accuracy for frame-based stereotactic radiosurgery was less than or equal to 1.0 mm and less than or equal to 3.0 mm for stereotactic radiotherapy using a relocatable frame.

Robotic radiosurgery consists of a mobile LINAC mounted on a robotic arm with six different axes of motion, thereby allowing for a virtually limitless number of beam angles and approaches. This advantage in mobility permits nonisocentric beam delivery unlike the kinematic restrictions of gamma knife and LINAC-based radiosurgery (16). Unlike gamma knife radiosurgery, this freedom in beam delivery also provides accessibility of stereotactic beam delivery to a full range of cranial, spinal, and body lesions (32, 81). The structural design of the robotic arm and couch unit, however, does result in limited beam access to posteriorly located lesions. In addition, the particular system arrangement of early models posed the potential for LINAC and camera collisions (102). Updated systems, however, eliminate this geometric restriction by positioning flat cameras parallel to the floor.

Frameless stereotactic radiosurgical systems with relocatable frames and live image acquisition also introduce the capacity for staged or fractionated treatment. Even with a frameless system and the unique advantage of repeated application, robotic radiosurgery has demonstrated an overall accuracy that may be comparable to frame-based radiosurgical systems (17). With a fixed-beam technique, we have measured the mechanical accuracy of our gamma knife unit over a 7-year period to be 0.14 ± 0.05 mm with a total clinical error of 0.66 ± 0.06 mm. Conversely, robotic radiosurgery systems have demonstrated an overall reported accuracy of less than 1 mm of the planned target (17, 67, 105).

Dosimetry

Although both gamma knife and LINAC-based radiosurgery provide conformal beam therapy through isocenter beam delivery, the two modalities have significant differences with respect to dosimetry. Gamma knife radiosurgery is conducive to delivery of complex multi-isocenter plans with conformal treatment of irregularly shaped lesions (96, 102). With the fixed-beam technique and APS, the treatment time per isocenter and between shots with a gamma knife unit is rapid. Using a conventional LINAC modified for radiosurgical use, accommodating a similarly complex multi-isocenter plan can pose a far greater challenge with respect to treatment planning and duration. Because multiple table positions and gantry angles must be used to deliver a conformal dose plan, treatment of irregular targets or multiple lesions in the past has typically been far more cumbersome with LINACs in comparison with gamma knife units (96, 104). Using simpler multi-arc single-isocenter plans with LINAC-based radiosurgery can also result in a greater volume of normal brain tissue irradiation (104).

Modern LINAC technology, particularly with dedicated LINAC radiosurgery units, however, has largely circumvented these limitations through several measures. Multileaf collimation and dynamic beam shaping provide for conformal radiation to irregular volumes through single isocenter delivery (5, 54). Alternatively, current high-dose rate LINAC units rapidly deliver radiation to an isocenter in less than 10 minutes, therefore allowing for multi-isocenter treatment with improved conformality and treatment times that compare favorably to the gamma knife unit. In addition, the use of intensity modulation planning and delivery techniques can result in workflows that are, in many instances, superior to gamma radiosurgical methods, at least for single lesions that are highly irregular. Treatment of multiple spheroid lesions, such as those that may be encountered with metastatic disease, however, continues to be more easily performed with gamma knife radiosurgery.

Gamma knife radiosurgery is characterized by its own dosimetric limitations and is generally reserved for lesions less than 3 cm in size (68). Because field sizes are limited, with the largest single spherical isodose being 18 mm in diameter, the stacking of multiple isocenters is necessary to construct larger dose volumes (64). However, with the increase in the number of isocenters, there is a consequent increase in entrance beams, resulting in a decrease in dose falloff surrounding the

lesion (96). In contrast, LINACs can be outfitted with a variety of collimators with a wide range of aperture sizes. As a result, LINAC-based radiosurgery has no practical field size limitation with appropriate collimation being used to treat lesions as large as 15 cm^3 (24, 60, 102).

The use of multiple isocenters in gamma knife radiosurgery can also result in significant dose inhomogeneities within the target volume (64, 96, 102). With additional isocenters, overlapping entrance beams can combine to escalate areas of substantially higher dose within the lesion. Dose inhomogeneities are further affected by the prescription isodose line. With a gamma knife unit, treatment to the 50% isodose line can create "hot spot" areas with an appreciably greater dose at the center of the target as compared with the periphery (71). LINAC-based radiosurgery with single isocenter treatment and higher percentile prescription dosing (e.g., 85 to 90%) generates a fairly homogeneous dose throughout the target (63, 102, 104). The clinical significance of dose inhomogeneities is unclear. Whereas previous reports indicate that dose inhomogeneities are correlated with patient complications (68), others suggest that when treating tumors, areas of escalated dose can contribute to improved tumor control (12, 71, 82).

Finally, current planning software for gamma knife radiosurgery creates isodose curves without accounting for heterogeneities of bone or air cavities. The operational program assumes that the cranium and its contents consist of uniform water density. Small aberrations in cranial thickness or sinus cavities, however, can contribute to slight differences in the attenuation of converging photon beams, thereby altering the resulting treated volume. The clinical significance of these minor tissue heterogeneities on treatment outcome is unclear. This marginal loss in dose precision may ultimately be offset by other variables such as consistency of frame immobilization, accuracy of image acquisition, translation of stereotactic coordinates, and instrument mechanical tolerances. For lesions that are close to, or involving, air sinuses, however, more sophisticated dose calculation algorithms, for example, Monte Carlo simulation, may be necessary to reduce dose calculation errors.

Economics

There are currently more than 100 gamma knife radiosurgical units in the United States (28). For a relative comparison, Novalis (BrainLAB, Heimstetten, Germany) and Trilogy (Varian Medical Systems) units, two competitive LINAC-based radiosurgical systems, alone number at approximately 100 centers in the United States (11, 95). This figure does not take into account other manufacturers' systems or the innumerable other hospitals using conventional LINACs modified for radiosurgical use. LINAC-based radiosurgery certainly offers an economic advantage in that a single clinical LINAC can be used for conventional radiotherapy and be modified for radiosurgery. In addition, staged radiosurgery and full fractionation stereotactic radiotherapy are possible with LINAC-based devices. The resource restraints of using one LINAC for multiple clinical services depend on optimizing scheduling and treatment times and accounting for appropriate quality assurance testing between uses. Installing a gamma knife radiosurgical unit comes at a substantial cost. Because gamma knife radiosurgery is currently limited to the treatment of only cranial-based lesions, implementation of a gamma knife unit may only be cost-effective for those centers with an appropriate clinical volume to support a dedicated gamma knife unit and its staff (29, 49).

Active robotic radiosurgery centers are numbered at greater than 50 in the United States and almost 100 facilities worldwide (1). Robotic radiosurgery provides several advantages, including the capability for both cranial and extracranial radiosurgery, as well as fractionated radiotherapy. The overall clinical equivalency of robotic radiosurgery to gamma or LINAC-based radiosurgery, however, remains to be determined before the economic benefit of widespread robotic radiosurgery implementation can be advocated.

Emerging Technology and Instrumentation

Leksell Gamma Perfexion. The Leksell Gamma Perfexion (Elekta, Stockholm, Sweden) is a new gamma knife design that provides several updated features that address some of the aforementioned issues. The primary advancement is a redesign of the collimator helmet to allow for expanded treatment reach and a wider range of accessible anatomic structures. The traditional hemispheric collimator helmet is replaced by a cylindrical design that permits extended caudal reach to include upper cervical lesions as well as extracranial head and neck tumors. The axial diameter of the collimator is also increased to facilitate positioning of peripheral lesions within the isocenter while reducing potential collimator-frame collisions (*Fig. 10, A–C*).

Whereas previous models provide multiple exchangeable collimator helmets with fixed apertures that necessitate manual changing between shots, the Perfexion contains a single collimator within the housing unit. The Perfexion collimator has built-in modulating apertures that automatically adjust to the appropriate size and can be blocked to shield critical structures. By automatically shifting the apertures internally, the time-consuming process of manually switching out helmets is eliminated. The final update of the Perfexion unit is to operate the robotic drivers for the automatic positioning system through the couch unit rather than the head frame. This improves patient comfort and provides for fully automated smooth transitioning between "shots" in a multi-isocenter treatment plan.

Image Guidance Radiotherapy and Radiosurgery: Extracranial and Fractionated Radiosurgery

As stated previously, precision in stereotactic radiosurgery relies on the accuracy by which any arbitrary point or volume within the head or body can be identified and accessed with the treatment beam. The goal is precise alignment of the treatment field with the target volume to allow for escalated radiation dose to the target with diminished radiation to adjacent normal tissue or organs at risk. The early development and success of stereotactic radiosurgery for the treatment of intracranial lesions may in large part be the result of the facility by which the cranium can be rigidly fixated and the relative lack of internal organ movement.

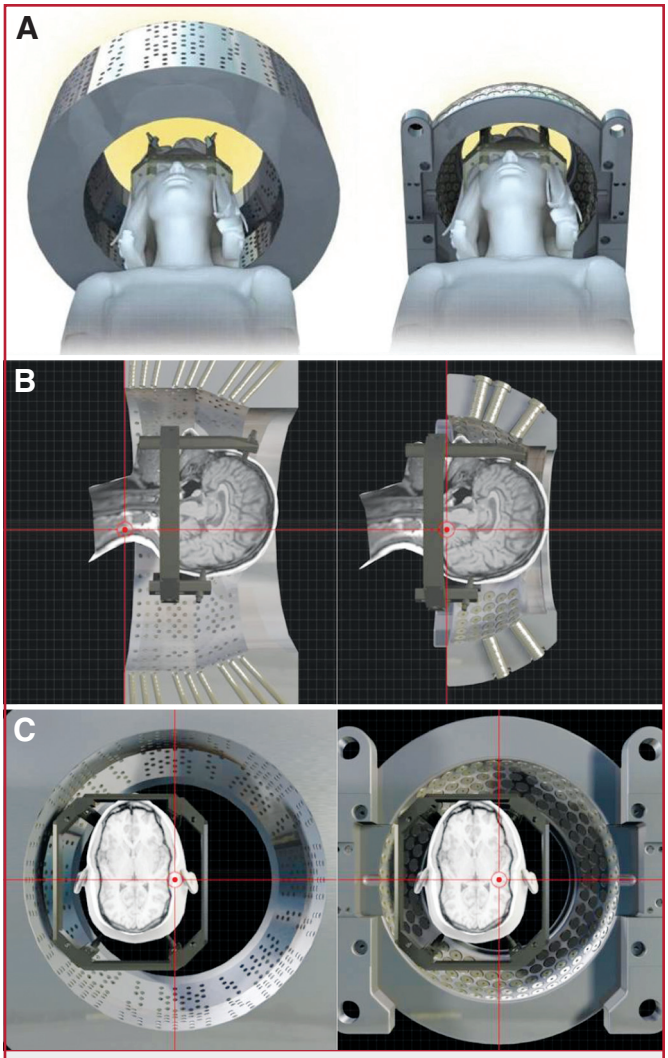


FIGURE 10. **A**, *the new design of the Leksell Gamma Perfexion (Elekta) collimator* (left) *is compared with the traditional Model C unit* (right). **B**, *extended caudal reach is demonstrated.* **C**, *with improved peripheral coverage.* Courtesy of, *Elekta, Stockholm, Sweden.*

Applying radiosurgery for the treatment of extracranial lesions or performing fractionated stereotactic radiotherapy, however, proves to be more challenging. Extracranial tumors can move during and between treatment sessions. Interfraction motion can occur with day-to-day changes in patient positioning, variable filling of gastrointestinal or urinary organs, and even changes in body weight. Intrafraction motion can occur with normal physiological processes such as respiration, cardiac and gastrointestinal organ movement, and voluntary patient motion. The combined variability of these factors can significantly alter the position of target lesions from moment to moment.

To circumvent these obstacles, several frameless technological strategies have been developed to allow precision radiation delivery for the treatment of extracranial lesions as well as capability for fractionated stereotactic radiotherapy. Further developments for robotic radiosurgery include a spine-tracking system, which uses enhanced digital x-ray registration of spinal bony landmarks to automatically locate and track tumors along the spinal column without the need for implanting fiducials. Respiratory tracking systems, for the treatment of lung tumors, correlate fiducials implanted near the pathology with infrared tracking markers on a specially designed vest worn by the patient. Information is relayed along fiberoptic cables to identify changes in target position during normal respiratory movements to appropriately align the beam in phase with the patient's breathing. In doing so, improved accuracy of target dosing, optimized patient comfort, and reduced treatment times are achieved by allowing the patient to breathe normally throughout the treatment.

Several dedicated LINAC units have been designed with image guidance technology to perform image-guided radiotherapy and radiosurgery for the treatment of extracranial lesions and for fractionated radiosurgery. Current gantry-based LINAC radiosurgical units are generally the result of multiple revisions to update these systems from initially frame-based cranial radiosurgery units to modern frameless image-guided units for the treatment of both intracranial and extracranial lesions. The majority of technological advancements, therefore, have largely been focused toward improving the image guidance component of the system to expand their treatment capabilities.

One such development is the use of stereoscopic x-ray imaging and infrared camera monitoring combined with a robotic treatment table that can correct for patient positioning in any of six dimensions. It, therefore, differs fundamentally from robotic radiosurgery in that instead of repositioning the radiation source to correct for patient motion, the couch unit moves the patient to align the target with the treatment beam. The image guidance is performed in two steps, the first of which uses infrared camera monitoring to visualize the movement of infrared markers attached to the patient's body. The second step uses two kilovolt x-ray tubes and an amorphous silicon flat panel detector to perform stereoscopic fluoroscopy for comparison with digitally reconstructed x-rays. The optical tracking system and the stereoscopic x-ray imaging are integrated with the treatment machine to automatically control couch movements for patient and target alignment.

Other developments in LINAC-based technology include on-board imagers designed to target and track tumors. The on-board imager integrates a kilovolt x-ray tube mounted on the gantry through two retractable robotically controlled arms that can each position along three axes for optimal imaging (45). The x-ray source is placed orthogonal to the treatment beam and a large flat-panel detector to perform radiography, volumetric cone-beam CT, or fluoroscopy. Cross-calibration of the imaging and delivery systems allows for high-quality volumetric CT imaging and treatment of soft tissue targets (i.e., lung, prostate, liver, etc.) without the use of implanted fiducials.

CONCLUSION

The evolution of technological measures for manipulating energy beam delivery has demonstrated the ability to effectively contain energy within a tight focus. The advent of stereotactic radiosurgery and the subsequent development of radiosurgical instruments reveal the immense potential for technology to harness energy forms for therapeutic benefit. The current implementation of stereotactic radiosurgery for a variety of neurological conditions underscores the importance of this development in neurosurgical practice. As described in an earlier article in this series (42), neurosurgeons have explored various methodologies to optimize energy containment with the use of radiation energy. Whereas particle therapy harnesses the biophysical properties of beam generation to concentrate energy within a target, stereotactic radiosurgery exploits technological means for manipulating beam delivery. With these preceding advancements in mind, Part 3 of this series of articles will introduce strategies for refinement of lesion localization, modulating radiation biological effect, and exploration of effective new energy modalities for radiosurgery.

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COMMENTS

The authors have provided an excellent summary of the various radiosurgical devices available at the present time. The authors not only summarize the differences between these devices, but also point out limitations that exist for each machine. Stereotactic radiosurgery continues to evolve and will play an increasing role in the future of neurosurgery. It is critical that neurosurgeons remain involved with the continued evolution of this field.

Steven D. Chang
Stanford, California

This article adds to the authors' initial publication (1) by addressing the technology of current radiation therapy techniques with a focus on how different strategies can be clinically useful. Like the first report, this is a lengthy article that covers a large amount of material. This review offers a comprehensive assessment that will be valuable to the readers. Lightning strikes twice in the same journal!

Joseph M. Piepmeier
New Haven, Connecticut

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1. Hoh DJ, Liu CY, Pagnini PG, Yu C, Wang MY, Apuzzo ML: Chained lightning, part 1: Exploitation of energy and radiobiological principles for therapeutic purpose. **Neurosurgery** 61:14–28, 2007.

Hoh et al. are to be congratulated on their informative review of the state of the art of the technological methodologies for stereotactic beam delivery in radiosurgery, as presented in Part II of their "*Chained Lightning*" series. This article represents a scholarly undertaking. Each of the systems has its unique advantages and disadvantages, which are outlined by the authors. Some of us who perform stereotactic radiosurgery may have experience with only one of the available systems reviewed. I look forward to Part III of their planned series.

Robert Goodkin
Seattle, Washington

Radiosurgery has gone through a rapid evolution in the past 10 years, and I am sure the field will continue to evolve with better software, faster computers, and more sophisticated means of localizing targets throughout the central neuraxis and beyond. If Moore's Law applies to this technology, we will witness treatment plans that will be automated and optimized for any target and systems that will be driven robotically to maximize daily patient volumes. The authors have taken on a heroic task and succeeded in doing a reasonable job summarizing this progress to date.

David W. Andrews
Philadelphia, Pennsylvania

CONGRESS OF NEUROLOGICAL SURGEONS' MISSION STATEMENT

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SURGICAL TREATMENT OF HIGH-RISK INTRACRANIAL DURAL ARTERIOVENOUS FISTULAE: CLINICAL OUTCOMES AND AVOIDANCE OF COMPLICATIONS

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OBJECTIVE: An increasing number of intracranial dural arteriovenous fistulae (DAVFs) are amenable to endovascular treatment. However, a subset of patients with high-risk lesions requires surgical intervention for complete obliteration. We reviewed our experience with the surgical management of high-risk intracranial DAVFs and offer recommendations to minimize complications based on fistula location and type.

METHODS: Hospital records for 53 patients (16 women, 37 men) with high-risk intracranial DAVFs treated surgically between 1995 and 2004 were reviewed to determine their presenting symptoms, location, endovascular and surgical interventions, angiographic outcome, and treatment complications. Most patients (76%) presented with intracranial hemorrhage, progressive neurological deficits, or seizures. All patients had high-risk angiographic features such as cortical venous drainage or venous varix. Preoperative embolization was performed in 27 patients. Surgical approaches were tailored to the lesion location. Fistulae were located in the transverse-sigmoid junction (n = 18), tentorium (n = 17), ethmoid (n = 7), superior sagittal sinus (n = 6), torcula (n = 4), and sphenoparietal sinus (n = 3).

RESULTS: At the time of the last follow-up evaluation, 49 patients (92%) had good or excellent outcomes (Glasgow Outcome Scale score, 4 or 5) and three (6%) were deceased. Five patients had a residual fistula. One residual spontaneously thrombosed, one was treated with gamma knife radiosurgery, and two were successfully embolized. The overall morbidity and mortality rate was 13%.

CONCLUSION: Despite fulminant presenting symptoms, high-risk intracranial DAVFs can be successfully managed with good outcomes. When anatomic features prevent endovascular access, or embolization fails to obliterate the lesion, urgent surgical treatment is indicated. Patients with residual filling of the DAVF should be considered for adjuvant therapy, including further embolization or radiosurgery.

KEY WORDS: Dural arteriovenous fistula, Endovascular treatment, Surgical results

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Dural arteriovenous fistulae (DAVFs) are defined as abnormal connections between an arterial feeder and a dural venous sinus or leptomeningeal vein with the nidus located within the dural leaflets. They compose 10 to 15% of all intracranial vascular malformations (17, 19, 31). DAVFs are uniquely suited for endovascular treatment. Endovascular techniques allow both arterial and venous access to the site of the fistulous connection. Endovascular strategies have become the treatment of choice for fistulae involving the cavernous sinus, transverse-sigmoid junction, and torcula (5, 6, 18).

DAVFs with leptomeningeal venous drainage or an associated venous varix are defined as high risk and are associated with a dismal natural history (11, 20). High-risk fistulae typically present with hemorrhage or progressive neurological deficits. Rarely are they clinically quiescent.

The majority of intracranial arteriovenous fistulae (AVFs) can be successfully managed with endovascular techniques. However, a

subset of patients harbors AVFs with anatomic features that require surgical treatment. We reviewed our experience with 53 patients with high-risk DAVFs that were not amenable to endovascular treatment. Based on this experience, we offer surgical techniques and caveats for treating DAVFs at various locations.

PATIENTS AND METHODS

All intracranial DAVFs with high-risk features were evaluated by a combined neurovascular team. The endovascular team determined whether patients were candidates for preoperative embolization and potential endovascular cure. If a fistula was not amenable to endovascular management (e.g. a lack of appropriate arterial or transvenous access) or not cured by embolization, the patient underwent surgical treatment.

Between 1995 and 2004, 53 patients (37 men, 16 women; mean age, 53.8 yr; age range, 4–85 yr) were identified as harboring high-risk DAVFs that were not amenable to endovascular cure. A database of patient information was maintained prospectively. Patient records, cerebral angiograms, operative reports, and clinical notes were analyzed retrospectively.

Twenty-two (42%) patients presented with intracranial hemorrhage, 13 (25%) with progressive neurological deficits, 10 (19%) with headache or bruit, and five (9%) with seizures. Fistulae were discovered incidentally in three (6%) patients. Eighteen fistulae were located in the transverse-sigmoid junction, 17 in the tentorium, seven in the ethmoid, four in the torcula, six in the superior sagittal sinus, and three in the sphenoparietal sinus. Two patients had multiple AVFs. Fifteen patients in this series have been reported previously (16).

Angiographic Findings

All patients had angiographic evidence of a high-risk AVF such as retrograde leptomeningeal venous drainage or the presence of a venous varix. All AVFs were Borden Type III and University of California, San Francisco Type III or IV.

Endovascular Treatment

Twenty-seven patients underwent preoperative embolization. However, anatomic features of the fistula such as tortuosity of arterial supply and lack of transvenous access precluded an endovascular cure in their cases.

Surgical Technique

Certain surgical principles of AVF obliteration are uniformly applicable regardless of the location of the fistula. Careful review of preoperative angiographic studies is crucial. The precise location of the draining vein must be identified. The ideal approach to that point is then determined based on the location of the draining vein and the site of the fistula. Although not as important as preoperative angiography, frameless stereotaxy using magnetic resonance imaging or computed tomographic angiography for stereotactic imaging is often useful for identifying the point of the fistula. Frameless stereotaxy guides the placement of the craniotomy and can help localize the associated dural venous sinus precisely.

During surgical exposure, the surgeon must be aware that scalp, transosseous, and dural feeders may be markedly enlarged, thereby increasing the complexity of the exposure. A craniectomy should be considered for lesions with significant dural and osseous feeders. The retrograde leptomeningeal draining vein must be interrupted as it exits the fistula. Our experience and the literature suggest that a dural nidus need not be excised (10, 30). Intraoperative angiography is recommended to verify obliteration of the fistula and to identify accessory fistulae that were not appreciated before surgery.

RESULTS

The results are summarized in *Tables 1* and *2*. The fistula was obliterated completely in 48 (91%) patients. Five patients (9%) had residual filling of the AVF on postoperative angiography. All five patients had undergone preoperative embolization. The residual fistula was embolized successfully in two patients. These patients were evaluated by the endovascular team (FCA, CGM) and were deemed curable by embolization. One patient had spontaneous thrombosis of the residual AVF 2 years after surgery. At the time of the last follow-up evaluation, 50 patients had a Glasgow Outcome Scale (GOS) score of 4 or 5 (95%) and three patients were deceased (6%).

Of the 18 patients with transverse-sigmoid AVFs, five presented with a focal or progressive neurological deficit, five with intracranial hemorrhage, four with headache or pulse synchronous bruit, and three with seizures. One fistula was discovered incidentally. In nine patients, the transverse sinus was skeletonized and packed with coils or cotton. In the remaining cases, a single point of fistulization was identified and obliterated. Postoperatively, three patients had residual AVFs. Of these three patients, two had a diffuse fistula involving the entire sinus. All three underwent additional postoperative embolization with successful obliteration. One patient's fistula recurred and required further embolization for cure. At discharge or the time of the last follow-up evaluation, 15 patients had a GOS score of 5 and two had a GOS score of 4. One patient died as a result of perioperative venous infarction.

Of the 17 patients with tentorial AVFs, six presented with intracranial hemorrhage, five with headaches, five with a progressive neurological deficit, and one with a seizure. The supracerebellar/infratentorial approach was used in nine patients, the retrosigmoid approach in six, and the orbitozygomatic approach in two patients. Postoperatively, the fistula was completely obliterated in all patients. Surgical complications included a unilateral superior cerebellar artery infarct of uncertain etiology and one cerebrospinal fluid leak treated with lumbar drainage. At the time of discharge, 14 patients had a GOS score of 5 and three had a GOS score of 4.

Of the seven patients with ethmoidal DAVFs, one presented with intracranial hemorrhage, two with headaches, and one with progressive neurological deficit. Two were discovered incidentally, whereas the remaining fistula was discovered after hemorrhage from a separate lesion. A unilateral modified orbitozygomatic approach or pterional craniotomy was used in all patients, and all of the AVFs were obliterated successfully. At the time of the last follow-up evaluation, all patients had a GOS score of 5.

Of the five patients with a fistula involving the superior sagittal sinus, two presented with a focal or progressive neuro-

TABLE 1. Summary of patient characteristics and results

Demographics		
Total	53	
Male	37 (70%)	
Female	16 (30%)	
Mean age (yr)	53.8 (range, 4–85)	
Mean follow-up (mo)	12 (range, 0–84)	
Presenting symptoms		
Intracranial hemorrhage	22 (42%)	
Progressive neurological deficit	13 (25%)	
Headache/bruit	10 (19%)	
Seizure	5 (9%)	
Incidental	3 (6%)	
Preoperative embolization	27 (51%)	
Surgical obliteration	48 (91%)	
Postoperative residual	5 (9%)	
Postoperative embolization	2	
Gamma knife radiosurgery	1	
Spontaneous thrombosis	1	
Untreated	1	
Glasgow Outcome Scale		
5	43 (81%)	
4	6 (11%)	
3	3 (6%)	
Not available	1 (2%)	
	Perioperative	**Long-term**
Complications		
Death	3	3
Infection	2	
Deep vein thrombosis	1	
Seizure	2	1
Stroke	2	2
Hydrocephalus/ ventriculoperitoneal shunt	4	
Facial palsy	1	
Spasm	1	
Aphasia	1	
Cerebrospinal fluid leak	1	
Imbalance	1	1
Total	19 (36%)	7 (13%)

logical deficit, two with intracranial hemorrhage, and one with seizure. Two had diffuse fistulae and three had a single point of connection. In two patients, the dura was stripped circumferentially around the extent of the sinus. In two patients, the focal fistulous point was disconnected. One patient with multiple AVFs underwent treatment of his posterior fossa fistulae, but he has not yet returned for treatment of his superior sagittal sinus fistula. One patient died from a subdural hematoma after an external ventricular drain was placed to treat hydrocephalus. Three patients had a GOS score of 5, one had a GOS score of 4, and one had a GOS score of 1.

Of the four patients who presented with torcular AVFs, two presented with a progressive neurological deficit, one with intraparenchymal hemorrhage, and one with a seizure. Three patients had a diffuse AVF that required packing of the sinus for treatment. One patient had a single point of fistulization, which was obliterated with ligation. Of the three patients with diffuse torcular AVF, two had residual AVF after treatment. One patient underwent gamma knife radiosurgery. The second patient sustained a large delayed venous infarction from which he died. The third patient sustained a stroke in the distribution of the posterior cerebral artery after preoperative embolization. At the time of the last follow-up evaluation, two patients had a GOS score of 5, one had a GOS score of 4, and one patient died.

Of the three patients with sphenoparietal sinus AVFs, all presented with intracranial hemorrhage related to the fistula. Two patients underwent preoperative embolization. A temporal or frontotemporal craniotomy was performed to ligate the fistulous site. None of the patients had residual fistulae after surgery, and all had a GOS score of 5 at the time of the last follow-up evaluation.

In our series, the perioperative (within 30 d) mortality rate was 6% (*Table 1*). One patient died from status epilepticus related to a hemorrhagic venous infarct; one from a delayed spontaneous intraparenchymal hemorrhage in the contralateral hemisphere, and one from a subdural hematoma related to ventriculostomy placement for hydrocephalus. Altogether, there were 19 (36%) perioperative complications. During the follow-up period (mean, 12 mo), the overall morbidity and mortality rate was 13% (*Table 1*).

DISCUSSION

Tentorial DAVFs

Tentorial DAVFs make up only approximately 4% of all intracranial fistulae (1, 14). They often demonstrate leptomeningeal venous drainage, a feature known to be a marker of aggressive behavior (1). They drain through the pontine, perimesencephalic, and basal veins into the Galenic system. They are characteristically supplied by the artery of Bernasconi and Cassinari as well as by the petrosal and petrosquamosal branches of the middle meningeal artery.

Picard et al. (24) classified patterns of venous drainage. Venous drainage can be located anteriorly along the tentorial notch. In these cases, the tributaries are often the basilar vein and lateral mesencephalic vein. Venous drainage of DAVFs at the lateral aspect of the tentorium may be superiorly through supratentorial tributaries, including the inferior temporal, temporal basal, and occipital basal veins, or inferiorly through

the vermian and cerebellar veins. Angiographic identification of the venous drainage pattern allows the fistula to be localized along the tentorium. Venous drainage also has implications for presenting signs and symptoms (10, 14).

Tentorial DAVFs typically present with hemorrhage because of their exclusive leptomeningeal venous drainage (28). An associated venous varix is also thought to indicate a propensity for intracranial hemorrhage. Neurological symptoms are dictated by the pattern of venous drainage. In several cases, tentorial fistulae with venous drainage through the spinal veins have caused progressive or acute myelopathy, as in Patient 1 (23). Pulsatile tinnitus and trigeminal neuralgia are rare presentations of this disease entity. One of our patients (Patient 32) with a tentorial DAVF presented with hemifacial spasm that resolved after the fistula was obliterated. The fulminant presenting symptoms and propensity for intracranial hemorrhage justify aggressive endovascular and surgical treatment.

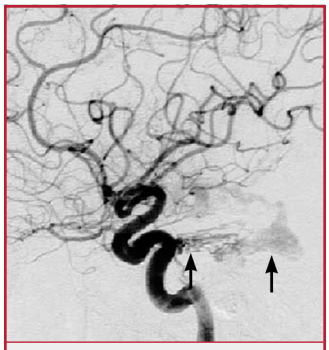


FIGURE 1. *Angiogram showing the branches of the meningeohypoglossal trunk* (arrow) *supplying this tentorial AVF. The draining vein follows the course of the basal vein of Rosenthal* (arrow). *An orbitozygomatic approach allows ligation of this fistulous site.*



FIGURE 2. *Angiogram showing that the draining vein originates at the posterior fossa* (arrow) *and is readily approached with a retrosigmoid craniotomy.*

Preoperative angiograms must be reviewed carefully to identify the site of the fistulous connection. In our series, three cranial base techniques were used to expose tentorial DAVFs based on the point of connection. The orbitozygomatic approach is used if the fistula is located in the anterior third of the tentorium (*Fig. 1*) with drainage through the basal vein of Rosenthal. The sylvian fissure is opened wide. A temporal lobe retractor can be used to increase exposure but is seldom necessary. The tentorium is followed posteriorly until the venous drainage of the fistula is identified. The vein is then coagulated or obliterated with an aneurysm clip at the point of dural attachment.

For lesions in the middle third of the tentorium (*Fig. 2*) with drainage through the petrosal vein or Dandy's vein, we used the retrosigmoid-suboccipital approach. Patients are positioned supine with a shoulder roll on the side ipsilateral to the lesion to facilitate head turning. The park bench position can be used for patients who are obese or who do not have a supple neck. External feeders are interrupted when the skin flap is raised and the dura is opened. Lumbar drainage allows cerebellar relaxation. The need for cerebellar retraction is obviated by further release of cerebrospinal fluid at the cisterna magna or by opening the cistern of the cerebellopontine angle. The wing of the tentorium is followed medially to the point of the fistula. The network of normal draining veins in this region can complicate identification of the leptomeningeal drainage of the fistula. In such cases, use of microvascular Doppler ultrasonography to demonstrate retrograde venous flow or intraoperative angiography can be very helpful. The venous drainage of the tentorial fistula is then obliterated by coagulation or clip ligation (*Fig. 3*).

For DAVFs involving the posterior aspect of the tentorium (*Fig. 4*), we used the midline supracerebellar-infratentorial approach. The patient is placed prone with the head in the neutral position, capitally distracted, and flexed. Cauterization of occipital artery feeders during elevation of the skin flap for the posterior fossa craniotomy significantly reduces the blood supply to the fistula. Cauterization of the meningeal supply

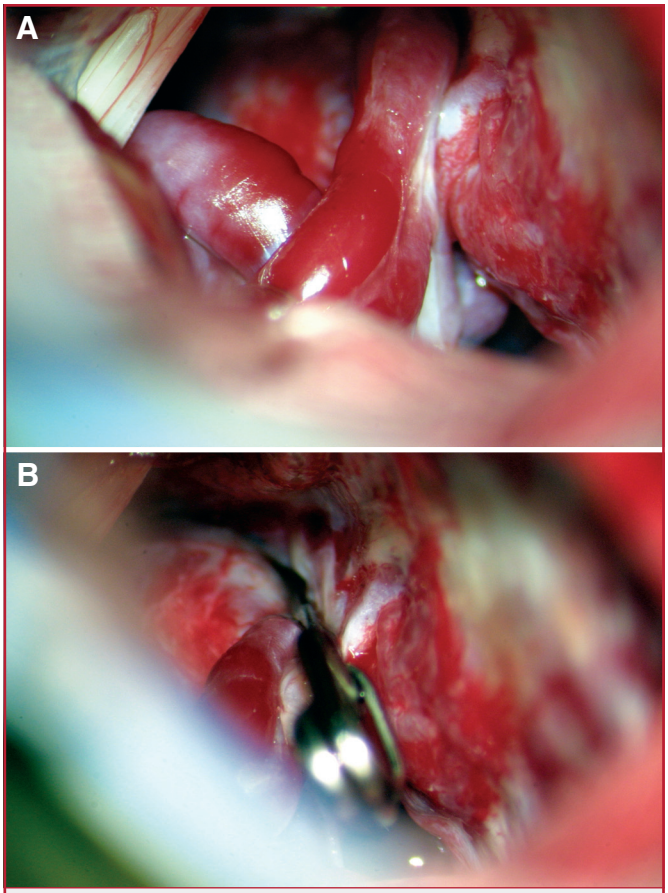


FIGURE 3. A, *the draining vein of this tentorial DAVF is located below the tentorium at the cerebellopontine angle.* **B**, *a straight titanium clip is applied to the draining vein as it exits the tentorium.*

during the dural opening further facilitates surgical extirpation. Preoperative arterial embolization of external carotid artery feeders helps mitigate blood loss during this portion of the procedure. After the dura is opened, the arterialized cortical draining vein is identified and followed to the point of the fistulous connection. The vein and site of the fistula are then cauterized or clip-ligated. After the fistula is obliterated, the previously arterialized veins regain a normal venous hue.

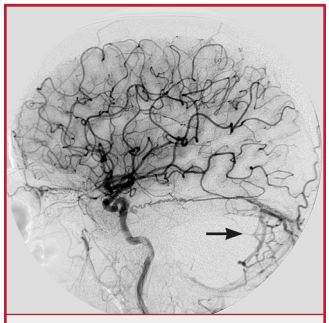


FIGURE 4. *Angiogram showing that the tentorial AVF is located posteriorly and is best treated with a supracerebellar infratentorial approach. The* arrow *delineates venous drainage.*

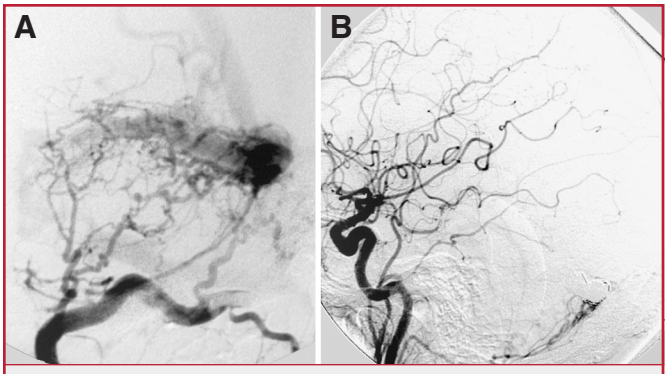


FIGURE 6. **A**, *the external carotid artery provides extensive supply to this diffuse fistula involving the transverse sinus.* **B**, *a craniotomy overlying the transverse sinus allows percutaneous coil embolization of the transverse sinus. No further fistula is identified.*

Transverse-sigmoid Junction DAVFs

The transverse-sigmoid junction is the most common location for DAVFs. These lesions typically manifest with headache and pulse synchronous bruit. Most AVFs in this location are aptly treated or cured with embolization techniques (3, 13). Fistulae without transvenous access or with multiple sites of fistulization along the sinus may not be amenable to endovascular cure. We have seen two types of DAVFs involving the transverse sinus or transverse sigmoid junction: those with a single leptomeningeal vein along the tentorium in the supratentorial compartment (*Fig. 5*) and those in which the entire sinus is involved (*Fig. 6*).

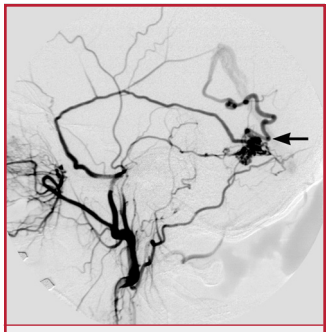


FIGURE 5. *Angiogram showing a single point of connection (arrow) between the multiple feeding arteries and the draining vein.*

In patients with a single fistulous point, the craniotomy should expose the transverse sinus and the region of the tentorium at the origin of the retrograde draining vein. The patient is placed supine with a large shoulder roll ipsilateral to the operative site. A park bench position should be considered if the neck is not supple or if the patient is obese. A lumbar drain should be placed to relax the brain. The arterialized draining vein is identified and obliterated with bipolar cauterization or clip ligation. If there are multiple fistulous sites, the transverse sinus must be skeletonized and the dural borders above, below, and medial to the sinus must be coagulated. In such cases, an excellent alternative to skeletonization of the transversus sinus, and often the method of choice, is for the surgeon to expose a sufficient portion of the sinus for direct vascular access. The sinus can then be cannulated intraoperatively and obliterated with coils (4, 9). Care must be taken to avoid interrupting normal anterograde venous drainage, particularly from the vein of Labbé. One of our patients with a transverse-sigmoid junction fistula sustained a large hemorrhagic venous infarction, presumably from loss of normal venous drainage in this region (*Fig. 7*). If there is retrograde venous flow into the vein of Labbé, this portion of the sinus can be sacrificed safely.

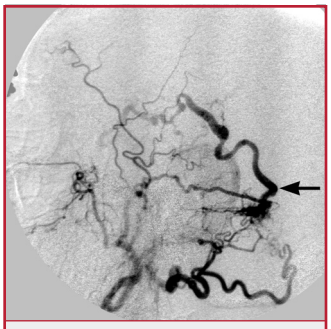


FIGURE 7. *Lateral angiogram showing a left transverse sinus AVF with retrograde cortical venous drainage. In this patient, loss of a tributary of the vein of Labbé resulted in a hemorrhagic venous infarction.*

Ethmoidal DAVFs

Because of their exclusive leptomeningeal venous drainage, ethmoidal AVFs are uniformly high risk (7, 15, 30). They are rarely amenable to endovascular treatment. Ethmoidal feeders arise from the ophthalmic artery. Embolization of the ophthalmic artery places the central retinal artery at risk. The caliber of these vessels is small, and they are remarkably tortuous, precluding catheterization with current technology.

Traditionally, we have approached these lesions through a unilateral modified orbitozygomatic approach when the draining vein is clearly lateralized. However, bilateral leptomeningeal venous drainage is common. In two of our cases, intraoperative angiography after obliteration of the draining vein on the side of the approach demonstrated contralateral venous drainage. In these cases, the falx was incised to provide access for obliteration of the contralateral draining vein (*Fig. 8*). In one of these patients, the bilateral drainage was apparent on retrospective review of the preoperative angiogram. We now position all patients for a possible bifrontal approach. One should be prepared to perform a bifrontal approach and use intraoperative angiography, when available. Unilateral cran-

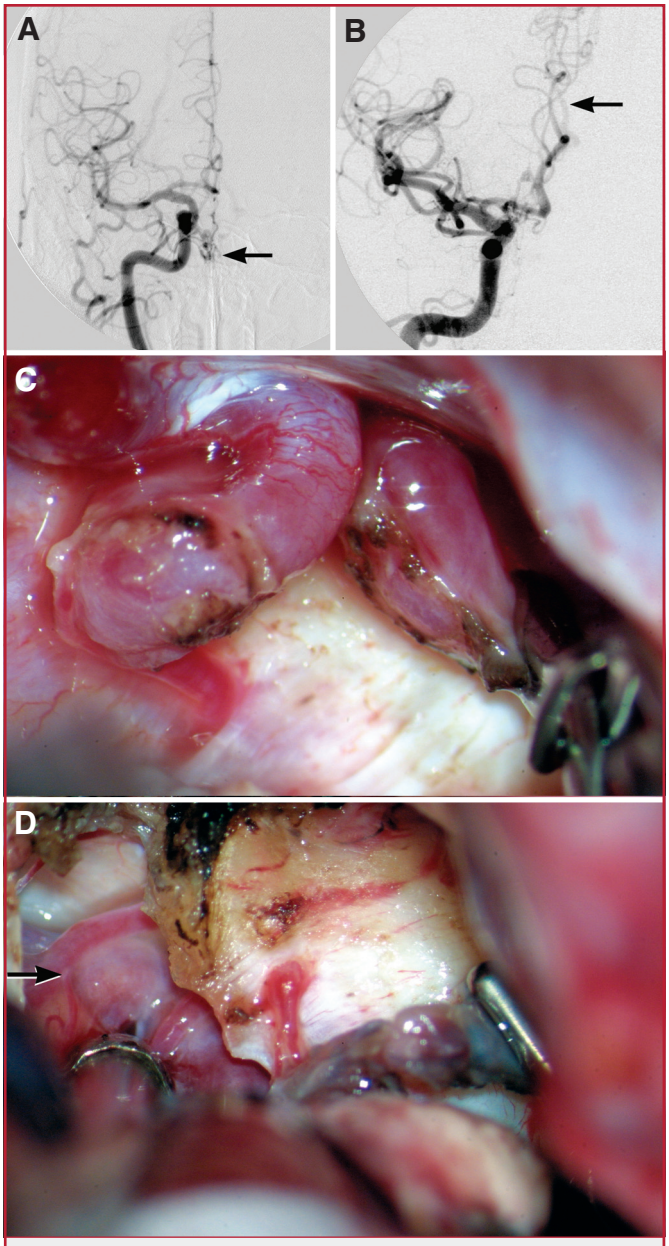


FIGURE 8. A, *posteroanterior angiogram showing an ethmoidal AVF.* **B**, *intraoperative angiogram revealing contralateral venous drainage* (arrow), *which was not apparent on preoperative angiography.* **C**, *the ipsilateral vein is ligated.* **D**, *a falcine incision allows identification of the contralateral vein. Parasitization of the falx by arterial feeders can make this falcine incision treacherous. (***C*** and* **D** from, *Deshmukh VR, Chang S, Albuquerque FC, McDougall CG, Spetzler RF: Bilateral ethmoidal dural arteriovenous fistulae: A previously unreported entity: Case report.* ***Neurosurgery*** *57:E809–E810, 2005.)*

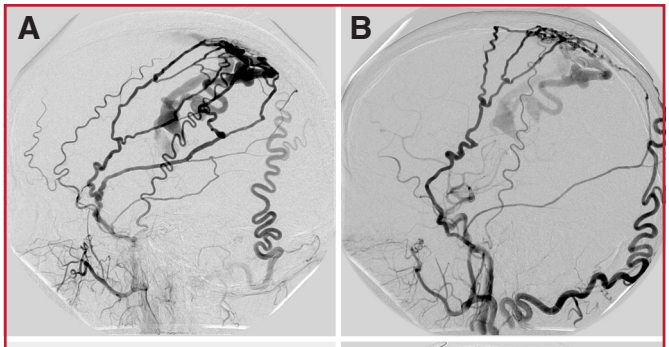


FIGURE 9. A, *external carotid artery injection with a lateral view showing a superior sagittal sinus fistula.* **B**, *the fistula is supplied by both external and internal carotid arteries, the norm for fistulas involving the superior sagittal sinus.* **C**, *a single vein exiting from the dura was ligated. Intraoperative angiography with bilateral common carotid artery injections confirms complete obliteration of the fistula.*

iotomy with incision of the falx is possible; however, the falx is usually parasitized with numerous arterial feeders, which makes this maneuver more treacherous.

Superior Sagittal Sinus DAVFs

DAVFs of the superior sagittal sinus comprise approximately 8% of all intracranial fistulae (2, 25). The first angiographic distinction that must be made is whether a single point or multiple fistulous points are present. If a single arterialized draining vein is identified, simple interruption of this vein is sufficient (*Fig. 9*). If multiple DAVFs are present along the length of the sinus (*Fig. 10A*), a bifrontal biparietal craniotomy is required. Bilateral arterial supply is the norm for these cases.

The patient is positioned supine with the neck flexed and the head positioned neutrally. In the case of a single draining vein, frameless stereotaxy with magnetic resonance imaging and magnetic resonance venography helps locate the craniotomy and site of the fistula. When multiple DAVFs are present, the surgical approach should allow for possible bilateral dural exposure. The dura is opened on the side of the fistulous draining veins, and exposure proceeds to the edge of the sagittal sinus. Preservation of normal bridging veins may require leaving strips of dura intact. The retrograde draining veins are identified and obliterated. Intraoperative angiography is crucial. We have found that a localizing clip placed adjacent to the sinus helps to identify the precise location of the fistulous veins (*Fig. 10, B–C*). Because of the bilateral supply, both external carotid arteries should be examined angiographically intraoperatively.

TABLE 2. Summary of surgically treated patients with high-risk dural arteriovenous fistulae[a]

Patient no.	Age (yr)/ sex	Presentation/ symptoms	Location	Embolization	Approach	Treatment	Outcome		Follow-up (mo)	Follow-up Glasgow Outcome Scale score
							Clinical	Angio		
1	59/M	Paraplegia	Tentorial	N	L RS	Clip ligation	Bilateral lower extremity improved to 3/5	CO	12	4
2	51/M	IPH	Tentorial	N	S/I	Clip ligation	No deficits	CO	46	5
3	36/M	PND	Torcular/TSJ	Y	Stage 1 and 2 occipital and torcular	Packing of sinus	Death from venous infarction, status epilepticus	Residual	0	0
4	53/F	HA, bruit	TSJ	Y	R RS	Clip ligation	Residual	CO on 2-year follow up	24	5
5	13/F	Seizure	SSS multiple sites	Y	Stage 1 and 2 bilateral frontal–bilateral parietal	Dural transection	Death from EVD-related SDH	CO	0	0
6	64/F	SAH Fisher 3	R ethmoidal	N	R OZ	Clip ligation	No deficits	CO	1	5
7	41/F	HA	R ethmoidal	N	R MOZ	Clip ligation	No deficits	CO	1	5
8	60/M	HA	Tentorial	Y	S/I	Clip ligation	No deficits	CO	74	5
9	54/M	R IPH	R TSJ and R cerebellar AVM	Y	Stage 1 and 2 R presigmoid and R RS	Skeletonization transverse and sigmoid sinus	Recurrent fistula treated with obliteration	CO	24	4
10	55/M	SAH	R tentorial	N	R OZ	Clip ligation	No deficits	CO	84	5
11	49/M	Seizure	L transverse sinus	N	L temporal–occipital in 1995 and 1997	Clip ligation	Recurrent fistula with seizure	CO	0	5
12	56/M	PND	L tentorial	Y	L OZ	Clip ligation	No deficits	CO	12	5
13	35/M	Bruit, headaches	L TSJ	N	L RS	Skeletonization transverse and sigmoid sinus	No deficits	CO	38	5
14	52/M	R temp IPH	R spheno-parietal sinus	Y	R pterional	Clip ligation	No deficits	CO	1	5
15	54/M	Incidental	L ethmoidal		L OZ	Clip ligation	No deficits	CO	9	5
16	63/M	R temp IPH	TSJ	Y	R temporal–occipital	Clip ligation	No deficits	CO	0	n/a
17	8/M	PND	R transverse sinus	Y	S/I	Resection of sinus	No deficits	CO	2	5
18	74/M	IPH	Tentorial	Y	S/I	Clip ligation	No deficits	CO	5	5

continues

TABLE 2. Summary of surgically treated patients with high-risk dural arteriovenous fistulae[a] *(continued)*

Patient no.	Age (yr)/ sex	Presentation/ symptoms	Location	Embolization	Approach	Treatment	Outcome		Follow-up (mo)	Follow-up Glasgow Outcome Scale score
							Clinical	Angio		
19	51/M	Seizure	Tentorial	Y	L RS	Clip ligation	No deficits	CO	1	5
20	59/M	Facial pain	Tentorial	N	L RS	Clip ligation	L SCA spasm with infarct	CO	24	5
21	74/M	Aphasic seizure	L TSJ	N	L temporal–occipital	Clip ligation	Death secondary to delayed R hemisphere IPH	CO	0	0
22	50/M	Cerebellar IPH/SAH	R ethmoidal + tentorial	Y	R MOZ and torcular	Clip ligation	No deficits	CO	0	5
23	50/F	Seizure	SSS	N	S/I	Clip ligation	No deficits	CO	17	5
24	52/F	IPH	Tentorial	N	L RS	Clip ligation	No deficits	CO	1	4
25	32/F	HA bruit	TSJ	N	L RS/L PO	Clip ligation	No deficits	CO	24	5
26	49/M	IVH	Tentorial	Y	S/I	Clip ligation	No deficits	CO	0	5
27	67/M	PND	L TSJ	Y	L RS	Sinus packing	No deficits	CO	0	5
28	69/M	IPH, SAH	Tentorial	N	Bilateral suboccipital	Clip ligation	Temporary tracheostomy	CO	1	4
29	66/M	IPH R basal ganglion	Tentorial	Y	S/I	Clip ligation	No deficits	CO	60	5
30	37/F	HA	Tentorial	N	S/I	Clip ligation	No deficits	CO	12	5
31	85/M	Aphasia	L TSJ	N	L RS	Cotton packing	Improved aphasia	CO	10	5
32	51/M	PND	L tentorial	N	L RS	Clip ligation	No deficits	CO	1	5
33	51/M	PND	Torcular	Y	Bilateral occipital	R transverse sinus packing	No deficits	Residual, GKRS	60	5
34	39/M	L occipital IPH/L SDH	SSS	N	Bilateral PO	Clip ligation	R homonymous inferior quadrantanopsia	CO	6	5
35	51/M	HA	L ethmoid	N	L pterional	Clip ligation	No deficits	CO	6	5
36	60/M	HA	SSS	Y	R PO	Clip ligation	No deficits	CO	1	5
37	78/F	SAH	L TSJ fistula	N	RS	Packing with coils	No deficits	CO	1	5
38	71/M	Seizure, aphasia	Torcular	Y	Torcular	Packing with coils	L PCA, stroke	CO	2	4
39	49/M	IPH	SSS	N	Bilateral PO	Strip SSS bilateral	No deficits	CO	0	5
40	53/M	IPH	SSS	N	Bilateral PO	Cautery and excision	Wound infection	CO	1	5
41	71/M	PND	L ethmoidal	Y	L OZ	Cautery and division	No deficits	CO	1	5
42	80/F	Incidental	R ethmoidal	N	R frontal	Clip ligation	GOS 5	CO	3	5

TABLE 2. Summary of surgically treated patients with high-risk dural arteriovenous fistulae[a] *(continued)*

Patient no.	Age (yr)/ sex	Presentation/ symptoms	Location	Embolization	Approach	Treatment	Outcome		Follow-up (mo)	Follow-up Glasgow Outcome Scale score
							Clinical	Angio		
43	59/M	L temp IPH	L TSJ	Y	L temporoparietal	Clip ligation	No deficits	Residual coil embolization	36	5
44	68/F	HA	R TSJ	Y	S/I	Bipolar cautery	No deficits	CO	1	5
45	76/M	PND, dementia	SSS, torcula, L TSJ	Y for SSS fistula, no access to others	Torcular/RS approach	Sinus packing	Dementia improved	No residual except SSS fistula	0	4
46	4/F	PND	Transverse	Y	Occipital/ suboccipital	Obliteration of transverse sinus	No deficits	Residual, had follow-up embolization in 1995	12	5
47	44/F	SAH	R spheno-parietal sinus	Y	R pterional	Excision	No deficits	CO	1	5
48	45/F	SAH	R spheno-parietal sinus	N	R pterional	Clip ligation	No deficits	CO	0	5
49	55/M	L temp IPH, HA	L TSJ	N	L temporo-parietal	Cautery and excision	No deficits	CO	6	5
50	74/M	Incidental	L TSJ	Y	L occipital	Coil obliteration	No deficits	CO	10	5
51	47/F	IPH/IVH	Tentorial	N	Torcular	Clip ligation	No deficits	CO	1	5
52	59/F	Seizure	R TSJ	Y	R torcular/occipital	Coil obliteration	No deficits	CO	3	5
53	50/M	SAH	Tentorial	Y	L RS	Clip ligation	No deficits	CO	26	5

[a] IPH, intraparenchymal hemorrhage; PND, progressive neurological deficit; HA, headache; SAH, subarachnoid hemorrhage; R, right; temp, temporal; IVH, intraventricular hemorrhage, L, left, SDH, subdural hematoma; TSJ, transverse sigmoid sinus junction; SSS, superior sagittal sinus; AVM, arteriovenous malformation; N, no; Y, yes; RS, retrosigmoid; S/I, supracerebellar/infratentorial; OZ, orbitozygomatic; MOZ, modified orbitozygomatic; PO, parieto-occipital; PCA, posterior cerebellar artery; GOS, Glasgow Outcome Scale; CO, complete obliteration; SCA, superior cerebellar artery; EVD, external ventricular drain; GKRS, gamma knife radiosurgery.

Torcular DAVFs

Lesions involving the torcula are among the most complex intracranial DAVFs. Preoperative angiography and embolization are crucial to simplify the angioarchitecture. Surgical treatment is typically warranted if high-risk features are present and if the sinus appears to be isolated. Wide exposure is invaluable for these lesions.

The patient is typically placed prone with the neck flexed. A craniotomy or craniectomy is performed to expose the torcula as well as adjacent portions of the sagittal and transverse sinuses. Intraoperative lumbar cerebrospinal fluid drainage is vital to provide a relaxed surgical field. Options for treatment include intraoperative transvenous embolization of the diseased segment or intraoperative surgical packing of the sinus. With refinements in coil embolization and intraoperative angiography, intraoperative coil embolization is preferred. Staged treatment is often necessary.

Sphenoparietal Sinus DAVFs

The middle meningeal artery is the principle arterial feeder to DAVFs in this location. In most reported cases, a traumatic etiology has been theorized (12, 21, 22, 26, 29). Cortical venous drainage in our patients predicted the fulminant presentation (*Fig. 11*). Typical cortical drainage is through the superficial middle cerebral vein. For these reasons, the patient is placed supine with the head turned 45 degrees. A pterional or temporal craniotomy suffices for clip ligation of the draining vein from the fistula. The middle meningeal artery and the orbitomeningeal arteries may be interrupted extradurally (12). Intradural exploration reveals an enlarged superficial middle cerebral vein that is followed proximally to the region of the sphenoparietal sinus. This connection is then clip ligated.

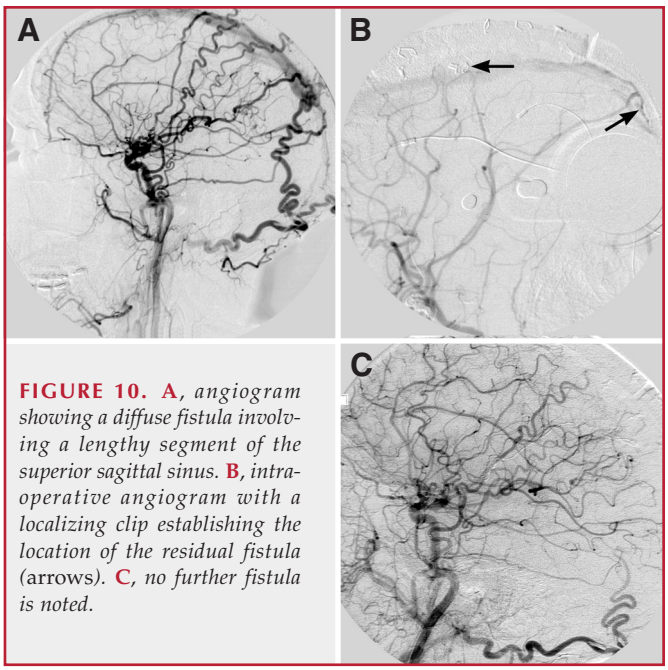


FIGURE 10. A, *angiogram showing a diffuse fistula involving a lengthy segment of the superior sagittal sinus.* **B**, *intraoperative angiogram with a localizing clip establishing the location of the residual fistula* (arrows). **C**, *no further fistula is noted.*

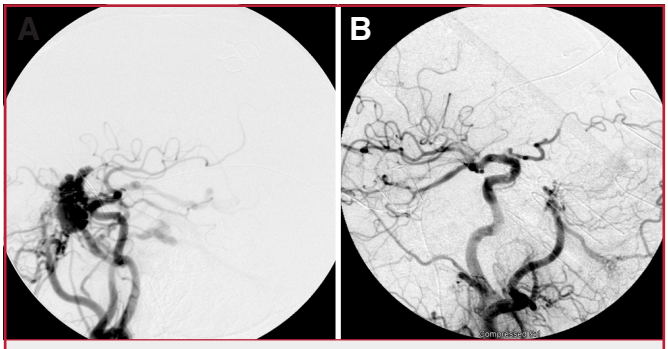


FIGURE 11. A, *the external carotid artery significantly supplies this sphenoparietal fistula.* **B**, *intraoperative angiogram confirming complete obliteration of the fistula.*

Role of Endovascular Therapy

All DAVFs should be explored endovascularly with the intent of embolization to obtain a cure. At minimum, endovascular exploration guides the surgical approach and treatment of the fistula. Arterial embolization of the fistula reduces the risks of the surgical approach and also simplifies the angiographic anatomy. Its importance cannot be overstated; however, the lack of transvenous or transarterial access can prevent effective endovascular management of the fistula. In some cases, simply exposing the sinus with a craniotomy or craniectomy can provide access and enable endovascular obliteration of the fistula. In other cases, residual filling of the fistula after surgery can be obliterated with embolization. In this manner, endovascular and surgical techniques complement each other in the management of these lesions.

Surgical Innovations

Continued refinements in surgical technique, including the introduction of frameless stereotaxy and improved software for fusing multiple diagnostic imaging studies, have simplified the operative exposure and management of DAVFs. That only obliteration of the draining vein is necessary to treat most of these lesions has greatly reduced the risks of management. Liberal use of lumbar drainage and the use of cranial base approaches have limited the need for brain retraction. Intraoperative angiography, when available, is a valuable tool in the management of these patients. In difficult cases, it can accurately identify the draining vein, and it is useful for confirming complete obliteration of the lesion. At a minimum, perioperative angiography is recommended to confirm obliteration of these lesions given their dismal outcome.

CONCLUSION

High-risk intracranial AVFs manifest with fulminant symptoms. With appropriate use of endovascular and surgical techniques, complete obliteration and excellent outcomes can be achieved in most patients with these lesions. In patients with residual AVF, further embolization or stereotactic radiosurgery must be considered. In our experience, the natural history of partially treated AVFs is dismal.

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COMMENTS

Kakarla et al. describe their extensive experience in the treatment of 53 patients with high-risk intracranial dural arterivenous fistulae (dAVFs). As is known from other series, three-quarters of the patients presented with intracranial hemorrhage or progressive neurological deficit related to venous hypertension. All of the patients treated were at high risk for reasons such as cortical venous drainage in the presence of a varix. Only half of the patients underwent embolization before treatment, which I suspect has increased in the current era. Many of the cases to which the authors allude can now be treated with endovascular techniques as a result of advances in embolic materials and catheter design. However, certain cases must still be dealt with primarily by surgical means. Cases of the ethmoid complex are not amenable to endovascular treatment, and the risk to the optic apparatus is so high that these should not even be attempted unless there is a significant single pedicle, which is usually not the case. Many other lesions, such as carotid cavernous fistulae, can now be treated via a superior ophthalmic approach, performed either by direct exposure or percutaneous catheterization of the superior ophthalmic venous system.

There is no question that the surgical experience gained by this group is probably the largest in the world, and many of their surgical tips and clinical pearls are extremely valuable. The most important point to take home is that these lesions should be treated very aggressively using all modalities available, including endovascular therapy, gamma knife radiosurgery, and aggressive microsurgical intervention. As shown by the authors' experience, if these lesions are treated aggressively, the majority of these patients have excellent or good outcomes, as evidenced by 95% of their patients having Glasgow Outcome Scale scores of 4 or 5 at the time of follow-up. One thing that should be stressed is that these lesions can recur; thus, these patients need to be followed indefinitely, usually with magnetic resonance imaging, magnetic resonance angiography, and magnetic resonance venography.

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Much has been written on the natural history of dAVFs and the potential role of surgical intervention for high-risk lesions. When endovascular therapies fail to cure the lesions or eliminate leptomeningeal drainage, surgery has been advocated, and many small series have reported its feasibility and success. In recent years, several authors, including our group, have advocated a number of surgical adjuncts, including cranial base approaches, intraoperative angiography, intraoperative physiological monitoring, and, more recently, frameless stereotaxy, to enhance success and minimize complications of these difficult procedures that are often performed with patients in poor neurological condition (e.g., recent bleed or significant brain edema).

The authors are to be congratulated on reporting a very large case series aiming to analyze various adjuncts with a concept of "complications avoidance" for lesions in different locations. They are also commended on truly avoiding many complications by achieving superb outcomes in this series. In most cases, we agree with their analysis of cases, choice of approaches, and adjuncts. However, any such case series is plagued by a methodological trap, confusing association with causation, and, hence, attributing successful or poor outcomes to specific maneuvers or interventions, without the crudest controls or other comparisons.

Nevertheless, one cannot argue with recipes of success, and this study is filled with technical pearls, in the great Spetzleresque tradition, with ergonomic flap design and patient positioning, minimizing retraction, and enhancing the safety and reach of each approach. We can only state that we have also achieved good outcomes in a comparable number of cases by using the presigmoid transpetrosal approach, while also avoiding retraction of the vein of Labbé, rather than the orbitozygomatic approach for lesions involving the anterior tentorial incisura. We use a similar transpetrosal approach for other lesions involving the petrosal dura or sigmoid sinus. For more posterior tentorial lesions, we

have successfully used the far posterior subtemporal or suboccipital approaches, supratentorial or infratentorial, depending on the propensity of leptomeningeal drainage.

We have also used ventricular drainage (frontal or occipital image-guided through the surgical field) to enhance brain relaxation when needed, rather than lumbar drainage, to avoid the increasingly reported cases of brain sagging with intraoperative lumbar drains. We find computed tomographic angiography-guided frameless stereotactic navigation infinitely more valuable than magnetic resonance guidance for these lesions. When available, intraoperative angiography performed with an experienced team can be quite useful. We always supplement it by higher resolution and quality postoperative angiograms to insure complete cure.

The authors do not mention cases in which dAVFs recurred after previous successful transvenous embolization. We have encountered several such cases with fistula recurrence in the wall of a coiled transverse-sigmoid sinus necessitating resection of the involved sinus segment, in addition to disconnection of leptomeningeal drainage. The large surgical experience and excellent outcomes in this series will insure that this study will become a classic reference in the literature on dAVFs.

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The authors present a series of 53 high-risk intracranial dAVFs, which were all treated surgically because they were not amenable to endovascular cure. Seventy-five percent of the patients presented with major or severe symptoms. Surgical approaches and techniques corresponding to the location of the fistulae are described and discussed extensively. Complications and failures are reported very openly. This impressive surgical series constitutes an update to one published in 1997 (1), including a recent case report. The reader profits from the clear and straightforward manner in which this difficult topic is presented. The article is written as a practical guide, in a "how to" fashion, which is dominated by the senior author's expertise. I concur with its general concept and have a slightly different opinion on only a few points.

According to my experience, cranial base approaches, frameless stereotaxy, intraoperative digital subtraction angiography, or a combination of these is not mandatory for these operations but might be helpful in selected cases. The only thing that is essential is some form of immediate intra- or postoperative angiographic proof of complete obliteration and an angiographic follow-up in diffuse, aggressive subtypes. For example, the ethmoidal dAVF shown in *Figure 8* is not a convincing case to argue for the necessity of intraoperative angiography. In a diffuse dAVF, such as the one shown in *Figure 10,* however, it may be very helpful. Furthermore, an orbitozygomatic approach to tentorial (e.g., *Fig. 1*) or ethmoidal dAVFs (e.g., *Fig. 8*) is just one of many options. Both can be tackled via simpler approaches.

Finally, one should keep in mind that the conclusions of this study are the equivalent of an expert opinion but are not necessarily borne by hard data. This is because the essentials are recorded in a retrospective fashion and the rate and length of follow-up were very moderate. Therefore, the conclusion drawn is actually that the natural history of these dAVFs is dismal, and surgery, although difficult and risky, is justified because it is the only choice.

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1. Lucas CP, Zabramski JM, Spetzler RF, Jacobowitz R: Treatment for intracranial dural arteriovenous malformations: A meta-analysis from the English literature. **Neurosurgery** 40:1119–1132, 1997.

In this retrospective study, Kakarla et al. examine the clinical presentation and surgical treatment of 53 patients with intracranial dAVFs with cortical venous reflux (Borden Shucart Grades II or III), a subset of patients known to carry very significant risk for cerebral hemorrhage or nonhemorrhagic neurological deficits. The mode of presentation for the series was consistent with that of previous studies, with most patients presenting with hemorrhage, seizures, or progressive neurological deficits. Endovascular embolization was used as a preoperative surgical adjunct in approximately 50% of these patients. Surgical approaches were tailored to the dAVF location, and cranial base techniques were frequently used. The overall treatment strategy for most patients appears to have been complete dAVF obliteration, as assessed by intra- or postoperative cerebral angiography, through direct obliteration of the fistula, including disconnection of the venous outflow and/or packing of the involved sinus with coils or cotton. This goal was achieved in 48 of the 53 patients. Of the five with persistent fistulae after surgery, only one was left with a persistent fistula after adjunctive therapy. The reported rates of perioperative complications and overall morbidity or mortality were 36 and 13%, respectively.

The authors provide a review of their considerable experience with the surgical management of high-risk intracranial dAVFs. The major contribution of this study is as a review of the many surgical techniques and approaches that can be used for these lesions. The authors' discussion regarding choice of surgical approach towards specific dAVF locations (tentorial, transverse-sigmoid junction, ethmoidal, superior sagittal sinus versus torcular) and surgical strategy for certain types of dAVFs (single versus multiple fistulous points) is particularly insightful. Unfortunately, other aspects of dAVF management were less completely assessed and discussed, making firm conclusions regarding the optimal treatment of these lesions difficult. For example, the authors state that only obliteration of the draining vein is necessary to treat most of these lesions and that this more conservative strategy has greatly reduced the risks of management, but it is not clear which patients in their series were treated in this manner and no attempt to compare results between a strategy of complete dAVF obliteration versus venous outflow disruption alone was provided. The role of endovascular therapy was also incompletely defined. Although the authors identify the importance of endovascular therapy for dAVF management, including a statement that all dAVFs should be explored endovascularly with the intent of embolization to obtain a cure, the exact nature of the use of this modality in their management algorithm was difficult to determine. How many patients with high-risk dAVFs were treated with endovascular therapy as a stand alone procedure? Of those undergoing preoperative embolization, was an attempt at cure pursued or was the overall goal to simply assist the planned surgical obliteration? Finally, patients presented in this study were drawn from a long time period, and experience with endovascular methods and radiosurgery evolved considerably during that time. It is possible that many of the patients treated early in the authors' experience would not be treated surgically today.

At the end of the day, we have little hard evidence to guide our decisions regarding the optimal treatment of patients with aggressive dAVFs, other than that they should be treated. We have a good understanding of the natural history of this disorder, particularly for those patients who are symptomatic. Fortunately, this natural history risk greatly exceeds the surgical complication rate observed in the present case series and previous reports of surgical and endovascular treatment. Given the anatomic complexity and variability of dAVFs, treatment decisions will continue to be tailored to individual patients. When surgical management is pursued, the algorithm delineated in this study

will serve as a useful guide toward the optimal surgical management of high-risk intracranial dAVF patients.

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Despite the increasing role of embolization in the treatment of dAVFs, we may still encounter lesions that can be best treated only by surgical intervention. The merit of this meticulous analysis of 53 patients is that it provides a good overview of most clinical and surgical aspects of these particular vascular malformations and shows the results of treatment in the hands of experienced surgeons in a well-known vascular center. We can clearly see that, although the principle of surgical treatment may appear rather simple, it is often quite complex in clinical reality. Surgery may be associated with significant morbidity and even with mortality. On the other hand, considering the heterogeneity of dAVFs and the deep location of many of these lesions, the overall outcome of this series is very good. While I agree with the authors in terms of indication for surgical treatment, I would have chosen different surgical approaches in some of the cases. For instance, ethmoidal dAVFs can be nicely approached using the interhemispheric approach (1) rather than the more elaborate orbitozygomatic or bifrontal surgical access routes. Also, in my experience, most tentorial arteriovenous fistulae can be easily exposed by using a limited subtemporal approach with transtentorial access to the fistula site. The advantage is a very short skin incision with minimal craniotomy compared with the orbitozygomatic route. However, such preferences may not necessarily influence the result. In my personal experience, I have also found that intraoperative Doppler sonography is the most important technical tool, and is superior to neuronavigation in localizing the arteriovenous fistula point and most helpful for understanding a very complex hemodynamic situation with large, ecstatic, and tortuous veins in at least some of my cases. In addition to the dAVF subtypes described in this interesting article, I would like to mention those involving the jugular bulb (2) because they belong to the same group of high-risk lesions with which the authors have dealt.

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The Other End of the Whale (1877), oil on panel, Charles S. Raleigh. (Courtesy of New Bedford Whaling Museum). *From*: Matthews, LH: *The Whale*. New York, Simon & Schuster, 1968.

NEUROFORM STENT-ASSISTED COIL EMBOLIZATION OF WIDE-NECK INTRACRANIAL ANEURYSMS: STRATEGIES IN STENT DEPLOYMENT AND MIDTERM FOLLOW-UP

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OBJECTIVE: To evaluate the midterm results of intracranial stent-assisted coil embolization in the treatment of wide-necked cerebral aneurysms and to assess the efficacy of various strategies used in stent deployment.

METHODS: A retrospective study of 42 patients with 46 wide-necked cerebral aneurysms enrolled in a prospective single-center registry of patients treated with a Neuroform stent (Boston Scientific/Target, Fremont, CA), a flexible self-expanding nitinol stent, was performed. Twenty-seven of 46 aneurysms were unruptured aneurysms, 14 were recanalized aneurysms, and five were acutely ruptured. Thirty-nine aneurysms were located in the anterior and seven in the posterior circulation. Mean aneurysm size was 9.8 mm. Stenting before coiling was performed in 13 of 45 aneurysms (29%), coiling before stenting in 27 of 45 aneurysms (60%), and stenting alone in five of 45 aneurysms (11%). The balloon remodeling technique for coiling before stenting was performed in 77% of patients. Angiographic and clinical follow up was available in 31 patients with 33 aneurysms and ranged from 3 to 24 months.

RESULTS: Neuroform stenting was attempted in 46 wide-necked aneurysms (42 patients). Forty-nine stent sessions were performed, including three poststent retreatments. In 46 of 49 sessions (94%), successful deployment of 47 stents for 45 aneurysms was obtained. In 40 aneurysms treated with stent-assisted coiling, angiographic results showed 14 (35%) aneurysm occlusions, 18 (45%) neck remnants, and eight (20%) residual aneurysms. In five recanalized aneurysms treated with stenting alone, no changes were observed in four (80%) aneurysms and one (20%) neck remnant reduced in size. At angiographic follow-up in 30 aneurysms treated with stent-assisted coiling, there were 17 (57%) aneurysm occlusions, seven (23%) neck remnants, and six (20%) residual aneurysms. In three recanalized aneurysms treated with stent alone, two (67%) neck remnants remained unchanged and one (33%) neck remnant decreased in size. Procedural morbidity was observed in two of 42 patients (4.8%) and one patient died. On clinical follow-up, the modified Rankin Scale score was 0 in 27 patients (87%), 1 in three patients (10%), and 2 (3%) in one patient. No aneurysm bled during the follow-up period.

CONCLUSION: These results indicate that Neuroform stent-assisted coil embolization is a safe and effective technique in the treatment of wide-necked cerebral aneurysms. Further studies are needed to evaluate the long-term durability of stent-assisted aneurysm occlusion and tolerance to the stent.

KEY WORDS: Aneurysm, Coils, Endovascular, Intracranial, Neuroform, Stent

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Nontotal occlusion is still a major limitation of coil therapy, especially in wide-necked and large aneurysms. Recanalization is observed despite the use of coated platinum coils and the balloon remodeling technique. The development of intracranial stents has increased the options for the treatment of wide-necked aneurysms (1, 2, 10,

15, 19, 27). Stent-assisted coil embolization allows for adequate coil placement and prevents coil protrusion into the parent vessel. In addition, intracranial stents might help prevent aneurysm recanalization. Different stent techniques are used regarding the timing of stent deployment in relation to coiling. The purpose of our study was to evaluate the angiographic and clinical results and midterm follow-up of intracranial stent-assisted coil embolization using different strategies of stent deployment in the treatment of wide-necked aneurysms.

PATIENTS AND METHODS

We performed a review of the clinical and radiological records of all patients included during a 31-month period from November 2002 to June 2005 in a prospective single-center registry of patients treated with a self-expandable nitinol Neuroform stent (Boston Scientific/Target, Fremont, CA). The study was carried on a consecutive series of 42 patients with 46 intracranial aneurysms.

There were 35 women and seven men. Mean age was 57 years with a range from 11 to 88 years.

Thirty-nine aneurysms were located in the anterior and seven in the posterior circulation. Aneurysm locations are reported in *Table 1*. Twenty-six aneurysms were on the left side, 17 on the right, and three involved the basilar artery. According to the International Study of Unruptured Intracranial Aneurysms size classification (28), 24 aneurysms were small, nine medium, nine large, and four giant (two partially thrombosed). Recanalized aneurysm size was evaluated on the basis of the circulant portion during the stent session. Mean aneurysm size was 9.8 mm. All aneurysms had a large (>4 mm) neck and/or dome/neck ratio (≤1.5 mm). Twenty-seven of 46 (59%) aneurysms were de novo unruptured aneurysms, 14 (30%) were recanalized (five unruptured and nine ruptured in the past, which had been previously treated using coils in 12 patients and clips in two), and five (11%) aneurysms were acutely ruptured. Among the 27 unruptured aneurysms, 10 were incidental, 10 presented with headache, two with cranial nerve palsy, two with visual deficit, and three others with trigeminal neuralgia, mass effect, and embolic events. Among the 37 patients with unruptured (24 patients with 27 aneurysms) or recanalized (13 patients with 14 aneurysms) aneurysms, 26 patients had a modified Rankin scale (mRS) of 0, seven patients had a score of 1, and four patients had a score of 2. In five patients presenting with acute subarachnoid hemorrhage (SAH), the World Federation of Neurosurgical Societies scale was Grade 1 in one patient, Grade 2 in two, Grade 3 in one, and Grade 4 in one. The five patients with SAH were treated at Days 1, 2, 4, 5, and 7 after the bleeding. In this series of 42 patients, other clinical findings included arterial hypertension in 12 (28.6%) patients, fibromuscular dysplasia in three (7%), smoking in five (12%), and a family history of intracranial aneurysms in three (7%). Multiple (>2) aneurysms (including small aneurismal dilations) were observed in 17 of 42 (40.5%) patients.

All patients underwent endovascular treatment under general anesthesia. In nonacutely ruptured aneurysms, pharmacological therapy included 325 mg of aspirin per day and 75 mg of clopidogrel (Plavix; Bristol-MyersSquibb/Sanofi Pharmaceuticals, New York, NY) for 3 days before the endovascular treatment followed by 1 month of clopidogrel and aspirin indefinitely. In patients with SAH, only aspirin was given in the acute phase. In patients with nonacutely ruptured aneurysms in whom the use of a stent was not planned, abciximab was administrated intravenously during the endovascular procedure and aspirin and clopidogrel were started after the procedure.

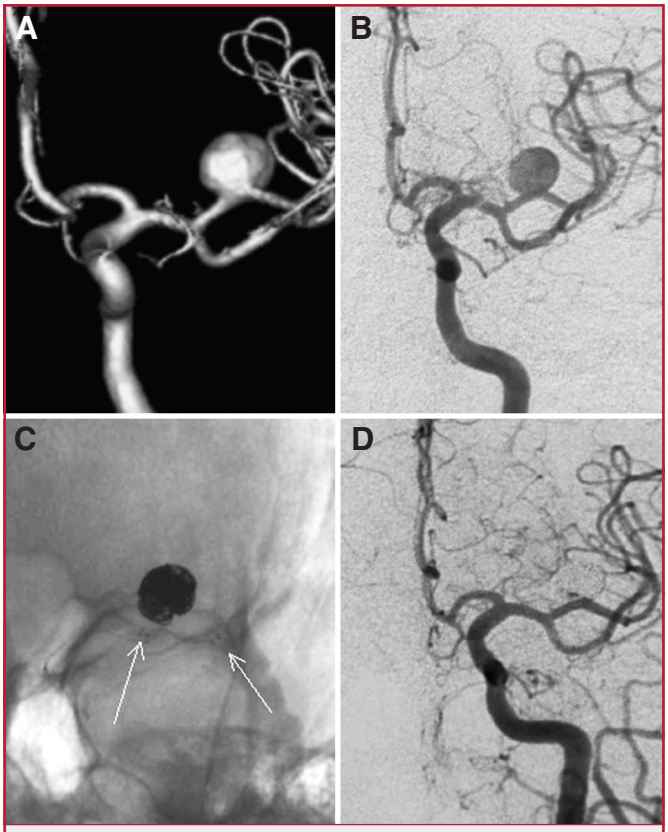


FIGURE 1. A, *Three-dimensional angiographic reconstruction and (**B**) digital angiogram of the left internal carotid artery in anteroposterior view of Patient 5 showing an aneurysm of the left middle cerebral artery in a 66-year-old woman presenting with headache.* **C**, *Stenting was performed before coiling in the same session* (arrows, *stent markers). The microcatheter was positioned in the aneurysm through the struts of the stent.* **D**, *After the procedure, a small neck remnant is visualized.*

Angiographic results were classified in three classes as total occlusion, neck remnant, and residual aneurysm. On angiographic follow-up, the aneurysm could change from one class to another or remain unchanged. Changes in size of the neck remnant and residual aneurysm were also classified as "increased" or "decreased." Clinical and angiographic findings are summarized in *Table 1*.

Stenting Sessions

Neuroform stenting was attempted in 46 aneurysms (42 patients). Stent deployment was successful in 44 of 46 patients at the first procedure, at the second attempt in one of 46 patients (Patient 6), and failed in the first patient of this series (Patient 1). One aneurysm (Patient 39) was treated with a double stent placement (stent within stent) in the same session. Five aneurysms needed retreatment with additional coils positioned through the stent. An attempt to deploy a second stent within a previously positioned stent was performed during three retreatments (successful deployment in two patients and failure in one).

TABLE 1. Angiographic and clinical results and follow-up in 42 patients with 46 aneurysms treated with the Neuroform stent[a]

Patient no.	Age (yr)/sex	Clinical findings	mRS/ WFNS (degrees)[c]	Side	Location	Size	Previous treatment	Complications	Embolization results	Angiographic follow-up	Angiographic results at follow-up	Retreatment/ result	Angiographic follow-up after retreatment	Clinical follow-up	mRS follow-up
1	52/F	Incidental	0	L	Pcom	S	Clip		Stenting failed						
Stenting before coiling															
Stenting before coiling in the same session															
2	77/F	Visual deficit	1	L	Ophthalmic	L		Subdural hematoma	Neck remnant	7 mo	Residual	Occlusion	7 mo, occlusion	20 mo	1
3	45/F	CN palsy	2	NA	Basilar	S			Neck remnant	7 mo	Neck remnant unchanged			7 mo	0
4	88/F	Incidental	1	L	Ophthalmic	L		Vessel perforation	Residual	Deceased	—			Died	6
5	68/F	Headache	0	L	MCA, M2	M			Neck remnant	Lost	—			Lost	
6[d]	55/F	Headache	0	L	Ophthalmic	S		Groin hematoma	Occlusion	9 mo	Occlusion			9 mo	0
7	51/F	Headache	0	L	ICA cavernous	S			Occlusion	7 mo	Occlusion			7 mo	0
8	53/F	Past headache	0	L	Superior hypophyseal	S	Coiling		Occlusion	6 mo	Occlusion			6 mo	0
9	56/M	Past transient ischemic attack L leg	1	R	ACA, A2	M	Coiling		Neck remnant	6 mo	Occlusion			6 mo	0
10	63/F	Past SAH	1	R	Ver bas	S	Coiling		Occlusion	6 mo	Occlusion			6 mo	0
Stenting before coiling performed in a second session															
6[e]	55/F	Headache	0	R	Ophthalmic	S	Stenting failed		Occlusion	Scheduled				Scheduled	
11	44/F	Headache	0	R	Superior hypophyseal	S		Asymptomatic stenosis	Neck remnant	18 mo	Occlusion			18 mo	0
12	43/F	Past SAH	0	L	Pcom	S	Clip		Occlusion	12 mo	Occlusion			12 mo	0
13	44/M	Past SAH	0	R	Ophthalmic	M	Coiling	Coil loop protrusion	Occlusion	7 mo	Occlusion			7 mo	0
Coiling before stenting															
Coiling before stent deployed at the end of the session															
14	73/F	CN palsy	2	L	Pcom	M			Residual	13 mo	Neck remnant			13 mo	0
15	58/M	Visual deficit	2	L	Basilar PCA	G thrombosed			Neck remnant	6 mo	Occlusion			6 mo	0
16	67/F	Headache	0	R	MCA, M1	M			Neck remnant	4 mo	Neck remnant increased			4 mo	0
17	35/M	Past SAH	0	L	Basilar	L	Coiling		Neck remnant	Lost				Lost	
18	49/F	SAH/5 d	1	L	Ophthalmic	S			Occlusion	Scheduled				Scheduled	
19	11/F	Headache	0	R	Superior hypophyseal	L			Residual[b]	7 mo	Occlusion			7 mo	0
20	66/F	Incidental	0	L	Ophthalmic	S			Residual[b]	18 mo	Occlusion			18 mo	0
21	37/F	Headache	1	L	Superior hypophyseal	L		Asymptomatic dissection	Residual	3 mo	Neck remnant			6 mo	0

TABLE 1. ***continued***

22[d]	52/F	Incidental	0	L	Ophthalmic	S			Neck remnant	16 mo	Occlusion			16 mo	0
23	49/M	Headache	0	L	Ophthalmic	M			Neck remnant	6 mo	Neck remnant unchanged			9 mo	0
24	67/F	Incidental	0	L	Ophthalmic	L			Neck remnant	7 mo	Residual	Occlusion	8 mo, occlusion	15 mo	2
25	59/F	Incidental	0	L	ICA cavernous	M			Neck remnant	13 mo	Occlusion			13 mo	0
26	39/F	Incidental	0	L	Ophthalmic	S			Occlusion	7 mo	Occlusion			7 mo	0
27	63/M	Incidental	0	L	ICA cavernous	S			Occlusion	7mo	Occlusion			7 mo	0
28[d]	66/F	Incidental	0	R	Ophthalmic	M			Neck remnant	5 mo	Residual	Neck remnant	8 mo, residual	13 mo	0
28[e]	66/F	Incidental	0	L	Ophthalmic	S			Occlusion	8 mo	Occlusion			8 mo	0
29	70/F	CN V neuralgia	1	R	Pcom	L			Occlusion	Scheduled				Scheduled	
30	54/F	Embolisms	1	NA	Basilar	M			Neck remnant	Scheduled				Sche-	
31	52/M	SAH/7d	2/Fisher 3	NA	Basilar	G		Transient ophthalmoparesis	Residual	24 mo	Residual increased			24 mo	1
32	68/F	SAH/4 d	3	L	ICA/choroidal	S			Neck remnant	8 mo	Residual	Neck remnant		8 mo	1
33	50/F	Past SAH	0	R	Superior hypophyseal	L	Coiling		Neck remnant	7 mo	Neck remnant unchanged			7 mo	0
34	57/F	Past SAH	0	L	Pcom	S	Coiling		Neck remnant	Scheduled				Sche-	
Coiling before stenting and additional coils after deployment of the stent in the same session														duled	
35	77/F	SAH/1 d	4/Fisher 3	R	Pcom	S			Residual	Deceased	Deceased			Deceased	6
36	83/F	SAH/2 d	3/Fisher 3	L	Pcom	S			Occlusion	Lost				Lost	
37	60/F	Incidental	0	L	Ophthalmic	L			Occlusion	8 mo	Occlusion			8 mo	0
38	53/F	Headache	0	R	Pcom	G			Residual	6 mo	Residual	Occlusion		6 mo	0
39	59/F	Mass effect	2	L	Vertebral	G thrombosed			Neck remnant	6 mo	Neck remnant unchanged			6 mo	0
Stenting alone															
40	54/F	Headache	0	R	Superior hypophyseal	S	Coiling		Neck remnant unchanged	7 mo	Neck remnant decreased			7 mo	0
22[e]	52/F	Past SAH	0	R	Ophthalmic	S	Coiling		Neck remnant unchanged	13 mo	Neck remnant unchanged			13 mo	0
41	61/F	Past SAH	0	R	Pcom	S	Coiling		Neck remnant decreased	8 mo	Neck remnant unchanged			8 mo	0
42[d]	64/F	Past SAH	0	R	Pcom	S	Coiling		Residual unchanged	Scheduled				Sche-	
42[e]	64/F	Incidental	0	R	Superior hypophyseal	S	Coiling		Residual unchanged	Scheduled				Sche-	

[a] mRS, modified Rankin Scale; WFNS, World Federation of Neurological Surgeons; Pcom, posterior communicating; L, left; S, small; CN, cranial nerve; NA, not applicable ; MCA, middle cerebral artery; M, middle; ICA, internal carotid artery; R, right; ACA, anterior cerebral artery; SAH, subarachnoid hemorrhage; Ver bas, vertebrobasilar; PCA, posterior cerebral artery; G, giant.

[b] Residual small flakes of contrast medium filling the aneurysm.

[c] According to mRS, 0 means no symptoms, 1 minor symptoms, and 2 some restriction in lifestyle.

[d] First aneurysm in a patient with two aneurysms.

[e] Second aneurysm in the same patient.



FIGURE 2. A, *Right internal carotid artery angiogram in anteroposterior view of Patient 19 showing an aneurysm of the carotid siphon in a 11-year-old girl presenting with headache.* **B**, *Coiling with the balloon remodeling technique was performed before the deployment of the stent at the end of the session* (arrows, *stent markers*). **C**, *Angiographic results showed residual opacification of the aneurysm.* **D**, *Seven-month angiographic follow-up showed occlusion of the aneurysm.*

Consequently, 49 stent sessions were performed. In 46 of 49 stent sessions (94%), we obtained successful deployment of 47 stents for 45 aneurysms, including three aneurysms with stent within stent and one patient with two adjacent aneurysms of the carotid siphon treated with the same stent (Patient 42). The 47 Neuroform stents deployed were seven Neuroform 1, 17 Neuroform 2, 20 Neuroform 2Treo, and three Neuroform 3. In most coiling procedures (70%), Matrix coils (Boston Scientific) were used. Other coils included GDCs (Boston Scientific) and HydroCoils (Microvention, Inc., Aliso Viejo, CA).

Stenting Strategies

Strategies used and evaluated regarding the deployment of the stent in relation to coiling in 45 treated aneurysms were the following:

1. Stenting before coiling in 13 of 45 aneurysms (29%).
   a. Stenting before coiling in the same session (*Fig. 1*). The stent was deployed before coiling in nine of 45 treated aneurysms (20%). In six of nine aneurysms (67%), the microcatheter was introduced into the aneurysm through the struts of the stent. In three of nine aneurysms (33%), the microcatheter was "jailed" between the arterial wall and the stent.
   b. Stenting before coiling performed in a second session. In four of 45 aneurysms (9%), the coils were positioned in the aneurysm in a second session performed from 2 to 3 months (mean, 2.5 mo) after the stenting procedure. The main reason in using this option was the impossibility of aneurysm catheterization for coiling after the deployment of the stent and/or stent movements during attempts to pass the microcatheter through the stent struts.
2. Coiling before stenting in 27 of 45 aneurysms (60%).
   a. Coiling before stent deployed at the end of the session (*Fig. 2*). In 22 of 45 aneurysms (49%), the coils were introduced before the deployment of the stent. Because all aneurysms had a large neck and/or unfavorable dome/neck ratio, the balloon remodeling technique for coiling was performed in 17 of 22 aneurysms (77% of patients). In five patients, the deployment of the stent was not planned in advance, and stent deployment was performed to reverse coil protrusion and/or if the coil mass appeared unstable.
   b. Coiling before stenting and additional coils after deployment of the stent in the same session. In five of 45 aneurysms (11%), after coiling and stenting, additional coils were positioned after stent deployment (microcatheter through the stent in three patients and the "jail" technique in two). The deployment of the stent before the occlusion of the aneurysm by coils was attributable to protrusion of the coils into the parent artery despite the fact that in four of five patients, the coiling was being performed using the balloon remodeling technique. After stenting, aneurysm treatment could be completed with additional coils thanks to the stent scaffold. In one patient (Patient 39), a second stent within the first one was also deployed.
3. Stenting alone in five of 45 aneurysms (11%).
   a. In five aneurysms, only the stent was deployed because, before and/or after stenting, it was not possible to obtain coil placement even using the remodeling balloon technique. All of these aneurysms have been previously treated by coiling, and the small residual aneurysm or neck remnant of these recanalized aneurysms was very difficult to be occluded. Three of these five lesions were ruptured in the past.

RESULTS

Table 1 summarizes the major findings and results for each of the 46 aneurysms in 42 patients.

Immediate Angiographic Results

Immediate angiographic results after the stent procedure in 45 aneurysms were evaluated in relation to the different strategies of stent deployment. In the 40 aneurysms treated with stent-assisted coiling, angiographic results showed 14 (35%) aneurysm occlusions, 18 (45%) neck remnants, and eight (20%) residual aneurysms.

Stenting before coiling was performed in 13 aneurysms and angiographic results showed complete occlusion in seven (54%) aneurysms, neck remnants in five (38%), and a residual aneurysm in one (8%). Coiling before stenting was performed in 27 aneurysms and angiographic results showed complete occlusion in seven (26%) aneurysms, neck remnants in 13 (48%), and residual aneurysms in seven (26%).

Stenting alone was performed in five recanalized aneurysms and immediate angiographic results showed no change in four (80%) aneurysms (two residual aneurysms and two neck rem-

nants) and one (20%) neck remnant reduced in size. In all patients, on unsubtracted images, the stent appeared correctly deployed with regard to the aneurysm neck.

Complications

Procedural morbidity was observed in two of 42 patients (4.8%) (two of 46 procedures [4.3%]). In one patient (Patient 31, *Fig. 3*), an internuclear ophthalmoparesis developed after the endovascular treatment (thromboembolism or, less likely, mass effect) and regressed within 1 week under steroid therapy. In another patient (Patient 2) who previously underwent surgery for another ruptured aneurysm, a subdural hematoma requiring surgical evacuation occurred during the stent procedure. This patient's 1 month mRS was 4 but significantly improved by 6 months to a mRS of 1. Mortality was observed in one of 42 patients (2.4%) (one of 46 procedures [2.2%]) attributable to perforation of the anterior cerebral artery by a microwire causing massive subarachnoid and intraventricular hemorrhage (Patient 4). The latter two patients were both under high-dose antithrombotic therapy (aspirin, clopidogrel, and abciximab) for planned Neuroform stent-assisted coil embolization. Another patient died from SAH complications unrelated to the endovascular procedure.

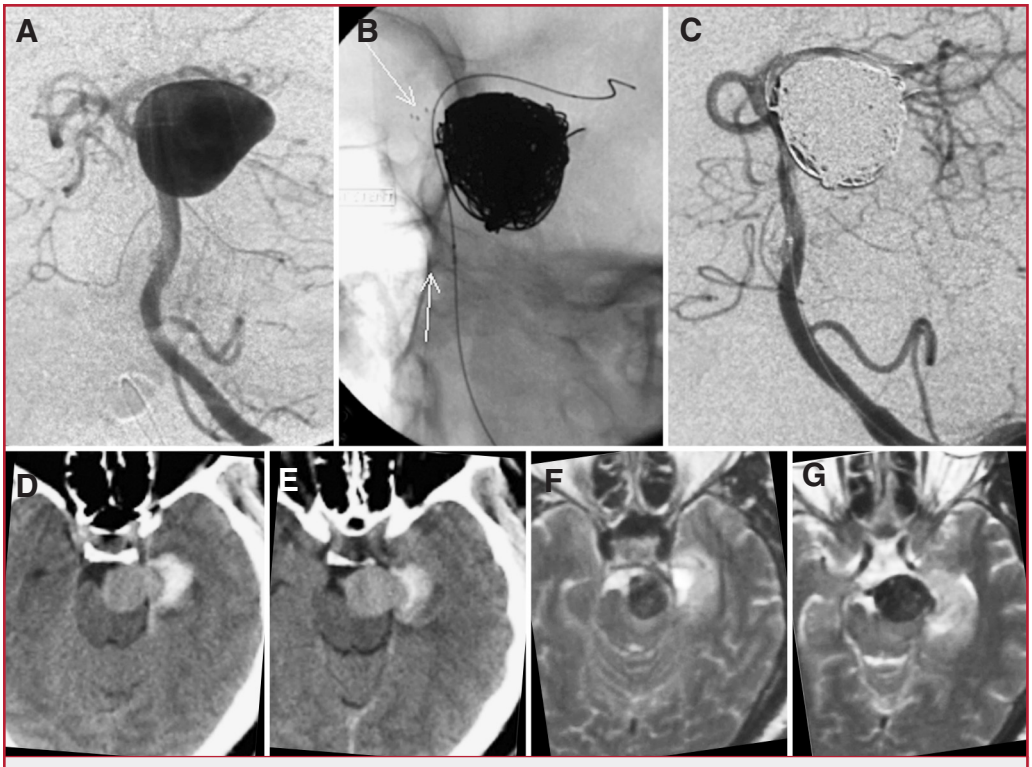


FIGURE 3. A, left *vertebral artery angiogram in anteroposterior view of Patient 31 showing an aneurysm of the superior third of the basilar artery in a 52-year-old man presenting with SAH 7 days before.* **B**, *Coiling with the balloon remodeling technique was performed before the deployment of the stent at the end of the session* (arrows, *stent markers).* **C**, *Angiographic results showed residual opacification of an aneurysmal aneurysm. One day after the procedure, internuclear ophthamoparesis (INO) developed but resolved within 1 week after steroid therapy. Computed tomographic scan before (***D*** and* **E***) and magnetic resonance imaging scan after (***F*** and* **G***) the stenting procedure. Diffusion-weighted study (not shown) was normal.*

Asymptomatic complications were observed in three of 42 patients (7.1%) (three of 46 procedures [6.5%]), including one stenosis of the parent artery at the proximal end of the stent. This stenosis was observed on follow-up angiography and successfully treated by angioplasty (Patient 11). The other complications included one small dissection located at the C2 segment of the carotid siphon, which spontaneously healed on angiographic follow-up (Patient 21) and one groin hematoma (Patient 6). In another patient, a loop of a coil protruded into the parent artery without consequence (Patient 13).

Angiographic Follow-up

Angiographic follow-up was available in 33 of 45 treated aneurysms and ranged from 3 to 24 months (mean, 9 months). Thirty aneurysms were treated with stent-assisted coiling and three with stent alone.

The evolution of 30 aneurysms treated with stent-assisted coiling showed that all 10 initially occluded aneurysms stayed occluded. Five of 14 (36%) neck remnants progressed to complete occlusion, four (28.5%) remained unchanged, one (7%) increased in size, and four (28.5%) evolved to residual aneurysm (*Fig. 4*). Two of six (33%) residual aneurysms progressed to complete occlusion, two (33%) evolved to neck remnant, one (16.5%) remained unchanged, and one (16.5%) increased in size. Overall, in 30 aneurysms treated with stent-assisted coiling, angiographic follow-up showed 17 (57%) aneurysm occlusions, seven (23%) neck remnant, and six (20%) residual aneurysms.

Aneurysm evolution was analyzed in relation to different stenting techniques. In 10 aneurysms treated by stenting before coiling (six aneurysm occlusions and four neck remnants), follow-up showed eight (80%) aneurysm occlusions, one (10%) neck remnant, and one (10%) residual aneurysm. In 20 aneurysms treated by coiling before stenting (four aneurysm occlusions, 10 neck remnants, and six residual aneurysms), follow-up showed nine (45%) aneurysm occlusions, six (30%) neck remnants, and five (25%) residual aneurysms. In three recanalized aneurysms treated with stent alone (three neck

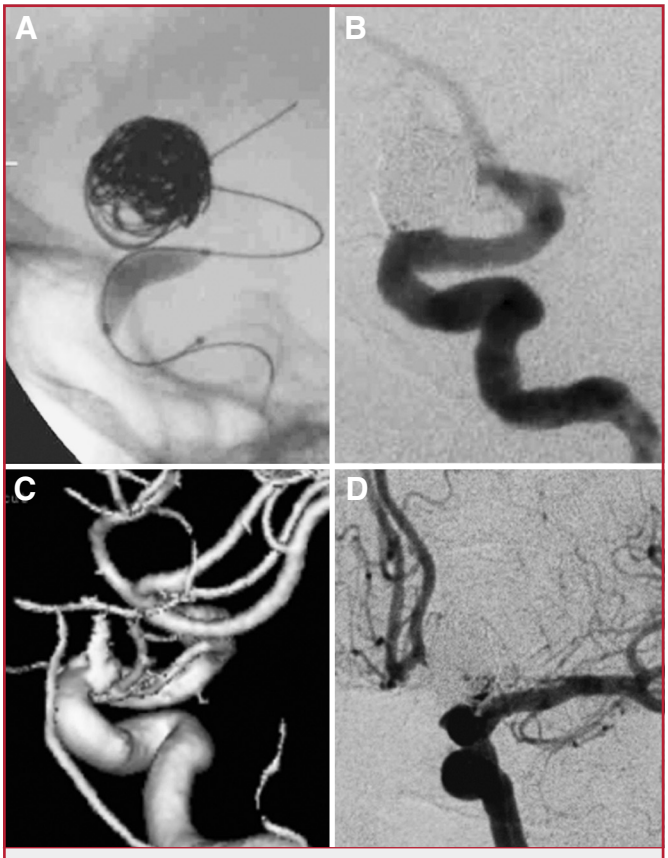


FIGURE 4. *Incidental ophthalmic aneurysm is shown in Patient 24, a 67-year-old woman.* **A**, *Coiling with the balloon remodeling technique is demonstrated.* **B**, *After the deployment of the stent at the end of the session, a left internal carotid artery angiogram in lateral view shows a small neck remnant. At 7-month follow-up,* (**C**) *three-dimensional angiographic reconstruction and* (**D**) *digital angiogram in oblique view showed recurrence. At a second procedure, coils were added through struts and complete occlusion was obtained. Eight-month follow-up (not shown) demonstrated persistent occlusion.*

remnants), two (67%) neck remnants remained unchanged and one (33%) neck remnant decreased in size.

Retreatment

Retreatment was performed in five residual aneurysms (Patients 2, 24, 28, 32, and 38) from 5 to 8 months (mean, 6.8 mo) after the first stent procedure. In all patients, retreatment was performed using additional coils positioned through the stent. An attempt to deploy a second stent within the previously positioned stent was also performed in three patients with successful deployment in two patients (Patients 28 and 38) and failure in the remaining patient. Angiographic results showed three aneurysm occlusions and two neck remnants. Angiographic follow-up was available in three patients. At 7- and 8-month follow-up, respectively, two aneurysms (Patients 2 and 24) remained occluded. At 8-month follow-up, one neck remnant (Patient 28) had evolved to residual aneurysm.

Clinical Follow-up

Two patients died (one from severity of her SAH and one from a procedural complication). Clinical follow-up was available in 31 of 42 patients and ranged from 4 to 24 months (mean, 10 mo). Twenty-seven of 31 patients (87%) had an mRS of 0, three patients (10%) an mRS of 1, and one patient (3%) an mRS of 2. This latter patient also had Parkinson's disease. No aneurysm ruptured or reruptured during the follow-up period.

DISCUSSION

Endovascular treatment of wide-necked aneurysms remains a technically challenging procedure. Although the use of the balloon remodeling technique and three-dimensional shaped and bioactive coils helps obtain better immediate results in the treatment of intracranial aneurysms, recurrence is still a major problem. Stent-assisted aneurysm embolization is a new tool in the management of intracranial aneurysms and may be particularly useful in the case of a broad-necked or a large/giant aneurysm. The stent serves as a mechanical scaffold for the placement of aneurysm coils, prevents coil protrusion into the parent vessel, and may allow for safer packing of the aneurysm with a denser coil mesh. In addition, intracranial stents may help prevent aneurysm recanalization by redirecting flow and facilitating endothelialization at the aneurysm neck.

Several case reports and initial practice with aneurysm stenting have been published, including the use of stents in fusiform and dissecting aneurysms (4, 14, 18, 20, 21, 25). Preliminary experience in animal models using a self-expandable stent with an open-cell design specifically created and optimized for intracranial use has been obtained using the Neuroform stent (6). More recently, series of patients treated with self-expandable stents devoted to intracranial aneurysms such as the Neuroform stent (1–3, 7, 10, 11, 15, 19, 24), the Cordis Enterprise stent (13) (Cordis Endovascular, Miami Lakes, FL) or the Balt Leo stent (23) (Balt, Montmorency, France) have been reported. As reported in other series (1, 10, 15, 19), we observed that the intracranial navigation of the Neuroform stent, even in tortuous cerebral vasculature, was usually successful and that this stent could be placed into small vessels such as the M1–M2 segments of the middle cerebral artery and the A1–A2 segments of the anterior cerebral artery. In addition, technical advances in the newer generation of this stent (Neuroform 3), which is mounted in a more suitable delivery system, significantly facilitated stent deployment.

Lylyk et al. (19) reported difficulties in placing the Neuroform stent in 31% of patients, mostly at the beginning of their experience; however, a second generation of devices resolved this limitation. Fiorella et al. (10) confirmed that using the second-generation Neuroform2 delivery system alleviated the technical problems with stent delivery and deployment encountered in their initial results (11).

Stenting Strategies

Different strategies regarding the timing of stent deployment in relation to coiling are practiced. In the majority of

reports, stenting was performed before coiling (1–3, 10, 17, 26). Coiling was usually performed with the microcatheter placed in the aneurysm through the mesh of the stent or less frequently using the "jailed technique" in which the microcatheter is caged between the vessel wall and the stent (1, 2, 10, 19). This "jailed technique" permits stabilization of the microcatheter during coil delivery. After stent deployment, most authors have reported coiling of the aneurysm in the same sessions (1–3, 10, 17, 26) or, rarely, in a successive second session (1, 15). In our series, when trans-stent aneurysm catheterization was difficult and/or stent movements were encountered during attempts to pass the microcatheter through the stent struts, the procedure was interrupted and coil embolization was delayed for 1 to 2 months. This staged treatment allows for stent stabilization and endothelialization, enabling safer catheterization of the aneurysm. This strategy has also been reported by Howington et al. (15).

In our series, the strategy of stenting after coiling was predominantly used, usually in conjunction with balloon remodeling. Of course, this was performed only when safe coil positioning could be obtained without initial stenting. The choice of this strategy was based on our good experience with the balloon-assisted coiling technique in wide-necked intracranial aneurysms and our opinion that it is safer and easier to deploy a stent at the end of the procedure. In this method, the role of the stent is coil mass stabilization and the prevention of aneurysm recanalization. This strategy is less frequently reported in the literature and results of this strategy have not been detailed (19, 23). In addition, trapping of an extruded coil by means of stent placement obviates the need for coil removal and avoids the risk of coil mass manipulation (8). In 10 patients in our series, the deployment of the stent was not planned in advance and was decided during the procedure to reverse coil protrusion and/or if the coil mass appeared unstable. In five of these patients, additional coils were placed after stent deployment.

Complications Related to Stenting

In our series, we observed a relatively low rate of complications (4.8% mild morbidity and 2.4% mortality), which appeared unrelated to the type of stent strategy used. In other series, morbidity ranged from 5.8 to 20% and mortality from 2.1 to 8.9% (1, 3, 7, 11, 12, 19). Lee et al. (17) reported stent thrombosis during the procedure in one of 22 (4.5%) patients. Hemorrhagic complications on the 25th day after the procedure was noted in another patient. Fiorella et al. (9, 10) reported delayed and severe in-stent stenosis in three of 64 (4.7%) patients. In our series, asymptomatic stenosis of the parent artery at the proximal end of the stent occurred in one patient. The thrombogenicity of endovascular stents represents an important limitation with respect to the treatment of aneurysms and appears to be the main drawback of this technique (1, 11, 19). A rigorous pre-, peri-, and postprocedural pharmacological regimen can avoid or limit some thromboembolic complications. However, in our series, two complications were hemorrhagic and related to high antiplatelet regimen. Overall, results in stenting therapy for intracranial aneurysms compare well with the large series of Murayama et al. (22) reporting an overall morbidity/mortality rate of 9.4% in 818 patients harboring 916 aneurysms treated by coil embolization.

Angiographic Results and Follow-up

In our series, all initially occluded aneurysms remained occluded on midterm follow-up, and 36% of neck remnants and 33% of residual aneurysms progressed to complete occlusion. Recanalization to residual aneurysm was observed in 28% of the neck remnants (13% of wide-necked aneurysms treated with stent-assisted coiling). In the series of Murayama et al. (22), the overall recanalization rate of coiling without stenting was 20.9%.

The comparison of angiographic outcomes across reported series is difficult. A standard definition of what constitutes complete occlusion and residual aneurysm filling is lacking and quantification and analysis of the results is subjective (16). In addition, few papers report angiographic follow-up in stenting procedures for aneurysms.

Fiorella et al. (10) reported initial (3–6 mo) angiographic follow-up in 58% of aneurysms treated with Neuroform stent-assisted coil embolization showing progressive thrombosis in 52% of patients, recanalization in 23%, and no change in 25%. In our study, midterm (6–18 mo) follow-up data were available in 88% of aneurysms and confirmed a significant advantage of the stent-assisted coil embolization of wide-necked aneurysms without recanalization in completely occluded aneurysms. According to our results, Sani et al. (24) reported persistent occlusion in nine of 10 aneurysms at initial angiographic follow-up and one residual neck remained unchanged. In other series (1, 3), short-term angiographic follow-up was performed in a small percentage of lesions and results were not detailed. Dos Santos et al. (7) reported short-term follow-up angiography for only one of 17 aneurysms, whereas a favorable clinical outcome was reported in 88% of the patients (average follow-up time, 4.7 mo). The good clinical midterm outcome observed in our series demonstrates that stenting in intracranial aneurysms is a relatively safe technique when performed at institutions with experience in endovascular aneurysm treatment. Although complete or subtotal aneurysm occlusion was not always obtained, no aneurysm ruptured or reruptured during the follow-up period. Lylyk et al. (19) reported that follow-up was obtained in 63% of their patients and stressed that there were no cases of repeated hemorrhage.

In conclusion, our results and midterm follow-up show that Neuroform stent-assisted coil embolization is a safe and effective technique in the treatment of wide-necked cerebral aneurysms. The stent can be deployed before or after the coiling. We think that stenting before coiling is a more risky procedure because the subsequent (after stenting) endovascular manipulations to coil the aneurysm can displace the stent itself (5). In addition, coil loops can be trapped and tangled to the stent struts. Consequently, we usually perform stenting before coiling in selected cases in which coiling with the balloon remodeling technique does not seem feasible. In our series,

the most frequently used strategy was balloon-assisted coiling followed by stenting. In our experience, coiling with the balloon remodeling technique offers better protection against coil protrusion into the parent artery and allows for better packing than stenting. However, the rate of recanalization of nonstented wide-neck aneurysms is high. A stent placed across the aneurysm neck may prevent recanalization because of the hemodynamic changes induced by the struts crossing the aneurysm neck and stent endothelialization. Therefore, our philosophy is to use the stent to prevent recanalization more than to assist in coil delivery.

Although results at midterm follow-up are encouraging, further studies are needed to evaluate the long-term stability of aneurysmal occlusion and tolerance to the stent.

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COMMENTS

The authors reported their series of Neuroform (Boston Scientific/Target, Fremont, CA) stenting for intracranial aneurysms with a focus on both technique and the interim follow-up period. They report their treatment strategy on 46 aneurysms, 45 of which underwent stenting, in a group of 42 patients. This single-center experience spanned 31 months, and included 24 small aneurysms, nine medium aneurysms, nine large aneurysms, and four giant aneurysms, two of which were partially thrombosed. The mean aneurysm size was 9.8 mm, and all had a neck diameter greater than 4 mm and a neck-to-dome ratio of 1.5 or less. The majority (37 out of 45) of aneurysms were unruptured, and five were acutely ruptured. The techniques used were coiling followed by stenting (22 out of 45), and stenting followed by coiling (13 out of 45), or stenting alone when the aneurysm could not be coiled after repeat attempts (5 out of 45). The majority of patients treated with coiling before stenting underwent balloon remodeling (17 out of 22; 77%), whereas an additional five cases in this group were not planned but were placed when coils protruded into the parent artery. The interim follow-up period angiographic results in 33 of the 45 aneurysms followed for a mean duration of 9 months demonstrated that 57% (an increase from the initial 35%) were occluded, 23% (a

decrease from 45%) had remnants, and 20% had a residual aneurysm, which is unchanged from the initial results.

The majority (32 out of 46) of aneurysms in this series were in the internal carotid distribution, including three in the intracavernous carotid artery. Only three were in the distribution of the middle cerebral artery (n = 2) or anterior cerebral artery (n = 1). Based on location alone, this should be where the stent is most effective. However, the overall residual aneurysm rate was 20% after less than 1 year of follow-up. Stenting of intracranial aneurysms is not a panacea. Those aneurysms with wide-based necks involving the supraclinoid carotid can have challenging neck origin anatomy, as demonstrated by the five cases the authors were unable to reaccess and coil. In the majority of cases, balloon remodeling was used to buttress the coils. Although this is a very effective technique, it is not without increased thromboembolic risks, and the ability to maintain coil packing may be compromised when removing the balloon and placing a stent. In most cases, repeat access to the aneurysm becomes acutely more difficult. As demonstrated by this experienced group of operators, this technique is usually reserved for unruptured aneurysms given the requirement for antiplatelet medication.

In review, some of the aneurysms that were most difficult to treat were small, previously ruptured, and in the distribution of the superior hypophyseal, ophthalmic, or posterior communicating artery. Direct surgery on these aneurysms without the presence of a stent or previous coils facilitates clipping of the neck without the risk of stent deformation or parent vessel aneurysm neck avulsion. Therefore, the judicious application of stenting or coiling should be balanced early on with open microsurgical treatment, which may afford the most direct, definitive, and safest option.

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With this article, Biondi et al. add to the growing body of literature supporting the use of the Neuroform stent for the treatment of wide-necked intracranial aneurysms. The authors report a high technical success rate and low patient morbidity and mortality rates with the use of this device. An interesting observation with this work was the use of the stent after initial coil embolization. At our institution, we have adopted a similar technique. Despite these promising results, this patient population will need careful long-term follow-up to assess for the potential sequelae of stenting, namely aneurysm recurrence and in-stent stenosis or thrombosis. Only long-term follow-up evaluation will establish the true efficacy of this novel device.

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The authors have demonstrated that stent-assisted aneurysm coiling is relatively safe. Various strategies of stent placement are described in this report. Most intriguing is the concept of placing the stent with balloon assistance after coiling. The authors describe the primary role of stenting in this setting to be the prevention of aneurysm recanalization rather than the prevention of coil herniation. However, stents were placed in 10 patients to stabilize the coil mass or to reverse coil protrusion. The authors seem convinced that stent placement after coiling is a better strategy, despite the fact that the angiographic follow-up results were actually better in the group that underwent stenting before coiling.

At our institution, we typically place the stent before coiling. If the placement of the stent is difficult or if the stent is placed in a very tortuous segment of the parent vessel, we usually wait several weeks before placing coils through the stent. Otherwise, we proceed with coiling in the same session as the stent placement. We have found this strategy relatively safe.

The main point to be learned from this study is that the endovascular treatment of aneurysms has technical variations, all of which have advantages and some disadvantages. Given that long-term follow-up data is still lacking for most endovascular techniques, we must not be dogmatic with our individual biases. This study opens our minds to a different stenting strategy that may ultimately prove to be better than what we are currently doing. We need larger numbers of patients with much longer follow-up periods to determine which strategy is better. Unfortunately, by the time that occurs, a new endovascular strategy will have been devised to treat aneurysms.

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FUTURE MEETINGS—CONGRESS OF NEUROLOGICAL SURGEONS

The following are the planned sites and dates for future annual meetings of the Congress of Neurological Surgeons:

2007	San Diego, CA	September 15–20
2008	Orlando, FL	September 20–25
2009	New Orleans, LA	October 24–29
2010	San Francisco, CA	October 23–28
2011	Washington, DC	October 1–6
2012	Chicago, IL	September 29–October 4
2013	San Francisco, CA	October 19–24

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Improving Prediction of Outcome in "Good Grade" Subarachnoid Hemorrhage

OBJECTIVE: We hypothesize that subtle neurological signs at baseline could be present in some "good grade" subarachnoid hemorrhage (SAH) patients and that they would have negative prognostic implications.

METHODS: We analyzed data from 1000 patients randomized to the Intraoperative Hypothermia for Aneurysm Surgery Trial (World Federation of Neurological Societies Grades I, II, and III). Nine hundred and forty-four patients had a complete National Institutes of Health Stroke Scale (NIHSS) examination performed at baseline. We analyzed the relationship between baseline NIHSS scores and Glasgow Outcome Scale scores at 3 months. Using stepwise logistic regression, we identified the individual NIHSS items that independently predicted outcome to construct a useful shorter version of the scale for SAH.

RESULTS: The NIHSS was abnormal at baseline in 23% of the Grade I patients and 82% of the Grade II patients. Baseline NIHSS scores strongly predicted 3-month outcomes ($P < 0.001$). The NIHSS items that were relevant to predict outcome were level of consciousness, dysarthria, visual fields, and worst motor score for the arms. Baseline NIHSS-SAH scores also independently predicted 3-month outcomes ($P < 0.001$).

CONCLUSION: Subtle neurological signs at baseline are common in World Federation of Neurological Societies Grades I and II patients and are associated with a worse outcome at 3 months. These signs are not detected by the World Federation of Neurological Societies classification. A better stratification of "good grade" SAH patients to predict long-term outcomes may be desirable for clinical trials and practice. Either using the full NIHSS or a shortened version testing level of consciousness, visual fields, dysarthria and worst arm motor score will help to better stratify "good-grade" SAH patients.

KEY WORDS: Aneurysm, National Institutes of Health Stroke Scale, Outcome, Prognosis, Scales, Subarachnoid hemorrhage

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There is a direct relationship between the severity of the initial neurological deficit and long-term outcome in subarachnoid hemorrhage (SAH) patients (10). Consequently, several neurological scales use initial neurological status to predict outcome among patients with SAH (4). One of the most commonly used scales in this setting is the World Federation of Neurological Societies (WFNS) scale (2). The WFNS scale is based on a combination of the Glasgow Coma Scale score and the presence of either aphasia or hemiparesis. However, the WFNS scale does not include other neurological signs. This is a potential limitation of the WFNS because neurological signs other than weakness or aphasia could also indicate initial neurological injury and, thereby, portend a less than optimal outcome. In fact, the classic work by Hunt and Kosnik (8) suggested that patients who had drowsiness, confusion, or mild focal deficit (Grade III) were less likely to survive. We hypothesize that a subgroup of SAH patients who would otherwise be classified as "good grade" may have neurological signs on admission, other than aphasia or hemiparesis, that are not detected by the WFNS examination. We also hypothesize that those undetected but subtle neurological signs might identify a subset of "good grade" SAH patients with a poorer long-term prognosis.

PATIENTS AND METHODS

We conducted a secondary analysis of patients who were enrolled in the Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST), an international randomized clinical trial enrolling patients with a "good-grade" SAH (WFNS Grades I, II, or III). In this trial, patients undergoing surgical clipping for ruptured intracranial aneurysms were randomized to receive either intraoperative hypothermia (33°C) or normothermia (36.5°C). The trial's methods and results are described in detail elsewhere (11). Because the tested intervention did not influence outcome, we considered all patients in the intention-to-treat analysis as a prospective cohort in this study.

In addition to their WFNS score, all patients underwent preoperative testing with the National Insitutes of Health Stroke Scale (NIHSS), a quantitative scale designed to comprehensively and quantitatively assess a variety of neurological deficits. Complete preoperative NIHSS examinations were obtained in 944 patients. Patients with incomplete NIHSS examinations (n = 56) were excluded from analysis. Although the NIHSS was not specifically designed for SAH patients, it is a well-validated instrument with outcome-predictive abilities for ischemic stroke (3), and is, therefore, useful as a detailed assessment of focal neurological signs. All patients had baseline WFNS grade and NIHSS scores recorded before surgery and randomization. At 3 months postoperatively, Glasgow Outcome Scale (GOS) scores were determined. All examinations were performed by IHAST study investigators who had previously undergone a detailed training and certification process in the use of the three scales by using videotapes or written examples followed by Internet-based assessments. We used the NIHSS certification program created by the National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Trial group, and we designed a similar program for the WFNS and GOS scales.

We analyzed the relationship between baseline total NIHSS score and 3-month GOS scores with Cochran-Mantel-Haenszel test statistics, using a 5% level of significance. We performed a multivariate backward logistic regression analysis using "unfavorable" 3-month outcome (GOS > 1) as the response variable, with each individual component of the NIHSS, age, sex, and baseline WFNS score as predictors. We sequentially removed those variables with a P value greater than 0.1, and used the baseline NIHSS component that remained in the model to construct an abbreviated version of the NIHSS (NIHSS-SAH). We then tested the baseline NIHSS-SAH score as an independent predictor of unfavorable outcome (GOS > 1) at 3 months in a multivariate logistic regression analysis with age, sex, and baseline WFNS scale score as covariates. All statistical analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC).

RESULTS

We analyzed the IHAST patients in the intention-to-treat population. Their mean age was 51.7 years (standard deviation, 12.5 yr); 65% were women and 80% were Caucasian. The median time from the onset of SAH to the baseline preoperative examination was 2 days (range, 0–14 d). The distribution of the preoperative WFNS and NIHSS scores is shown in *Figure 1*. Although neurological signs were recorded in only 5% of these patients using the WFNS scale (i.e., WFNS Grade III), almost half of all patients in this study scored at least one point on their NIHSS examination. Neurological signs (NIHSS score of at least 1 point) were observed in 148 out of 634 (23%) of the patients classified as WFNS Grade I and in 215 out of 263 (82%) of the patients classified as WFNS Grade II.

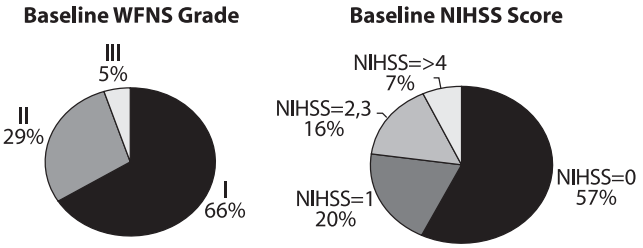


FIGURE 1. *Pie charts comparing the baseline NIHSS and WFNS scores in 944 patients with "good grade" SAH.*

Figure 2 shows the strong univariate association between baseline NIHSS score and 3-month outcome by GOS scores ($P < 0.001$). A multivariate logistic regression analysis confirmed the strong association between baseline NIHSS score and 3-month outcome ($P < 0.001$). This association was independent of the all other baseline characteristics, including WFNS scale score.

In multivariate backward logistic regression analyses using age, sex, and baseline WFNS score as covariates, the following four NIHSS items were each independently associated with outcome at 3 months: 1) worst arm motor score, 2) visual fields, 3) dysarthria, and 4) level of consciousness. Accordingly, we used these four NIHSS items to create a shortened NIHSS-SAH. The NIHSS-SAH was abnormal in 7% of the patients classified as WFNS Grade I and in 45% of those classified as WFNS Grade II. *Table 1* shows the impact of having an abnormal NIHSS-SAH score on 3-month outcome for WFNS Grades I and II. The likelihood of a favorable outcome at 3 months for a WFNS Grade I patient decreased from 74 to 48% if the patient had at least one point in the NIHSS-SAH.

The univariate relationship between baseline total NIHSS-SAH score and 3-month outcome is shown in *Figure 3*. *Table 2* shows the odds of an unfavorable outcome at 3 months (GOS > 1) for different baseline NIHSS-SAH scores compared with 0 (no abnormalities) in a multivariate logistic analysis using age, sex, and baseline WFNS score as covariates. SAH patients who scored even a single point on the reduced NIHSS-SAH were twice as likely to have an unfavorable outcome at 3-months (odds ratio, 1.8; 95% confidence interval, 1.2–2.6).

DISCUSSION

In this large cohort of SAH patients, we found that many patients considered to be "good grade" on the basis of the WFNS score had subtle neurological signs. We attribute this observation to the use of a more sensitive diagnostic tool for neurological focal findings, the NIHSS. The NIHSS characterizes a diversity of both major and minor neurological deficits in a way not covered by the SAH scales (3). To our knowledge,

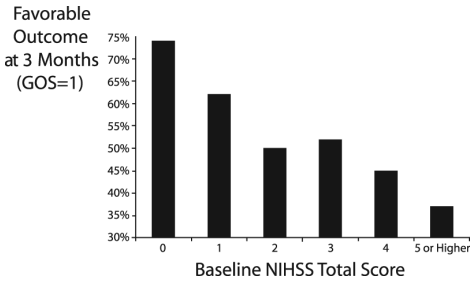


FIGURE 2. *Bar graph showing the relationship between the baseline NIHSS score and favorable outcome at 3 months by GOS scores.*

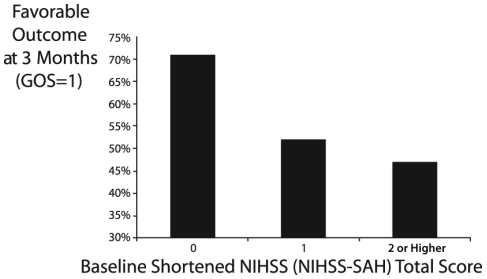


FIGURE 3. *Bar graph showing the relationship between the baseline shortened NIHSS (NIHSS-SAH) score and favorable outcome at 3 months by GOS score.*

TABLE 1. Impact of detecting focal neurological symptoms with the National Institutes of Health Stroke Scale-Subarachnoid Hemorrhage scale on the long term prognosis of World Federation of Neurological Societies Grades I and II[a]

WFNS grade	Favorable 3-month outcome (GOS = 1)	WFNS + NIHSS-SAH	Favorable 3-month outcome (GOS = 1)
Grade I (n = 472) (GCS = 15, no hemiparesis or aphasia)	72%	NIHSS-SAH = 0 (n = 440) (93%)	74%
		NIHSS-SAH > 0 (n = 32) (7%)	48%
Grade II (n = 168) (GCS = 13 or 14, no hemiparesis or aphasia)	52%	NIHSS-SAH = 0 (n = 93) (55%)	59%
		NIHSS-SAH > 0 (n = 75) (45%)	41%

[a] WFNS, World Federation of Neurological Societies; GOS, Glasgow Outcome Scale; NIHSS, National Institutes of Health Stroke Scale; SAH, subarachnoid hemorrhage; GCS, Glasgow Coma Scale.

TABLE 2. Odds of unfavorable outcome at 3 months (GOS > 1) by baseline National Institutes of Health Stroke Scale-Subarachnoid Hemorrhage score in a multivariate logistic analysis using age, gender, and baseline World Federation of Neurological Societies score as covariates[a]

Compared levels of total NIHSS-SAH scores	Adjusted OR of having 3-month GOS >1
1 (n = 143) versus 0 (n = 751)	1.8 (95% CI, 1.2–2.6)
2 (n = 57) versus 0	3.7 (95% CI, 1.9–6.9)
3 or higher (n = 49) versus 0	2.8 (95% CI, 1.4–5.8)

[a] WFNS, World Federation of Neurological Societies; NIHSS, National Institutes of Health Stroke Scale; SAH, subarachnoid hemorrhage; OR, odds ratio; GOS, Glasgow Outcome Scale; CI, confidence interval. $P < 0.001$.

the NIHSS has not been systematically studied in a population of SAH patients previously. The discovery of the high prevalence of subtle neurological signs at baseline in "good grade" SAH patients has important prognostic implications. These neurological findings in the initial NIHSS examination, which would otherwise go undetected by use of the WFNS, convey a significantly worse long-term prognosis. The mechanism causing these subtle neurological deficits is probably multifactorial, including parenchymal extension of a hematoma, compression of brain tissue by a subarachnoid clot, edema, secondary ischemia from early vasospasm and/or compression of penetrating vessels, or remote effect from increased intracranial pressure.

Our findings show that aphasia or hemiparesis are not the only signs that identify SAH patients with more severe disease. Therefore, it seems that the current WFNS classification does not adequately discriminate outcome among "good grade" SAH patients. Accurate risk stratification may facilitate the design of future clinical trials testing interventions in SAH patients. In addition, better prognostic accuracy would also be useful for discussing long-term outcomes with patients and families. In these circumstances, our findings indicate that the NIHSS can be a highly useful addition to the WFNS. The NIHSS is a familiar and widely accepted tool in the initial evaluation of stroke patients. In addition, because the NIHSS is commonly used in the evaluation of a suspected stroke before neuroimaging, it is likely that is already being used in the baseline assessment of many SAH patients who present with focal neurological findings. Finally, the NIHSS has well established certification programs already in place (9), which facilitates reproducibility among examiners. The NIHSS can be used reliably by different health professionals after minimal training (7). Although the NIHSS is already in common use, there could be some reluctance to add the entire NIHSS examination in the setting of SAH due, in part, to time constraints. The full NIHSS typically takes experienced practitioners approximately 7 minutes to perform (3), which, although comparatively brief, is still substantially longer than the time required to assign a WFNS score. In an attempt to shorten the examination time, we

used a multivariate regression analysis technique to identify those items of the NIHSS that are specifically relevant to outcome in SAH patients. Inclusion of the worst arm motor score, visual fields, dysarthria, and level of consciousness retained nearly all the predictive value of the full NIHSS.

We found that, as also observed with both ischemic stroke (1) and intracerebral hemorrhage (5), the baseline NIHSS score is a strong predictor of 3-month outcome in patients with "good-grade" SAH. This is an important finding because the NIHSS was not specifically designed for SAH. The use of a single unified scale to assess neurological status to predict outcome has always been appealing (6). These results broaden the scope of applicability of NIHSS to patients with suspected stroke, even when SAH is a consideration. The predictive ability of NIHSS is independent of the WFNS scale, which suggests that NIHSS is assessing different domains that are relevant to SAH outcome. Our hypothesis is supported by the large number of patients without focal findings by WFNS criteria that scored at least one point in the NIHSS.

However, we are not proposing substituting the current WFNS with NIHSS. Clearly, in the SAH population, it is apparent that NIHSS and NIHSS-SAH alone have relatively low discriminatory value. Furthermore, the WFNS scale will still be helpful for those patients with poor WFNS grades in whom the usefulness of the NIHSS has not been tested. NIHSS is not an appropriate scale to examine comatose patients, and the need for better detection of neurological signs is only an issue for "good-grade" patients (2). Instead, we suggest adding the four-point NIHSS-SAH only to patients with WFNS Grades I and II. The combination of WFNS scale and NIHSS-SAH results in a more refined predictive ability for WFNS Grades I and II (*Table 1*) by better stratification of patients in discrete categories that have different likelihoods of poor outcome. This additional step would require very little additional time for the evaluator, particularly if we consider the level of consciousness as part of the WFNS scale.

We are also aware of the limitations of this research. Because IHAST only included patients with baseline WFNS Grades I, II, and III, it is unknown whether or not the NIHSS and SAH-NIHSS add predicative value in WFNS Grades IV and V. Another limitation is the timing of the scales. Both the NIHSS and WFNS scales were performed within 12 hours of randomization but not necessarily at the time of initial presentation. Because there was a time gap between the onset of SAH and the measurement with these scales, it is possible that some of the focal findings recorded could be the result of early vasospasm. Nevertheless, the prognostic significance of the NIHSS-SAH remains.

CONCLUSION

We have discovered that a large number of SAH patients characterized as "good grade" by use of the WFNS have otherwise unrecognized focal neurological signs and that the presence of these signs convey a significantly less favorable prognosis. Assessing these few NIHSS items during the evaluation of a "good grade" SAH patient can be performed rapidly and significantly improves prediction of 3-month outcome by identifying patients with focal neurological signs not otherwise noted by the WFNS scale.

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Acknowledgments

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COMMENTS

The authors used data from the Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST) to evaluate the power of the World Federation of Neurological Societies (WFNS)-subarachnoid hemorrhage (SAH) grading scale in predicting outcome for patients with good grades. Grade I or II patients who had positive National Institutes of Health Stroke Scale (NIHSS) scores had significantly worse 3-month outcomes than patients who scored 0 on the stroke scale. Positive scores on the NIHSS suggest some type of brain dysfunction. More than 30 years ago, we learned from the pioneering work of William Hunt that SAH patients with brain dysfunction (Hunt and Hess [HH] Grade III) fared much worse after treatment than patients who presented with normal brain function (HH Grades I and II). The

NIHSS is an eloquent way to quantify brain dysfunction and accurately assign patients to HH Grade III.

In my opinion, there are only three groups of SAH patients who need to be defined before treatment: 1) those with normal brain function, 2) awake patients with any form of brain dysfunction, and 3) comatose patients. Both the HH grading scale and the WFNS grading scale aim at differentiating these three groups in a quantifiable fashion. This study using the NIHSS serves to highlight the limitations of the WFNS grading scale.

Robert A. Solomon
New York, New York

In this report, data from the IHAST study were analyzed to determine whether or not subtle preoperative neurological signs could be used to improve outcome prediction in patients defined as having good grades by the WFNS grading system. The NIHSS was used to detect these neurological signs, which were present in 23% of WFNS Grade I patients and 82% of Grade II patients. Four NIHSS items were predictive of a less favorable outcome: level of consciousness, visual field deficit, dysarthria, and arm motor score. Based on this observation, an abbreviated NIHSS-SAH scale was proposed to better predict outcome after SAH, which the authors recommend as a quick assessment tool and perhaps a measure in future clinical trials that test interventions in SAH.

There have been many attempts to improve simple grading scales, such as the widely used HH scale and the WFNS scale, typically by adding clinical information or radiographic data. The end result is more complicated schemes with more accurate outcome prediction. However, the value of the HH scale is not as an outcome predictor, but rather as an indicator of the severity of aneurysm rupture. Neurosurgeons who answer pages from emergency rooms appreciate how difficult it is to obtain reliable clinical information on patients with ruptured aneurysms from non-neurosurgeons. Consequently, we continue to embrace the HH scale because it is simple, reproducible, and informative. The NIHSS-SAH Scale is quite simple and easy to use, but less as a gauge of rupture severity and more as a refined predictor of outcome later in the clinical course. It is relevant only to good grade patients and is not relevant to poor grade patients. The scale should become part of the design of future clinical trials involving good grade SAH patients, as the authors suggest. This report also exemplifies the value of retrospectively analyzing datasets like the one from IHAST to answer important clinical questions outside of their intended purpose.

Michael T. Lawton
San Francisco, California

Extrapolating data from the IHAST, Leira et al. examine outcomes of SAH patients classified as good grade based on the traditional WFNS scale. In this secondary analysis of the IHAST data, the authors compare NIHSS and Glasgow Outcome Scale (GOS) scores at presentation and at 3 months. They purport that the NIHSS is a more sensitive and specific predictor of long-term functional outcomes than the WFNS scale.

Based on their analysis, the authors were able to identify specific parts of the NIHSS battery that predicted a worse outcome at 3 months; among these were level of consciousness, dysarthria, visual fields, and worst arm motor score. They propose a shortened version of the NIHSS, the NIHSS-SAH, as a complementary scale to be applied to SAH patients for clinical or research purposes. It is interesting, for example, that 45% of their patients classified as WFNS Grade II had an abnormal NIHSS-SAH score, and that this decreased the rate of favorable 3-month outcome from 59% for Grade II patients with a NIHSS-SAH score of 0 to 41% for Grade II patients with an abnormal NIHSS-SAH score.

This work is both novel and important. Of course, the elegance of the WFNS scale is in its simplicity and ease of use. Adding complexity to any grading scale will add time and perhaps decrease the utilization of such an analysis. Yet, the proposed shortened scale seems a reasonable and beneficial approach to enhancing our ability to predict outcomes after SAH.

Edward Duckworth
H. Hunt Batjer
Chicago, Illinois

There are several well established factors associated with predicting the long-term outcome after aneurysmal SAH. One of the most important factors is the clinical grade on admission. Both the WFNS and HH grading scales are used routinely in clinical practice. However, the limitations of these scales are manifestly obvious, especially in predicting outcome in good grade SAH patients (Grades 1 and 2).

This study is commendable in examining how the prognostic value of the WFNS score could be improved in good grade SAH patients. The authors have shown that the inclusion of the NIHSS can further stratify good grade patients and improve the predictive value of the WFNS grading scale. They have also shown that the level of consciousness, visual field defects, presence of dysarthria, and the worst arm motor score as particularly predictive of outcome and have suggested that these four points be used with the WFNS score in assessing the prognosis for outcome of good grade SAH patients. As a minor point, the authors use a GOS score of 1 as the best outcome, with a GOS score of 5 representing death. The original publications of the GOS scale designated a GOS score of 5 as the best outcome and a GOS score of 1 as death.

The ability to predict outcome accurately is important for both the optimal management of patients and assessing new treatments in SAH patients. Other factors, such as age, volume of SAH, presence of intraventricular blood, medical comorbidities, degree of vasospasm, and the size and location of the aneurysm are all important determinants in outcome from aneurysmal SAH when considering all grade patients. However, the relative importance of these factors in influencing the outcome of good grade SAH patients has yet to be determined and the inclusion of these with the NIHSS will no doubt further improve our prognostic power in the future. It is still unclear how widely the NIHSS-SAH scale will be used when compared with the familiarity, simplicity, and applicability of the WFNS and HH scales.

Marco B. Lee
Gary K. Steinberg
Stanford, California

Leira et al. performed a retrospective analysis of data from 1000 patients with SAH (WFNS Grades I, II, and III) by use of the NIHSS, NIHSS-SAH, and GOS at 3 months. We agree that the WFNS grading system is not perfect for the prediction of outcome among good grade SAH patients. The authors used the NIHSS-SAH scale to assess worst arm motor area, visual fields, dysarthria, and level of consciousness and showed that a combination of the WFNS and NIHSS-SAH scales was a more refined predictor for Grade I and II patients. This system is very simple, can be performed very quickly at the bedside, and could be practical for the assessment of good grade SAH patients. This article will contribute to the daily management of good-grade SAH patients with WFNS Grades I and II.

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EFFECTS OF TOBACCO DOSE AND LENGTH OF EXPOSURE ON DELAYED NEUROLOGICAL DETERIORATION AND OVERALL CLINICAL OUTCOME AFTER ANEURYSMAL SUBARACHNOID HEMORRHAGE

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OBJECTIVE: The association between smoking and intracranial aneurysms is now well recognized. However, the relationship between tobacco use and outcome after aneurysmal subarachnoid hemorrhage (SAH) is not as well understood and published results are contradictory. The purpose of this study is to examine the degree to which the amount of tobacco exposure/dose impacts delayed neurological deterioration and overall clinical outcome after aneurysmal SAH.

METHODS: We reviewed our retrospective database of patients with aneurysmal SAH. We assessed the impact of four independent tobacco variables: smoker (ever smoked), current smoker (actively smoking within the past yr and with at least a 10 pack per yr history of smoking), long-term smoker (at least a 20 pack per yr history), and salient (combination of current and long-term) smoker as well as tobacco dose (categorized according to number of packs per yr) on two outcome variables, delayed neurological deterioration and dichotomized Glasgow Outcome Scale score. Covariates included in the analysis were age, sex, Hunt and Hess grade, Fisher grade, and medical comorbidities. Stepwise elimination with logistic regression was used to arrive at a final multivariate model for each outcome and independent tobacco variable in the presence of covariates.

RESULTS: A total of 320 patients were analyzed. As expected, Hunt and Hess grade was a significant predictor of both delayed neurological deterioration and clinical outcome. Tobacco use (smoker variable) showed an independent association with the development of delayed neurological deterioration ($P = 0.0409$; odds ratio, 1.78; 95% confidence interval, 1.02–3.08). In addition, patients who were long-term or current smokers (salient smoker variable) showed a trend toward a slightly stronger association with the occurrence of delayed neurological deterioration ($P = 0.0229$; odds ratio, 1.85; 95% confidence interval, 1.09–3.14). No tobacco use variable was associated with clinical outcome (Glasgow Outcome Scale) in the multivariate analysis.

CONCLUSION: The duration and timing of tobacco use, rather than the dose of tobacco per se, seem to be risk factors for delayed neurological deterioration after aneurysmal SAH. Although we did not find an association between tobacco use and overall clinical outcome after aneurysmal SAH, these results suggest that the distribution of various patterns of tobacco use within a given data set may influence the overall results.

KEY WORDS: Cerebral aneurysm, Cerebral vasospasm, Outcome, Smoking, Subarachnoid hemorrhage, Tobacco

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The association between tobacco smoking and the development and rupture of intracranial aneurysms is now well recognized. However, the relationship between tobacco use and outcome, particularly as it relates to the occurrence of vasospasm and overall morbidity, after aneurysmal subarachnoid hemorrhage (SAH) is not as well understood. In addition, the degree to which the amount of tobacco exposure (tobacco dose) impacts vasospasm and outcome is not known. In the

present study, we examined the relationship between varying amounts of tobacco use and the incidence of delayed neurological deterioration as well as overall clinical outcome. We chose to use the term "delayed neurological deterioration" rather than vasospasm (angiographic or transcranial Doppler-derived) as an end point because it emphasizes the clinical status of the patient rather than the radiological findings.

PATIENTS AND METHODS

We reviewed our single-hospital retrospective database of patients with aneurysmal SAH who presented between 1991 and 2001. To be included in the analysis, all patients must have had a documented SAH, either by computed tomographic scan or bloody/xanthochromic cerebrospinal fluid after lumbar puncture, and must have subsequently been found to have an intracranial aneurysm on digital subtraction angiography. For patients with SAH in whom no aneurysm was found, so-called "angio-negative SAH" were not included.

The patients' demographic characteristics and premorbid medical conditions were recorded at the time of admission. Patients were considered hypertensive if they were found to be taking antihypertensive medication at the time of their SAH or if their admission echocardiogram showed changes consistent with left ventricular hypertrophy. Tobacco use (cigarettes) was quantified according to pack-years (the number of cigarette packs consumed per day multiplied by the number of years of use) as reported by the patient or nearest relative if the patient was unable to provide the information. If no information was available regarding the patient's tobacco use (n = 6; < 2%), the patient was assumed to be a nonsmoker. A smoker was defined as any patient who had previously smoked regardless of duration or quantity. A current smoker was defined as a person who had smoked within the past year and had smoked a pack per day for at least 10 years (10 pack-yr history). A long-term smoker was defined as anyone with a 20 pack-year or greater history of tobacco use. Patients were considered previous smokers if they had not smoked in more than 1 year. A salient smoker was defined as a person who had smoked within the past year and had at least a 10 pack-year history or had a 20 pack-year or greater history of tobacco use (i.e., a combination of "long-term" and "current" smokers).

We assessed the impact of these four tobacco variables (smoker, current smoker, long-term smoker [more than 20 pk-yr], and salient smoker) as well as tobacco dose (stratified in pack-yr categories) on two outcome variables, delayed neurological deterioration and Glasgow Outcome Score (GOS) (6). Because we were using it as a proxy for clinical "vasospasm," delayed neurological deterioration was specifically defined as a neurological deterioration occurring at least 2 days after surgical or endovascular intervention and not attributable to any other cause such as hydrocephalus, rehemorrhage, seizure, or metabolic abnormality. Clinical outcome (GOS) was determined at the time of the most recent follow-up evaluation by direct clinical interview and examination. GOS was dichotomized with the category "excellent/good" representing GOS 4 and 5. Covariates included in the analysis were age, sex, Hunt and Hess grade, Fisher grade, and medical comorbidities. Medical comorbidities included major medical illnesses such as, asthma, cancer, chronic obstructive pulmonary disease, congestive heart failure, coronary artery disease, chronic liver disease, peptic ulcer disease, and renal insufficiency/failure.

Statistical Analysis

Pearson's χ^2 test was used to test for a univariate association between each outcome variable and each categorical, but not ordinal, independent variable (covariate). A two-sample *t* test was used as the univariate test for continuous variables. A Cochran-Armitage trend test was used as a univariate test for trend. Tobacco dose (0, 1–9, 10–19, and 20 or greater pack-yr), Hunt and Hess grade, Fisher grade, and major medical illness were analyzed in this way with regard to either delayed neurological deterioration or clinical outcome (GOS category). Logistic regression was used to test the association of each independent variable of interest with each outcome while adjusting for the effects of covariates. For each outcome, a stepwise process of elimination with logistic regression was used to choose the covariates that were most significant to the outcome collectively from age, sex, diabetes, hypertension, Hunt and Hess grade, Fisher grade, and other major medical illness. The inclusion/exclusion level of significance for the stepwise procedure of choosing covariates for the models was set at 0.15. These covariates were combined with the independent variable of interest in the final multivariate logistic regression model. A Hosmer and Lemeshow goodness-of-fit test was performed with each model to check the representativeness of the model.

RESULTS

A total of 520 patient data records were initially reviewed from patients treated between 1987 and 2001. After exclusion of those patients with unruptured aneurysms, "angiographically negative SAH," and unknown treatment dates, 320 patients treated between 1991 and 2001 remained and were included in the final data set. Demographic characteristics and descriptive statistics are summarized in *Table 1*. The average patient age was 53 years (range, 8–88 yr). The majority of the patients were female (n = 221; 69%). Approximately two-thirds of these (n = 213; 67%) had some history of tobacco use. Approximately half of the patients were current smokers (n = 165; 52%), whereas 41% (n = 130) were long-term smokers (more than 20 pack-yr

TABLE 1. Baseline characteristics and outcome variables[a]

No. of patients	320
Age, yr (mean ± SD)	53.5 ± 14.6
Male (%)	99 (31)
Median Hunt and Hess grade	3
Median Fisher grade	3
Smoker (%)	213 (67)
Current smoker (%)[b]	165 (52)
Long-term smoker (%)[c]	130 (41)
Salient smoker (%)[d]	190 (59)
Delayed neurological deterioration (%)	119 (43)
GOS score of excellent/good (%)	193 (61)
Median GOS score	4

[a] SD, standard deviation; GOS, Glasgow Outcome Scale.
[b] Defined as a person who has smoked within the past year and has smoked a pack per day for at least 10 years (10 pack-yr history).
[c] Defined as a person with a 20 pack-year or greater history of tobacco use.
[d] Defined as a person who had smoked within the past year and had at a 10 pack-year history or had a 20 pack-year or greater history of tobacco use (i.e., a combination of "long-term" and "current" smokers).

TABLE 2. Summary of relationship between tobacco variables and delayed neurological deterioration by univariate analysis

Variable	Delayed neurological deterioration (no.)	Odds ratio	95% confidence interval	*P* value
Smoker	86	1.5	0.89–2.50	0.1241
Current smoker	67	1.34	0.83–2.16	0.2314
Long-term smoker	49	0.94	0.58–1.52	0.7904
Salient smoker	80	1.66	1.01–2.71	0.045

TABLE 3. Summary of relationship between tobacco variables and clinical outcome by univariate analysis[a]

Variable	GOS (excellent/good)	Odds ratio	95% confidence interval	*P* value
Smoker	136	1.53	0.95–2.46	0.0807
Current smoker	108	1.57	1.00–2.48	0.0512
Long-term smoker	85	1.41	0.89–2.25	0.1448
Salient smoker	121	1.4	0.89–2.22	0.1466

[a] GOS, Glasgow Outcome Scale.

history). Hypertension was present in 165 patients (52%). Only 23 patients (7%) were diabetic. The median Hunt and Hess grade was 3; the median Fisher grade was 3. One hundred nineteen patients (43%) experienced delayed neurological deterioration at some point during their hospital stay. The median GOS score was 4, and the mean duration of the follow-up period was 15 months (range, 1–155 mo).

Univariate Analysis

The results of the univariate analysis are summarized in *Tables 2* and *3*. Notably, the salient smoker group (i.e., current smoker or long-term smoker) was significantly associated with delayed neurological deterioration ($P = 0.045$) with an odds ratio of 1.66 (95% confidence interval [CI], 1.01–2.71), which means that a patient with at least a 10 pack-year history who was still smoking during the past year before admission or had a 20 pack-year or greater history of tobacco use was 1.66 times more likely to experience delayed neurological deterioration than a patient who never smoked or smoked only briefly in the past. There was no difference between the mean ages of patients with delayed neurological deterioration versus those without. There was a significant difference in the mean age of patients in the GOS category of "dependent/deceased" (57.7 yr) compared with those in the "excellent/good" category (50.6 yr) (two-sample *t* test, $P < 0.0001$).

Multivariate Analysis

Delayed Neurological Deterioration

The significant covariates resulting from the process of stepwise elimination with logistic regression for delayed neurological deterioration included Hunt and Hess grade ($P = 0.0083$) and seizures ($P = 0.0394$). The independent variables of interest adjusted for these significant covariates were smoker ($P = 0.0409$) and salient smoker ($P = 0.0229$). The current smoker ($P = 0.2108$), long-term smoker (more than 20 pack-yr) ($P = 0.6079$), and tobacco dose groups ($P = 0.1524$) did not demonstrate a significant association with delayed neurological deterioration after adjustment for the previously described covariates. Patients with any history of tobacco smoking (smoker) had a significantly increased risk of delayed neurological deterioration (odds ratio, 1.78; 95% CI, 1.02–3.08) compared with patients who have never used tobacco. Salient smokers also showed a significant association with delayed neurological deterioration, with an odds ratio of 1.85 (95% CI, 1.09–3.14), meaning that a patient who is a "salient" smoker (current and/or long-term) is almost twice as likely to experience delayed neurological deterioration when compared with a patient who is not a smoker or who has smoked for less than 20 pack-years and quit more than 1 year previously (*Table 4*).

After finding these significant relationships, we performed a more specific multivariate analysis such that each smoking category was separately assessed in comparison with nonsmokers. Compared with nonsmokers, long-term smokers did not show a significantly increased risk of delayed neurological deterioration ($P = 0.1206$). However, status as a current smoker versus a nonsmoker was a significant predictor of delayed neurological deterioration ($P = 0.0419$; odds ratio, 1.84; 95% CI, 1.02–3.32). When current smokers were combined with long-term smokers in the salient smoker variable, the association became somewhat stronger, with "salient" smokers being almost twice as likely to experience delayed neurological deterioration when compared with nonsmokers ($P = 0.0238$; odds ratio, 1.92; 95% CI, 1.09–3.37).

TABLE 4. Summary of multivariate analysis of impact of tobacco variables on delayed neurological deterioration

Variable	Odds ratio	95% confidence interval	*P* value
Comparison with entire study sample			
Smoker	1.78	1.02–3.08	0.0409
Current smoker	1.38	0.83–2.29	0.2108
Long-term smoker	1.14	0.68–1.91	0.6079
Salient smoker	1.85	1.09–3.14	0.0229
Tobacco dose	1.41	0.61–3.27	0.1524
Comparison with nonsmokers			
Current smoker	1.84	1.02–3.32	0.0419
Long-term smoker	1.62	0.88–3.00	0.1206
Salient smoker	1.92	1.09–3.37	0.0238

TABLE 5. Summary of multivariate analysis of impact of tobacco variables on clinical outcome[a]

Variable	Odds ratio	95% confidence interval	*P* value
Smoker	1.09	0.55–2.14	0.8110
Current smoker	1.15	0.60–2.21	0.6744
Long-term smoker	1.09	0.55–2.14	0.8083
Salient smoker	0.97	0.50–1.90	0.9277
Tobacco dose	1.14	0.41–3.13	0.6539

[a] GOS, Glasgow Outcome Scale.

Clinical Outcome

The significant covariates resulting from the process of stepwise elimination with logistic regression for GOS category included age ($P = 0.0199$), Fisher grade ($P = 0.0425$), Hunt and Hess grade ($P < 0.0001$), and major medical illness ($P = 0.0351$). Because delayed neurological deterioration is known to have a significant association with clinical outcome, we also included that variable as a covariate in the models for GOS category. The independent variables of interest, smoker ($P = 0.8110$), current smoker ($P = 0.6744$), long-term smoker (more than 20 pack-yr) ($P = 0.8083$), salient smoker ($P = 0.9277$), and tobacco dose ($P = 0.6539$), did not have a significant association with GOS category when adjusted for the aforementioned covariates (*Table 5*).

DISCUSSION

After numerous studies, tobacco exposure is now widely accepted as a risk factor for the development and rupture of intracranial aneurysms (8, 10, 12, 15, 22). However, the influence of tobacco exposure (smoking) on outcome after SAH has not been studied as thoroughly and conflicting results have been reported (7, 18, 20). Likewise, the impact of smoking on clinical vasospasm, the leading cause of morbidity and mortality after the initial SAH, is controversial (9, 13, 23). Furthermore, although there is evidence that risk of aneurysmal SAH may increase in a dose-dependent manner (1, 15, 21), the influence of tobacco dose on clinical vasospasm and delayed neurological deterioration and overall clinical outcome is unclear.

In general, tobacco use has been thought to increase the chances of a poor outcome. However, actual published results regarding outcome after aneurysmal SAH have by no means been uniform. In 1992, a United Kingdom-based study reported a twofold increase in the relative risk of aneurysmal SAH for smokers versus nonsmokers (18). Smokers had more postoperative pulmonary complications, but overall management outcome at 6 months was similar for both groups. Although not directly assessing clinical outcome, in 1997, Lasner et al. (13) first reported that cigarette smoking was an independent predictor of symptomatic vasospasm after aneurysmal SAH. Analyzing almost 3500 patients from the Cooperative Aneurysm Study, Weir et al. (23) also found an increased incidence of vasospasm in smokers with aneurysmal SAH. In a review of more than 800 cases from the United Kingdom, Pobereskin (20) found case-fatality rates to be lower among smokers when compared with nonsmokers and proposed that increased immediate vasospasm in smokers may reduce the severity of the initial hemorrhage. None of these previous studies examined differences in outcome or vasospasm risk in relation to the amount (dose) of tobacco used.

In the present study, we sought to examine the influence of tobacco smoking on delayed neurological deterioration and overall clinical outcome with a focus on the influence of dose as a means of exploring a potential explanation for some of the differences previously reported. In an attempt to better characterize these controversial tobacco effects, we devised four distinct "tobacco" variables as well as a fifth "tobacco dose" variable. The majority of previous studies have assessed tobacco use in patients by designating them as either smokers or nonsmokers. This dichotomy mirrors our smoker variable. Among the other categories, the salient smoker variable was created to reflect the group of smokers in which tobacco use would most likely produce some influence. This category, therefore, excludes short-term smokers who quit more than 1 year before their SAH. To more specifically scrutinize the influence of the amount of tobacco used, we also created the "tobacco dose" variable, in which the "dose" of tobacco is represented as pack-years.

The choice of definitions for smoking categories was based largely on the distribution of our data set. Specific definitions in the literature are sparse. The American Lung Association defines a current smoker as a person who has smoked a total of 100 cigarettes (five packs) during their lifetime and who currently smokes everyday or some days. However, no similar definition exists for terms such as "long-term" or "heavy" smoker. Further complicating matters, the quantity of tobacco smoked is typically recorded in pack-years (number of packs per day multiplied by the number of years the patient has smoked). In addition, studies in the oncology and vascular disease literature use various breakpoints from 10 pack-years to 60 pack-years to define long-term or heavy smokers (3, 4, 11, 14, 16, 19).

In our series of 320 patients with aneurysmal SAH, 67% had a history of tobacco use and 43% of patients experienced some form of delayed neurological deterioration during their hospitalization. Not surprisingly, admission Hunt and Hess grade was an independent predictor of this deterioration. Also, as expected, Hunt and Hess grade, Fisher grade, and the presence of major medical illness were all predictors of outcome by GOS. Smoking did not prove to be an independent predictor of clinical outcome regardless of dose or duration. However, the influence of smoking on the occurrence of delayed neurological deterioration proved to be much more complex. Tobacco use in general (any amount, any duration) showed a significant association with delayed neurological deterioration. In the initial multivariate analysis, current and long-term smokers showed no independent association with delayed neurological deterioration, but patients in the salient smoker category (cur-

rent and long-term smokers combined) showed a significant independent association with the occurrence of delayed neurological deterioration ($P = 0.0229$). "Salient" smokers were more than 1.5 times more likely to experience delayed neurological deterioration than other patients (odds ratio, 1.85; 95% CI, 1.09–3.14). Tobacco dose, categorized independent of whether or not a patient was a current smoker, had no impact on the incidence of delayed neurological deterioration. When a multivariate analysis was performed in comparison with nonsmokers (rather than all other patients), current smokers, but not long-term smokers, showed a significantly increased risk of delayed neurological deterioration. The combination of current and long-term smokers (salient smokers) had the strongest association with this group being almost twice as likely to experience delayed neurological deterioration as their nonsmoking colleagues ($P = 0.0238$; odds ratio, 1.92; 95% CI, 1.09–3.37).

These findings may provide a clue to the seemingly contradictory results currently in the literature regarding smoking and outcome after SAH. If, as our study indicates, the pool of current and long-term smokers (especially current smokers) truly does have an increased risk of delayed neurological deterioration relative to nonsmokers and short-term smokers who have quit for more than 1 year, the percentage of "inactive" short-term smokers in any given study population may have a significant impact on the overall results. The etiology of such differences is unclear. However, it is reasonable to speculate that the cerebrovascular dysfunction promoted by tobacco smoking is most pronounced in active smokers, and perhaps to a lesser extent in long-term smokers, and that such dysfunction is less prominent in short-term or inactive smokers. Although we were not able to demonstrate an effect of smoking of any kind on outcome, it is not hard to suppose that a similar effect may be occurring in this regard.

Like any other retrospective case series, this study has some potential methodological issues. As a tertiary referral center, there is likely to be a degree of selection/referral bias with regard to the patients included. However, the patients' condition, as indicated by the Hunt and Hess grade and suggested by the Fisher grade, is controlled for in the multivariate analysis. We chose to use delayed neurological deterioration as a measure of in-hospital deterioration and a proxy for clinical vasospasm. The use of this term emphasizes the clinical status of the patient rather than acting as a measure of radiographic findings such as angiographic or transcranial Doppler vasospasm, which may or may not actually manifest in a clinically significant change. Nevertheless, determining this form of delayed neurological deterioration from a retrospective record review may lead to recording errors. To minimize inaccuracies as much as possible, record reviewers were warned of potential pitfalls and care was taken to avoid recording neurological changes related to rebleeding, hydrocephalus, infection, or metabolic abnormalities. Questionable cases were reviewed by the senior author (KMC), who was blinded to the patient's smoking status. Likewise, smoking status and quantification of tobacco use relied on a review of records obtained at the time of the patient's admission. In some cases, the next of kin rather than the patient reported tobacco information. In cases in which varying amounts of use were reported, the highest recorded amount was entered as the "dose." When no information regarding tobacco use was found, the patient was entered as a nonsmoker. Overall, this method of recording smoking status likely results in an under-reporting of tobacco use and as such biases the results in favor of a negative finding. Finally, it is quite possible that the sample size may have limited our ability to detect an association between tobacco use and GOS score. The fact that no association was found, therefore, does not warrant the conclusion that one does not exist, but only that one was not detected in the present study.

Obviously, there are likely to be additional reasons for the discrepancies in the literature. Some differences may stem from the inconsistent use of certain covariates in the statistical analyses. Many factors other than tobacco use are known to influence the incidence of delayed neurological deterioration/vasospasm and the overall clinical outcome after SAH. For example, age, clinical grade (Hunt and Hess Grade or World Federation of Neurological Surgeons Grade), and Fisher computed tomographic grade are all known to predict outcome, yet all of these variables are not always controlled in any given analysis. Clinical grade and computed tomographic grade are also predictors of vasospasm. In the present study, these variables were all included in the analysis. The finding that these variables did, in fact, predict delayed neurological deterioration and outcome lends validity to the data set. As a related issue, the inclusion or exclusion of patients with angiographically negative SAH may also influence results. Traditionally, so-called "angio-negative" patients have been thought to have a better outcome than their counterparts with aneurysmal SAH (2, 5), yet these patients are sometimes included in studies of aneurysmal SAH. For instance, Pobereskin (20), although showing an improved outcome for smokers after SAH, reported a 17% angiogram-negative rate and a 35% overall aneurysm-negative rate, including patients who died and underwent autopsy. Whether or not the angiogram-negative rate varied with smoking status was not reported. However, such a high rate of "angio-negative" patients with SAH could easily bias the results in favor of good overall outcomes.

There is also evidence that treatment modality may also influence outcome. However, a specific comparison of surgery versus endovascular treatment was not performed in this particular case because endovascular techniques were largely unavailable at our institution during the majority of the period covered by this study. Certainly, future series that include a large proportion of endovascularly treated patients will need to consider the influence of treatment type on outcome, especially because evidence suggests that the incidence of vasospasm is significantly lower in endovascularly treated patients (17).

In summary, our present study supports the conclusion that tobacco smoking does increase a patient's risk of delayed neurological deterioration after aneurysmal SAH. In addition, the data suggest that the amount and duration of tobacco use may have a subtle influence on the incidence of delayed neurological deterioration and overall clinical outcome after SAH.

Specifically, in the present study, patients who were current and/or long-term smokers (salient smokers as defined in our analysis) were almost twice as likely to experience delayed neurological deterioration when compared with other patients with aneurysmal SAH. These differences may explain, at least in part, the discrepancies currently reported in the literature with regard to the influence of tobacco use on delayed neurological deterioration/vasospasm and outcome. Prospective studies of larger cohorts of patients may provide further information in this regard.

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COMMENTS

This carefully conducted retrospective analysis of aneurysmal subarachnoid hemorrhage (SAH) patients adds to the literature suggesting adverse effects of smoking on outcome and vasospasm. I have three comments regarding this study. The first is that the vasospasm described here is not an angiographic vasospasm. The authors are discussing delayed neurological deterioration, one cause of which may be angiographic vasospasm. It is increasingly being recognized that there may be other causes for delayed neurological deterioration than angiographic vasospasm, i.e., after excluding metabolic causes, hydrocephalus, seizures, and anything detectable by laboratory and radiological testing or treatable. Other terms such as delayed cerebral ischemia have been used, but delayed neurological deterioration avoids the assumption that all deterioration is on the basis of ischemia.

Secondly, the statistical analysis is complex and requires a great deal of thought for appropriate interpretation. I am not a statistician, but I have concluded that a close working relationship between the physician researcher and a knowledgeable statistician is needed in order to conduct such work. Modern statistical software allows those of us with little knowledge to conduct complex analyses without any idea as to what any of the output means. The present analysis, for example, makes the important observation that smoking is associated with delayed neurological deterioration. The prognostic factors associated with outcome after SAH have been discussed frequently and with conflicting results, but many studies show that delayed deterioration is associated with poor outcome. Therefore, why does this study not show that smoking is associated with poor outcome? It simply shows that no significant relationship could be found within this small, retrospective review. It cannot be concluded that one does not exist.

Thirdly, the mechanisms by which smoking exerts detrimental effects are not known. Patients sometimes ask if the smoking information also applies to pipes, cigars, and chewing tobacco; the answer to this question seems to be unknown.

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In this retrospective analysis, Krishnamurthy et al. investigate an intriguing issue regarding the relationship between cigarette use and both delayed neurological deficit and clinical outcome after aneurysmal SAH. Although they fail to detect a statistically significant correlation between tobacco smoking and Glasgow Outcome Score, the authors find that tobacco use was associated with an increased propensity toward delayed neurological deterioration, a clinically meaningful correlate of vasospasm. The authors extend the findings of previous work by stratifying smoking patients into different groups based on the timing of

tobacco use in relation to SAH, the duration of tobacco exposure, and tobacco dose. Notwithstanding concerns about the adequacy of their study's power, these results do introduce, but do not necessarily answer, questions that may explain discrepancies in previous investigations. For instance, the ability to accurately identify those patients who are current or long-term smokers may decrease variability when examining links between tobacco use and various sequelae of aneurysmal SAH.

On a practical level, this study warns clinicians to raise their suspicion of delayed neurological deterioration when managing SAH patients with a significant smoking history. Beyond clinical correlation, studies such as this provide a clinical impetus for future mechanistic analyses of cerebrovascular responsiveness and smoking-induced vascular stress in the context of SAH.

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In this study, the authors review 10 years of data from one center, providing more than 320 consecutive patients with aneurysms and SAH. The authors investigated tobacco use as a variable of outcome such as developed neurological deterioration. The methodologies of such studies are always difficult and the authors discuss this. This includes the definition of SAH. In this case, the authors only include SAH from a proven aneurysm. They excluded bleeds from other sources and unruptured aneurysms. The next issue is the definition of vasospasm, which is a clinical definition in their study (i.e., delayed neurological deterioration) and, without angiographic proof, is capable of creating some confusion with other diagnoses of delayed deterioration. Finally, the dose and presentation of smoking is debated here. The authors provide several different reviews in an attempt to get at the idea of total dose of tobacco using traditional methodology, the history of current smoking, and current heavy smoking. They also see that most of the positive results are obtained by combining two groups of overlapping patients, which they call "salient smokers," combining recent smoking with any period of heavy smoking in the past. The results suggest that there is a relationship with clinical deterioration associated with smoking and probably with recent or heavy smoking. They provide conflicting data, as they first say they do not see an effect on outcome. Nevertheless, they also suggest that tobacco dose demonstrates a significant increase in trend for Glasgow Outcome Scale category, i.e., the outcome is improved as the tobacco dose increases. This is not discussed in further detail in the article. The authors need to clarify this statement in the context of their conclusions. Other reports have suggested that there may be a dichotomous relationship to smoking; whether it is a survival effect or whether it suggests that there is some important difference in the vasospasticity of a smoker's vessels has never been clarified. The authors would do well to expand upon this in detail.

The authors do understand the limitations of such studies due to methodological differences because of the use of one center, the clinical definition of vasospasm, and the multiple ways in which smoking is represented in their study. Nevertheless, the possibility of a Type 2 error is real in that their failure to show an outcome difference with smoking may be the result of sample size and does not necessarily prove that no difference exists. Further information regarding these questions would strengthen the study's presentation.

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Krishnamurthy et al. have reviewed their database with the goal of examining the degree to which tobacco exposure and dose impacts delayed neurological deterioration and overall clinical outcome after aneurysmal SAH. The authors found tobacco use to be independently associated with the development of delayed neurological deterioration, with long-term or current smokers trending towards a stronger association. Interestingly, the no tobacco use variable was associated with clinical outcomes. The authors concluded that duration and timing of tobacco use, rather than dose, are risk factors for delayed neurological deterioration after aneurysmal SAH.

Although the association between smoking and intracranial aneurysms is well established, the authors have contributed to the literature by demonstrating that tobacco use is also related to delayed neurological deterioration after aneurysmal SAH. This is not entirely unexpected, as increases in cortical cerebral blood flow may be induced by stimulation of basal forebrain cholinergic neurons. This response is mediated in part by nitric oxide and involves nicotinic receptors. Thus, it may be that patients exposed to chronic tobacco have impaired cerebrovascular autoregulation and, thereby, more likely to develop cerebral vasospasm. This theory has already been shown in animal models, as chronic nicotine exposure blunts NO-induced vasodilation of pial vessels and diminishes cortical blood flow (1).

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Clinical Features, Treatment, and Prognosis of Patients with Acute Subdural Hematomas Presenting in Critical Condition

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OBJECTIVE: Spontaneous acute subdural hematoma (aSDH) may be caused by aneurysm rupture. Patients can present in very poor clinical condition with anisocoria or even bilaterally dilated pupils, absent brainstem reflexes, and cardiac insufficiency. For the clinician, the question is how should these patients be treated? Large series on this subject do not exist because aSDH is a rare event. This report focuses on the prognosis and adverse prognostic factors of these patients.

CLINICAL PRESENTATION: We present eight cases of aSDH and subarachnoid hemorrhage attributable to aneurysm rupture. All patients were World Federation of Neurosurgical Societies Grade 5. Four presented with anisocoria, three presented with bilaterally fixed and dilated pupils, and one developed anisocoria in the course of treatment.

TREATMENT: As a result of prolonged hypoxia before admission, one patient was not treated and died. In one patient, surgical decompression could not be performed in the acute phase as a result of significant comorbidity. All other patients received decompressive surgery, obliteration of the aneurysm, and medical therapy as well as extensive rehabilitation measures. After 6 months, four had no or only minor neurological deficits; one patient was independent despite hemiparesis. Two patients whose surgical decompression had to be delayed as a result of severe cardiac instability recovered poorly, showed severe neurological deficits, and required permanent care. However, none of the patients survived in a persistent vegetative state.

CONCLUSION: Within the spectrum of aneurysmatic hemorrhage, patients with aSDH represent a distinct subgroup. Despite a very poor clinical condition on admission, recovery with only minor deficits or even without neurological deficit is possible. Mass effect and herniation induce a poor clinical condition, which is not directly related to the underlying subarachnoid hemorrhage. Hence, clinical grading systems such as the Hunt and Hess scale or World Federation of Neurosurgical Societies grading are not applicable. We suggest that whenever the medical condition allows, rapid surgical decompression should be performed even in patients who present in very poor neurological condition.

KEY WORDS: Aneurysm, Aneurysmatic subdural hematoma, Coma, Decerebration, Outcome, Subarachnoid hemorrhage, Subdural

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Sudden and spontaneous onset of neurological deterioration and pupillary disturbance suggests intracranial hemorrhage with significant mass effect. This may be attributable to spontaneous acute subdural hematoma (aSDH) caused by aneurysm rupture. The incidence of aneurysmal aSDH has been reported to be 5 to 22% in autopsy studies, including patients with small amounts of subdural blood and those who died before reaching medical treatment (8, 13). In computed tomographic (CT)-based clinical studies, the incidence of aneurysmal aSDH has been found to be 2 to 10.3% (16, 22).

Since the 1950s, several authors have discussed the appropriate management of patients

with aneurysmal aSDH. In 1953, Clarke and Walton (6) classified aneurysmal aSDH based on published case reports: 1) patients with rapidly fatal hemorrhage, 2) patients with an insignificant amount of subdural blood, and 3) patients with clinically significant hematoma, which was not rapidly lethal. It was concluded that Group 3 alone was suitable for treatment. Since then, several groups have reported good outcome after rapid surgical decompression, although patients presented in poor neurological condition (17, 18). In general, early decompression of significant mass lesions has shown to be favorable and has been recommended even in larger studies (10, 16, 22). However, in larger series, a significant number of patients did not receive surgical treatment or were not treated at all. However, the reasons for withdrawing therapy in poor-grade patients were not discussed in detail.

Improvements in emergency treatment and resuscitation help a growing number of patients survive the first hours and reach hospitals in very poor neurological condition. The situation is challenging because it requires rapid evaluation of whether angiography should precede surgery, whether surgery should be postponed because of severe comorbidities, or if therapy should be completely withheld to prevent vegetative survival. Large systematic series focusing on the outcome and prognosis of patients with aneurysmal aSDH who present in very poor clinical condition do not exist. Currently, decisions must be based on personal experience and case reports. In this article, we report eight patients with aneurysmal aSDH who presented in a comatose state with pupillary disturbance.

Illustrative Cases

We present a series of eight patients with aneurysmal aSDH who were admitted in a comatose state and with pupillary disturbance within a 3-year period. In this period, a total of 115 patients with aneurysmal SAH were admitted to our department. Eight patients, all women, had aSDH visible on CT scans. On admission to our department, all of the reported patients were intubated and mechanically ventilated. Five patients were primarily admitted to our department and three were transferred from external hospitals. The clinical state before intubation was reported by emergency physicians who accompanied the transfer to our department. According to their initial examination, all patients were graded as World Federation of Neurosurgical Societies Grade 5 (*Table 1*).

Except for one patient who was not specifically treated and died subsequently (Patient 8), all patients were discharged into rehabilitation centers. Neurological outcome was assessed after 6 months and is presented using the Glasgow Outcome Scale (GOS) and the Barthel Index.

Patient 1

A 55-year-old woman was admitted to an external hospital with severe headache. Four hours later, she deteriorated to Glasgow Coma Scale [GCS] 6, was intubated, and transferred to our hospital. On admission, she had no pupillary disturbance. CT scans showed a right frontotemporal and interhemispheric subdural hematoma (*Fig. 1*). External ventricular drainage was implanted for intracranial pressure monitoring and cerebrospinal fluid drainage. Angiography demonstrated an aneurysm of the anterior communicating artery, which was treated by endovascular coiling. Twenty-four hours later, intracranial pressure increased and anisocoria developed. Immediate craniectomy and evac-

TABLE 1. Details of clinical presentation, treatment, and outcome[a]

Patient no.	Age (yr)/sex	State on admission, pupillary state	Location of subdural hematoma	Aneurysm	Treatment of hematoma and aneurysm	Complications, infarction	Outcome
1	55/F	WFNS 5, anisocoria after 24 hours	Right frontal and interhemispheric	Acom	Endovascular coiling; decompression as anisocoria developed	Vasospasm, angioplasty, right frontobasal infarction	GOS 4 Barthel 70
2	56/F	WFNS 5, MI, bilaterally fixed pupils	Right frontotemporal and ICH	MCA	Delayed treatment; decompression and vasospasm, clipping after 24 hr	Cardiac instability, right MCA and partial ACA infarction	GOS 3 Barthel 20
3	55/F	WFNS 5, anisocoria	Right frontotemporal	Pcom	Surgical decompression; endovascular coiling	Vasospasm, right parietal infarction	GOS 4 Barthel 70
4	55/F	WFNS 5, anisocoria	Right frontal and interhemispheric	Acom	Surgical decompression; endovascular coiling	Vasospasm, right frontobasal infarction	GOS 5 Barthel 100
5	43/F	WFNS 5, bilaterally fixed pupils	Left frontotemporal	Pcom	Surgical decompression; endovascular coiling	Vasospasm, angioplasty, partial left MCA infarction, VP shunt	GOS 3 Barthel 70
6	54/F	WFNS 5, MI, resuscitated anisocoria	Right frontotemporal	Acom	Delayed treatment ventriculostomy; endovascular coiling	Cardiac instability, vasospasm, right MCA and partial ACA infarction	GOS 3 Barthel 0
7	42/F	WFNS 5, anisocoria	Right frontotemporal	Pcom	Surgical decompression and clipping	Vasospasm, angioplasty, no infarction	GOS 5 Barthel 100
8	55/F	WFNS 5, hypoxic, bilaterally fixed pupils	Right frontotemporal and ICH	MCA	No therapy as a result of prolonged hypoxia before admission	Deceased	GOS 1

[a] WFNS, World Federation of Neurological Surgeons, clinical classification; Acom, anterior communicating artery; GOS, Glasgow Outcome Scale; MI, myocardial infarction; ICH, intracerebral hemorrhage; MCA, middle cerebral artery; ACA, anterior cerebral artery; Pcom, posterior communicating artery; VP, ventriculoperitoneal.

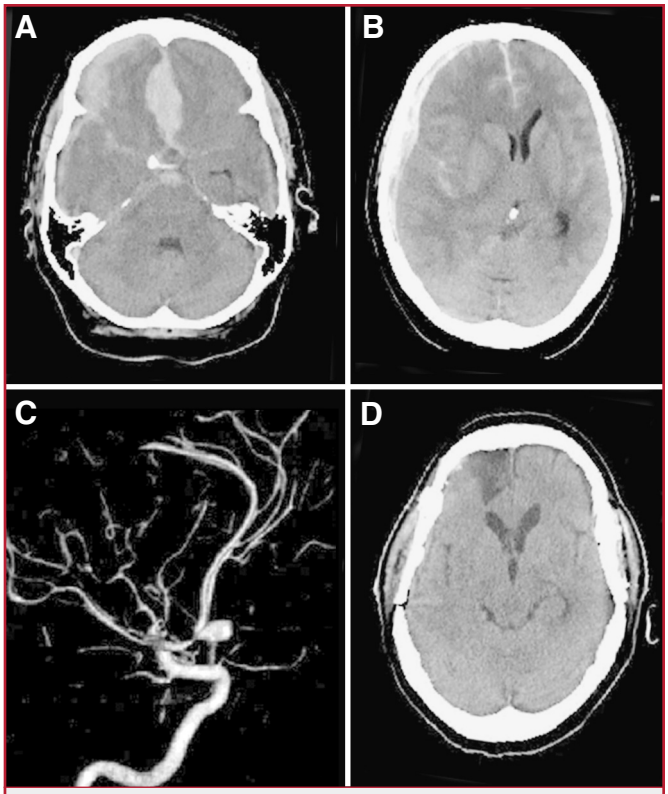


FIGURE 1. **A** *and* **B**, *CT scans showing Patient 1 after deterioration.* **C**, *three-dimensional angiography showing an aneurysm of the anterior communicating artery.* **D**, *CT scan obtained 5 months after bleeding showing partial infarction of the right anterior cerebral artery territory.*

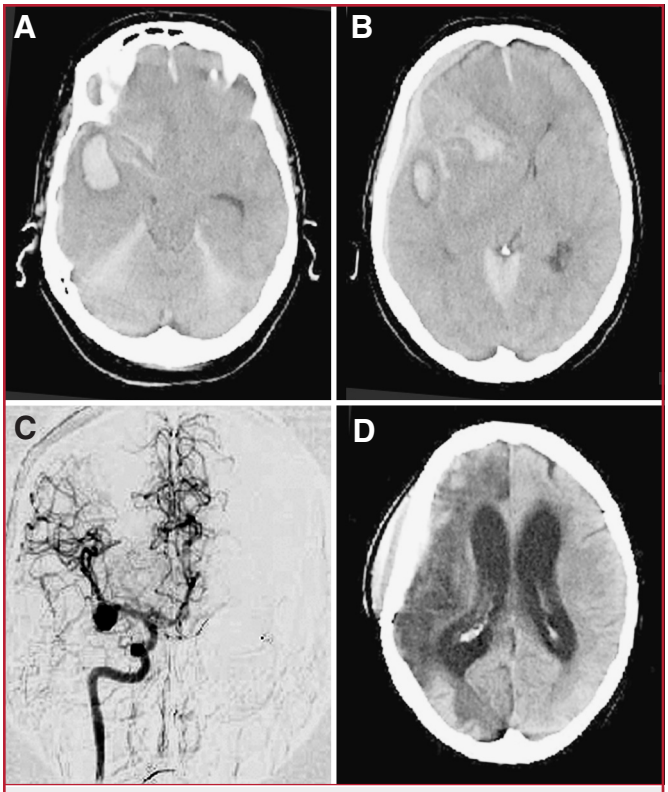


FIGURE 2. **A** *and* **B**, *CT scans showing Patient 2 at the time of admission.* **C**, *anteroposterior view showing a large middle cerebral artery aneurysm.* **D**, *CT scan obtained 6 months later showing infarction in the right middle cerebral artery and frontal anterior cerebral artery territory.*

uation of the hematoma was performed and anisocoria resolved. Despite angioplasty for treatment of consecutive vasospasm, a small right frontobasal infarction developed. After 6 months, the patient had no formal neurological deficit, was independently mobile for short distances, and was able to communicate freely (GOS 4, Barthel 70).

Patient 2

A 56-year-old woman collapsed at home and was found in a deep coma with bilaterally fixed and dilated pupils and insufficient respiration. She was intubated and transported to our hospital. CT scans showed an acute subdural hematoma over the right hemisphere and intracerebral hemorrhage (*Fig.* 2). Immediate surgery was not feasible because of acute myocardial infarction and persistent cardiocirculatory instability with recurrent phases of bradycardia and hypotension requiring high doses of catecholamines. One hour after admission and repeated infusions of mannitol, the left pupil became reactive to light again. Twenty-four hours after the event, cardiac function was slightly improved; angiography was performed and showed a large aneurysm of the right middle cerebral artery. A craniectomy was performed, the hematoma was evacuated, and the aneurysm was clipped. Pupillary reactivity returned on both sides. In the further course of intensive care treatment, the patient had to be mechanically resuscitated, experienced cerebral vasospasm, and developed infarction of the right middle cerebral artery territory and anterior cerebral artery territory. After 6 months, verbal communication on a simple level was possible, she had severe left hemiparesis, and she remained dependent on permanent care (GOS 3, Barthel 20).

Patient 3

A 55-year-old woman had been complaining about neck pain for several days. During a car trip, she suddenly felt a severe headache and rapidly deteriorated neurologically. She was found comatose with anisocoria and no motor response (GCS 3) and was immediately intubated and transported to our hospital. CT scans showed subarachnoid hemorrhage and a right subdural hematoma. An immediate craniectomy was performed, the hematoma was evacuated, and an external ventricular drainage was placed. The pupillary state normalized after surgery. Angiography and endovascular therapy of an aneurysm of the posterior communicating artery were performed the next day. She experienced vasospasm, which was not accessible to angioplasty, and developed right temporoparietal infarction despite hyperdynamic therapy. After 6 months, the patient returned home with minor left hemiparesis (GOS 4, Barthel 70).

Patient 4

A 55-year-old woman reported a severe headache and was admitted to an external hospital in a soporous state. CT scans showed subarachnoid hemorrhage and right frontotemporal and interhemispheric subdural hematoma. Her condition deteriorated further, and she became comatose and developed anisocoria. On arrival at our department, an

immediate craniectomy was performed and an external ventricular drainage was placed. The patient's pupils normalized. On the next day, an aneurysm of the anterior communicating artery was treated by endovascular coiling. After 6 months, she had no residual deficit and had returned to the office (GOS 5, Barthel 100).

Patient 5

A 43-year-old woman was found comatose (GCS 3) with anisocoria but spontaneously breathing and was transported to an external hospital. There, she was intubated as a result of progressive respiratory insufficiency. During the transport to our hospital, she developed bilaterally fixed and dilated pupils. CT scans showed subarachnoid hemorrhage and a left subdural hematoma. She underwent an immediate craniectomy and evacuation of the hematoma and pupillary reactivity normalized. Angiography was performed thereafter and an aneurysm of the left posterior communicating artery was treated by endovascular coiling. She experienced vasospasm and developed partial infarction of the left middle cerebral artery territory despite balloon angioplasty on Day 7. Two months later, a ventriculoperitoneal shunt was implanted. After 6 months, the patient returned home with right hemiparesis using a wheelchair for longer distances. She had no speech disorder and was largely independent (GOS 3, Barthel 70).

Patient 6

A 54-year-old woman collapsed during work and had to be mechanically resuscitated. She was found comatose with no motor response and anisocoria and was immediately intubated (GCS 3). Admission CT scans showed subarachnoid hemorrhage and a right subdural hematoma. As a result of myocardial infarction and sustained cardiac instability, she received an external ventricular drainage as a primary measure. Pupillary state returned to normal and remained so during the further course of treatment. A follow-up CT scan performed the next day showed a decrease of midline shift. As a result of the normalized pupillary state, decreased mass effect on CT scans, and persistent cardiac instability, surgical decompression was not performed in the acute stage. An aneurysm of the anterior communicating artery was treated by endovascular coiling. She developed bilateral frontobasal infarctions and partial infarction in the right middle cerebral artery territory. Three weeks later, the hematoma was evacuated through a burr hole. A ventriculoperitoneal shunt was implanted 2 months after the insult. After 6 months, she was able to communicate verbally on a simple basis and had no formal paresis. She was transferred home but was not able to walk and remained dependent on permanent care (GOS 3, Barthel 0).

Patient 7

A 42-year-old woman collapsed suddenly during gardening work. She was found deeply comatose without motor response and with anisocoria and was immediately intubated. CT scans showed subarachnoid hemorrhage, right subdural hematoma, and acute occlusive hydrocephalus (*Fig. 3*). She primarily received an external ventricular drainage and pupillary state normalized. Angiography showed five aneurysms. Three aneurysms were clipped, and evacuation of the subdural hematoma was performed. She experienced vasospasm and angioplasty was performed. After 6 months, the patient returned to normal life without neurological deficits (GOS 5, Barthel 100).

Patient 8

A 55-year-old woman had experienced nausea/vomiting during the previous evening. In the morning, she was found unconscious and gasping by her husband. Because he was not able to wake her, an ambulance was called. She was found deeply comatose with no motor response and with bilaterally fixed and dilated pupils (GCS 3). She had aspirated and was cyanotic and hypoxic. She was intubated and transported to our hospital. CT scans showed right subdural hematoma, subarachnoid hemorrhage, and intracerebral hematoma most likely originating from an aneurysm of the middle cerebral artery (*Fig. 4*). Therapy was discontinued because of prolonged hypoxia before admission (7, 20).

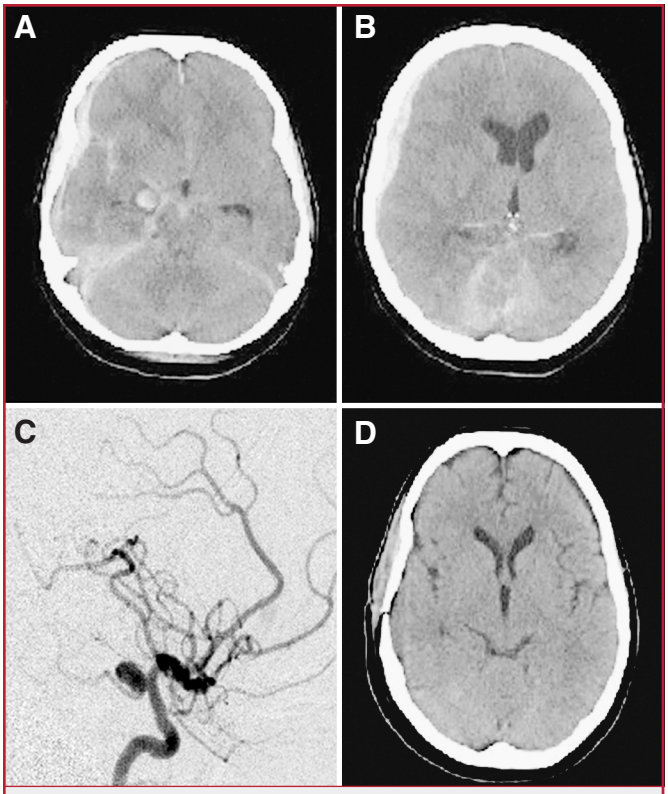


FIGURE 3. **A** *and* **B**, *CT scans showing Patient 7 at the time of admission demonstrating an aneurysm of the right posterior communicating artery, the origin of bleeding.* **C**, *angiography demonstrating further aneurysms of the right middle cerebral artery, the left middle cerebral artery, the left pericallosal artery, and a basilar tip aneurysm.* **D**, *CT scan obtained 6 months later showing no signs of infarction.*

DISCUSSION

Most previous studies of aneurysmal aSDH report that some of the patients presented in good neurological condition on hospital admission (6, 9, 22). In contrast, all patients presenting in our department with aneurysm rupture and aSDH visible on CT scans were graded World Federation of Neurosurgical Societies Grade 5. The patients were graded according to the statements of emergency physicians who performed the primary evaluation before intubation. If a patient shows signs of acute cardiac or respiratory insufficiency, time may be scarce and primary evaluation may be difficult. However, classification according to the GOS before intubation and pupillary state has been well documented in the reported patients.

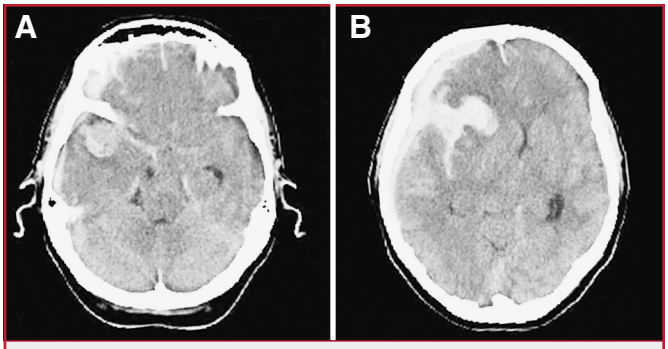


FIGURE 4. A *and* **B**, *CT scans of Patient 8 on admission showing right subdural hematoma, subarachnoid hemorrhage, and intracerebral hematoma. This patient was not treated because of prolonged hypoxia before hospital admission.*

Overall mortality in poor-grade subarachnoid hemorrhage (World Federation of Neurosurgical Societies Grade 5) with or without intracranial hematoma has been reported to be as high as 60%. Functional outcome is achieved in only a small portion of patients (4, 21).

The mortality rate after traumatic aSDH has been reported to be as high as 60% in adults (12, 23). The mortality rate of patients with traumatic aSDH presenting with unilaterally or bilaterally unreactive pupils has been reported as 81 and 97%, respectively (11). Again, only a small portion of patients with anisocoria on admission regain functional outcome. With bilaterally fixed and dilated pupils, the chance of good recovery is close to zero (1). Traumatic aSDH usually appear together with primary structural damage to the brain tissue. The latter seems to be the decisive factor determining outcome after traumatic brain injury with aSDH rather than the subdural hematoma (12, 23). In contrast, there is no primary damage of brain tissue in aneurysmal aSDH and those patients seem to have a more favorable prognosis.

After the first publications in the 1950s, several reports have been published showing varying results. Sachs and Bernat (18) and Ryan (17) each published a case of aneurysmal aSDH presenting with signs of brainstem herniation. Both patients underwent immediate evacuation of the hematoma and recovered well. Barton and Pitts (2) reported mainly good recovery after aneurysmal aSDH in 10 out of 11 patients who underwent surgical decompression. In contrast to our patients, most patients in this series presented in good neurological condition. Other series report mixed results ranging from death to recovery without deficit (9, 14) or report mainly unfavorable results with only a few patients regaining functional recovery (15, 22). In those studies, however, a significant number of patients was not treated and died. The reasons or conditions for withdrawing treatment are not discussed. In our series, only one patient was not treated because she had aspirated and was hypoxic for several hours before intubation and admission to our hospital. She subsequently died a few hours after admission.

The aim of surgical treatment in the acute stage was to perform decompressive craniectomy and remove the subdural hematoma. In contrast to the other patients who underwent operation in the acute stage, Patient 7 showed no significant brain swelling after removing the hematoma and the bone flap was reinserted. All other patients received decompressive craniectomy.

If osmotherapy and/or external ventricular drainage were sufficient in reversing signs of herniation as expressed by pupillary disturbance, angiography preceded surgical decompression. If not, we performed immediate decompression without angiography. We did not face any bleeding complications during the decompressive procedures even in those patients whose aneurysms had not been obliterated. If angiography was performed before decompression and the aneurysm was not found suitable for endovascular obliteration, decompression and clipping were performed in one procedure. Generally, we consider decompression the primary target in this acute situation, in particular, if signs of herniation cannot be reversed by primary measures such as osmotherapy, sedation, or external ventricular drainage.

Two patients developed major deficits and had an unfavorable outcome. Both patients sustained acute myocardial infarction and acute heart failure, making an immediate operation unfeasible. It is difficult to distinguish whether poor medical condition or the resulting delay of surgical decompression had a greater negative impact on final outcome. Insufficient cardiac output causes a global decrease of brain perfusion. Extraaxial masses, in turn, cause focally reduced brain perfusion (5, 19). The combination of both is likely to be particularly unfavorable, especially because subarachnoid hemorrhage itself is associated with acutely reduced brain perfusion (3). Rapid removal of the mass lesion by surgical decompression is the only procedure able to reverse the acute reduction of brain perfusion in this situation.

Local pressure on the underlying brain and blood vessels may also gate cerebral vasospasm and infarction, as suggested by the fact that all but one patient (Patient 7; *Fig. 3*) developed infarctions in the area of the subdural hematoma. Patient 1 did not undergo operation immediately because she had no pupillary disturbance at the time of admission. Earlier surgical decompression might have resulted in faster and even more complete recovery in this patient.

We suggest that whenever possible, rapid surgical decompression should be performed in poor-grade patients with aneurysmal aSDH unless significant comorbidities exist and there is doubt that the patient will survive the surgical procedure, e.g., Patients 2 and 6. Considering the poor recovery of the two patients who could not be treated immediately, it may be discussed whether or not patients in an unstable medical condition should receive delayed treatment at all, particularly if cardiocirculatory stabilization requires excessive time.

Five patients in this series reached a favorable outcome, although they also experienced cerebral vasospasm and other complications of prolonged therapy. However, they remained in a stable medical condition throughout the course of therapy and demonstrate that aneurysmal aSDH can be survived with only minor residual deficits, even if patients present in very

poor neurological condition. Midline shift and uncal herniation may mimic a clinical condition that appears to be worse than the accompanying subarachnoid hemorrhage can be held responsible for.

CONCLUSION

Aneurysmatic subarachnoid hemorrhage complicated by aSDH is a critical condition. Patients may present in exceptionally poor neurological condition with signs of apparent uncal or transtentorial herniation. However, if rapid surgical decompression and maximum medical treatment can be performed, prognosis can be favorable.

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COMMENTS

The authors have reported a small series of patients presenting with extension of subdural hemorrhage after aneurysmal subarachnoid hemorrhage (SAH). Each of these patients presented in poor condition; however, after 6 months, four had no or only minor neurological deficits. I agree with the authors that aggressive therapy is worthy of consideration in this group of patients. Although these patients may present with severe neurological deficits, urgent evacuation of the subdural and/or intracerebral hemorrhage can be lifesaving and improve the chances for a good neurological recovery.

However, I question the logic of performing endovascular therapy in this series of patients who are already undergoing a surgical procedure. In the first case, endovascular therapy was performed before surgery, thus unnecessarily delaying surgical treatment. Four of the other treated patients underwent a separate endovascular procedure after the surgical procedure. This required the patient to be exposed to two separate therapeutic procedures, each with their attendant risks, rather than treating the hematoma and aneurysm at the same time. With rare exceptions, the only benefit of endovascular therapy is to avoid a surgical procedure. If a surgical procedure needs to be performed for evacuation of a subdural or intracerebral hematoma, I think the aneurysm should be treated during the same procedure, if at all possible.

When patients present with a life-threatening subdural or intracerebral hemorrhage associated with aneurysmal rupture, we make every attempt to avoid unnecessary preoperative diagnostic studies and plan the urgent surgical procedure based on the distribution of blood. Once the offending hematoma has been removed, we typically perform intraoperative angiography to better understand the angioarchitecture of the intracranial circulation so definitive treatment of the aneurysm can be accomplished during the same procedure. Regardless of differences in philosophy, the authors are to be congratulated on the good outcomes in a significant number of these patients.

Daniel L. Barrow
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In this series, Westermaier et al. present the results of aggressive surgical treatment in seven out of eight patients with an aneurysmal acute subdural hematoma (aSDH). One patient was not treated because of prolonged anoxia before presentation. All patients were scored as WFNS Grade 5 and had pupillary disturbances. Of the seven treated patients, three underwent decompression of the aSDH followed by endovascular coiling, two underwent decompression of the aSDH and aneurysm clipping, one had a ventriculostomy followed by aneurysm coiling, and one underwent coiling followed by delayed surgical decompression. The patient who was not treated died. Two of the remaining seven patients had an excellent outcome (Glasgow Outcome Scale 5), three patients were graded as Glasgow Outcome Scale 4, and two patients were graded as Glasgow Outcome Scale 3. None of the patients survived in a persistent vegetative state.

The conclusion of this case series is that patients with aneurysmal aSDH who present in a WFNS Grade 5 condition with pupillary abnormalities may have a better prognosis with aggressive surgical therapy than Grade 5 SAH patients without an acute subdural hematoma. Thus, in selected poor grade aneurysmal SAH patients with an aSDH, aggressive surgical treatment of the subdural hematoma with either immediate aneurysm clipping or delayed aneurysm coiling should remain a consideration.

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This report describes a single institution's 3-year experience with aSDH accompanying aneurysm rupture. This is an eight patient case series derived from a total of 115 patients with ruptured aneurysms treated in their department during that time period (5.3%). Subdural hematomas accompanying aneurysm rupture large enough to cause, or contribute significantly to, uncal herniation are not common and are most often associated with middle cerebral artery and posterior communicating artery aneurysms. In this series, however, three patients had ruptured anterior communicating artery aneurysms. The central idea that grew out of this unusual clinical experience is that, although aneurysmal aSDHs are associated with severe rupture and poor neurological condition and prognosis, they should nevertheless be considered for aggressive surgical management when causing uncal herniation and when there is otherwise no vital brain destruction apparent. Their own treatment approach varied according to individual patient features, but one that was interesting and successful in several patients was that of a rapidly performed large craniectomy, subdural hematoma evacuation, insertion of an external ventricular drain, and subsequent cerebral angiography and endovascular occlusion of the aneurysm. Depending on the relative expertise of the operating surgeon in acute aneurysm clipping and the availability of an endovascular team, this particular approach deserves consideration.

J. Max Findlay
Edmonton, Canada

Approximately 80% of our patients with ruptured aneurysms undergo operation within 24 hours and those with hematomas are taken into the operating room immediately. As we treat patients with population responsibility and cannot exclude anyone, we must also care for poor-grade patients. This study is in parallel with our experience, showing the benefits of early surgery, even in poor-grade patients, to save lives. This report also addresses the necessity of neurosurgeons and interventionalists to work together when selecting patients for each modality. Why would one not clip the aneurysm after taking the subdural hematoma out as the cranium is already open and one could do it using the same approach? Therefore, we need dedicated neurovascular centers to treat these patients to guarantee the best possible outcome.

Reza Dashti
Mika Niemelä
Juha A. Hernesniemi
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"Flensing" (1954), woodblock and paper, copied from a 1773 picture scroll, Taiyo Fishing Company. (Courtesy of New Bedford Whaling Museum). *From*: Matthews, LH: *The Whale*. New York, Simon & Schuster, 1968.

POSTOPERATIVE HYDROCEPHALUS IN PATIENTS UNDERGOING DECOMPRESSIVE HEMICRANIECTOMY FOR ISCHEMIC OR HEMORRHAGIC STROKE

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OBJECTIVE: We have frequently observed the development of postoperative communicating hydrocephalus in patients undergoing decompressive hemicraniectomy. This condition may persist in some patients after cranioplasty and require permanent cerebrospinal fluid (CSF) diversion. To confirm an independent correlation between hemicraniectomy and the development of communicating hydrocephalus, and to detail the frequency and potential clinical factors contributing to this complication, we evaluated our series of patients undergoing hemicraniectomy for life-threatening increases in intracranial pressure secondary to ischemic or hemorrhagic stroke.

METHODS: A retrospective analysis was performed with a cohort of consecutive patients who underwent emergent hemicraniectomy for medically refractory elevations in intracranial pressure. Patients with known independent risk factors for the development of communicating hydrocephalus were excluded. Clinical and imaging data were reviewed to determine the incidence and type of hydrocephalus after hemicraniectomy, the persistence of hydrocephalus after cranioplasty, and the need for permanent CSF diversion.

RESULTS: Eighty-eight percent of the eligible patients undergoing hemicraniectomy in our cohort developed postoperative communicating hydrocephalus. Half of these patients harbored persistent hydrocephalus after cranioplasty and required placement of a ventriculoperitoneal shunt. We noted a strong correlation between prolonged time to replacement of the bone flap and persistence of hydrocephalus.

CONCLUSION: Communicating hydrocephalus is an almost universal finding in patients after hemicraniectomy. Delayed time to cranioplasty is linked with the development of persistent hydrocephalus, necessitating permanent CSF diversion in some patients. We propose that early cranioplasty, when possible, may restore normal intracranial pressure dynamics and prevent the need for permanent CSF diversion in patients after hemicraniectomy.

KEY WORDS: Hemicraniectomy, Hydrocephalus, Stroke, Surgical management

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Malignant elevation of intracranial pressure (ICP) is a predictably devastating consequence of catastrophic neurological injury. In cases in which medical therapy fails to control life-threatening increases in ICP, emergent surgical hemicraniectomy can be performed to provide for immediate decompression. This procedure has been shown to improve survival in carefully selected cases involving trauma, hemispheric cerebral infarction, and subarachnoid hemorrhage (3, 6, 10). However, improvements in long-term functional outcomes and quality of life, when compared with standard medical therapies, have been less tangible (3, 7, 8).

Since 1998, the senior author (ESC) has been performing emergent hemicraniectomy in selected patients with medically refractory elevations in ICP secondary to hemispheric cerebral infarction, deep intracerebral hematoma, or subarachnoid hemorrhage. We have observed that a large proportion of our cohort developed communicating hydrocephalus within a short time period after the

surgical procedure. In addition, a significant number of these patients ultimately required permanent cerebrospinal fluid (CSF) diversion after bone flap replacement. Although the presence of subarachnoid or intraventricular blood is a known cause of communicating hydrocephalus, patients with isolated ischemic infarction or deep intracerebral hematoma are not expected to develop this complication as a result of their initial neurological injury. We, therefore, hypothesized that hemicraniectomy may be an independent risk factor for the development of communicating hydrocephalus. To investigate this possibility, we reviewed the records and imaging studies of a consecutive series of patients undergoing emergent decompressive hemicraniectomy for ICP elevations secondary to ischemic cerebral infarction or deep intracerebral hematoma. Patients with other clinical risk factors known to contribute to the development of hydrocephalus were excluded. The cohort was evaluated for the incidence and nature of hydrocephalus, the need for permanent CSF diversion, and any factors potentially contributing to either of these outcomes.

MATERIALS AND METHODS

Study Design

The study was performed under the auspices of the Columbia University Institutional Review Board protocol number AAAB6537. All patients in the study were admitted to the Neurological Intensive Care Unit (NICU) at Columbia–Presbyterian Medical Center between 1998 and 2005 with either hemispheric cerebral infarction or deep intracerebral hematoma. All patients developed medically refractory elevations in ICP secondary to their neurological insult, which were diagnosed by a combination of computed tomographic (CT) scans, evidence of elevated ICP on physical examination, or invasive ICP monitoring. The determination of failure of maximal medical therapy, including head elevation, sedation, hyperventilation, and hyperosmolar therapy through administration of intravenous mannitol or hypertonic saline, and the decision to proceed with hemicraniectomy were made in the preoperative period by the senior author (ESC) and the NICU attending neurologist (SAM). Surgical procedures were performed as we have previously described (3), including removal of the frontotemporoparietal calvarium to the level of the zygoma as well as expansive durotomy. Bone flaps were typically placed in a subcutaneous pouch in the abdomen; in several patients, however, the flaps were discarded and computer-guided synthetic flaps were used for cranioplasty (Synthes Inc., West Chester, PA; Lorenz Inc., Jacksonville, FL). After surgery, all patients were returned to the NICU for ICP monitoring and further medical management of cerebral edema, during which time they underwent serial CT scanning.

During the 8 years covered by the study, a total of 43 patients underwent decompressive hemicraniectomy. We excluded patients who had confounding variables known to independently contribute to the development of hydrocephalus, including subarachnoid and intraventricular hemorrhage (n = 19) and intracranial infection (n = 1). An additional group of patients who died in the immediate postoperative period (n = 3) or were lost to follow-up in the early postoperative period, before bone flap replacement (n = 3), were also excluded. Thus allowing for correlative analysis between hemicraniectomy and the development of communicating hydrocephalus, the final cohort included a total of 17 patients. Presenting diagnoses and demographic data are outlined in *Table 1*. Relevant clinical data and serial CT images were compiled and reviewed for each patient. For the purposes of this study, communicating hydrocephalus was defined as radiographic evidence of ventricular dilatation and/or the presence of an enlarging extraaxial CSF collection on serial CT imaging; measurement of ICP was not included in this definition. Clinical examination was not included as a defining element in the determination of hydrocephalus given the poor baseline neurological status of most patients in the acute period, secondary to their initial neurological insult, which resulted in an inability to quantify subtle clinical changes possibly referable to hydrocephalus.

Study outcomes focused specifically on the development of hydrocephalus after hemicraniectomy and the ultimate need for permanent CSF diversion. Fisher's exact test was used to evaluate associations between patient gender, presenting diagnosis, or laterality of hemicraniectomy and the development of hydrocephalus. The Mann-Whitney *U* test was used to determine potential associations between the following variables: 1) patient age and the development of hydrocephalus after hemicraniectomy; 2) time (in days) from diagnosis to hemicraniectomy and the development of hydrocephalus after hemicraniectomy; 3) time from hemicraniectomy to development of hydrocephalus and persistent hydrocephalus after cranioplasty; and 4) time from hemicraniectomy to cranioplasty and persistent hydrocephalus after cranioplasty.

RESULTS

The cohort meeting selection criteria consisted of 17 patients, including nine men and eight women, ranging in age from 20 to 73 years (mean, 47.8 yr). Eleven of these patients presented with hemispheric infarction (seven middle cerebral arteries, four internal carotid artery bifurcations), whereas the remaining six patients sustained deep intraparenchymal hemorrhage (three basal ganglia hemorrhages, three deep cortical hemorrhages). After failure of maximal medical therapy to control malignant ICP elevations in these patients, emergent hemicraniectomy was performed on the side of the lesion (seven left-sided, 10 right-sided). All patients underwent hemicraniectomy within 5 days of their admission to the NICU.

After hemicraniectomy, we observed the development of postoperative communicating hydrocephalus, as defined previously, in 15 of the 17 patients (88.2%). Historically, neither of the initial neurological injuries resulting in study inclusion (cerebrovascular accident or isolated ICH without intraventricular hemorrhage) nor the medical treatment of the consequential elevations in ICP are independently associated with communicating hydrocephalus. The time to radiographic evidence of hydrocephalus ranged from postoperative Day 1 to postoperative Day 16 (mean, 7.7 d). Ten patients developed an enlarging extraaxial CSF collection (*Fig. 1A*; 66.7%), whereas an additional three patients demonstrated a combination of ventricular enlargement and extra-axial CSF accumulation (*Fig. 1, C* and *D*; 20%). Only two patients had isolated enlargement of the ventricular system (*Fig. 1B*; 13.3%).

We specifically focused the remainder of our analysis on the 15 patients who developed posthemicraniectomy hydrocephalus before cranioplasty. One of the patients died in the

TABLE 1. Patient cohort presenting diagnoses and demographic data[a]

Patient no.	Age (yr)/sex	Presenting diagnosis	Side of lesion	Location of lesion	Diagnosis to hemicraniectomy (d)	Hydrocephalus posthemicraniectomy	Subtype of hydrocephalus	Time to cranioplasty (d)	Postcranioplasty hydrocephalus	Shunt post-cranioplasty
1	52/F	CVA	L	ICA	4	Y	E, V	177	Y	Y
2	50/M	ICH	R	BG	5	Y	E	22	N	N
3	49/M	CVA	L	MCA	3	Y	E	35	[c]	—
4	53/M	CVA	R	ICA	1	Y	V	183	[c]	—
5	48/M	CVA	R	MCA	2	Y	E, V	19	N	N
6	67/M	CVA	R	MCA	3	N	—	—	—	—
7	56/M	CVA	R	MCA	0	Y	E	21	[d]	—
8	36/M	ICH	R	BG	2	Y	E	28	Y	Y
9	33/M	ICH	R	BG	2	Y	E	20	[d]	—
10	54/F	CVA	L	MCA	1	N	—	—	—	—
11	73/F	CVA	R	ICA	0	Y	E, V	[b]	—	—
12	20/F	ICH	R	Parietal	2	Y	E	21	Y	Y
13	46/F	CVA	L	MCA	1	Y	V	24	N	N
14	51/F	CVA	R	MCA	2	Y	E	81	Y	N
15	39/F	ICH	L	Fronto-temporal	0	Y	E	56	Y	Y
16	38/M	CVA	L	ICA	0	Y	E	89	Y	Y
17	48/F	ICH	L	Temporal	0	Y	E	24	N	N

[a] CVA, cerebrovascular accident; L, left; ICA, internal carotid artery; E, external/extraaxial cerebrospinal fluid collection; V, ventricular enlargement; ICH, intracerebral hemorrhage; R, right; BG, basal ganglia; MCA, middle cerebral artery.
[b] Patient with early infection of bone flap (requiring removal) after cranioplasty.
[c] Patient lost to follow-up in early postoperative period after cranioplasty.
[d] Patient with delayed death before bone flap replacement.

delayed postoperative period before bone flap replacement, and two patients were discharged and lost to follow-up before bone flap replacement. An additional two patients developed early postcranioplasty infections, requiring removal of the implant, and were, therefore, necessarily excluded from further analysis. Of the remaining 10 patients, the median time from hemicraniectomy to cranioplasty was 32 days (range, 19–183 d; mean, 63 d). Eight of these patients underwent autologous bone flap replacement, and two received a computer-guided synthetic cranioplasty. After cranioplasty, a total of six patients (60%) demonstrated evidence of persistent hydrocephalus (*Fig. 2A*). Five of these patients ultimately required permanent CSF diversion through placement of a ventriculoperitoneal shunt. The remaining four patients (40%) demonstrated rapid resolution of hydrocephalus after replacement of their bone flap (*Fig. 2B*). Statistical analysis demonstrated no association between postcranioplasty hydrocephalus and patient age, presenting diagnosis (ICH versus ischemic stroke), subtype of hydrocephalus (external versus ventricular), or time from hemicraniectomy to the development of hydrocephalus. However, there was a strong trend between postcranioplasty hydrocephalus and length of time between hemicraniectomy and cranioplasty; patients with persistent hydrocephalus underwent bone flap replacement at a median of 69 days (mean, 75.3 ± 23.1 d; range, 21–904 d), whereas patients who had spontaneous resolution of their hydrocephalus had bone flaps replaced at a median of 23 days (mean, 22.3 ± 1.2 d; range, 19–35 d) ($P = 0.067$).

DISCUSSION

Over the past decade, there has been a dramatic increase in the number of studies evaluating the therapeutic benefits of emergent decompressive hemicraniectomy in patients with malignant ICP elevations secondary to large ischemic infarcts or deep intracerebral hemorrhages. Although cautionary data emphasize poor outcomes in elderly patients, patients with prolonged elevations in ICP before hemicraniectomy, or patients with dense aphasia before hemicraniectomy (1, 2, 7, 13), most studies note significantly decreased mortality for individuals undergoing this procedure (15–30%) (7, 9, 11, 13) when compared with matched patients managed with medical therapy alone (approaching 80%) (5). However, the data have been considerably less convincing regarding improvements in long-term quality of life or functional status for patients after hemicraniectomy (4, 13).

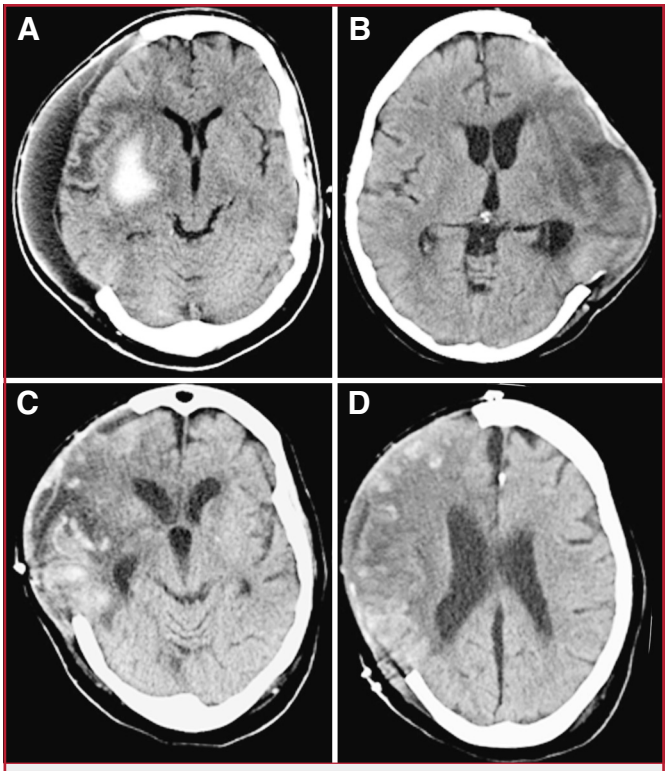


FIGURE 1. *Representative CT scans showing patients developing various subtypes of communicating hydrocephalus after hemicraniectomy.* **A**, *an enlarging extra-axial CSF collection is seen over the right hemisphere after hemicraniectomy in a patient who had a right basal ganglia hemorrhage.* **B**, *evidence of isolated ventricular enlargement after hemicraniectomy is shown in a patient with left middle cerebral artery territory infarction.* **C** *and* **D**, *ventricular enlargement with concomitant convexity and interhemispheric CSF collections is shown in a patient who had a hemorrhagic right middle cerebral artery infarct. All changes in these patients were slowly progressive throughout serial imaging (not shown).*

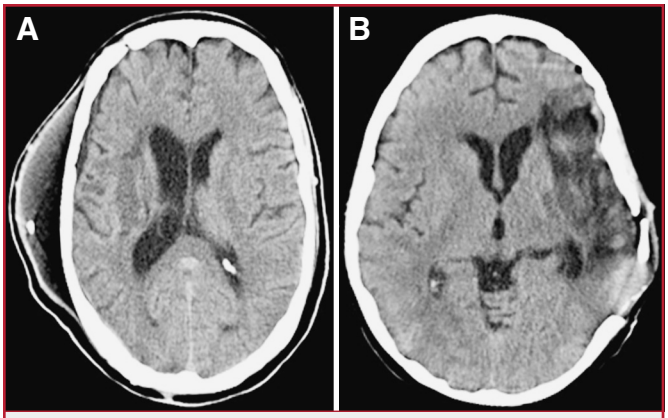


FIGURE 2. *Delayed postcranioplasty CT scans showing patients included in* Figure 1, A *and* B. **A**, *persistent hydrocephalus, after cranioplasty in the patient documented in* Figure 1A, *as evidenced by a large right subgaleal CSF collection. The enlarged right lateral ventricle seen in this patient is likely secondary to ipsilateral hemispheric atrophy.* **B**, *resolution of the ventricular enlargement after cranioplasty in the patient previously documented in* Figure 1B.

Our case series is the first to identify communicating hydrocephalus as an almost universal finding in the immediate postoperative period after hemicraniectomy. Although exclusion of patients with complicating factors known to contribute to the development of hydrocephalus (most notably, subarachnoid hemorrhage) left a small cohort for analysis, a direct correlation between the hemicraniectomy procedure and hydrocephalus could not be otherwise reasonably explored. We expect that evaluation of similar cohorts from other centers would strengthen and confirm our findings.

Diagnosis of hydrocephalus in the hemicraniectomy population is necessarily subjective, because criteria based on measurements of intracranial pressure or details of ventricular structure are often unreliable in the setting of an open cranial vault. However, the almost universal propensity for progressive accumulation of CSF in these individuals, frequently manifested as enlarging extraaxial collections over the hemispheric convexity, indicates an inability to adequately balance CSF production with drainage into the venous sinuses. Through our experience in the postoperative management of hemicraniectomy patients, we believe that increasing CSF accumulation generally mandates temporary diversion through frequent lumbar puncture or placement of an external ventricular or spinal drain. We have found that management of fluid dynamics after hemicraniectomy can be quite challenging as a result of issues of hemispheric shift or compartmentalization, emphasizing that definitive resolution of CSF accumulation is a significant priority. Importantly, our data demonstrate that a portion of patients will experience spontaneous resolution of hydrocephalus after cranioplasty, particularly if the bone flap is replaced at an earlier time point. However, because the timing of bone flap replacement was largely guided by residual swelling, it must be considered that delayed cranioplasty may be a surrogate for more severe brain injury. This may have in turn predisposed patients to persistent hydrocephalus and the need for shunting.

The physiological mechanism by which hydrocephalus develops after hemicraniectomy remains to be determined. It is possible that factors other than altered intracranial pressure dynamics, such as mechanical blockage or inflammation of arachnoid granulations by postsurgical debris, may play a role. However, we have repeatedly observed a "flattening " of the normally dicrotic ICP waveform in patients harboring intraparenchymal pressure monitoring devices after hemicraniectomy, hypothetically as a result of transmission of the pressure pulse out of the open cranium. Because the arachnoid granulations function as pressure-dependent one-way valves from the subarachnoid space to the draining venous sinuses (14), it is possible that disruption of pulsatile ICP dynamics secondary to opening the cranial vault results in decreased CSF outflow. If this is the case, early cranioplasty should lead to restoration of normal intracranial pressure

dynamics and spontaneous resolution of hydrocephalus as witnessed. In contrast, late cranioplasty, in prolonging this disruption, might be expected to result in permanent dysfunction of the arachnoid granulations as is seen with hydrocephalus induced by long-term CSF drainage (12).

The issue of persistent hydrocephalus in the hemicraniectomy population is of clinical relevance when considering long-term outcomes for these patients. Although the potential for elevated ICP secondary to CSF accumulation is less of a concern during the early postoperative period after hemicraniectomy, continued imbalance between CSF production and outflow would not be similarly well tolerated after cranioplasty. In these cases, permanent CSF diversion becomes a clinical necessity. Because the avoidance of permanent instrumentation is desirable, attributable to predictable concerns for hardware malfunction or infection, our data provide an impetus for early cranioplasty when clinically possible. Ultimately, the contribution of postcranioplasty hydrocephalus to decreased functional outcomes or quality of life will be important considerations in the ongoing discussion regarding hemicraniectomy for patients with ischemic or hemorrhagic stroke.

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COMMENTS

The authors have made note of an important issue after massive decompressive craniectomy. Our experience has largely focused on the ischemic infarction population. In our series of several dozen hemicraniectomy patients for hemispheric infarcts, we have only infrequently had to perform permanent cerebrospinal fluid (CSF) diversion. When this has occurred, bone flap replacement has been delayed beyond 8 weeks. In these cases, we similarly observed a progressive "expansion" of cerebral tissue through the craniotomy defect, with associated ventricular enlargement. Hence, we agree with the authors that this phenomenon can occur and that early bone flap replacement may decrease the propensity for this to occur. In our practice, we tend to strive for bone flap replacement within 4 to 8 weeks.

We also agree with the authors that a reasonable hypothesis to explain this phenomenon may be transmission of the intracranial pressure pulse over time through the open cranium to the highly compliant scalp. In one of our patients who experienced an 11-month interval between decompressive craniectomy and bone flap placement, there was a noticeable expansion of the skin over time, similar to what one might see with a scalp expander. At the time of cranioplasty, the patient's ventricle was tapped for 45 cc of CSF, which led to a marked involution of the skin and allowed for bone flap replacement with no requirement for ventricular peritoneal shunting. In this situation, it is possible that the scalp overlying the craniotomy defect gradually expands over time in a way that would not occur in the presence of the intact cranium, leading to hydrocephalus.

Bob Carter
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The authors have made a potentially important observation that patients undergoing decompressive hemicraniectomy for the management of intractable intracranial hypertension have a high incidence of postoperative hydrocephalus. Based on the authors' perception that a significant number of their patients developed delayed ventricular and/or enlarging extra-axial CSF collection, the authors hypothesize that hemicraniectomy alone may be an independent risk factor for the development of hydrocephalus. This stimulated the authors to perform a retrospective review of a consecutive series of patients undergoing emergent decompressive hemicraniectomy for increased intracranial pressure secondary to ischemic and hemispheric infarctions or deep intracerebral hemorrhages.

Of 43 patients undergoing decompressive hemicraniectomy between 1998 and 2005, 26 were excluded from the analysis because they had confounding clinical conditions that are known to be associated with the development of hydrocephalus, three patients died in the immediate postoperative period, and three patients were lost to follow-up. The 17 remaining patients all had ischemic infarctions or deep intracerebral hemorrhages, and 15 (88%) of these patients developed some form of hydrocephalus. In the majority of patients (n = 10), this was manifested by enlarging extra-axial fluid collections, with three of these patients exhibiting a combination of ventricular enlargement and extra-axial CSF collection, whereas only two developed ventriculomegaly.

In addition to this important observation of the increased incidence of hydrocephalus after ventriculomegaly, the authors have demonstrated that there was no correlation between the development of hydrocephalus and the age of the patient, presenting diagnosis, subtype of hydrocephalus, or time from surgery to the development of hydrocephalus. There was, however, a strong correlation between the development of postcranioplasty hydrocephalus and the length of time between decompressive hemicraniectomy and cranioplasty.

As decompressive hemicraniectomy becomes a more acceptable therapeutic option for managing intractable intracranial hypertension, this observation by the Columbia neurovascular group may prove to be exceedingly important and may lend insight into our knowledge of CSF dynamics. As stated by the authors, verification of these findings in other centers would enhance the importance of this observation.

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There is a growing enthusiasm towards hemicraniectomies in selected patients with subarachnoid hemorrhage, trauma, and ischemia. According to our experience, the results are often promising in patients younger than 50 years who have an otherwise severe outcome. Waziri et al. describe a series of patients who developed hydrocephalus after hemicraniectomy for stroke. The mechanisms remain unknown and may be different in different types of stroke. Therefore, histopathological and larger clinical studies are needed to provide us with more data on the mechanisms to be able to predict and prevent this complication. When to perform cranioplasty after hemicraniectomy is often difficult to decide in these often severely ill patients. Experience with time and more treated patients will guide us.

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In this series, a retrospective cohort of patients undergoing decompressive hemicraniectomy for malignant swelling from stroke or deep intracerebral hemorrhages were analyzed. Forty-three patients underwent decompressive craniotomy, 17 of whom met the selection criteria for having communicating hydrocephalus. Hydrocephalus was defined as radiographic evidence of ventricular dilatation and/or the presence of an enlarging extra-axial CSF collection upon serial computed tomographic imaging. No clinical information or follow-up data regarding the patients is given.

The authors conclude that communicating hydrocephalus is an almost universal finding in patients after hemicraniectomy and that delayed time to cranioplasty is linked with the development of persistent hydrocephalus, necessitating permanent CSF diversion in some patients. They propose that early cranioplasty, when possible, may restore normal intracranial pressure dynamics and prevent the need for permanent CSF diversion in patients after hemicraniectomy.

We commend the authors on their work. However, we feel there are two major issues that arise in this study. The first issue relates to the fact that the operational definition given for hydrocephalus is a purely radiographic one. More accurately, this would be termed "ventriculomegaly" if the cranial vault were intact. In our opinion, hydrocephalus connotes a clinical syndrome based predominantly on neurological signs and symptoms rather than radiographic findings. There is no mention of the patient's clinical condition or whether or not there are signs or symptoms of "true" hydrocephalus.

The second issue is related to the first. There is no information provided regarding the clinical outcomes of the patients. For this reason, we are unable to draw any conclusions regarding the impact of the radiographic ventriculomegaly and external fluid collection on patient outcome.

This is an important study for the neurosurgical literature. One must be thorough in the evaluation and follow-up of hemicraniectomy patients to avoid complications related to altered CSF hydrodynamics.

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De Novo versus Transformed Atypical and Anaplastic Meningiomas: Comparisons of Clinical Course, Cytogenetics, Cytokinetics, and Outcome

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OBJECTIVE: The clinical course of atypical and anaplastic meningiomas is heterogeneous. As malignant gliomas, aggressive meningiomas may arise de novo or transform from a benign tumor. This study aims to compare differences in clinical behavior, cytogenetics, cytokinetics, receptor status, and outcome between de novo malignant meningiomas and meningiomas that progressed to malignancy.

METHODS: Data from 36 patients with atypical or anaplastic meningiomas were selected for retrospective analysis and divided into two subgroups: 1) de novo atypical or anaplastic tumors and 2) tumors that progressed from a lower grade. We analyzed data concerning patients' sex, age, tumor location, number of operations, status of hormone receptors, proliferative indices, cytogenetic findings, additional therapy, and survival. For meningiomas with progression, we calculated the interval between initial diagnosis and tumor progression.

RESULTS: For atypical meningiomas, the subgroups had significant differences in status of progesterone receptors, proliferative indices, cytogenetics, and patients' outcome. The anaplastic group had similar differences, but they did not reach statistical significance because of the small numbers. There was a loss of part or monosomy of chromosome 10 and an increased monosomy or derivative chromosome 1 combined with monosomy of chromosome 14. These phenomena occurred mainly in patients with malignant transformation who had a worse outcome.

CONCLUSION: De novo malignant meningiomas and meningiomas with malignant transformation may represent distinct subgroups of atypical and anaplastic meningiomas.

KEY WORDS: Anaplastic meningioma, Atypical meningioma, Brain tumor, Cytogenetics, Tumor progression

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Atypical and anaplastic meningiomas are rare and challenging intracranial tumors, and their diagnosis and grading, which have been topics of debate for a long time, have recently been well reviewed (48). The clinical course and prognosis of these meningiomas, especially atypical tumors, seem to be heterogeneous (54). The understanding of the natural history of these tumors is still poor, however, and clear clinical separation of atypical and anaplastic meningiomas with definition of possible subtypes is not made in the literature (6, 10, 14, 30, 45, 73). For example, the clinical behavior of radiation-induced meningiomas differs from similar meningiomas of the same pathological grade (4). Meningiomas can progress from benign to atypical or anaplastic variants, as is well documented with gliomas (3, 25, 26, 62). This phenomenon, in which a neoplasm changes irreversibly in one or more characteristics, has been termed tumor progression (16). Such a biological and clinical progression reflects the sequential appearance of cytogenetically acquired changes (51, 52). Glioblastomas can develop de novo or progress from a low-grade or anaplastic astrocytoma termed primary and secondary glioblastoma (33, 76). Literature about comparisons of possible subtypes of aggressive meningiomas is lacking. In this study, we retrospectively analyzed the clinical data from our patients with atypical and anaplastic meningiomas to investigate whether there is a difference in clinical behavior, proliferative indices, receptor status, and cytogenetics between so-called de novo malignant meningiomas and meningiomas with malignant progression from a previously lower-grade tumor (transformed meningioma).

MATERIALS AND METHODS

We reviewed the records of all patients who underwent operation for a Grade II or III meningioma (World Health Organization [WHO] classification 2000 [76]) from 1994 through 2005 by the senior author (OA). Data from subgroups of Grade II and III meningiomas such as radiation-induced, clear cell, chordoid, rhabdoid, and papillary meningiomas were not included because the groups were too small and the clinical behavior of these lesions, even if classified as higher grades, may differ from that of atypical and anaplastic meningiomas.

The pathological diagnosis of atypical and anaplastic meningiomas was reported according to the WHO 2000 classification criteria. Ki-67 and proliferating cell nuclear antigen (PCNA) were not the basis of our diagnosis of atypical or anaplastic meningiomas. Atypical and anaplastic meningiomas were then further divided into two subgroups. The first subgroup consisted of de novo meningiomas if the patients had no history of biopsy, surgery, or radiation before the diagnosis of the atypical or anaplastic meningioma. The second subgroup comprised meningiomas with malignant progression (transformed meningioma). In these patients, histological slides or outside pathology reports were reviewed to confirm the more benign grade before transformation. These subgroups were then compared according to several parameters: the patients' sex and age, the location of the tumor, and the number of operations. Biological markers such as hormone receptor status (29 patients), proliferative indices (31 patients), and cytogenetic findings (28 patients) were compared. For patients with tumor progression, we compared the time from first diagnosis to malignant transformation. The steps used for differentiation were also analyzed. We then compared the survival period from the time of diagnosis of the higher-grade tumor to each patient's death or last follow-up evaluation between atypical and anaplastic meningiomas and among their subgroups.

Cytogenetic Analysis

Cytogenetic analysis was performed using standard in situ culture techniques done on 20 trypsin-Giemsa banded metaphase cells from 20 independent tumor cell colonies, as described elsewhere by Sawyer et al. (65). Cytogenetic abnormalities were defined as any structural or numerical changes present in two or more cells. The presence of a single cell with an abnormal karyotype was not considered a true clone.

Statistical Analysis

For statistical analysis, we used the Statistical Analysis System macro surv.sas (Department of Biostatistics, Mayo Clinic, Rochester, MN) to calculate the Kaplan-Meier survival curves along with the log rank test and the *P* value. For comparison between subgroups, either the χ^2 or rank sum test and Fisher's exact test was used.

RESULTS

Patient Population

We reviewed data from 36 patients who met our criteria. Of these patients, 26 (72%) had atypical meningiomas and 10 (28%) had anaplastic meningiomas. The male-to-female ratio was 1:1.17 for atypical and 1:0.25 for malignant meningiomas. The mean age at the time of diagnosis was 54.5 years (range, 14–76 yr) for the atypical group and 54 years (range, 40–74 yr) for the anaplastic group. The mean age of atypical meningiomas was the same for both de novo and transformed meningiomas (54 versus 55 yr); in the anaplastic group, de novo meningiomas occurred at a mean age of 49 years (range, 40–51 yr), whereas meningiomas with transformation occurred at a mean age of 59 years (range, 46–74 yr) (*Table 1*).

Tumor location is listed in *Table 1*. The high percentage of cranial base meningiomas may relate to our referral pattern. Despite the small number of cases, when we combined the subgroups of anaplastic and atypical lesions, tumors located in the falcine/parasagittal region tended to predominate in the group with malignant transformation. On the other hand, de novo atypical and anaplastic meningiomas seemed to predominate at the cranial base (*Table 2*).

The clinical features of de novo tumors and tumors that progressed to malignancy are listed in *Table 1*. The average number of operations performed in the groups with transformation was 3.3 and 3.6 for atypical and anaplastic tumors, respectively, and 1.3 for both types in the de novo group.

In the atypical group, 10 patients (38%) had a meningioma that transformed from a Grade I tumor, whereas seven (70%) of those in the anaplastic group had transformation from a lower

TABLE 1. Clinical findings in patients

	Atypical (n = 26)		Anaplastic (n = 10)	
	De novo	With progression	De novo	With progression
Men	7	5	2	6
Women	9	5	1	1
Total	16 (62%)	10 (38%)	3 (30%)	7 (70%)
Age				
Range	14–76	41–72	40–51	46–74
Mean	54	55	49	59
Location				
Convexity	1 (6%)	0	0	2 (29%)
Falx/parasagittal	2 (12%)	3 (30%)	1 (33%)	2 (29%)
Cranial base[a]	12 (76%)	7 (70%)	2 (67%)	1 (14%)
Tentorium	1 (6%)	0	0	1 (14%)
Posterior fossa[b]	0	0	0	1 (14%)
No. of operations (range)	1.3 (1–2)	3.3 (2–6)	1.3 (1–2)	3.6 (3–5)

[a] Sphenoid wing meningiomas are included in the cranial base group.
[b] Meningiomas of the posterior fossa convexity; all others are included in the cranial base group.

TABLE 2. Proportion of de novo and transformed meningiomas by location

Location	De novo Grade II–III meningiomas	Transformed Grade II–III meningiomas
Falcine/parasagittal	37%	63%
Cranial base	64%	36%

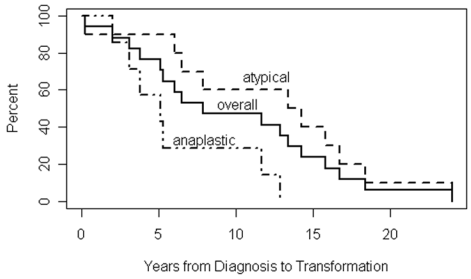


FIGURE 1. *Kaplan-Meier curve showing the length of time from diagnosis to transformation in atypical and anaplastic meningiomas.*

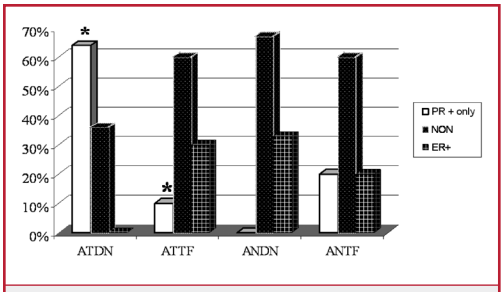


FIGURE 2. *Bar graph showing the receptor status of patients with atypical de novo (ATDN) meningiomas, atypical transformed (ATTF) meningiomas, anaplastic de novo (ANDN) meningiomas, and anaplastic transformed (ANTF) meningiomas.* Asterisk, *P = 0.024.*

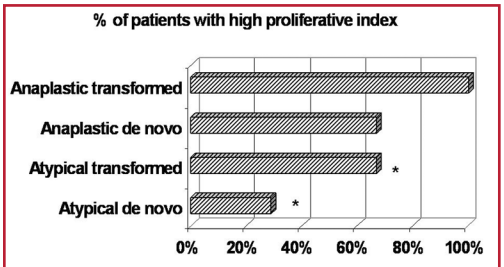


FIGURE 3. *Bar graph showing the percentage of patients with high proliferative indices (Ki-67 more than 5% and PCNA more than 10%).* Asterisk, *P = 0.036.*

grade. Of the tumors that transformed to anaplastic, three (42%) changed from benign to anaplastic, two (29%) from atypical to anaplastic, and two (29%) from benign to atypical and then to anaplastic. In these tumors, the second transformation took place in less than 1 year. The average time for tumor transformation in the atypical group was 13.84 years (range, 0.25–24.02 yr). In the anaplastic group, it was 5.12 years (range, 2.02–12.91 yr) ($P = 0.009$) (*Fig. 1*). Three out of 10 transformed atypical meningiomas had radiation before transformation and three out of seven with anaplastic meningioma had radiation before transformation.

Immunohistochemical Studies

Hormone Receptors

Receptor status was determined in 21 patients with atypical meningiomas and eight with anaplastic meningiomas. In the atypical de novo group, 64% of the lesions were positive for progesterone receptors (PR), 0% were positive for estrogen receptors (ER), and 36% were negative for both receptors. In the group of atypical meningiomas with malignant transformation, only 10% of the patients were positive for PR, 60% were negative for both receptors, and 30% were positive for ER with either positive or negative PR (*Fig. 2*). There was a significantly increased number of tumors positive for PR alone among the de novo atypical meningiomas compared with atypical tumors with transformation ($P = 0.024$).

In the anaplastic de novo group, none of the lesions were positive for PR alone, 67% were negative for both receptors, and 33% were positive for ER with or without PR. In the anaplastic group with transformation from a lower grade, 20% of lesions were positive for PR alone, 60% were negative for both receptors, and 20% were positive for ER with or without PR. Because of the small numbers in the subgroups, no statistical analysis was done for the anaplastic meningioma group.

Proliferation Index

Immunohistochemical staining for Ki-67 was done in 20 patients and for PCNA in 11 patients. For Ki-67, more than 5% and PCNA more than 10% were considered high. *Figure 3* shows the percentage of patients in each group with high proliferative indices. There was a statistically significant increase in the number of cases with high proliferative indices in atypical transformed meningioma patients compared with atypical de novo patients ($P = 0.036$).

Cytogenetic Findings

Cytogenetic analysis was done in 18 atypical meningiomas (nine de novo, nine with transformation) and 10 anaplastic lesions (three de novo, seven with transformation). In our study, the atypical and anaplastic tumors generally had complex karyotype abnormalities, including multiple translocations between different chromosomes and monosomy of multiple chromosomes (*Table 3*), which is common for these types of meningiomas (74).

Some patients in both subgroups of atypical meningiomas showed a normal chromosomal analysis. In the de novo atypical group, three patients (33%) had a normal karyotype, whereas six (67%) had an abnormal karyotype. In atypical meningiomas with transformation, two patients (22%) had a normal karyotype and seven (77%) had an abnormal karyotype. In the anaplastic group, neither subgroup had a normal karyotype.

TABLE 3. Chromosome changes in de novo and transformed atypical and malignant meningiomas[a]

Patient no.	Group	Sex	Chromosome						Rest of chromosome
			1	14	22	10	18	19	
	Atypical de novo								
1		M		−14	−22				
2		F	der 1						
3		M		+14	−22				der 2; der 7; +9, der 13, der 16
4		M		−14	−22				−13; −Y
5		F							der 2; der 4; −6; +9, der 15
6		M							−Y
7		F							normal
8		F							normal
9		M							normal
	Atypical transformed								
1		M	−1	−14	−22		−18		−6; −8; der 9; −12; −16
2		F			−22				
3		M	−1	−14	−22	−10	−18		+11; −Y
4		F	+1 (q41)			−10		add 19 (p13.3)	der 3; der 5, der 6; der 12, der X
5		M				der 10			der 2
6		F	der 1	−14	−22	−10	−18		+13; −X
7		M							−Y
8		F							normal
9.		F							normal
	Anaplastic de novo								
1		F	der 1	−14	−22	−10		der 19 (p13.3)	−4; +6; der 7
2		M			−22				−Y
3		M							−Y
	Anaplastic transformed								
1		M	−1	−14	−22	−10	−18		−15; der Y
2		M	−1	−14	−22				
3		M			−22	−10			−Y
4		M	−1	−14	−22				
5		M							−Y
6		F	der 1	−14	+22 (q12)	−10	−18	add 19 (q13.4)	−3; −4; −5, der 6; der 7; der 8; −11; −12, ; der 13, +16; −17
7		F	der 1	−14	−22	der 10		add 19 (q13.4)	der 2; der 4, −12; der 13

[a] der, derivative. Translocations and dicentric chromosomes are not included.

The exact distribution of the cytogenetic changes is shown in *Table 3*. A combination of changes, including chromosomes 1, 14, and 22, were observed in 22% of atypical meningiomas with progression but no changes occurred in the atypical de novo patients. Monosomy or a derivative chromosome 10 (44%) and monosomy of chromosome 18 (33%) were found only in atypical meningiomas with progression (*Fig. 4*; *Table 3*).

In the anaplastic tumors, a combination of changes, including chromosomes 1, 14, and 22, were found in 33% of the de novo meningiomas and in 71% of the patients with progres-

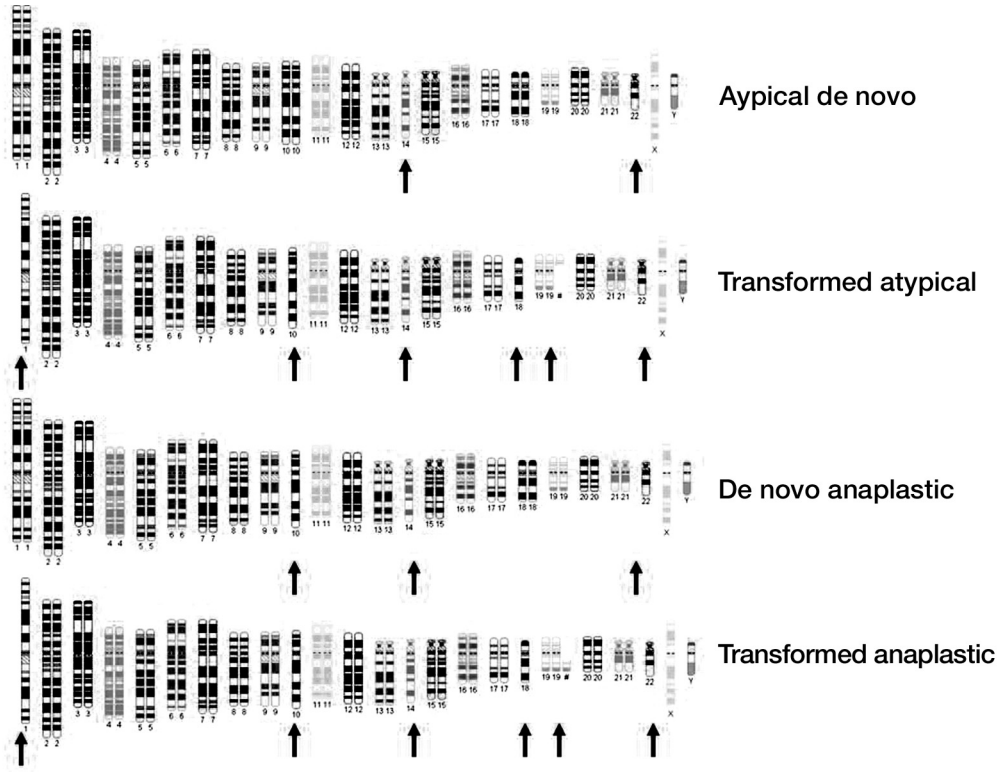


FIGURE 4. *Drawing of a karyogram, using CyDAS software (CyDAS; Institute for Human Genetics and Anthropology, Dusseldorf, Germany) (20) showing the different sites of chromosomal changes according to* Table 3.

sion. Monosomy or a derivative chromosome 10 and monosomy of chromosome 18 (*Fig. 4*) were found in 33 and 0%, respectively, of the anaplastic de novo cases and in 57 and 29%, respectively, of the patients with progression.

Because of the small number of patients in the subgroups of atypical and anaplastic meningiomas, no statistically significant differences were found. When comparing the combined atypical and anaplastic meningiomas with transformation to the combined group of de novo atypical and anaplastic meningiomas, we found a statistically significant increase in the number of cases showing loss of part or monosomy of chromosome 10 ($P = 0.039$) in the transformed subgroup. We also found a significant increase in the number of patients having monosomy or a derivative chromosome 1 in combination with monosomy of chromosome 14 (-1p, -14) in the group with malignant transformation ($P = 0.036$), and there was a tendency in the appearance of an additional part of chromosome 19 in transformed meningiomas.

Outcome

The overall average survival time for patients with atypical and anaplastic meningiomas was 4.54 years (range, 0.07–15.95 yr) and 1.48 years (range, 0.18–13.26 yr), respectively. In the subgroups, the average survival time for patients with de novo atypical meningiomas was 5.36 years (range, 1.02–15.95 yr) compared with 1.95 years (range, 0.07–7.71 yr) for those with malignant transformation, a difference that was statistically significant ($P = 0.01$) (*Fig. 5*). In patients with anaplastic meningiomas, the de novo subgroup had an average survival time of 6.56 years (range, 1.69–13.26 yr) compared with 1.13 years (range, 0.18–5.82 yr) in patients with transformation. Because of the small numbers, however, no statistical conclusion could be drawn (*Fig. 6*). Additional treatment of either conventional or stereotactic radiation was given to 31% of patients with de novo atypical tumors, 60% with atypical tumors with progression, 33% with de novo anaplastic tumors, and 86% with anaplastic meningiomas with transformation. None of the other patients received additional treatment.

DISCUSSION

Tumor Progression

Glioblastomas can develop de novo or progress from a low-grade or anaplastic astrocytoma (33, 76). These subtypes, termed primary and secondary glioblastomas, not only evolve through different genetic pathways but also affect patients at

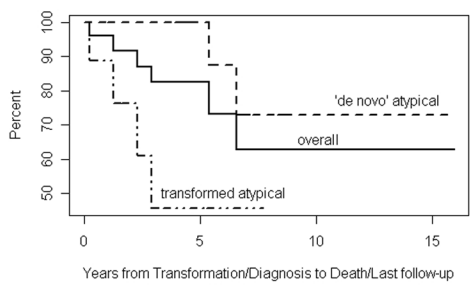


FIGURE 5. *Kaplan-Meier curve showing the overall survival of patients with atypical meningiomas and a comparison of de novo atypical meningiomas with meningiomas that progress.*

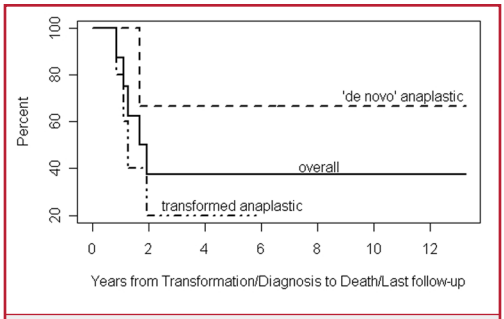


FIGURE 6. *Kaplan-Meier curve showing the overall survival of patients with anaplastic meningiomas and a comparison of de novo anaplastic meningiomas with meningiomas that progress.*

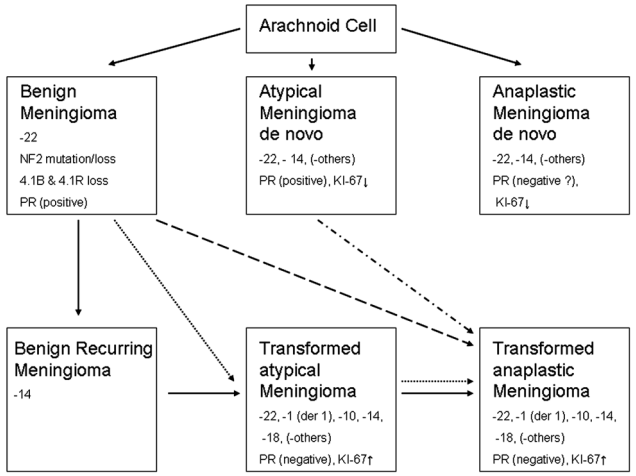


FIGURE 7. *Illustration showing a possible hypothesis of tumorigenesis and progression based on the findings of our small group. The* dotted lines *indicate alternative pathways of tumor progression.* -others *may include factors mentioned in other models (34, 56) that were not investigated in our study or could not be attributed to one specific subgroup.* uparrow, *increased;* downarrow, *decreased.*

different ages. Whether or not there is a significant difference in survival between these subgroups is still not clear (5, 13, 75).

In comparing our meningioma cases, we found several significant differences between de novo atypical and anaplastic meningiomas and meningiomas with malignant transformation. These tumors differ not only in hormone-receptor expression, value of proliferative indices, and cytogenetic profile, but also in their clinical course. This difference in our findings, although in a relatively small sample size, is the reason we propose a different model of possible meningioma tumorigenesis than what has been described by others (34, 55) (*Fig. 7*). Certainly, there are several limitations to this model because only the previously mentioned factors have been analyzed and the number of cases, especially in the anaplastic group, was low. Furthermore, there is still the uncertainty of whether some of the tumors we call de novo may arise from a Grade I meningioma. The presence of malignant transformation from a previously lower grade may also present a sampling error at the time of the first surgery. However, our study should stimulate further investigation of these subtypes to confirm this hypothesis.

We present a series of atypical and anaplastic cranial base meningiomas, which are known to recur frequently because of the difficulty of removal (54, 56). Our findings in the patients' overall survival data are similar to those of other reports (19, 30, 31, 53). The longer survival of patients with atypical or anaplastic de novo meningiomas compared with those that transformed from a lower grade may be the result of increased technical difficulty of total removal in patients who have undergone previous operations. However, the fast recurrence despite more operations and a higher frequency of radiation treatment in the groups with transformation may reflect their more aggressive behavior. All of these factors lead us to believe that these subtypes constitute different diseases.

The overall rate of progression from a tumor that was originally Grade I to a higher-grade tumor ranges from 0.16 to 2% (3, 26, 27, 36, 62). As many as 28.5% of recurrent meningiomas transform to malignant varieties (3, 25), and the risk of progression from atypical to malignant ranges from 26 to 33% (26, 54). In our series of 30 meningiomas that were atypical at one point, only four (13%) have shown further transformation to an anaplastic type. Tumors with malignant transformation represented 38% in the atypical group and 70% in the anaplastic group, which is much higher, especially in the group of anaplastic meningiomas, than the 14 to 29% reported in the literature (57, 62). Unfortunately, further clinical information regarding malignant transformation and the frequency of so-called de novo atypical and anaplastic meningiomas is lacking in the literature, because these tumors are not usually distinguished from each other (6, 10, 11, 19, 30, 45, 47, 54, 73, 78).

The period of time that elapses between the appearance of a tumor and its transformation to malignancy is considerably shorter for tumors progressing to the anaplastic variant than for tumors progressing from benign to atypical (3). Thus, the grade of malignancy is probably defined from the beginning and the process is not just a generalized stepwise progression. One possible explanation is that the tumors might have a specific, complex, genetic alteration leading them to become anaplastic or atypical at the point of time at which they are first classified as benign (3). Whether or not all meningiomas with transformation to the anaplastic variant passed the stadium of atypical is not clear. If they do so, they remain atypical for a short time. Furthermore, it is not clear whether or not the tumors we classify as de novo also derive from an originally benign meningioma. Because we found several differences, we believe that de novo tumors, especially de novo atypical meningiomas, represent a distinct group.

General Features

The rates of atypical and anaplastic meningiomas reported in the literature vary considerably, ranging from 4.7 to 19.8%

for atypical and from 1 to 7.2% for anaplastic tumors (3, 17, 25–27, 45, 48, 57). The male predominance of anaplastic meningiomas was confirmed in our study. In contrast to findings from the WHO (76) and a recent review (48), however, we found an equal male-to-female ratio for atypical meningiomas, which is similar to other reports (4, 54). There are even a few series that show a female predominance for atypical meningiomas (22, 23). Furthermore, as previous studies and our findings suggest, atypical and anaplastic meningiomas appear earlier in life (42).

Our cases present the largest series of atypical cranial base meningiomas, which may be the results of the referral patterns for our patients. Although most other studies either do not present exact data or mix atypical and anaplastic meningiomas, when we added our numbers to those of other reports in the literature, we found that, of 151 atypical meningiomas, 31% occurred over the convexity, 28% at the falx or the parasagittal area, 36% at the cranial base, 3% on the tentorium, and 2% in the posterior fossa (17, 22, 28, 30, 54, 73). The distribution of anaplastic meningiomas, however, was different. Of 184 tumors, 42% occurred at the convexity, 31% at the falx or parasagittal region, 21% at the cranial base, 4% at the tentorium, and 2% in the posterior fossa (6, 9, 24–26, 28, 30, 53, 54, 61, 62, 68, 72, 73). Adding the large series of Maier et al. (43), who did not differentiate between convexity and parasagittal meningiomas, changes the percentages for atypical meningiomas to 65% (convexity, falx, parasagittal), 31% (cranial base), 2% (tentorium), and 2% (posterior fossa). For anaplastic meningiomas, the percentages change to 77% (convexity, falx, parasagittal), 18% (cranial base), 3% (tentorium), and 2% (posterior fossa). Our group had a low number of convexity and falx/parasagittal meningiomas because our department specializes in cranial base tumors. Sixty-three percent of the atypical and anaplastic meningiomas with falx/parasagittal location were tumors with progression and only 37% of the de novo tumors in both groups were located there.

The grade of resection is one of the most important prognostic factors for recurrence (1, 25, 29, 47, 64, 71). Because convexity meningiomas can be removed with an additional margin (Grade 0 removal) (32), their numbers, especially as tumors with transformation, should be low. We could not verify this hypothesis, however, because our number of patients was low. There are only a few reports of atypical and anaplastic spinal meningiomas, suggesting that tumors in this location have a different pathological behavior because they rarely show malignant transformation or recurrence even if not totally resected (2, 59).

Hormone Receptors and Proliferation Indices

PR expression in meningiomas relates to the tumor's grade and recurrence. A PR-positive status is more frequent in benign than malignant tumors (18, 50, 63), and there is an association between recurrence and PR-negative status (15). Proliferative indices in PR-positive meningiomas are lower than those in PR-negative tumors (21, 50). Thus, negative PR and a higher mitotic activity, expressed by a higher Ki-67 index, indicate more aggressive behavior (15, 18, 21, 50, 56, 60, 63). The significant differences in the atypical meningioma subgroups may be one reason for the difference in patient outcome. Transformed atypical meningiomas, which have a negative PR and higher proliferative index, seem to have much more aggressive behavior than the de novo subgroup. We found a high percentage of ER in atypical meningiomas with transformation and anaplastic meningiomas, but their numbers were small. So the role of ER in aggressive behavior still has to be defined.

Cytogenetic Differences

Genetic alterations in meningiomas are known to increase as the tumors become more aggressive (12, 74, 79). In addition to abnormalities of chromosome 22, alterations of chromosomes 1, 6, 9, 10, 14, 16, 18, and 19 and sex chromosomes are most often detected (12, 35, 38, 46, 66, 67, 69, 70, 79). Partial loss or monosomy of chromosomes 1, 10, and 14 is associated with more aggressive behavior (7, 8, 12, 31, 37, 39, 40, 41, 44, 49, 58, 70, 79). In our group, loss of part or monosomy of chromosome 10 and an increased monosomy or derivative chromosome 1 in combination with monosomy of chromosome 14 occurred mainly in the groups with malignant transformation that had a worse outcome. These findings were statistically significant. It is known that the expression of several genes linked to cell-cycle regulation is upregulated in atypical and anaplastic meningiomas and that expression of several members of the insulin-like growth factor and wingless signaling cascade is increased in atypical and anaplastic meningiomas with loss on chromosome 10 and 14, suggesting that aberrations of these pathways may also play a role in progression (77). Cai et al. (8) found that the combination of the deletion of 1p and 14q correlated with decreased survival in patients with atypical meningiomas. In addition, tumors with progression frequently showed a loss of chromosome 18, which was not found in the de novo groups.

CONCLUSION

The clinical behavior, hormone receptor status, proliferative indices, and cytogenetic profile of de novo atypical and anaplastic meningiomas may differ from tumors with malignant transformation, which suggests that these tumors can comprise distinct subgroups of aggressive meningiomas. The different time period to transformation for atypical and anaplastic meningiomas may be the result of a preset pattern defined by cytogenetic alterations and not just a stepwise differentiation. Further studies with larger numbers are needed to confirm our hypothesis, which may have influence on treatment strategies.

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COMMENTS

It is very interesting to learn that the haphazard and uncontrolled growth of cancer cells may be the result of a very precise stepwise sequence of mutations. Although this phenomenon is better understood in the evolution of low-grade gliomas to high-grade ones, as well as the development of de novo glioblastomas, it is less understood in other tumors of the central nervous system. This study details the cytogenetic profile, proliferative index, hormone receptor status, and clinical behavior of a small group of de novo atypical and anaplastic meningiomas, as well as those that have progressed into these entities.

The median proliferation index was much higher in the atypical group with progression than in the de novo group, implying that the former was more active and aggressive. This may be the reason why some atypical meningiomas can progress to an anaplastic state more rapidly than a benign one to an atypical state. Similarly, the investigators also conclude that the tumors that progressed required surgery more often than the de novo ones.

It was also determined that de novo atypical meningiomas are more likely to have receptors to progesterone, whereas those that have progressed to an atypical state are more likely to have receptors to neither estrogen nor progesterone or to have estrogen receptors only. The progesterone receptor of negative atypical tumors seemed to have a more aggressive behavior. However, both de novo and progressive anaplastic lesions are likely to have receptors to both hormones. Future studies should attempt to address why there is a difference between these groups, as well as the clinical importance of this finding.

In the cytogenetic analysis, there were several tumors with a normal karyotype, suggesting that there are more than just chromosomal mutations contributing to the development of some atypical meningiomas. In addition, other investigators have found other chromosomal changes (chromosomes 12, 15, 17, and 20) in atypical and anaplastic meningiomas that were not noted in this series.

Krayenbühl et al. provide further information about how meningiomas can evolve into higher-grade tumors but, at the same time, also

suggest that there is more to the development of a cancer cell than just a collection of stepwise mutations. We agree with the concept that the grade of malignancy a meningioma will achieve may be defined from the beginning and is not just a consequence of stepwise genetic changes.

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Most studies and clinical applications of the Ki67 proliferation index use a percentage of labeled cells based on specific criteria published in the literature. The Ki67 index is often not estimated if the mitotic index is high enough to establish the diagnosis of Grade II or III. The method for calculating the Ki67 index in this case series is not given. The median number for the proliferation index has no meaning. The most reproducible method is to calculate the percentage of labeled nuclei counting approximately 1000 tumor cells in the region with the highest density of labeled cells. In addition, it would be interesting to know how many Grade I tumors were seen by the authors in the same period of time and how many of them had the same investigations to establish that the changes described can be generalized to a larger population of meningiomas.

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This is a very interesting and important study that defines the differences in clinical behavior and outcome of patients who have atypical and/or anaplastic meningiomas that develop from progression, i.e., transformation from a lower grade, versus the de novo malignant variants. The authors of this study found differences not only in hormone receptor status, but also in the proliferative indices and cytogenetic findings. This translated out to differences in survival in this patient population, which is an important distinction that has not been recognized previously. In essence, patients tend to have a longer survival with the de novo atypical and anaplastic meningiomas compared with those in whom transformation occurred from a lower grade. This, in comparison to the de novo glioblastoma, is the opposite of what one would expect in the latter histological tumor. In this setting, de novo glioblastoma patients tend to have a shorter period of survival than those in whom the tumor transforms as a secondary variant. Although it is true that the presence of a malignant transformation from what was previously felt to be a low-grade tumor could represent a sampling error, it is unlikely that that is the case. Indeed, I think the authors have found a true association between outcome and development of these tumors from a de novo versus progressive transformation. Thus, this is a very innovative and novel study, and the authors are to be congratulated for a major contribution to the meningioma literature.

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The authors present a comprehensive clinical, histopathological, cytogenetic, and outcomes analysis on 36 patients with atypical and anaplastic meningiomas (World Health Organization Grades II and III). These patients were then appropriately subdivided into categories of de novo and secondarily transformed tumors. Comparisons were made between the tumor subtypes with respect to patient-specific (demographic data) and tumor-specific (hormone receptor status, proliferative indices, and cytogenetic data) factors. Despite the small numbers of this type of relatively rare primary central nervous system tumor, statistical significance was achieved with respect to intersubgroup analysis of transformation time, hormone receptor positive histology, proliferation index, cytogenetics, and outcome. Included within the data presented is a comprehensive review of the volume of literature to date pertaining to these rare meningioma histopathologies.

Although numerous studies have documented the histopathological, immunohistochemical, cytogenetic, and outcome differences among the meningioma grades, no study to date has examined the differences between the subclasses of de novo atypical/anaplastic and secondarily atypical/anaplastic meningiomas. This fact supports the importance of the data presented here. Of particular importance is the finding of statistically significant cytogenetic differences between the groups. These differences, in the absence of other patient-specific data, likely contribute greatly to the survival differences between the groups. This study represents an important first step as we move away from classic cytogenetic techniques toward molecular classification of tumors. The advent of copy number variation and other array-based analysis will not only aid in the microscopic cytogenetic analysis of these tumors (3, 5), but also tease out molecular differences and potential therapies.

High-resolution array based analysis would have likely provided more detailed analysis of the cytogenetic architecture of the tumors in which no cytogenetic abnormality was appreciated by Giemsa stain karyotyping. Although the authors correctly point out that meningiomas can malignantly transform in a similar fashion to gliomas, such a comparison may be misleading. In gliomas, both older and newer outcomes analyses suggest that survival times are longer for secondary (malignantly transformed) than for de novo gliomas (2, 4) and, with respect to survival during the malignant phase of the disease, no differences have been demonstrated (1, 2). The data presented here demonstrates the opposite finding for meningiomas. This is obviously an important fact and clinical difference to note when counseling a patient.

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INTRASELLAR ARACHNOID CYSTS

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OBJECTIVE: To evaluate the clinical, endocrinological, and radiological presentation of nine cases of surgically verified intrasellar arachnoid cysts and to discuss the physiopathological mechanisms of formation of these cysts.

METHODS: Among 1540 patients presenting with pituitary lesions, nine presented with an intrasellar arachnoid cyst. Their charts were retrospectively reviewed.

RESULTS: Presenting symptoms included headache (n = 2), visual symptoms (n = 3), menstrual irregularities (n = 2), rapid weight gain (n = 1), vertigo (n = 1), and/or confusion (n = 1). Two cysts were discovered incidentally. T1-weighted magnetic resonance imaging scans showed an intrasellar cystic lesion in all cases, with a huge suprasellar extension in six cases. The cyst was of the same intensity as the cerebrospinal fluid (CSF) in only two patients. A transsphenoidal approach allowed the transdural aspiration of fluid and injection of a water-soluble contrast agent under mild pressure. In three patients, the contrast infiltrated along the pituitary stalk toward the subarachnoid spaces; in the other patients, it remained in the intrasellar compartment. Cyst membranes were removed as completely as possible with fenestration toward the subarachnoid spaces in communicating cysts. In spite of tight packing of the sella and sphenoid sinus, CSF fistulae requiring reoperation developed in two patients.

CONCLUSION: The clinical picture of an intrasellar arachnoid cyst resembles that of a nonfunctional pituitary adenoma. Magnetic resonance imaging scans typically show a cystic intrasellar lesion with suprasellar extension, containing isointense or, more often, hyperintense fluid on T1-weighted sequences. In spite of the risk of CSF fistulae, the preferred surgical approach is transsphenoidal. A physiopathological mechanism is proposed according to anatomic variations of the sellar diaphragma allowing penetration of subarachnoid spaces into the sellar compartment and their enlargement by a ball-valve mechanism.

KEY WORDS: Arachnoid cyst, Magnetic resonance imaging, Non-neoplastic cysts, Pituitary diseases, Sella turcica, Transsphenoidal approach

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Intrasellar arachnoid cysts (IAC) are rare. A review of the literature using Medline revealed that only 42 of these surgically treated cysts have been reported in the English- and French-language literature since 1980 (3, 10, 14, 15, 17, 20, 21, 22, 23, 26, 27, 28, 31, 35). The presenting clinical picture of IAC mimics that of a nonsecreting pituitary adenoma. With the use of sophisticated radiological studies, the differential diagnosis between the two conditions should be easy. However, the cysts can appear hyperintense compared with the cerebrospinal fluid (CSF) on T1-weighted magnetic resonance imaging (MRI) scans.

A strong difference between these and other arachnoid cysts is that IACs are not associated with normal CSF cisterns because leptomeninges are considered to be absent in the sella turcica. Their pathogenesis remains unclear. In the literature, surgical morbidity for arachnoid cysts seems to be higher than that for pituitary adenomas after the transsphenoidal procedure. Serious complications have been reported, including one death from Klebsiella meningitis (20), CSF fistulae in seven cases (3, 15, 23, 26, 28), and postoperative blindness in one case (29).

We present nine cases of IACs treated by the transsphenoidal approach. The preoperative data are analyzed, including a thorough analysis of MRI findings in seven patients. The surgical procedure, results, and morbidity rates are presented and discussed along with the 42 previously reported cases. Our operative findings yield some information regarding possible mechanisms of cyst formation.

PATIENTS AND METHODS

Patient Population

Among 1540 patients with pituitary lesions observed by the senior author (AS) between 1968 and 2004, nine patients with IACs were retrospectively reviewed. Data collected included the age and sex of the patient; past medical history; preoperative clinical presentation; preoperative neurological, endocrinological, and ophthalmological status; and postoperative outcome.

Endocrinological Evaluation

Anterior pituitary functions were assessed in all patients. The following hormonal dosages were obtained: serum prolactin, growth hormone, thyroid-stimulating hormone, adrenocorticotropic hormone, luteinizing hormone, follicle-stimulating hormone, free thyroxine, free triiodothyronine, serum cortisol, and urinary free cortisol. Dynamic endocrine testing was performed by injection of thyroid-releasing hormone, luteinizing hormone-releasing hormone, and the insulin tolerance test.

Radiological Studies

Neuroradiological studies included sella turcica polytomography in the anteroposterior and lateral planes in eight patients and computed tomographic scanning in seven patients before and after intravenous contrast injection. Seven patients were studied by MRI scans, using T1-weighted sequences before and after gadolinium injection in all seven patients, T2-weighted sequences in three patients, and proton density sequences in one patient. Angiograms were performed for the first two patients, and four patients underwent pneumoencephalography.

Surgical Procedure

All patients underwent operation using the transsphenoidal approach. The operative findings were collected from the operative notes, as well as the surgical therapeutic procedure.

Postoperative Follow-up

Relief of preoperative symptoms and the occurrence of postoperative complications were noted from the charts. All patients underwent at least one postoperative ophtalmological examination. A repeated endocrinological work-up was performed at 7 to 10 days postoperatively in all patients and at 2 to 10 months postoperatively in seven patients. An annual follow-up examination in the Pituitary Diseases Clinics was noted in the charts of three patients; four other patients or their general physician were contacted by phone at the end of the study to obtain long-term follow-up data.

RESULTS

Clinical Presentation

The clinical data are summarized in *Table 1*. There were five men and four women with a mean age of 45 years (range, 20–80 yr). One patient (Patient 3) had undergone radiotherapy without any surgical treatment in another institution for a suspected pituitary adenoma in 1976, 14 years before admission to our department. Detailed data regarding the former diagnosis were not available.

Three patients presented with visual symptoms, including bitemporal hemianopsia and diminished visual acuity. Headache was the presenting symptom in two patients. Two women had menstrual irregularities, and one of them experienced a weight gain of 21 kg over a 1.5-year period. The preoperative duration of symptoms varied from 2 weeks to 5 years. Two arachnoid cysts were discovered incidentally, one by a sella turcica enlargement identified on a cranial x-ray for a patient experiencing post-traumatic epilepsy and one on a cervical spine x-ray for a patient presenting with paresthesias in both hands.

Endocrinological Evaluation

The results of the endocrinological evaluation are presented in *Table 1*. The patient who had been irradiated was found to have panhypopituitarism; two patients had a mixed gonadotrophin/growth hormone insufficiency; and an isolated growth hormone or gonadotrophin insufficiency was found in one and two patients, respectively. Two patients had no pituitary hormonal insufficiency. A mild or moderate hyperprolactinemia was found in three patients.

Radiological Studies

The radiological findings are summarized in *Table 2*. On sella turcica polytomography, performed in eight patients, a balloon-shaped sella with erosion of the floor cortex and dorsum sellae was found in five patients; asymmetry of the sellar floor was present in the three remaining patients. In the ninth patient, enlargement of the sella turcica was visualized on computed tomographic scans. A hypodense non-enhancing lesion within an enlarged sella was observed on the computed tomograpic scans of seven patients, five of which had suprasellar extension.

The lesion appeared cystic on the MRI scans of seven patients (*Fig. 1*). The sella turcica was markedly increased in size in six patients, with marked ballooning and sagging of its floor. On T1-weighted images, the lesion was homogeneously more intense than the CSF in five patients. In two patients, the cystic fluid had a signal similar to that of the CSF on T1- and T2-weighted sequences. All lesions were ovoid and regular. Six patients presented a suprasellar extension, expanding in a posterosuperior (n = 3), anterosuperior (n = 1), or superior direction (n = 2). Their largest diameter ranged from 12 to 35 mm (mean, 24 mm). The chiasma and anterior part of the third ventricle were pushed up by a huge suprasellar extension in six patients. In the seventh patient, the lesion only gained contact with the chiasma. A close contact with the medial aspect of the cavernous sinus was present, with the lesion perfectly molding but not invading the sinus wall. In Patients 3, 4, 5, and 9, the lesion appeared to distort the medial wall of the cavernous sinus between the carotid arteries segments. Normal pituitary tissue was recognized with certainty in only one case (Patient 6) and was pushed in the left part of the sella by the right-sided cyst; no normal pituitary tissue was visualized in five patients. Lack of complete studies in the sagittal plane rendered the evaluation of the gland difficult in the last patient. The pituitary stalk remained on the midline in one patient, was

TABLE 1. Clinical and endocrine data in nine cases of intrasellar arachnoid cysts[a]

Patient no.	Age (yr)/sex	Duration of symptoms (mo)	Symptoms and signs	GH	LH/FSH	TSH	ACTH	PRL (mUI/l)
1	20/M	10	Headache, weight loss, asthenia	N	↓	N	N	365
2	42/M	Incidental	Incidental	N	N	N	N	399
3	62/M	2.5	Confusion, ↓VA, ↓VF	↓	↓	↓	↓	554
4	45/F	60	Amenorrhea, ↓VA, ↓VF	↓	↓	N	N	618
5	43/M	3	Dizziness	↓	↓	N	N	144
6	20/F	42	Amenorrhea, weight gain	N	↓	N	N	296
7	27/F	0.5	Headache	N	N	N	N	1102
8	50/M	Incidental	Incidental	↓	N	N	N	114
9	80/F	3	↓VA	N	N	N	↓	4275

[a] GH, growth hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; TSH, thyroid-releasing hormone; ACTH, adrenocorticotropic hormone; PRL, prolactin; Incidental, incidental discovery; VA, visual acuity; VF, visual fields; ↓, reduced; N, normal function. Normal ranges of prolactin levels are 62–400 for men and 62–700 for women.

TABLE 2. Radiological data in nine cases of intrasellar arachnoid cysts[a]

Patient no.	X-rays/tomography/ ST CT scan	CT scan	T1- weighted MRI scan	Angiography	Encephalography
1	Vol. ST ↑ Asymmetric floor	—	—	N	no communic no SSE
2	Vol. ST ↑	Hypodense lesion density = CSF, no SSE	—	N	no communic no SSE
3	Vol. ST ↑↑ Thinned floor	Hypodense lesion density > CSF, SSE	Vol.ST ↑↑; sagged floor I = CSF; SSE Diam. 35 mm	—	no communic SSE 18 mm
4	Asymmetric floor	Hypodense lesion density > CSF, SSE	Vol. ST ↑; ballooned floor I > CSF; SSE Diam. 29 mm	—	no communic SSE 20 mm
5	Vol. ST ↑↑ Thinned floor	Hypodense lesion density > CSF, SSE	Vol. ST ↑; ballooned floor I > CSF; SSE Diam. 32 mm	—	—
6	Asymmetric floor	Hypodense lesion density > CSF, no SSE	Vol. ST : N I > CSF; no SSE Diam. 12 mm	—	—
7	Asymmetric floor	Hypodense lesion density > CSF, SSE	Vol. ST ↑ I > CSF; SSE Diam. 19 mm	—	—
8	Vol. ST ↑↑	Hypodense lesion density > CSF, SSE	Vol. ST ↑; ballooned floor I > CSF; SSE Diam. 22 mm	—	—
9	Vol. ST ↑↑	—	Vol. ST ↑; ballooned floor I = CSF; SSE Diam. 18 mm	—	—

[a] ST, sella turcica; CT, computed tomography; MRI, magnetic resonance imaging; Vol., volume; CSF, cerebrospinal fluid; N, normal; Communic., communication; SSE, suprasellar extension; Diam., largest diameter of the lesion; I, intensity. Arrows indicate an increase.

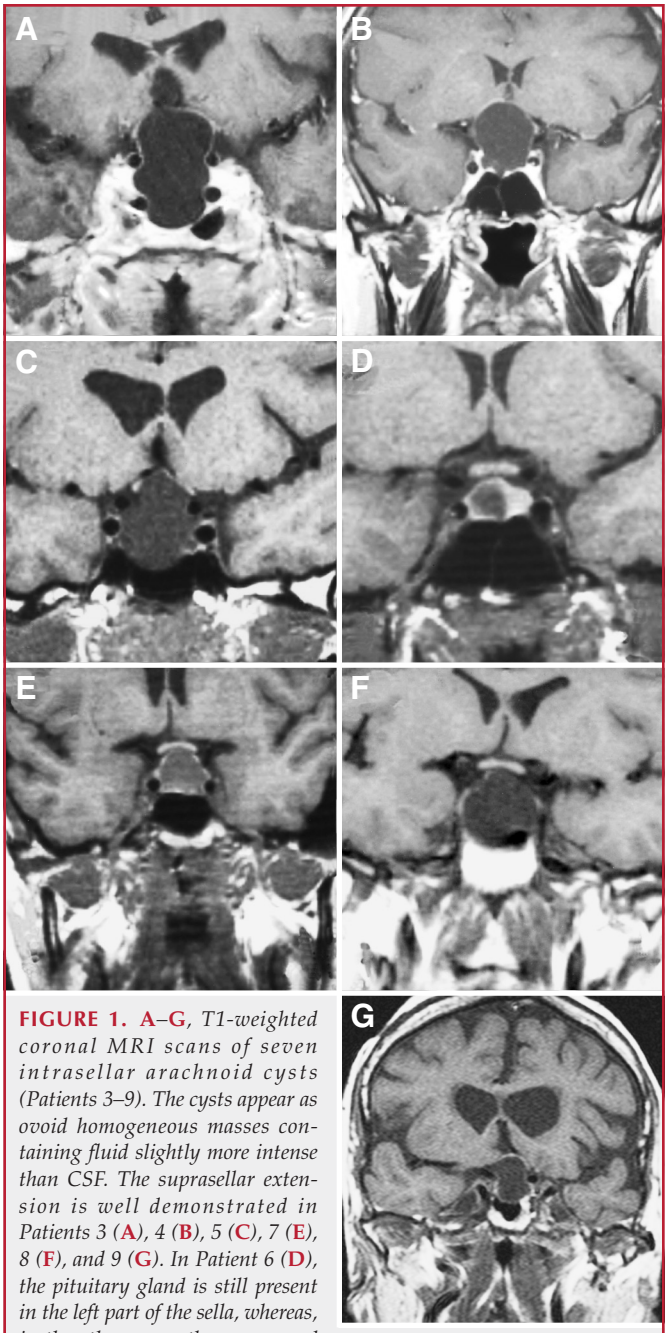


FIGURE 1. A–G, *T1-weighted coronal MRI scans of seven intrasellar arachnoid cysts (Patients 3–9). The cysts appear as ovoid homogeneous masses containing fluid slightly more intense than CSF. The suprasellar extension is well demonstrated in Patients 3 (**A**), 4 (**B**), 5 (**C**), 7 (**E**), 8 (**F**), and 9 (**G**). In Patient 6 (**D**), the pituitary gland is still present in the left part of the sella, whereas, in the other cases, the compressed pituitary gland is reduced to a thin layer at the periphery of the cyst.*

displaced posteriorly and laterally in four patients, and was not recognized in two patients.

Angiograms, obtained in two patients, were normal. Using pneumoencephalography (four patients), the cysts were found not to communicate with the chiasmatic cistern or ventricular system. A suprasellar extension of the cyst causing

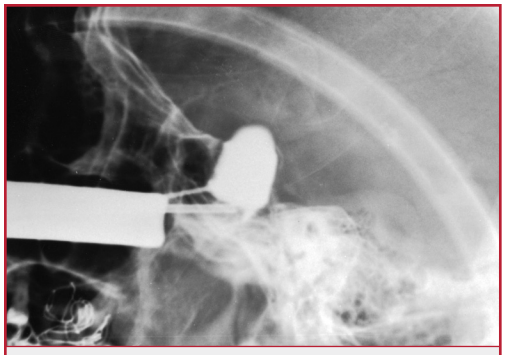


FIGURE 2. *Intraoperative x-ray taken after aspiration of the content of an IAC through the punctured dura and injection of watersoluble contrast material. The contrast delineates the intrasellar cavity and its suprasellar extension. The diaphragma is seen to bulge upward. No communication with the subarachnoid spaces is visualized (Patient 5).*

amputation of the anterior part of the third ventricle was found in two patients.

Surgical Procedure

All patients underwent operation via the transsphenoidal route. The sellar floor was found to be completely destroyed in the patient who had undergone radiotherapy, whereas it was reduced to a thin osseous layer in two others. Upon aspiration through the punctured dura mater, 2 to 8 cc of clear (Patients 1, 3, and 6), mildly xanthochromic (Patients 2, 4, 5, 7, and 8), or mildly hemorrhagic (Patient 9) fluid were withdrawn. After aspiration of the cyst content, air or a water-soluble agent was injected through the puncturing needle in eight patients. A communication toward the subarachnoid space (SAS) was demonstrated in that way, before dura opening, in three patients (Patients 4, 5, and 7). In the remaining five patients, the contrast delineated the intrasellar cavity and its suprasellar extension when present (*Fig. 2*). The dura was then opened and the cyst cavity was drained completely. The cyst wall was made of a thin arachnoid layer. The arachnoid membrane was totally (n = 2) or partially (n = 7) excised, depending on the adhesions with the pituitary gland, using a careful dissection technique. When present, the communication with the suprasellar cisterns was located at the pituitary stalk (n = 5). In Patient 8, no communication was demonstrated by injection of air or water-soluble contrast through the dura puncturing needle, even when injecting under some pressure. In this case, after drainage of the cyst and partial resection of the arachnoid membrane, however, a small amount of CSF was observed seeping around the pituitary stalk, with no evidence of a localized communication. The same leakage of CSF around the pituitary stalk was observed in the patient not studied by contrast intraoperative injection. In four of the five communicating cysts, a broad wall fenestration was performed toward the SAS. Membrane excision and drainage of the cyst were done for the four non-communicating

cysts and one communicating cyst. Packing of the sella itself with fat was performed in four cases in which the cyst cavity was left very large after drainage. The floor of the sella was reconstructed with nasoseptal bone pieces and the sphenoid sinus was packed with abdominal fat and biological glue.

Nasal tampons were left in place for 5 days postoperatively. Upon awakening from anesthesia, patients were recommended to maintain the sitting position. Fifteen to 20 cc of CSF were withdrawn daily by lumbar puncture for 5 days.

Pathology

Histologically, the cyst wall was composed of connective tissue containing a few mononucleated cells and a few small vessels, covered by a thin arachnoid cell layer. Protein concentration was measured in three patients (300 mg/l [Patient 2], 3650 mg/l [Patient 8], and 25500 mg/l [Patient 7]).

Postoperative Course

The follow-up period ranged from 2 months to 27 years (mean, 11 yr). The 62-year-old patient who had undergone radiotherapy 14 years preoperatively developed CSF rhinorrhea on the sixth postoperative day. The fistula did not resolve in spite of spinal CSF drainage. At the time of reoperation on the 16th postoperative day, the sellar and sinusal cavities were filled more compactly, and biological glue was used again. During the postoperative period, the patient developed a right hemiparesis from an ischemic event of the left basal ganglia; he died as a result of bronchopneumonia 6 years postoperatively. Another patient developed recurrent rhinorrhea, which was initially thought to consist of nasal secretions. A CSF fistula was finally diagnosed and the patient underwent a transsphenoidal reoperation 3 years later.

The three patients with preoperative visual deficits showed significant improvement. Prolactin was almost normalized in the three patients with preoperative elevation. The two patients with normal preoperative anterior pituitary function retained normal function. Among five patients with a preoperative partial hypopituitarism, normal pituitary function was restored in four patients and one developed complete hypopituitarism. Two patients with preoperative isolated corticotroph insufficiency and preoperative panhypopituitarism, respectively, remained unchanged. One patient developed permanent diabetes insipidus needing substitutive treatment. One of the two patients who presented with headaches improved.

DISCUSSION

Pathophysiology of IACs

An arachnoid cyst is a collection of CSF-like fluid whose wall is made of arachnoid structures. The cyst can develop at any site in the SAS along the cerebrospinal axis (24). In normal conditions, there is no arachnoid tissue below the diaphragma sellae. The pituitary gland is surrounded by a capsule that can be identified anatomically and during surgery as a membranous layer enveloping the two lobes of the gland and the pituitary stalk (9). At the histological level, this capsule is clearly not arachnoid but a derivative of the pia. There is no evidence of differentiation of a leptomeningeal layer surrounding the pituitary gland. During development, the sellar mesenchyma progressively transforms into dura mater and completely surrounds the gland and closes the aperture of the sella turcica (ST) to form the diaphragma (33). The diameter of the diaphragmatic aperture is highly variable. In 1951, Busch (8) described several types of diaphragmatic apertures in 788 autopsy cases: 1) the opening is very narrow, allowing passage of the stalk only (42%); 2) the aperture is larger than the stalk (37.5%); and 3) the diaphragma is reduced to a rim of dura or is nonexistent (20.5%). Likewise, Bergland et al. (5) found that the opening of the stalk was larger than 5 mm in diameter in 39% of the 225 fresh autopsy cases they studied. Moreover, the pituitary gland was at least 2 mm shorter than the ST depth in 23% of specimens, allowing extension of the SAS into the ST. The volume of the pituitary gland varies during development; in a series of seven autopsied children, Sunderland (29) observed that the ST was completely filled by the gland. On the contrary, the volume of the gland was smaller than the volume of the ST in 76 adult or elderly patients.

The presence of a large diaphragmatic aperture, or even the absence of diaphragma, and the discrepancy between the volume of the pituitary gland and that of the ST are factors that allow penetration of SAS into the ST. Liliequist (19), Ferner (12), Yaşargil et al. (34) and later Brasil and Schneider (6) demonstrated that leptomeninges form a collar around the hypophyseal stalk or are located dorsally to the infundibulum. SAS have been demonstrated to penetrate into the ST in normal conditions (11, 24). Under pathological conditions, including intracranial hypertension or gland atrophy, SAS may also penetrate the ST (1, 11). In the empty sella syndrome, SAS extend largely into the sella, freely communicating with the suprasellar SAS. No pressure gradient exists between the sellar and suprasellar compartments. On the contrary, IACs either do not communicate with the suprasellar SAS (four of our nine patients) or communicate by a small pinhole (3) or a slit (17). Benedetti et al. (4) postulate an aetiopathogenic correlation between primary empty sella syndrome and IACs. According to their theory, IACs are initially formed by largely communicating SAS expanding into the ST. The SAS are secondarily isolated by closure of the communication because of some meningitic, hemorrhagic, or inflammatory event. Another pathophysiological hypothesis could be based on the anatomic particularities of the diaphragmatic aperture and pituitary stalk (*Fig. 3*). In our opinion, empty sella syndrome is likely to occur in a "Bush Type 3" diaphragma, one with a very large diaphragmatic aperture or with an nonexistent diaphragma (*Fig. 4*). On the contrary, IACs might occur with a "Bush Type 2" diaphragma. In this anatomic variation, a diaphragmatic opening slightly larger than the pituitary stalk allows intrasellar penetration of SAS. A narrow communication exists between the suprasellar and intrasellar SAS. Thus, IACs are not true intra-arachnoid cysts (24) but rather arise from the chiasmatic citern extending into the confines of the sella (2). In this

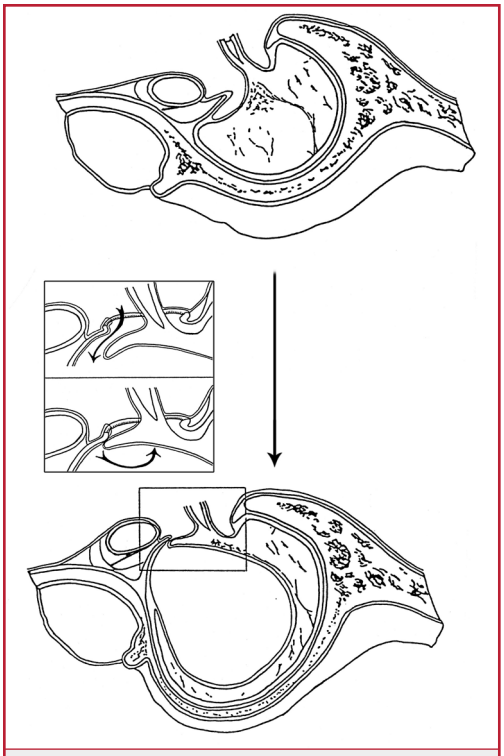


FIGURE 3. *Illustration of a pathophysiological hypothesis for intrasellar arachnoid cysts. A large diaphragmatic aperture and the pulsatile CSF force allows the suprasellar SAS to penetrate into the ST. The pituitary stalk and gland participate in a ball-valve mechanism, reoccluding the dural defect after CSF entrance (communicating cyst). Apposition of arachnoid membranes at some point of evolution leads to a non-communicating cyst (not shown).*

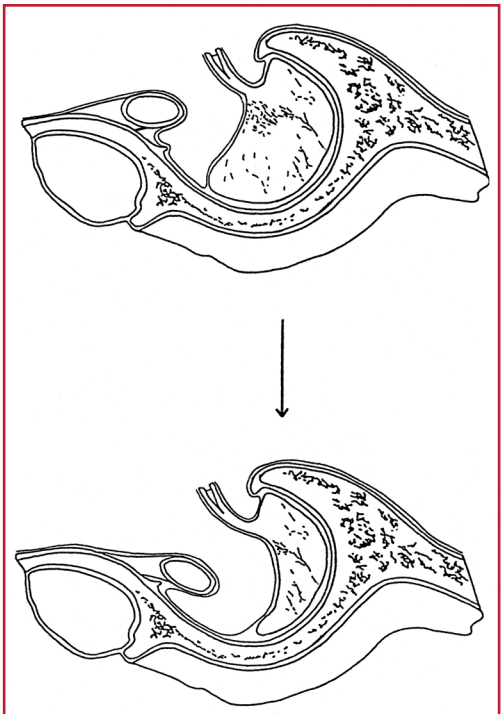


FIGURE 4. *Illustration of the pathophysiological steps leading to a primary empty sella. A very broad diaphragmatic opening allows free penetration of SAS into the ST. CSF freely enters and exits the ST; neither a ball-valve mechanism nor a pressure gradient occurs.*

situation, CSF can enter the sellar compartment propelled by the pulsatile intracranial force. The CSF can be trapped within the ST because of the narrowness of the passage and of very light or virtually absent pulsatile force in the ST. In this way, the IAC enlarges by a ball-valve mechanism. Such a mechanism has been evoked for arachnoid cysts in other locations, such as spinal extradural. Rohrer et al. (25) observed a spinal arachnoid cyst in which a dural defect in the thecal sac allowed extravasation of CSF into the cyst. Two rootlets of the L1 nerve root were acting as a ball-valve through the dural rent. The rootlets could be reduced into the thecal sac, producing CSF flow directed to the extradural arachnoid cyst, after which the rootlets reoccluded the dural rent. Similarly, in IACs, the pituitary stalk could act in the same way. This mechanism was observed operatively in one of our patients in whom we visualized a rhythmic CSF leak around the stalk. In Hornig and Zervas' (17) case report, CSF was seen squirting through a 1 mm slit perforation of the anterior diaphragma in a rhythmic fashion. After some time, the pituitary gland could participate in the ball-valve mechanism. The deformed gland could act as a piston, blocking itself against the diaphragma after CSF entrance into the ST, and, therefore, occluding the dural defect. The frequently observed suprasellar extension would be explained by the fluid collection pushing up the pituitary gland and diaphragma. Cystic enlargement leads to increased intrasellar pressure. As a consequence, the CSF leak progressively diminishes and may stop when the intrasellar pressure counteracts the intracranial pressure. Cessation of CSF passage through the narrow communication at some point of evolution could allow apposition of the arachnoid membranes and lead to anatomic closure of the communication. The latter hypothesis could explain the four non-communicating cysts in our series. One of the four non-communicating cysts occurred in Patient 3, who had received radiotherapy for a pituitary adenoma 14 years earlier. In this case, the secondary gland/tumor atrophy might have played a role by facilitating the passage of arachnoid spaces through a large diaphragmatic opening. The following pathophysiological steps are similar to the other cysts, leading to closure of the narrow transdiaphragmatic communication and transformation into a non-communicating cyst.

Clinical Presentation

Since 1980, there have been 14 published series (3, 10, 20, 21, 23, 27, 28) or case reports (14, 15, 17, 22, 26, 31, 35) describing a

TABLE 3. Clinical presentation of 51 reported intrasellar arachnoid cysts

Series (ref. no.)	No. of patients	Mean age, yr	M/F	Incidental Asymptomatic	Headache	Visual trouble	Endocrine trouble
Harter et al., 1980 (14)	1	24	1 M/0 F	0	0	1	0
Spaziante et al., 1981 (28)	3	55	0 M/3F	0	2	2	2
Baskin and Wilson, 1984 (3)	8	42	6 M/2 F	4	4	0	4
Meyer et al., 1987 (20)	13	46	5 M/8 F	0	7	7	Unknown
Hasegawa et al., 1991 (15)	1	53	1 M/0 F	0	0	1	0
Hornig and Zervas, 1992 (17)	1	57	1 M/0 F	0	0	1	0
Nomura et al., 1996 (23)	2	55	2 M/0 F	0	0	2	0
Dietemann et al.,1997 (10)	2	48	0 M/2 F	0	0	2	0
Saeki et al., 1999 (26)	1	62	1 M/0 F	0	0	1	0
Miyamoto et al., 1999 (21)	2	63	1 M/1 F	0	2	2	Unknown
Shin et al., 1999 (27)	5	53	2 M/3 F	Unknown	3	3	2
Weil, 2001 (31)	1	Unknown	1 M/0 F	0	0	1	0
Murakami et al., 2003 (22)	1	48	1 M/0 F	0	0	1	0
Yasuda et al., 2005 (35)	1	67	1 M/0 F	0	1	1	1
Current series	9	45	5 M/4 F	2	2	3	2
Total	51	47	28 M/23 F	6	21	28	11

total of 42 operated IACs; the current report adds nine more cases. The clinical presentation of these 51 patients is summarized in *Table 3*.

This series includes 28 men and 23 women, ranging in age from 16 to 80 years. The cyst was found incidentally in six patients when sellar abnormalities were noted on cranial x-ray films obtained for head trauma or epilepsy or C-spine x-rays for arm paresthesia. Headaches (21 patients) and visual troubles (28 patients) were the prominent presenting symptoms. Endocrine symptoms were less common; most complaints involved the gonadotropic axis, including menstrual irregularities, infertility, decreased libido, or impotence. Even if there were no or few complaints, an extensive endocrine work-up with pituitary stimulation tests, could reveal biological alterations, including panhypopituitarism, as was the case in three of our patients.

As seen above, an IAC expresses itself as a mass lesion within and above the pituitary fossa, producing optochiasmatic compression, diminished anterior pituitary function, hyperprolactinemia, or headaches. The headaches may arise from dura distension caused by the cyst. In some cases, the headaches are probably not related to the arachnoid cyst, the latter being incidentally discovered in a work-up done for the headaches. No oculomotor disturbances have been reported related to an IAC.

Diagnosis

The radiological diagnosis of an intrasellar mass is provided essentially by MRI scan. The tomographic, angiographic, and encephalographic data are given for historical reasons. Encephalography, which has been abandoned, was an examination capable of demonstrating the presence or absence of a communication toward the suprasellar SAS preoperatively. Arachnoid cysts in other locations are typically described as well-demarcated collections of fluid having almost the same intensity as the CSF on all MRI sequences (13, 30). In all 28 cases of arachnoid cysts studied by Heier et al. (16) and 16 cases reported by Wiener et al. (32), the intensity of the cyst matched that of CSF on all pulse sequences but none was of intrasellar location. In some cases, an elevated protein concentration in the fluid may cause the cyst to appear slightly more intense than the CSF on T1-weighted images. In the seven cases we studied by MRI scan, five had a signal significantly different from that of CSF. The cystic fluid was of slightly higher intensity than CSF on T1-weighted sequences. This aspect has already been pointed out by Meyer et al. (20), who studied two of their 13 patients by MRI scan. Moreover, in our seven cases, the cyst usually appeared spherical or ovoid, regular, and molding but not invading the cavernous sinus wall. The two cysts that were of same intensity as the CSF did (n = 1) or did not (n = 1) communicate with the suprasellar spaces, whereas four of the five cysts with higher signal were communicant. The communication is usually a narrow slit. Therefore, the cystic fluid is stagnant, probably explaining the signal differences on MRI examination. Sophisticated MRI techniques are able to demonstrate the pulsatile motion of CSF within arachnoid cysts, although definitive anatomic evaluation of the lesions is not obtained (7).

MRI scans may suggest the diagnosis of an intrasellar arachnoid cyst when showing a cystic intrasellar lesion with suprasellar extension, balloon-shaped, regular, iso-or slightly hyper-intense to the CSF, molding but not invading the medial wall of the cavernous sinus (18, 27, 36). Differential diagnoses

on MRI scans include Rathke's cleft cysts, cystic adenomas, and craniopharyngiomas. A definitive diagnosis is difficult to obtain before surgery.

Surgical Management

The indications for surgical treatment are the same as those for a non-secreting adenoma, including pituitary dysfunction, signs of optochiasmatic compression, and severe headaches. The operative indication in the two incidentally diagnosed lesions was the presence of a large pituitary lesion of unknown origin, suspected to be a non-functioning adenoma, in a young patient in 1978 and the presence of pituitary somatotroph dysfunction in the second patient. The transsphenoidal route is the one of choice. The definitive diagnosis is usually obtained preoperatively; the operative goals are to evacuate the CSF-like fluid, to excise all or part of the cyst membranes and, if present, to largely open a communication with the suprasellar CSF spaces. Partial or total membrane excision allows histological diagnostic confirmation and does not produce pituitary damage if done using delicate dissection techniques. At the completion of the procedure, the floor of the sella turcica must be reconstructed hermetically, and the sphenoid sinus must be efficiently packed with fat to prevent the occurence of CSF fistula. Two of our nine patients and seven of the 42 reported cases (3, 15, 23, 26, 28) developed CSF rhinorrhea, with most of them requiring reoperation. We are not sure whether or not the only death reported (20), which resulted from Klebsiella meningitis, originated with a CSF fistula. This serious morbidity, much more frequent than after transsphenoidal surgery for pituitary adenomas, illustrates the importance of a meticulous closure of the sella and sphenoid sinus, associated with postoperative postural intracranial hypotension and daily CSF drainage for a few days. Moreover, prolapsus of the optic structures in a emptied sella caused postoperative blindness in one reported case (28). This complication should also be prevented by efficient packing upon closure. Except for this complication, visual deficits improved postoperatively in the majority of our patients and the previously published cases. Hyperprolactinemia resolved in seven out of eight cases. Partial pituitary insufficiency often recovered, whereas complete pituitary insufficiency frequently did not improve. The pulsatile mass effect on the pituitary tissue could explain progressive gland atrophy and irreversible alteration of the pituitary function.

CONCLUSIONS

IACs are very rare, as there is no differentiation of leptomeninges in the ST and, therefore, no arachnoid membrane below the diaphragma sellae. Under particular anatomic circumstances, discrepancies between the diameters of the pituitary stalk and the diaphragmatic aperture and between the volumes of the gland and the ST allow the suprasellar SAS to enter the ST. A ball-valve mechanism may be produced by the narrowness of the communication, with the pituitary gland and stalk acting as a piston, and the CSF pulsatility. Closure of the communication at some point of evolution leads to a non-communicating cyst. The clinical picture resembles that of a non-secreting pituitary adenoma. MRI scans typically show a cystic intrasellar lesion, often with suprasellar extension, balloon-shaped, containing fluid iso- or hyperintense to CSF. Using the transsphenoidal procedure, the cyst is drained and, if communicating, largely opened to the suprasellar CSF spaces. Meticulous closure and packing are important to prevent postoperative CSF fistulae.

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COMMENTS

The authors present nine new patients with intrasellar arachnoid cysts, with good magnetic resonance imaging (MRI) studies on seven. They claim that this is a rare entity with only 42 previously published cases. I do not believe it is that rare, but rather that it is just not published often. This study demonstrates the MRI characteristics well, demonstrating the difficulty in correctly diagnosing some of these patients. Often, the diagnosis is very evident on the MRI scans.

The issue of treatment is interesting. Early in my series, even with considerable transsphenoidal experience, I approached intrasellar arachnoid cysts through a craniotomy, believing that the surgery needs to communicate the cyst with the subarachnoid space to prevent recurrence. It seemed antithetical to me to create a larger opening via the transsphenoidal route into the intracranial subarachnoid space, while minimizing the risk of postoperative rhinorrhea. Subsequently, I have altered my approach to the transnasal transsphenoidal route and have not observed postoperative cerebrospinal fluid leak problems. I have, however, witnessed recurrence with both a craniotomy and transsphenoidal approach. Long-term follow-up is necessary with both serial visual fields and MRI scans.

The etiology of these cysts is unclear, but the suggestions made in this article are worthy of consideration. I do believe it is a slow ball-valve phenomenon, but the stimulus to the formation may be variable.

Kalmon D. Post
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True arachnoid cysts of the sella are rare, as the authors observed in this retrospective analysis of nine cases out of more than 1500 pituitary lesions treated at a single institution over a 36-year period. I agree that these lesions can be successfully treated by the transsphenoidal approach, although a minimally invasive pterional or supraorbital approach is also effective and minimizes the risk of cerebrospinal fluid leak. I am not certain that injection of air or contrast agent to delineate the fistula to the intracranial subarachnoid space is necessary; fenestration with a cerebrospinal fluid repair will usually suffice.

Marc R. Mayberg
Seattle, Washington



Stove boat with harpooner taking aim at a sperm whale (painting, 1879). (Courtesy of New Bedford Whaling Museum). *From*: Matthews, LH: *The Whale*. New York, Simon & Schuster, 1968.

ATLANTO-OCCIPITAL DISLOCATION: PART 1—NORMAL OCCIPITAL CONDYLE-C_1 INTERVAL IN 89 CHILDREN

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OBJECTIVE: Although atlanto-occipital dislocation has long been recognized as an extremely unstable and often lethal injury, no single radiodiagnostic criterion published to date has achieved failure-proof status. This is because most existing diagnostic tests exploit bony landmarks remote from the injured condyle–C_1 (OC_1) joint so that patient positioning could inadvertently line up these landmarks and conceal actual disruption of the joint. Many of the landmarks used are wide apart and/or noncoplanar; their measurements are subject to errors related to x-ray angle, target–film distance, and superimposed bony outlines. We propose using the actual occipital condyle–C_1 interval (CCI) obtained from high-resolution reconstructed computed tomographic scans as the indicator for OC_1 joint disruption. We hypothesize that the normal CCI is very small and has great left-right symmetry and that atlanto-occipital dislocation is always manifested by an abnormal widening of the CCI and/or by left-right joint asymmetry irrespective of the shifting of other remote bony landmarks. Part I of this study establishes standard normal values for CCI in children.

METHOD: Sagittal and coronal reformatted images were obtained from thin axial computed tomographic scans performed on 89 children, 18 for nontraumatic complaints and 71 as part of a minor head trauma protocol but later exonerated for cervical injury. The interval between condyle and C_1 was measured at four equidistant points on the joint surface on the sagittal and coronal images of all 178 joints (left and right) in the group. Sagittal and coronal CCIs are the means of four sagittal and four coronal measurements, respectively. The combined or true CCI for an individual joint was taken as the mean of both the sagittal and coronal (total of eight) measurements.

RESULTS: The mean combined CCI of all 178 joints was 1.28 mm ± 0.26 (standard deviation [SD]). None of the 178 CCIs exceeded 1.95 mm, and none of the individual joint interval measurements exceeded 2.5 mm. Left-right symmetry was tested by computing the mean left-right difference in CCI from all 89 subjects equal to 0.047 mm ± 0.002 (SD); or only 3% of the mean combined CCI. When the mean of all right CCIs (1.333 mm ± 0.31 SD) is contrasted with the mean of all left CCIs (1.327 mm ± 0.30 SD), the difference is 0.006 mm, or 1.09% of the mean total CCI ($P = 0.792$). Left-right symmetry is also apparent in conformational anatomy in both sagittal and coronal images. Linear regression analysis between CCI and age shows no statistical difference in CCI between age groups from 0.5 to 18 years. Linear regression performed separately on the right and left CCIs suggests that left-right symmetry is also stable through this age range.

CONCLUSION: The normal OC_1 joint in children 0 to 18 years is tightly held together by ligaments with a mean CCI of 1.28 mm in the 89 subjects tested. There is great left–right joint symmetry in both CCI and conformational anatomy. CCI and left-right symmetry do not appear to change significantly with age. It is reasonable to set a maximum CCI as a discriminator between normal and disrupted OC_1 joints to indicate atlanto-occipital dislocation.

KEY WORDS: Atlanto-occipital dislocation, Diagnostic criteria, Left-right joint symmetry, Normative measurements, Occipital condyle-C_1 interval

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Traumatic atlanto-occipital dislocation (AOD) is one of the most common fatal cervical spine injuries (1, 2, 3, 5, 14, 15). Autopsy and postmortem radiographic examination of traffic fatalities revealed 20 to 35% incidence of AOD (1, 3, 5). Improvements in emergency resuscitation and prehospital care have increased survival in this previously almost invariably lethal injury. AOD is a particularly important entity in pediatric spine trauma, not only because it occurs more than twice as frequently in children as in adults (3), but also because those children who survive the initial catastrophe often make good recoveries despite severe presenting neurological deficits (17, 18).

Survival of AOD depends on prompt recognition. Ironically, the diagnosis of this most devastating and disruptive injury often rests on subtle shifts of structures within the complex matrix of the occiput–C_1–C_2 joints, making AOD the most elusive deadly injury in the child's spinal column (2, 14, 15). The literature contains a veritable catalog of radiodiagnostic criteria for AOD (7, 9, 10, 12–14, 20, 23, 27), but no single criterion has yet reached failure-proof status.

The explanations for this inadequacy in diagnostic method are threefold. First, most existing radiodiagnostic criteria exploit a change in normal relationships between bony landmarks to reflect atlanto-occipital instability, yet these landmarks are not part of the condyle-C_1 articulation, but are rather remote from it such as the basion and opisthion of Powers et al.'s (20) and Lee et al.'s (14) criteria; the posterior border of the C_2 body of Harris et al.'s criterion (9, 10); the odontoid tip of Wholey et al.'s criterion (27); and the laminae of the upper three cervical segments of Sun et al.'s criterion (23). For the pathological shifts to be detectable, secondary forces must act on these remote landmarks *after* the initial destabilization of the joints. Given the highly unstable nature of AOD, the postimpact relationship between the cranium and C_1–C_2 can be profoundly affected by patient handling (11, 26); thus, careful lining-up of the head and neck of the victim at the time of the x-rays could unintentionally "normalize" these shifted landmarks and thus inadvertently conceal the true extent of the injury to the occiput–C_1 joints (23).

Second, because some of the landmarks used are wide apart (Powers et al.'s [20]; Lee et al.'s [14], and Sun et al.'s [23]) or even noncoplanar (Dublin et al.'s [7]), the actual measurements between designated points are subject to change with the incident angle of the x-ray beam (rotational distortion) as well as the distance between the target and the x-ray film. The wider the spread between target points, the larger the error (17).

Finally, congenital anomalies of C_1, C_2, and at the foramen magnum, and immature or delayed ossification of the odontoid segments, preclude use of many available criteria.

The aforementioned considerations led us in 1994 to explore the possibility of measuring the actual gap interval within the occipital condyle–C_1 articulation as an indicator of joint integrity, thus eliminating all the logistical and technical weaknesses of the other diagnostic methods. Our thesis is based on three hypotheses:

1. The normal occiput-C_1 (OC_1) joint is held tightly together by strong ligaments and operates physiologically with a narrow condyle-C_1 interval (CCI).
2. The left and right OC_1 joints are normally highly symmetrical in their configuration.
3. Any forces that disrupt the integrity of the OC_1 joints will necessarily enlarge the CCI and/or produce left–right asymmetry in the joint configuration. These two situations will be detectable radiographically irrespective of "extraneous" shifts of bony landmarks remote from the OC_1 joints, and because the target points are coplanar and adjacent, the measurements are unaffected by rotational and other distortions. Bony anomalies and developmental stages of neighboring structures will also not affect the CCI.

The present study, first of a two-part AOD series, was undertaken to test the first two hypotheses, namely, using reformatted computed tomographic (CT) images to measure the CCI of normal children and to verify symmetry between the left and right OC_1 joints. Part II of the study will test the third hypothesis by applying a new diagnostic criterion for AOD using abnormal CCI on a cohort of children with proven AOD and comparing the merits of CCI against the published diagnostic methods.

MATERIALS AND METHODS

Subject Demographics

The study cohort comprised two groups of children. Seventy-one children were admitted through the emergency room after trivial trauma to the upper body. Our trauma protocol dictated performance of axial CT scans of the craniovertebral junction and upper cervical spine on any child younger than 8 years whenever there was the slightest suspicion of craniospinal trauma. Any children later found to have neurological deficits, persistent neck pain, or abnormalities on the x-rays were excluded. Most of the subjects were sent home within 24 hours, and the parents or children were contacted by telephone 1 to 2 weeks later to ensure absence of neck symptoms. These 71 subjects were thus younger children, 0.5 to 8 years old, with a mean age of 3.3 years.

Eighteen additional children had CT scans of the craniovertebral junction because of headaches (10), fever workup (3), ear infection (3), and ischemic symptoms (2). These were older children, 5.6 to 17.1 years old, with a mean age of 10.3 years.

The total cohort therefore comprised 89 children, 59 males and 30 females, aged 0.5 to 17.1 years with a mean age of 4.7 years.

Imaging Technique and Protocol

The imaging sequence was part of the head and neck protocol used for trauma. One and one half to 2.5 mm nonoverlapping axial CT scans were obtained from the midclivus to the bottom of C_2. Orthogonal coronal and sagittal reconstructions were generated to display the two occiput-C_1 joints.

Measurements

All measurements were obtained from the reformatted images that cut through the largest surface of the OC_1 joint. In the coronal plane,

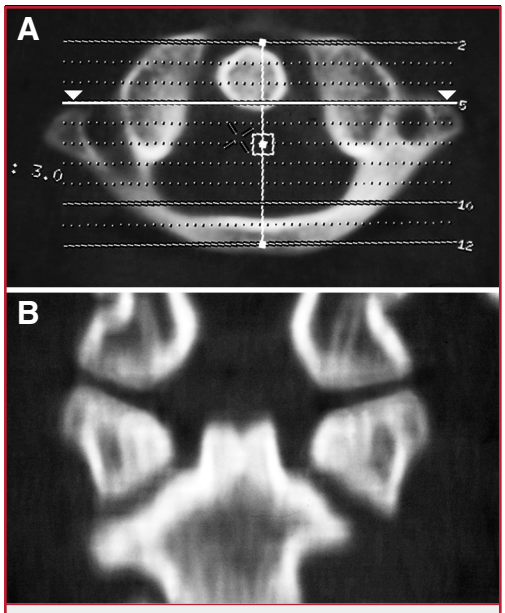


FIGURE 1. *Coronal CT reconstruction showing the OC_1 joint in a normal 6-year-old child.* **A**, *Coronal section indicators are at C_1. Slice five is highlighted.* **B**, *Slice five from* **A** *through the midpoint of the OC_1 joint showing a slightly wider medial portion of the joint space.*

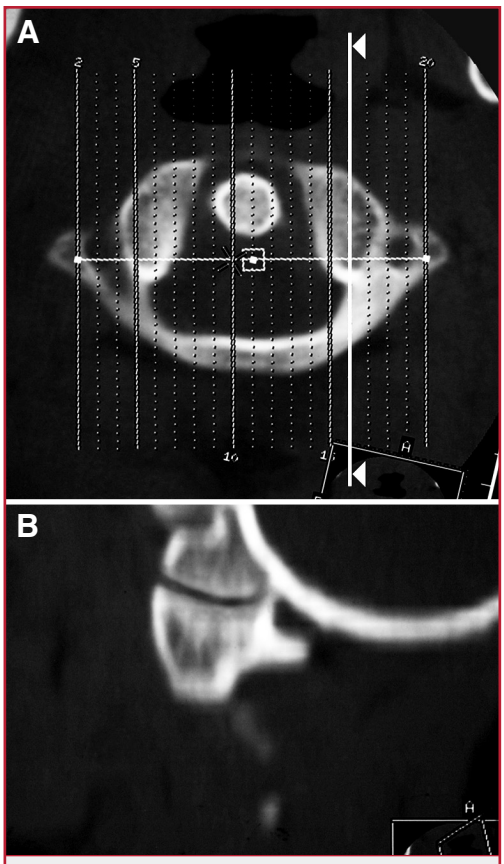


FIGURE 2. *Sagittal CT reconstruction showing the OC_1 joint in a normal 6-year-old child.* **A**, *Sagittal section indicators are at C_1. Note orthogonal parasagittal cuts are not in line with the long axis of the OC_1 joint surface. Slice 16 is highlighted.* **B**, *Slice 16 from* **A** *showing very narrow and homometric joint space throughout the whole articulating surface of the left OC_1 joint.*

this was usually the image through the midpoints of the two foramina transversaria (*Fig. 1*). In the sagittal plane, the oblique orientation of the OC_1 joint precluded any parasagittal images from cutting through the joint's longest axis, but as a result of considerations of convenience for later clinical application of this technique, we continued with parasagittal images and selected the cut approximately midpoint between midsagittal and the tip of the transverse process (*Fig. 2*).

Four equidistant points were designated on the opposing joint surfaces both in the coronal and sagittal images (*Fig. 3*). The gap interval between opposite points within each of the four point sets was measured with appropriate adjustments of contrast and magnification on the computed images. The best estimate was obtained in multiples of 0.25 mm. The mean of the four readings was obtained for both the sagittal and coronal images of each side. Correlations between sagittal and coronal measurements and between the left and right joints were made.

Statistical Analysis

Mean values of CCI between the left and right joints and between sagittal and coronal measurements, were compared using a two-tailed *t* test for unequal variance. CCI values were correlated with age using linear regression analysis with reports of Pearson correlation coefficient and 95% confidence intervals.

RESULTS

There were a total of 1424 measurements of the joint interval counting all 178 OC_1 joints with eight measurements per joint from both the sagittal and coronal images. The range of individual interval measurements of the entire series was 0.25 to 2.5 mm. Joint spaces were by and large very narrow in all projections with few measurements exceeding 2.0 mm. The exceptions were in children younger than 5 years, in whom there was frequently a wedge-shaped "crevice" on the joint surface of the occipital condyle related to ossification borders (*Fig. 4*). These crevices were avoided when possible in selecting points of measurements.

The CCI for each joint may be computed either from the sagittal or coronal image as the mean of four measurements. The combined or actual CCI for the joint is taken here as the average of both the sagittal and coronal CCIs and is thus the mean of eight measurements.

The CCIs for all 89 subjects in *Table 1* were tabulated according to the right and left sides as well as the respective sagittal or coronal image from which the measurements were made.

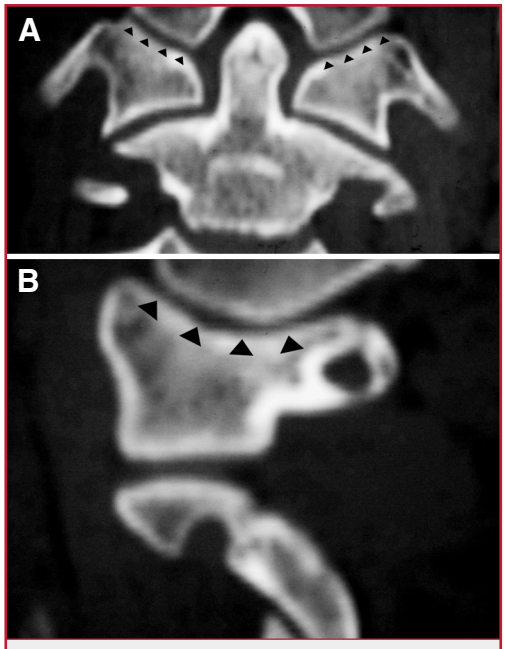


FIGURE 3. *Placement of the measurement points (*arrowheads*) on the coronal (***A***) and sagittal (***B***) OC_1 joint surfaces shown in a normal 7-year-old boy.*

The mean combined CCI for all 178 joints is 1.28 mm ± 0.26 mm (standard deviation [SD]). None of the 178 CCIs were greater than 1.95 mm.

There are no significant sex differences in the combined CCI among the 89 subjects.



FIGURE 4. *Sagittal reconstructed CT showing synchondrosis intraoccipitalis anterior (SIA) (*arrow*) on the condyle side of the OC_1 joint of a 7-year-old child corresponding to the ossification border between the basioccipital and exoccipital portions of the chondrocranium.*

Comparison Between Sagittal and Coronal Measurements

The sagittal and coronal measurements were compared for cohesiveness in two ways. First, the algebraic difference between the sagittal and coronal CCI for each individual joint, given as sagittal CCI–coronal CCI, was calculated and then summated for all 178 joints. The mean difference was found to be 0.146 mm, or 11.6% of the mean combined CCI (P = 0.00062), suggesting the CCI obtained from sagittal measurements is significantly greater than that obtained from coronal measurements.

Next, the entire array (178) of sagittal CCIs (mean = 1.33 mm ± 0.30 SD) were compared with that of coronal CCIs (mean = 1.17 mm ± 0.31 SD). The difference of means is 0.158 mm greater for sagittal CCI, or 12.2% of the whole group, which is also statistically significant (P = 0.00059).

The differences between sagittal and coronal CCIs are illustrated in a typical data set (*Table 2*) for a typical OC_1 joint. Besides a discrepancy in the respective CCI values, there is also a difference in the shape of the joint spaces when viewed in the two planes. In the sagittal plane, the four readings are more or less equal from the anterior to the posterior points on the joint surface (*Fig. 3B*), but in the coronal plane, the joint gap in the medial part of the joint is considerably wider than in the lateral part (*Fig. 1B*).

Comparison Between Left and Right Sides

Left and right symmetry of the OC_1 joints was examined in two ways. First, the difference between the CCI of the left and right joints of each individual subject was calculated for the entire cohort. Because there is no logistic priority of left or right side, we used the absolute rather than the algebraic difference between the sides. The mean left–right difference was 0.049 mm ± 0.002 SD, representing 3% of the mean combined CCIs. The difference is thus negligible ($P > 0.9$).

Next, the entire array of right-sided CCIs (mean = 1.28 mm ± 0.273 SD) were contrasted with that of the left side (mean = 1.273 mm ± 0.257 SD). The difference of means is 0.007 mm, representing 0.54% of the mean combined CCIs. The P value is 0.841, again suggesting homogeneity between the left and right populations.

Because of the difference in sagittal and coronal measurements, we compared the sagittal and coronal CCIs separately for left–right symmetry to eliminate the possibility of mutual influence of variables. The difference of means between the right sagittal CCIs (mean = 1.333 mm ± 0.31 SD) and left sagittal CCIs (mean = 1.327 mm ± 0.30 SD) is 0.006 mm, or 0.47% of the mean total CCIs (P = 0.915). The difference of means between the right coronal CCIs (mean = 1.180 mm ± 0.32 SD) and left coronal CCIs (mean = 1.166 mm ± 0.31 SD) is 0.014 mm, or 1.09% of the mean total CCIs (P = 0.792). Thus, left–right symmetry is maintained in both the sagittal and coronal planes (*Fig. 5, A–B*; *Fig. 6*).

Stratification of CCIs by Age Groups and Sex Differences

The CCIs for all 178 joints are plotted against the subjects' ages in *Figure 7*. There is a preponderance of younger subjects (less than 5 yr) owing to the selection criteria. Only 15 subjects were 8 years or older. Linear regression analysis shows no significant difference in CCIs between age groups (Pearson correlation coefficient = + 0.1009, with a 95% confidence interval of −0.05–0.24). Although the mean CCIs of the 15 children older than 8 years is 0.06 mm (or 4.7% of the mean total) greater than that for children younger than 8 years, the difference is not significant (P = 0.2137).

Linear regression correlation between CCI and age was also performed separately for the right and left OC_1 joints (*Fig. 8*). The two linear plots are essentially superimposable with

TABLE 1. Sagittal, coronal, and combined (actual) CCI from the right and left OC_1 joints in 89 children[a]

OC_1 joints	Sagittal CCI[b]	Coronal CCI[b]	Combined CCI[c] (mean of sagittal and coronal CCI)
Right (89)	1.333 mm ± .31 (SD)	1.180 mm ± .32 (SD)	1.28 mm ± .273 (SD)
Left (89)	1.327 mm ± .31 (SD)	1.166 mm ± .31 (SD)	1.27 mm ± .257 (SD)
Total (178)	1.33 mm ± .30 (SD)	1.17 mm ± .31 (SD)	1.28 mm ± .26 (SD)

[a] CCI, condyle–C_1 interval; OC_1, condyle–C1; SD, standard deviation.
[b] Sagittal and coronal CCIs are from the mean of four individual measurements from the respective plane.
[c] Combined CCIs are from the mean of both sagittal and coronal measurements, thus from the mean of eight individual measurements.

TABLE 2. Typical work sheet for a single subject showing relatively even joint spaces on the sagittal plane but wider medial than lateral gaps in the coronal plane[a,b]

Sagittal CT reconstruction: point measurements (mm)					
	1 (anterior)	2	3	4 (posterior)	χ (sagittal CCI)
Right	1.5	1.75	1.25	1.75	1.56
Left	1.75	1.50	1.25	1.75	1.56
Coronal CT reconstruction: point measurements (mm)					
	1 (medial)	2	3	4 (lateral)	χ (coronal CCI)
Right	2.0	1.50	1.0	0.5	1.26
Left	2.0	1.50	1.0	0.75	1.31

[a] CT, computed tomography; CCI, condyle–C_1 interval.
[b] Note left–right symmetry and larger sagittal than coronal CCI.
Right CCI = 1.41 mm
Left CCI = 1.44 mm Difference = 0.03 mm.
Right–left difference in sagittal CCI = 0.
Right–left difference in coronal CCI = 0.06 mm.
Difference between sagittal CCI and coronal CCI (right) = 0.31 mm.
Difference between sagittal CCI and coronal CCI (left) = 0.25 mm.



FIGURE 5. *Left–right symmetry in the sagittal plane at two different ages is shown.* **A**, *Similarities in both CCI and conformational anatomy between left and right OC_1 joints shown in a 4-year-old child.* **B**, *Same strong CCI and conformational left–right symmetry in a 12-year-old child as in the 4-year-old is shown.*



FIGURE 6. *Left–right symmetry in the coronal plane in a 4-year-old child is shown.*

nearly identical correlation coefficients (Pearson coefficients for the right side = +0.0926, and for the left side = +0.108). This describes closely related paired left and right values throughout the age range, suggesting that left–right symmetry is stable for age.

There were no significant differences between males and females in combined, sagittal, or coronal CCI.

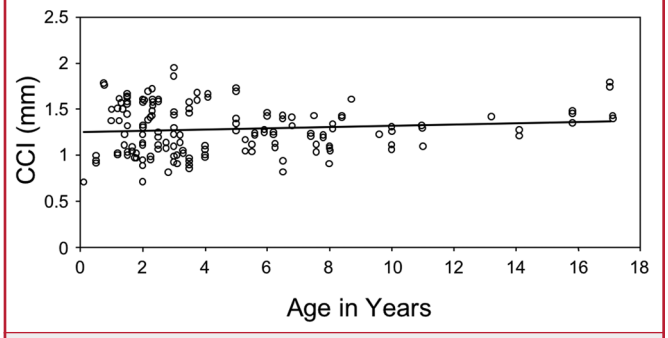


FIGURE 7. *"Combined" CCI of all (right and left) 178 joints were plotted against ages of subjects. Linear regression analysis showings no significant difference in CCIs between age groups. Pearson correlation coefficient = +0.1009 with a 95% confidence interval of −0.05 to 0.24 (P = 0.2137).*

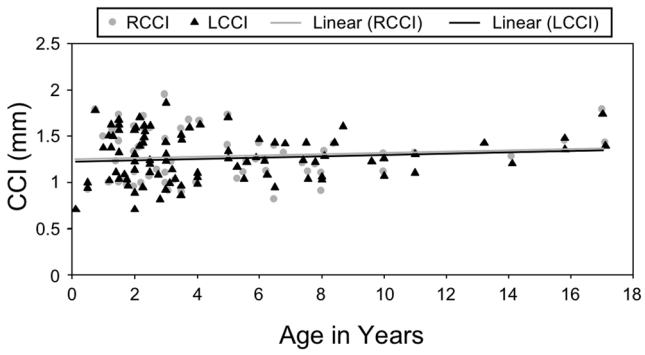


FIGURE 8. *Linear regression correlation between CCI and age was performed separately for the right and left OC_1 joints. The nearly superimposable right and left linear plots and almost identical Pearson coefficients (right = +0.0926; left = +0.108) suggest left–right symmetry is conserved through infancy to 18 years.*

DISCUSSION

The current method of assessing CCI has its roots in studies by Kaufman et al. (12, 13) who measured the occipital condyle–C_1 lateral mass separation on crosstable lateral cranium x-rays in 100 normal children. Compared against our more modern reformatted CT technique, the shortcomings of Kaufman's findings now seem quite obvious. Their visualization of the OC_1 joint on plain x-ray was often obscured by overlying structures such as ear lobes and the mastoid tip. Biometric evaluation of the joint, even when visualized, was further subject to errors related to head rotation, x-ray beam angles, target–film distance, and confusion between overlapping bony lines of paired joints superimposed on each other. It was thus not surprising that in the studies by Kaufman et al. (12, 13), measurements could not be made in 16% of the radiographs examined, and in only 60% were all five designated points on the joint seen well enough to be measured. Moreover, assessment of left–right symmetry and comparison between sagittal and coronal joint dimensions are not possible with the Kaufman method.

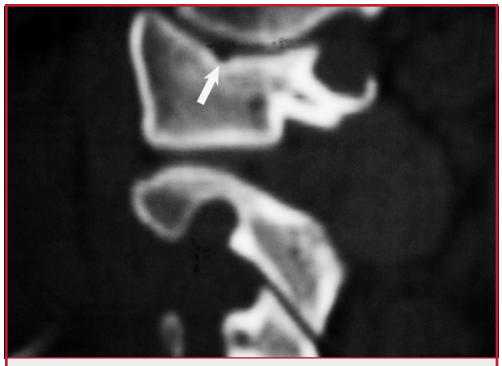


FIGURE 9. *A slight "crevice" on the C1 side of the OC_1 joint (arrow) in a 6-year-old child, probably related to ossification border zones.*

Our method with reformatted CT obviated all of the aforementioned weaknesses associated with plain x-rays. We encountered no situation in which interpretable reconstructions were not obtainable. The measurability of our designated points on both the sagittal and coronal images is 100%. With 2 mm or thinner axial CT slices, the reformatted images are sharp enough to withstand considerable magnification to facilitate measurement. The one small technical challenge for unfamiliar users is the choosing of the best reconstruction slice, as specified in the Materials and Methods section. By and large, the best slice is the one that displays the most joint surface. For sagittal computations, the corresponding slice on the other side is selected for left–right consistency.

Biplanar display shows that there is considerably more variability in the individual coronal measurements than in the sagittal measurements. In the coronal image, the medial one-third of the joint space tends to be twice or even three times as wide as the lateral part. The sagittal measurements tend to be more uniform in children older than 5 years, but in younger children, there is often a wedge-shaped crevice on the condyle side corresponding to the synchondrosis between the ossification centers from the basioccipital and exoccipital portions of the chondrocranium (16), termed synchondrosis intraoccipitalis anterior (24). This synchondrosis usually ossifies completely between 4 and 6 years of age, but it may remain partially cartilaginous until 10 to 12 years (*Fig. 4*) (16, 24). In infants and young children, this radiolucent site is situated just rostral to the midcoronal plane of the OC_1 joint, so some of the measurements in the anterior half of the sagittal image may be unusually wide in young subjects.

In two children, we also encountered a similar crevice on the C_1 side of the joint (*Fig. 9*), which may also be related to ossification border zones, but these are rarities and should not confound the clinical application of CCI.

Biometric analysis also showed that sagittal CCIs are consistently larger than coronal CCIs by an average of 12 to 13%. Because of this discrepancy and because of the variability of the

individual measurements, we chose to characterize the "true" CCI of each joint as the mean of all eight measurements from both the sagittal and coronal readings. This is in contrast to the Kaufman study in which only individual sagittal measurements were evaluated.

The mean combined CCI for all 178 joints was 1.28 mm. No individual joint had a CCI greater than 1.95 mm. Even with the higher sagittal readings, the mean sagittal CCI was 1.33 mm with no single value greater than 1.9 mm. In fact, no measurement among all 1424 data points was greater than 2.5 mm. Thus, the normal OC_1 joint is tightly held together by strong ligaments and it maintains a very narrow joint space within its physiological operating limits. Given the huge mass of the head and a correspondingly large angular moment, it is reasonable to expect that disruption of the OC_1 joint that results in atlanto-occipital instability should instantaneously lead to widening of the CCI and that this abnormal widening should not revert back to normal proximation with patient positioning. It is noted that our mean CCI and maximum individual measurement are approximately half of the values obtained in the studies by Kaufman et al. (12, 13) (mean and maximum joint intervals in the studies by Kaufman et al. are, respectively, 2.42 and 5 mm). We attribute this difference to the technical advantage of high-resolution CT scanning.

There is great left–right symmetry in the normal OC_1 joints not only in CCI in both the sagittal and coronal planes, but also in the conformation of the articular surfaces, best shown in the coronal reconstructed image. If there is a left–right discrepancy of greater than 20% of the mean CCI or a conformational mismatch suggesting one condyle has swung forward or backward in relation to the other OC_1 joint, pivoting, as it were, on the other side, pathological disruption of the paired atlanto-occipital articulation may be presumed.

The CCI seems to be fairly constant within the age range of 0.5 to 18 years. Given the uneven distribution of age in the series, this conclusion should theoretically be tentative, but with the considerable sample size of 178 joints and the very low correlative coefficient between CCI and age, we are confident that the normal CCI at any age up to 18 years should fall very close to the predicted mean of 1.28 mm, i.e., well below 4 mm. (Even with two standard deviations, the gap should be less than 1.8 mm.) The slightly larger CCI in children older than 8 years may be related to tissue thickness. It should be remembered that the measured joint interval is really the combined thickness of two articular cartilages and whatever joint space in between. Older children may well have more robust articular cartilage and not necessarily a laxer joint. Judging from the almost superimposable linear regression lines of the right and left CCI against age, implying nearly identical left and right paired values throughout the age range, it may also be concluded that left–right symmetry in CCI is conserved from infancy through age 18 years.

The major drawback of this study is that it contains only static and not dynamic data. We do not know what the CCI would be under "normal" stresses such as nondisruptive distraction. This is particularly germane in very young children whose ligaments and muscles are known to be elastic and yielding. The few known stress-induced "normal" changes in measurements in the upper cervical spine of young children include the atlantal-dens interval, which could increase from 2 to 4 mm (4, 6, 8, 22) and the posterior vertebral body alignment at C_2/C_3, which could widen from 1.5 to 3.5 mm with forced flexion in "pseudosubluxation" (6, 19, 21, 22, 25). Keeping to this approximate range of variability, and considering the largest single CCI obtained in the entire group is 1.95 mm, we set a discriminator of 4 mm between normal and AOD. This number is approximately 10 standard deviations from the mean normal "unstressed" value and so is also unlikely to underrepresent the maximum limit of normal "stressed CCI," whatever that may turn out to be. Part II of this study will deal specifically with the diagnostic sensitivity and specificity of this chosen discriminator in the clinical setting of patients with AOD.

CONCLUSION

The normal occipital condyle–C_1 joint in children is tightly held together by strong ligaments with a condyle–C_1 interval of less than 2 mm measurable on high-resolution CT images. There is strong left–right symmetry in both the condyle–C_1 interval and in the conformation of the joint. There is no significant change in the condyle–C_1 interval or left–right symmetry with age between birth and 18 years.

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COMMENTS

Pang et al. extensively studied the occipital-C_1 condyle joint in 89 normal children. They found that the normal occipital-condyle-C_1 joint in children is tightly apposed. The normal interval between these two structures was less than 2 mm on high-resolution computed tomographic (CT) scans. There was a strong left-right symmetry in both the condyle-C_1 interval and in the configuration of the C_1–C_2 joint. Surprisingly, there was no significant change in the condyle-C_1 interval or left-right symmetry between birth and the age of 18 years. These are all interesting findings and will help clinicians to detect an abnormal occipital-condyle C_1 dislocation.

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This is a very detailed analysis of high resolution CT reconstructions of the occipital cervical joint in children scanned for trivial trauma or non-traumatic concerns. The authors propose normal parameters for the occipital-C_1 joint that could be used to determine instability in subtle cases. The method used is easy to apply and seems robust. The usual wisdom is that atlanto-occipital dislocation is a fatal disease, and few of these patients are salvageable. For this normative data to be clinically useful, there must be a subset of patients with subtle clinical and radiographic findings in whom reduction and fusion are beneficial and in whom an abnormal joint discovered by CT scans would be clinically relevant. I have personally not seen such a patient. We tend to use magnetic resonance imaging to "clear the spine" in trauma patients, and the relative usefulness of CT versus magnetic resonance imaging in this setting also remains to be defined. One wonders what the clinical relevance of an increased occipital-C_1 separation on static images is without instability on dynamic images. I await the authors' future work in which this normative data is shown to be clinically useful.

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A Shoal of Sperm Whale off the Island of Hawaii (1833), aquatint, paper, Cornelius B. Holsart, Thomas Birch, and J. Hill. (Courtesy of New Bedford Whaling Museum). *From*: Matthews, LH: *The Whale*. New York, Simon & Schuster, 1968.

NONOPERATIVE MANAGEMENT OF ODONTOID FRACTURES USING A HALOTHORACIC VEST

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OBJECTIVE: Despite various reports in the literature, the appropriate treatment of Type II odontoid fractures remains controversial. Although there is an increasing tendency toward surgical treatment of these fractures in recent years, nonoperative treatment strategies are still regarded as a practicable method, particularly in elderly patients with significant comorbidities. One purpose of this study was to determine the functional and radiographic long-term results after rigid immobilization of Type II odontoid fractures using a halothoracic vest. The second aim was to present a case-control series of patients with nonunion of Type II odontoid fractures compared with patients with successful fracture healing to determine specific risk factors for failure of halo immobilization.

METHODS: We reviewed the clinical and radiographic records of 90 patients with an average age of 69 years at the time of injury who had undergone nonoperative treatment of odontoid fractures using a halothoracic vest between 1988 and 2004. To identify potential risk factors for failure of halo fixation, patients were divided into "cases" and "controls." Cases were defined as patients with nonfusion after halo immobilization, and controls were patients with successful fracture healing attained with this treatment option.

RESULTS: Seventy-five patients returned to their preinjury activity level and were satisfied with their treatment. The Smiley-Webster scale showed an overall functional outcome score of 1.64. Successful fracture healing was achieved in 76 patients (84%). In 14 patients, nonunion was diagnosed by standard x-rays and additional computed tomographic scans within 6 to 12 months after trauma. Referring to possible risk factors for failure of halo fixation, nonunion was found significantly more often in older patients and in those with displaced fractures of the odontoid. Secondary loss of reduction and delay of treatment were identified as further risk factors for nonfusion.

CONCLUSION: With regard to successful fracture healing and functional results of the patients, we had a satisfactory outcome after halo fixation of Type II odontoid fractures. Although a fusion rate of 84% should not be deemed as optimal, nonoperative management of these fractures using a halothoracic vest seems to be an appropriate treatment strategy in patients who are not suitable for surgical treatment.

KEY WORDS: Halo vest treatment, Odontoid fractures, Outcome, Risk factors for failure

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The appropriate treatment of Type II odontoid fractures has been the subject of many investigations but still remains a matter of debate (19, 21, 26, 33, 35). In the recent literature, there seems to be an increasing tendency toward primary surgical stabilization of these fractures because the technique of direct anterior screw fixation has shown encouraging results with high fusion rates and a good outcome on cervical function (1, 5, 11, 12, 25). Nevertheless, there are several studies that argue against primary surgical treatment of odontoid fractures, particularly in elderly patients with enhanced anesthesiological risk and diminished bone quality (3, 15, 30, 32). In this subset of patients, external immobilization by a halo vest or a rigid cervical collar has been reported to be a preferable approach for the management of these fractures (3, 23, 32). At our department, patients with Type II odontoid fractures according to the classification of Anderson and D'Alonzo

usually undergo primary surgical treatment by anterior screw fixation, irrespective of their age (2). Nonoperative management by a halothoracic vest is indicated if patients show an unacceptably high presurgical anesthesiological risk or are not willing to undergo surgical procedures.

There were two major goals in this study. One aim was to determine the functional and radiographic long-term results in patients who had undergone nonoperative treatment of Type II odontoid fractures at this Level I trauma center. We retrospectively analyzed the outcome after rigid immobilization of these fractures by using a halothoracic vest with particular regard to bony fusion, cervical spine motion, and treatment-related complications. The second purpose of this study was to present a case-control series of patients with nonunion of Type II odontoid fractures compared with patients with successful fracture healing after halo immobilization to determine specific risk factors for failure of this treatment option.

PATIENTS AND METHODS

This study reviewed the clinical records and trauma database of Vienna General Hospital, Medical University of Vienna and identified all patients with fractures of the odontoid (n = 265) who were admitted to this Level I trauma center between 1988 and 2004. The trauma database of Vienna General Hospital is a prospectively gathering database that was established for registration of injury characteristics (type, mechanism, etc.) and demographic data of trauma patients.

Eligibility Criteria

Patients who had undergone nonoperative treatment of Type II odontoid fractures by using a halothoracic vest were sorted and their data set of follow-up monitoring was examined for completeness and accuracy. According to our inclusion criteria, patients with complete sets of collected data and a follow-up period of at least 2 years after trauma were enrolled in this study. Collected data included variables such as age, sex, mechanism of injury, fracture type, presence of neurological deficits, associated injuries, preexisting systemic disease that may affect bone healing, and clinical and radiographic outcome after nonoperative treatment. The exclusion criteria for this study were patients with Type III odontoid fractures, incomplete data sets, or penetrating mechanism of injury or congenital cervical spine anomalies. An incomplete data set was determined if pertinent clinical or radiographic follow-up data (e.g., documents of clinical findings or functional results, x-rays, computed tomographic [CT] scans, etc.) were missing.

Clinical and Radiographic Examination

For analysis of the clinical and radiographic long-term results as well as the morbidity and mortality rate after nonoperative management of odontoid fractures, all follow-up data were meticulously reviewed for each patient. Follow-up data included accurate clinical and radiographic examination of the patients before discharge and at 6, 12, and 24 weeks after trauma. Further regular examinations were performed at 12 and 24 months after injury. All patients were monitored for a period of at least 2 years.

Radiographic assessment consisted of a three-view cervical spine series (anteroposterior, lateral, and open-mouth) at each follow-up visit. Additional flexion/extension views were performed at 3 and 12 months after trauma. Bony fusion was defined by evidence of bony trabeculae crossing the fracture site, absence of motion on functional flexion/extension views, and absence of sclerotic borders adjacent to the fracture site. Fine-cut CT scans with helical reconstruction were routinely obtained during the primary assessment of the patients and 6 to 12 months after trauma if the adequacy of bony fusion could not be determined on the standard x-rays.

TABLE 1. Smiley-Webster scale for assessment of functional results

Score	Description
I) Excellent	Patient returned to full-time work/activity like before onset of symptoms; no pain medication required
II) Good	Patient returned to full-time work/activity; occasional consumption of pain medication
III) Fair	Patient not able to return to former level of work/activity; occasional pain medication; improved over preoperative status
IV) Poor	Patient not able to return to work/former activity level; regular consumption of pain medication

For clinical examination, range of motion, local pain, and activities of daily living were routinely assessed. To quantify the clinical results, the patients were asked to grade their functional outcome according to the Smiley-Webster scale as excellent, good, fair, or poor (see *Table 1*). For evaluation of neurological function, patients were assessed by a neurological consultant, and American Spinal Injury Association (ASIA) grades were provided to quantify the severity of neurological deficits.

Treatment Protocol

According to the institution's treatment protocol, nonoperative management of Type II odontoid fractures was performed in patients with considerably enhanced anesthesiological risk (American Society of Anesthesiologists Grades 3, 4, and 5) as a result of other severe injuries or preexisting systemic disease and in patients who declined to undergo surgery. Standard nonoperative treatment involved external immobilization of these fractures by using a halothoracic vest for 8 to 12 weeks. In cases of uncertain fracture healing after that time period, immobilization was continued by a cervical collar for an additional 4 weeks.

During application of the halo ring and jacket, patients usually remained awake to enable them to report sensations and pain in the extremities. If necessary, the fractures were reduced by longitudinal traction of the head using an image intensifier control. Four halo pins (two frontal, two temporal) were inserted under local anesthesia into the lamina externa of the cranium, and the halo ring was attached and finally connected to the jacket by using compounding rods.

Analysis of Data

To identify potential risk factors for failure of halo vest treatment, patients were divided into "cases" and "controls." Cases were defined as patients with nonfusion after halo immobilization, and controls were patients with successful fracture healing attained with this treatment option.

In a univariate analysis, "cases" and "controls" were compared using Student's t test for quantitative data and χ^2 analysis for qualitative data. Statistical significance was defined as a P value of less than 0.05. We also performed a multivariate analysis using logistic regression and odds ratio to determine relative risk for nonfusion. The covariates that were analyzed included age, sex, mechanism of injury, frac-

ture type, initial fracture displacement, secondary loss of reduction, beginning of treatment, presence of neurological deficits, associated injuries, and preexisting systemic disease.

RESULTS

From a database of 251 trauma victims with fractures of the odontoid, an analysis of clinical records revealed that we had 102 patients (41%) who underwent nonoperative treatment of their odontoid fractures by using a halothoracic vest. Twelve of these patients were not considered for analysis of clinical and radiographic results because they had sustained Type III odontoid fractures (n = 7) or because relevant follow-up data were missing (n = 5; four patients died during the follow-up period and one patient was lost to follow-up because he refused to come to further examinations). The remaining 90 patients (48 women and 42 men), with an average age of 69 years (range, 32–91 yr) at the time of injury, met the criteria for inclusion and were enrolled in this series.

Mechanism of Injury, Fracture Types, and Initial Displacement

Clinical records showed several mechanisms of injury. The injuries resulted from motor vehicle accidents in 36% (n = 32) of the patients, falls that were of low energy (e.g., falls from a standing position, falls from a chair, etc.) in 23% (n = 21) of the patients, falls from a considerable height or down stairs in 22% (n = 20) of the patients, sports-related injuries (climbing, diving) in 16% (n = 14) of the patients, and from other causes in 3% (n = 3) of the patients.

Fractures were classified based on the classification systems described by Anderson and D'Alonzo (2) and Roy-Camille et al. (29). According to the classification of Anderson and D'Alonzo, all patients had sustained odontoid fractures of Type II. Using the classification scheme of Roy-Camille et al., there were 52 patients with horizontal fractures, 17 patients with anterior oblique fractures, and 21 patients with posterior oblique fracture lines.

Initial displacement of the odontoid was measured on a cervical CT scan, which was obtained routinely during the primary examination. Sixty-three patients with nondisplaced or slightly displaced (less than 2 mm) fractures of the odontoid were identified, whereas there was a significant displacement on the initial CT scan in 27 patients. The average displacement for all odontoid fractures was 2.4 mm (range, 0–8 mm).

Associated Injuries, Neurological Deficits, and Preexisting Systemic Diseases

Significant associated injuries were noted in 34 patients, whereas 56 patients had isolated injuries of the odontoid process. Three patients had an associated injury at the cervical spine. Two cases involved nondisplaced fractures of the anterior ring of the atlas, and the third patient had a slightly displaced fracture of C3. Fifteen patients showed evidence of a severe head injury; seven patients had signs of a severe thoracic, abdominal, or pelvic trauma; five patients had significant injuries of the limbs; and four patients sustained a combination of multiple severe injuries. The average Injury Severity Score for patients with odontoid fractures and significant concomitant injuries in this study was 29 points. None of these patients had an Injury Severity Score greater than 45. Nineteen patients underwent one or more surgical procedures as a result of their concomitant injuries.

Neurological deficits related to the odontoid fracture were found in nine patients. One patient showed motor deficits, three patients incurred sensory deficits, and five patients had motor and sensory deficits. ASIA grades were provided to quantify the severity of the spinal cord injury and the impairment of neurological function; the deficits were graded as ASIA D in seven patients and as ASIA C in two patients (10).

Relating to preexisting systemic diseases and risk factors that may influence bone healing (e.g., diabetes mellitus, rheumatoid arthritis, or renal insufficiency), we had 68 patients with significant contributory medical conditions (see *Table 2*). The average American Society of Anesthesiologists score, which was determined to evaluate anesthesiological risk, was 3.7 in this series (29).

Treatment Analysis

Reduction, if required, and immobilization were obtained within 24 hours of the injury in 59 patients, within 3 days in 19 patients, and within 1 week in 10 patients. Two patients presented with older injuries of the odontoid process, 19 days after trauma in one case and 27 days in the other. Both patients were admitted to the hospital because of increasing neck pain after low-energy trauma.

TABLE 2. Preexisting systemic diseases and contributory medical conditions

Preexisting systemic diseases/ contributory medical conditions	No. of patients (n = 68)
General risk factors	
Cardiac diseases	6
Pulmonary diseases	8
Infections	1
Tumor diseases	2
Sever adipositas	7
Other	3
Risk factors for nonunion	
Renal diseases/insufficiency	3
Diabetes mellitus	9
Rheumatoid arthritis	7
Thyroid disorders	1
Cushing disease/corticoid therapy	4
Osteoporosis	6
Chronic tobacco use and alcohol consumption	11
Other	0

Reduction of displaced fractures using longitudinal traction of the cranium was performed in 11 patients for a mean duration of 4 days (range, 1–6 d). Halo vest treatment was accomplished for a mean duration of 74 days (range, 56–122 d). In 17 patients, immobilization was continued by a cervical collar (stiff neck) for a mean duration of 15 days (range, 7–28 d).

Radiographic Results

An analysis of radiographic results revealed that successful fracture healing was achieved in 76 patients (84%). In 14 patients (16%), adequate bony fusion could not be determined on standard x-rays and nonunion was diagnosed by cervical CT scan between 6 and 12 months after trauma. Five of these patients underwent surgical treatment because they had severe motion pain at the upper cervical spine or because the pseudarthrosis was clinically unstable. All of them were stabilized by posterior fusion with transarticular C1–C2 screws and bone grafting after a mean period of 32 weeks after trauma. In the remaining nine patients with nonunion, no surgical interventions were found to be necessary because the patients were free of symptoms and did not show any relevant residual instability at the cervical spine.

Failures of reduction were noted in 11 patients (12%). In four cases, we failed to achieve correct anatomic reduction of the odontoid, and in seven patients, we noted a secondary loss of reduction within 4 to 19 days after halo fixation. The odontoid fragment was left in slight posterior displacement in four patients and in anterior displacement in one patient. Two patients had laterally displaced fragments and the odontoid was overcorrected and distracted in four cases. In eight of these patients, the fractures healed uneventfully, whereas in six others, the adequacy of bony fusion could not be determined within 6 to 12 months.

Clinical Results

An analysis of the clinical follow-up data showed that 75 (83%) patients had returned to their preinjury activity level 1 year after trauma and were fully satisfied with their treatment. Fifteen patients (17%) reported certain limitations in daily living, occasional or chronic pain symptoms, and a decrease of cervical spine motion. Using the Smiley-Webster scale to quantify the clinical outcome of the patients by grading their results from excellent (= 1) to poor (= 4), we had an overall functional outcome score of 1.64. Clinical characteristics, including range of cervical spine movement, presence and severity of pain, and activities of daily living, are presented in *Table 3*.

Neurological deficits after the removal of the halothoracic vest were evaluated in five patients (5%). One patient showed motor deficits, two patients had sensory deficits, and two additional patients incurred motor and sensory deficits. The deficits were graded as ASIA D in four patients and ASIA C in one patient. In four of these five patients, we saw a complete recovery of neurological function after rehabilitation and incomplete resolution of neurological deficits in one patient. All other patients with neurological deficits during the primary examination recovered fully during halo immobilization.

TABLE 3. Clinical characteristics

Characteristic	No. of patients (n = 90)
Activities of daily living	
No impairments	75
Limitations in certain sport activities/professions	14
Limitations in (nearly) all activities	1
Cervical spine motion	
Full range of movement	79
Movement restriction >30%	10
Movement restriction >50%	1
Pain	
Presence of pain	
No pain	79
Occasional pain	8
Regular pain	3
Severity of pain	
Mild symptoms	9
Severe symptoms	2

Morbidity and Mortality

To determine morbidity and mortality rates during halo immobilization, we also included the five patients who were excluded from analysis of clinical and radiographic results. General and treatment-related complications occurred in 16 of the 95 patients, resulting in an overall morbidity rate of 17% (see *Table 4*). Eighteen patients required intensive care treatment, 16 of them as a result of significant associated injuries and two patients after profound deterioration of their general state of health. The average length of time spent in the intensive care unit was 22.8 days.

Four patients died during halo vest treatment, resulting in an overall mortality rate of 4% (see *Table 4*). Three of these patients showed severe concomitant injuries, and one patient had an isolated injury of the odontoid process. Regarding the causes of death, two patients died as a result of cardiac arrest, one patient developed severe pneumonia with respiratory insufficiency, and another patient died of pulmonary embolism. The deaths occurred between 12 and 50 days after beginning treatment.

Comparison of "Cases" and "Controls"

When cases (n = 14) and controls (n = 76) were compared using univariate analysis, statistical results revealed that the age of the patients and initial fracture displacement had a significant influence on the outcome. Patients with successful fracture healing were significantly younger than patients with inadequate bony fusion (cases, 77.2 yr; controls, 60.8 years; $P < 0.05$), and nonunion was found significantly more often in patients with an initial fracture displacement of more than 2 mm (cases, 11 out of 14 [79%]; controls, 16 out of 76 [21%];

TABLE 4. General and specific complications after halo immobilization

Complication	No. of patients
General complications	
Cardiac failure	2
Respiratory failure	1
Pneumonia	1
Severe infections	0
Thromboembolism	1
Treatment-related complications	
Nonunion	14
No or incorrect reduction	2
Secondary loss of reduction	3
Pin site infections	1
Loosening/dislodging of the pins	2
Pressure sores of the vest	2
Late pain/prolonged stiffness	1
Deaths	4

$P < 0.05$). All the other variables did not show significant differences in univariate analysis (see *Table 5*).

The results of logistic regression and odds ratio showed that two other variables may have influenced the outcome of fracture healing in this series. Secondary loss of reduction and beginning treatment 3 days after trauma or later were identified as further risk factors besides advanced age and fracture displacement. Combining two of these covariates, we had an enhanced risk for inadequate bony fusion of 57%. With three of these covariates, the risk increased to 70.2%. With all four covariates, the risk was 81.4%. The combination of other covariates failed to reach statistical significance, predicting fewer than 50% of the outcomes (union or nonunion) correctly (see *Table 5*).

DISCUSSION

A review of the literature shows that the best treatment strategy for Type II odontoid fractures remains controversial (19–22, 26, 34, 37). Although Type I and III fractures are treated well using nonoperative methods, different opinions have been advanced regarding the management of Type II fractures (7, 8, 27, 37). In recent years, there has been an increasing tendency toward primary surgical treatment of these injuries (1, 5, 11, 12, 25). Because the technique of direct anterior screw fixation has shown encouraging results with high fusion rates and a good outcome on cervical spine function, it seems to be preferred both by surgeons and patients (4, 6).

Nevertheless, nonoperative treatment strategies are still regarded as a practical method for management of Type II odontoid fractures (3, 15, 30, 32). Several authors propose rigid immobilization by a halothoracic vest as a preferable treatment option for these fractures, particularly in patients with significant comorbidities (3, 22, 23, 31). They have presented similar long-term results referring to bony fusion and functional outcome and lower rates of morbidity and mortality compared with operative treatment (3, 20, 33, 35). Other authors have suggested nonrigid immobilization of Type II odontoid fractures using a cervical collar (26, 34). In stable fracture types, they have also shown acceptable fusion rates demonstrating no remarkable differences in fracture healing and late instability between rigid and nonrigid fixation (26, 34).

At our department, patients with Type II odontoid fractures usually undergo primary surgical treatment by anterior screw fixation, irrespective of their age. However, in nearly half of the cases (41%), we had to attain nonoperative management of these fractures using a halothoracic vest because surgical treatment was not feasible. Considerably enhanced presurgical risk or the unwillingness of the patients to undergo surgery convinced us to abstain from operative treatment. This fact and the lack of profound scientific information in the literature have encouraged us to analyze the clinical and radiographic outcome after rigid immobilization of these fractures at our unit.

Based on supporting data in the literature, successful fracture healing of Type II odontoid fractures after halo fixation varies to a great extent (19, 21, 26, 34, 35). Several authors have achieved acceptable fusion rates, ranging from 70 to 90%, whereas others have experienced a noticeably worse outcome and presented union rates of less than 50% (18, 21, 34, 35). These considerable variations in fracture healing might be attributed to different inclusion criteria and inhomogeneous groups of patients, biasing the results toward higher or lower success rates (19). Vieweg and Schultheiss (35) summarized a series of reliable articles describing experiences with halo vest treatment of Type II odontoid fractures and revealed a combined fusion rate of 85%. A further review of relevant literature by Julien et al. (18) showed an average union rate of 70%. In our series, we had an overall fusion rate of 84%, underscoring that an acceptable success rate of fracture healing can be achieved using rigid immobilization by a halothoracic vest. Consistent with current data in the literature, our results also demonstrated that nonunion was not obligatorily equivalent to a bad result (26, 31). In more than half of the patients without solid bony fusion, halo fixation resulted in some degree of fibrous union, requiring no surgical interventions because the patients were free of symptoms and did not show any residual instability at the cervical spine.

Relating to successful fracture healing, a number of reports have enumerated potential risk factors for nonunion of odontoid fractures (8, 19, 21, 26, 30, 31, 33, 35). Factors such as age of the patients, degree and direction of fracture displacement, delay in treatment, and presence of neurological deficits have been reported to influence the outcome of bony fusion. Several authors have considered increased age as the most relevant risk factor for nonfusion (21, 27, 30, 31). Lennarson et al. (21), for example, analyzed a series of patients with Type II odontoid fractures and ascertained that patients aged 50 years or older were 21 times more disposed to failure of halo immobilization than patients younger than 50 years of age. Other

TABLE 5. Statistical analysis comparing cases and controls

Risk factor	Group		Statistical analysis	
	Cases (n = 14)	Controls (n = 76)	Univariate analysis significant	Multivariate analysis influence
Age, sex, and injury-related factors				
Age			Yes	Yes
Younger than 65 yr	4	43		
Older than 65 yr	10	33		
Sex			No	No
Female	8	40		
Male	6	36		
Mechanism of injury			No	No
Low-energy trauma	3	16		
High-energy trauma	11	60		
Fracture displacement			Yes	Yes
No or slight displacement	6	57		
Displaceemnt > 2 mm	8	19		
Fracture			No	No
Anterior oblique	3	14		
Posterior oblique	3	18		
Fracture type			No	No
Horizontal	8	42		
Other	0	2		
Associated injuries	5	29	No	No
Neurological deficit	1	8	No	No
Systemic diseases/medical conditions				
Renal diseases/insufficiency	0	3	No	No
Diabetes mellitus	1	8	No	No
Rheumatoid arthritis	0	7	No	No
Thyroid disorders	0	1	No	No
Cushing disease/corticoid therapy	0	4	No	No
Osteoporosis	1	6	No	No
Chronic tobacco use/alcohol consumption	2	9	No	No
Treatment-related factors				
No or incorrect reduction	0	2	No	No
Secondary loss of reduction	1	2	Yes (?)	Yes
Delay in treatment (>3 d)	2	10	No	Yes

reports have highlighted the importance of fracture displacement on the healing rate (8, 19, 31). A fracture gap of more than 5 mm as well as displacement to posterior have been presented as further determining risk factors for nonunion of Type II odontoid fractures after halo immobilization (8, 15, 16, 19). Koivikko et al. (19) have stated that union probably fails to occur in these cases as a result of insufficient bony contact of the fragments, compromised blood supply, or because posterior displacement reflects more extensive ligamentous injuries. In our series, inadequate bony fusion correlated with increased age of the patients and initial fracture displacement, confirming the results of previous studies in the literature. Patients with pseudarthrosis were significantly older than those with successful fracture healing, and nonunion was found significantly more often in patients with displaced fractures of the odontoid. A delay in treatment of more than 3 days as well as secondary loss of reduction might also influence the outcome of fracture healing because the combination of these factors additionally enhanced the risk for failure of halo immobilization in our study.

A further controversial issue of halo vest treatment is the clinical outcome of the patients after rigid fixation of the cervical spine for several weeks. A number of authors argue against halo immobilization because they have observed a high incidence of treatment-related complications and decreased ranges of movement (13, 17, 24). Pin site infections, loosening or dislodging of the screws leading to secondary loss of reduction, pressure sores of the vest, and late pain and prolonged stiffness at the cervical spine level are well-known clinical findings after halo fixation, particularly in elderly patients (9, 20, 35). However, other series have presented lower rates of these complications and functional long-term results that are comparable to those after surgical treatment (7, 14, 35). Buchholz and Cheung (7) and Glaser et al. (14) have reported on a morbidity rate of less than 5%, evaluating the incidence of complications associated with halo vest treatment in their series. In our study, we had good functional results after halo fixation but a relatively high rate of general and treatment-related complications. The overall morbidity rate of 17% in our series might be attributed to the fact that most of the patients (76%) had preexisting systemic diseases or severe associated injuries leading to a higher risk for subsequent illness. Despite the increased incidence of complications during halo immobilization, most of the patients (83%) returned to their preinjury activity level 1 year after trauma and were free of pain symptoms. According to the Smiley-Webster scale, the vast majority of the patients even graded their outcome as "excellent" to "good," indicating satisfactory clinical results after halo vest treatment.

CONCLUSION

With regard to successful fracture healing and functional results of the patients, we observed a satisfactory outcome after halo fixation of Type II odontoid fractures. Although a fusion rate of 84% and a complication rate of 17% should not be deemed as optimal, nonoperative management of these fractures using a halothoracic vest seems to be an appropriate treatment strategy in patients who cannot tolerate or refuse to undergo surgical procedures. With increasing experience, well-coordinated follow-up care, and exclusion of unsuitable patients (e.g., those with increased fracture displacement, delay in treatment, or secondary loss of reduction), a further improvement of the outcome should be achievable.

Although this study does not add substantially new information for the treatment of Type II odontoid fractures, several important aspects for halo vest treatment of these fractures are still given. No other authors have presented reliable long-term results after halo fixation in a subset of patients with a considerably decreased state of health, and no other series have shown a more detailed documentation of functional results for a follow-up period of 2 years. We may be criticized for potential weaknesses linked to a retrospective design but because this series contains patients from a prospectively gathered database with previously determined exclusion criteria and because Class I and Class II data are very scarce in the current literature, a thoroughly important and meaningful contribution for clinical science in the spine literature can be given.

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COMMENTS

Platzer et al. performed a case-control study examining 90 patients who had undergone nonoperative treatment for odontoid fractures. They report a successful fracture healing rate of 84%. Patients were followed for 20 months, and non-unions were diagnosed with standard x-rays and additional computed tomographic scans. Because computed tomographic scans were not obtained on every patient, the nonunion rate may be slightly underreported. Failure to heal with halo fixation was noted to occur significantly more often in elderly patients and those with displaced fractures. Significant displacement was defined as greater than 2 mm. This determination was made using a computed tomographic scan at the time of primary evaluation.

This study provides further evidence that elderly patients with Type II odontoid fractures do not fare well with nonoperative management. Displacement is a difficult issue. Throughout the literature, displacement has been defined vaguely. Many reports discuss displacement, but the reader is left wondering whether the displacement refers to maximal displacement, displacement on the first x-ray obtained, displacement on the first x-ray obtained at the treating institution, etc. The authors are to be commended for clearly defining displacement in their work. The standard set here may be useful if applied to future series.

The morbidity in treating odontoid fractures surgically, even in elderly patients, is rather small. I do take some issue with the fact that, out of the 14 patients who did not heal with halo immobilization, the authors chose to manage only five of these with surgical intervention. It could be argued that all 14 should be treated with surgery. Unless there are extremely unusual circumstances, these patients would be expected to fare well.

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The authors provide us with a refreshing revisitation of bracing for Type II odontoid fractures. They are absolutely correct in stating that the treatment remains controversial, a point that may not be obvious from a recent perusal of the peer-reviewed literature, which has focused predominantly on contemporary methods for atlas and axis fixation. Although the 84% arthrodesis rate could be viewed as either high or low depending on the reader's perspective, it is important to note that the study group (41% of candidate patients) was a selected population (high American Society of Anesthesiologists risk, preexisting injury, systemic illness, and patient self-selection). In addition, of the five medical complications, at least four may have been just as likely with surgical treatment (cardiac failure, respiratory failure, and pneumonia). One of the take home points seems to be that halo fixation should always attempt to achieve and maintain fracture realignment. To accomplish this, the authors utilized traction liberally before vest fixation, a practice that is less and less common in the United States.

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The authors provide us a retrospective description of their experience with the treatment of Type II odontoid fractures with halo immobilization. Overall, the results were quite good, especially considering that the patients selected for this treatment were older and had a significant incidence of medical comorbidities. The findings that advanced age and displacement of the fracture fragments lead to poor fusion rates are neither novel nor surprising. Overall, I believe the study provides evidence that halo vest immobilization is an acceptable treatment option for Type II odontoid fractures and should be considered along with screw fixation and collar immobilization as an alternative based on medical comorbidity, age, fracture anatomy, and patient preference.

Daniel K. Resnick
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Platzer et al. present a retrospective review of their results of halo brace management among 90 patients with Type 2 odontoid fractures who were too high risk for acute surgical treatment. The results of halo management were acceptable in the majority of patients. Eighty-four percent of patients (n=76) developed an osseous union. Among the 16% (n = 14) of patients who had nonunions, five patients had atlantoaxial instability which required surgical treatment, whereas nine patients had painless stable pseudoarthrosis, also referred to as fibrous unions.

The radiographic success rate of stable healing of the fractures was actually 94% (76 osseous unions plus nine fibrous unions). This very high success rate of halo brace treatment is notable. Naturally, there were complications that occurred. The most significant ones were inability to reduce the fractures or to maintain alignment in the halo brace (12%). Patients with a malaligned odontoids are potentially at risk for nonunion or neurological sequelae. The authors did not observe any neurological deterioration among their patients during treatment. Four patients died and were excluded from the data analysis; however, their deaths were more likely the result of their injuries and medical comorbidities rather than the halo brace treatment per se.

This report confirmed the findings of other authors that advanced age and displacement of the dens more than 5 mm create a higher risk of nonunion with a halo brace. It would have been helpful if the authors also analyzed and presented the results of their patients who were treated surgically, with odontoid screw fixation or posterior C1–C2 fusion. It would be interesting to compare the complications and the outcomes in the two populations. Clinically, we do not yet have enough scientific data to create treatment standards or guidelines for the treatment of odontoid fractures. Treatment options include external bracing or internal fixation, depending on the patient's risk factors and the surgeon's skills and experience.

My treatment preferences for the treatment of Type 2 odontoid fractures are simple. I usually recommend a rigid cervical collar (Philadelphia type) in patients with nondisplaced fractures, as long as they can be compliant with wearing the brace and following up. I usually recommend a halo brace for patients with displaced fractures

(≤ 5 mm) or patients who are likely to be noncompliant with treatment. Surgical fixation is offered to patients who have widely displaced fractures (> 5 mm) with a high risk of nonunion or to patients who prefer surgical treatment as an alternative to wearing a halo brace. Surgically, I prefer to use odontoid screw fixation if the fracture can be anatomically realigned, the fracture is acute (< 8 wk old), and the bone is dense. I advocate posterior C1–C2 fusion or occipitocervical fusion in patients with severe osteoporosis, chronic fractures, nonunions, or unsuitable anatomy for an anterior odontoid screw.

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Logbook page of the whaler, *William Baker*, which sailed on July 11, 1838 and returned on April 19, 1839. The page describes sightings of whales on November 1838. The whaler returned with 180 barrels of sperm oil and 620 barrels of whale oil. (Courtesy of New Bedford Whaling Museum). *From*: Matthews, LH: *The Whale*. New York, Simon & Schuster, 1968.

SEGMENTAL POLYMETHYLMETHACRYLATE-AUGMENTED PEDICLE SCREW FIXATION IN PATIENTS WITH BONE SOFTENING CAUSED BY OSTEOPOROSIS AND METASTATIC TUMOR INVOLVEMENT: A CLINICAL EVALUATION

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OBJECTIVE: Instrumentation of the osteoporotic spine may result in bone failure because of pedicle screw loosening and pullout. A clinical evaluation of a novel fenestrated bone tap used in pedicle screw augmentation was performed to determine the performance and safety of this technique.

METHODS: Over a 2.5-year period, the clinical and radiographic results of 119 consecutive patients who underwent instrumented arthrodesis were reviewed. Of these patients, 23 had bone softening secondary to osteoporosis and/or metastatic spinal tumor involvement. These patients underwent surgical decompression and spinal instrumentation.

RESULTS: Six patients (26%) had metastatic spine disease (squamous cell lung carcinoma, renal cell carcinoma, bladder carcinoma, breast, prostate, and uterine adenocarcinoma); five patients (22%) had a degenerative spondylolisthesis; and 12 patients (52%) had burst fractures, eight as a result of benign causes and four as a result of metastatic disease. Four (17%) patients underwent revision surgery of previous pedicle screw failure resulting from bone softening and pseudarthrosis. A total of 98 levels were fused using 158 polymethylmethacrylate-augmented screws. None of the patients experienced operative death, myocardial infarction, hypoxemia, intraoperative hypotension, radiculopathy, or myelopathy. Asymptomatic anterior cement extravasation was observed in nine patients (39%). There was one asymptomatic polymethylmethacrylate pulmonary embolus and one wound infection. There was no significant relationship between cement extravasation and the quantity used, levels augmented, or location ($P > 0.05$). There were no construct failures.

CONCLUSION: Polymethylmethacrylate-augmented pedicle screw fixation reduces the likelihood of pedicle screw loosening and pullout in patients with osteoporosis requiring instrumented arthrodesis.

KEY WORDS: Metastasis, Osteoporosis, Pedicle screw augmentation, Polymethylmethacrylate, Spinal fracture

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In the United States, approximately 1.5 million fractures annually are attributable to osteoporosis with approximately 700,000 occurring in the spine (42). Because of our aging population, the frequency of osteoporotic fractures is increasing, necessitating improved preventative and surgical strategies.

Unstable spinal fractures occur in patients with bone softening secondary to osteoporosis and metastatic tumor involvement both with and without an inciting traumatic event. Spontaneous osteoporotic burst fractures are far less common than compression fractures, but they are well documented in the literature (3, 7, 27, 28, 31, 47). Resulting neurological deficits in patients with these fractures are extremely low with estimates approximating 0.05% (27, 28, 31, 47). The surgical treatment of patients with bone softening and spinal instability can be complicated. Although there are those who advocate minimally invasive percutaneous procedures such as vertebroplasty (32), this would be contraindicated in patients with mechanical and/or neurological instability. In these patients the ideal treatment would include surgical decompression of the neural elements followed by rigid spinal fixation. However, instrumenta-

tion of the osteoporotic spine may be fraught with complications (26). Osteoporosis has been implicated as a cause of hardware failure and more specifically pedicle screw loosening and pullout (19, 45). As such, a number of different techniques have been proposed to increase pedicle screw pullout strength, including the use of bicortical purchase (4), pedicle undertapping (19), offset laminar hooks (19), and pedicle screw-bone interface augmentation including the use of expandable pedicle screws (12), resorbable polymers (21), rib grafts (20), milled bone (37), matchstick bone (37), and bone cement (14, 20, 23, 29, 37, 44, 45, 50–52).

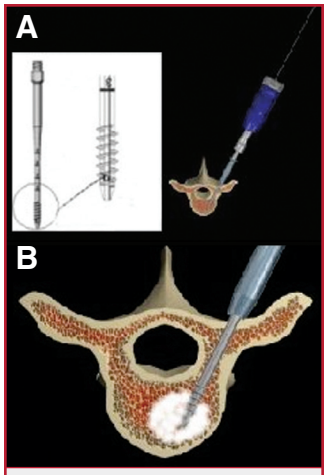


FIGURE 1. *Surgical technique for placement of the Pedestal (Abbott Spine, Austin, TX) fenestrated tap (**A**, inset) into a vertebral body (**A**), followed by cement injection (**B**).*

Recent advances in minimally invasive percutaneous vertebroplasty and balloon kyphoplasty procedures have improved surgical techniques and the ability to use bone cements such as polymethylmethacrylate (PMMA) more safely in this context. A number of laboratory studies in cadaver spines (20, 29, 44, 45, 51) and sawbones (14) have demonstrated significantly increased axial pullout force and transverse bending stiffness in bone cement-augmented pedicle screw fixation. Despite this, clinical reports of bone cement use in this capacity are sparse (11, 44, 50, 52). We describe the largest clinical series reported on this topic consisting of 23 patients with unstable spinal fractures and bone softening secondary to osteoporosis and/or metastatic disease. Screw augmentation procedures were performed using a novel and effective technique for cement delivery, a fenestrated bone tap system. In this device, tap threads serve a dual purpose in that they prevent backflow of cement toward neural elements while allowing for a custom form for subsequent screw placement.

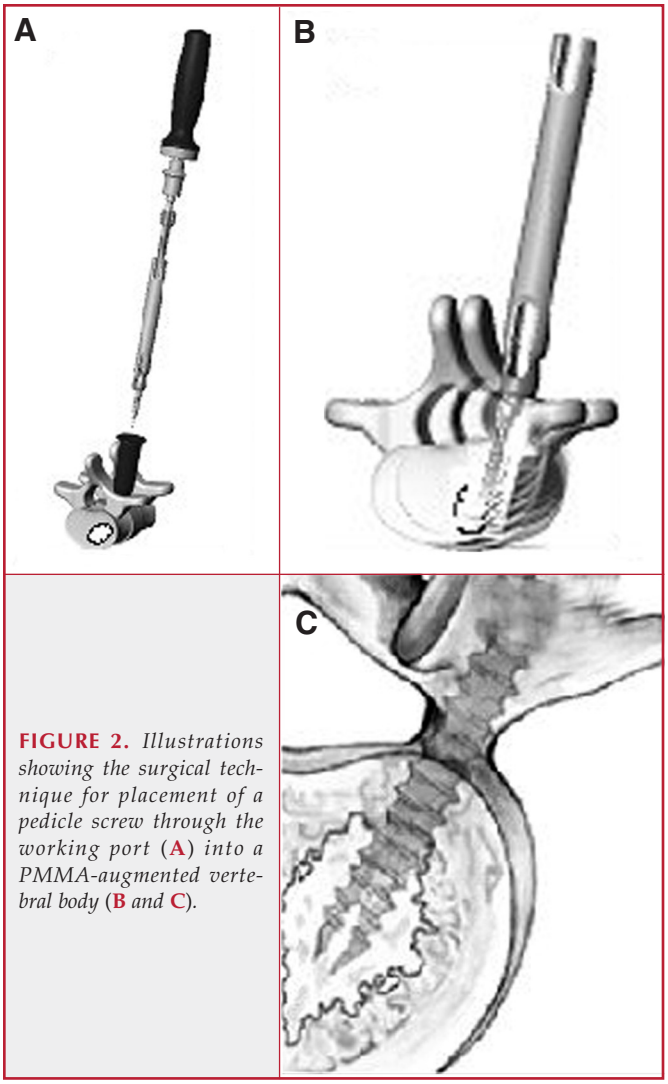


FIGURE 2. *Illustrations showing the surgical technique for placement of a pedicle screw through the working port (**A**) into a PMMA-augmented vertebral body (**B** and **C**).*

MATERIALS AND METHODS

Clinical Series

Over a 2.5-year period, the clinical and radiographic results of 119 consecutive patients who underwent instrumented arthrodesis were reviewed. Of these patients, 23 had bone softening secondary to osteoporosis and/or metastatic spinal tumor involvement. These patients underwent surgical decompression and spinal instrumentation by the senior author (BMF). In these 23 individuals, a total of 98 levels were fused and 177 pedicle screws were placed. Of the 177 screws placed, 158 were augmented with Simplex bone cement (Stryker Instruments, Kalamazoo, MI) using the Pedestal Fenestrated Tap System (Abbott Spine, Austin, TX). The decision to augment was made on the basis of a combination of preoperative radiographic findings and intraoperative tactile feel of resistance of the vertebral body to the pedicle probe.

The operative techniques performed in this series of 23 patients (*Figs. 1* and *2*) are briefly described. To decrease potential morbidity in this elderly patient population (mean age, 64.7 years), all approaches to the spine were posterior with the fewest number of segments exposed and instrumented. No thoracotomies or thoracoabdominal approaches were used. After exposure and decompression, pedicles were probed and the fenestrated tap was threaded into the anterior one-third of the vertebral body (*Fig. 1*) using fluoroscopic guidance (OEC Workstation; GE Healthcare, Barrington, IL). The smallest tap (4.5 mm) was used in the thoracic spine, and the largest tap (6.5 mm) was used in the lumbar spine. After insertion, the tap was flushed into the vertebral body with 3 to 5 mL of saline. Spineplex bone cement (Stryker Instruments) was mixed according to the manufacturer's recommendations. An average of 2.9 mL of cement was injected through the tap into the vertebral body using a 10-mL Luer-Lok syringe (BD, Franklin Lakes, NJ) and monitored during continuous lateral fluoroscopy (*Fig. 1*). The bone tap was left in place for approximately 1 minute to allow for partial cement

consolidation and then unscrewed from the vertebral body. This was followed by placement of pedicle screws into the curing cement within the vertebral bodies (*Fig. 2*). No difficulty was encountered in unthreading the tap from the vertebral body or threading the screws through the curing PMMA. All screws were cemented in short constructs spanning one or two segments. In longer constructs, screws were augmented at both ends and the center skipping intermediate levels to reduce the number of cemented levels and potential toxicity. As such, of the 177 screws placed, 158 were augmented.

After screw placement, decortication of the facet joints and posterolateral elements, including transverse processes, was performed. Local bone obtained from the decompression (except in metastatic cases) was stripped of its soft tissue, morselized, and added to a demineralized bone matrix-calcium sulfate-cancellous chip mixture (Allomatrix Custom Graft; Wright Medical Technology, Arlington, TN) reconstituted with iliac crest bone marrow aspirate (approximately 10 mL of bone marrow aspirate per graft). This composite graft mixture was then placed posterolaterally over the decorticated bone.

Patients were followed clinically and radiographically for a minimum of 9 months postoperatively. The mean follow-up period was 24 months (range, 12–36 mo). The mean patient age was 64.7 years (range, 38–80 yr); there were six men and 17 women. The mean Jikei grade (44) was 2.3 (range, 1–3). The Jikei scale is used to radiographically grade the degree of osteoporosis as follows: Grade 0, a normal pattern of transverse and vertical trabecula; Grade I, a decrease in transverse trabecula with the prominent appearance of vertical trabecula and endplates; Grade II, a further decrease in vertical and transverse trabecula; and Grade III, near disappearance of the transverse trabecular pattern and unclear vertical trabecula appearing as ground glass (44).

Clinical data were reviewed for construct failure, quantity of bone cement used, and complications such as cement extravasation, radiculopathy, myelopathy, pulmonary embolus, infection, and death (*Table 1*). Fusion was considered successful when plain postoperative x-rays demonstrated clear trabecular bone bridging across intended fused segments at a minimum of 6 months postoperatively.

Statistical Analysis

The Spearman rank order correlation was used to analyze the relationship between cement extravasation and the quantity of cement used, number of levels augmented, and location (thoracic or lumbar).

RESULTS

The clinical results are summarized in *Table 1*. All patients had primary or secondary osteoporosis of Jikei Grade I or greater (mean, 2.3; range, 1–3). A total of 158 cement-augmented pedicle screws were placed. Six patients (26%) had metastatic spine disease (squamous cell lung carcinoma, renal cell carcinoma, bladder carcinoma, breast, prostate, and uterine adenocarcinoma). Operative exposure of the spine in patients with metastatic disease was limited to posterior and posterolateral techniques (laminectomy ± transpedicular/transversectomy approach to the anterior column) to reduce potential morbidity. Five patients (22%) had degenerative spondylolisthesis (*Fig. 3*). Twelve patients (52%) had burst fractures, eight of which resulted from benign causes and four of which resulted from metastatic disease. This included four short segment fusions in four elderly patients (mean age, 75 yr) with osteoporotic burst fractures. Short segment fusions with pedicle screw augmentation were chosen in these individuals to reduce exposure and operative times to minimize potential morbidity. Four (17%) of the patients underwent revision surgery for previous pedicle screw failure resulting from bone softening and pseudarthrosis (salvage procedures). *Figure 4* illustrates a representative revision procedure. Four cases were pure thoracic (17%), three cases were thoracolumbar (13%), and 16 cases were lumbar (70%). The mean cement injection per pedicle was 2.89 mL ± 0.72 (range, 2.0–5.0 mL).

Patients were followed for a minimum of 9 months postoperatively. The mean follow-up period was 21 months (range, 9–30 mo). There were no cases of operative deaths, myocardial infarctions, hypoxemia, or intraoperative hypotension in this series. There was no cement extravasation resulting in radiculopathy or myelopathy. Asymptomatic cement extravasation was observed in 9 of the 23 patients (39%). All extravasation was anterior, primarily into the external venous plexus (n = 6); however, cement flow into the ascending lumbar vein (n = 1) and hemiazygous vein (n = 1) was noted postoperatively in two cases. There was no posterior cement flow into the basivertebral or intervertebral veins. One case of asymptomatic PMMA pulmonary embolus (4.3%) was noted in the patient with cement in the ascending lumbar vein. This was diagnosed on a routine follow-up chest x-ray. Oxygen saturation remained at 98% on room air throughout hospitalization. In addition, one case of asymptomatic cement extravasation through the superior endplate into the disc space was observed. There was no significant relationship between the cement extravasation and the quantity of cement used ($P > 0.05$ for all comparisons), the number of levels augmented ($P > 0.05$ for all comparisons), and the location (thoracic or lumbar) ($P > 0.05$ for all comparisons).

There was one postoperative superficial wound infection with methicillin-resistant *Staphylococcus aureus* treated with a 6-week course of intravenously administered vancomycin, wound packing until granulation, and closure. There were no cases of construct failure, screw fracture, or pullout. Posterolateral fusion was demonstrated in 14 out of of 17 patients (82%) without metastatic disease. Fusion was not assessed as an end point in patients with metastatic disease to the spine because of their relative short survival periods and adjuvant therapies such as chemotherapy and radiation, making fusion less likely. Regardless, there were still no construct failures in this subgroup of patients.

DISCUSSION

The use of PMMA in pedicle screw augmentation and in balloon kyphoplasty and vertebroplasty must be done with caution because of a number of potential serious complications that may occur with intraosseous injection of bone cement. The risk of PMMA extravasation in various series ranged between 27 and 74% (13, 18, 25, 34, 35, 43), with resultant neurological deficits such as radiculopathy and cord compression occurring in 3.7 and 0.5%, respectively (9). We report a rate of PMMA extravasation of 39% consistent with these series, but without the posterior migration of cement that can be associated with myelopathy (0%) and radiculopathy (0%).

TABLE 1. Clinical data for patients undergoing pedicle screw augmentation[a]

Patient no.	Age (yr)/Sex	Jikei Grade	Preoperative diagnosis	Fixation levels	PMMA/level	Complication	PMMA extravasation
1	51/F	3	Degenerative spondylolisthesis, stenosis	L3–L5	2.5 cc/pedicle L3–L5	None	Superior endplate/disc, asymptomatic
2	68/M	2	L3 burst fracture	L2–L4	2.5 cc/pedicle L2–L4	None	External venous plexus, asymptomatic
3	68/F	2	Degenerative spondylolisthesis, stenosis	L2–L5	5.0 cc/pedicle at L2 and L3	None	External venous plexus, asymptomatic
4	68/F	2	L4 burst fracture	L2–S1	4.0 cc/pedicle at L2, L3, L5, and S1	None	None
5	74/F	3	L2 and L3 burst fractures	T11–S2	3.0 cc/pedicle at L4–S1	asymptomatic pulmonary embolus	Ascending lumbar vein
6	61/F	2	Salvage proc. L5–S1 pedicle screw failure	L4–S1	4.0 cc/pedicle at L4	None	External venous plexus, asymptomatic
7	71/F	2	Degenerative spondylolisthesis, stenosis	L4/L5	2.5 cc/pedicle at L4–L5	None	External venous plexus, asymptomatic
8	63/F	3	T4 burst fracture, met. breast CA	T2–T6	2 cc/pedicle at T5 and T6	None	None
9	80/F	2	L4 burst fracture	L3–L5	3.0 cc/pedicle at L3 and L5	None	None
10	61/F	2	Salvage proc., pedicle screw failure	L3–L5	4 cc/pedicle at L5	None	None
11	44/F	1	Salvage proc., pedicle screw failure	L3–S1	3 cc/pedicle on right at L3	None	None
12	76/F	2	Degenerative spondylolisthesis, stenosis	L3–L5	3.0 cc/pedicle at L3 and L5	MRSA superficial wound infection	None
13	74/M	3	Salvage proc., pedicle screw failure	L2–L4	3.0 cc/pedicle at L2–L4	None	External venous plexus, asymptomatic
14	38/M	1	T7 burst fracture, kyphosis	T5–T10	2.5 cc/pedicle at T5 and T10	None	None
15	72/F	2	L4 burst fracture	L3–L5	2.5 cc/pedicle at L3 and L5	None	None
16	51/M	3	Cauda equina syndrome, met. squamos cell CA	L2–L5	2.5 cc/pedicle at L2, L4, and L5	None	External venous plexus, asymptomatic
17	69/F	3	Cauda equina syndrome, met. renal cell CA	L1–L4	3 cc/pedicle on right at L4	None	None
18	79/F	2	Degenerative spondylolisthesis, stenosis	L3–L5	2.5 cc/pedicle at L3–L5	None	None
19	80/F	2	L2 burst fracture	L1–L3	2.0 cc/pedicle at L1 and L3	None	None
20	49/M	3	Met. bladder CA, T3–T4 burst	T1–T7	2.5 cc/pedicle at T5–T7	None	None
21	76/M	2	Met. prostate, T3 burst	C7–T5	2.5 cc/pedicle at T4 and T5	None	None
22	67/F	3	T12, L1 burst uterine adeno CA	T10–L4	2.5 cc/pedicle at T10, T11, L3, and L4	None	Hemiazygous, asymptomatic
23	47/F	2	L1 burst	T10–L3	2.5 cc/pedicle at T10, T11, L2, and L3	None	None
Total	**17F/6M**	**Mean, 2.26**		**158 augmented screws**	**Mean PMMA, 2.89 cc**	**2 out of 23, 8.7%**	**9 out of 23, 39%**

[a] PMMA, polymethylmethacrylate; proc., procedure; met. metastatic; CA, carcinoma; MRSA, methicillin-resistant Staphylococcus aureus.

This is thought to be the result of proper surgical technique in placing the fenestrated bone tap into the anterior one-third of the vertebral body and the tap threads that prevent posterior flow of cement along the tap and into the basivertebral and intervertebral veins. Posterior flow has not been demonstrated in either this clinical series or cadaveric studies using the Pedestal Fenestrated Tap System. The risk of epidural migration of PMMA has been reported to be minimized by the use of smaller volumes of bone cement, slow injection times under low pressures, and limitation of use above T7 (43). However, there was no significant correlation between cement extravasation and volume or between the number and



FIGURE 3. *X-rays showing preoperative multilevel degenerative spondylolisthesis with stenosis (**A** and **B**) and postoperative (**C** and **D**) decompression, reduction, and instrumented fusion from L3 to L5 using a PMMA-augmented pedicle screw construct (Patient 8).*

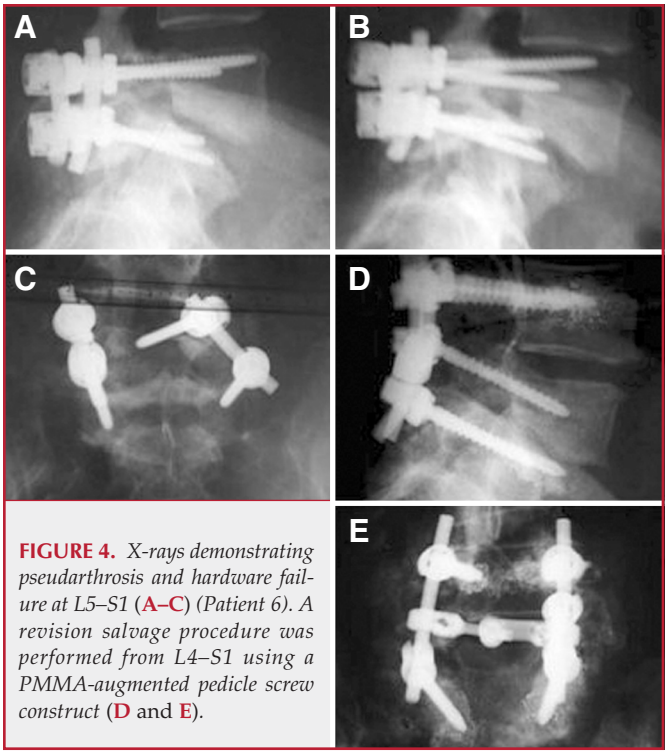


FIGURE 4. *X-rays demonstrating pseudarthrosis and hardware failure at L5–S1 (**A–C**) (Patient 6). A revision salvage procedure was performed from L4–S1 using a PMMA-augmented pedicle screw construct (**D** and **E**).*

location of levels augmented in this series. There is no substitution for careful surgical technique using correct tap positioning with adequate anteroposterior and lateral fluoroscopy to image the extent and direction of PMMA injection by qualified, experienced surgeons. Any fluoroscopic demonstration of cement extravasation should immediately result in the termination of injection and either repositioning of the tap or abandonment of further injection. Furthermore, the use of lower volumes of cement seems to be as effective as higher volumes. Overall, the mean volume of PMMA used in our cadaver study was 3.7 mL per pedicle (range, 2.5–8.0 mL/pedicle) in two groups of cadavers, a low cement group (≤2.8 mL/pedicle) and a high cement group (≥5.5 mL/pedicle). The pullout strength did not significantly change with increased cement use ($P > 0.05$ for all comparisons). As such, the mean cement volume used in this clinical series was 2.89 ± 0.72 mL per pedicle (range, 2.0–5.0 mL) based on our cadaveric studies, and it is the recommendation of the authors to use the described lower ranges of cement volumes for pedicle screw augmentation procedures.

In addition to local complications, systemic complications including fever, (17) infection (9), pulmonary embolism (1, 24, 33, 36), fat embolism (24, 48), hypoxia (17), hypotension (24, 38), myocardial infarction (24, 41), and sudden death have been reported with the use of PMMA (24, 38, 41). The majority of these cases have occurred in orthopedic procedures involving prostheses fixation and not with vertebroplasty-type operations per se. One methicillin-resistant *Staphylococcus aureus* wound infection was noted in this series and not thought to be related to pedicle screw augmentation with bone cement. No operative deaths, myocardial infarctions, hypoxia, or hypotension were demonstrated in these patients; however, one must be mindful of these potential complications when PMMA is used.

Pulmonary embolism after vertebroplastic procedures has been well documented in the literature (1, 2, 5, 6, 8, 10, 15, 16, 22, 30, 33, 36, 39, 40, 46, 49, 53), with its incidence ranging from 1 to 11% (1, 2, 10, 22). In these series, there have been a total of 23 reported cases of pulmonary emboli (10 symptomatic, nine asymptomatic, and four deaths) (1, 2, 5, 6, 8, 10, 15, 16, 22, 30, 33, 36, 39, 40, 46, 49, 53). One case of asymptomatic pulmonary embolism was observed, an incidence of 4.3%, consistent with the vertebroplasty literature. This was an incidental finding on a routine postoperative chest x-ray, and the patient was asymptomatic with 98% saturation on room air. A pulmonary embolus is caused by cement migrating into the external venous plexus, then ascending into the lumbar veins, connecting to the azygous and/or the hemiazygous system emptying into the superior vena cava, then into the heart, and subsequently into the pulmonary arteries and lungs. An understanding of the relevant venous anatomy (*Fig. 5*) is crucial in performing vertebral augmentation procedures to reduce complication occurrence. Again, great care must be used by the surgeon to prevent unwanted migration of PMMA into the venous system.

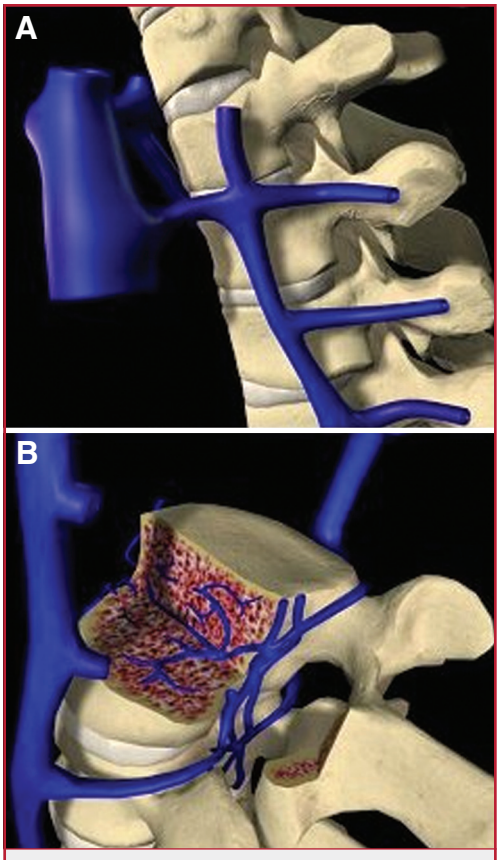


FIGURE 5. *Illustrations demonstrating relevant venous anatomy for vertebral augmentation procedures.* **A**, *the azygous and hemiazygous veins are seen draining into the superior vena cava in the thoracic spine.* **B**, *the basivertebral veins, anterior internal and anterior external venous plexuses, intervertebral veins, and ascending lumbar veins are seen in the lumbar spine.*

Clinically, this procedure was used in 23 patients with moderate to severe bone softening caused by osteoporosis and metastatic spine disease. Screw augmentation procedures were performed using a novel and effective technique for cement delivery, a fenestrated bone tap. In this device, tap threads serve a dual purpose in that they prevent the backflow of cement toward neural elements while allowing for a custom form for subsequent screw placement. Solid instrumentation, without hardware failure, was achieved with a low complication profile consistent with previous reports of use of bone cement in the spine.

CONCLUSION

Segmental PMMA-augmented pedicle screw fixation for instrumentation of the osteoporotic spine can be performed relatively safely. This technique may reduce the likelihood of pedicle screw loosening and pullout in patients with osteoporosis requiring instrumented arthrodesis. However, careful attention to surgical technique is necessary to prevent complications related to cement migration, such as pulmonary embolus.

Disclosure

Bruce M. Frankel, M.D., is the surgeon-inventor of the Pedestal Fenestrated Tap System (patent pending) used in these procedures.

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COMMENTS

Frankel et al. have presented a unique strategy for augmenting screw-bone fixation with polymethylmethacrylate (PMMA). Their clinical results demonstrate relative safety and clinical efficacy. They have provided an alternative strategy in this difficult to manage patient population. For this, they are to be congratulated.

Edward C. Benzel
Cleveland, Ohio

This small series describes the results of twenty-six patients who underwent PMMA vertebral augmentation to improve pedicle screw fixation when the bone was weakened due to metabolic or neoplastic disease. Although the use of PMMA to improve screw fixation for a variety of purposes is not novel, the authors used a newer technique of injecting the cement through the screw tapping device. This has particular advantages, most notably controlling cement delivery, encouraging PMMA deposition deep into the vertebral body, and also reducing the egress of PMMA from bony back bleeding through the pedicle tract. It should be noted that similar fenestrated pedicle screws are now commercially available for the same purpose, which may be more efficient for this purpose.

It should be remembered, however, that PMMA augmentation simply increases the physical interaction of titanium implants with the interstices of cancellous bone. Ultimately, repetitive cyclic loading in the absence of an effective interbody or posterolateral fusion will result in implant and PMMA loosening and progressive bony erosion, a phenomenon familiar to orthopedic surgeons who use PMMA in hip replacement surgery. Thus, careful attention to a bony arthrodesis is still necessary until a bioactive or osteoinductive bone cement becomes available.

Nevertheless, this report is quite timely in that the treatment of the "aging spine" will be a critical issue for neurosurgeons engaged in

spinal reconstruction procedures. As the population of potential surgical patients ages, the need to effectively anchor onto or fixate the osteoporotic spine will become increasingly important. This report is a small but meaningful step in that direction.

Michael Y. Wang
Miami, Florida

Frankel et al. describe a technique used for pedicle fixation in 23 patients with osteoporosis. A unique fenestrated tap was used to facilitate the injection of PMMA before placement of the pedicle fixation. The authors report an 82% fusion rate in the patients without metastatic disease with a 6-month assessment. I suspect that the fusion rate would be less at a 2-year follow-up evaluation. The potential complications do not seem to differ from other techniques of vertebral body augmentation with methylmethacrylate. There was anterior dye extravasation primarily into the external venous plexus, the ascending lumbar vein, and the hemiazygous vein. Augmentation of pedicle screw fixation with methylmethacrylate has been used for many years. This new device may improve the ease with which this technique can be performed.

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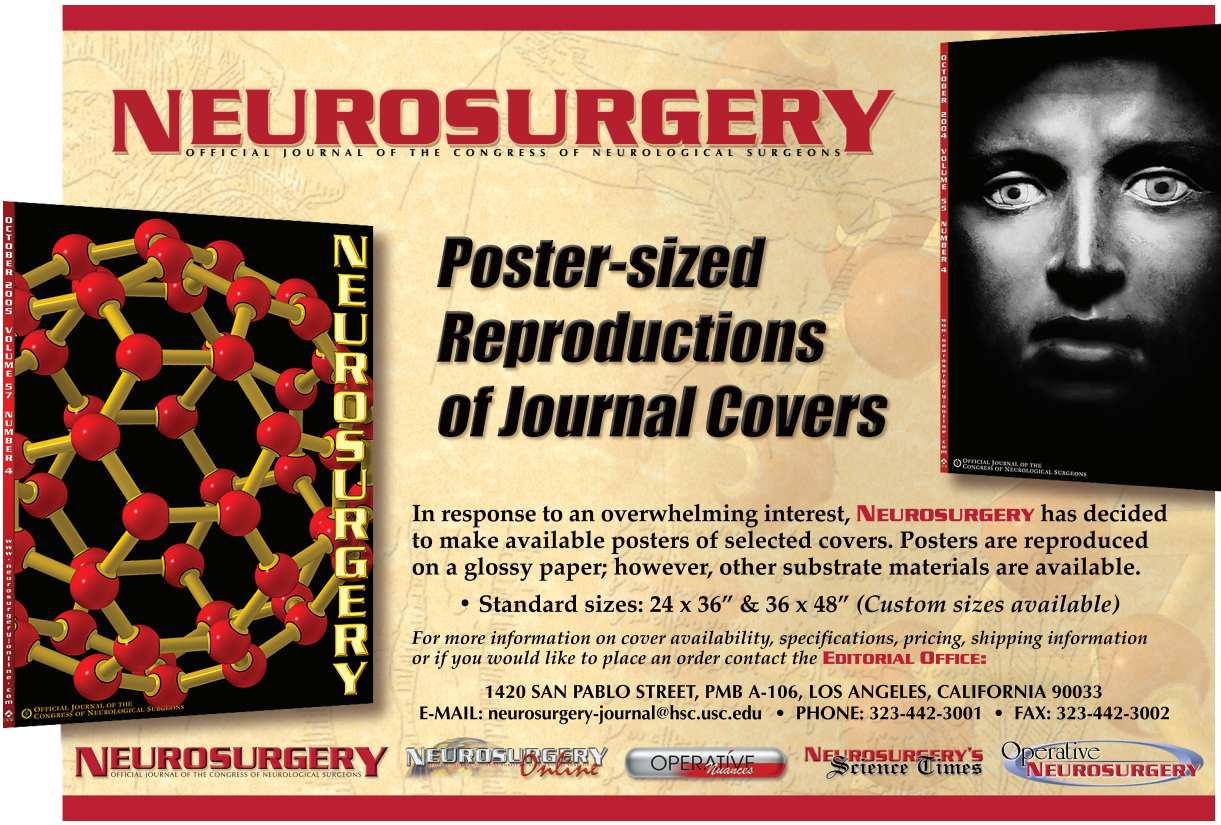
The authors address the relatively common problem of trying to place pedicle screws in osteoporotic bone or in bone involved with metastatic disease. They did so successfully by placing PMMA in the anterior aspects of the involved vertebral body using relatively novel instrumentation. There was some extravasation of the PMMA, primarily anteriorly, and one patient also developed pulmonary emboli. Some of these patients developed clinically significant symptoms.

Augmentation of PMMA with pedicle screws is not new. Nevertheless, the authors provide a unique way of delivering the PMMA, emphasizing that it should be placed in the anterior third of the vertebral body. They also have a good clinical series. Their long-term fusion rate, however, was not addressed. Once the surgeon determines that the bone is osteoporotic, the criteria for placing PMMA are unclear. Nevertheless, the success rate for obtaining firm pedicle fixation by augmenting the vertebral body with PMMA was excellent in these authors' hands.

Volker K.H. Sonntag
Phoenix, Arizona

This study describes the authors' experience with PMMA augmented pedicle screw fixation. The authors used the technique in 23 patients and observed few complications. It is noted that the first author (BMF) is the developer of the device used to perform the procedure. The primary use of short segment posterior instrumentation to treat osteoporotic or pathological burst fractures, with or without PMMA augmentation, is a controversial strategy. In addition, the study illustrates the fact that intraoperative injection of PMMA in this patient population is associated with a high (39%) rate of extravasation. Although the technique does appear to improve resistance to pull out, use of the technique will not protect against failure due to deficiencies of the ventral load bearing column in the long term.

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MINIMALLY INVASIVE LUMBAR DISCECTOMY IN OBESE PATIENTS

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OBJECTIVE: To assess patient outcomes and complication rates after minimally invasive lumbar microdiscectomy in an obese patient population.

METHODS: A retrospective clinical review of 32 patients with a body mass index of 30 kg/m^2 or greater undergoing lumbar minimally invasive discectomy was performed. The initial chart review was followed by phone interview if all information could not be obtained from chart review. Demographic and pertinent pre-, peri-, and postoperative data were obtained.

RESULTS: Favorable clinical outcomes were obtained in all patients except one, indicating that they would undergo operative intervention again. Most patients reported minimal or no leg or back pain. Twenty-five of the patients did not require any chronic analgesia. The overall complication rate was 12.5%. Two patients had recurrent disc herniations requiring reoperation and one patient required fusion for a pars defect and subsequent subluxation.

CONCLUSION: Lumbar minimally invasive discectomy is our preferred surgical technique for symptomatic disc herniations in this patient population. Decreased incision length and a trend toward reduced infectious complications are the primary reasons. We feel that, given the comorbidities often found in this patient population, a minimally invasive technique will supplant open approaches in the near future.

KEY WORDS: Minimally invasive lumbar discectomy, Obesity

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Obesity is defined as a body mass index (BMI) of 30 kg/m^2 or greater and morbid obesity as a BMI greater than 40 kg/m^2. Both afflictions are rapidly becoming epidemic in the United States (5, 6). Unfortunately, these patients are often affected by medical comorbidities, and obesity has been shown to be a risk factor for infectious complications in spinal surgery. The excessive subcutaneous fat deposition in this patient population can be daunting with regard to the surgical approach to the bony structures of the spine. The general rule has been to increase the length of the incision to allow adequate visualization at depth. The additional tissue injury associated with an increase in incision length and depth is likely a factor in the operative site morbidity. In 1997, Foley and Smith (5) introduced a tubular retractor system for performing a minimally invasive discectomy. The original system was designed for use with an endoscope and was subsequently modified for use with an operative microscope. Microendoscopic discectomy has been applied to multiple patients with excellent results and low morbidity rates (3, 9). Our approach uses an operative microscope and, thus, is referred to as a minimally invasive discectomy (MID). Given the growing proportion of the population that is either obese or morbidly obese, application of a surgical technique that can reduce surgical morbidity seemed the best course of action. Benefits of the minimally invasive approach in the literature have included decreased use of narcotic analgesia in the perioperative period, decreased tissue trauma, and a low infection rate (9, 12). This case series reports our experience with MID in the obese population at the University of Kentucky. This study was performed to evaluate outcomes after MID in patients who are obese to ascertain whether or not this application was safe and efficacious.

MATERIALS AND METHODS

A total of 42 consecutive cases of MID in patients who are obese were performed between July 2003 and May 2006 by a single surgeon (TRJ). The operative indication for all patients was radiculopathy or neurological deficit on physical examination corroborated by imaging. The Institutional Review Board approved of this protocol before collection of data. The clinic and hospital charts from these patients were retrospectively reviewed and each patient's BMI was calculated using an Internet-based program (4). Patients eligible for inclusion were adults between 18 and 80 years old who were classified as obese (BMI greater than or equal to 30 kg/m^2). Two incarcerated patients were excluded

from this analysis. Eight other patients were excluded from the study, including one patient who refused to participate with the phone interview, one patient who died of undisclosed causes during the follow-up period, and six patients who were lost to follow-up. The patient who died did so more than 1 year after surgery. Further analysis of each individual with a BMI greater than or equal to 30 kg/m^2 was then undertaken. Thirty-two evaluable patients were reviewed and underwent a total of 34 procedures. The patient demographics as well as operative information and clinical outcome were reviewed. If the estimated blood loss was dictated as "minimal," this was assigned a value of less than or equal to 50 mL. Blood loss was estimated from the operative report and anesthesia intraoperative record; if there was a discrepancy, the larger value was used. All data were collected by chart review and/or phone interview. If phone contact was necessary, verbal consent was obtained before collection of missing data. Patient outcome was determined with a numerical score assigned to each outcome measure (*Tables 1* and 2). In this study, active was defined as being able to perform regular activities of daily living and the ability to ambulate without assistance. Active was not meant to reflect the ability to return to a previous job, which was evaluated separately. The minimal follow-up period for patients included in this study was 3 months.

Operative Technique

After the induction of general anesthesia, the patient is placed in the prone position on a Wilson frame (ideally radiolucent) (Mizuho OSI, Union City, CA). The patient is prepped and draped in a sterile fashion. The midline is accurately marked using the spinous processes and gluteal cleft as guides. If the spinous processes are not readily palpable, a Kirschner wire can be placed on the patient's back and an anteroposterior fluoroscopic image obtained to find the midline. Failure to accurately mark the midline can make identifying the anatomy difficult. Next, a line parallel to the disc space is identified using a 22-gauge spinal needle with lateral fluoroscopy. If the image quality is poor, the buttock adipose can be retracted caudally to improve the image. The adipose can also be taped in place once retracted. Once the disc space is identified, an 18- to 20 mm incision is made 1.5 cm off the midline ipsilateral to the disc herniation. The METRx (Medtronic Sofamor Danek, Memphis, TN) tubular retractor system is used to sequentially dilate the muscle and subcutaneous tissue docking the 18 mm diameter tube over the disc space of interest. In patients who are obese, longer tubular retractors are used (typically 7–9 cm). Adipose tissue is somewhat compressible; thus, even if the first dilator indicates the depth to be greater than 9 cm (the longest tube available), it is typically possible to compress the adipose tissue to allow for placement of the 9 cm tube. If the anatomy does not appear normal, it is necessary to ensure that passage of the dilator contralaterally has not occurred inadvertently by taking an anteroposterior fluoroscopic image. At this point, the operative microscope is brought into the field and a laminotomy/medial facetectomy is performed like a typical discectomy. A sequestrectomy is performed rather than an aggressive discectomy. After adequate decompression is performed, the tubular retractor is removed. If possible, the fascia is closed followed by the subcutaneous tissue. The wound is dressed with Mastisol (Ferndale Laboratories, Inc., Ferndale, MI) and Steri-Strips (3M Healthcare, St. Paul, MN). The patients are given antibiotics before the incision (typically cefazolin unless allergic). Assuming there are no complications, the procedure is performed as an outpatient surgery. In two-level procedures, the distance between the two discs can be divided and the tube "wanded" up and down or two separate incisions may be made in cases with multiple herniations at noncontiguous levels.

TABLE 1. Leg pain outcome score

Score	Description
1	Minimal to no leg pain at present
2	Moderate leg pain but still able to be active
3	Moderate leg pain; unable to be active
4	Severe leg pain; no improvement from preoperative status

TABLE 2. Back pain outcome score

Score	Description
1	Minimal to no back pain at present
2	Moderate back pain but still able to be active
3	Moderate back pain; unable to be active
4	Severe back pain; no improvement from preoperative status

RESULTS

All patient data are presented in an anonymous fashion (*Tables 3* and *4*). The mean age of patients in the study was 38; their mean BMI was 35.9 kg/m^2 (range, 30–51.2 kg/m^2)with nearly equivalent sex and operative side breakdown. The most common spinal level was L5–S1, with L4–L5 nearly matching in total number of cases. Two two-level operations were performed, and the results of these cases represent an aggregate of both levels of operative intervention. The average operative time was 86.1 minutes (range, 36–128 min). The estimated blood loss was 50 mL or less in 24 cases and more than 50 mL in eight cases (range, 5–300 mL). The majority of patients (78%) were discharged on the same day as their operation. However, all patients with durotomies were admitted overnight. All patients had a single incision ranging from 18 to 20 mm in length.

The overall complication rate was 21.8% with seven overall complications; however, several of these complications were late. The complications presented are separated categorically in the manner described by Kraemer et al. (6). Intraoperative complications included three durotomies (9.4%), which were resolved without the need for additional operative intervention. In terms of immediate postoperative complications, there was a single case of urinary retention, which resolved spontaneously. Combined, these resulted in an early complication rate of 12.5%. Two late recurrent disc herniations occurred (6.3%) necessitating additional operative intervention. For these cases, the patients noted initial relief but developed refractory recurrent pain prompting new imaging and resection of disc material. These patients had interval leg pain but noted good recovery after their additional operation. An additional patient had an undiagnosed but operatively noted pars defect, which eventually resulted in lumbar fusion. Initially, positive results were obtained, but refractory radicular pain necessitated her subsequent fusion. The patient eventually noted an excellent out-

TABLE 3. Patient data[a]

Patient no.	Age (yr)/sex	Body mass index (kg/m2)	Level	Side	Estimated blood loss	Operating room time (min)
1	30/M	32.7	L5–S1	R	<50	93
2	34/F	47	L5–S1	R	100	97
3	47/M	30.4	L5–S1	R	30	97
4	41/M	31.6	L4–L5	R	<20	56
5	24/M	35.9	L5–S1	R	10	101
6	60/F	38.3	L5–S1	L	125	116
7	49/M	37.1	L4–L5	L	30	82
8[b]	37/M	32.4	L4–L5	L	<50/<10	87/39
9	56/M	32.4	L4–L5	L	250	103
10	56/F	30.6	L4–L5, L5–S1	L	25	92
11	31/M	36	L5–S1	L	10	67
12	46/M	32.8	L5–S1	L	<50	103
13	52/F	37.8	L4–L5	L	250	93
14	34/F	35	L3–L4, L4–L5	L	150	128
15	34/F	31.8	L4–L5	L	100	126
16	44/M	35.2	L4–L5	R	100	70
17	27/M	30	L4–L5	L	5	103
18[b]	36/M	34.8	L4–L5	R	10/<50	68/80
19	37/F	30.2	L5–S1	R	<50	95
20	48/F	37.1	L4–L5	L	15	118
21	36/F	49.3	L5–S1	L	<50	105
22	27/F	51.2	L4–L5	R	10	76
23	37/F	30	L5–S1	R	30	72
24	25/M	43.3	L5–S1	R	<50	66
25	37/M	35.7	L5–S1	R	30	89
26	40/M	31.7	L4–L5	L	50	62
27	36/F	43.1	L5–S1	R	<50	96
28	35/M	30.5	L5–S1	L	20	86
29	21/F	39	L4–L5	R	300	90
30	30/F	35.8	L5–S1	L	20	36
31	38/F	38.2	L4–L5	L	10	43
32	33/M	33	L4–L5	L	<50	40

[a] R, right; L, left.
[b] Patients who underwent a second operation at the same level with estimated blood loss and operating room time listed for each case separated by a backslash.

come. The late complication rate was 9.4% overall. No patients had a postoperative infection. A number of patients have required prolonged postoperative analgesia, but only two (6.3%) have required prolonged narcotic analgesia. One patient requiring prolonged narcotic analgesia developed cancer and takes chronic opioid analgesia for systemic pain.

Nineteen patients were employed preoperatively, 18 of whom returned to work. One patient who was previously unemployed found a job postoperatively, whereas two patients did not return to work (one was disabled and one returned to school).

Twenty patients (62.5%) noted no to minimal leg pain and 11 (34.3%) noted moderate leg pain, which did not restrict their activity. A single patient (3.1%) noted significant leg pain, which was activity-limiting. In terms of back pain, 17 (53.1%) noted no to minimal back pain, whereas 13 (40%) noted moderate back pain, which did not limit activity. Two patients (6.3%) had moderate activity-limiting back pain. The aforementioned patient with systemic cancer had pre- and postoperative chronic leg and back pain, which was activity-limiting. This patient still felt the operation was helpful to some degree and would undergo the procedure again. Overall, 31 (97%) reported they would undergo the procedure again. The single patient who felt he or she was not helped had a profound preoperative foot drop, which did not resolve postoperatively.

TABLE 4. Patient data[a]

Patient no.	Hospital days	Leg pain	Back pain	Postoperative medication	Preoperatively employed	Postoperatively employed	OR again	Complications
1	1 (SDS)	1	1	N	Y	N	Y	N
2	1 (SDS)	2	1	Y[d]	N	N	Y	N
3	2	2	2	N	Y	Y	Y	Y (durotomy)
4	2	2	2	N	Y	Y	Y	Y (Ur. Ret.)
5	1 (SDS)	1	2	N	Y	Y	Y	N
6	2	2	2	Y[d]	N	N	Y	N
7	1 (SDS)	2	1	N	Y	Y	Y	N
8[b]	1 (SDS)/1 (SDS)	1	1	N	Y	Y	Y	Y (recurrence)
9	1 (SDS)	1	1	N	Y	Y	Y	N
10	2	1	1	Y[d]	N	N	Y	Y (instability)
11	1 (SDS)	1	1	N	Y	Y	Y	N
12	1 (SDS)	1	1	N	Y	Y	Y	N
13	1 (SDS)	1	1	N	Y	Y	Y	N
14	1 (SDS)	1	1	N	Y	Y	Y	N
15	2	1	1	N	Y	Y	Y	Y (durotomy)
16	2	2	2	Y[d]	N	N	Y	N
17	1 (SDS)	1	1	N	Y	Y	Y	N
18[b]	1 (SDS)/1 (SDS)	1	1	N	Y	Y	Y	Y (recurrence)
19	1 (SDS)	2	3	Y[d]	Y	Y	Y	N
20	1 (SDS)	3	3	Y[c]	N	N	Y	N
21	1 (SDS)	1	1	N	Y	Y	N	N
22	1 (SDS)	2	1	N	N	Y	Y	N
23	1 (SDS)	1	2	N	Y	Y	Y	N
24	1 (SDS)	2	2	Y[c]	N	N	Y	N
25	2	1	1	N	Y	Y	Y	Y (durotomy)
26	1 (SDS)	1	2	N	N	N	Y	N
27	1 (SDS)	2	2	N	N	N	Y	N
28	1 (SDS)	1	1	N	Y	Y	Y	N
29	1 (SDS)	2	2	N	N	N	Y	N
30	1 (SDS)	1	2	N	N	N	Y	N
31	1 (SDS)	1	2	N	N	N	Y	N
32	1 (SDS)	1	2	N	Y	Y	Y	N

[a] SDS, same-day surgery; Leg pain, leg pain score; Back pain, back pain score; OR again, would the patient have surgery again?; N, no; Y, yes; Ur. Ret., urinary retention.
[b] Patients who underwent a second operation at the same level with estimated blood loss and operating room time listed for each case separated by a backslash.
[c] Narcotic.
[d] Non-narcotic.

DISCUSSION

Microendoscopic discectomy and MID have been shown to be safe and efficacious in a number of applications (2, 9, 12, 13). The benefits of this technique include decreased muscle denervation, shorter hospital stay, and a smaller scar. Although some surgeons debate the applicability of the technique, we feel that MID is the preferred technique in the obese. Other authors have noted the applicability of this technique in the obese (11). We present the first case series of MID's application to an obese population.

Spine surgery in the obese is a challenging endeavor for many reasons, including anesthetic considerations, intravenous access, and positioning, as well as the procedure itself. Most spine surgeons would agree that intervention is more difficult in this population. Before the development of minimally invasive discectomy, lumbar microdiscectomy usually involved a longer incision than usual in this patient population. Retraction

was difficult and visualization of the important elements of the operation was obscured by the patient's depth. The literature would support operating on these individuals when necessary. However, obesity should not be ignored either. Andreshak et al. (1) found that although surgery could be safely performed in this population, the infectious complication rate was approximately doubled. Other studies have noted obesity as a risk factor for infectious complications during spinal procedures. Telfeian et al. (14) noted a 33% infectious complication rate in a population of patients who were morbidly obese. Wimmer et al. (15) noted that obesity played a role in 31% of the 22 infectious complications noted after a survey of 850 spinal operations. Additionally, Olsen et al. (8) showed that 29% of the spinal surgical site infections were in patients with BMI higher than 35 kg/m^2. However, in that study, patients with BMIs lower than 35 kg/m^2 were not shown to have an increased risk of infection. The infectious complication rate of microendoscopic discectomy and MID is as low as 0.7% in the literature and we experienced no infectious complications in our study population (9). Given the large incision necessary for discectomy in this patient population, the likely etiology of the increased incidence of infection is tissue devitalization or gross contamination. Other postulated causes include elevated blood glucose in these patients and poor preoperative antibiotic penetration in fat (8). However, without a concurrent or retrospective control group, an absolute reduction in infectious complications cannot be established. The trend noted in our small cohort is suggestive of a potential benefit.

The most common complication in our series was incidental durotomy, which occurred in 9.4% of our patients. The literature has noted rates ranging from 3 to 5% for this complication previously (9, 10). We had one durotomy during incision of the annulus and the other durotomies were related to Kerrison punch use (Codman/Johnson & Johnson, Raynham, MA). These were closed primarily when possible and sealed with fibrin sealant (TISSEEL; Baxter, Deerfield, IL) when primary closure proved impossible. All patients with durotomies were kept flat overnight and discharged the next morning without further intervention. Although the tubular retractor allows for excellent visualization with a minimal incision, the working depth in these patients is still formidable. These complications were not encountered in the largest patients. The level of training of the assistant surgeon varied from second-year neurosurgery resident to chief resident. Because minimally invasive spinal techniques are relatively new to our institution, the experience of the residents with the procedure was quite limited. The increased rate of durotomy could potentially be related to the greater working distance necessary in patients who are obese. A recent open spinal surgery series in the morbidly obese had a durotomy rate of 16.7% (two out of 12 patients) (14). Thus, durotomy may be more common in patients who are obese overall.

The second most common complication we encountered was the need for reoperation. The interval between the first and second operations ranged from 56 days to 6 months. This occurred in three (9.4%) patients, two (6.3%) of whom required simple discectomy. The other patient required reoperation for an occult pars defect. Eventually, instability at this operative level with refractory radiculopathy prompted lumbar fusion. These patients were in great distress related to their recurrent symptoms. Their interim satisfaction scores were not collected, but we must assume they were quite low. No additional reoperation was necessary during the study period.

The limitations of our study relate to its design. As a retrospective case series, it has potential biases. Several patients were lost to follow-up and, given the low numbers of patients in the study, could certainly adversely affect the satisfaction scores. The chart review of the patients lost to follow-up did not reveal additional complications. In addition, a single patient refused inclusion in the study, which could also affect outcome measures. The follow-up period ranged from 3 to 33 months with all but five patients having at least 6 months of follow-up. The median follow-up period was 14.5 months and the mean follow-up period was 15.3 months. Some would argue that this follow-up duration is not extensive enough. We agree that a longer follow-up period would prove useful and will endeavor to publish long-term results in our patient population.

In addition, a lack of preoperative assessment and the lack of a validated outcome measurement tool in this publication are limitations. The support staff necessary for collection and collation of prospective data in large numbers of patients was not available. Although the return to work is an indication of economic outcome, our scales of leg and back pain are not validated and reliable measures of functional outcome on the whole. This case series is useful because of the relative dearth of information available about this patient population.

Lumbar MID in patients who are obese has become our preferred surgical approach to this challenging patient population. The decreased incision length and a trend toward reduced infectious complications are the chief reasons. Despite the limitations of this study, it has provided valuable insight into this patient population and has prompted a change in our practice patterns. Given that obesity prevalence is on the rise, we feel that this technique will become more common as our society struggles with this health problem.

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COMMENTS

Cole and Jackson have presented a series of difficult to manage patients, utilizing emerging technology in a thoughtful manner. They make a good case for the utilization of the minimally invasive discectomy (MID) technique as a treatment of choice in this patient population. Their results are compelling. They are to be congratulated for their results and the presentation of these results in a clear and concise manner.

Edward C. Benzel
Cleveland, Ohio

Cole and Jackson report the results of a retrospective study of obese patients who underwent MID for presumably symptomatic lumbar disc herniations. Of 42 eligible patients, 32 (76%) were studied. These 32 patients underwent 34 operations. Follow-up data for more than 6 months were available for 27 patients.

The results showed an early complication rate of 12.5%, a late complication rate of 9.4%, and an overall complication rate of 21.8%. There were no postoperative infections. Three patients underwent repeat operations, including one who underwent arthrodesis. As indicated by the questionnaire, most patients reported minimal or moderate symptoms at the time of their last follow-up evaluation.

This study serves to highlight the utility of minimally incisional techniques in a perhaps unexpected group of patients. The ability of current retractor systems to provide adequate exposure of relevant anatomy while, at the same time, excluding redundant adipose tissue, may make them particularly suited to this patient population. Although the lack of a control group limits the power of this retrospective study, the data certainly suggest a possible reduction in wound related complications. Confirmation of this suggested effect awaits a randomized controlled trial.

Christopher E. Wolfla
Milwaukee, Wisconsin

The authors present a retrospective review of 32 obese patients treated with MID using tubular retractors and the microscope. The authors conclude that such procedures are associated with acceptable morbidity and that they may offer an advantage over standard open techniques in lowering the risk of infection. Although I agree with both conclusions, the evidence provided by the study to support these conclusions is weak. It should be noted that there was a 25% loss to follow-up rate (42 patients underwent operation), making any conclusions regarding outcome suspect. The use of a nonvalidated subjective outcome measure and the lack of long-term follow-up data further limit the conclusions that can be drawn. It is very difficult to make definitive statements or justify a novel clinical practice without the use of validated outcome measures and near complete follow-up data.

Daniel K. Resnick
Madison, Wisconsin

Cole and Jackson retrospectively reviewed their experience with MID in 32 obese patients and concluded that it was their preferred surgical technique in this patient population. The work is compromised by the lack of a control group and the exclusion of an additional 10 obese patients treated in this manner during the study period. Complication rates for durotomy and infection were lower in this report than those listed in previous publications focused on outcomes after traditional surgical approaches for lumbar discectomy in the obese.

The muscle splitting approach and tubular retractors used to maintain exposure are probably most beneficial for obese patients, and the technical aspects of this portion of the procedure as described by Cole and Jackson are useful. The authors should be congratulated for providing this information, albeit limited. Ideally, more data regarding the management of this difficult group will be presented in the future.

Vincent C. Traynelis
Iowa City, Iowa

CALL FOR *CONCEPTS AND INNOVATIONS* CONTRIBUTIONS

The ***Concepts and Innovations*** section has been conceived to establish a new dimension in journalistic presentation. Because of individual variations in the creative mind and the ability to effectively carry ideas through to fruition, many concepts or novel ideas are left "on the shelf" or are unheard because, for one reason or another, individuals do not have the capability to see them through to absolute or practically developed completion.

This section of the ***Journal*** will offer a forum for all those who wish to present new concepts or ideas related to neurosurgery and neuroscience, as applied to neurological disorders, and will offer the opportunity for the logical and substantive presentation of ideas and novel issues without absolute confirmation within clinical or laboratory sectors.

New concepts with potential application to all foci of practice will be welcomed.

COMPARISON OF OPEN DISCECTOMY WITH MICROENDOSCOPIC DISCECTOMY IN LUMBAR DISC HERNIATIONS: RESULTS OF A RANDOMIZED CONTROLLED TRIAL

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OBJECTIVE: We compared the intra- and postoperative differences, as well as the final outcome of patients with herniated lumbar discs who underwent either open discectomy (OD) or microendoscopic discectomy (MED).

METHODS: We performed a prospective controlled randomized study of 40 patients with sciatica caused by lumbar disc herniations nonresponsive to conservative treatment who underwent OD or MED with a 24-month follow-up period. Pre- and postoperative neurological status, pain, and functional outcome were evaluated. Other studied variables were the duration of the procedure, blood loss, time of hospital stay, and time to return to work. Statistical analysis with a P value less than 0.005 was carried out.

RESULTS: The only statistically significant differences found were for size of the incision, length of hospital stay, and operative time. The former two were greater in the OD group ($P < 0.01$ and $P = 0.05$, respectively), and the latter was greater in the MED group ($P < 0.01$).

CONCLUSION: The few parameters that were found to be statistically significant between the groups did not affect the overall outcome. In the current series, the final clinical and neurological results were similarly satisfactory in both the OD and the MED groups.

KEY WORDS: Comparative study, Lumbar disc herniation, Microendoscopic discectomy, Open discectomy, Surgery

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Lumbar disc herniations are a common cause of sciatica (16). More than half of the affected patients respond to conservative treatment (10, 13). Surgical discectomies, either through an open approach or using the more modern microscopic or endoscopic approaches, are indicated for those patients with persistent incapacitating low back pain and sciatica after at least 6 weeks of treatment or in those with early or progressive neurological impairment (8, 10).

In 1934, Mixter and Barr (9) first described laminectomy and discectomy to treat herniated lumbar discs. Surgical results using these techniques were often poor, especially regarding pain, mostly because of the extensive muscular dissection required for the open approach (3, 20). To address these issues, Caspar (2), Yaşargil (20), and Williams (19) described the microsurgical discectomy technique that involved a monosegmentar, minimally invasive approach using specially designed instrumentation and a surgical microscope. In 1971, Simeone (15) described the use of a surgical telescope (loupe) to substitute the microscope, acquiring similar results.

Thus, "microsurgical discectomy" is a term currently used to describe a surgical technique involving a small incision with minimal paravertebral muscle dissection using magnification, which may be either microscopic (19) or using a loupe (16). This is considered the "gold standard" for the treatment of disc herniations.

In 1997, Foley and Smith (7) developed an endoscopic approach as a minimally invasive surgical alternative for the treatment of lumbar disc herniations. The herniated tissue is resected endoscopically through a posterior

approach using a small incision and a tubular retractor (16 or 18 mm in diameter). This microendoscopic discectomy (MED) is thought to cause less tissue damage than standard open microdiscectomy with a marked reduction in postoperative pain and muscle spasm, allowing the procedure to be performed in an outpatient setting and enabling patients to return to their activities sooner (7, 8, 11). It also allows direct vision of the nerve root and bone decompression (12).

Despite all of the technical refinements, surgical treatment of herniated discs still remains controversial (18). Although excellent results have been reported after discectomy, relief of low-back pain has been less predictable (1, 4, 16, 18). Only a small number of studies have compared the outcome of patients using the open discectomy (OD) and MED techniques (14, 16). The objective of the current prospective randomized study was to compare the outcome of patients with persistent sciatica secondary to lumbar disc herniation treated with either OD or MED technique.

MATERIALS AND METHODS

After institutional review board approval, patients with sciatica caused by herniated lumbar discs who did not respond to conservative treatment were randomly enrolled in the treatment protocol to undergo either OD or MED between June 2001 and September 2004. The inclusion criteria were the presence of a posterolateral herniated lumbar disc observed on magnetic resonance imaging scans and the persistence of sciatica after 4 to 8 weeks of conservative treatment with rest, analgesia, nonsteroidal anti-inflammatory drugs, and physical therapy. The exclusion criteria were as follows: age older than 60 years, previous surgery, associated lumbar spine stenosis, foraminal or extraforaminal disc herniations, spondylolisthesis, and workers' compensation payments. Only those patients with a final postoperative follow-up period of at least 2 years were included in this study.

After the inclusion criteria were met and informed consent was obtained, patients were allocated randomly into one of two groups: Group 1 underwent OD; and Group 2 underwent MED. The surgical procedures were performed under general anesthesia with the patient in the prone position. Prophylaxis with a first-generation cephalosporin was introduced 1 hour before anesthesia and kept for 8 hours after the procedure.

Patients in Group 1 underwent OD following Caspar's technique modified only by the use of a surgical magnifying loupe of $\times 2.5$ (Designs for Vision, Inc., Ronkonkoma, NY) and a halogen headlight (Designs for Vision, Inc.), instead of the surgical microscope (3). In this technique the paravertebral muscles are swept laterally from the lamina in a subperiosteal plane, using the lamina as a landmark. A self-retaining retractor is placed, and the discectomy is performed using a magnifying surgical loupe. Patients in Group 2 underwent MED following the technique described by Foley and Smith (7).

The surgical variables analyzed were the level and side of the herniated disc, side of root compression, duration of the procedure, blood loss, presence of complications, duration of hospital stay, opioid administration, and incision size. Postoperative braces were not used, and the patients were kept in the hospital until adequate pain control was achieved.

Pre- and postoperative evaluation consisted of a neurological examination, the Visual Analogue Scale (VAS), and the Oswestry Disability Index (5, 6, 17). The surgical wound pain was assessed 12 hours after surgery by using the VAS. The VAS scores the intensity of pain from 0 (absence of pain) to 10 (worst pain ever experienced) (17). Clinical neurological status was evaluated using the Lasegue test, motor assessment by muscle strength, and testing of the reflexes and sensibility. Functional outcome was evaluated using the Oswestry Disability Index (6). The patients were reevaluated 1, 3, 6, 12, and 24 months after surgery. The time required for patients to return to work was also registered.

Data were analyzed using the χ^2 and Fisher exact tests, as well as Student's t and Mann-Whitney tests when applicable, with a significance level established at 95% ($P < 0.05$) and statistical power established at 90% ($\beta = 0.10$).

RESULTS

A total of 40 patients were enrolled, 19 in Group 1 and 21 in Group 2 (*Table 1*). The mean postoperative follow-up period was 36 months in Group 1 (range, 24–46 mo) and 36.2 months in Group 2 (range, 25–56 mo).

In Group 1 (OD), there were 13 men and 6 women, with a mean age of 46 $\pm$ 12.4 years. The vertebral level affected was L4–L5 in 11 patients (57.9%) and L5–S1 in eight patients (42.1%); the left side was most commonly affected (12 patients [63%]). All patients in Group 1 presented with preoperative neurological impairment; 100% had a positive Lasegue sign (19 out of 19), 100% had motor deficits (19 out of 19), 74% had sensory deficits (14 out of 19), and 63% had impaired or absent reflexes (12 out of 19). After 6 months of follow-up, 37% had motor deficit, 42% had sensory deficit, and 63% had altered reflexes. After 12 months, these percentages changed to 26, 42 and 63%, respectively, and after 24 months, they changed to 26, 37, and 58%, respectively. One patient presented recurrence of the herniation 24 months after surgery and underwent another operation.

Group 2 (MED) was composed of 10 men and 11 women with a mean age of 42.0 $\pm$ 10.7 years. The vertebral level affected was L2–L3 in one patient (4.8%), L3–L4 in one patient (4.8%), L4–L5 in 11 patients (52.4%), and L5–S1 in eight patients (38.1%). The left side was most commonly affected (13 patients, 61.9%). All patients in this group presented with preoperative neurological impairment; 90% with a positive Lasegue sign (19 out of 21), 100% with motor deficits (21 out of 21), 91% with sensory deficits (20 out of 21), and 86% with impaired or absent reflexes (18 out of 21). After 6 months of follow-up, 67% had motor deficit, 67% had sensory deficit, and 62% had altered reflexes. After 12 months, these percentages changed to 38, 48, and 57%, respectively, and after 24 months, they changed to 33, 38, and 48%, respectively (*Table 2*). Opioid therapy was used in three patients (14%). The complications observed in this group were a recurrence of the disc herniation after 18 months requiring surgical treatment in one patient, a seroma that resolved spontaneously with complete recovery in one patient, and a dural tear that resolved with conservative treatment prolonging hospital stay to 48 hours in one patient.

When comparing Group 1 (OD) with Group 2 (MED), the only statistically significant differences found were for the following variables: the size of the incision, length of hospi-

TABLE 1. Comparison between Groups 1 (open discectomy) and 2 (microendoscopic discectomy)[a]

Variable	OD n = 19	MED n = 21	*P* value
Age (yr)	46.0 ± 12.4	42.0 ± 10.7	0.28
Sex, no. (%)			0.31
Male	13 (68.4)	10 (47.6)	
Female	6 (31.6)	11 (52.4)	
Duration of symptoms (d)	60 (30–210)	60 (30–180)	0.71
Length of hospital stay (h)	26 (16–72)	24 (11–72)	0.05[b]
Surgical time (min)	63.7 ± 15.5	82.6 ± 21.9	<0.01[b]
Blood loss (mL)	40 (11–450)	50 (10–700)	0.98
Size of incision (cm)	2.6 ± 0.4	2.1 ± 0.2	<0.01[b]

[a] OD, open discectomy; MED, microendoscopic discectomy. Data are represented as mean ± standard deviation, median (minimum and maximum), or percentage.
[b] Statistically significant difference.

TABLE 2. Neurological status of Groups 1 (open discectomy) and 2 (microendoscopic discectomy) before and after surgery[a]

Variable	OD n = 19	MED n = 21	*P* value
Motor deficit			
Preoperative	19 (100)	21 (100)	NA
1 mo postoperative	16 (84)	17 (81)	0.99
3 mo postoperative	15 (79)	17 (81)	0.99
6 mo postoperative	7 (37)	14 (67)	0.11
12 mo postoperative	5 (26)	8 (38)	0.51
24 mo postoperative	5 (26)	7 (33)	0.74
Sensory deficit			
Preoperative	14 (74)	19 (91)	0.23
1 mo postoperative	12 (63)	17 (81)	0.29
3 mo postoperative	12 (63)	16 (76)	0.49
6 mo postoperative	8 (42)	14 (67)	0.20
12 mo postoperative	8 (42)	10 (48)	0.76
24 mo postoperative	7 (37)	8 (38)	0.99
Altered reflexes			
Preoperative	12 (63)	18 (86)	0.15
1 mo postoperative	12 (63)	14 (67)	0.99
3 mo postoperative	12 (63)	13 (62)	0.99
6 mo postoperative	12 (63)	13 (62)	0.99
12 mo postoperative	12 (63)	12 (57)	0.76
24 mo postoperative	11 (58)	10 (48)	0.55

[a] OD, open discectomy; MED, microendoscopic discectomy; NA, not available. Data are presented as percentages.

tal stay, operative time, and immediate postoperative pain at the incision. The two former variables were greater in the OD group ($P < 0.01$ and $P = 0.05$, respectively), and the latter two were greater in the MED group ($P < 0.01$ in both) (*Tables 1* and *3*).

The VAS score (*Fig. 1*) and Oswestry Disability Index (*Fig. 2*) improved significantly in Groups 1 and 2 postoperatively, and there was only one statistically significant difference in VAS after 12 hours of surgery (*Table 3*). The mean time to return to work and normal activities was 21 days in both groups, ranging from 7 to 60 days in Group 1 and from 4 to 45 days in Group 2. The difference between the groups was not found to be statistically significant ($P = 0.79$).

DISCUSSION

The demands of modern society create the need for faster recoveries, allowing patients to resume their normal activities sooner. Technical developments in the past decades have made the treatment of herniated discs safer and less invasive. By using microsurgical or microendoscopic approaches through small incisions, nerve root decompression is achieved with minimal risk of complication and preserving normal anatomy (19). Foley and Smith (7) believe that MED is superior to other percutaneous techniques for combining the standard lumbar microsurgical technique with endoscopy, allowing the surgeon

TABLE 3. Comparison between surgical Groups 1 (open discectomy) and 2 (microendoscopic discectomy)[a]

Variable	OD n = 19	MED n = 21	*P* value
VAS for pain			
Preoperative	9 (7–10)	7.9 (6–10)	0.03
12 h postoperative	1.2 (0–5)	2 (1–4)	<0.01[b]
1 mo postoperative	1.2 (0–3)	1.5 (0–6)	0.33
3 mo postoperative	1 (0–2)	0.8 (0–6)	0.50
6 mo postoperative	1 (0–3)	1 (0–6)	0.27
12 mo postoperative	0 (0–3)	0 (0–3)	0.67
24 mo postoperative	0 (0–6)	1 (0–3)	0.15
Oswestry Disability Index			
Preoperative	50 (22–96)	54 (28–100)	0.65
1 mo postoperative	10 (0–48)	12 (2–44)	0.39
3 mo postoperative	11 (0–36)	8 (0–42)	0.49
6 mo postoperative	10 (0–24)	10 (0–40)	0.89
12 mo postoperative	8 (0–20)	10 (2–34)	0.23
24 mo postoperative	10 (0–30)	10 (0–22)	0.87

[a] OD, open discectomy; MED, microendoscopic discectomy; VAS, Visual Analogue Scale. Data are represented as mean ± standard deviation, median (minimum and maximum), or percentage.
[b] Statistically significant difference.

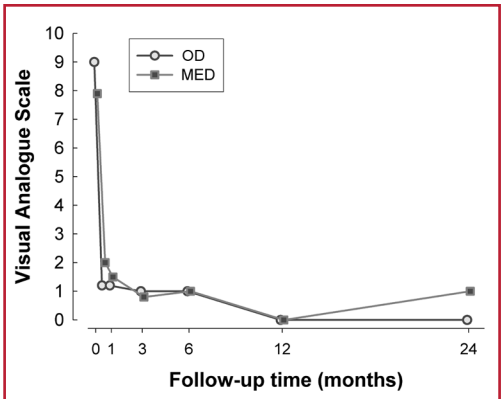


FIGURE 1. *Line graph demonstrating the comparative results of the postoperative pain between Groups 1 (OD) and 2 (MED) using the VAS.*

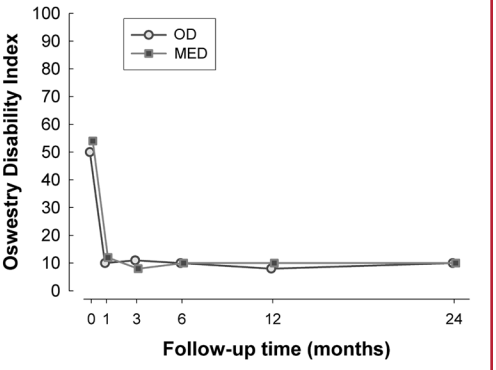


FIGURE 2. *Line graph demonstrating the results of the Owestry Disability Index for evaluation of functional outcome after surgical repair of lumbar herniated disc comparing Groups 1 (OD) and 2 (MED).*

to address free-fragment disc pathology and lateral recess stenosis through an even smaller incision than OD and with less trauma. The improved optical conditions allow better differentiation of the anatomic structures with gentler manipulation of the nerve root and dural sac (2, 3).

The high rate of early neurological deficits reported in the current series may reflect the greater number of acute cases and the volume of the herniation. Although no statistically significant differences were found regarding neurological recovery between the groups, the OD group recovered both motor and sensory functions earlier than the MED group. However, after a 24-month follow-up period, both groups presented similar results.

The operative time was greater in the MED group, but within the average reported by surgeons experienced with the technique (2, 3, 11, 19). The hospital stay was longer in the OD group, but only by an average of 2 hours, which represents little significant clinical or economical difference. Clinical outcome was satisfactory and comparable in both groups.

The superiority of microdiscectomy over traditional discectomy has been widely proven (7, 10, 11, 20). However, there is no randomized clinical study comparing the OD and MED techniques. To our knowledge, this is the first prospective randomized clinical study to compare the clinical outcome and technical aspects of both techniques.

CONCLUSION

The few parameters that were found to be statistically different between the groups (incision size, length of hospitalization, operative time, and VAS at 12 hours) did not affect the overall outcome. Up to the present, the current study included, the technical superiority of the videoendoscopic technique has not been proven, but it may become an interesting alternative for those patients who require faster recoveries.

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COMMENTS

Righesso et al. performed a prospective randomized study of 40 patients with sciatica due to lumbar disc herniations. Patients were treated with either an open microsurgical discectomy or a microendoscopic discectomy (MED). The follow-up period was just over 3 years. Essentially, there was no significant difference between the clinical outcomes of the two groups. Those having an open procedure had a larger incision and a hospital stay lasting 2 hours longer, both of which were significantly different compared with these parameters for the MED group. The MED procedure required approximately 20 minutes longer than the open procedure, which was also statistically significant.

This study highlights the similarities in terms of outcome between these two procedures. It should be noted that the authors used a muscle-splitting approach in their open procedure very similar to that used for MED. This is probably a key factor in minimizing postoperative morbidity and earlier return to function. Once the exposure is achieved, whether the surgeon chooses to use a microscope or endoscope does not seem to make much difference.

Vincent C. Traynelis
Iowa City, Iowa

The authors performed a randomized controlled study comparing MED and microsurgical discectomy. They found that the results of both procedures were generally excellent and that there were no important differences between the groups. The "significant" differences noted in incision length and length of stay were clinically meaningless (5 mm and 2 hours, respectively). The MED procedures required approximately 20 minutes longer and used more expensive equipment. The results of this study indicate that modern microsurgical procedures provide excellent results in correctly selected patients. Surgeons should select the procedure they are most comfortable with and become familiar with the tools necessary for the facile performance of such procedures. More expensive and trendy procedures should not be adopted over well proven alternatives unless there is a benefit in patient outcome.

Daniel K. Resnick
Madison, Wisconsin

In the present study, Righesso et al. describe the results of a randomized study of open discectomy versus MED in a select group of 40 patients. All harbored posterolateral disc herniations and experienced symptoms unresponsive to nonoperative treatment. Patients in both groups recovered to a similar degree. The size of incision and length of hospital stay were significantly longer in the open discectomy group, whereas operative time was significantly longer in the MED group. The authors conclude that the procedures yield similarly satisfactory results.

Overall, this is an interesting study within its limitations, the primary one being sample size. Although many would argue that the use of loupes and a headlight is not equivalent to the use of an operating microscope, it is instructive to note that there were still no significant outcome differences. These data highlight the difficulty of improving on the "gold standard."

Christopher E. Wolfla
Milwaukee, Wisconsin

Righesso et al. are to be congratulated for putting together a prospective randomized trial comparing open discectomy to MED in the treatment of lumbar herniated discs. I am mystified by the fact that we derive our knowledge of a procedure performed hundreds of thousands of times each year from 40 patients. Be that as it may, the authors state that the statistical power of this study is 90%.

The authors' conclusion is that it is hard to improve on the standard procedure for herniated lumbar disc. The most important endpoint, time to return to work, is not affected by the procedure performed. The three statistically significant differences are operator-dependent. The authors performed open surgery using loupe magnification. The operating microscope affords the surgeon three-dimensional vision through a smaller opening. Thus, a 5 mm difference in the length of the incision could be reduced by the use of the operating microscope. It is not clear how it was decided when to discharge the patients after surgery. Thus, it is hard to know that the 2 hour difference in duration of hospitalization was a result of the surgical procedure. Although I imagine that the MED operation takes longer to perform, the exact operating time will depend on the skill and experience of the surgeon. It is hoped that others with a focused interest in spine surgery will repeat this study.

Allan H. Friedman
Durham, North Carolina

This is a well-organized, simple study comparing standard microdiscectomy techniques with microendoscopic techniques. Importantly, it is a rare prospective, randomized study comparing the two techniques. The authors' results show equivalence in outcomes for the two techniques. Despite the vigorous industry promotion of new instruments for microendoscopic techniques and the popularity of this topic at professional meetings, the superiority of these "minimally invasive" techniques has not yet been established.

After many years of experience with rod-lens scopes and tubular retractors at our institution, we have adopted a combination of these two techniques. We have returned to using the operating microscope with tubular retractors and the muscle-dilating approach described by Foley and Smith (1). The enhanced ability to focus the beam of light and improved microscope optics in general have rendered the rod-lens scope obsolete in microdiscectomy procedures in our institution.

Lastly, it should be noted that one significant advantage of the sequential muscle-dilating and tubular retractor placement is in obese patients. Any open technique that involves subperiosteal stripping of the paraspinal muscles and placement of blade retractors in obese patients usually requires a much larger incision, whereas tubular retractors are now available in a variety of extended lengths. The diameter of the tube and length of skin incision can be quite small and reproducible, yet presumably less painful and cosmetically more satisfactory.

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Comparison of Section of Filum Terminale and Non-neurosurgical Management for Urinary Incontinence in Patients with Normal Conus Position and Possible Occult Tethered Cord Syndrome

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OBJECTIVE: Patients with persistent urinary incontinence and a normal location of the conus on magnetic resonance imaging scans may have occult tethered cord syndrome (OTCS). We compare outcomes in such patients after filum section versus non-operative treatment.

METHODS: We performed a retrospective analysis of a consecutive series of children with refractory urinary incontinence and normal location of the conus who were offered section of the filum for treatment of possible OTCS.

RESULTS: Eight children, aged 4.4 to 9.8 years, underwent filum section, with one child undergoing two such operations. Clinical urological improvement occurred in seven children at a mean follow-up period of 3.1 years, with improved urodynamic findings in four of the seven children tested postoperatively. Other non-urological back or lower limb abnormalities improved in five out of six children with such findings. None of the patients underwent additional urological operations after filum section. Seven children, aged 3.1 to 13.5 years, all of whom had abnormal urodynamic findings, did not undergo filum section. At a mean follow-up period of 3.3 years, two patients had urological improvement and three patients had undergone bilateral ureteric reimplantations. Other non-urological back and/or lower limb abnormalities were present in five patients and did not improve. One patient had the filum cut after 8 years and improved thereafter.

CONCLUSION: Section of the filum in children with refractory urinary incontinence and OTCS may produce better urological outcomes than continued medical management. A definitive answer to the question of whether section of the filum is better than non-neurosurgical medical management for children with OTCS awaits the conclusion of a randomized controlled trial.

KEY WORDS: Filum terminale, Occult tethered cord syndrome, Surgery, Urinary incontinence

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The tethered cord syndrome secondary to a tight filum terminale is a well-accepted entity (2, 3, 6). In this condition, the filum is thickened and often fatty, and the conus medullaris ends lower than normal.

The concept of a so-called occult tethered cord syndrome (OTCS) was recently proposed. OTCS is characterized by clinical findings consistent with a tethered cord syndrome but with the conus ending in a normal position with or without a thickened filum. The most common clinical abnormalities include urological dysfunction, usually incontinence, and back pain, with minor or no neurological abnormalities in the lower limbs. OTCS as an entity has been espoused to explain the improvements reported after sectioning of the filum terminale in children with the conus ending in a normal position (4, 5, 7, 8, 13–15).

The above reports of beneficial effects of filum section in children with OTCS are either anecdotal or case series, and there is no strong scientific evidence that cutting the filum in such children is beneficial. The concept of

OTCS and the advisability of sectioning the filum terminale in a patient with neurogenic urinary incontinence and the conus in a normal position is still controversial, with much disagreement among pediatric neurosurgeons (1, 10, 12). This study compares outcomes in patients with possible OTCS after filum section versus those who did not undergo filum section.

PATIENTS AND METHODS

The databases of the Division of Neurosurgery and Urology were searched to identify children who met the following criteria: 1) referred to neurosurgery by a pediatric urologist because of persistent urinary incontinence despite medical treatment with a possible diagnosis of a tethered cord syndrome; 2) magnetic resonance imaging (MRI) scans and/or computed tomographic (CT) myelography showing a normal position of the conus, with the conus ending above the lower end plate of the L2 vertebral body; and 3) no other explanation for the urinary incontinence except a possible OTCS.

The neurosurgical clinic charts of the patients identified from the database search were reviewed. Patients were entered into the study if the option of cutting the filum had been discussed, as documented in the clinic chart. During the time covered by the study, children who fit the diagnosis of OTCS were offered the option of filum section as an unproven but possibly beneficial procedure. After discussion of the pros and cons, parents were advised to consider the option and decide whether to have their child undergo surgery or to continue with medical management. For all patients in the study, data were extracted regarding demographics, date of the neurosurgical clinic visit, urological findings, urodynamic studies, back or lower limb pain, other symptoms in the lower limbs, neurological and orthopedic abnormalities, and ability to touch the toes. The radiology reports and radiographic studies were reviewed to identify the level of termination of the conus, the size of the filum, the presence of fat in the filum, and other associated spinal and spinal cord abnormalities (e.g., a syrinx). The date and clinical and urodynamic outcomes at the time of the most recent follow-up evaluation were recorded. A change in the child's urinary continence from baseline to the time of follow-up was determined from review of the office/clinic charts, physician impression, and comparison of before and after 24-hour elimination diaries. For patients who underwent surgery, the operative report was reviewed to identify the level at which the surgery was performed, the amount of bone removal, the size of the filum at surgery, the presence of fat in the filum at surgery, and whether or not the filum retracted when sectioned. The latter three factors were subjectively determined by the surgeon.

The data were entered into an Excel (Microsoft Corp., Redmond, WA) spreadsheet for ease of analysis. The children treated by section of the filum were compared with those who were not treated with filum section. Only descriptive analysis was done because of the small number of patients.

The research protocol was approved by the Ethics Committee of the University of British Columbia. It is helpful for the interpretation of the results of this study to know that approximately 1200 patients were assessed annually at our institution for voiding dysfunction of some sort. The majority of these were treated with behavioral and dietary modification, medications, and/or biofeedback. Only a small select subgroup of patients who were refractory to these interventions went on to have urodynamics and spinal MRI performed each year. Voiding cystourethrograms were not performed routinely, but only selectively for children with pyelonephritis.

Urodynamic studies were performed using saline at body temperature, using a fill rate of 10% of predicted capacity for age per minute according to the Koff formula (capacity = [age + 2] $\times$ 30 mL). Compliance was defined as the change in pressure with a given change in volume ($\delta V/\delta P$). Normal compliance was defined by the following pressure-volume relationship: 95% of healthy children will store urine at less than 20 cm of H_2O pressure up to a volume according to the following: 17 $\times$ age + 55 mL.

RESULTS

Fifteen patients met the study criteria and were included in this analysis. Between 1993 and 2005, approximately 12,000 children with voiding dysfunction were assessed. The 15 patients in this study comprised eight who underwent filum section and seven who did not undergo filum section. Spinal MRI scans were performed in all patients, and CT myelography was also performed in one patient to rule out a possible abnormality that might have been missed on the MRI scan. The mean age was 8.0 years (range, 4.4–9.8 yr) for the surgical group versus 8.2 years (range, 3.1–13.5 yr) for the nonsurgical group. The male-to-female ratio was 5:3 for the surgical group and 4:3 for the nonsurgical group. In all patients, the urinary incontinence was diurnal, and all children had received behavioral and dietary modification, medications, and/or biofeedback under the care of a urologist for at least 1 year. There were two patients younger than 5 years at the time of neurosurgical assessment. One boy was 3.1 years old, had undergone multiple urological operations, and was referred for neurosurgical consultation because he also had associated multiple spinal anomalies. This boy is mentioned later in the text as the child who was initially treated without filum section and then many years later underwent a filum section. The other child younger than 5 years old was a 4-year-old boy who is described in detail below in the first case history. None of the patients, with the exception of the one mentioned above with the spinal anomalies, underwent urinary tract surgery before evaluation by the neurosurgeon for possible OTCS. The urinary incontinence was secondary in two patients in the medical group and primary in all of the other patients. Seven of the eight patients in the surgical group and all the six patients tested in the nonsurgical group had abnormal urodynamic findings at the time of the initial assessment (*Table 1*).

Seven of the eight children in the surgical group and five of the seven children in the nonsurgical group had additional clinical symptoms and signs, as detailed in *Table 2*. One of the most common findings, which was noted in 7 of the 12 children tested, was an inability to touch the toes on maximal forward flexion with the knees extended. On MRI scans and/or CT myelography, none of the patients had a thickened filum and one patient in the surgical group had fat involving the entire length of the filum. In three children, two of whom were in the surgical group, there were spinal radiographic abnormalities: multiple vertebral anomalies in one patient (nonsurgical group), small syrinx at T3–T11 in one patient, and bony spina bifida at L5 in one patient. In the sur-

TABLE 1. Baseline urodynamic findings for the surgical and nonsurgical groups, and postoperative urodynamic findings for the surgical group[a]

	Patient no.	Baseline urodynamics	Postoperative urodynamics	Change from baseline	Change in clinical incontinence
Surgical group	1	Normal capacity, instability	Normal capacity, instability resolved	Improved	Improved
	2	Small capacity, instability, poor compliance	Improved capacity and compliance, instability persistent	Improved	Improved
	3	Small capacity, poor compliance	Capacity, compliance improved, but new instability	Improved	Improved
	4	Large capacity, instability	Not done	Not done	Improved
	5	Large capacity, insensate bladder	Large capacity, insensate bladder	No change	Improved
	6	Normal	Normal	No change	No change
	7	Small capacity, poor compliance, instability	Instability, compliance improved, no change in capacity	Improved	Improved
	8	Small capacity, poor compliance	Small capacity, poor compliance, new instability	Worse	Improved
Nonsurgical group	1	Multiple early unstable contractions, small volume	N/A	N/A	Improved
	2	Large capacity, insensate bladder	N/A	N/A	No change
	3	Not done	N/A	N/A	Improved
	4	Reduced capacity and compliance with increased sensation	N/A	N/A	No change
	5	Large capacity, insensate bladder	N/A	N/A	No change
	6	Small capacity with instability	N/A	N/A	No change
	7	Small capacity	N/A	N/A	No change

[a] N/A, not applicable.

TABLE 2. Clinical abnormalities other than urinary dysfunction in the surgical and nonsurgical groups[a]

	Filum section (n = 8)	No filum section (n = 7)
Fecal incontinence	2	0
Unable to touch toes	6/8[b]	1/3[b]
Pain in back and/or lower limbs	2	1
Toe walking	1	1
Abnormal lower limb reflexes	2	0
Weakness lower limb	1	3
One foot smaller	0	1

[a] Some patients exhibited more than one abnormality.
[b] The denominator indicates the number of patients in whom this finding was sought.

TABLE 3. Outcomes for the surgical group versus the nonsurgical group

	Filum cut	No filum cut
Duration follow-up, mean (range)	3.1 yr (1–10 yr)	3.3 yr (4 mo–5 yr)
Improved incontinence	7/8	2/7
Improved urodynamics	4/7[a]	Not repeated
Other improvement	6/7[a]	0/5[a]

[a] One patient in the surgical group did not have repeated urodynamic assessments and four children, including two in the surgical group, had no clinical abnormalities except for their urinary dysfunction; thus, the numbers used as denominators.

gical group, two of the children were non-twin siblings and one child's father had similar symptoms as a child (Patient 3). One child in the nonsurgical group had an uncle with an intraspinal lipoma. No other children had vertebral abnormalities, cutaneous abnormalities, imperforate anus, or other coexisting anomalies that might be associated with a tethered cord and urinary incontinence.

The clinical outcomes are tabulated in *Table 3*. At a mean follow-up period of 3.1 years (range, 1.0–10.0 yr), seven of the eight patients who had the filum cut improved with respect to their urinary incontinence. There was no incontinence in one child, rare incontinence in four children, usually at night, and less improvement in two children. In five of the six children

who had other non-urological clinical findings as outlined in *Table 2*, there were improvements in these findings. The only child who did not improve was the one with normal urodynamic findings preoperatively. Postoperative urodynamic assessments were performed at 1 year or later in seven children and showed variable improvements in four (*Table 1*) and possible worsening in one. None of the patients underwent urological operations after the filum was sectioned. One child's condition improved initially after the filum was sectioned but deteriorated with respect to urinary continence 8 years later. At repeat surgery, the proximal cut end of the filum had adhered to the dorsal dura and this adhesion was lysed. Postoperatively, she improved again and had maintained her improvement at the time of her 1-year follow-up examination. In the group without filum section, at a mean follow-up period of 3.3 years (range, 4 mo–5 yr), two of the children improved with respect to urinary continence, with one becoming fully continent. None showed improvements in their other non-urological clinical findings. Three children in this group underwent bilateral ureteric reimplantations during the follow-up period. A fourth child, who had congenital lumbar spinal abnormalities, back pain, and toe walking, had already undergone bilateral ureteric reimplantations, vesicostomies, and closure of a vesicostomy before neurosurgical assessment. This child had a repeat vesicostomy and then augmentation cystoplasty and Mitrofanoff after being offered a filum section. After 8 more years, urinary incontinence persisted, in-turning of the feet developed, and the normal filum was cut. Postoperatively, the child claimed to have some "sensation" of bladder filling, and his toe walking, in-turning of the feet, and back pain improved. He went on to require a renal transplantation for renal failure.

In eight of the nine operations to cut the filum, including the patient from the nonsurgical group who later went on to filum section, the operations were performed at a single interlaminar space between L4 and S1, with removal of no bone (one patient with bifid spine), a single lamina (four patients), or the inferior part of the superior lamina and superior part of the inferior lamina (three patients) at one interlaminar level. In one patient, the conus was exposed initially via a L1 laminectomy, and the filum was cut after also removing the L2 lamina. At the time of operation, according to the subjective opinion of the surgeon, the filum appeared thickened in one patient, fatty in two patients, and tight in one patient. In four cases, the surgeon thought the edges of the filum had retracted after the filum was cut. Intraoperative electrophysiological monitoring was not performed routinely during the operations.

Illustrative Cases

Patient 4

Patient 4 (*Table 1*) was a boy who initially presented at 4 years of age with urinary and stool incontinence. He also had some discomfort in his calves and fatigued easily when running. His urological assessment had shown abnormal findings suggestive of upper motor neuron bladder dysfunction and hydronephrosis. On neurosurgical examination, the ankle jerks were absent, but the remainder of the neurological

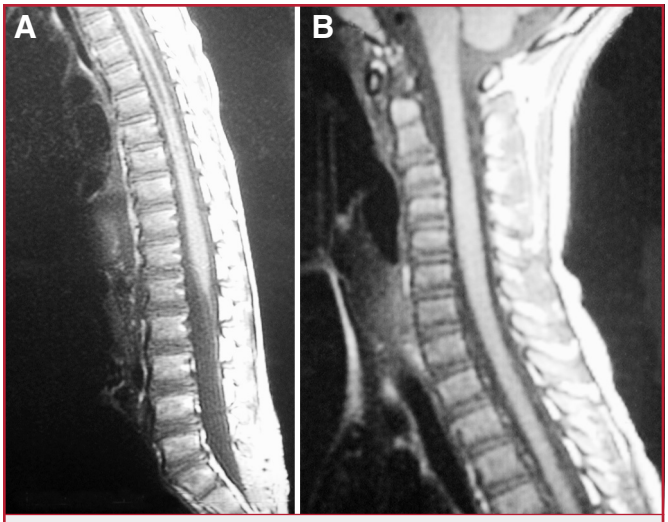


FIGURE 1. A *and* **B**, *sagittal MRI scans showing the conus ending at L1–L2, a normal filum, a small syrinx in the lower thoracic cord, and no Chiari malformation in Patient 4.*

examination findings were otherwise normal, as were his back examination results. An MRI scan of the spine showed the conus to end at L1 with a normal filum (*Fig. 1*). There was a small syrinx from T5 to T8, but no Chiari malformation. Six months later, the patient was being catheterized intermittently for urinary retention and a suprapubic cystostomy was advised by the urologists. Instead, it was opted to cut the filum. At the time of surgery, the filum looked normal and was cut. The cut edges of the filum did not retract. Postoperatively, the patient rapidly improved starting in the immediate postoperative period. At 3 years after surgery, he had no episodes of urinary retention and no urinary incontinence with a timed voiding schedule, on which he had been unsuccessful before surgery, and his hydronephrosis had improved. In addition, his leg fatigue and calf discomfort had disappeared, and his ankle jerks, although diminished, were present. The child refused a repeat urodynamic assessment. A repeat MRI scan showed no change in the syrinx.

Patient 3

Patient 3 (*Table 1*) was an 8-year-old girl who presented with secondary urinary incontinence, increasing toe walking, and pain in her legs. On examination, her heel cords were tight and she was unable to touch her toes. The neurological and back examination results were normal. Urodynamic findings were abnormal, with small capacity and increased compliance. An MRI scan of the spine showed normal results, with the conus ending at mid-L2 and a normal filum (*Fig. 2*). Her father had shown similar symptoms as a child; a CT myelogram showed normal results, but he had a bony S1 spina bifida occulta. Intradural exploration had been carried out from the conus to the bottom of the thecal sac, and no abnormalities had been found. A normal-appearing filum was cut. Postoperatively, the father improved dramatically: He could walk on his heels, his leg pain disappeared, and his urinary function improved. In light of this family history, the child had her filum cut. The filum appeared normal and did not retract. On the day after surgery, she noted sensation of bladder filling, which was new for her. At the time of her last follow-up evaluation 1.3 years later, she was fully continent except for rare nocturnal enuresis, her lower limb pain had disappeared, and her walking had improved

such that she no longer toe walked. Repeat urodynamic findings showed improvement.

DISCUSSION

The current series of children presenting with urinary incontinence and features consistent with a diagnosis of OTCS differs from other reported series in that it comprises two groups of patients: one group in whom the filum was cut and the other in whom the filum was not cut, but continuing management by a pediatric urologist was pursued. This was not a randomized trial, but it is probable that the groups were similar. During the time period of the study, parents were routinely told that the concept of OTCS and the option of cutting the filum when the conus ended in a normal position, especially if the filum appeared normal on MRI scans, were controversial. Cutting the filum was provided as an option, but parents were always asked to go home, think about it, and make a decision in a delayed manner. Approximately half of the parents chose to proceed with surgery.

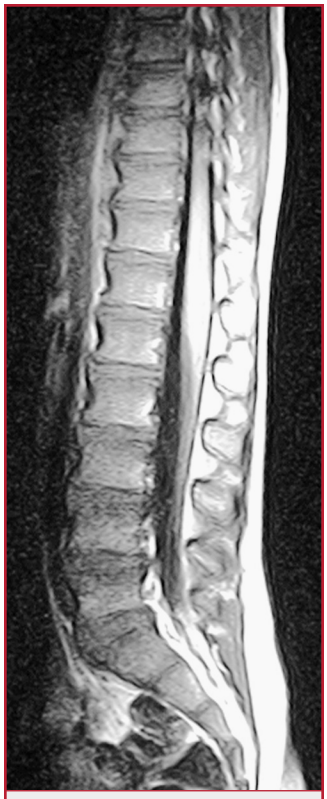


FIGURE 2. *Sagittal MRI scan showing the conus ending at L2 and a normal filum in Patient 3.*

The results of this study suggest that the outcome was better in the patients who underwent filum section compared with those who did not undergo filum section. In seven of the eight patients (88%) treated with section of the filum, improvement in urinary continence was demonstrated at a reasonably long follow-up period ranging from 1 to 10 years (mean, 3.1 yr). None of the children underwent bladder or ureteric surgery after the filum was cut. These results are consistent with other series reported previously, in which improvement rates ranged from 60 to 97% (4, 5, 7, 8, 13–15). On the other hand, there was urological improvement in only two of the seven children in whom this surgery was not performed. In addition, three of the seven children in whom the filum was not cut underwent bilateral ureteric reimplantations for persistent vesicoureteral reflux and urinary infection. One other child underwent vesicostomy and later augmentation cystoplasty and Mitrofanoff, and then developed renal failure. Many years later, the child underwent a filum section when new lower limb findings developed and the child started to have bladder sensation. One might question whether or not an earlier section of the filum might have affected bladder function more and avoided the poor urological outcome. In six out of seven children in the filum section group and in the child with filum section after initial urological management, other clinical abnormalities, such as lower limb weakness or pain, abnormal gait, or restricted forward flexion, improved after surgery. This never occurred in the absence of filum section.

It is interesting that the one surgical patient who did not improve urologically had normal preoperative urodynamic findings. This child also had back and lower limb pain, which, together with the urinary incontinence, suggested a possible OTCS. Thus, surgery was offered and, although there was no urological improvement, the back and lower limb pain disappeared after the operation. One might question whether or not the urological outcome in this case lends support to use of this test as a screening tool for OTCS. However, one must recognize that urodynamic studies are invasive, and the fact that the patient had normal urodynamic findings in the face of persistent incontinence suggests several possibilities. Urodynamics may simply be an insensitive tool for detecting subtle or intermittent bladder dysfunction, or clinical assessment of incontinence may be flawed. Currently, we do not advocate urodynamics as a screening tool for OTCS but consider urodynamics to be an adjunct to the assessment of pediatric voiding dysfunction. In general, we would be reluctant to recommend section of the filum terminale for a presumed OTCS in the face of normal urodynamic findings.

If OTCS is a real condition, one has to postulate that the conus can be tethered by the filum and does not have to be too low. This is reasonably easy to accept per se. It could be simply that the conus is slightly lower than it otherwise would have been had it not been tethered and could still be located normally above the lower endplate of L2. Whatever the location of the termination of the conus, one would expect that the filum would have to be less elastic than normal to pull on the conus in an abnormal fashion. Recognizing that in most cases of reported OTCS and in almost all cases in this series the filum was normal in diameter on the MRI scans, one would have to postulate that perhaps the MRI scans missed abnormal thickening of the filum or that the structure of the filum was abnormal even though the diameter was within normal limits. In this series, only one patient, in whom the MRI scan indicated a normal thickness of the filum, was thought at surgery to have a thickened filum, and discrepancy in the size of the filum on the MRI scan and at surgery has rarely been reported (5, 7). Thus, it is more probable that there is an alteration in the structure of the filum. In one of our patients, the filum was fatty on the MRI scan, although it was not abnormally thick, and at surgery one additional filum was fatty in appearance. There are some data on histopathological examination of the fila from patients with OTCS that indicate excess fibrous tissue and fat compared with normal fila in children (9, 11). If one accepts that the conus can be tethered by a grossly normal-appearing filum, which may be abnormal in structure, one would expect that there would be some evidence of tension in the filum at the time of surgery. Such tightness of the filum was observed in only one of our nine patients, and in only three did there appear to be any

retraction of the cut edges of the filum. Despite what appeared to be a lack of tension in the filum, most patients improved postoperatively. If one accepts that the improvement resulted from the operation, one has to postulate that in this condition of OTCS tethering is intermittent and not necessarily present in the prone position during surgery.

In the current series, one of the associated findings commonly observed in the children was a restriction in forward flexion of the back, with inability to touch the toes with the knees straight. This finding was also observed by the authors in children with the more well-recognized tethered cord syndrome, wherein the conus is too low and the filum is too thick. One might reasonably hypothesize that this is indicative of tension on the lower end of the spinal cord and may be a clinical indicator of tethering.

CONCLUSION

The results of this study suggest that section of the filum for children with refractory urinary incontinence consistent with OTCS may produce better urological outcomes than continued medical management. However, there is a caveat. This was not a randomized study, and there may be sources of bias and other mechanisms to explain the findings. A definitive answer to the question of whether or not section of the filum is better than urological medical management for children with OTCS awaits the conclusion of a randomized controlled trial.

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COMMENTS

The authors report results from a small number of patients undergoing surgical lysis of the filum terminale for the controversial diagnostic entity, occult tethered cord syndrome (OTCS). They also report similar patients from the urological clinic at their institution who were offered surgery but declined. Previously, almost 200 patients undergoing filum lysis for OTCS have been described in uncontrolled case series, with generally favorable results. The current report, however, represents the first case-controlled study of filum lysis for OTCS.

The critical issue with regards to OTCS is the denominator. How many school-aged children are sent to an urologist for voiding dysfunction? How many of these children are refractory to standard medical therapy, such as timed voiding and anticholinergic medications? Finally, what proportion of the latter is diagnosed with OTCS based on radiological and/or functional urodynamic criteria? Diagnostic criteria and referral patterns may make dramatic differences in the perceived incidence of OTCS and in the number of children undergoing intradural spine surgery in an attempt to correct it (2).

It is fascinating that the only child operated upon in this series, despite normal urodynamic bladder function, is also the only operated child who failed to improve. Although it is impossible to draw conclusions from such a small number of patients, this finding emphasizes the importance of identifying specific diagnostic criteria for OTCS and defining their sensitivity, specificity, and positive predictive value.

Despite inconsistent findings regarding the morphology of the filum terminale in their surgical series, Steinbok and colleagues speculate that intermittent pathological tension in the filum terminale causes OTCS. Of interest, the only two systematic studies of filum terminale morphology and histology report thickened and excessively fibrous fila terminale in this condition (1, 3).

Numerous confounding variables are present in this and other studies of surgical filum lysis for OTCS. Surgery for OTCS could dramatically increase the number of North American children undergoing filum lysis. Furthermore, clinical equipoise exists with regards to this indication (4). I agree with the authors that a prospective randomized trial is indicated.

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This is a retrospective study with small numbers that has been very carefully performed. The results are compelling. Although its tentative conclusion that filum sectioning is beneficial under the specified circumstances may not yet be considered a standard recommendation, it

certainly justifies the prospect of a larger randomized controlled study.

I would like to recommend the following in the authors' future efforts. First, "normal" filum diameter should be defined. Secondly, histology should be performed on a segment of the cut filum to specifically look for the amount and density of the collagen, fat, and other anomalous contents. Also, "normal" and "abnormal" appearance of the filum on magnetic resonance imaging scans should be defined. In this last context, we have found axial T2-weighted images cut sequentially from the conus to the end of the thecal sac most helpful. A thick, fatty, or otherwise densely fibrotic (proven by histology) filum appears distinctly stout and intensely black amongst the grayer, slender nerve roots. The thick black dot often has a contrasting bright "bloom" next to it that is decidedly not subtle.

I should also comment on the lack of a "tight" appearance of most of these fila at the time of surgery. The highly controlled and artificial condition for the child's spine during surgery has nothing to do with real life, in which unimaginable states of bending and stretching are routine antics for an active child. The intermittent tugging on the conus by an unyielding, though not too tight-looking, filum may actually be more harmful than chronic sustained tension, a phenomenon related to the physiological adaptation of conductive membranes under changing versus constant conditions.

Dachling Pang
Oakland, California

This provocative article addresses a very controversial area in pediatric neurosurgery, namely the problem of a child with undefined urinary incontinence and no clear radiographic evidence of tethered cord. To date, a number of anecdotal reports have suggested that a subset of these children seem to benefit from filum terminale sectioning, which carries a very low rate of morbidity.

The current report is a nonrandomized series of such patients, in whom the decision to operate or not was largely made by the parents. This obviously introduces bias, as acknowledged by the authors. Perhaps some issue of the severity of incontinence or associated signs or symptoms may have pushed the clinician and, therefore, the patients' parents to lean toward or away from surgery. However, pending a more formal randomized trial, this report offers the most convincing evidence to date to support the value of surgery in this setting. It also raises the even more difficult issue of what to do with the thickened filum with normal conus level in asymptomatic children or younger children who have not yet achieved bowel and bladder continence.

It is also interesting that the degree of filum separation in the operated patients did not clearly predict success of the procedure. On the basis of this and other reports, it would seem reasonable to offer filum sectioning in the setting of an incontinent child with abnormal urodynamic studies, even if the magnetic resonance imaging scans are not convincing for tethering.

Leslie N. Sutton
Philadelphia, Pennsylvania

Steinbok et al. describe a series of 14 children affected by urinary incontinence and other nonurological back or lower limb abnormalities. All patients had a normally located conus medullaris, and all were offered surgical section of the filum terminale. The families of eight patients chose surgical treatment; six refused surgical treatment and were managed medically. In the first group, seven out of eight patients had improved with a mean of 3 years after filum section. In the second group, only two patients improved. The two groups were not randomized. However, in spite of this major bias, this study remains a well written, concise, and informative report that compares, for the first time, two treatment modalities (surgical versus nonsurgical) in two similar groups of patients affected by probable OTCS in which the only criteria for treatment modality was parental choice. These results are interesting and warrant further larger, multicentric, randomised studies. If the effectiveness of surgical management of urinary incontinence was confirmed, the whole management and pathophysiology of this clinical entity should be reconsidered. The authors do not consider the role of intraoperative monitoring and stimulation to identify the filum among the sacral rootlets that come into vision through an L4–L5 laminotomy. Identification of a thick, fatty filum is relatively easy anatomically, but isolation of a normal filum could be more difficult through a limited approach on a pure anatomical basis and the role of intraoperative monitoring for a safe procedure should not be underestimated.

Giuseppe Cinalli
Naples, Italy

In this article, Steinbok et al. suggest that filum section in children with normal location of the conus medullaris may improve urinary incontinence. They have conducted a retrospective analysis as well as they could despite inherent limitations. I would like to note, however, that the outcome assessment was purely qualitative and the changes in urinary incontinence were based on the physicians' notes in the office and clinic charts. The addition of a nonsurgical group does not provide statistical analysis in this retrospective analysis of a small number of patients. As the authors concluded, we should await the conclusions of a randomized study.

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SUBMISSIONS, PEER-REVIEW, AND DISCLOSURE

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VENTRICULOPERITONEAL SHUNT COMPLICATIONS IN CALIFORNIA: 1990 TO 2000

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BACKGROUND: Risk factors for ventriculoperitoneal (VP) shunt complications have not been assessed with population cohort data since the advent of modern surgical techniques. We examined demographic factors and VP shunt complications in a population-based retrospective cohort study of all nonfederal California hospital admissions between 1990 and 2000.

METHODS: We identified all admissions in a statewide administrative hospital discharge database that indicated a VP shunt insertion. Repeat hospital admissions within California generating a discharge diagnosis of surgical shunt complication, defined as a shunt replacement, revision, removal, or exploration, represented the primary outcome of interest. We performed Kaplan-Meier survival analyses and Cox proportional hazards modeling to analyze sex, age, ethnicity, socioeconomic status based on payer status, and type of hydrocephalus in relation to the risk of shunt complications.

RESULTS: The annual population incidence of VP shunt placement was 5.5 per 100,000. Among 14,455 individuals with 65,040 person-years of follow-up, the cumulative complication rate at 5 years was 32%. Children demonstrated a higher rate of shunt complications than did adults at 5 years (48 versus 27%, $P < 0.0001$). The following demographic factors were independently associated with increased risk of shunt complications: male sex (hazard ratio [HR], 1.1; 95% confidence interval [CI], 1.03–1.2), low socioeconomic status (HR, 1.2; 95% CI, 1.1–1.3), and age younger than 19 years (HR, 1.6; 95% CI, 1.4–1.7). Compared with communicating hydrocephalus, obstructive hydrocephalus was also associated with increased risk of shunt complications (HR, 1.7; 95% CI, 1.5–1.9).

CONCLUSION: VP shunt complications are common, especially in children. Further study is needed to explain the associations between demographic factors and elevated shunt complication rates.

KEY WORDS: Epidemiology, Hydrocephalus, Ventriculoperitoneal shunt

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Hydrocephalus is a common condition accounting for 69,000 hospital discharges each year in the United States (1). Congenital hydrocephalus is the second most common congenital brain malformation after spina bifida (22), and there are approximately 30,000 cerebrospinal fluid (CSF) shunt procedures performed annually in the United States (1, 16), amounting to $94 million of medical costs per year (1).

CSF shunt procedures have dramatically reduced the morbidity and mortality of hydrocephalus, but they have potential complications that may require multiple surgical procedures during a patient's lifetime. Causes of shunt malfunction include obstruction, mechanical disconnection or breakage, infection, and overdrainage. In pediatric surgical series, shunt failures occur in 14% of patients just within the first month after shunt placement (13), and 40 to 50% of shunts will fail within the first year (12, 19). Adults also experience a relatively high (29%) shunt failure rate within the first year (7). Long-term studies suggest that 45 to 59% of all patients, regardless of age, will require a shunt revision (2, 7). Multiple shunt failures (11, 19, 21) and infections (10) are common, and revisions account for 48% of all shunt-related procedures performed in the United States (1).

Studies of CSF shunt complications based on experiences from a single hospital (2, 6, 9, 11, 13, 14, 17, 19, 21) have shown that younger age, prematurity, increasing number of previous revisions, and shorter time to first revision increase the risk of shunt complications (13, 17, 19). Specific causes of hydrocephalus, such as intraventricular hemorrhage and brain tumor, have also been reported to increase the risk of shunt failure (7, 11, 19), although not all studies have supported this association (13, 17).

Few population-based studies of CSF shunts have been reported in the United States. One study predates the 1980s (8), whereas the other two are cross-sectional studies that lack follow-up data (1, 16). Thus, the demographic factors that influence the risk of shunt complications have yet to be determined in an unselected population. We analyzed California hospital discharge data over an 11-year period to examine ventriculoperitoneal (VP) shunt complication rates and to determine factors that may be associated with increased risk of shunt complications.

PATIENTS AND METHODS

The Office of Statewide Health Planning and Development collects administrative data regarding discharge diagnoses and procedures for all hospital admissions to nonfederal hospitals in California. Using this database, we identified all individuals admitted to a California hospital during the years 1990 to 2000 who received a discharge procedure code (International Classification of Diseases, 9th Revision-Clinical Modification [ICD-9-CM], 02.34) indicating insertion of a VP shunt. Patients who had a revision, replacement, or removal of a CSF shunt were only included in this study if they also carried a discharge procedure code indicating the placement of a new VP shunt during a previous hospitalization within the study period. The incidence rate of CSF shunt insertion was calculated as the total number of new placements per year, divided by the California population for that given year (4). Patients whose zip codes indicated residence outside the state of California were excluded, as were patients with an age of greater than 100 years when their CSF shunts were placed (n = 9).

Patients who have a social security number are given a unique identifier in the Office of Statewide Health Planning and Development database and, thus, could be followed over subsequent hospitalizations within California during the 10-year study period. However, patients without a unique identifier could not be tracked over time and were, therefore, excluded from analyses regarding shunt complications.

We analyzed the following individual characteristics in relation to shunt complication rates: sex, ethnicity, age at the time of the first shunt placement (<1 month [neonate], 1 to 12 months [infant], 1 to 18 years [child], >18 years [adult]), hydrocephalus type (spina bifida, congenital excluding spina bifida, communicating, obstructive), and socioeconomic status (SES) based on source of payment (high SES indicates private insurance or self-pay; low SES indicates Medicare/Medicaid or indigent).

Our primary outcome of interest was the time to the first surgical shunt complication. A surgical shunt complication was defined as the presence of at least one of the following procedure codes in a subsequent hospital discharge record: replacement or revision of ventricular shunt (ICD-9-CM, 2.42), removal of ventricular shunt (ICD-9-CM, 02.43), exploration of ventricular shunt (ICD-9-CM, 02.41), or distal shunt revision (ICD-9-CM, 54.95).

In a survival analysis modeling time to first shunt complication, we considered the period at risk to begin at the time of VP shunt placement. Because the exact date of procedure was not available to us, we estimated the beginning of the risk period as the 15th of the month when the VP shunt was placed. The failure event was defined as the first surgical shunt complication. Patients were censored or removed from analysis at the time of death during any hospitalization. Patients who were not identified as deceased in the dataset were assumed to have been followed until the end of the study period and, thus, were censored in December of 2000. Because we were unable to account for patients who left the state of California or to identify those who died outside of a California hospital, our methods overestimate the true at-risk period. Thus, our study provides a conservative or lower-bound estimate of the rate of VP shunt complication.

We constructed Kaplan-Meier curves to model complication-free shunt survivals and performed log-rank tests to identify factors that are associated with lower shunt survivals in a univariate analysis. We then constructed multivariate models using Cox proportional hazard regression analysis and calculated hazard ratios (HRs) and 95% confidence intervals (CIs). All individual factors that were significant predictors in the univariate analysis were included in the multivariate model. Statistical analyses were performed using the Stata statistical software package (v. 7; Stata Press, College Station, TX).

RESULTS

The incidence rate of new VP shunt placements was 5.5 per 100,000 per year, based on the 19,284 patients identified during the study period. Children represented one-third of all patients who received a VP shunt during the study period (*Table 1*). Obstructive hydrocephalus (49%) was the most common accompanying diagnosis, followed by congenital hydrocephalus, including spina bifida (17%) and communicating hydrocephalus (14%).

The rate of shunt complications could only be determined in the 75% of patients who had a social security number and who could, thus, be followed over time. Infants aged younger than 1 year were more likely to lack a social security number and, thus, to be excluded from follow-up analyses than were patients aged more than 1 year at the time of initial shunt insertion (67 versus 14%, $P < 0.0001$). Hispanics were also more likely than non-Hispanics to lack a social security number (40 versus 20%, $P < 0.001$).

Shunt Complications

The remaining analyses are restricted to the 14,455 patients (of whom 80% were aged > 18 yr) with a VP shunt whose subsequent hospitalizations could be identified. The mean length of follow-up was 54 months (standard deviation, 38 mo), and children were followed on average longer than adults (57.4 versus 53.1 mo, $P < 0.001$). Three percent of patients died during the initial hospitalization when the VP shunt was placed. Another 11% of patients died during a subsequent hospitalization within California. Children were less likely to die in a hospital during the study period than were adults (6.2 versus 16.7%, $P < 0.0001$). Among those who died during a subsequent hospitalization, the median time from

TABLE 1. Characteristics of 19,284 patients who received a ventriculoperineal shunt in California between 1990 and 2000

	%
Male	52.4
Age at shunt placement	
Neonate (<1 mo)	7.9
Infant (1 mo-1 y)	12.2
Child (1–18 y)	13.8
Adult (>19 y)	66.2
Ethnicity	
Caucasian	60.1
Hispanic	18.7
African-American	7.2
Asian	5.9
Native American	0.4
Unknown	7.8
Low socioeconomic status	50.2
Hydrocephalus type	
Obstructive only	48.5
Communicating only	14.3
Communicating and obstructive	11.5
Congenital, not spina bifida	11.5
Spina bifida	5.7
None of the above	8.5

TABLE 2. Surgical shunt complication rates among 14,455 children and adults who received a ventriculoperineal shunt in California between 1990 and 2000[a]

	All patients (%) n = 14,455	Children (%) n = 2905	Adults (%) n = 11,550
Any shunt complication	29.0	46.4	24.6
Shunt replacement	21.6	36.4	17.9
Shunt removal	11.0	20.8	8.6
Distal shunt complication	5.2	7.9	5.9
Shunt exploration	0.7	1.1	0.5

[a] Note that all types of shunt complications were statistically more common in children than in adults ($P < 0.0001$).

shunt placement to in-hospital death was 8 months (interquartile range, 2–30 mo).

Among patients with a VP shunt who could be followed over time, 35% experienced at least one surgical shunt complication during the study period, and 11% had multiple (two or more) shunt complications. Patients with multiple complications had a mean of three complications each (standard deviation, 1.8), and 16 patients underwent 10 to 23 hospitalizations for shunt complications during the follow-up period.

Shunt replacement or removal occurred in 95% of patients with a shunt complication, whereas distal shunt complications and shunt explorations were less common (*Table 2*). All forms of shunt complications were significantly more frequent in children.

Time to First Shunt Complication

The shunt survival analysis included 11,550 adults and 2905 children who received a VP shunt, with 51,150 and 13,889 person-years of follow-up, respectively. Children consisted of patients aged 1 to 18 years (56%), infants aged 1 to 12 months (32%), and neonates aged less than 1 month (12%).

Overall, the cumulative VP shunt complication rate was 15% in the first month, 25% at 1 year, 32% at 5 years, and 34% at 10 years. Children had higher rates of shunt complications than adults (26 versus 12% in the first month, 39 versus 21% at 1 year, 48 versus 27% at 5 years, and 55 versus 29% at 10 years, $P < 0.0001$, log-rank test). Compared with adults, neonates (univariate HR, 2.5; 95% CI, 2.2–2.9) had the worst outcome (*Fig. 1A*). Infants (HR, 2.0; 95% CI, 1.8–2.2) and older children (HR, 2.0; 95% CI, 1.9–2.2) also exhibited an increased risk of complications when compared with adults.

Patients with obstructive hydrocephalus (*Fig. 1B*) exhibited a higher shunt complication rate than patients with communicating hydrocephalus (HR, 1.9; 95% CI, 1.7–2.1). The shunt failure rates did not differ significantly between patients with spina bifida and those with other types of congenital hydrocephalus ($P = 0.45$). Male sex (HR, 1.14; 95% CI, 1.1–1.2) and lower SES (HR, 1.5; 95% CI, 1.4–1.6) were also associated with a higher rate of shunt complications.

Caucasians and Asians (*Fig. 1C*) exhibited similar survival curves that were not statistically different ($P = 0.38$), and survival curves for African-Americans and Hispanics also were not statistically different ($P = 0.71$). In univariate analysis, African-Americans and Hispanics together experienced an increased risk of VP shunt complications when compared with Caucasians and Asians (HR, 1.3; 95% CI, 1.2–1.4). The 54 Native Americans identified in our cohort had the highest complication rate compared with Caucasians (HR, 1.7; 95% CI, 1.2–2.6).

Multivariate Analysis

We included the following variables in a Cox proportional hazards model: sex, ethnicity, age group, type of hydrocephalus, and SES. The type of hydrocephalus was the strongest independent risk factor for VP shunt complications (*Table 3*). Compared with patients with communicating hydrocephalus only, those with congenital hydrocephalus (HR, 3.1; 95% CI, 2.6–3.6) or obstructive hydrocephalus (HR, 1.7; 95% CI, 1.5–1.9) were at increased risk of shunt complications, as were patients with both communicating and obstructive hydrocephalus (HR, 2.4; 95% CI, 2.1–2.7). Male sex (HR, 1.1; 95% CI, 1.03–1.2) and low SES (HR, 1.2; 95% CI, 1.1–1.3) were also associated with increased risk of shunt complications, whereas ethnicity no longer demonstrated a significant effect on outcome

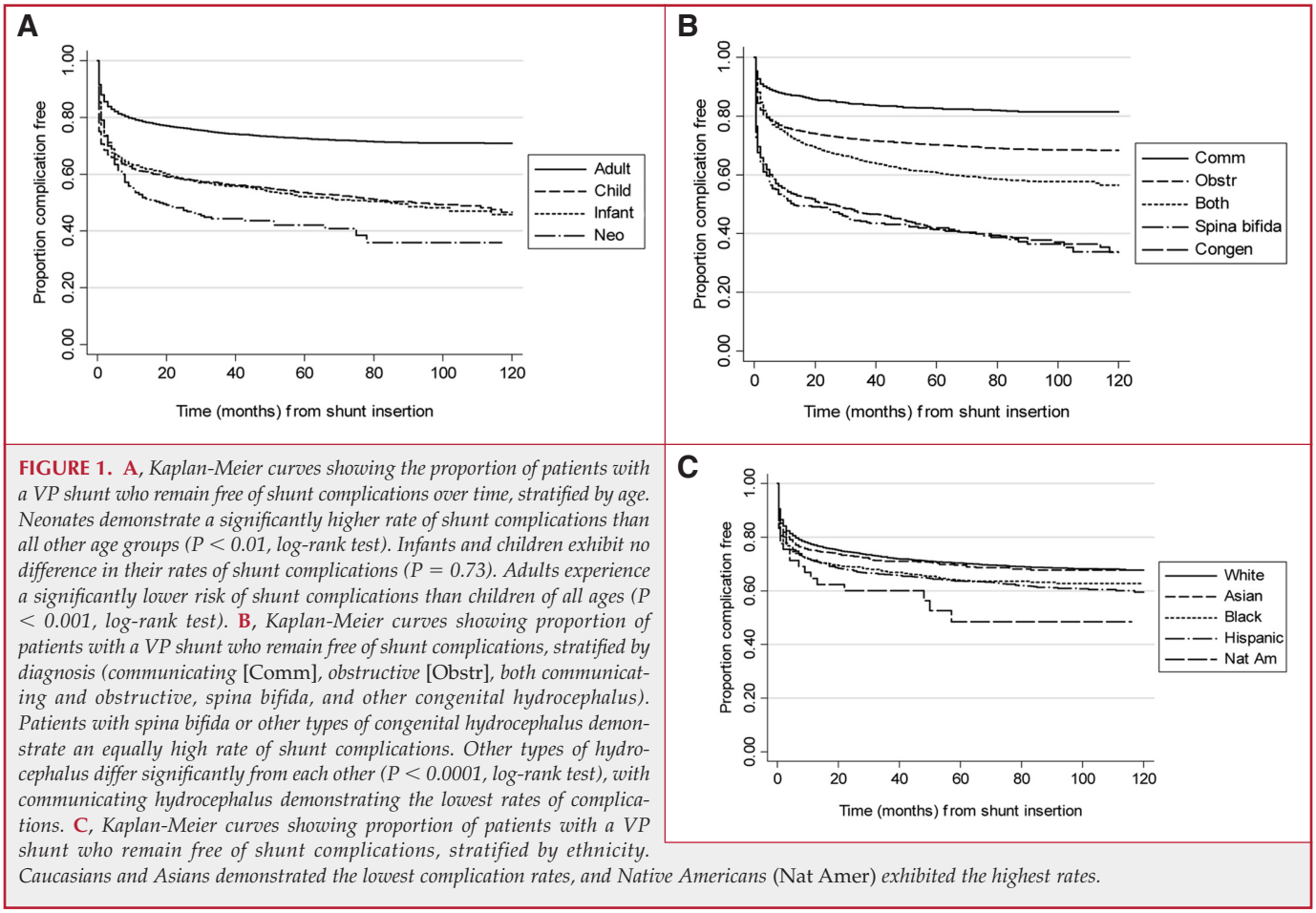


FIGURE 1. A, *Kaplan-Meier curves showing the proportion of patients with a VP shunt who remain free of shunt complications over time, stratified by age. Neonates demonstrate a significantly higher rate of shunt complications than all other age groups ($P < 0.01$, log-rank test). Infants and children exhibit no difference in their rates of shunt complications ($P = 0.73$). Adults experience a significantly lower risk of shunt complications than children of all ages ($P < 0.001$, log-rank test).* **B**, *Kaplan-Meier curves showing proportion of patients with a VP shunt who remain free of shunt complications, stratified by diagnosis (communicating* [Comm], *obstructive* [Obstr], *both communicating and obstructive, spina bifida, and other congenital hydrocephalus). Patients with spina bifida or other types of congenital hydrocephalus demonstrate an equally high rate of shunt complications. Other types of hydrocephalus differ significantly from each other ($P < 0.0001$, log-rank test), with communicating hydrocephalus demonstrating the lowest rates of complications.* **C**, *Kaplan-Meier curves showing proportion of patients with a VP shunt who remain free of shunt complications, stratified by ethnicity. Caucasians and Asians demonstrated the lowest complication rates, and Native Americans* (Nat Amer) *exhibited the highest rates.*

after adjustment for other factors such as SES. Compared with adults, children of all age groups also demonstrated an increased risk of shunt complications, after adjustment for potential confounders (neonate: HR, 1.4; 95% CI, 1.1–1.7; infant: HR, 1.3; 95% CI, 1.2–1.5; and child: HR, 1.7; 95% CI, 1.5–1.8).

Of the patients who had a first shunt complication, 31% went on to experience at least one more complication during the study period. A shorter time to first shunt complication (<6 mo) was associated with a greater probability of having a subsequent shunt complication in children (odds ratio, 1.3; 95% CI, 1.02–1.7) but not in adults (odds ratio, 0.85; 95% CI, 0.71–1.03).

DISCUSSION

In this first longitudinal study of VP shunts within a United States population since the 1970s, we found that the overall rate of surgical shunt complications was 35% during a mean follow-up period of 4.5 years. Children, and especially neonates, experienced the highest complication rates. Almost half of the children required a repeat surgical procedure by 5 years of follow-up. Although African-Americans and Hispanics demonstrated a significantly higher rate of VP shunt complications than Caucasians and Asians in univariate analyses, ethnic differences were no longer apparent after adjusting for SES in the multivariate analysis. Male sex and type of hydrocephalus also independently increased the risk of surgical shunt complications.

This study is subject to a number of important limitations. Only patients with a social security number were able to be followed over time, leading to potential selection bias and an underrepresentation of infants and Hispanics. We lacked data regarding mortality outside of California hospitals during the study period, as well as information regarding which patients might have left the state, again leading to potential bias if patients remaining in California differed systematically from those who were unknowingly lost to follow-up. Furthermore, our shunt complication and mortality rates represent lower-bound estimates of the true population rates, given our lack of knowledge of how many patients left the state. We relied on hospital discharge codes that may not have been recorded reliably. For instance, the accuracy with which communicating and obstructive hydrocephalus was coded is unknown. These study limitations are offset by a number of advantages, including the large, ethnically diverse population base, a relatively

TABLE 3. Multivariate hazard ratios of individual characteristics associated with increased risk of developing a ventriculoperineal shunt complication[a]

	HR	95% CI	*P* value
Male	1.1	1.03–1.2	0.003
Age group			
Adult	Reference	Reference	
Neonate	1.4	1.1–1.7	0.002
Infant	1.3	1.2–1.5	<0.001
Child	1.7	1.5–1.8	<0.001
Ethnicity			
Caucasian	Reference	Reference	
African-American	1.0	0.9–1.2	0.48
Hispanic	1.0	0.9–1.1	0.98
Asian	1.0	0.8–1.1	0.49
Native American	1.5	0.98–2.2	0.06
Low socioeconomic status	1.1–1.3	<0.001	
Type of hydrocephalus			
Communicating	Reference	Reference	
Obstructive	1.7	1.5–1.9	<0.001
Communicating and obstructive	2.4	2.1–2.7	<0.001
Congenital (including spina bifida)	3.1	2.6–3.6	<0.001

[a] HR, hazard ratio; CI, confidence interval.

recent cohort, and our ability to follow a large number of patients over a significant period of time, whereas previous population-based studies have been primarily cross-sectional in design (1, 16).

The incidence rate of first-time VP shunt placements in our population was 5.5 per 100,000. This approximates the average age- and sex-adjusted incidence of initial CSF shunts during the early 1970s in Minnesota (4.6 per 100,000) (9). During the study period, the mean number of new VP shunts placed in California was 1300 per year. Because the population of California is approximately one-tenth that of the United States, our study would suggest that approximately 13,000 new VP shunts are placed each year in patients in the United States. This number falls directly between the two previous population estimates of new VP shunts inserted annually in patients in the United States (8300 and 17,000) (1, 16).

Children are known to experience a high rate of shunt complications. The children in our study had a 39% shunt complication rate at 1 year, with an overall complication rate of 52% by 10 years. Others have reported similar pediatric VPS shunt failure rates in the 40 to 53% range during a mean follow-up period of 1 to 3 years (11–13, 19). Possible explanations for the higher shunt failure rates include the higher growth rate and higher risk of shunt infections experienced by children (3, 5). In one large European multicenter study, 80% of shunt infections occurred in infants aged younger than 6 months (7). In our study, the in-hospital mortality rate of pediatric patients with VP shunts was 6.2% after a mean follow-up period of 4.8 years. This rate is an underestimate of total mortality because we did not have access to outpatient death records. A recent report of children who received a CSF shunt at a single institution suggests that overall mortality rate is 8.9% at 5 years (20).

Male patients are disproportionately represented among those who receive a CSF shunt (6, 7, 15). The male-to-female ratio of patients receiving CSF shunts is 1.17 to 1 (1). We found that the risk of shunt complications was also elevated in male patients by approximately 10%. Obstructive hydrocephalus was also associated with an increased risk of shunt complications in our cohort when compared with communicating hydrocephalus and congenital hydrocephalus. Others have also reported an increase in shunt failure rates among patients with obstructive hydrocephalus caused by a tumor (19), although not all studies have found that the type of hydrocephalus affects the risk of shunt complications (6, 13, 17). Differences in underlying cause or mechanical factors may be responsible for the higher shunt complication rates in patients with obstructive hydrocephalus, although future studies are needed to confirm this hypothesis.

To our knowledge, this is the first study that addresses the risk of VP shunt complications in relation to ethnicity and SES. African-Americans, Hispanics, and Native Americans fared worse, as illustrated by the Kaplan-Meier graphs, whereas Caucasians and Asians demonstrated a significantly lower rate of shunt complications on univariate analyses. However, these differences were no longer significant after adjusting for the effect of SES. Lower SES was independently associated with a 20% increased hazards ratio for VP shunt complications. To determine whether this is the result of disparities in hospital characteristics and surgeon volume (18) or to other factors is beyond the scope of this study.

VP shunt procedures represent a significant health care expenditure, costing, by one estimate, approximately one billion US dollars during the year 2000 (16). Approximately half of the cost associated with VP shunt procedures are spent on shunt revisions (1). The fact that 32% of our population with VP shunts experienced a surgical complication reminds us that the current treatment for hydrocephalus is unsatisfactory for a large proportion of patients. More studies are needed to elucidate the risk factors that contribute to shunt complications, so that preventative strategies can be devised to improve the long-term outcome of patients with hydrocephalus.

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COMMENTS

This carefully constructed population-based study provides us with contemporary data that will be a useful resource for future epidemiological investigations of ventriculoperitoneal shunting for the treatment of hydrocephalus. Although none of the findings are surprising, they do at least support the results of a wide range of previous studies. It is a bit disappointing that we have not made greater inroads into the epidemiological problems associated with shunts over the past 25 years.

Paul H. Chapman
Boston, Massachusetts

This is a population-based survey performed over a 10-year period in California examining the outcomes of 14,455 shunt placements. Via uni- and multivariate analysis, the authors found that younger age, male sex, low socioeconomic status, and obstructive hydrocephalus were independent risk factors for shunt complications. As the authors discuss, there are a number of inaccuracies related to inaccurate coding, missing patients (patients not entered because of lack of social security number), patients lost to follow-up or moving out of state, patients dying, etc. in large data sets such as this. These inaccuracies are somewhat compensated for by large numbers; thus, the estimates for the patients identified are reasonably accurate and are likely lower estimates of complications. Suffice it to say that shunt complications remain 32% overall and 48% in children and have likely not changed much over the previous several decades. Studies such as this remind us that the success of treatment of hydrocephalus with shunts is not satisfactory and is worthy of every effort to improve things.

James M. Drake
Toronto, Canada

This is a review of adult and pediatric shunts performed in California over a 10-year period, with data on reoperation for shunt complications obtained from a state registry. The results are not surprising and basically confirm earlier and smaller single institution studies. Children had a higher rate of shunt problems than adults, and lower socioeconomic status was an independent risk factor for shunt complications. The study probably underestimates the true incidence of problems because patients who died or moved out of state were lost to follow-up and infants were underreported because they often lacked social security numbers. The analysis of obstructive versus communicating hydrocephalus is probably erroneous because there was no way to really distinguish these from each other in a study of this type.

Despite the hope that endoscopic third ventriculostomy would eliminate the need for shunts and shunt complications, shunts with all of their attendant problems remain. The fact that patients of lower socioeconomic status had more problems is unexplained. I suspect this is because this group of patients had more complex forms of hydrocephalus, such as postinfectious, posttraumatic, and posthemorrhagic types, which tend to lead to multicompartmental ventricles, infections, and other risk factors.

Leslie N. Sutton
Philadelphia, Pennsylvania

This study examines a number of factors related to the incidence of ventriculoperitoneal shunt complications in the state of California from 1990 to 2000, thereby providing a large cohort to analyze. As the authors note, there were a number of limitations to the data available, including the fact that 25% of the patients had no social security number and could not be followed. The accuracy of coding is also subject to question. Coding for sex was highly accurate and the reliability of males being at higher risk for shunt complications leaves little doubt, as does younger age. The validity of coding for types of hydrocephalus is very suspect and differentiation of complication rates for communicating hydrocephalus, obstructive hydrocephalus, and communicating and

obstructive hydrocephalus leaves much room for question. How is it possible to accurately separate communicating and obstructive hydrocephalus from hydrocephalus that is only communicating versus hydrocephalus that is only obstructive? This is pure fiction. As a side note, all hydrocephalus are obstructive with the exception of that related to cerebrospinal fluid overproduction associated with a choroid plexus papilloma. A neonate born with hydrocephalus will be correctly coded as having congenital hydrocephalus. On subsequent admissions, this distinction is often lost. Even in our office records, I note discrepencies for older children as to whether the hydrocephalus is properly coded as congenital versus acquired.

The incidence of hydrocephalus associated with an open neural tube defect (spina bifida/myelomeningocele) has dropped markedly. A study covering the time interval from 2000 to 2010 will have but a fraction of the 5.7% incidence noted in the present study.

Fifty-four of the 14,455 patients in the study group were classified as Native American. What are the criteria to be classified as Native American? To be considered as such, does one have to be 100% Native American or will 51% suffice? Presumably, the selection was made by the individual checking off a box on a questionaire. Were genealogy studies performed for confirmation? It would take but few complications to skew the outcomes. To draw conclusions based on 54 Native Americans seems suspect.

This study does put into broad overview the complication rates associated with ventriculoperitoneal shunts. As long as hydrocephalus is treated with mechanical devices, there will be complications. To say that the current treatment of hydrocephalus is unsatisfactory for a large proportion of patients is a bit harsh. One has only to remember the prognosis for patients with hydrocephalus before shunts became available. The complication rate has slowly diminished, but do we need to do better? Yes, much better.

J. Gordon McComb
Los Angeles, California



19th century English whaling gear, illustrated by William Scoresby, Jr. *From*: Matthews, LH: *The Whale*. New York, Simon & Schuster, 1968.

CRANIOTOMY AND CLIPPING OF INTRACRANIAL ANEURYSM IN A STEREOSCOPIC VIRTUAL REALITY ENVIRONMENT

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OBJECTIVE: The release of results of International Subarachnoid Aneurysm Trial in 2003 caused a shift in the paradigm of management of ruptured intracranial aneurysms. The cases selected for microsurgical clipping nowadays are usually those patients with aneurysms that are not suitable for embolization, and are often complex and difficult. We devised an innovative application of operative planning and training for craniotomy and microsurgical clipping of intracranial aneurysms in a stereoscopic virtual reality environment.

METHODS: Patient-specific Digital Imaging and Communications in Medicine data from computed tomographic angiography of the intracranial circulation and cranium were transferred to the workstation (Dextroscope; Volume Interactions Pte. Ltd., Singapore, Singapore). An aneurysm clip database was loaded into the patient data set. Three-dimensional volume rendering was followed by data coregistration and fusion.

RESULTS: Virtual head positioning and craniotomy were carried out to simulate the microscopic visualization. Clip selection could be carried out with reference to the angle of application. This allows one to see the exposure and degree of obliteration of an aneurysm with the various angles of approach.

CONCLUSION: The virtual craniotomy and microsurgical clipping application simulated the operative environment. Its role in neurosurgical training is encouraging and should be further developed.

KEY WORDS: Intracranial aneurysm, Microsurgical clipping, Surgical simulation, Virtual reality

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The microsurgical clipping of intracranial aneurysms is a crucial part of vascular neurosurgery. The release of the results of the International Subarachnoid Aneurysm Trial in 2003 caused a shift in the paradigm of the management of ruptured intracranial aneurysms (17, 18). Although this study suffered from a number of weaknesses in methodology and criticism in applicability, the management of ruptured and unruptured intracranial aneurysm has swung from microsurgical clipping to endovascular embolization as the preferred mode of treatment in many neurosurgical centers (6, 15). The aneurysm patients who are referred for microsurgical clipping are usually those with aneurysms that are not suitable for embolization, which are sometimes complex and difficult. Neurosurgical training for microsurgical clipping becomes a great challenge.

Virtual reality simulation has long been used for training in military and civilian arenas, such as pilot training. The advantage of training in a no-risk virtual reality environment is appreciated by the surgical community. Recently, simulators have been developed for laparoscopic surgery, endoscopy, and interventional radiology. A similar application in neurosurgery (Dextroscope; Volume Interactions Pte. Ltd., Singapore, Singapore) is also available. This system uses patient-specific, coregistered, fused radiology data sets that may be viewed stereoscopically and can be manipulated in a virtual reality environment. It allows some degree of rehearsal of bone drilling and brain retraction using the "erase" function. The use of the Dextroscope in intracranial tumor cases was demonstrated previously (10). The application of the Dextroscope to operative

planning and training for craniotomy and the microsurgical clipping of intracranial aneurysm has not been tested and described. We have developed a means to provide instruments and implants for preoperative planning and rehearsal of microsurgical clipping of intracranial aneurysms using the Dextroscope-based virtual reality environment.

MATERIALS AND METHODS

The details of the Dextroscope have been described previously (10). Briefly, a computer-generated stereoscopic image is displayed on a monitor (1024 × 768 pixels) and is reflected into the user's eyes via a mirror. The user works from a seated position, with his or her forearms positioned on comfortable armrests. Wearing liquid crystal display shutter glasses (Crystal Eyes; Sterographics Inc., San Rafael, CA), which are synchronized with the time-split display, the user looks into the mirror and sees a stereoscopic image that seems to float behind the mirror. The positions of the virtual holder and stylus in the user's hands are calibrated so that the user perceives them in the same spatial position and orientation.

Patient-specific radiology data sets were processed as described. A Standard 16-row multislice computed tomographic (CT) scanner (GE LightSpeed 16; GE Healthcare, Waukesha, WI) was used to obtain three-dimensional CT angiography data sets. Contrast solution (Omnipaque 300 [GE Healthcare], 100ml, 3.5–4m l/s) was given with a delay of 20 to 25 seconds. Data was acquired with a thickness of 0.625 mm from the foramen magnum to the vertex. Digital Imaging and Communications in Medicine data using patient-specific CT scans of the cranial bone and CT angiography of intracranial circulation were loaded into the Dextroscope workstation. Three-dimensional volume rendering was followed by data coregistration and fusion. A three-dimensional color-adjustment table allowed individual color and transparency adjustments for the cranial bone and cerebral arteries. Structures, such as aneurysms, could be selected, shaped, and colored. The process was straightforward because all data were CT-based.

Aneurysm clips and clip applicators were scanned using a standard 16-row multislice CT (GE LightSpeed 16). Using the Dextroscope, the data were processed by cropping out the empty space and useless information. Further coloring could then be performed. The data sets were saved as the aneurysm clip database. The aneurysm clip database could then be loaded into an individual patient data set.

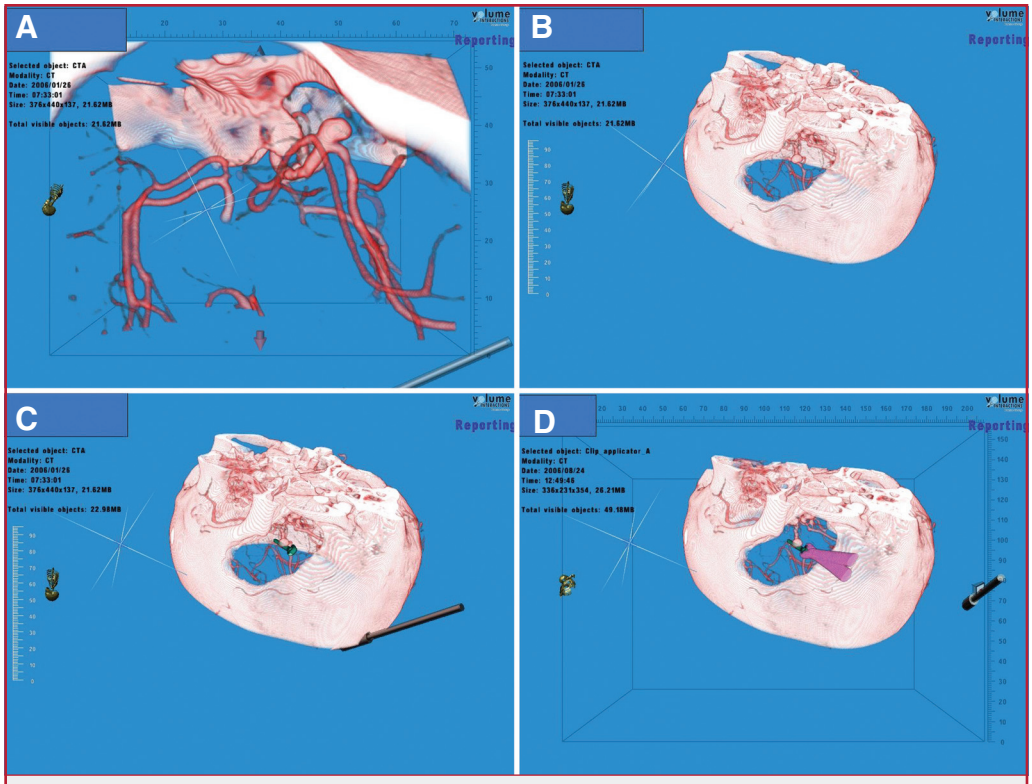


FIGURE 1. **A**, *screen shot showing the right middle cerebral artery aneurysm after bone subtraction for planning before virtual craniotomy.* **B**, *screen shot showing the effect after virtual bone drilling.* **C**, *screen shot showing the application of aneurysm clip.* **D**, *screen shot showing the clip applicator position with reference to the viewing angle and craniotomy.*

RESULTS

The patient-specific data set was transferred, colored, and highlighted. The user could then visualize the anatomy with various available functions, including zoom, rotate, move, crop, and cut plane. The measurement function could be activated to measure the dimension of aneurysm.

Using the "crop" function for the cranial bone, the best angle and position could be selected with respect to clip placement at this juncture (*Fig. 1A*). The selected angles of positioning could be visualized from the left-sided logo, and that position would be the ideal position for the microscope.

The user then returned to the complete cranial view using the "uncrop" feature and positioned the head in accordance with the selected angles of positioning. Craniotomy can then be performed using the drill function. In the case of a right middle cerebral artery aneurysm, a pterional craniotomy was performed (*Fig. 1B*). The user could then provide feedback regarding the adequacy of different extension of the craniotomy and the effect of drilling of the sphenoidal ridge and temporal bone with respect to the visualization of the aneurysm, internal carotid artery, and middle cerebral artery.

The method used to bring in the clip and clip applicator is described here. In the registration session, the user could use

freehand registration for the CT angiography and the suitable clips. One can then move the clip to the neck of aneurysm as appropriate (*Fig. 1C*). The same principle of freehand registration could be performed to the clip and clip applicator beforehand. In that case, the subsequent visualization of the aneurysm clip applicator could tell the user whether or not the clip applicator would be obstructing the working microscopic view in reality (*Fig. 1D*). By repeating the procedures in different angles and degrees of zoom, the user could gain a better understanding of the best approach for microsurgical clipping for the patient.

As in the above case of a middle cerebral artery aneurysm, we performed similar work in other data sets, including patients with internal carotid artery aneurysms (*Fig. 2*), anterior communicating artery aneurysms (*Fig. 3*), and vertebral artery aneurysms, amounting to a total of 13 cases. Difficult cases, such as a giant internal carotid artery aneurysm, were useful to obtain a better appreciation of the anatomy and neurosurgical approach.

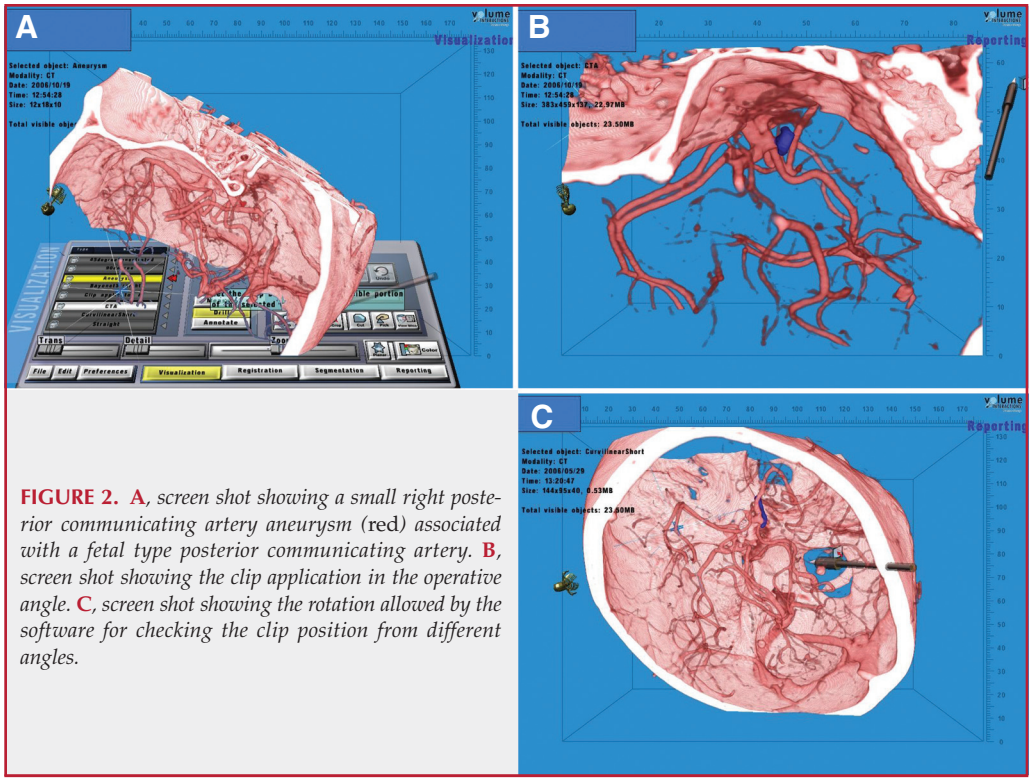


FIGURE 2. **A**, *screen shot showing a small right posterior communicating artery aneurysm* (red) *associated with a fetal type posterior communicating artery.* **B**, *screen shot showing the clip application in the operative angle.* **C**, *screen shot showing the rotation allowed by the software for checking the clip position from different angles.*

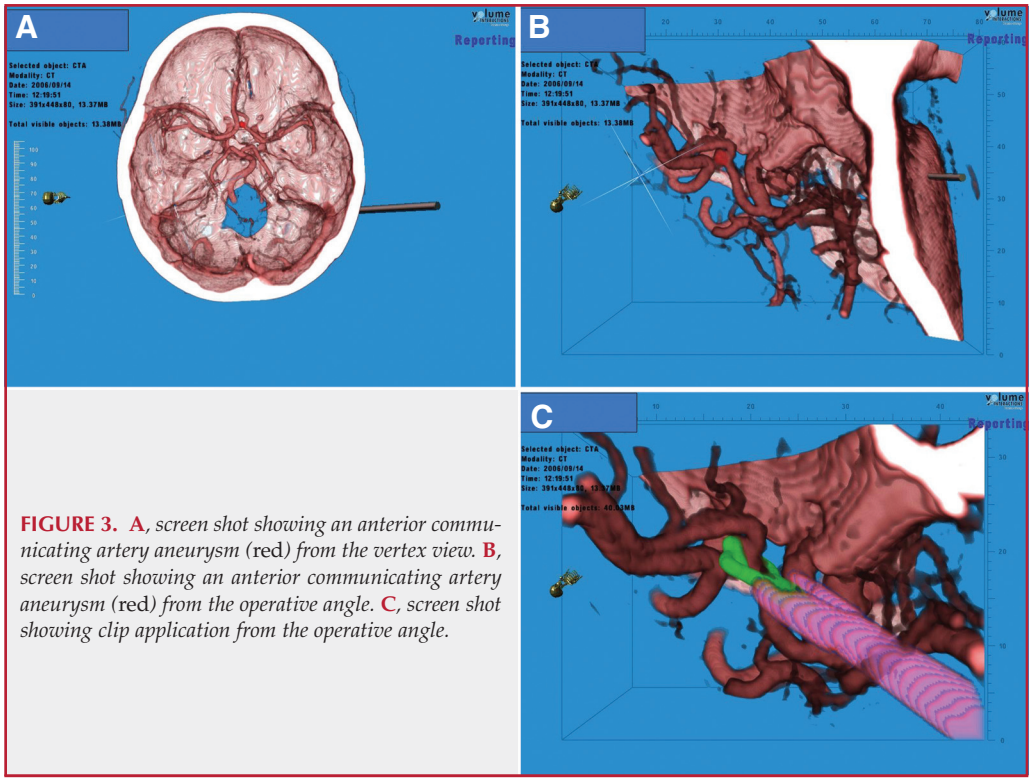


FIGURE 3. **A**, *screen shot showing an anterior communicating artery aneurysm* (red) *from the vertex view.* **B**, *screen shot showing an anterior communicating artery aneurysm* (red) *from the operative angle.* **C**, *screen shot showing clip application from the operative angle.*

DISCUSSION

Technology has improved our methods of understanding neurosurgical anatomy and approaches. With the advance of three-dimensional angiography technology, one can easily manipulate three-dimensional intracranial vasculature in the computer console, whether from CT angiography, magnetic resonance angiography, or catheter angiography (2, 16, 20, 23). Advances in neuronavigation

technology allow neurosurgeons to look at anatomic structures and lesions in a different plane, which allows better decision making for neurosurgical approaches (7, 26). Neurosurgeons can now manipulate a two-dimensional projection of a three-dimensional cerebral vasculature with a different degree of rotation and magnification. This has certainly improved the neurosurgeon's preoperative anatomic understanding of the cerebral vasculature and pathology. The projected views, however, are still significantly inferior, in terms of visual quality, to the intraoperative binocular microscopic views. Traditional training methods for microsurgical clipping involve training of microsurgical techniques in animals, case observations, and a step-by-step increase in participation during the operation. This tradition of training has raised concern among professionals and the public. The problem is further complicated by a decrease in case load, which reduces the frequency of opportunities for neurosurgical trainees to observe and participate in the operation. Worse still is that the aneurysms now faced by the neurosurgeons would be the aneurysms that are not suitable for coiling, which may be large, wide-necked, and partially thrombosed aneurysms associated with intracranial stenosis or with important vessels coming out from the aneurysm complex. Virtual reality simulation has long been used for training in military and civilian arenas, such as air pilot training. The advantage of training in a no-risk virtual reality environment is appreciated by the surgical community. Recently, simulators have been developed for laparoscopic surgery, endoscopy, and interventional radiology (3–5, 9, 19, 21, 22). A similar application, the Dextroscope, is also available in neurosurgery. Virtual reality simulation seems to have come at the right time to provide a good solution for the appropriate training of the microsurgical clipping of aneurysms.

The Dextroscope allows real-time manipulation of the three-dimensional data set and provides a suite of registration, segmentation, and planning tools, including tools for simulating bone drilling. The three-dimensional views obtained from the stereoscopic virtual reality environment are in keeping with what one attained with the binocular microscopic views, as compared with the two-dimensional projections of the three-dimensional CT angiography. We further enhance its applicability by incorporating aneurysm clips and aneurysm clip applicators to the data set, in which movement in relationship to the three-dimensional CT angiography data (and, thus, the aneurysm) is feasible. It allows the option of preoperative rehearsal and training for microsurgical clipping.

The use of virtual reality simulation for the training of microsurgical clipping allows for the development of a "pretrained novice" so that basic psychomotor and visual-spatial skills, with reference to positioning, craniotomy, and clip application, have been developed and become reasonably automatic before proceeding to the operating room. In conjunction with cadaveric dissection training for microsurgical skills, this allows for more efficient and safer use of operating room training time, such that intraoperative training can be focused on avoidance of errors and other technical perils. However, when one considers the implementation of virtual reality simulation into the training program, it is important to realize that virtual reality simulation is most effective when incorporated into a well-designed training program of vascular neurosurgery with close supervision and participation of vascular neurosurgeons. A high fidelity laparoscopic training model has been shown to improve resident performance of basic skills in the animate operating room environment and provides evidence that virtual reality simulation training may lead to improved operating room performance (1). The next stage would be to develop a validated assessment tool for operative performance of microsurgical clipping and to assess the results of microsurgical clipping training with or without the availability of the stereoscopic virtual reality environment. Effectiveness, in terms of operative time and clinical outcome, would be another important aspect to be explored in the next stage of study.

The other spectrum of utilization would be for the vascular neurosurgeons to understand complex vascular cases. This virtual reality system allows the appreciation of the anatomy from different angles. It can highlight different areas of interest, such as the aneurysm, main trunk, important branches, and the relationship to bony structures. It allows better preoperative planning, better decisions regarding operative approaches, and a preoperative rehearsal. It may be used for the training and decision to use the keyhole approach. The system can also be used in the clinic and ward settings to facilitate the acquisition of informed consent for the operative procedures, allowing patients a view to help relieve anxiety and build confidence.

The same principle could be applied to other vascular cases, including cerebral arteriovenous malformations. It provides better appreciation of the arterial and venous anatomy and better pre-operative planning. However, the current hardware and software cannot account for the many intraoperative variations that can change management, including brain swelling, brain retraction, movement of structures on manipulation, and calcification of the aneurysm neck, that could alter clip application and aneurysm rupture. Future development would involve the simulation of brain retraction, clip opening and closure with the associated aneurysm deformation, haptics, simulation of intraoperative aneurysmal rupture, and so on (11–14, 24, 25). We believe that it will ultimately become an indispensable tool for neurosurgical training and planning in every major vascular neurosurgery center (8).

CONCLUSION

The virtual microsurgical clipping application enhances the understanding of the surgical anatomy and simulates the operative environment encountered in microsurgical clipping. It provides an opportunity for preoperative rehearsal, microsurgical training, and assessment.

Disclosure

George K.C. Wong and W.S. Poon are honorary key opinion leaders for Volume Interactions Pte. Ltd. and provide input for future research and development. None of the authors have received any direct funding from Volume Interactions Pte. Ltd.

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COMMENTS

This is an interesting article that introduces us to surgical planning of the future. The authors correctly state that the numbers of surgical clipping decrease as endovascular coiling has proven to be an effective and safe technology of aneurysm occlusion in properly selected patients. Thus, neurovascular training will benefit from virtual craniotomy and microsurgical clipping application simulating the operative environment. Moreover, virtual craniotomy and clipping also provide more experienced surgeons with a unique opportunity to foresee some of the difficulties of selecting the proper clip and may even change the side or angle of approach, especially in paraclinoid and anterior communicating artery aneurysms.

Andreas Raabe
Frankfurt, Germany

The authors present an eloquent array of three-dimensional images that help recreate operative findings in patients with intracranial aneurysms. Trainees could use this technology to perform "virtual craniotomies" before real operative intervention. Unfortunately, previous applications of similar technologies have not proven useful for neurosurgical training, and we have no information that the virtual reality training proposed in this report will be useful. The goal of computer-generated surgical simulation is important and may be essential for future training purposes. It seems evident that the technology as presented needs further refinement and validation.

Robert A. Solomon
New York, New York

Wong et al. describe a technique by which computer-generated stereoscopic images may be used for preoperative planning and rehearsal of aneurysm clipping in a virtual reality environment. With the advances in microcatheter techniques and devices, coil embolization is increasingly used for the treatment of intracranial aneurysms. Concomitantly, the number of open operative cases being performed has decreased. This decrease is making it more difficult for young neurosurgeons to gain the operative experience needed to perform these complex procedures with confidence. Thus, the remaining aneurysms referred for operative clipping tend to be the most difficult to treat. The result is a deficit in the training needed for young neurosurgeons to develop their surgical skills.

The virtual reality technique reported by Wong et al. is one means by which neurosurgical training can be attained if operative cases are lacking. However, this technique is not a perfect simulation of the operative environment. It may help surgeons determine optimal positioning of patients, the bony removal needed for an operative approach, and the angle of clip application. Nonetheless, a virtual environment will never exactly reproduce the unpredictability associated with actual surgery. In the future, most complex aneurysms in need of operative clipping will likely be referred to large centers that perform enough cases each year for the attending surgeons to gain and maintain the necessary experience to treat such cases appropriately.

Elisa Beres
Robert F. Spetzler
Phoenix, Arizona

The authors have described the training of surgical trainees in the microsurgical clipping of cerebral aneurysms using virtual reality. This is unfortunately going to have to be part of the future as the training of surgeons is evolving. Firstly, with the restriction of work hours to 80 hours a week for residents in the United States, and fewer abroad, this will result in a decrease in the hours spent in the operating room. Secondly, as the authors state, with the endovascular treatment of aneurysms rapidly becoming the first line treatment, the surgical training of trainees in aneurysm surgery will be difficult. This may result in a new generation of microvascular surgeons with less skills and worse results than the surgeons of today and provide a self-fulfilling prophecy that endovascular treatment is better for the patient. This will be a disadvantage to the patients as some cases will always require surgical treatment. Therefore, virtual reality may be what is needed to keep surgeons somewhat experienced in the surgical management of aneurysms. However, virtual reality is just that, and no amount of time behind the computer can replace the tactile and emotional training required when treating aneurysms surgically, particularly with an intraoperative rupture.

Gavin W. Britz
Seattle, Washington

Recent clinical data has shown that treatment-related morbidity is smaller with endovascular treatment when compared with open surgery with aneurysms that are amenable to both modalities. This has resulted in a decrease in the number of surgically treated aneurysms in many centers across the world. Aneurysms that are not amenable to endovascular treatment tend to be surgically challenging, and this raises a very real problem among training programs: how will the next generation of neurovascular surgeons achieve the level of expertise required to successfully treat these difficult lesions in the face of a declining surgical case load?

This article is quite timely in this regard. Using a three-dimensional database generated from computed tomographic angiography slice data, the reconstructed cranium, blood vessels, clips, and instruments are placed in a virtual reality environment to simulate the experience of exposing and treating aneurysms. Ideally, time spent with the simulation would provide trainees the "case volume" required to become proficient at aneurysm surgery.

Unfortunately, the software in its current incarnation seems relatively primitive in truly replicating the surgical experience. Choice of trajectory is clearly important. However, positioning and removal of bone is only the first step in achieving adequate exposure. In real life, the brain is in the way, and visualization of important structures is a dynamic process, looking around corners and moving brain tissue and vessels to provide adequate visualization of the aneurysm and surrounding important structures. There is no tactile feedback to teach the user how to handle tissue, how to open the fissure and cisterns in the setting of acute subarachnoid blood, or how to safely dissect around the neck and dome of an aneurysm.

The system described in this article is clearly an important first step, and I encourage the authors to continue to develop and refine their system. However, it is unclear to me whether or not time spent with these simulations in their present form translates into increased proficiency in the clinical setting compared with other teaching methods. Perhaps some more objective measures would make this a stronger article. One simple idea would be to measure the amount of time it would take for three groups of residents to expose the anterior communicating artery on a cadaver through a pterional approach. The first group would perform the exposure five times on a cadaver. The second group would perform the exposure four times using the software and then the fifth time on a cadaver. The third group would watch the exposure on a cadaver four times and then perform the cadaveric exposure the fifth time. A comparison of the three groups would be quite enlightening.

Paul P. Huang
Patrick J. Kelly
New York, New York

CALL FOR *CLINICAL TRIALS* CONTRIBUTIONS

Clinical trials are an increasingly important part of daily neurosurgical practice that can change management paradigms and influence decision-making. Accordingly, NEUROSURGERY is pleased to announce a new ***Clinical Trials*** section effective January 2006. This section will focus on clinical trial design and comprehensive reviews of trials treating neurosurgically relevant disease processes. Submissions describing results of single or multi-center clinical trials are also encouraged. A future online offering to this section will allow neurosurgeons to list their own clinical trials as part of NEUROSURGERY-*Online*. We look forward to better informing our readers about clinical trials so that the most recent, validated results can be integrated into daily practice.

Please contact Andrew T. Parsa M.D., Ph.D. directly regarding any questions attendant to this expanding area of NEUROSURGERY'S content and focus at:
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PREFERENTIAL EXPRESSION OF CHEMOKINE RECEPTOR CXCR4 BY HIGHLY MALIGNANT HUMAN GLIOMAS AND ITS ASSOCIATION WITH POOR PATIENT SURVIVAL

OBJECTIVE: CXCR4 is implicated in the growth, metastasis, and angiogenesis of malignant tumors. We investigated the potential role of CXCR4 in human gliomas.

METHODS: The expression of CXCR4 messenger ribonucleic acid and protein by human glioma cell lines was examined by reverse-transcriptase polymerase chain reaction and immunocytochemistry analysis. Tumor cell chemotaxis and production of vascular endothelial growth factor induced by the CXCR4 ligand SDF-1β were measured. Xenograft models were used for evaluation of glioma cell tumorigenesis. CXCR4 expression by xenografted tumors and primary human glioma specimens were evaluated for CXCR4 protein expression. The relationship between CXCR4 expression and patient survival was analyzed. A synthetic lipoxygenase inhibitor, Nordy, was tested for its effects on glioma cell expression and function of CXCR4, as well as on glioma cell tumorigenicity.

RESULTS: CXCR4 expression correlated directly with the degree of malignancy of the human glioma cell lines and primary tumors. Activation of CXCR4 induced tumor cell chemotaxis and increased production of vascular endothelial growth factor. Glioma cells expressing higher levels of CXCR4 formed more rapidly growing and lethal tumors in nude mice. Primary human glioma specimens expressing CXCR4 contained high-density microvessels. Patients with CXCR4-positive gliomas had poorer prognosis after surgery. The lipoxygenase inhibitor Nordy diminished CXCR4 expression by glioma cell lines in vitro and reduced their tumorigenicity in nude mice.

CONCLUSION: The level of CXCR4 expression seems to correlate with the degree of malignancy of human gliomas and may contribute to their rapid growth.

KEY WORDS: Angiogenesis, Chemotaxis, CXCR4, Glioma, Vascular endothelial growth factor

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Malignant gliomas, composed mainly of anaplastic astrocytomas and glioblastomas arising from astrocytes, account for more than 60% of the primary tumors within the central nervous system (6). These tumors are characterized by rapid expansion, invasion of adjacent central nervous system tissues, and aberrant neovascularizion (14). Despite rigorous treatment with surgery, radiation, and chemotherapy, the median survival period of patients with malignant gliomas after diagnosis is less than 1 year, and only 2% of the patients survive beyond 3 years (34). Because the incidence of glioblastoma is increasing with very poor prognosis (10), a better understanding of glioma pathogenesis and progression is crucial for the development of more effective therapeutic approaches to this deadly tumor type.

Malignant tumor cells interact with a number of tissue-derived cytokines and growth factors to their advantage. Among these factors, members of the chemokine family, originally identified as mediators of leukocyte trafficking and homing (37), are relevant because of their participation in tumor progression and metastasis by promoting tumor cell growth and angiogenesis and by inducing directional migration of tumor cells (1, 41). In fact, many tumor cells of nonhematopoietic origin express one or multiple functional G protein coupled chemokine receptors. For instance, CCR7,

which was cloned from an Epstein-Barr virus-positive Burkitt lymphoma (4, 26), may be responsible for the lymph node metastasis of esophageal squamous cell carcinoma (11), gastric carcinoma (20), and malignant melanoma (22). However, CXCR4 has been reported to promote the spread of melanoma metastasis to the lung, prostate cancer metastasis to the bone, and neuroblastoma metastasis to the bone marrow (5, 13, 21). In human breast cancer cell lines, CXCR4 is highly expressed, and injection of anti-CXCR4 antibody or silencing of this receptor significantly reduced the metastasis of breast cancer cells in mice (19, 23). Human glioma cell lines have also been reported to express CXCR4, which may transduce growth signals in response to the ligand SDF-1 (33, 45). In a small-scale study of six patients with human primary glioblastoma multiforme (GBM), CXCR4 and its ligand SDF-1 were detected in tumor cells closer to the necrotic regions. Moreover, in animal xenograft experiments, a small molecule CXCR4 antagonist significantly inhibited the tumorigenicity and the growth of tumors formed by human glioma cell lines (30). These results suggest that CXCR4 may play an important role in promoting the progression of human gliomas. However, it is not known how CXCR4 contributes to the malignant phenotype of glioma cells and whether or not the observations made thus far bear clinical relevance.

The purpose of the present study was to examine the relationship between the levels of CXCR4 expression and the degree of malignancy of human glioma cell lines and primary tumors, as well as the implications for prognosis. Herein we report that the level of CXCR4 expression correlated with the degree of malignancy of human primary gliomas as well as established glioma cell lines. Activation of CXCR4 in glioma cells not only promoted tumor cell chemotaxis, but also promoted the production of vascular endothelial growth factor (VEGF). Furthermore, a novel lipoxygenase inhibitor, Nordy (*Fig. 1*) (8), synthesized based on the structure of natural nordihydroguaiaretic acid (NDGA), diminished CXCR4 function in human glioma cells and markedly reduced the growth of xenograft tumors formed by human malignant glioma cells. Our study demonstrates the potential for CXCR4 and SDF-1 as molecular targets for the treatment of human malignant gliomas.

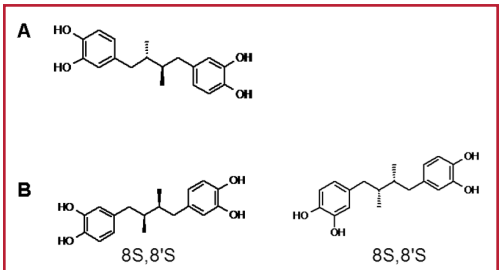


FIGURE 1. *Diagrams illustrating the chemical structures of (**A**) natural NDGA (meso-NDGA) and (**B**) Nordy (dl-NDGA).*

PATIENTS AND METHODS

Patients and Surgical Specimens

Human brain glioma tissues were obtained from surgically removed tumors for diagnostic and therapeutic purposes (Southwest Hospital and Daping Hospital, Third Military Medical University, Chongqing, China). All glioma specimens were diagnosed and graded according to the World Health Organization (WHO) classification of tumors of the central nervous system (6). No patient had received radiation or chemotherapy before surgery. Normal brain tissues from five patients with brain trauma were used as controls. Written informed consent was obtained from all patients before diagnostic and surgical procedures according to the institutional policy.

Tumor Cells

A human glioblastoma cell line, U87 (WHO Grade IV), from American Type Culture Collection (ATCC, Manassas, VA) was used. Human anaplastic astrocytoma cell line SHG-44 (WHO Grade III) was from the Laboratory of Brain Tumors, Suzhou University (Suzhou, China), and astrocytoma cell line CHG-5 (WHO Grade II) was established from surgically removed tumors from patients (Southwest Hospital, Chongqing). Primary human glioblastoma cells from seven additional fresh surgical specimens were cultured and examined by immunostaining for expression of glial fibrillary acidic protein (GFAP) and vimentin. The cells were grown in Dulbecco's modified Eagle's medium with 10% fetal calf serum (HyClone, Logan, UT).

Reverse-transcriptase Polymerase Chain Reaction

Analysis of CXCR4 messenger ribonucleic acid (mRNA) was performed by reverse-transcriptase polymerase chain reaction (RT-PCR). Total ribonucleic acid was extracted from human glioma cell lines using Tripure Reagent (Roche Diagnostics Shanghai Ltd., Shanghai, China). Sense primer 5′-AATCTTCCTGCCCACCATCT-3′ and antisense primer 5′-GACGCCAACATAGA CCACCT-3′ were used to yield a 367-base pair product of CXCR4. Experiments were performed with a two-step RT-PCR kit (DingGuo Biotechnologic Inc., Beijing, China). Primers for human glyceraldehye-3-phosphate dehydrogenase (GAPDH) were sense 5′- CCATGGAGAAGGCTGGGG and antisense 3′-CCAGTAGGTACTGTTGAAAC to yield a 195-base pair product as controls. The primers were custom synthesized by Stratagene Co.-Genetimes Technology, Inc. (Shanghai, China), and the RT-PCR procedures were followed according to the manufacturer's instructions. The procedures included 1 minute at 94°C, 1 minute at 54°C, and 1 minute at 72°C for a total of 35 cycles. RT-PCR products were separated on 1.5% agarose gel and were visualized by ethidium bromide staining. Densitometry was performed using a 200TM-Image Universal Hood (Bio-Rad Laboratories, Rome, Italy) and the level of CXCR4 mRNA was calculated by normalization with the density of GAPDH mRNA.

Chemotaxis Assays

Chemotaxis assays were performed using 48-well chemotaxis chambers (NeuroProbe, Gaithersburg, MD) (16). Aliquots of 27 μl of CXCR4 ligand SDF-1β were placed in the wells of the lower compartment of the chamber and 50 μl of tumor cells (1×10^6/ml in RPMI1640 containing 1% bovine serum albumin and 25 mmol/L *N*-2-hydroxyethylpiperazine-*N*′-2-ethanesulfonic acid 5-HETE, 5-hydroxy-6,8,11,14-eicosatetraenoic acid) were placed in the wells of the upper compartment. The upper and lower compartments were separated by a 10-μm pore-sized polycarbonate filter (GE Osmonics Labstore, Minnetonka, MN) coated with 50 μg/ml of collagen type I (BD

Biosciences, San Jose, CA). A 270-minute incubation period at 37°C was used for measurement of tumor cell migration. After incubation, the filters were removed and stained, and cells that migrated across the filters were counted under a light microscope after coding the samples. The results were expressed as the mean (±standard deviation) of migrated cells in three high-powered fields in triplicate samples or as a chemotaxis index, which represents the fold increase in the number of migrated cells in response to chemoattractants over spontaneous cell migration in response to control medium.

To test the effect of the antilipoxygenase compound Nordy, tumor cells were preincubated with different concentrations (10 ~ 200 μmol/L) of Nordy (99.87% high-performance liquid chromatography pure; Institute of Pathology, Southwest Hospital, Chongqing) for 24 hours. Then, the samples were examined for their expression of CXCR4 and the capacity to migrate in response to SDF-1β.

Immunostaining

Human primary and xenograft glioma specimens were paraffin embedded and sectioned. A mouse antihuman CXCR4 monoclonal antibody (Sigma-Aldrich China Inc., Shanghai, China) was used for detection of CXCR4 protein, and a mouse antihuman CD34 monoclonal antibody (Zymed Laboratories, Inc., South San Francisco, CA) was used for quantitation of microvessel density. The Envision$^+$ kit for visualization of immunostaining was a product of DakoCytomatin (Carpinteria, CA). A semiquantitative system was used to measure microvessel density as described previously (3). The levels of positive staining of CXCR4 in human glioma specimens were defined by a labeling index, representing the percentage of CXCR4-positive cells in the total number of cells counted (200 cells per specimen). As a quantitative measurement, the labeling (++) represents 50% or more CXCR4-positive tumor cells in a specimen, (+) defines specimens with 5 to 49% CXCR4-positive tumor cells, and (−) indicates specimens with less than 5% CXCR4-positive tumor cells. All evaluations were performed independently by two pathologists (XB, HX), with highly consistent reproducibility. For the evaluation of the state of differentiation of glioma cell lines, mouse antihuman GFAP and vimentin monoclonal antibody (Gene Co. Ltd, Chengdu, China) were used. Immunocytochemistry analysis for GFAP, vimentin, and CXCR4, respectively, was carried out on glioma cells grown on poly-L-lysine–coated glass coverslips and fixed in 4% paraformaldehyde. The slips then were treated with 1% H_2O_2 and 5% normal horse serum to quench endogenous peroxidases and to block nonspecific binding of the antibodies. After incubation with primary antibodies, the EnVision system was used to visualize the proteins. Isotype-matched normal mouse immunoglobulin G was used as a control (3). The quantitative detection of the expressed proteins was performed on 100 cells under ×400 magnification. An average optical density from 300 cells was presented as the expression levels.

VEGF Production by Glioma Cells

VEGF in the supernatants of cultured glioma cells stimulated with 30 ng/ml SDF-1β for different periods was measured by enzyme-linked immunosorbent assay kits (Boster Biotechnological Ltd., Wuhan, China). To test the effect of Nordy, tumor cells were preincubated with different concentrations (10–200 μmol/L) of Nordy for 24 hours and were then examined for the capacity to produce VEGF in response to SDF-1β.

Xenografts

Cells (5×10^6 cells in 150 μl phosphate-buffered saline) from three human glioma cell lines, U87, SHG-44, and CHG-5, were injected into the flank regions of each of the male or female athymic (Balb/c nu/nu) mice (3–4 wk of age; Laboratory Animal Center, Third Military Medical University). Ten mice were used in each group of SHG-44 cell implantations and five mice were used as normal controls without tumor implantation. For evaluation of the effect of Nordy, 12 mice were divided randomly into Nordy and saline treatment groups (n = 6 for each group). In the Nordy treatment group, each mouse was injected intraperitoneally with Nordy at a dosage of 27 mg/kg body weight every 2 days starting on Day 7 after implantation with SHG-44 cells. The tumor volumes were measured daily by a Vernier caliper and were calculated by the formula: volume = l (length) x w^2 (width) / 2. Mice were sacrificed on Day 30, and tumors were collected and fixed in 10% neutral formalin for histological and immunohistochemical examination.

Statistical Analysis

All experiments were performed at least three times and the results were from representative experiments. Data were analyzed with computer-aided SPSS statistical software (version 10.0; SPSS Inc., Chicago, IL). Parametric data are expressed as the mean values (±standard deviation). When two groups were compared, the unpaired dependent-samples t test was used. A one-way analysis of variance was used to determine the statistical significance of the differences among multiple groups. For comparison of protein expression levels, an independent-samples t test was used. Statistical significance was set at a P value less than 0.05.

RESULTS

Phenotypes of Human Glioma Cell Lines and the Expression of CXCR4

We first investigated the expression and function of CXCR4 in three human glioma cell lines. As described previously, the levels of intracellular GFAP and vimentin are important markers for the degree of glioma malignancy (8, 42). U87 cells were derived from human glioblastoma and expressed low levels of the glial cell differentiation marker GFAP (122.17 ± 9.47; n = 300). These cells, in contrast, contained higher levels of vimentin (148.31 ± 12.57; n = 300), a protein expressed by immature or poorly differentiated glial cells. In contrast, CHG-5 cells were derived from a relatively well-differentiated human astrocytoma that expressed higher levels of GFAP (143.97 ± 4.58; n = 300) but very low levels of vimentin (115.56 ± 4.53; n = 300). In comparison with U87 and CHG-5 cells, another human glioma cells line, SHG-44, expressed moderate levels of both GFAP (132.16 ± 6.49; n = 300) and vimentin (132.10 ± 4.53; n = 300; *Fig. 2, A–F*). All three human glioma cell lines expressed CXCR4 mRNA as detected by RT-PCR and based on the normalization against GAPDH mRNA. U87 cells expressed the highest level of CXCR4 gene, but CHG-5 cells expressed the lowest level (*Fig. 2, G* and *H*). The expression of CXCR4 protein by human glioma cell lines was measured by immunocytochemistry, which also detected the highest CXCR4 expression in U87 cells as compared with SHG-44 and CHG-5 cell lines (*Fig. 3, A–C*). CXCR4 expressed by human glioma cell lines was functional as assayed by the ability of the CXCR4 agonist SDF-1β to induce directional cell migration in a dose-dependent manner. It is interesting to note that, in agreement with the expression levels of CXCR4 gene and pro-

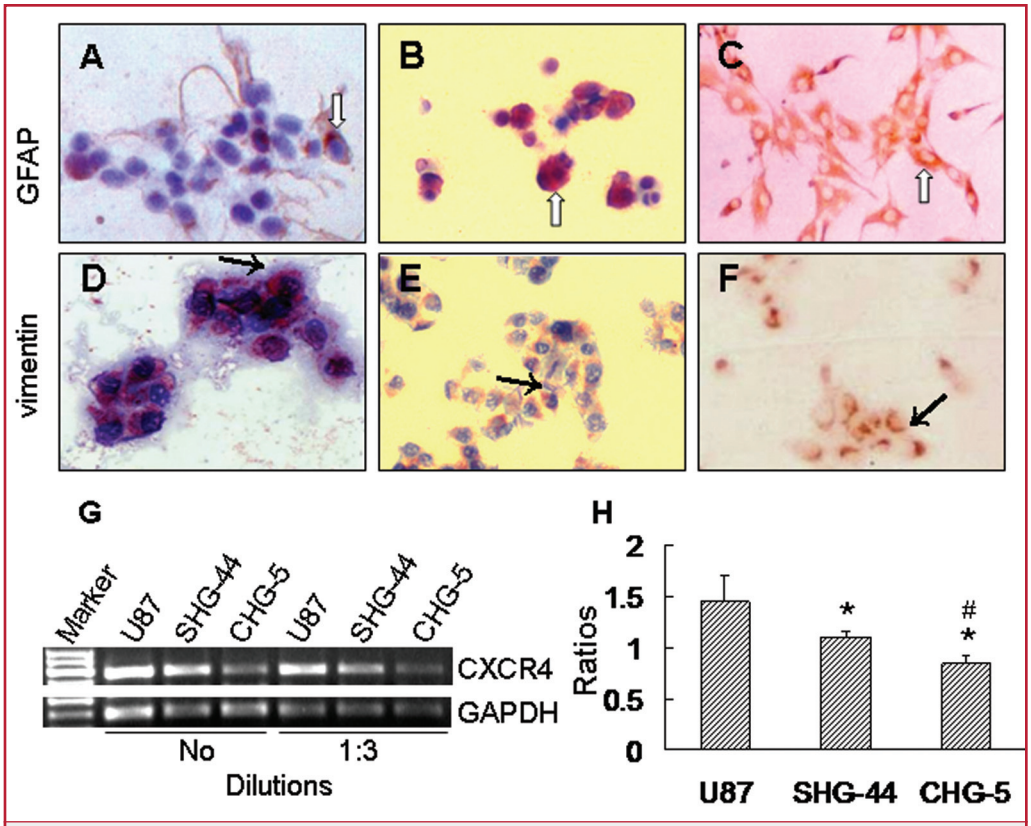


FIGURE 2. *Differentiation states of human glioma cell lines. Photomicrographs demonstrating immunohistochemistry analysis used to detect GFAP (***A–C***,* white arrows*) and vimentin (***D–F***,* black arrows*) in the cytoplasmic regions of the cells.* ***A*** *and* ***D****, U87 cells;* ***B*** *and* ***E****, SHG-44 cells;* ***C*** *and* ***F****, CHG-5 cells.* ***G****, RT-PCR results of CXCR4 mRNA in human glioma cell lines, measured as a 367-bp product. Human GAPDH mRNA was measured as a standard in RT-PCR. RT-PCR products at different dilutions were electrophoresed on agarose gel.* ***H****, bar graph demonstrating densitometry of measured CXCR4-to-GAPDH ratio values at 1:3 RT-PCR product dilutions. The densitometry ratios of CXCR4 mRNA to GAPDH transcripts in U87, SHG-44, and CHG-5 were 1.443 ± 0.257, 1.092 ± 0.063, and 0.893 ± 0.080, respectively. The* asterisks *indicate significantly lower ratios of CXCR4 mRNA to GAPDH mRNA of SHG-44 and CHG-5 cells as compared with U87 cells (*$P < 0.01$*). The* pound sign *indicates significantly lower ratios of CXCR4 mRNA to GAPDH mRNA of CHG-5 cells as compared with SHG-44 cells (*$P < 0.01$*). The colors of immunocytochemically stained glioma cells were revealed by AEC in* red *(with hematoxylin counterstaining) or by DAB in* brown *(without counterstaining)* ***A–F****, original magnification, ×200).*

after implantation, all nude mice injected with U87, SHG-44, and CHG-5 cells grew palpable tumor nodules. However, tumors formed by U87 and SHG-44 cells exhibited growth rates markedly more rapid than those formed by CHG-5 cells, as measured on Days 15 and 25 after implantation in nude mice (*Fig. 4A*). For example on Day 25, the size of U87 and SHG-44 tumors were at 810 ± 254 mm^3 and 651 ± 147 mm^3 (n = 10), respectively, and all mice bearing U87 tumors had to be sacrificed because of their large tumor mass or the appearance of necrotic lesions in the tumors. In contrast, the mean value of CHG-5 tumors on Day 25 was 354 ± 95 mm^3 (n = 10). All implanted tumors showed pathological features resembling glioblastoma. The tumors formed by CHG-5 cells were apparently better differentiated than the tumors formed by U87 or SHG-44 cells. Immunohistochemical staining of tumor sections formed by human glioma cell lines was positive for CXCR4 (*Fig. 4, B–D*). Thus, human glioblastoma cell lines expressing higher levels of CXCR4 have the capacity to form more rapidly growing tumors in xenograft models.

tein, U87 cells exhibited the most potent chemotactic responses to SDF-1β (*Fig. 3D*). Moreover, stimulation with SDF-1β increased the production of VEGF, an important angiogenic factor implicated in the growth of malignant tumors, by glioma cells (*Fig. 3E*). Similarly, functional CXCR4 receptors were expressed by cells isolated from seven highly malignant primary gliomas (*Fig. 3F*). These results indicate that functional CXCR4 is expressed in more highly malignant human glioma cells and that activation of CXCR4 in glioma cells promotes tumor cell migration and the production of the angiogenic factor VEGF.

In Vivo Growth of Human Glioma Cell Lines in Nude Mice

Tumor xenograft models in nude mice were then used to more precisely determine the tumorigenicity and the growth rate of tumors formed by human glioma cell lines. On Day 5

CXCR4 Expression and Microvessel Density in Primary Human Gliomas

We then examined the expression CXCR4 in a greater number of primary human gliomas and its relationship to the degree of tumor malignancy. CXCR4 was detectable in 53 (73.6%) out of 72 surgically removed human gliomas by immunohistochemistry. The expression of CXCR4 protein was correlated with the degree of malignancy and size of human gliomas (*Table 1*) because higher levels of CXCR4 were detected in Grade III anaplastic astrocytomas and Grade IV glioblastomas (*Fig. 5, A* and *B*), but not Grade II astrocytomas (*Fig. 5C*). A number of vascular endothelial cells of tumor blood vessels were also positive for CXCR4 (*Fig. 5B*), suggesting that the chemokine ligand SDF-1β may stimulate both tumor cells and blood vessel epithelial cells (ECs) for activation and promote angiogenesis.

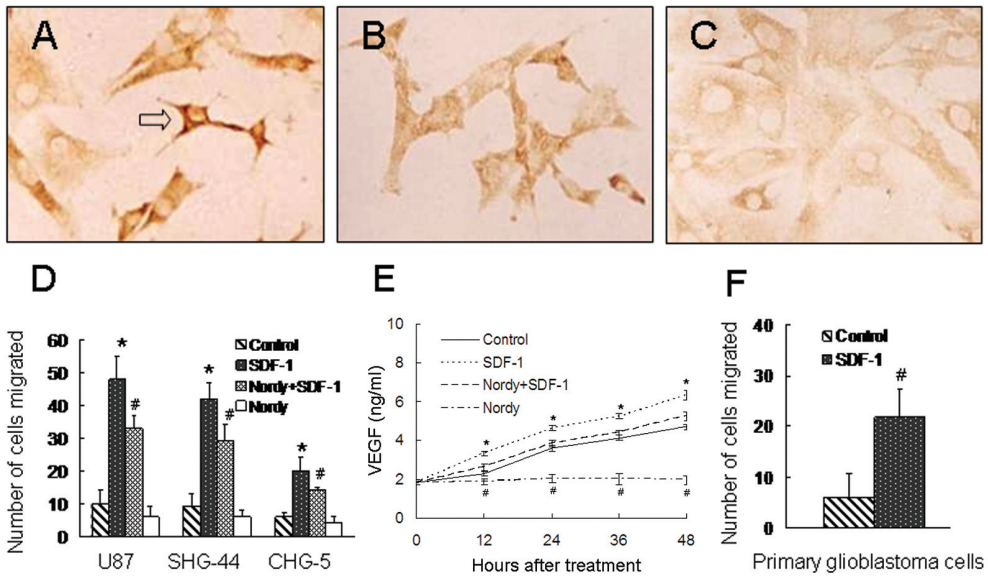


FIGURE 3. *The expression and function of CXCR4 in human glioma cell lines and primary human glioma cells. Photomicrographs demonstrating the results after human glioma cell lines U87 (A), SHG-44 (B), and CHG-5 (C) were cultured on coverslips and stained with anti-CXCR4 monoclonal antibody (original magnification, ×200;* arrow *indicates positive CXCR4 staining).* D, *bar graph demonstrating the migration of human glioma cells, with or without Nordy treatment (200 μmol/L), in response to SDF-1β (30 ng/ml). The* asterisks *indicate significantly increased migratory responses of U87 and SHG-44 cells compared with CHG-5 cells ($P < 0.01$). The* pound signs *indicate significantly decreased migratory responses of the glioma cells pretreated with Nordy (200 μmol/L) and then stimulated by SDF-1β compared with the cells without the pretreatment ($P < 0.01$).* E, *graph demonstrating VEGF protein in the supernatants of human glioma cells stimulated with 30 ng/ml SDF-1β for different hours, measured by enzyme-linked immunosorbent assay. The* asterisks *indicate significantly increased VEGF production by SDF-1β-stimulated glioma cells compared with cells treated with Nordy (200 μmol/L) followed by SDF-1β stimulation ($P < 0.01$). The* pound signs *indicate significantly decreased VEGF production compared with cells treated with control medium ($P < 0.01$).* F, *bar graph demonstrating the migration of primary human glioblastoma cells in response to SDF-1β (30 ng/ml). Cells from seven primary glioblastoma cases were used. The* pound sign *indicates significantly increased migratory responses of primary tumor cells to SDF-1β compared with control medium ($P < 0.01$).*

To support this notion, the density of microvessels in CXCR4-positive tumor sections was found to be much higher (56.03 ± 16.39; n = 16) than that in CXCR4-negative sections (35.36 ± 12.67; n = 32; $P < 0.05$; *Fig. 5, D–F*). In addition, analysis of postoperative prognosis revealed a significantly reduced length of survival for patients with CXCR4-positive tumors as compared with those with CXCR4-negative tumors (*Table 1*). The CXCR4-positive tumors were also larger (*Table 1*).

Inhibition of CXCR4 Function in Human Glioma Cells and their Tumorigenesis by the Compound Nordy

Having observed that higher levels of CXCR4 were expressed by more aggressive human primary gliomas and cell lines, we investigated the effect of a synthetic antilipoxygenase compound Nordy, which has been shown to inhibit intracranial implanted tumors in mice (7), on the expression and function of CXCR4 in human glioma cells. *Figure 6, A–D* shows that the levels of CXCR4 expression by human glioma cell lines were reduced significantly after incubation with 100 μmol/L Nordy. This was associated with diminished chemotactic responses to SDF-1β (*Fig. 3D*). Nordy also inhibited SDF-1-induced VEGF production by the glioma cells (*Fig. 3E*). In nude mice with tumor xenografts, Nordy administration markedly inhibited the tumorigenicity of human glioma cells and reduced the growth rate of established tumors (*Fig. 6E*). These results indicate that Nordy, as an inhibitor of CXCR4 expression and function in human glioma cells, has the potential to act as a novel antiglioma therapeutic agent.

DISCUSSION

Although chemokines and receptors are proven key mediators of leukocyte trafficking and homing (37), several chemokine receptors are also expressed by malignant tumors of nonhematopoietic origin. Among such receptors, CXCR4 is the most predominant and has been detected in more than 20 epithelial and mesenchymal tumors (1, 41). However, the distribution of CXCR4-positive cells in a single tumor and the intracellular localization of CXCR expression are often highly heterogeneous, such as in the case of non–small-cell lung carcinomas (36). In our study, we observed that in low-grade primary human gliomas, CXCR4 generally was expressed at levels much lower than in higher grade tumors. But even in the extremely aggressive GBM, not all tumor cells were CXCR4 positive. This raised the possibility that CXCR4-positive glioma cells may represent a subpopulation of actively growing cells that are prone to invasion and metastasis. This notion was supported by our study of glioma cell lines, in which the U87 glioblastoma cells expressed CXCR4 at higher levels than the astrocytoma and anaplastic astrocytoma cell lines. In accordance with the level of CXCR4 expression, U87 cells were more responsive to stimulation by SDF-1 in the chemotaxis assays and in the production of VEGF; furthermore, U87 formed more rapidly growing tumors in xenograft models. Our analyses of clinical data suggest that patients with CXCR4-positive gliomas exhibited poorer postoperative life expectancy compared with those with CXCR4-negative gliomas. It is interesting to note that the positivity of CXCR4 is correlated with glioma size, but

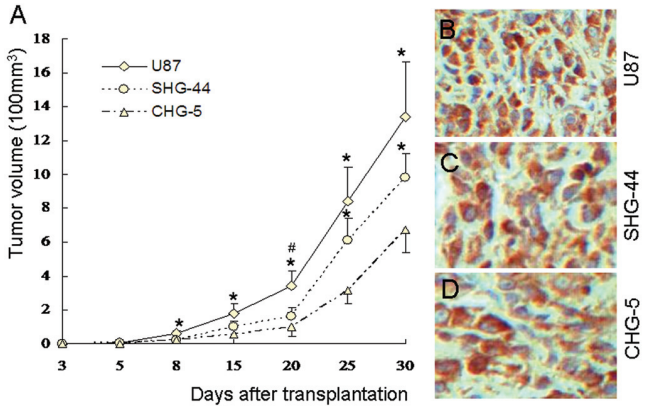


FIGURE 4. *The growth of tumors formed by injection of human glioma cells in nude mice.* **A**, *graph demonstrating the growth curves of xenografted tumors formed by human glioma cell lines. The* asterisks *indicate significantly higher volumes of tumors formed by U87 and SHG-44 cells compared with tumors formed by CHG-5 cells ($P < 0.01$).* **B–D**, *photomicrographs demonstrating immunostaining of CXCR4 protein in tumor sections formed by human glioma cell lines in nude mice. DAB was used to reveal CXCR4 in red with hematoxylin counterstaining (original magnification, ×200).*

not with the age or sex of the patients (Bian, unpublished observation), suggesting that CXCR4 may be considered a prognostic indicator and that more rigorous postsurgical adjunctive therapy may be required.

Although the mechanistic basis for CXCR4 to promote cancer progression requires further investigation, CXCR4 may contribute to tumor growth in several important ways. First, CXCR4 is a classic G protein-coupled receptor and its first defined functions were as a coreceptor for T-lymphocyte tropic human immunodeficiency virus and a mediator of the chemotactic responses of diverse leukocytes to its sole cognate agonist SDF-1 (24, 39, 43). Since the introduction of the concept that chemokines may mediate the organ-specific metastasis of malignant tumors (40, 41), CXCR4 was found to be involved in the metastasis of a variety of human cancer cells in animal models by virtue of its capacity to direct tumor cell migration and extravasation in response to the locally elevated agonist SDF-1 (25, 47). Thus, CXCR4 expression may be responsible for the increased motility; hence, the capacity for invasion and metastasis of tumor cells. Second, CXCR4 has been shown to affect tumor progression through induction of other host factors that support tumor cell survival and proliferation. For instance, stimulation of CXCR4 on ovary cancer cell lines and ascite cells enhanced the production of tumor necrosis factor-α, a proinflammatory cytokine and a promoter of mouse skin cancer (35). In some human glioma cells lines, CXCR4 may act as a survival factor in vitro, and in selected ovarian cancer cells, CXCR4, through MAP kinase and Akt pathways, transactivated the receptor for epidermal growth factor (29), which is expressed at high levels on tumor cells of the epithelial lineage. Third, as discovered in the present study, activation of CXCR4 in glioma cells markedly increased the production of VEGF, a major angiogenic factor implicated in a vast majority of malignant tumors (2). These observations indicate a strong linkage of CXCR4 signaling pathway to tumor cell motility, growth, and angiogenesis, events that are crucial for tumor progression and metastasis. During the final stage of preparation of this manuscript, Ehtesham et al. (12) reported that the CXCR4 expression in glioma cells is correlated with tumor cell invasiveness. These findings, together with our present results, strongly implicate the role of CXCR4 in promoting the malignant behavior of human glioma cells.

TABLE 1. CXCR4 expression in human primary gliomas and correlation with patient survival[a]

	No. of cases	CXCR4 expression	
		Negative	Positive
Normal brain	5	5	0
World Health Organization grade[b]			
II	28	13 (46.4%)	15 (53.6%)
III and IV	44	6 (13.6%)	38 (86.4%)
Tumor sizes (cm3)[c]			
≤3.0	29	12 (41.4%)	17 (58.6%)
>3.0	43	8 (18.6%)	35 (81.4%)
Postoperative survival (yr)[d]			
>3	28	22 (78.6%)	6 (21.4%)
≤3	44	15 (34.1%)	29 (65.9%)

[a] CXCR4 expression was detected in surgical specimens by immunohistochemistry and the results were scaled semiquantitatively as negative (–) or positive (+ and ++) reactions.
[b] Significantly higher levels of CXCR4 protein were detected in Grade III anaplastic astrocytomas and Grade IV glioblastoma as compared with Grade II tumors ($P < 0.05$).
[c] There was a correlation between tumor size and the level of CXCR4 expression ($P < 0.05$).
[d] Patients with CXCR4-positive tumors showed a lower rate of 3-year postoperative survival than those with CXCR4-negative tumors ($P < 0.05$).

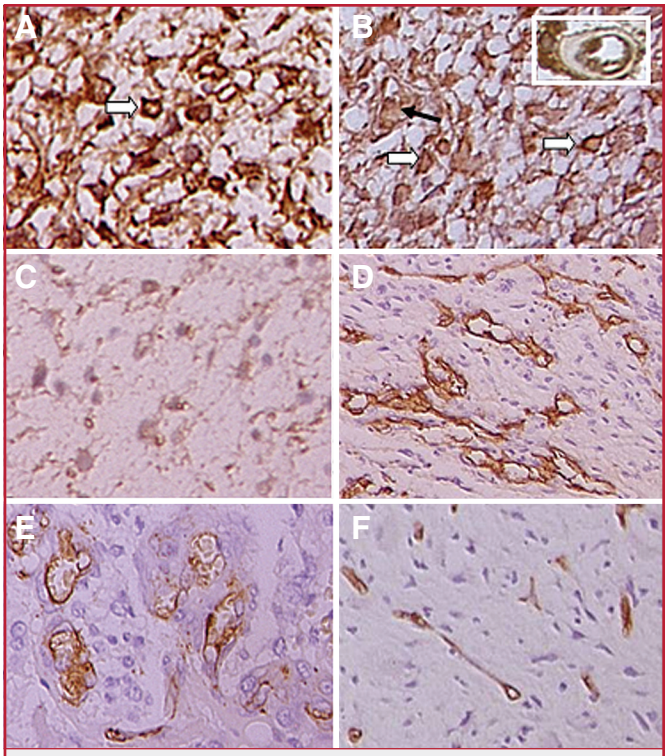


FIGURE 5. *Photomicrographs demonstrating CXCR4 expression and microvessel density in sections of primary human gliomas. A human anaplastic astrocytoma (A, WHO Grade III) and a glioblastoma (B, WHO Grade IV) are highly positive for CXCR4 protein in tumor cells (*white arrows*). Endothelial cells of microvessels were also positive for CXCR4 (*black arrow *and* inset *in B). C, Astrocytoma (WHO Grade II) with low levels of CXCR4 staining in tumor cells. D and E, endothelial cells in two CXCR4-positive Grade III anaplastic astrocytoma sections were in a proliferative state in association with higher microvessel density in tumor section. F, in a section of CXCR4-negative Grade II astrocytoma, endothelial cells were in a quiescent state associated with lower microvessel density in tumor tissue. A–F, immunostaining was revealed by DAB in* brown. *Sections were counterstained with hematoxylin (original magnification, ×200 (A–C) and ×150 (D–F).*

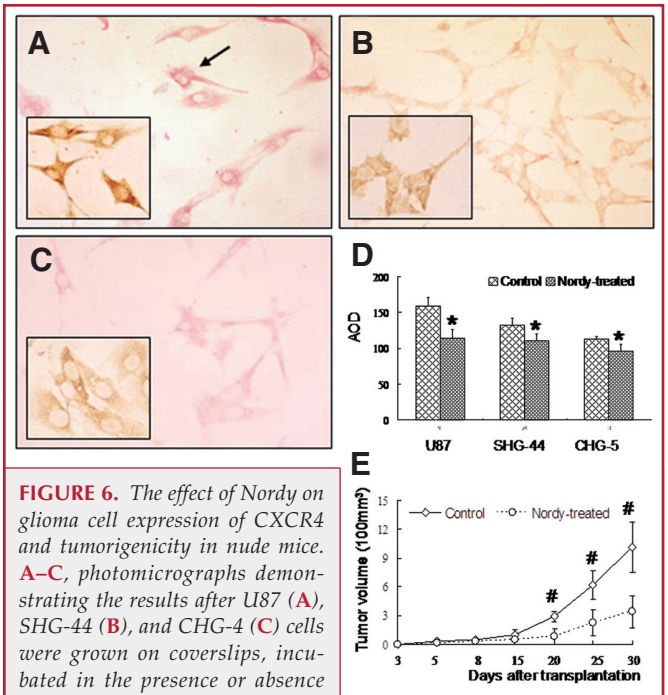


FIGURE 6. *The effect of Nordy on glioma cell expression of CXCR4 and tumorigenicity in nude mice. A–C, photomicrographs demonstrating the results after U87 (A), SHG-44 (B), and CHG-4 (C) cells were grown on coverslips, incubated in the presence or absence (*insets*) of Nordy (at 100 μmol/L for 24 h) and then stained with anti-CXCR4 monoclonal antibody. CXCR4 protein is indicated by a* black arrow. *D, bar graph demonstrating the quantitative measurement of CXCR4 in glioma cells cultured in the presence or absence of Nordy (at 100 μmol/L for 24 h). The* asterisks *indicate significantly reduced CXCR4 expression in Nordy-treated glioma cells ($P < 0.01$). E, graph demonstrating the volumes of tumors formed by SHG-44 cells 30 days after implantation in nude mice treated with phosphate-buffered saline alone (control) or with Nordy (27 mg/kg, once every 2 d for 30 d). The* pound signs *indicate significantly higher volumes of tumors formed in control mice compared with those in Nordy-treated mice ($P < 0.01$).* AOD, *average optical density.*

It is of great interest that we and other investigators also observed that microvessel ECs express CXCR4 in highly malignant human gliomas. Because highly malignant glioma cells have been shown to secrete the CXCR4 agonist SDF-1 (CXCL12) (33), it is plausible that ECs in tumors may sense its ligand in the tumor microenviroment for their increased infiltration to facilitate the angiogenic processes. As reported, CXCR4 was expressed by ECs of other origins, including the umbilical cord vein, aorta, and pulmonary artery (9, 31). These ECs responded to SDF-1 by chemotaxis and formation of vascular structures (32). To support the angiogenic activity of CXCR4 and SDF-1, CXCR4 is detected at high levels in the endothelium of developing vessels of the brain, and deletion of either CXCR4 or SDF-1 resulted in severe deformation of the cardiovascular systems in animals (1, 38, 46). Thus, CXCR4 expressed on glioma vessel ECs may participate actively in tumor angiogenesis in response to SDF-1 in tumor parenchyma.

It should be pointed out that CXCR4 may not be the sole molecule that is associated with the degree of glioma malignancy. We also recently found that another G protein-coupled receptor, namely formylpeptide receptor (FPR), which was mainly expressed by myeloid cells and mediates their chemotaxis to the bacterial peptides (17), was expressed selectively by most Grade III and IV malignant gliomas (44). Furthermore, glioma cells that express FPR respond to FPR agonist peptides with increased chemotaxis, proliferation, and production of VEGF. Depletion of FPR with small interfering ribonucleic acid reduced the tumorigenicity of highly malignant human glioma cell lines in nude mice. Thus, the progression of human gliomas may be multifactorial and is likely to be a complex process that involves close interaction of transformed cells with different molecules in their microenvironment. Further studies are required to define more precisely the key molecules that contribute to the development and expansion of human glioma.

Nevertheless, based on the functional role of CXCR4 in experimental tumor models and its relevance to clinical observation, as reported here in glioma patients, it is important to search and develop agents that may interfere with key signaling events of CXCR4 in tumors. It has been reported that anti-CXCR4 antibodies or a synthetic inhibitor of CXCR4 were capable of abrogating the metastasis to different organs of a number of human cancer cells in animal models (18, 23). In xenograft models, a small molecule compound, which inhibited CXCR4 functions as a chemoattractant receptor and a human immunodeficiency virus coreceptor, also reduced the tumorigenicity of human glioma cells in mice (30).

Nordy is a synthetic compound with a chiral structure of natural NDGA (*Fig. 1*). NDGA is a ligand found in creosote bush (*Larreu tridentala*) and is an inhibitor of 5-lipoxygenase. At one time, it was used to treat actinic keratoses but was later removed from the market as a result of side effects such as skin hypersensitivity (27). Along with other investigators, we have found that NDGA inhibits the growth of malignant tumors (15). However, the limited source and the side effects restrict the medical use of NDGA. Our present results showed that synthetic Nordy was capable of suppressing the expression of CXCR4 in malignant human glioma cells, reducing tumor cell chemotaxis and VEGF production in response to SDF-1β. Nordy treatment was also found to reduce calcium flux response induced by SDF-1 in glioma cells (28). More importantly, Nordy markedly inhibited the growth of tumors formed by CXCR4-expressing human glioma cells, with no toxicity to the animals. In addition to inhibiting CXCR4 function, Nordy also suppresses the function of another G protein-coupled receptor FPR in glioblastoma cells (8). Thus, although it is possible that inhibition of CXCR4 in glioma cells may not be the only biological activity of Nordy, this compound has nevertheless demonstrated its potential as candidate for the design of novel antiglioma agents.

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COMMENTS

This is a well executed investigation into the biological significance of CXCR4 in the growth, angiogenesis, and malignancy of gliomas. There is potential for capitalizing on this by way of therapeutic benefit to patients; this remains to be seen.

Nelson M. Oyesiku
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Bian et al. report interesting findings correlating the expression of the CXCR4 chemokine receptor with the degree of glioma malignancy via the proposed mechanisms of angiogenesis, cell migration, and proliferation as tested in vitro and in a mouse xenograft model. CXCR4 expression correlates with tumor size and relates to activation of angiogenesis in more malignant or larger hypoxic tumors. They also show the ability of an intriguing synthetic compound, Nordy, to decrease CXCR4 expression and reduce "tumorigenicity" in mice. Further studies will be needed to better characterize the CXCR4's role in determining biological characteristics of glioma malignancy, thereby potentially leading to translational therapeutics targeting this pathway.

John S. Kuo
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Recent reports suggest a crucial role for CXCR4 expression in the metastasis of multiple malignancies. The work presented by Bian et al. contributes to this growing knowledge by showing an association between high CXCR4 levels, increased vascular endothelial growth factor secretion, and accelerated angiogenesis. The authors also show that gliomas with high levels of CXCR4 expression are associated with poor postoperative prognosis, indicating that CXCR4 may be an important clinical target. The therapeutic potential of a CXCR4 antagonist in primary intracranial tumors is currently being explored. Rubin et al. (1) have shown that systemic administration of a CXCR4 antagonist decreases growth of intracranial glioblastoma and medulloblastoma xenografts through increased apoptosis and decreased proliferation. However, CXCR4 is widely expressed on hematopoietic cells, and high doses of CXCR4 antagonism lead to unacceptably high levels of bone marrow toxicity, limiting clinical applications (2). At this time, it is unclear what long term effects the CXCR4 antagonist has on bone marrow function and if related ana-

logues will also elicit similar side effects. The data suggest that continued evaluation of this pathway is warranted.

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1. Rubin JB, Kung AL, Klein RS, Chan JA, Sun Y, Schmidt K, Kieran MW, Luster AD, Segal RA: A small-molecule antagonist of CXCR4 inhibits intracranial growth of primary brain tumors. **Proc Natl Acad Sci U S A** 100:13513–13518, 2003.
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The search for markers differentiating low-grade gliomas from anaplastic gliomas and glioblastomas is an important one because, once found, these markers can become targets for directed therapies or act as prognostic factors for patients. In the present study, the authors investigate the role that CXCR4, a member of the chemokine family, may play in glioma tumor progression, degree of malignancy, chemotaxis, and tumor growth, both in vitro and in limited in vivo studies. They also attempt to correlate the expression of this tumor marker with patient survival.

The authors have performed some very nice in vitro studies demonstrating the expression of CXCR4 in gliomas by immunohistochemistry and reverse-transcriptase polymerase chain reaction. They also show that activation of CXCR4 is related to cell migration and the production of vascular endothelial growth factor protein, a known angiogenic factor. This effect is inhibited by Nordy. One criticism of this work is that the authors use a long-standing multiple passaged and cultured glioblastoma line, U87, and compare it with primary cultures from patients for the low-grade and anaplastic tumors. It is known that tumors in culture can change their receptor characteristics as well as their genetic profiles as a result of multiple passage and continued culture in vitro.

The in vivo work suggests a decrease in tumor growth when CXRC4 is blocked by Nordy. However, these studies are limited in clinical relevance because they are performed in a subcutaneous tumor model in nude mice and measure only tumor growth. We look forward to seeing survival studies with an intracranial tumor model, preferably in immune competent mice, in order to assess efficacy and toxicity.

Finally, the finding that CXRX4 correlates with patient survival is intriguing, but the numbers are too small at this time. In addition, we do not know if the patients were all treated comparably with respect to surgery, radiation, and chemotherapy. We look forward to further studies from this productive group.

Roberta Glick
Chicago, Illinois



Sperm whale skull and lower jaw. The wide basin-shaped upper surface of the skull holds the "case" full of spermaceti, a waxy substance consisting of fatty acids used in cosmetics and candles or as an emollient. *From*: Matthews, LH: *The Whale*. New York, Simon & Schuster, 1968.

A Study of the Correlation between Morphological Findings and Biological Activities in Clinically Nonfunctioning Pituitary Adenomas

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OBJECTIVE: The aims of this study are to review the histology of the clinically nonfunctioning pituitary adenomas (CNFPAs) we have observed and to determine whether or not the frequency of cavernous sinus invasion is different among each type of morphology.

METHODS: In addition, several proliferative markers, including Ki67, p53, E-cadherin, matrix metallo-proteinase 9 and pituitary tumor derived fibroblast growth factor receptor 4 (ptd-FGFR4), were also investigated in invasive and non-invasive tumors.

RESULTS: Our consequent 213 CNFPAs were diagnosed as follows: 64% were silent gonadotroph adenomas, 18% were null cell adenomas, 12% were silent corticotroph adenomas, 4% were silent Subtype 3 adenomas, and 1% were other types of adenomas. Female patients or younger patients showed a significant preponderance in silent corticotroph adenomas and in silent Subtype 3 adenomas, respectively. Cavernous sinus invasion occurs most frequently in silent corticotroph adenomas (85%) followed by Subtype 3 adenomas (67%), null cell adenomas (38%), and silent gonadotroph adenomas (11%). There were no significant differences in the Ki67, p53, E-cadherin, matrix metallo-proteinase 9, and ptd-FGFR4 expression between tumors with and without cavernous sinus invasion.

CONCLUSION: From a clinical standpoint, it is quite important to differentiate morphological type in CNFPAs to aid the clinician in assessing the clinical behavior and prognosis of the tumor. Therefore, we suggest that all CNFPAs be examined not only by conventional light microscopy but also by immunohistochemistry, preferably by electron microscopy, to achieve a correct morphological diagnosis.

KEY WORDS: Cavernous sinus invasion, Morphology, Non-functioning pituitary adenoma, Null cell adenoma, Proliferative marker, Silent pituitary adenomas

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The term clinically nonfunctioning pituitary adenoma (CNFPA) relies on a clinical definition that has no evidence of hormone excess. CNFPAs are usually macroadenomas associated with visual disturbances and/or various degrees of hypopituitarism; they are the most common type of pituitary adenoma, comprising 25 to 30% of all pituitary tumors (1, 7, 19). They are morphologically heterogeneous and are classified into two groups, those which have the same hormone immunoreactivity and morphological features of known adenohypophysial cell types but are clinically silent and those composed of cells that have no specific markers and do not resemble nontumorous adenohypophysial cell types (1, 7, 19). Included among the former are silent somatotroph adenomas, silent corticotroph adenomas, silent thyrotroph adenomas, and silent gonadotroph adenomas. Among the latter are null cell adenomas, oncocytomas, and silent Subtype 3 adenomas. However, there are very few studies reporting differences of biological activity or follow-up results after surgery among each type of morphology. The aims of this study are to review the histology of the CNFPAs we have observed and to determine whether or not the

frequency of cavernous sinus invasion is different among each type of morphology. In addition, several factors, including Ki67, P53, E-cadherin, matrix metallo-proteinase 9, and pituitary tumor-derived fibroblast growth factor receptor 4 (ptd-FGFR4), were investigated between invasive tumors and non-invasive tumors to clarify the mechanism of the cavernous sinus invasion.

PATIENTS AND METHODS

Two-hundred thirty-five consecutive patients underwent transsphenoidal surgery for presumptive diagnosis of CNFPA at Toranomon Hospital between 2001 and 2005. Of these, only 213 were included in this study. The others were ultimately diagnosed with a different histology, including craniopharyngiomas, Rathke's cleft cysts, or other granulomatous diseases. All of the tumors were studied by routine histological methods, including immunohistochemistry. For the purpose of histology and immunohistochemistry, the tissues were fixed in 10% buffered formaldehyde, dehydrated in graded ethanol, and embedded in paraffin. Microsections were stained with hematoxylin and eosin. The avidin-biotin-peroxidase complex (ABC) technique was used for the immunohistochemistry. The following antiserums were applied: polyclonal antisera to growth hormone (1:800; Dakopatts, Glostrup, Denmark) and adrenocorticotropic hormone (1:1600; Dakopatts), and monoclonal antibodies to prolactin (1:1000; Immunotech, Marseille, France), the β-subunit of luteinizing hormone (1:1000; Immunotech), follicle-stimulating hormone (1:1000; Immunotech), thyroid-stimulating hormone (1:100; Chemicon, Temecula, CA), and the α-subunit of glycoprotein hormone (1:100; INC Immuno-Biological, Lisle, IL), Ki-67, clone MIB-1 (1:100, Lot.012; DAKO, Kyoto, Japan), p53 protein, clone DO-7 (1:60, Lot.121; DAKO), E-cadherin (1:400, Lot.9; BD Biosciences, San Diego, CA), and matrix metallo-proteinase 9 (1:5, Lot.MO69333; BD Biosciences). Immunohistochemical studies for anterior pituitary hormones were performed at both Toranomon Hospital and Tokushima University. Regarding Ki67, p53, E-cadherin, and MMP9, results were obtained by manually counting immunopositive cells in random fields by a technical assistant (MW) who was blinded to all clinical data. Ultrastructural features were studied using electron microscopy (EM) in patients when we were not able to reach a final morphological diagnosis using only conventional histological examinations. In addition, the ultrastructural diagnosis of silent Subtype 3 adenomas were finally confirmed by Drs. Kalman Kovacs, M.D., and Eva Horvath, Ph.D. (Department of Laboratory Medicine and Pathobiology, St. Michael's Hospital, Toronto, Canada).

Ptd-FGFR4 messenger ribonucleic acid (mRNA) expression has been reported to reflect the presence of ptd-FGFR4 protein (4). To evaluate the expression of ptd-FGFR4 mRNA, amplification of not only the FGFR4 kinase domain (exon 10~11) but also the FGFR4 extracellular immunoglobin-like and kinase domain (exon 4~11) were performed using GeneAmp PCR System 9700 (Applied Biosystems, Foster City, CA). In the presence of ptd-FGFR4 mRNA expression, only the kinase domain (exon 10~11) can be amplified. We used the mRNA sample of MCF-7, a breast-carcinoma cell line, as the positive control expressing full-length FGFR4, and were thus able to amplify both exon 10~11 and exon 4~11. For amplification of exon 10~11, we used the oligonucleotide 5′-TCAAGCTCATCCCTGGTACG-3′ as the forward primer and 5′-GCCACAGTGCTGGCTTGGTCAG-3′ as the reverse primer. For amplification of exon 4~11, we used the oligonucleotide 5′-GCAAGCACCCTACTGGACAC-3′ as the forward primer and 5′-GCCACAGTGCTGGCTTGGTCAG-3′ as the reverse primer; both primers were designed by Abbass SA and collaborators. After denaturation for 5 minutes at 95°C, exon 10~11 amplification was performed over [94°C × 1 minute, 55°C × 1 minute, 72°C × 1 minute] × 40 cycles, followed by 72°C × 7 minutes with TaKaRa Ex-Taq (TaKaRa Biochemicals, Tokyo, Japan), and exon 4~11 amplification was performed over [94°C × 1 minute, 55°C × 1 minute, 72°C × 2 minutes] × 40 cycles and 72°C × 7 minutes with TaKaRa LA-Taq (TaKaRa Biochemicals).

The χ^2 independence test, the Fisher test, the Kruskal-Wallis test, and Student's t test were performed to determine the significance of associations between different variables. A P value of less than 0.05 was considered statistically significant.

RESULTS

Background Factors

Out of 213 patients, 136 were diagnosed with silent gonadotroph adenomas (41 women and 95 men), 39 were diagnosed with null cell adenomas (22 women and 17 men), 26 were diagnosed with silent corticotroph adenomas (22 women and 4 men), 9 were diagnosed with Subtype 3 adenoma (3 women and 6 men), and the remaining 3 were diagnosed with silent thyrotroph adenomas (2 cases) or a silent somatotroph adenoma (1 case). Regarding the sex distribution in each morphological type, the χ^2 test showed that female patients had a significant preponderance in silent corticotroph adenomas compared with silent gonadotroph adenomas ($P < 0.0001$), null cell adenomas ($P = 0.0172$), or Subtype 3 adenomas ($P = 0.0073$). The age of the patients at the time of operation was 54.2 ± 2.5 years (mean ± standard error of the mean) in silent gonadotroph adenomas, 51.9 ± 2.3 in null cell adenoma, 52.1 ± 2.5 in silent corticotroph adenomas, and 28.3 ± 1.8 in Subtype 3 adenomas. The Student's t test showed that the patients with Subtype 3 adenomas were significantly younger than the other morphological types (*Table 1*).

Cavernous Sinus Invasion

Cavernous sinus invasion was analyzed based on preoperative magnetic resonance imaging scans, and the patient in whom cavernous sinus invasion was confirmed during surgery was only assessed as having "cavernous sinus tumor invasion." Cavernous sinus invasion was found in 15 out of 136 silent gonadotroph adenomas (11%), 15 out of 39 null cell adenomas (38%), 22 out of 26 silent corticotroph adenomas (85%), and 6 out of 9 silent Subtype 3 adenomas (67%). Cavernous sinus invasion occurred significantly more frequently in silent corticotroph adenomas than silent gonadotroph adenomas ($P < 0.0001$) and null cell adenomas ($P < 0.0001$), and more frequently in Subtype 3 adenomas than silent gonadotroph adenomas ($P < 0.0001$) using the χ^2 test. In order to clarify the differences in expression of proliferative markers, adhesion molecules, or Ptd-FGFR4 mRNA expression between the adenomas with cavernous sinus invasions and those without, 20 patients were arbitrarily selected from both groups. However, no significant difference was noted in Mib-1 index, p53, E-cadherin, or MMP9 immunohistochemistry between the two groups. In addition, no significant difference was noted as to Ptd-FGFR4

TABLE 1. Clinical data of each type of morphology in 210 clinically nonfunctioning pituitary adenomas[a]

Histological type	No. of cases (%)	Sex (F/M)	Age (yr), mean ± SE (range)	No. of patients with CSI (%)
Silent gonadotroph adenoma	136 (64)	41/95	54.2 ± 1.9 (35–72)	15 (11)
Null cell adenoma	39 (18)	22/17	51.9 ± 2.3 (32–75)	15 (38)
Silent corticotroph adenoma	26 (12)	22/4	52.1 ± 2.5 (35–72)	22 (85)
Silent Subtype 3 adenoma	9 (4)	3/6	28.3 ± 1.8 (19–34)	6 (67)

[a] SE, standard error of the mean; CSI, cavernous sinus invasion. Three cases were excluded, including two silent thyrotroph adenomas and one silent somatotroph adenoma.

mRNA expression between the two groups ($P = 0.285$), although Ptd-FGFR4 mRNA expression was found more frequently in patients with cavernous sinus invasion (10 out of 15) than those without invasion (7 out of 16) (*Table* 2).

DISCUSSION

Clinical Characteristics of Each Morphological Type of CNFPAs

Clinically nonfunctioning pituitary adenomas include several distinct morphological entities (1, 19). There have been no reports on the detailed frequency of each morphological type of CNFPAs, although it is known that the most frequent type of morphology is silent gonadotroph adenomas, followed by null cell adenomas and silent corticotroph adenomas (1, 7, 19). In contrast, other silent adenomas, including silent somatotroph, thyrotroph, or Subtype 3 adenomas are reported to be rare (1, 7, 19). These data are quite consistent with our current results; silent gonadotroph adenomas were present in 136 patients (63.8%), null cell adenomas were present in 39 patients (18.3%), silent corticotroph adenomas were present in 26 patients (12.2%), silent Subtype 3 adenomas were present in nine patients (4.2%), and others (two silent thyrotroph adenomas and one somatotroph adenoma) were present in three patients. Horvath and Kovacs (7) underscored the need for EM for the diagnosis of each morphological type, but EM is not absolutely necessary to identify each morphology because immunohistochemistry can provide a differential diagnosis in most cases. EM, however, often offers additional insights into subtle differences between functioning adenomas and the morphologically similar silent adenomas. In contrast, EM is an indispensable tool in making a final diagnosis of silent Subtype 3 adenomas, which are of undetermined cellular derivation at present, because immunohistochemical results are not consistent in this type of tumor and immunohistochemistry alone may lead to misleading conclusions (8). Therefore, in our present cases, in which ordinary pathological findings are equivocal, EM was performed to confirm histological diagnosis. With regard to sex- or age-related differences in incidence, female patients showed a significant preponderance toward silent corticotroph adenomas such as functioning corticotroph adenomas, and patients with Subtype 3 adenomas were significantly younger than those with other morphological types. This is in agreement with our previous findings (26) and those of others (8). Horvath and Kovacs reported that silent Subtype 3 adenomas are strikingly age-related, especially in female patients. Most women underwent operation between the ages of 20 and 35 years (7). Similarly, the age of the patients at the time of operation was 28.3 ± 1.8 in our patients with silent Subtype 3 adenomas.

Biological Activity in Each Morphological Type of CNFPAs

Furthermore, there are only two published reports concerning differences of biological activity or follow-up results after surgery among different types of morphologies (2, 3). However, in both reports, CNFPAs were morphologically divided into only ACTH immunopositive tumors and immunonegative tumors, and biological activity was compared between only two groups (2, 3). Thus, this is the first single-center comparative study reporting biological activities among each type of morphology in CNFPAs.

Tumor Cavernous Sinus Invasion

Previous reports showed that silent corticotroph adenomas or silent Subtype 3 adenomas behave more aggressively than other CNFPAs (2, 3, 8, 18, 25). In our present study, tumor aggressiveness was analyzed by studying tumor cavernous sinus invasion. The reported frequency of cavernous sinus invasion has varied greatly. The different definitions of invasiveness have been based on neuroimaging, as well as operative and histological findings (11, 17, 21). In our study, only tumors in which apparent cavernous sinus invasion was confirmed during surgery were defined as cavernous sinus invasion. Most of them showed the encasement of the intracavernous carotid artery, which is the most specific and reliable sign of cavernous sinus invasion (20). Cavernous sinus invasion occurred significantly more frequently in silent corticotroph adenomas than silent gonadotroph adenomas ($P < 0.0001$), and null cell adenomas ($P < 0.0001$). They also occurred more often in Subtype 3 adenomas than silent gonadotroph adenomas ($P = 0.0002$), indicating that silent corticotroph adenomas and silent Subtype 3 adenomas behave in an aggressive manner, as suggested in other reports (8, 18). Interestingly, cavernous sinus invasion was more common in null cell adenomas than silent gonadotroph adenomas ($P < 0.0001$). Young et al. (28) described that null cell and gonadotroph adenomas do not differ substantially in their biological behavior and prognosis. This may be due to the applica-

TABLE 2. Immunohistochemical data and ptd-FGFR4 gene expression[a]

Adenoma type	No. of cases	Ki67 (MIB1-index), mean ± SD	p53	E-cadherin	MMP9	Ptd-FGFR4, no. of positive cases/ total no. of cases
Adenomas with CSI	20	0.96 ± 0.28	–,4; +,8; ++,3; +++,5	–,1; +,3; ++,2; +++,4; ++++10	–,0; +,6; ++,6; +++,8	10/15
Adenomas without CSI	20	0.59 ± 0.10	–,7; +,5; ++,6; +++,2	–,0; +,1; ++,1; +++,4; ++++,14	–,0; +,8; ++,8; +++,4	7/16
P value[b]		0.417	0.216	0.124	0.476	0.285

[a] Ptd-FGFR4, pituitary tumor-derived fibroblast growth factor receptor 4; CSI, cavernous sinus invasion; –, all cells negative; +, less than 5% positive; ++, 5–15% positive; +++, 15–25% positive; ++++, 25–50% positive.
[b] *P* values were caluculated using the Fisher test in ptd-FGFR4 or the Kruskal-Wallis test in others.

tion of a different definition to null cell adenoma; the definition of null cell adenoma has changed from its original criteria. Presently, null cell adenomas are simply defined as pituitary adenomas without anterior hormone immunoreactivity by immunohistochemistry.

Proliferative Markers in Tumors with or without CSI

Several clinicopathological studies have been undertaken using biological markers for invasiveness of pituitary adenomas. These markers include Ki67, p53, nm23, c-myc, bcl-2, cathepsin B, MMP9, E-cadherin, polysialylated neural cell adhesion molecule, and vascular endothelial growth factor (13–15, 22–24). However, the results are not consistent among investigators. Some authors report that the overexpression of these factors is associated with cavernous sinus invasion and conclude that these factors can be considered a useful marker in determining the invasive behavior of pituitary adenomas (13–15, 22–27), whereas others claim that there is no significant difference between Ki-67, MMP-9, P53, or E-cadherin immunohistochemical expression and cavernous sinus invasion in pituitary adenomas (6, 9, 10, 12, 27). Similarly, we found no correlation between Ki-67, p53, E-cadherin, and MMP9 expression, and tumor cavernous sinus invasion. We recently reported that high levels of FGFR4 expression correlated significantly with Ki-67 ($P = 0.002$) and tended, although not significantly, to be found in invasive tumors (16). Indeed, ptd-FGFR4 gene expression was more frequent in invasive tumors (10 out of 15) compared with those without cavernous sinus invasion (seven out of 16), but no significant difference was noted between the groups ($P = 0.285$). Yokoyama et al. (27) postulate that most nonfunctioning pituitary adenomas involving cavernous sinus are neither aggressive nor invasive, but the question arises, which cannot be resolved at present, as to why cavernous sinus invasion is significantly more common in some types of adenomas. Moreover, from a clinical standpoint, cavernous sinus invasion is still of special interest because surgical cure is usually unlikely in this condition.

Tumor Recurrence

With regard to tumor recurrence or tumor regrowth, none of our present cases have shown definite tumor recurrence necessitating further additional treatment. This may be due to the relatively short follow-up period after surgery in this series. Baldeweg et al. (2) reported a higher recurrence rate (33.3%) in silent corticotroph adenomas. In contrast, Bradley et al. (3) indicated increased aggressiveness, but no increase in recurrence rate, in silent corticotroph adenomas when compared with adrenocorticotrophic hormone immunonegative and other CNFPAs. In general, tumor recurrence rates depend on the degree of tumor removal during surgery, and patients in whom gross total tumor removal was achieved by surgery have a low incidence of recurrence (5). Therefore, partial removal tends to occur in silent corticotroph or Subtype 3 adenomas because cavernous sinus invasion, which is difficult to be totally excised by surgery, is more frequent in those adenomas.

CONCLUSIONS

We suggest that all CNFPAs be examined not only by conventional light microscopy but also by immunohistochemistry, preferably by EM, to achieve a correct morphological diagnosis, which may provide useful information to aid the clinician in assessing the clinical behavior and prognosis of the tumor. In our view, close postoperative follow-up is an adequate primary approach when a CNFPA is diagnosed morphologically as a silent corticotroph, Subtype 3, or null cell adenoma. In addition, postoperative radiotherapy may be indicated to these types of tumors when gross total tumor removal cannot be achieved. Further studies will be necessary to clarify whether or not the recurrence rate or radiosensitivity is also different among these adenoma types. In addition, concern should be raised in attaching too much clinical significance to these biological markers, especially with respect to Ki67, p53, MMP9, E-cadherin as predictors of the clinical behavior of CNFPAs.

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COMMENTS

This is a large single-center series of 213 clinically nonfunctioning pituitary adenomas (CNFPA) that have been accurately subtyped and assessed by molecular markers. As CNFPAs represent a heterogeneous group of adenomas in terms of their biological behavior, we support the authors' opinion that these differences in growth potential and invasiveness justify careful examination by electron microscopy for subtyping and assessment of growth rate by proliferative markers.

The authors report magnetic resonance signs of invasiveness into cavernous sinus structures confirmed intraoperatively in 85% of silent corticotroph adenomas, 67% of silent Subtype 3 adenomas, 38% of null cell adenomas, and 11% of gonadotroph adenomas, with some significance on intersubgroup statistical analysis. A correlation of the status of invasiveness intraoperatively and on preoperative magnetic resonance imaging scans would be desirable and of paramount importance (2). This issue is even more contemporary, as current surgical techniques include endoscopy, which provides a direct judgement of the completeness of resection at the medial cavernous sinus wall.

Concerning expression of various factors and cavernous sinus invasion, no significant differences were found in this material. In our experience, however, MIB-1 can be used as a reliable marker for the assessment of growth potential and invasiveness (1, 3). In our opinion, both tumor cell proliferation markers and World Health Organization subtypes should be used as prognostic parameters to influence decisions of the individual postoperative patient management, such as the frequency of radiographic and endocrinological surveillance and considerations of radiotherapeutic interventions.

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Yamada et al. retrospectively analyzed immunohistochemical features of 213 CNFPAs surgically treated at a single institution. The distribution and sex characteristics of tumor types are similar to those reported in smaller and multi-institutional series. Tumor invasiveness, defined as cavernous sinus invasion, was seen more frequently in silent corticotroph and Subtype 3 adenomas. However, cavernous sinus invasion did not correlate with any of a series of cell markers, i.e., Ki-67, p53, cadherin, and fibroblast growth factor receptor 4 (FGFR4).

This study confirms the heterogeneity of nonfunctional pituitary adenomas. With the exception of silent corticotroph and Subtype 3 adenomas, however, the predictive significance of accurate subtype determination remains uncertain. Although we routinely characterize the hormone expression for all CNFPAs, decisions regarding adjunctive radiosurgery are based largely on radiological determinations of tumor residual and growth characteristics. One exception to this approach, however, is made when the initial proliferative index of the tumors is greater than 3%, in which case radiosurgery is recommended if the initial postoperative scan shows any residual tumor.

Clearly, there may be important prognostic information in the genomic and proteomic analysis of functional and nonfunctional adenomas. Such a determination will require a careful correlation of phenotype and long-term outcome measures.

Marc R. Mayberg
Seattle, Washington

This is an interesting study addressing a rather common problem: which pituitary adenomas are more likely to be invasive and which are more likely to recur? It is well studied and presented. I agree that too much clinical significance should not be placed on the markers we currently follow, yet an MIB-1 index greater than 3% remains troublesome to me. The final conclusion of this study, that all tumors should be studied for a correct morphological diagnosis, is something we do routinely, yet there were no alterations to therapy resulting from this process.

We still do not have an answer to the question of which, if any, of the incompletely removed adenomas demand immediate adjunctive therapy as opposed to a wait and watch philosophy with adjunctive therapy only if growth is seen. This study does not help in that regard. We need longer follow-up periods with stereotactic radiosurgery and the incidence of partial hypopituitarism seen afterward. If the results show that early single dose radiosurgery will yield a lower incidence of hypopituitarism, then early adjunctive therapy may be worthwhile after surgery while the residual adenoma is well away from the optic apparatus to allow single dose treatment.

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In this study, the authors correlate the various subtypes of CNFPAs with the incidence of cavernous sinus invasion. The data is gleaned from 213 consecutive CNFPA patients who underwent surgery between 2001 and 2005. Although the majority of CNFPAs were found to be gonadotroph or null cell adenomas, 16% were either silent corticotroph adenomas or silent Subtype 3 adenomas. Cavernous sinus invasion was present in only 11% of the patients with gonadotroph adenomas and 38% of those with null cell adenomas. However, a statistically significant increase in cavernous sinus invasion was seen in patients with silent corticotroph adenomas and silent Subtype 3 adenomas. Eighty-five percent of the silent corticotroph adenomas and 67% of the silent Subtype 3 adenomas showed evidence of cavernous sinus invasion. Proliferative markers, such as Ki67 and p53, did not correlate significantly with cavernous sinus invasion. The data support continued subtyping of CNFPAs and helps to justify the time and expense of immunohistochemical and electron microscopic analysis.

John A. Jane, Jr.
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This study follows a series of recent articles highlighting how different subtypes in the category defined as CNFPAs could be identified, each of them with different incidence and biological behaviour that are still under investigation. With the present study, the authors have shown that cavernous sinus invasion occurred more frequently in silent corticotroph and silent Subtype 3 adenomas. This might be a relevant result if proof bears a clinical implication, especially in terms of recurrence rate. The follow-up period needs to be longer to validate such a hypothesis. This study is expected to stimulate further research concerning the differences in the biological activity and/or follow-up results after surgery among this heterogeneous group of patients affected by CNFPAs.

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OBJECTIVE: Several reports recently suggested that vascular endothelial growth factor (VEGF) may have a therapeutic benefit against experimental cerebral infarction animal models. In addition, bone marrow stromal cells (BMSCs) are known to have therapeutic potency in improving neurological deficits after occlusive cerebrovascular diseases. In the present study, we evaluated the hypothesis that intracerebral transplantation of VEGF gene-transferred BMSCs could provide a greater therapeutic effect than intracerebral transplantation of native (non-gene-transformed) BMSCs by using a transient middle cerebral artery occlusion (MCAO) rat model.

METHODS: Adult Wistar rats (Japan SLC, Inc., Hamamatsu, Japan) were anesthetized. VEGF gene-transferred BMSCs engineered with a replication-deficient herpes simplex virus type 1 1764/4-/pR19-hVEGF165 vector, native BMSCs, or phosphate-buffered saline were administered intracerebrally 24 hours after transient MCAO. All animals underwent behavioral testing for 28 days, and the infarction volume was determined 14 days after MCAO. The brain water contents in the ipsilateral and contralateral hemispheres of the MCAO were measured 2 and 7 days after the MCAO. Fourteen days after MCAO, immunohistochemical staining for VEGF was performed.

RESULTS: The group receiving VEGF-modified BMSCs demonstrated significant functional recovery compared with those receiving native BMSCs. Fourteen days after the MCAO, there was a significantly lower infarct volume without aggravating cerebral edema in the group treated with VEGF gene-modified BMSCs compared with the control groups. The transplanted VEGF gene-modified BMSCs strongly expressed VEGF protein for at least 14 days.

CONCLUSION: Our data suggest that the intracerebral transplantation of VEGF gene-transferred BMSCs may provide a more potent autologous cell transplantation therapy for stroke than the transplantation of native BMSCs alone.

KEY WORDS: Bone marrow stromal cells, Cerebral infarct, Replication-deficient herpes simplex virus type 1 vector, Vascular endothelial growth factor

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Many previous studies showed that intracerebral or intravenous transplantation of bone marrow stromal cells (BMSCs), which have the ability to produce many kinds of important growth factors and cytokines, including fibroblast growth factor (FGF)-2, nerve growth factor, hepatocyte growth factor (HGF), and brain-derived neurotrophic factor (7), can improve neurological function after ischemic stroke (1, 4–6, 11, 16, 17, 19, 30, 34, 35). Therefore, BMSCs, including the primitive pluripotent mesenchymal stem cells, are thought to be a source for autoplastic therapy. If we could enhance the therapeutic

potential of BMSCs by ex vivo gene transfer of specific neurotrophic growth factors, such modified BMSCs might become even more promising tools for stroke treatment. In fact, the autologous transplantation of BMSCs modified with specific growth factor genes that have potential neuroprotective effects could help to improve the neurological function after ischemic cerebral stroke, as previously reported (12, 36).

It has been suggested that specific kinds of growth factors can ameliorate the neurological deficits caused by various neurological disorders (13, 25, 26, 29). Vascular endothelial growth factor (VEGF) is a strong angiogenic peptide with potent neurotrophic function in cerebrovascular diseases (14, 18) that also has a potential vascular permeability function (9, 10). Currently, the action of VEGF against acute ischemic disorders is considered a double-edged sword (15, 31, 35). Despite its neurotrophic function, application of this cytokine in cases of acute ischemic stroke is still controversial because of its vascular permeability-increasing effects, which can aggravate peri-infarct edema. In this study, we investigated whether or not the ex vivo gene modification of BMSCs with the VEGF gene could help to achieve greater therapeutic effects against acute cerebral infarction.

MATERIALS AND METHODS

Replication-deficient Herpes Simplex Virus Type 1 Vector Expressing the Human VEGF165 Gene

We prepared a replication-deficient herpes simplex virus type 1 (HSV-1) vector expressing human VEGF165 (HSV-1 1764/4-/pR19/hVEGF165), which originated from HSV-1 strain 17 and was made replication-incompetent by the deletion of the ICP4 and ICP34.5 genes and the inactivation of the VP16 gene (8, 20, 24). This vector contained the pR19 expression cassette driving a gene of interest under the control of fusion promoters, latency-associated transcript promoters, cytomegalovirus enhancers, and woodchuck posttranscriptional regulatory elements, as shown in *Figure 1A*.

Donor BMSC Preparation

We harvested donor BMSCs from 8-week-old Wistar rats (Japan SLC, Inc., Hamamatsu, Japan) as described previously (6, 12, 36). The bilateral femurs and tibias were sterilely dissected, and their bone marrow was extruded into a flask with the culture medium (Minimum Essential Medium with 10% fetal bovine serum, 1% antibiotic-antimycotic [GIBCO Invitrogen, Carlsbad, CA], and 2 mmol/L L-glutamine), and cultured at 37°C, 98% humidity, and 5% CO_2. After 48 hours, the nonadherent cells were removed by replacing the medium. When the cells had grown to confluence, they were lifted by 0.25% trypsin and 0.02% ethylenediamine tetraacetic acid in phosphate-buffered saline (PBS). The cells were passed five to seven times and were used in all procedures.

In Vitro Study

Human VEGF165 Secretion into the Culture Supernatant from VEGF Gene-enhanced BMSCs

The following eight experimental groups (n = 4 for each group) were used: Group 1, only culture medium (without BMSCs); Group 2, BMSCs without HSV-1 vector infection incubated in culture medium; and Groups 3, 4, 5, 6, 7, and 8: BMSCs infected with HSV-1 1764/4-/pR19/VEGF at multiplicities of infection of 0.1, 1, 2, 5, 10, and 20, respectively, in PBS-1% glucose for 1 hour and then incubated in the culture medium. Twenty-four hours after HSV-1 vector infection, we determined the VEGF concentration in the culture supernatant with an enzyme-linked immunosorbent assay (Endogen Human VEGF ELISA Kit; Pierce Biotechnology, Inc., Rockford, IL). Absorbency was measured with a microplate reader (450 nm; NALGEN-NUNC Immunoreader NJ-2001; Nalgen-Nunc, Rochester, NY) as previously described (12, 36).

In Vivo Study

Transient Middle Cerebral Artery Occlusion Model

All procedures and virus inoculates were approved by the Committees of Recombinant Deoyribonucleic Acid and Animal Experiments, Osaka Medical College. Eight-week-old male Wistar rats weighing 250 to 280 g (Japan SLC, Inc.) were anesthetized initially with 3.5% halothane and maintained with 1.0 to 2.0% halothane in 70% N2O and 30% O_2 using a face mask. Rectal temperature was maintained at 37°C throughout the surgical procedure. We induced transient middle cerebral artery occlusion (MCAO) using a previously described method of intraluminal vascular occlusion with minor modifications (12, 21, 32, 36). Two hours after MCAO, the animals were reanesthetized using the same procedure as for MCAO, and reperfusion was performed by withdrawing the suture; then, the end of the external carotid artery was tied. After recovery from anesthesia, the animals were allowed free access to food and water.

Experimental Groups: Intracerebral Transplantation of Donors

Twenty-four hours after MCAO, the animals were reanesthetized with halothane and maintained with intraperitoneal pentobarbital (10 μg/g body weight) administration, and then fixed with a stereotactic head holder (Model 900; David Kopf Instruments, Tujunga, CA). Donor cells were stereotactically transplanted by inserting a 26-gauge needle with a Hamilton syringe into the ipsilateral striatum of the MCAO, as previously described (12, 36). There were 1 x 106 cells in the total 10-μL fluid volume that was transplanted into each animal over a 10-minute period. The experimental groups included Group 1 (sham-operated group), consisting of rats given MCAO without cell administration but with 10 μL of PBS; Group 2 (native BMSC-treated group), consisting of rats given BMSCs without gene transfer (1 x 106 cells); and Group 3 (VEGF-modified, BMSC-treated group), consisting of rats given BMSCs (1 x 106 cells) into which the VEGF gene had been transferred by HSV-1 1764/4-/pR19/hVEGF165.

Ex Vivo Gene Transfer to BMSCs

BMSCs were prepared and passaged five to seven times. Twenty-four hours before the stereotactic transplantation, the VEGF gene was transferred to the BMSCs with HSV-1 1764/4-/pR19/hVEGF165 at a multiplicity of infection of five. Untreated BMSCs and VEGF-modified BMSCs were harvested just before the transplantation and diluted to 1 x 106 cells/10 μL of PBS, as previously described (12, 36).

Behavioral Testing

All animals (n = 5 for each group) underwent behavioral tests before MCAO and 1, 3, 7, 14, 21, and 28 days after MCAO. We used the modified neurological severity score (*Table 1*), which was described by Schallert et al. (27) to grade the aspects of neurological function. The

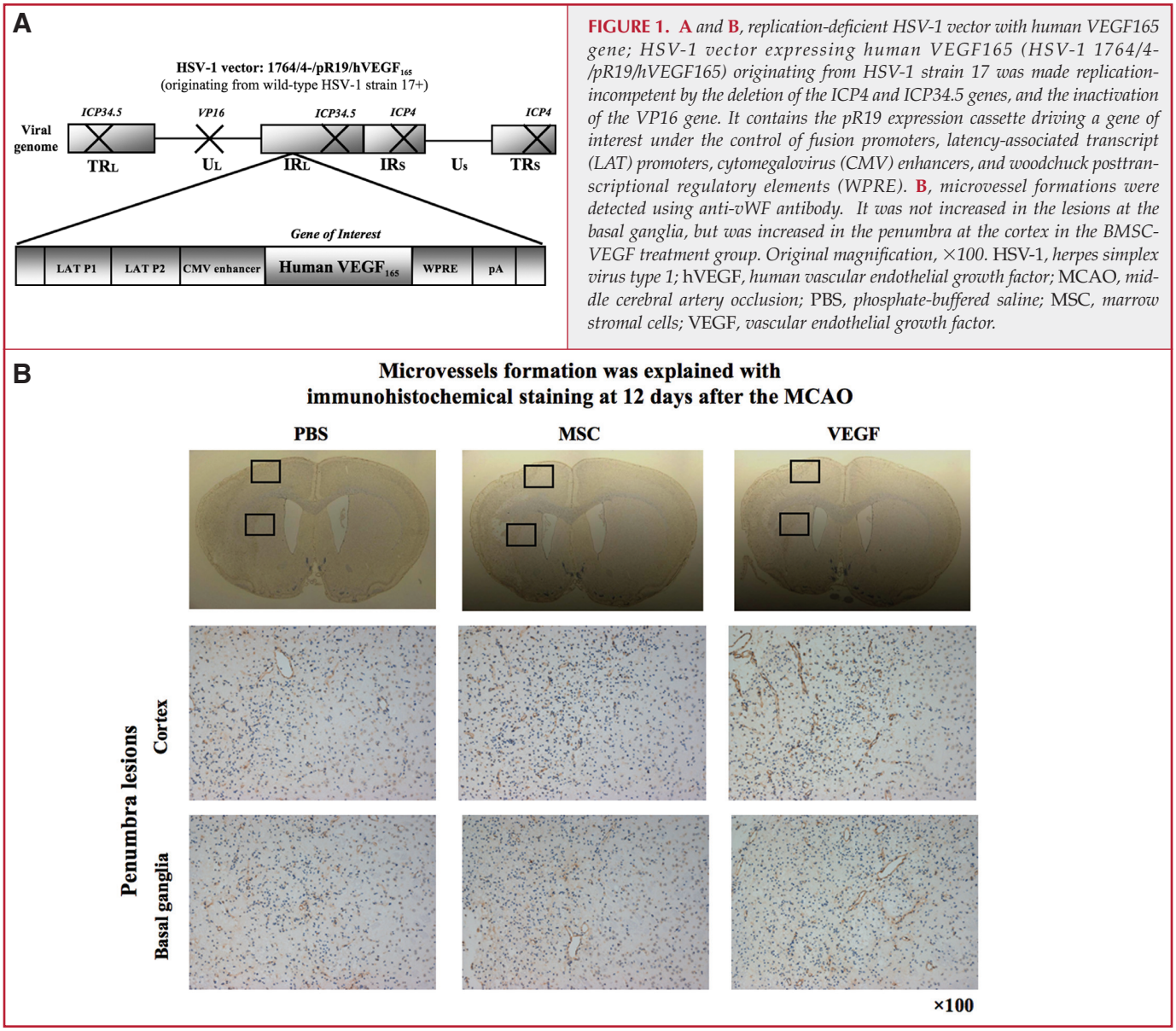


FIGURE 1. **A** *and* **B**, *replication-deficient HSV-1 vector with human VEGF165 gene; HSV-1 vector expressing human VEGF165 (HSV-1 1764/4-/pR19/hVEGF165) originating from HSV-1 strain 17 was made replication-incompetent by the deletion of the ICP4 and ICP34.5 genes, and the inactivation of the VP16 gene. It contains the pR19 expression cassette driving a gene of interest under the control of fusion promoters, latency-associated transcript (LAT) promoters, cytomegalovirus (CMV) enhancers, and woodchuck posttranscriptional regulatory elements (WPRE).* **B**, *microvessel formations were detected using anti-vWF antibody. It was not increased in the lesions at the basal ganglia, but was increased in the penumbra at the cortex in the BMSC-VEGF treatment group. Original magnification, ×100.* HSV-1, *herpes simplex virus type 1;* hVEGF, *human vascular endothelial growth factor;* MCAO, *middle cerebral artery occlusion;* PBS, *phosphate-buffered saline;* MSC, *marrow stromal cells;* VEGF, *vascular endothelial growth factor.*

tests used to determine the modified neurological severity score included motor (muscle status, abnormal movement), sensory (visual, tactile, and proprioceptive), and reflex tests. The higher the score, the more severe the neurological deficit.

Infarction Volume

Fourteen days after the MCAO, rats of all groups (n = 5 for each group) were deeply anesthetized with halothane. Then, transcardiac perfusion was performed with saline. The brain was immediately removed and sliced into seven equally spaced (2 mm) coronal sections using a rodent brain matrix. These sections were soaked in a 2% solution of 2-3-5-triphenyltetrazolium (Wako Pure Chemical Industries, Osaka, Japan) for 30 minutes at 37°C. The infarct area was defined as the area not stained with 2-3-5-triphenyltetrazolium, as described previously (2, 16). The lesion volume was calculated as the ratio of the volume of the lesion to the volume of the contralateral hemisphere.

Identification of the Transplanted BMSCs and Immunohistochemical Assessment for hVEGF165

Before transplantation, the BMSCs were incubated with culture medium containing 1 μg/mL bisbenzimide (Hoechst 33258; Polysciences, Eppelheim, Germany) over 24 hours to label the nuclei fluorescently. Twenty-four hours after MCAO, the rats were treated with PBS or fluorescence-marked native or VEGF-modified BMSCs as described above. Fourteen days after MCAO, the rats were deeply anesthetized with halothane and transcardially perfused with normal saline, followed by 4% paraformaldehyde. Then, the brains were removed and incubated overnight in 20% sucrose at 4°C. The samples were immediately frozen by liquid nitrogen, and 6-μm sections were

TABLE 1. Modified neurological severity score[a]

Motor tests	No. of points
Raising the rat by the tail	3
1 Flexion of forelimb	
1 Flexion of hindlimb	
1 Head moved more than 10 degrees to the vertical axis within 30 s	
Walking on the floor (normal, 0; maximum, 3)	3
0 Normal walk	
1 Inability to walk straight	
2 Circling toward the paretic side	
3 Fall down to the paretic side	
Sensory tests	2
1 Placing test (visual and tactile test)	
2 Proprioceptive test (deep sensation, pushing the paw against the table edge to stimulate limb muscles)	
Beam balance tests (normal, 0; maximum, 6)	6
0 Balances with steady posture	
1 Grasps side of beam	
2 Hugs the beam and one limb falls down from the beam	
3 Hugs the beam and two limbs fall down from the beam or spins on beam (<60 s)	
4 Attempts to balance on the beam but falls off (<40 s)	
5 Attempts to balance on the beam but falls off (<20 s)	
6 Falls off, no attempt to balance of hang onto the beam	
Reflexes absent and abnormal movements	4
1 Pinna reflex (head shake when touching the auditory meatus)	
1 Corneal reflex (eye blink when lightly touching the cornea with cotton)	
1 Startle reflex (motor response to a brief noise from snapping a clipboard and paper)	
1 Seizures, myoclonus, myodystony	
Maximum no. of points	18

[a] One point was awarded for the inability to perform the tasks or for the lack of a tested reflex. 1 to 6 indicates mild injury, 7 to 12 indicates moderate injury, and 13 to 18 denotes severe injury.

prepared with a cryostat for immunohistochemical staining. After permeabilization with 0.02% Triton X and blocking in 3% bovine serum albumin, these sections were treated with the mouse monoclonal antibody against hVEGF165 (Chemicon International, Inc., Temecula, CA) for 120 minutes at 4°C. Subsequently, the sections were washed with PBS, and fluorescein rhodamine-conjugated donkey secondary antibody against mouse immunoglobulin-G (Cosmo Bio, Ltd., Tokyo, Japan) was added, followed by incubation for 20 minutes at 4°C. The prepared sections were observed with a fluorescent microscope (Olympus AX70; Olympus Corp., Tokyo, Japan).

Brain Water Content

The rats (n = 4 for each group) were deeply anesthetized with halothane 2 and 7 days after MCAO, and the brains were removed and dissected immediately. The whole brain was separated into an ischemic hemisphere and a nonischemic hemisphere. Subsequently, the wet weight of each side was rapidly measured, and the brain was dried at 95°C for 24 hours to obtain the dry weight. The brain water content was calculated as (wet weight − dry weight)/dry weight, as previously described (11).

Statistical Analysis

Data are expressed as the means ± standard deviation. One-way analysis of variance followed by Bonferroni's post hoc analysis was used, and P values less than 0.05 were considered statistically significant.

RESULTS

In Vitro Study: Gene Transfer to BMSCs with HSV-1 Vector and hVEGF165 Secretion

The culture supernatant of hVEGF165 gene-transferred BMSCs was measured by enzyme-linked immunosorbent assay. hVEGF165 production by hVEGF165-modified BMSCs proportionately increased with the multiplicity of infection (*Fig. 2A*).

Neurological Outcome

Between 14 and 28 days after MCAO, the rats treated with native BMSCs or VEGF-modified BMSCs showed significant improvements in neurological function compared with PBS-treated rats ($P < 0.05$). In addition, the VEGF-modified BMSC group displayed more remarkable amelioration than the native BMSC group ($P < 0.05$) (*Fig. 3A*).

Measurement of Infarction Volume

Fourteen days after MCAO, the infarction volume was significantly less in the rats receiving BMSCs with the hVEGF165 gene (28.42 ± 2.65%) than in either the PBS group (38.95 ± 3.47%) or the native BMSC group (35.14 ± 2.66%; $P < 0.05$) (*Fig. 4*).

Identification of the Transplanted BMSCs and Immunohistochemical Assessment for VEGF

Fourteen days after MCAO, some Hoechst-positive cells were observed around the transplantation track, but no Hoechst-positive cells had migrated into the remote site from transplantation points such as the contralateral brain or ipsilateral cortex. VEGF expression by transplanted donor cells was detected with immunohistochemical staining at 14 days after MCAO at the region around the injection point. Some Hoechst-marked cells stained weakly for VEGF in the native BMSC-treated rats, whereas the Hoechst-marked cells stained strongly for VEGF in the VEGF-modified, BMSC-treated rats (*Fig. 5*).

Brain Water Content

Brain water content was measured in the three treatment groups 2 and 7 days after MCAO. With respect to the mean level of water content in the ischemic cerebral hemisphere,

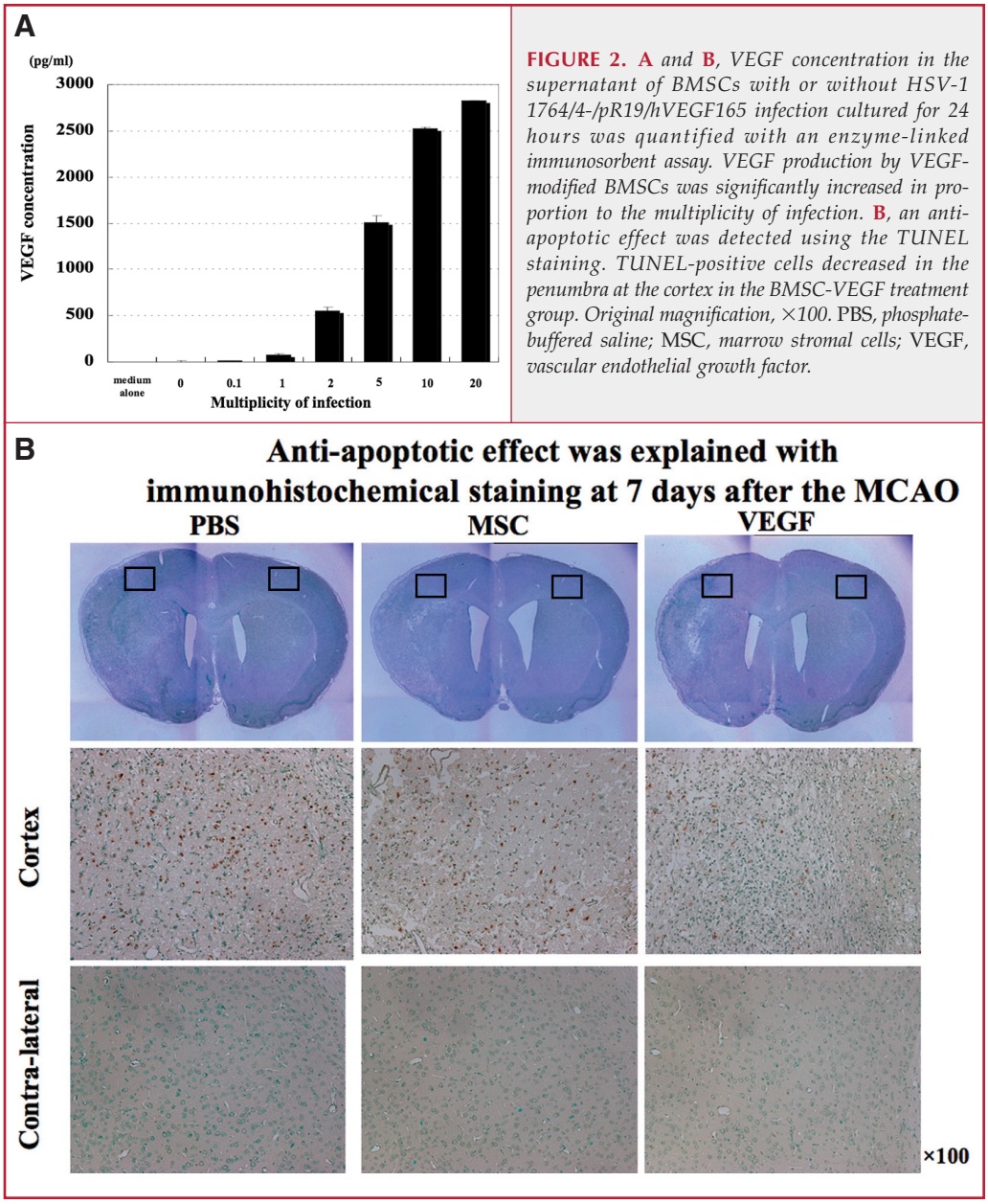


FIGURE 2. **A** *and* **B**, *VEGF concentration in the supernatant of BMSCs with or without HSV-1 1764/4-/pR19/hVEGF165 infection cultured for 24 hours was quantified with an enzyme-linked immunosorbent assay. VEGF production by VEGF-modified BMSCs was significantly increased in proportion to the multiplicity of infection.* **B**, *an anti-apoptotic effect was detected using the TUNEL staining. TUNEL-positive cells decreased in the penumbra at the cortex in the BMSC-VEGF treatment group. Original magnification, ×100.* PBS, *phosphate-buffered saline;* MSC, *marrow stromal cells;* VEGF, *vascular endothelial growth factor.*

there was no significant difference among the three groups at either analysis point (*Fig. 6*).

DISCUSSION

Recent animal studies have strongly suggested that cell transplantation therapy can be a promising therapeutic option for patients with ischemic stroke. Of the several kinds of cell candidates, including adult neural stem cells (NSCs), embryonic stem cells, and embryonic neural cells, BMSCs are by far the most accessible. Furthermore, their use is not associated with ethical or immunological problems. In fact, because many reports have insisted that only native BMSC transplantation could improve neurological function after cerebral ischemic stroke (1, 4–6, 16, 19), BMSCs have become one of the major cellular candidates for such treatments. Bone marrow mesenchymal stem cells have the potential to differentiate into neural cells (22, 33), and BMSCs can produce many kinds of important growth factors and cytokines, including FGF-2, nerve growth factor, HGF, brain-derived neurotrophic factor, and VEGF (7). Thus, BMSCs may provide important cues for neuron survival in the damaged brain, with or without direct commitment to brain tissue repair. With regard to the possible mechanisms for their therapeutic effect, it has been reported that BMSCs have the ability to differentiate into other cell types (22, 33) and have a potent ability to secrete multiple cytokines, including VEGF, in ischemic circumstances (7). Therefore, we believe that BMSCs may be useful vehicles for autotransplantation in both cell and gene therapy for ischemic cerebral stroke. In addition, many researchers have tried to deliver genes of interest directly into the brain. For example, Kurozumi et al. (16) reported the efficacy of direct gene therapy for a rat MCAO model using a glial cell line-derived neutrophilic factor-expressing fiber-mutant adenovirus vector.

In the present study, with the intent of enhancing the therapeutic potential of BMSCs, we prepared gene-modified BMSCs that strongly expressed VEGF using replication-deficient HSV-1 vectors. In a preliminary study, we confirmed that BMSCs could be efficiently gene-transferred by this HSV-1 vector with little cytotoxicity; their intracerebral transplantation did not result in greater immune reactions than transplantation of native BMSCs (data not shown). Just as we had intended, both BMSCs transferred with the HGF gene and those transferred with the FGF-2 gene using this vector seem to have achieved impressive thera-

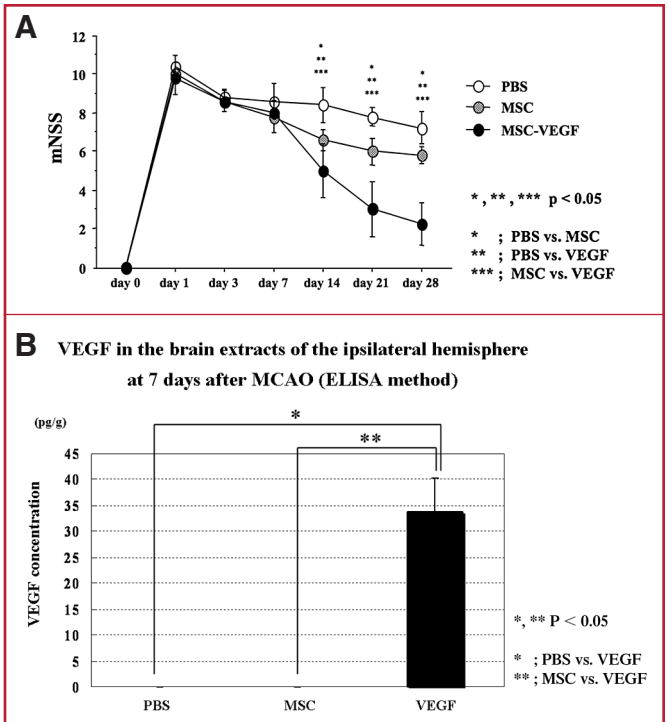


FIGURE 3. **A** *and* **B**, *neurological function of the experimental groups after MCAO determined by the modified neurological severity score. Significant neurological functional recovery was observed at 14, 21, and 28 days after MCAO in the rats treated with VEGF-modified BMSCs compared with the rats treated with native BMSCs alone (P < 0.05).* **B**, *VEGF concentration acquired from brain tissue at Day 7 was quantified with an enzyme-linked immunosorbent assay. VEGF concentration of the ipsilateral hemispheres in the BMSC-VEGF treatment group was significantly higher than that in the other groups (P < 0.05).*

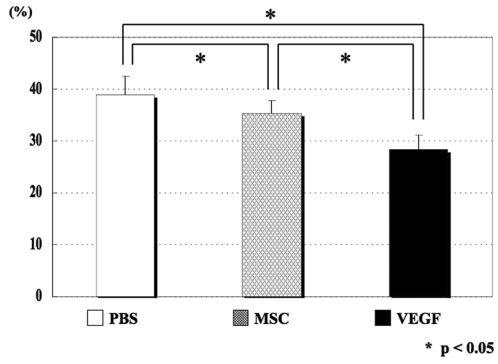


FIGURE 4. *Bar graph showing the ratio of the infarction volume of the lesion to the volume of the contralateral hemisphere detected with 2-3-5-triphenyltetrazolium staining at 14 days after the MCAO. There was a significantly lower infarction volume in the VEGF-modified, BMSC-treated group than in the other groups* (Asterisk, *P < 0.05*).

peutic effects in a rat stroke model. Therefore, our novel therapeutic strategy may be more beneficial than either direct gene therapy or cell therapy alone (12, 36).

It is widely known that VEGF is induced in hypoxic brains that have had an ischemic stroke and may play important roles in the remodeling of the damaged tissue. VEGF has two important biological properties. One is a strong angiogenic peptide (14, 18), and the other is a vascular permeability factor (9, 10). Many researchers have reported that VEGF has a strong therapeutic potency for ischemic stroke (11, 30, 34, 35). However, there is concern that VEGF increases blood-brain barrier leakage and might, as a consequence, induce a vasogenic brain edema in the acute stage of ischemic stroke (35). Indeed, some reports insist that the inhibition of VEGF in the super-acute stage of stroke attenuates brain edema and reduces infarction volume. For instance, Kimura et al. (15) demonstrated that inhibition of VEGF immediately after venous infarction attenuates vascular permeability and reduces cerebral venous infarction. Their results suggested that VEGF has a malignant influence on infarcts, especially in the super-acute stage. On the other hand, Sun et al. (30) indicated that VEGF reduced infarct size, improved neurological performance, enhanced the delayed survival of newborn neurons in the dentate gyrus and subventricular zone, and stimulated angiogenesis in the striatal ischemic penumbra. Shen et al. (28) also showed the efficacy of VEGF gene therapy in a rat cerebral ischemia model by using the adeno-associated virus vector with a hypoxia-responsive element controlling VEGF gene expression. The controlled overexpression of VEGF achieved a significant reduction of neuronal apoptosis and infarct volume. In the present study, we also observed an immunohistochemical increase in the formation of microvessels and an antiapoptotic effect in the cortex penumbra, especially in the VEGF-modified, BMSC-treated group (*Figs 1B and 2B*). We speculate that these beneficial effects may have been related to the surprising reduction of infarct volumes. On the other hand, some researchers revealed that although VEGF administration produced angiogenic effects, it did not increase cerebral blood flow (11, 34). Therefore, the therapeutic contribution of VEGF-induced angiogenesis to acute stroke remains obscure. The above discrepancy might arise from the fact that VEGF plays different roles in different stages of ischemic stroke. That is to say, the action of VEGF in patients with stroke is considered a double-edged sword, with the cytokine demonstrating both desirable and unfavorable activity.

Zhang et al. (35) demonstrated that administration of VEGF to ischemic rats in the late stage (48 hr after ischemic stroke) enhanced angiogenesis in the ischemic penumbra and significantly improved neurological recovery. On the other hand, administration of VEGF to ischemic rats in the early post ischemic stage (1 hr after ischemic stroke) significantly increased blood-brain barrier leakage, hemorrhagic transformation, and ischemic lesions. These data indicated that VEGF can markedly enhance angiogenesis in the ischemic brain and reduce neurological deficits during stroke recovery, and that inhibition of VEGF at the super-acute stage of stroke may reduce blood-brain barrier permeability and the risk of

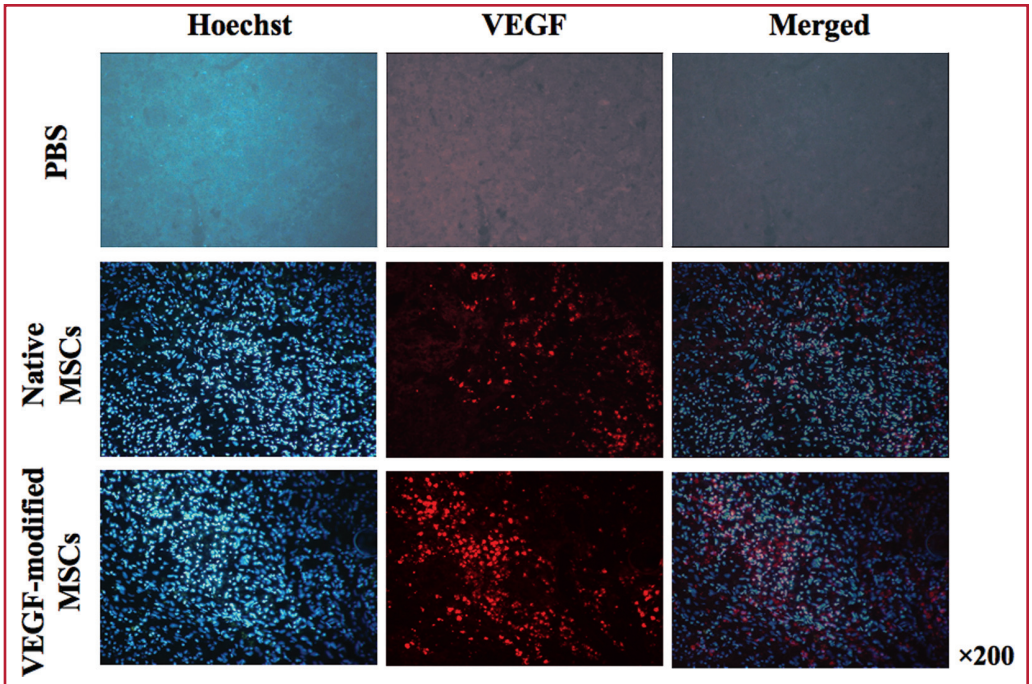


FIGURE 5. *VEGF production by transplanted BMSCs was detected by immunohistochemical staining 14 days after the MCAO. Some Hoechst 33258-marked transplanted BMSCs expressed weak VEGF production in the native BMSC-treated rat brains. On the other hand, VEGF-modified BMSCs expressed VEGF more abundantly. Original magnification, ×200.* VEGF, *vascular endothelial growth factor;* PBS, *phosphate-buffered saline;* MSC, *marrow stromal cells.*

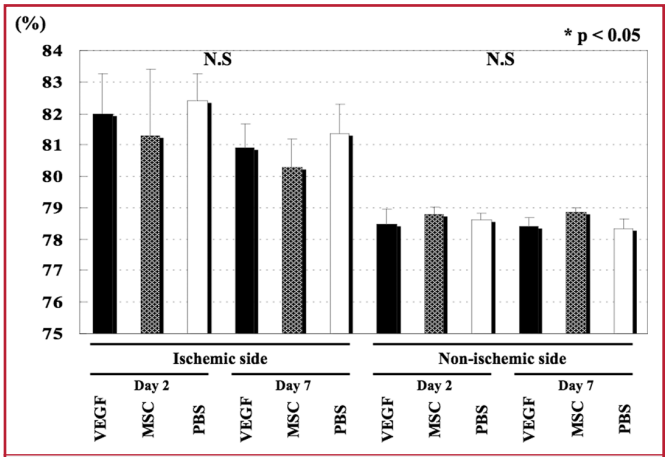


FIGURE 6. *Bar graph showing the brain water content in the three treatment groups 2 and 7 days after MCAO. There was not a significant difference among the three groups at either analysis point ($P < 0.05$).*

hemorrhagic events after focal cerebral ischemia. Thus, if we can determine the optimal timing, artificial enhancement of VEGF in the hypoxia-damaged brain may achieve desirable advantages without inducing adverse effects.

In our study, we performed therapeutic transplantation 24 hours after MCAO, and the VEGF gene-modified BMSC-treated group showed significantly higher therapeutic gain without any aggravation of brain edema in comparison with the control groups. We have no definitive explanation for why brain edema deterioration did not occur under our study conditions. One possibility is the participation of other cytokines. Cao et al. (3) showed that FGF-2 and VEGF induced significant angiogenic effects and that although VEGF-induced capillaries demonstrated numerous fenestrations, no fenestrations were detected in capillaries induced by FGF-2. Murohara et al. (23) demonstrated that VEGF, but not FGF-2 or HGF, significantly increased vascular permeability. BMSCs can also secrete FGF-2 and HGF, and it is probable that the combination of these cytokines can modify the VEGF function against the vessel permeability. Zhu et al. (37) showed that the direct transplantation of VEGF gene-transfected NSCs could confer sufficient neuroprotection against transient focal cerebral ischemia in rats. Their results demonstrated that the transplantation of nontransfected NSCs into the ischemic rat brain also improved the neurological symptoms in comparison with PBS-injected and sham-operated groups. The improvement of neurological symptoms occurred earlier in the VEGF gene-transfected NSC group than in the nontransfected NSC group. Their data suggested the possibility that overexpression of VEGF in the ischemic brain from gene-modified cells could accelerate the neurological recovery after stroke.

The therapeutic efficacy of BMSC therapy against brain ischemia has been clarified by several studies that used different methods of implantation (i.e., intracerebral, intra-arterial, or intravenous). We believe that intravenous administration of BMSCs is a less invasive method than direct transplantation. In our preliminary study, however, only approximately 3% of BMSCs successfully migrated into the ischemia-lesioned brain after intravenous injection. Most of them were trapped by other organs, including the liver, spleen, and lungs (data not shown). Under such conditions, the serum VEGF level would also increase and systemic edema might occur, as in Crow-Fukase syndrome. Thus, in the present study, we chose direct grafting of BMSCs to an ischemic lesioned brain because the purpose of this study was to clarify the impact of VEGF gene modification on BMSC therapy. Of course, if the delivery of BMSCs to the brain could be improved by some technical advance in the

future, the present method could be applied to the clinical treatment of patients with stroke.

CONCLUSION

In view of the accumulated data over the past several years, it is clear that the therapeutic benefit of BMSC transplantation against stroke may derive from multiple mechanisms, including providing focal growth factors with neuroprotective effects, enhancing angiogenesis, and providing for new neurons, or "exogenous neurogenesis," from marrow stromal stem cells. Although clinical trials for acute ischemic stroke with allograft bone marrow mesenchymal stem cells have already been initiated in Japan, the development of methods for improving cell grafting, intensifying its therapeutic potential, or evaluating subpopulations with specific properties, as well as clinical trials, will be required in the future to assess and improve the efficacy of this treatment. We think that the therapeutic modification of BMSCs using a gene-engineering method might be one way to realize the above requirements. In the present study, we proposed a gene-engineering strategy with replication-incompetent HSV-VEGF to treat acute stroke. In fact, 24 hours after the rat MCAO, the intracerebral transplantation of hVEGF165 gene-enhanced BMSCs contributed to remarkable functional recovery and infarct reduction without the exacerbation of acute brain edema compared with that of native BMSCs or administration of PBS. Although it is thought that VEGF is a double-edged sword against the ischemic brain, further examination of the mechanisms of this autoplastic gene-engineered cell therapy is suggested.

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COMMENTS

This report represents another study showing the value of cellular repair for ischemic stroke. In this experiment, the authors hypothesized that vascular endothelial growth factor (VEGF) producing cells would have better results than nonproducing marrow stromal cells (MSCs). The study was well designed but is limited by a rather simplistic method to measure infarct volume (magnetic resonance imaging was not used) and to assess animal function. Approximately 10% of transplanted cells appeared to survive in the authors' early analysis, which is in line with several other reports using different cell lines.

Certainly, animal models can be of value, but many questions remain to be addressed. These could include a study of the timing of cell delivery after stroke, cell number, use of additional compounds to promote graft viability, delivery method, or location. Other questions will require human clinical trials. I applaud the authors on their fine work.

Douglas Kondziolka
Pittsburgh, Pennsylvania

There has been increasing experimental evidence that cellular transplantation therapy may play a role in the treatment of ischemic stroke. Recently, bone MSCs have shown particular promise in animal models of ischemic strokes. The mechanism by which the beneficial therapeutic effect is exerted is still unclear, with secretion of various cytokines and differentiation potential being important. In previous work, the authors established that MSCs can be efficiently engineered to secrete cytokines at elevated levels by gene-transfer with herpes simplex virus type 1 vector. The engineered MSCs, when transplanted in a rat transient ischemia model, can secrete human growth factor and fibroblast growth factor-2 at elevated levels with beneficial effect. In this work, the authors extend their consideration to VEGF in a similar model. As the authors point out, VEGF has a potential downside in treating ischemic stroke due to its role in increasing vascular permeability and, thus, cerebral edema. This work demonstrates that MSCs can be engineered to secrete VEGF at increased levels, and that cellular transplantation therapy in the rat transient ischemia model improves outcome as determined by behavioral testing. Importantly, there was no significant increase in cerebral edema between the experimental animals and control animals receiving native MSCs. It is unclear why this is so. As the authors suggest, it may be the timing of the "treatment" at 24 hours that makes the difference. It would be interesting to see if this bears out in future experiments. It may also be that the other cytokines secreted by the MSCs ameliorates vascular permeability effect of VEGF. Although not statistically significant, it does appear that the animals treated with native MSC have less cerebral edema compared with those control animals receiving the phosphate-buffered saline injections. As with other work showing beneficial effects of cellular transplantation therapy, there remain many questions about the mechanism of action of the therapeutic intervention. Nevertheless, this work provides further optimism that this approach may ultimately be useful in the treatment of ischemic stroke. The fact that MSCs can be harvested easily with little ethical debate lends further enthusiasm.

Charles Y. Liu
Los Angeles, California

Decades of promising laboratory research has translated into failed clinical trials of neuroprotective or neuroregenerative therapy for acute ischemic stroke. It is hoped that stem cell therapy will succeed where other approaches have not. Previous studies have suggested that the important effect of stem cell transplantation is in VEGF expression as penumbral salvage of infarcted tissue has been demonstrated despite the failure of graft survival. The authors' experiment specifically addresses whether or not additional infarct survival results with enhancement of VEGF expression. They achieved a significant improvement in functional neurological recovery and infarct volume that seemed to be a graded response with VEGF-enhanced MSCs outperforming unenhanced MSCs.

As MSC therapy is already making its way into human clinical trials, it is critical that we have a better understanding of the potential mechanism of action and optimum timing of such therapy. To make the translational leap, laboratory experiments should parallel the typical

clinical scenario of MCA occlusion and major hemispheric stroke and be supported by serial neuroimaging, particularly with diffusion-weighted magnetic resonance imaging scans. Although the authors' conclusions are perhaps more hopeful than the data supports, their work provides another essential piece of the puzzle.

Cathy Sila
Cleveland, Ohio

Miki et al. have examined a VEGF expressing bone MSC-based transplant therapy after ischemic stroke in rats. They have utilized the transient MCA occlusion model in rats to test their hypothesis that VEGF expressing bone MSCs are more effective in limiting stroke volume and clinical deterioration after middle cerebral artery ischemia. This group has engineered a VEGF expressing MSC line that they have validated in previous publications as well as this one. These cells are directly transplanted into ischemic brain. Nuclear labeling is used to track cells and confirm that engraftment has occurred. The behavioral assessment of rats is done with a previously validated scale. The results are impressive for the VEGF expressing MSCs versus the MSCs in terms of behavioral improvement post infarct and reduction in stroke volume. There is a marked and significant improvement for the VEGF expressing MSC-treated group beginning at 7 days after infarct versus MSC alone or control. The stroke volume is also significantly reduced. Colabeling demonstrates that the engrafted cells express VEGF. Histology reveals neoangiogenesis in the VEGF-treated group, whereas little to no angiogenesis is demonstrated in the control and non-VEGF groups. The main complication of VEGF administration has been the exacerbation of cerebral edema. The authors demonstrate that this is not an issue in this model by performing water content measures from each group and demonstrating no significant difference. It is not clear why this is the case in this model versus direct VEGF administration. This study uses validated techniques and demonstrates the promising effects of VEGF expressing BMSCs as a tissue engineering approach to stroke protection and recovery.

Douglas J. Cook
James T. Rutka
Toronto, Canada

Miki et al. evaluated the hypothesis that intracerebral transplantation of VEGF gene-transferred MSCs could provide therapeutic benefit in a middle cerebral artery occlusion rat model. Results demonstrated that stroke animals receiving VEGF-modified MSCs had significant functional recovery compared with those receiving native MSCs. Moreover, there was a significantly lower infarct volume in the group treated with VEGF gene-modified MSCs compared with the control groups. Proof of principle was confirmed as the transplanted VEGF gene-modified MSCs strongly expressed VEGF protein for at least 14 days, leading the authors to conclude that intracerebral transplantation of VEGF gene-transferred MSCs may be a beneficial avenue for future stroke therapy.

Although only in the early stages, stem cell therapy holds much promise for the development of stroke treatment protocols. By reducing ischemic brain injury in animal models after safe administration at delayed time points, stem cells offer greater utility than currently available agents. Moving forward, caution should be exercised in future studies and eventual clinical trials, as previous failed attempts at translating stroke therapies to the bedside have shown that application of under-elucidated therapies leads to wasted resources and the potential for poor patient outcomes.

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"Oil Factory" (1954), woodblock and paper, copied from a 1773 picture scroll, Taiyo Fishing Company. (Courtesy of New Bedford Whaling Museum). *From*: Matthews, LH: *The Whale*. New York, Simon & Schuster, 1968.

COLLAGEN SCAFFOLDS POPULATED WITH HUMAN MARROW STROMAL CELLS REDUCE LESION VOLUME AND IMPROVE FUNCTIONAL OUTCOME AFTER TRAUMATIC BRAIN INJURY

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OBJECTIVE: Traumatic brain injury (TBI) causes extensive loss of cerebral parenchyma; however, no strategy for reconstruction has been clinically effective. Our group and others have used human marrow stromal cells (hMSCs) to treat rats subjected to TBI and found no significant changes in the lesion volume, although functional outcome was improved significantly. To identify new ways of delivering hMSCs into the injured brain and to maximize the therapeutic benefits of hMSC treatment, we investigated the use of collagen scaffolds implanted with hMSCs as a cell delivery system for treatment of TBI.

METHODS: Collagen scaffolds populated with 3×10^6 hMSCs were transplanted into the lesion cavity of the injured cortex 4 days after TBI, and the rats were euthanized 35 days after TBI. We measured sensorimotor function and spatial learning using an array of function tests, and the brain tissue was processed for histopathology analysis.

CONCLUSION: The data show that scaffolds populated by hMSCs improve spatial learning and sensorimotor function, reduce the lesion volume, and foster the migration of hMSCs into the lesion boundary zone after TBI in rats. hMSC-populated scaffolds may be a new way to reconstruct the injured brain and improve neurological function after TBI.

KEY WORDS: Human marrow stromal cells, Lesion volume, Scaffold, Traumatic brain injury

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Neuro- and cell transplantation have become widely recognized as powerful experimental tools for studying structure–function relationships, development, neuroplasticity, and regeneration in the adult central nervous system (21). Recently, they have also shown promise in the repair of brain injury and in the restoration of function after traumatic brain injury (TBI) (11, 14). Tissue and cell therapy may have advantages over single pharmacotherapy in the following ways: 1) the grafts may anatomically reconstruct the injured brain; 2) the grafts may establish connections with host cells; 3) exogenous cells entering the brain may produce neurotrophins and growth factors (3, 8); 4) exogenous cells provoke endogenous cell to express neurotrophins and growth factors (8); 5) the interaction between exogenous cells and endogenous cells is dynamic and sensitive to the microenvironment; 6) exogenous cells target the injured area (5); and 7) transplantation may also activate latent or silent pathways that exist in the brain or promote newly formed pathways after injury and thereafter benefit functional improvement (23). Our group has used human bone marrow stromal cells (hMSCs) to treat TBI and promising results have been achieved (14–16).

We used three different routes (i.e., intraarterial, intravenous, and intracranial) to administer hMSCs into injured brain (10, 15, 16). However, problems persist (e.g., relatively few hMSCs [less than 1×10^6] can be injected intracranially (10), intraarterial injection of hMSCs can cause brain ischemia (15), and intravenous injection results in bodywide distribution of hMSCs (14, 16). Although hMSC transplantation after TBI reduces neurological functional deficits, the lesion volume of cortex in the controlled cortical impact model used is not significantly reduced (2, 10, 17). Therefore,

in an effort to optimize hMSC therapy for TBI, we tested the use of hMSC-impregnated collagen scaffolds as hMSC delivery vehicles. The engineered scaffolds have been used for delivery of neural stem cells after ischemia (20) and for treating spinal cord injury (2); however, to date, this approach has not been used for the delivery of hMSCs within TBI sites. We have previously demonstrated the efficacy of silk fibroin scaffolds in the delivery of hMSCs for repair of various skeletal tissues, including bone, cartilage, and ligament tissue both in vitro and in vivo (1, 6, 7, 17–19, 22). We hypothesize that the scaffolds provide an effective platform for therapeutic delivery of hMSCs to injured tissue, likely as a result of enhanced anchoring, which leads to improved cellular survival in the hippocampus and overall function for the intended repair.

MATERIALS AND METHODS

All experimental procedures had been approved by the Institutional Animal Care and Utilization Committee of Henry Ford Hospital.

Animal Models

A controlled cortical impact model of TBI in the rat was used for the present study (4, 14). Male Wistar rats (300–400 g) were anesthetized intraperitoneally with 350 mg/kg/body weight chloral hydrate. Rectal temperature was kept at 37°C with a feedback-regulated water-heating pad. A controlled cortical impact device was used to induce the injury. Rats were placed in a stereotactic frame. Two 10-mm diameter craniotomies were performed adjacent to the central suture, midway between lambda and bregma. The second craniotomy allowed for movement of cortical tissue laterally. The dura was kept intact over the cortex. Injury was induced by impacting the left cortex (ipsilateral cortex) with a pneumatic piston containing a 6-mm diameter tip at a rate of 4 m per second and 2.5 mm of compression. Velocity was measured with a linear velocity displacement transducer.

Transplantation

Scaffolds were seeded with 3×10^6 hMSCs and transplanted into the lesion cavity of rats 4 days after TBI. Under aseptic conditions and general anesthesia with 40 mg/kg ketamine and 8 mg/kg xylazine, a 1-cm incision was made along the midline of the scalp. The TBI-induced lesion cavity was exposed in the left hemisphere. A scaffold seeded with hMSCs was placed directly into the cavity without removing any additional brain tissue and subsequently covered by surgical foam (polyurethane foam). The incision was closed with 4-0 absorbable gut surgical suture. The animals were euthanized 35 days after TBI.

Experimental Groups

Twenty-four male Wistar rats were randomly divided into four groups with six rats per group (i.e., TBI + saline, TBI + scaffold, TBI + hMSCs, and TBI + scaffold/hMSCs). All treatments were performed 4 days after TBI. Rats in the TBI + saline group were subjected to TBI and were injected intracranially with saline. Rats in the TBI + scaffold group were subjected to TBI, and 4 days later a scaffold was transplanted directly into the lesion core. Rats in the TBI + hMSCs group received 3×10^6 hMSCs injected directly into the lesion core 4 days after TBI. Rats in the TBI + scaffold/hMSCs group received transplantation of a scaffold seeded with 3×10^6 hMSCs. All rats were tested on the Morris Water Maze test during the last 5 days before being euthanized, and the neurological severity scores were measured before and after TBI at different time points.

Cells

hMSCs were isolated and expanded, as previously described (1). Briefly, human bone marrow aspirates obtained from a 25-year-old, consenting, nonsmoking donor (Clonetics-Poietics, Walkersville, MD) were resuspended in Dulbecco's modified eagle medium supplemented with 10% fetal bovine serum, 0.1 mmol/L nonessential amino acids, 100 U/ml penicillin and streptomycin, and 1 ng/ml basic fibroblast growth factor. They were then plated at 10 µl aspirate/cm^2 in tissue culture flasks and maintained at 37°C in an atmosphere of 95% air and 5% carbon dioxide. All tissue culture components were obtained from Life Technologies (Rockville, MD). hMSCs were selected based on their ability to adhere to the tissue culture plastic after approximately 10 days in culture; nonadherent hematopoietic cells were removed during medium replacement. Medium was changed twice per week thereafter. hMSCs were subsequently detached using 0.25% trypsin/1 mmol/L ethylenediamine tetra-acetic acid, replated at 5×10^3 cells/cm^2, and cultured to 90% confluency to passage-one cells. hMSCs were subsequently frozen in 10% fetal calf serum and 8% dimethyl sulfoxide in Dulbecco's modified eagle medium. They were then thawed and expanded ex vivo to passage-three cells as described previously and subsequently used for scaffold seeding.

Scaffold Preparation and Cell Seeding

Ultrafoam scaffolds, collagen type I, were obtained from commercial sources (Davol, Cranston, RI). Scaffolds were prewet overnight at 4°C (approximately 12 h) in culture medium consisting of Dulbecco's modified eagle medium supplemented with 10% fetal calf serum, 100 U/ml penicillin, 100 µg/ml streptomycin, 0.1 mmol/L nonessential amino acids, and 1 ng/ml of basic fibroblast growth factor (Life Technologies). The scaffolds were then transferred aseptically using tweezers to a 50-ml sterile centrifuge tube (VWR, West Chester, PA) (one scaffold per tube) and allowed to sit at the bottom of the tube. After trypsinization of the hMSCs from ex vivo expansion conditions, the cells were resuspended and transferred (3×10^6 hMSCs per scaffold) into 200 µl of culture medium. One hundred microliters of culture medium was then applied two times successively to opposite sides of the body of the cylindrical scaffold. The scaffold and cell solution were incubated for 30 minutes in a humidified incubator to facilitate primary cell seeding. The scaffolds were agitated gently within the solution manually twice every 15 minutes during this time. After primary seeding, the centrifuge tubes were filled with an additional 3 ml of culture medium and placed within a humidified incubator and incubated overnight until scaffold implantation. Before implantation, the scaffolds were collected from the medium. The scaffolds were approximately 60 µl.

Morris Water Maze Tests

All functional tests were performed by investigators blinded to the treatment. The testing procedure is a modification of that described previously (13). Data collection was automated by the Hversus Image 2020 Plus Tracking System (US Hversus Image, San Diego, CA). For descriptive data collection, the pool was subdivided into four equal quadrants formed by imaging lines. All animals were tested during the last 5 days before being euthanized. At the start of a trial, the rat was placed randomly at one of four fixed starting points randomly facing either toward the wall or the center (designated north, south, east, and west) and allowed to swim for 90 seconds or until they could find the platform. The platform was located in a randomly

changing position within the northeast quadrant throughout the test period (e.g., variously, equidistant from the center and edge of the pool, against the wall, near the center of the pool, and at the edges of the northeast quadrant). If the animal was unable to find the platform within 90 seconds, the training was terminated and a maximum score of 90 seconds was assigned. The percentage of time traveled within the northeast (correct) quadrant was calculated relative to the total amount of time spent swimming before reaching the platform and used for statistical analysis.

Neurological Functional Evaluation

Neurological functional measurement was performed using a modified Neurological Severity Scores (mNSS) test (12). The test was carried out on all rats preinjury and on days 1, 7, 14, and 35 after TBI. The mNSS is a composite of the motor (muscle status, abnormal movement), sensory (visual, tactile, and proprioceptive), and reflex tests and has been used in previous studies. Motor tests of the mNSS include seven items with a maximum of 6 points, which mainly reflect the function of the motor representation area in the contralateral cortex. Damage to this area causes contralateral limb paralysis leading to high scores on the mNSS motor tests. Sensory tests include two items with a maximum score of 2 reflecting a combination of visual, tactile, and deep sensation. Unilateral lesions of the sensory and motor representations of the forelimb in the somatosensory cortex can produce contralateral asymmetry. Indeed, the placing test included in sensory tests of the mNSS also reflects an aspect of the motor function, because the corticospinal pathway mediates the execution of the placing reaction (23) and lesions in the pathway produce an enduring forelimb placing deficit. Beam Balance Tests, as part of the asymmetry test, have seven items with a maximum score of 6, mainly reflecting hindlimb placing performance, which is controlled by the contralateral cortical representation of motor function. Damage to this area causes dragging of the contralateral hindlimb (the hindlimb is not placed on the beam) or the hindlimb is placed on the vertical surface of the beam to help support the animal's weight and to aid in maintaining balance, which results in a high score on Beam Balance Tests. The last part of the mNSS includes the pinna, corneal and startle reflexes, and abnormal movements. In this model, injury in the left hemispheric cortex of rats causes sensory and motor functional deficiency with elevated scores on motor, sensory, and Beam Balance Tests in the early phase after injury (Day 1 after injury). Absent reflexes and abnormal movements can be measured on rats with severe injury. Slow recovery in asymmetry deficiency as reflected by Beam Balance Test results has been reported in unilateral brain injuries, including brain trauma, brain hemorrhage, and ischemia. This test is suitable for evaluating long-term neurological function after unilateral brain injury.

Tissue Preparation and Measurement of Lesion Volume

Rats were anesthetized intraperitoneally with ketamine and xylazine and perfused transcardially first with saline solution containing heparin followed by 4% paraformaldehyde in 0.1 mol/L phosphate-buffered saline, pH 7.4. Their brains were removed, postfixed in 10% formalin for 1 to 2 days at room temperature, and then processed for paraffin sectioning. A series of 6-μm thick sections were cut with a microtome through every seventh standard block. One section from each block was processed for hematoxylin and eosin staining and then used to calculate lesion volume using a MCID system (9).

Immunohistochemistry Staining

Single staining was performed for identification of hMSCs using a primary mouse anti-human nuclei monoclonal antibody (MAB1281), specific for all human cell types, and a secondary Cy5-conjugated F $(ab')_2$ fragment rabbit anti-mouse IgG in the coronal sections of brains. Briefly, 6-μm thick sections from the TBI + hMSCs and TBI + scaffolds/hMSC groups were deparaffinized and the sections were put in boiling citrate buffer (pH = 6) in a microwave oven for 10 minutes for identification of neurons. After cooling at room temperature, the sections were incubated with a primary mouse anti-human nuclei monoclonal antibody (a human cellular nuclei antigen, MAB1281, dilution, 1:200) and a Cy5-conjugated F $(ab')_2$ fragment mouse anti-human IgG (dilution, 1:20). The slides were analyzed using a fluorescent microscope (BH-2; Olympus Optical Co., Tokyo, Japan). Negative control sections from each animal received identical staining preparation, except that the primary or secondary antibodies were omitted.

Estimates of Cell Number

For measurement of MAB 1281-reactive cells, an average number of five equally spaced slides (approximately 100-μm interval) were obtained from brain block E, and MAB 1281 reactive cells were counted within the boundary zone. To reduce biases introduced by sampling parameters, all sections for MAB 1281 identification were stained simultaneously. The criteria for MAB 1281-positive cells were defined before the cells were counted by observers blinded to the individual treatment.

To test the effect of the implant on the hippocampus, the density (cells/mm) of granular cells in the dentate gyrus and pyramidal cells in the CA3 region was calculated on the hematoxylin and eosin-stained slides.

Statistical Analysis

The data were analyzed by analysis of variance for multiple comparisons of functional test data (16). Paired *t* test was used to test the difference in cell counts and lesion volume between the scaffold/hMSC-treated group and the hMSC-treated group. All measurements were performed by observers blinded to individual treatments.

RESULTS

hMSC-populated Scaffolds Improve Spatial Learning

To test whether scaffold/hMSC treatment promotes spatial learning in the relatively late phase (approximately 1 mo) after TBI, rats were tested on the Morris Water Maze during the last 5 days (from Day 31 to Day 35 after TBI) before being euthanized. The mean percentages of time spent in the correct quadrant were significantly higher in the hMSC-treated group (TBI + hMSC) than in the saline-treated (TBI + saline) and scaffold-treated (TBI + scaffold) groups at Days 34 and 35 after TBI ($P < 0.05$, *Fig. 1*). However, treatment with scaffold/hMSCs significantly improved spatial learning as early as 33 days after TBI and the improvement continued at Days 34 and 35. In addition, the percentage of time spent in the correct quadrant was significantly higher than that of the TBI + hMSCs group ($P < 0.05$) (*Fig. 1*). These data demonstrate that both hMSCs and scaffold/hMSCs promote restoration of spatial learning in the relatively late phase after TBI. However, scaffold/hMSCs appear to be more effective in improving spatial learning therapy than hMSCs only.

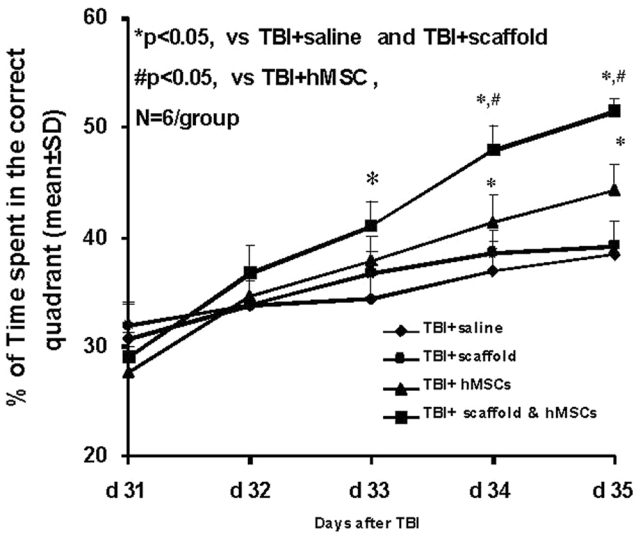


FIGURE 1. *The plot shows spatial learning deficits of rats from Days 31 to 35 after TBI and after TBI with different treatments. *P< 0.05 compared with the saline- and scaffold-treated groups; #P < 0.05 compared with the hMSC-only group.*

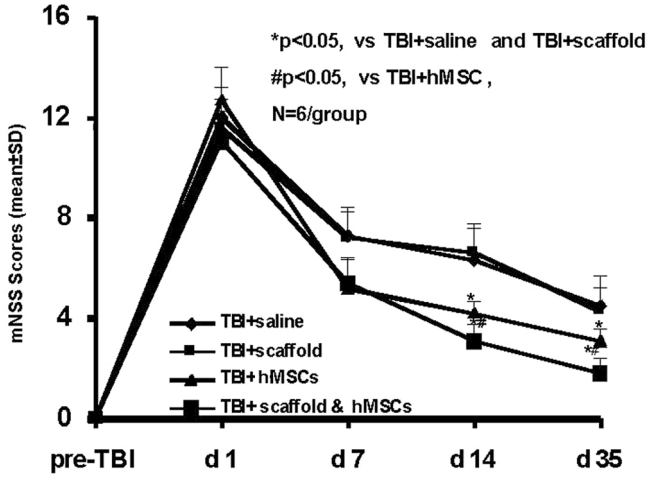


FIGURE 2. *The plot shows the functional improvement detected on the mNSS. *P < 0.05 compared with the saline- and the scaffold-treated groups; #P < 0.05 compared with the hMSC-treated group.*

hMSC-populated Scaffolds Improve Sensorimotor Functional Outcome After TBI

Figure 2 shows that there is no significant difference in the mNSS scores between the TBI + scaffold and TBI + saline groups ($P < 0.05$). However, significantly improved scores were measured at Days 7, 14, and 35 after TBI in both of the TBI + hMSCs and TBI + scaffold/hMSC groups compared with the TBI + saline and TBI + scaffold groups ($P < 0.05$). At Days 14 and 35, significantly lower (i.e., improved) scores were measured in the TBI + scaffold/hMSC group versus TBI + hMSC group ($P < 0.05$). These data demonstrate that both hMSCs and hMSC-populated scaffolds promote recovery of sensorimotor functional deficits, and scaffold/hMSC treatment is superior to hMSCs only.

hMSC-populated Scaffolds Reduce the Lesion Volume and Neuronal Loss After TBI

No scaffolds were found in the cavity of injured cortex, demonstrating the degradation of the scaffold in the brain. There were no significant differences in lesion volume among TBI + MSC (16.2 ± 1.4%), TBI + scaffold (17.7 ± 2.1%), and TBI + saline (18.1 ± 2.3%) groups ($P < 0.05$) (*Figs. 3* and *4*). Treatment with scaffold/hMSCs significantly reduced lesion volume to 11 ± 1.6% when compared with the other three groups ($P < 0.05$). *Figure 4* also shows that scaffold/hMSC treatment reduces the tissue loss in the injured cortex. These data demonstrate that seeding scaffolds with hMSCs reduces lesion volume of the injured cortex after TBI. Table 1 shows that hMSC transplantation and a combination of scaffold and hMSCs increase cell densities in the dentate gyrus and hippocampal CA3 region with the combination treatment showing more efficacy in protecting neurons in the hippocampus after TBI than treatment with hMSCs alone.

hMSCs Migrate Into The Lesion Boundary Zone From Scaffold

Because no MAB 1281-positive cells were detected in the lesion boundary zone in both TBI + scaffold and TBI + saline groups, we only counted MAB 1281-positive cells in the lesion boundary zone in the TBI + hMSC and the TBI + scaffold/hMSC groups. Some scattered MAB 1281-positive cells were detected in other areas of the ipsilateral cortex, but we focused on the lesion boundary zone. *Figures 5* and *6* show MAB 1281-positive cells in the lesion boundary zone in the TBI + MSC and the TBI + scaffold/hMSC groups. A signifi-

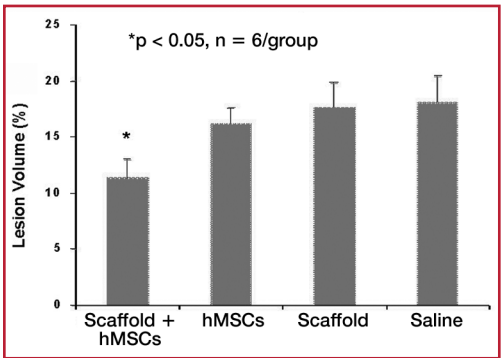


FIGURE 3. *The bar graph shows changes of lesion volume among different groups. *P < 0.05 compared with hMSC, scaffold, and saline treatments.*

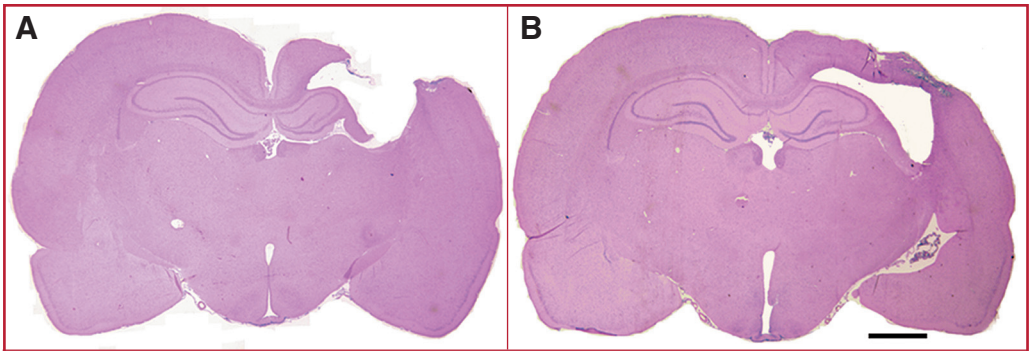


FIGURE 4. *Hematoxylin and eosin staining shows the representative sections from TBI + hMSC (**A**) and TBI + scaffold/hMSC (**B**) groups 35 days after TBI. Treatment with scaffold/hMSCs reduces lesion volume and prevents tissue loss in the cortex and hippocampus (**B**). The scale bar (in **B**) = 250 μm.*

TABLE 1. Cell numbers in the dentate gyrus and hippocampal CA3 region[a]

	TBI + saline	TBI + scaffold	TBI + hMSCs	TBI + scaffold/hMSCs
CA3	145 ± 23	162 ± 27	247 ± 32[b]	326 ± 36[b,c]
Dentate gyrus	265 ± 36	279 ± 42	382 ± 38[b]	473 ± 31[b,c]

[a] TBI, traumatic brain injury; hMSCs, human marrow stromal cells.
[b] $P < 0.05$ versus TBI + saline and TBI + scaffold groups.
[c] $P < 0.05$ versus TBI + hMSC group.

cantly increased number of MAB 1281-positive cells was present in the TBI + scaffold/hMSC group (14.3 ± 2.1/mm²) compared with the TBI + hMSC group (4 ± 1.3/mm²) ($P < 0.05$). These data demonstrate that scaffolds enhance the presence of hMSCs in the lesion boundary zone.

DISCUSSION

Our data demonstrate that scaffolds suffused with hMSCs improve spatial learning and sensorimotor function and reduce the lesion volume as well as increase the numbers of hMSCs into the lesion boundary zone after TBI compared with saline-, scaffold-, and hMSC-treated rats.

Our previous studies have shown that intracranial transplantation of 1×10^6 hMSCs was an effective treatment for TBI (15). However, there was no significant change in the lesion volume with intracranial or intravenous administration of hMSCs compared with controls (15, 16). Because hMSCs were injected in the lesion boundary zone, a limited volume of solution (10 μl) was used to dilute the hMSCs, which restricts the use of this approach. Large numbers of hMSCs (from 2×10^6 to 8×10^6) have been intravenously injected; however, hMSCs have been detected in almost all organs in the recipient rats (16). In the present study, each scaffold was seeded with 3×10^6 hMSCs, three times more than the single injection of intracranial hMSCs, thereby increasing the magnitude of hMSC delivery to the TBI defect site.

This is the first study to find that transplantation of scaffolds populated with hMSCs reduces spatial learning and sensorimotor function deficits after TBI. However, transplantation of scaffolds alone has no significant effect on functional outcome when compared with saline injection. Although hMSC treatment significantly improves the functional outcome compared with controls, the effect is reduced compared with that of the scaffolds populated with hMSCs. This finding demonstrates that transplantation of scaffolds populated with hMSCs may be an effective cell delivery vehicle for restoration and repair of neural injury after TBI. Mechanically engineered hydrogel scaffolds without cells have been used to treat spinal cord injury in the rat, and these scaffolds promote axonal growth and angiogenesis (2). However, there are no current data relating to whether this treatment promotes functional recovery. A synthetic biodegradable polymer (polyglycolic acid) has been used to recruit neural stem cells and to reconstitute lost tissue caused by hypoxia–ischemia in mice (20). These neural stem cell–scaffold complexes appeared to augment the reparative response by facilitating a series of reciprocal interactions between donor neural stem cells and host brain tissue; however, the behavioral responses of the recipients were not provided.

Reduction of the lesion volume by complexes of scaffolds and hMSCs may be mediated by the following mechanisms: 1) hMSCs within the scaffolds may provide neurotrophic support for the surrounding brain tissues, and 2) hMSCs that migrate into the lesion boundary zone may promote remodel-

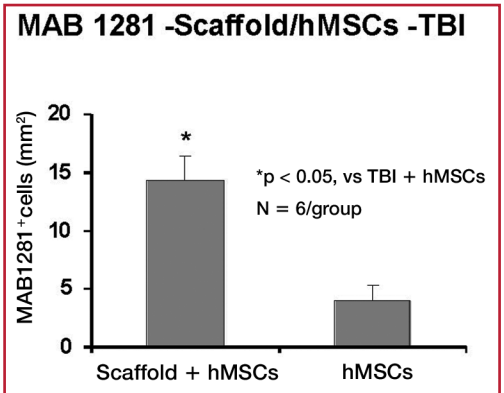


FIGURE 5. *The bar graph shows significantly increased MAB 1281-positive cells detected in the lesion boundary zone in the scaffold/hMSC-treated group versus the hMSC-alone treated group (*P < 0.05).*

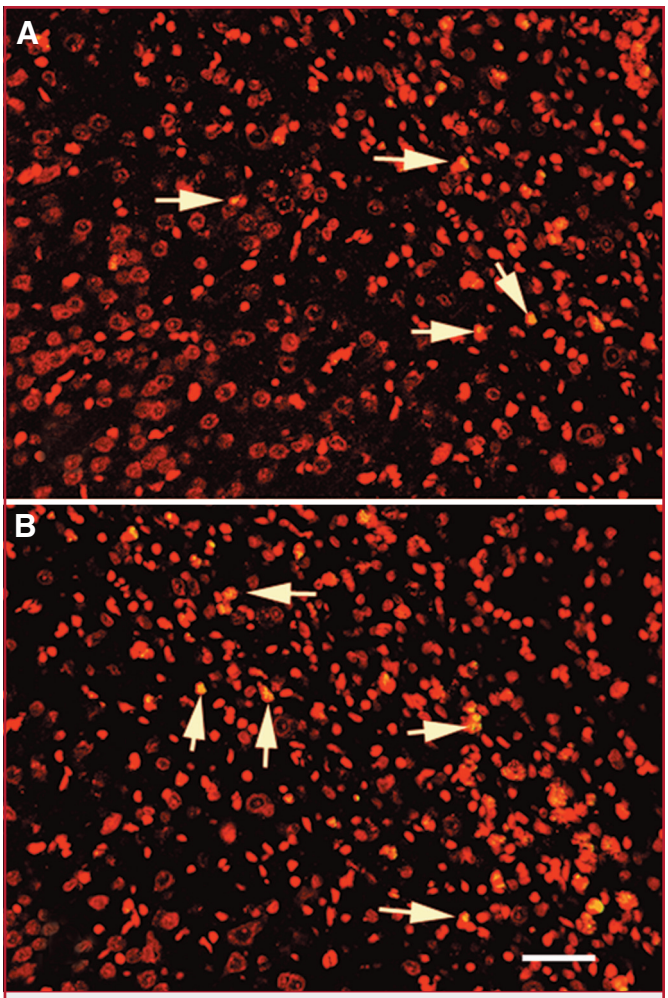


FIGURE 6. *Immunohistochemical staining shows the MAB 1281-positive cells in the lesion boundary zone from hMSC-treated (A) and scaffold/hMSC-treated (B) groups.* Arrows *show the positive cells* (yellow). *The scale bar (in B) = 50 μm.*

ing of the injured brain tissue. The scaffolds, by temporarily fixing the hMSCs in space and maintaining them in proximity to the injured tissue, are likely to foster such constitutive reciprocal interactions between hMSCs and the injured brain tissue. The fate of hMSCs is regulated by multiple interactions with the microenvironment (i.e., neighboring cells, soluble trophic factors, and mechanical stimuli) (11). hMSCs in the brain evoke increased expression of an array of neurotrophic and growth factors such as nerve growth factor, vascular endothelial growth factor, and brain-derived neutrotrophic factor (11). This may be one of the mechanisms by which hMSCs inhibit the progressive chronic processes of cell death or, alternately, repair the injured cerebral tissue. In addition, these factors are both secreted by hMSCs as well as induced within parenchymal cells by activation of the intrinsic neurorestorative mechanisms of hMSCs, which include angiogenesis, neurogenesis, and synaptogenesis (11). In turn, the surrounding injured brain tissue generates cytokines that not only stimulate and activate hMSCs to secrete growth factors, but also attract hMSCs to migrate into the lesion boundary zone. This may be one of the reasons that many more hMSCs have been detected in the lesion boundary zone in the TBI + scaffold/hMSC group than in the TBI + hMSC group. Additional studies are required to determine other possible mechanisms underlying the therapeutic benefit of collagen scaffolds suffused with hMSCs in the treatment of TBI.

CONCLUSION

The present study shows that scaffolds impregnated by hMSCs improve spatial learning and sensorimotor functions, reduce lesion volume, and enhance migration of hMSCs into the lesion boundary zone after TBI in rats.

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COMMENTS

Lu et al. continue their innovative work using marrow stromal cells, now testing the utility of a collagen scaffold for cell delivery. Cells on a scaffold seemed to improve rat behavior better than cells alone. Whether the "reconstruction" of the cortex was relevant to recovery or improvement occurred through some other means (improved cell viability or better cytokine release) is not known. It would be interesting to repeat this study in a higher animal model. Clearly, all of the experimental arms, including vehicle injection, were associated with recovery from injury, although stromal cells on scaffolds did best within this small animal series.

A number of investigators, including ourselves, are testing new methods for cell delivery. Solid tissue blocks, cells within an immunoprotective polymer, and other approaches have been used in different animal and human studies previously. The scaffold concept is unique for cortical injury and could also be used for subcortical brain injury if modified for implantation with a special injection device. It will be interesting to see if other investigators begin to use scaffold-based cell implants for traumatic brain injury studies.

Douglas Kondziolka
Pittsburgh, Pennsylvania

This represents another study from an established group that has previously demonstrated the beneficial role of human bone marrow stromal cells (hMSC) in the treatment of traumatic brain injury (TBI). Previous work from the authors has demonstrated a beneficial effect of hMSC administration via the intra-arterial, intravenous, and intracranial injection route in a rat model of TBI. In an attempt to further maximize the benefit of hMSC treatment, the authors chose a strategy to improve cell survival by presumed improved anchoring of the cells, i.e., by use of a collagen scaffold. The concept of scaffolds is well accepted in tissue engineering, and the authors themselves have explored their utility in both neural and non-neural tissue. However, the use of collagen scaffolds as a vehicle for hMSC transplantation is first reported in this current study. They elegantly demonstrate that the scaffolds populated by hMSCs improved spatial learning and sensorimotor funtion in the model. In addition, it appears to reduce lesion volume and increases the migration of hMSCs into the lesion boundary zone after TBI. The mechanisms of the beneficial effects continue to be unclear. Nevertheless, the data is compelling. I look forward to further work from this group.

Charles Y. Liu
Los Angeles, California

Cell replacement strategies are being studied as a means of treating numerous central nervous system disorders. It is generally accepted that a combination of therapeutic strategies will be required to effectively treat conditions such as brain and spinal cord injury. Cell replacement may be the cornerstone of such regimens. That this strategy improves outcome in neurotrauma seems plausible; a large number of publications demonstrate functional improvements despite the use of different cells of origin and a multitude of injury models. The functional improvements noted so far have been modest at best, however, and survival of these cells after transplantation is also a major issue.

In this study, the authors present an innovative approach to enhancing the efficacy of cell replacement therapy. The use of collagen scaffolds reduced lesion volume, increased cellular delivery to the perilesional zone, and was associated with functional improvement when compared with cellular transplantation alone.

We encourage the authors to determine what is responsible for the reduction in lesion volume: is it functional nervous tissue or merely scar or inflammatory infiltrate? Inflammatory cell infiltration is a possibility that is important to consider when implanting a foreign body. The authors also need to determine whether the benefits they saw arise from the ability to introduce more stromal cells or if the scaffolds in some way provide a structural framework for regenerative processes. Of some concern is the fact that the cellular control group involved transplantation into the lesion rather than the perilesional zone. Although some have used this as a control (3), others have noted very poor cell survival with transplantation into the hostile injury epicenter as compared with "penumbra" tissue (1, 2). This is likely a better standard against which new treatments should be compared.

This work is important, however, because of its innovative approach to enhancing the efficacy of cell replacement strategies. We look forward to further work from this group characterizing the mechanisms underlying the improvements seen with collagen scaffolds.

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In this intriguing report, the group from Henry Ford describes the most recent of its ongoing investigations into the use of hMSCs for the treatment of experimental TBI. An important problem is the route of delivery of hMSCs. As the authors state in their introduction, intra-arterial injection can cause cerebral ischemia; intravenous injection distributes these cells throughout the body; and direct intracranial injection may not deliver enough cells to the target site. The current report describes the use of hMSC-containing collagen scaffolds as delivery vehicles for these cells. Histological and behavioral measures reveal that these scaffolds produce greater improvement than direct injection of hMSCs, and they also reduce lesion volume. The next step is to sort out the mechanisms underlying these results.

Alex B. Valadka
Houston, Texas

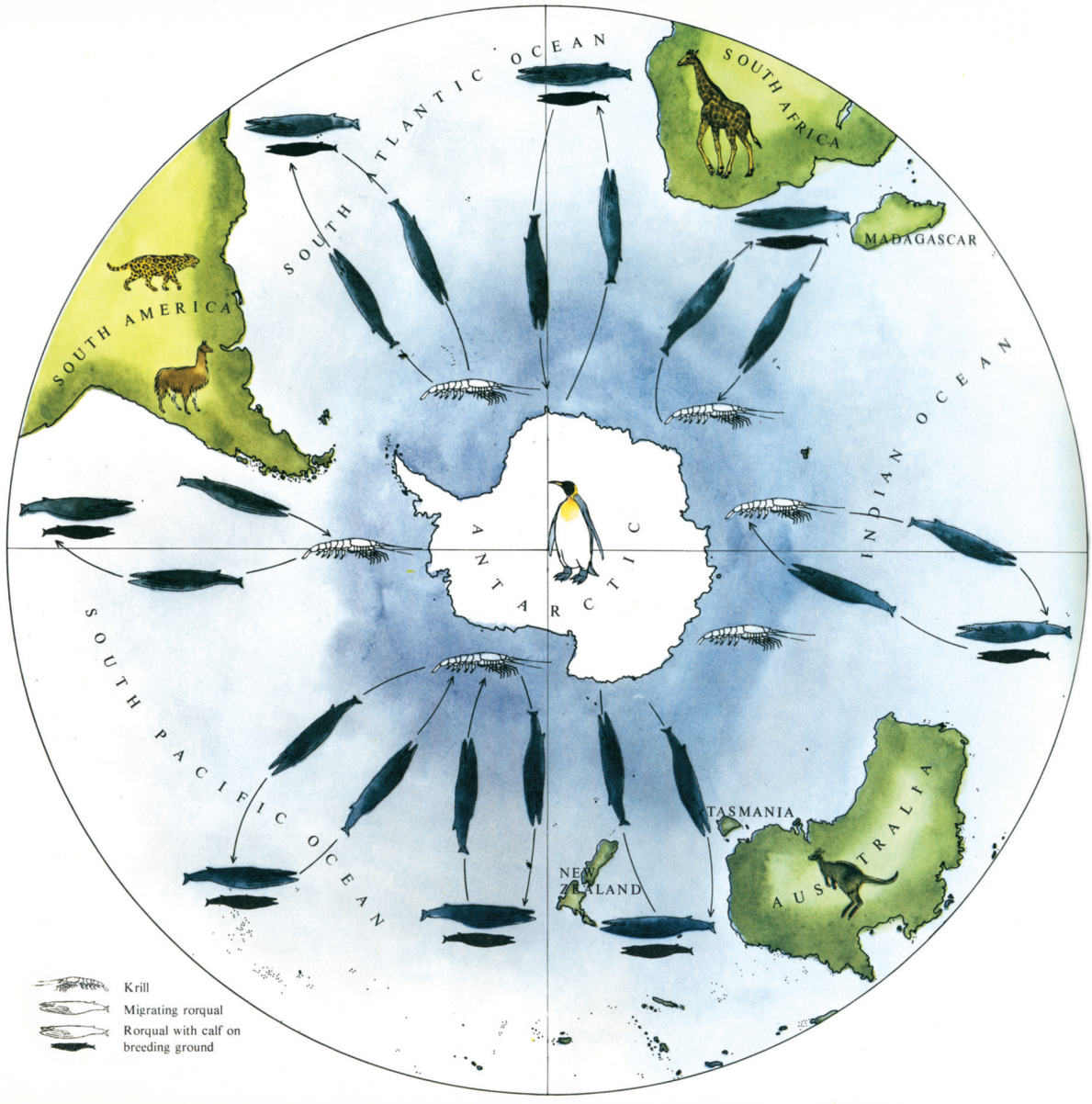


Diagram of whale migrations. In the spring and summer, whales migrate south to the Antarctic for feeding. In autumn, they go to more temperate seas to give birth. (Courtesy of National Institute of Oceanography, England). *From*: Matthews, LH: *The Whale*. New York, Simon & Schuster, 1968.

COADMINISTRATION OF LOW-DOSE LIPOPOLYSACCHARIDE AND SOLUBLE TISSUE FACTOR INDUCES THROMBOSIS AFTER RADIOSURGERY IN AN ANIMAL ARTERIOVENOUS MALFORMATION MODEL

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OBJECTIVE: Radiosurgery for arteriovenous malformations is limited to small lesions and may take 3 years to produce total occlusion. It has recently been shown that coadministration of low-dose lipopolysaccharide (LPS) and soluble tissue factor (sTF) selectively induces thrombosis in murine tumor models, attributable perhaps to the prothrombotic phenotype of tumor vasculature. Radiosurgery may induce changes in endothelial prothrombotic molecules similar to those found in tumors. This study aimed to determine if a similar strategy could be used to stimulate thrombus formation in an animal arteriovenous malformation model.

METHODS: Seventeen rats underwent creation of a carotid-to-jugular anastomosis. Animals were intravenously injected with sTF, low-dose LPS, a combination of both, or placebo 24 hours after stereotactic irradiation of the anastomosis. Control animals received both agents after sham irradiation.

RESULTS: Coadministration of sTF and LPS led to the formation of thrombi in up to 69% of small vessels and 39% of medium-sized vessels within the target region. The irradiated vasculature demonstrated intermediate rates of thrombosis after treatment with either sTF or LPS alone as did vessels within the fistula in the control group. Logistic regression analysis demonstrated significant associations between development of thrombi and treatment with radiation, sTF, or LPS ($P < 0.005$). There was no evidence of systemic thrombus formation or toxicity in any group.

CONCLUSION: Treatment with sTF and LPS selectively induces thrombosis of irradiated vessels in a rat model of arteriovenous malformation. Stimulation of thrombosis may improve the efficacy of radiosurgery, increasing the treatable lesion size and reducing latency.

KEY WORDS: Inducing thrombosis postradiosurgery, Intracranial arteriovenous malformations, Lipopolysaccharides, Radiosurgery, Tissue factor

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Rupture of intracranial arteriovenous malformations (AVMs) is a leading cause of stroke in children and young adults. Treatment options include surgery and highly focused radiation (stereotactic radiosurgery) (20). For lesions larger than 3 cm, the risks of surgery are high and radiosurgery has a disappointingly low efficacy and long latency. However, radiation mediates an array of changes that may be targeted to promote vessel occlusion analogous to vascular targeting of tumor endothelium to induce thrombosis (18). In murine tumor models, coadministration of low-dose lipopolysaccharide (LPS) and the extracellular domain of human tissue factor (TF) expressed in *Escherichia coli* and refolded into the soluble form (sTF) selectively occludes tumor vessels (26). We hypothesized that hemodynamic stress and radiation may induce AVM endothelial changes similar to those in tumor vessels (3, 17), providing the rationale for the trial of a similar strategy in an animal model of AVM.

A rat model, created by end-to-side anastomosis of the external jugular vein to the common carotid artery, shares many hemodynamic

TABLE 1. Experimental groups receiving intravenous administration of sTF, LPS, or combination therapies after radiosurgery[a]

Radiation dose (Gy)	Treatment	Number of animals
25	Control	3
	LPS/sTF	5
	LPS	3
	sTF	3
Sham	LPS/sTF	3
Total		17

[a] sTF, soluble tissue factor; LPS, lipopolysaccharide; Gy, Gray.

and histological hallmarks with human AVMs (28, 32). Several cell adhesion molecules, selectins, and coagulation regulators have similar levels of expression in AVM vessels and rat arteriovenous fistula vessels, differentiating them from normal vessels (28, unpublished data).

To examine whether coadministration of LPS and sTF induces thrombosis in this model, we undertook an experiment to determine the effect of these agents after radiosurgery.

MATERIALS AND METHODS

All experiments and animal care were approved by the Animal Care and Ethics Committee of the University of New South Wales. Seventeen 6-week-old male Sprague-Dawley rats weighing 323 ± 40 g (mean ± standard deviation) were used for this experiment. The experimental groups are detailed in *Table 1*. Each animal underwent a fistula formation procedure. After 6 weeks to allow maturation of the fistula, animals received either 25 Gy or sham radiosurgery. The radiation treatment plan specified a dose of 25 Gy to the region of the fistula and anastomosis, whereas contralateral carotid arteries and jugular veins received a dose of approximately 2 to 4 Gy. Twenty-four hours after irradiation, animals were injected intravenously with sTF, low-dose LPS, a combination of both, or placebo. Four days after injection, animals were euthanized by transcardiac perfusion of paraformaldehyde.

Recombinant soluble tissue factor (a gift of Diagnostic Stago, Asnières sur Seine, France) was produced by the expression of the extracellular domain of human tissue factor in *E. coli* that was then refolded into the soluble form. Purified LPS from *E. coli* serotype 055:B5 was purchased from Sigma-Aldrich (St. Louis, MO).

Animal Procedures

Fistula Creation

The fistula creation model has been described previously (32). General anesthesia for surgical procedures was induced in an anesthetic chamber with 4% isoflurane and then maintained with the animal self-ventilating 2 to 3% isoflurane through a nose cone with an oxygen flow rate of 1.5 L/minute. The anastomosis was performed using a sterile microsurgical technique with the animal positioned supine. A midline incision was made over the anterior neck. The left sternocleidomastoid muscle was identified and the left omohyoid muscle was divided to allow exposure of the left common carotid artery (CCA). The left external jugular vein (EJV) was dissected out. A ligature was placed around the EJV at its junction with the subclavian vein. The EJV was transected close to the ligature and then mobilized to allow approximation to the lateral side of the CCA. Blood flow through the CCA was measured using a 1-mm ultrasonic Doppler probe (Transonic Systems Inc., Ithaca, NY). After placement of clips proximally and distally on the CCA, a small arteriotomy was made and the distal end of the EJV was anastomosed to the CCA using running 10-0 Prolene suture (Ethicon, Inc., Somerville, NJ). The clips were removed and hemostasis was achieved using pressure at the site of the anastomosis. Blood flow was measured through the proximal CCA and the EJV using 1- and 2-mm ultrasonic Doppler probes, respectively. The wound was closed in layers with nonabsorbable sutures.

Unlike a previous rat aorta–vena cava fistula radiosurgical model (1), this model mimics the structural arrangement of an AVM (*Fig. 1*) with a large arterial inflow connecting to a "nidus" of branching vascular channels that then lead to a large draining vein with low resistance. This arrangement is possible because the normal venous anatomy of the rat differs from human anatomy. The sigmoid sinus, draining the brain, connects outside the skull with the facial vein, forming a type of plexus that then coalesces to form the external jugular vein. Reversing

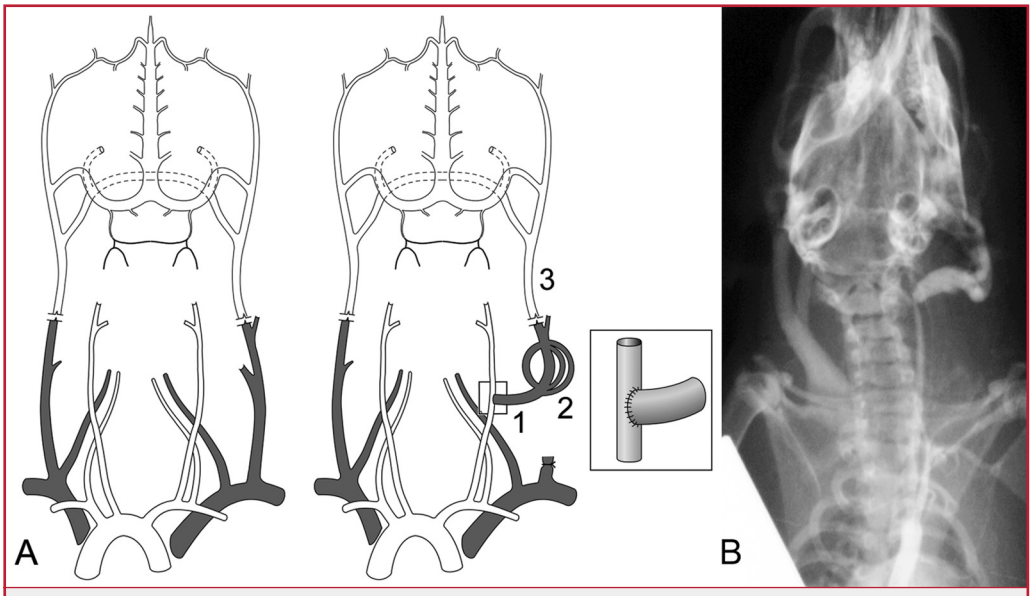


FIGURE 1. A, *Schematic diagram showing the vascular arrangement in the arteriovenous fistula model. Regions 1, 2, and 3 mimic the arterial inflow, nidus, and a large draining vein, respectively.* **B**, *Angiogram showing a rat 6 weeks after fistula creation.*

this flow with an arterial connection to the external jugular vein creates a feeding vessel (carotid artery and arterialized jugular vein), a nidus (arterialized venous plexus), and a draining vein (sigmoid sinus flowing to the opposite transverse and sigmoid sinuses).

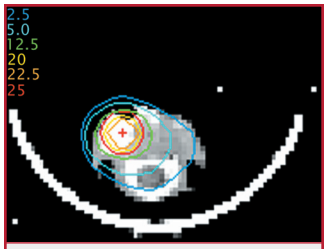


FIGURE 2. *Axial computed tomographic angiogram at the level of the fistula showing a rat 6 weeks after surgery. Radiosurgery planning information showing isodose lines (numbers represent radiation dose in Gray) has been superimposed.*

Radiosurgery

Initial dose planning was performed using computed tomographic angiography in a rat with an arteriovenous fistula that had been euthanized 6 weeks after surgery (*Fig. 2*). The plan specified a dose of 25 Gy of gamma irradiation to the site of the anastomosis with the 90% isodose line encompassing the fistula; the same treatment plan was used for all animals.

Radiosurgery was performed under intraperitoneal ketamine and midazolam anesthesia; sham-irradiated animals were treated identically but did not receive any radiation. Once sedated, the animal was placed on a stage attached to the head ring of the X-Knife linear accelerator (Radionics, Burlington, MA). Correct positioning of the animal relative to the planned treatment location was confirmed by ensuring that the fistula was placed at the intersection of the two targeting laser beams that designate the center of the radiation delivery arcs.

Intravenous Injection

Twenty-four hours after radiosurgery, animals received intravenous administration of LPS, sTF, a combination of both, or sterile saline. LPS was given as a dose of 0.1 mg/kg body weight. The dosage of sTF was 0.4 mg/kg body weight. All preparations were suspended in 0.5 ml 0.9% sterile saline.

Intravenous administration was performed as a slow push over 5 minutes through a cannula inserted in the right femoral vein. Briefly, cannulation was performed using a sterile microsurgical technique with the animal positioned supine under inhalational anesthesia. The femoral arterial pulse was palpated and a 1 cm incision was made over this point. The femoral neurovascular bundle was identified and the vein was separated from the artery and nerve. The femoral vein was cannulated with a 24-gauge cannula directed proximally. The vein was ligated after the intravenous injection.

Tissue Processing and Staining

At the completion of the experiment, animals were anesthetized and perfused with 4% paraformaldehyde through the aorta. Immediately after perfusion, vascular and soft tissue from the neck region was harvested; the brain, heart, lungs, and liver were also taken for analysis. Samples were embedded in paraffin and 5-μm sections were stained with hematoxylin & eosin or Martius Scarlet Blue to allow visualization of vessels and thrombi. Martius Scarlet Blue-stained red cells yellow, fresh fibrin orange/red, and old fibrin blue.

Microscopy and Statistical Analysis

Thrombosed and patent vessels were counted on five representative high-power fields of sections from each vascular region and from each of the harvested organs by an observer blind to the animal treatment group. Logistic regression analysis was performed with SPSS version 13 software (SPSS Inc., Chicago, IL) and was used to determine the contribution of radiosurgery and the intravenous agents to the formation of thrombi. $P < 0.05$ was considered statistically significant.

RESULTS

Ipsilateral to the Fistula

Thrombosis rates by region and treatment group are presented in *Table 2*. Very few irradiated vessels were thrombosed in animals that received saline alone (*Fig. 3*). Coadministration of sTF and LPS led to the formation of fibrin and erythrocyte thrombi in a mean of 57% of small vessels and 23% of medium-sized vessels within the 25-Gy target region (*Figs. 4–6*). Administration of LPS or sTF alone was associated with intermediate rates of thrombosis (mean of 17% and 34% in small vessels, respectively). Animals that received sham irradiation followed by coadministration of sTF and LPS demonstrated thrombosis in a mean of 27% of small vessels in the vessels draining the fistula on the ipsilateral side.

Contralateral to the Fistula

On the contralateral side, in a region that had received between 2 and 4 Gy, thrombosis was rarely seen in animals that received intravenous saline. Administration of LPS or sTF alone was associated with mean small-vessel thrombosis rates of 16% and 23%, respectively. After coadministration of both agents, thrombi were

TABLE 2. Thrombosis rates by treatment group for small and medium-sized vessels ipsilateral and contralateral to the fistula[a,b]

Treatment group	Ipsilateral		Contralateral	
	Small	Medium	Small	Medium
RS + saline	9.13 ± 10.2	3.51 ± 6.07	6.20 ± 8.32	0
RS + LPS	16.7 ± 2.54	8.66 ± 1.82	16.4 ± 6.99	9.09 ± 15.7
RS + sTF	34.3 ± 3.46	12.0 ± 7.47	22.6 ± 8.18	4.53 ± 4.21
RS + sTF + LPS	56.8 ± 11.5	23.4 ± 13.1	27.8 ± 11.0	10.8 ± 9.95
sTF + LPS	27.4 ± 3.44	11.4 ± 5.63	34.2 ± 0.94	14.6 ± 6.87

[a] RS, radiosurgery; LPS, lipopolysaccharide; sTF, soluble tissue factor.
[b] Rates expressed as mean ± standard deviation.

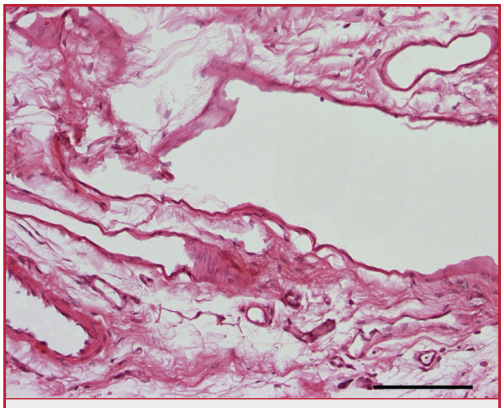


FIGURE 3. *Representative section of irradiated fistula tissue showing a rat 72 hours after treatment with normal saline. No evidence of thrombus formation is seen in the region of the fistula (hematoxylin & eosin; original magnification, × 20).*

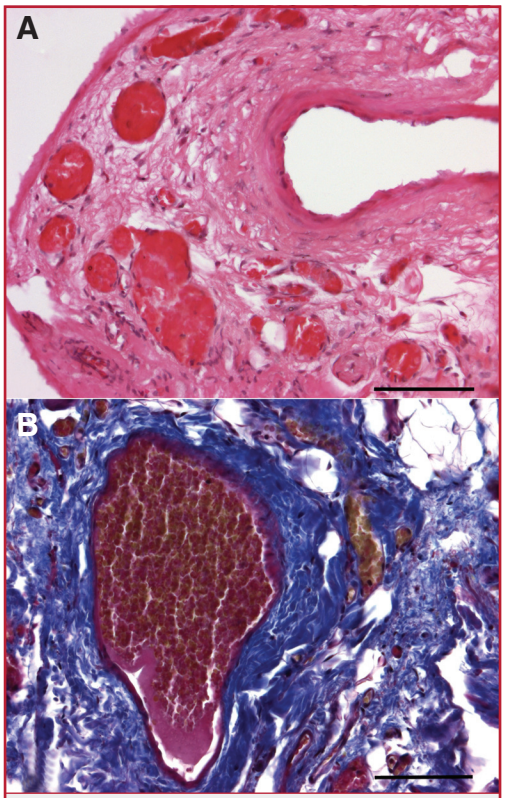


FIGURE 4. *Representative sections of irradiated fistula tissue showing rats 72 hours after combined treatment with sTF and LPS.* **A**, *Hematoxylin & eosin-stained section demonstrating extensive thrombus formation within small and medium-sized vessels (original magnification, × 20).* **B**, *Martius Scarlet Blue staining demonstrating the presence of fibrin and erythrocytes in multiple thrombi (original magnification, × 40).*

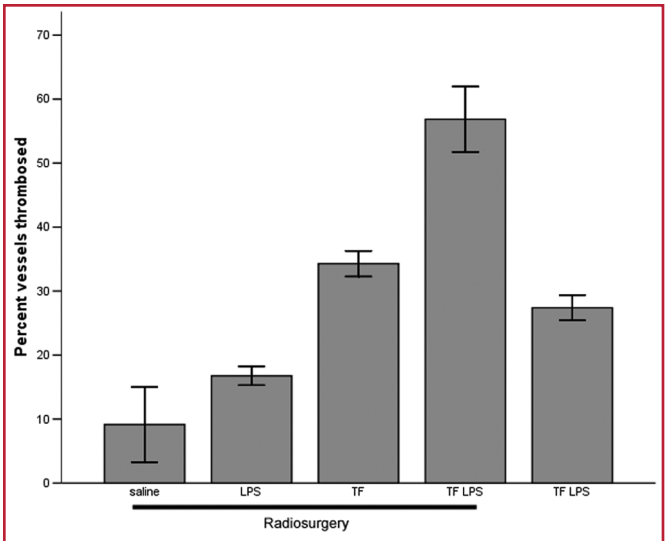


FIGURE 5. *Thrombosis rates in small (<50 μm) vessels in the region of the anastomosis, fistula, and draining vessels by treatment group are shown. Error bars represent standard error of the mean.*

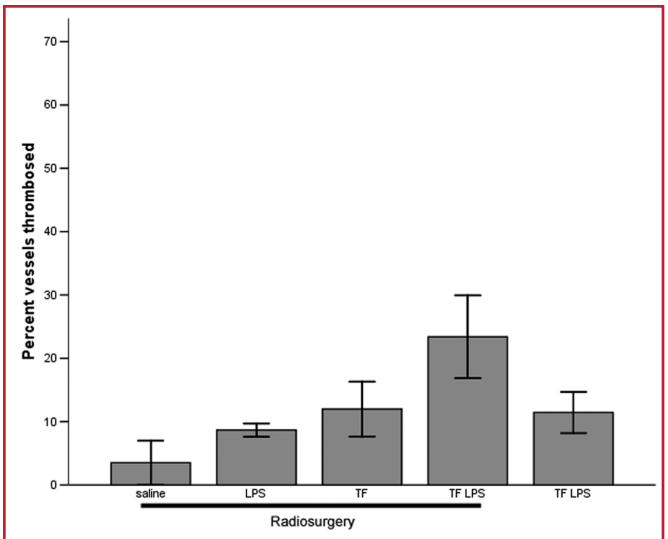


FIGURE 6. *Thrombosis rates in medium (50–200 μm) vessels in the region of the anastomosis, fistula, and draining vessels by treatment group are shown. Error bars represent standard error of the mean.*

present in 28% of small vessels and 11% of medium-sized vessels. Sham-irradiated rats receiving both agents had thrombi within up to 35% of high-flow small vessels draining into the contralateral external jugular vein.

Logistic regression analysis of the experimental data from all treatment groups demonstrated significant associations between development of thrombi and treatment with radiation, sTF, or LPS ($P < 0.005$).

Histologically, the thrombi displayed features typical of antemortem thrombi, being composed of fibrin, erythrocytes, and a few platelets while frequently exhibiting lines of Zahn. The majority of thrombi were seen in vessels less than 200 μm in size, although occasionally total or partial occlusion was seen in much larger vessels.

No animals were found to have thrombi in the vasculature of the nonirradiated organs studied (brain, lung, heart, or liver) and there was no evidence of infarction in these organs. Clinically, the animals tolerated the intravenous agents well with no change in behavior or significant loss of weight postinjection.

DISCUSSION

The results of this study indicate that the AVM model vessels are different from normal vessels and that these differences can be used to induce selective thrombosis by the administration of one or more procoagulant agents. Thrombosis rates were increased with radiation. The ability to use radiation to define a region in which significant vessel thrombosis occurs while causing no injury or thrombosis in normal tissues may have significant implications for the treatment of AVMs.

LPS

Lipopolysaccharide is a constitutive component of the outer membrane of Gram-negative bacteria. It is released as an endotoxin during bacterial multiplication or death (26) and plays a central role in Gram-negative sepsis. LPS has a multitude of prothrombotic and proinflammatory effects. Many of these effects are mediated by the induction of cytokines, including tumor necrosis factor-α (TNF-α) from inflammatory cells (14, 21). LPS also directly stimulates many endothelial processes, including the expression of TF (10, 27), interstitial cell adhesion molecule-1 (6, 8, 29), vascular cell adhesion molecule-1 (VCAM-1) (30), and E-selectin (8, 10, 22). Weibel-Palade body exocytosis is initiated by LPS with consequent increases in von Willebrand factor (31) and P-selectin expression (24). In addition, LPS is a potent inducer of endothelial apoptosis (2).

In animal models, LPS is used to induce disseminated intravascular coagulation and septic shock syndrome. Although LPS is a potent stimulator of TF production in cultured endothelial cells, endothelial expression of TF is rare in rat, rabbit, and baboon models of endotoxemia (10, 12, 16); only the baboon splenic microvascular EC expresses TF. However, many other cell types overexpress TF in response to LPS, including pulmonary and renal epithelial cells, astrocytes, and macrophages.

The LPS dose used for this current experiment was much lower than that used previously to induce septic shock in rats. Shock is induced by doses approximately 4 to 8 mg/kg (11, 13, 21), whereas in this experiment, only 0.1 mg/kg was used. At this low dose, there is still significant induction of TNF-α expression; plasma TNF-α levels are over 90% of those occurring at septic shock-inducing doses (21). In the murine tumor experiments, a dose of 0.05 mg/kg was found to have maximal thrombotic effects (26). In this current experiment, there was no evidence of LPS toxicity in the animals as demonstrated by minimal weight loss and no behavioral change postinjection. Soluble tissue factor was given at similar dose-to-weight ratio as was used in the murine tumor work (26).

Tumor Vasculature

For some time, high-dose LPS has been used to induce hemorrhagic necrosis in animal tumor models (5); a process in which TNF-α is thought to play a central role. Philipp et al. (26) postulated that the selective thrombosis after high doses of LPS arises as a result of the synergistic action of TNF-α and tumor cell-produced VCAM (4, 7) on LPS-induced TF expression. When low-dose LPS is given as a single agent, there is minimal coagulation within the tumor vasculature; it is only the coadministration with soluble TF that induces significant thrombus formation. It appears that although the nature of the TF changes induced by the lower dose of LPS is similar to those occurring at higher doses, the intensity of TF expression is insufficient to initiate coagulation. Only in the presence of sTF, bound to the endothelial surface after association with coagulation factor VIIa, is the surface density of TF sufficient to initiate coagulation (26). Of central importance in the thrombotic process after either high- or low-dose LPS administration is the unique expression of externalized phosphatidylserine on the tumor endothelium.

Irradiated Fistula Vasculature

The results of this experiment demonstrate that the hemodynamic derangements within the fistula and radiation have independent and additive effects on thrombosis after administration of low-dose LPS and sTF. In our prior work, no thrombosis has been observed in any untreated rats after formation of a carotid-to-jugular anastomosis. The nonirradiated fistula vessels overexpress VCAM (A Karunanayaka, unpublished data), perhaps as a direct consequence of high shear stress (15, 17), and may externalize phosphatidylserine. Radiation induces further vascular endothelial growth factor expression (19) and endothelial apoptosis (25) or disruption of membrane translocases may lead to increased externalization of phosphatidylserine (3). The net result of these changes is that the irradiated fistula and draining venous system exhibit significant phenotypic similarities with tumor vessels, making them susceptible to the combined effects of low-dose LPS and sTF in a similar manner. Normal vessels outside the irradiated region are resistant to the effects of LPS and sTF presumably through the action of the tissue factor pathway inhibitor, thrombomodulin, sequestration of TF, and the maintenance of phospholipid asymmetry. We administered LPS and sTF after radiosurgery to take advantage of the endothelial changes. Soluble tissue factor has a relatively short half-life and administration before radiosurgery is unlikely to be as effective.

Limitations and Future Directions

Although thrombosis occurred specifically within regions receiving radiation in this animal model, it is unclear if the

method would be safe or effective for use in humans. This approach lacks the obvious specificity of anti-phosphatidylserine antibodies or a coaguligand directed against E-selectin, for example. Further study is required to determine whether changes that occur in chronically inflamed or neovascularizing tissues may also trigger inappropriate thrombus formation. Adverse effects may also be limiting; in one clinical trial, administration of endotoxin (4 ng/kg) produced transient renal and hepatic toxicities and was accompanied by constitutional effects such as fever, chills, and hypotension (23).

This study does not indicate the long-term fate of thrombi in the animal model. Recanalization may occur as has been shown in irradiated human AVMs. Examination of tissue at later time points after irradiation will allow determination of the durability of the thrombotic process.

In this experiment, small vessels were preferentially thrombosed. These vessels are also the most vulnerable to radiation damage (9). In clinical use, if the AVM nidus is comprised of larger vessels, then this may lead to incomplete thrombosis of the nidus. Although occlusive thrombi were seen in medium and large vessels, further work is necessary to demonstrate the ability to occlude the majority of these larger vessels.

Nevertheless, this is the first time in which a pharmacological strategy has been used to induce thrombosis in vessels after radiosurgery and provides proof of principle for the use of a vascular targeting approach in the treatment of AVMs. The demonstration of the ability to stimulate thrombosis restricted to an irradiated region carries the promise of significant improvements in the treatment of AVMs. This strategy warrants safety and efficacy studies in a large animal model with a view to eventual use in clinical trials.

The findings of this study may have implications for areas beyond AVM management. The ability to induce thrombosis in blood vessels within a stereotactically defined target may have application in other fields, particularly in tumor treatment.

CONCLUSION

This study demonstrated that treatment with sTF and low-dose LPS selectively induces thrombosis of irradiated fistula vessels in a rat model of AVM. The hemodynamic derangements within the fistula and radiation appear to have independent and additive effects on the occurrence of thrombosis in this setting. Stimulation of thrombosis may improve the efficacy of radiosurgery, increasing the treatable lesion size and reducing latency.

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COMMENTS

Although it is a long way from mice to men, and applicability of this surgically created cervical caroticojugular fistula as a model of brain arteriovenous malformations (AVMs) is theoretical, the authors have nevertheless, in a straightforward and controlled experiment, given us proof of principle that coadministration of systemic agents might enhance the efficacy of stereotactic radiosurgery in causing early vascular thrombosis. The prothrombotic agents used here are low-dose lipopolysaccharide (LPS) and the extracellular domain of human tissue factor (TF), and the combination was associated with more than two-thirds of small and one-third of medium vessels being found thrombosed immediately after their administration and 24 hours after radiosurgery versus virtually no thrombosis seen in irradiated tissue given saline placebo. The mechanism of action requires clarification. The concept of sensitizing vascular tissue in a manner similar to the pharmacological sensitization of neoplastic cells to radiation is novel and potentially very important. It is hoped that the authors will continue to pursue this line of investigation with more animals, longer follow-up periods, different endpoints, and perhaps a search for cause and effect at a molecular level.

J. Max Findlay
Edmonton, Canada

The authors studied the effects of a low-dose bacteria-based LPS in promoting vascular obliteration in a rat radiosurgery model. They found that the agents led to an increased rate of occlusion versus the control. The use of other agents, such as estrogens, has been discussed in the past. I could certainly envision endovascular delivery of drugs during angiography as part of radiosurgery planning or administration the next day, if appropriate, based on drug pharmacokinetics. Clearly, more work needs to be done. It would be interesting to test these agents in the swine rete mirabile model.

Douglas Kondziolka
Pittsburgh, Pennsylvania

There are no perfect models of AVMs in animals. Mice heterozygous for endoglin gene deletion may develop brain AVMs, similar to the human condition of hereditary hemorrhagic telangiectasia (2). The carotid-jugular fistula model used here is probably the best, most practical method for studying some aspects of AVMs at present. The authors use the model to test the classic idea of "radiosensitizing" tissue to enhance differential effects of radiation on target and nontarget tissues. A variation on this was using radiation-inducible gene therapy for tumors (1). This approach is very worthy of extensive investigation, and the work presented here is a start.

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The radiosurgical management of intracranial AVMs has been studied more extensively than any other indication for radiosurgery. Reports on AVM radiosurgery over the past three decades have highlighted two primary weaknesses of this approach: size limitation and delay in obliteration. Using a rat carotid-to-jugular anastomosis, the authors showed an additive effect on thrombus formation within the fistulae in animals that received a combination of LPS and soluble TF after single fraction (25 Gy) irradiation of the fistula. The authors speculate that these molecules could potentially be used as radiation sensitizers for AVM radiosurgery. Questions still remain as to whether the rapid thrombus formation demonstrated here would lead to long-term vessel occlusion or simply vessel recanalization. Also, abrupt alterations in the flow of AVMs after radiosurgery could result in an increased risk of hemorrhage either from perfusion pressure breakthrough or occlusive hyperemia. Further study with longer follow-up periods, including some form of radiological imaging before sacrifice, would be helpful in determining the clinical usefulness of this strategy.

Bruce E. Pollock
Rochester, Minnesota

Storer et al. have elegantly investigated the role of LPS and soluble TF as adjuvant therapies to enhance thrombus formation in an animal AVM model. The authors created carotid-to-jugular anastomoses and injected either soluble TF, low-dose LPS, a combination of both, or placebo 24 hours after stereotactic irradiation of the vascular lesion. Control animals received both agents after sham irradiation. The authors found that coadministration of soluble TF and LPS caused thrombi formation in nearly 70% of small vessels and 40% of medium-sized vessels within the target region. In comparison, administration of LPS or soluble TF alone was associated with only 17 and 34% thrombosis, respectively, whereas sham irradiation followed by coadministration of soluble TF and LPS demonstrated thrombosis in 27% of small vessels. Of note, there was no evidence of systemic thrombus formation or toxicity in any group.

Considering the current limitations of AVM radiosurgery, the findings of this study provide preliminary data for further investigation into the coadministration of one or more procoagulant agents to induce vessel thrombosis. Previous literature has shown that irradiated vascular tissue exhibits significant phenotypic similarities to tumor vessels, making them susceptible to the combined effects of low-dose LPS and soluble TF, whereas normal vessels outside the irradiated region are resistant to these agents, presumably through the presence of tissue factor pathway inhibitor and thrombomodulin. Although encouraging, it remains unclear whether or not this technique would be safe or effective for use in clinical trials, as severe adverse effects have been seen with administration of LPS. In addition, this study does not address the long-term outcome of vessel thrombosis, as recanalization may occur. Nevertheless, the authors' work provides proof of principle utilizing adjuvant pharmacology to augment thrombosis after AVM radiosurgery. Moving forward, safety and efficacy studies in other animal models are warranted with eventual transition to clinical trials.

Ricardo J. Komotar
E. Sander Connolly, Jr.
New York, New York

In the past three decades, stereotactic radiosurgery has increased the therapeutic repertoire of the neurosurgeon in managing AVMs, a potentially devastating vascular disease. Concerns with radiosurgery still remain, however, due mostly to the delay in vessel obliteration after application of the technique, allowing for a window of up 3 years during which patients remain at risk for hemorrhage. Storer et al. utilize a novel, prothrombotic strategy inspired by the tumor literature to enhance the ability of radiosurgery to thrombose AVM vessels. Using a rodent model of AVM, the authors convincingly demonstrate that the systemic administration of LPS and soluble TF synergize with radiosurgery to increase both small and medium caliber vessel thrombosis within the AVM. These results suggest, at least in principle, that an adjuvant prothrombotic approach may be able to augment the clinical benefits of radiosurgery in human AVMs. At the same time, the authors appropriately mention the possibility of untoward side effects of encouraging thrombosis, especially given their data demonstrating increases in AVM vessel thrombosis with LPS and soluble TF in the absence of radiosurgery. The specters of myocardial ischemia, ischemic stroke, and deep venous thrombosis immediately come to mind; however, in light of the recent success with activated factor VII in hemorrhagic stroke and the generally young age of AVM patients, it is plausible, although still highly speculative, that the risk/benefit ratio for a prothrombotic maneuver in the setting of AVM radiosurgery may be favorable. Locally acting prothrombotic agents or local application of such agents provides other possibilities for increasing the spatial specificity of this strategy. Overall, the authors have introduced an intriguing and potentially therapeutic idea to bolster the effects of AVM radiosurgery.

Albert H. Kim
Robert M. Friedlander
Boston, Massachsetts

RESIDENT TRAVELING FELLOWSHIP IN PEDIATRIC NEUROSURGERY

The Joint Pediatric Neurosurgery Section of the ***American Association of Neurological Surgeons*** and the ***Congress of Neurological Surgeons*** has established a traveling fellowship for residents in accredited North American neurosurgical training programs. The fellowship is intended to cover the traveling and living expenses for one month for a resident who wishes additional experience in Pediatric Neurosurgery during residency. The one-month fellowship can be spent at any institution within North America to pursue an activity which broadens the resident's exposure to Pediatric Neurosurgery, including observation at a clinical or research center, participation in a research project, or any other relevant activity. Two fellowships per year are awarded on the basis of an evaluation by a committee of the Joint Pediatric Section. The maximum fellowship stipend is $2500.

The application must include:

1) Statements defining the purpose of the proposed fellowship and an estimate of expenses that will accrue to the applicant
2) Permission from the applicant's residency program director to pursue the one month fellowship if it is awarded
3) A letter of acceptance from the Pediatric Neurosurgical program where the applicant will seek the fellowship

The completed application should be sent to:

R. Michael Scott, M.D.
Department of Neurosurgery, The Children's Hospital
300 Longwood Avenue, Bader 319
Boston, Massachusetts 02115

or via e-mail to:
michael.scott@childrens.harvard.edu

THE ABSOLUTE DEADLINE FOR APPLICATION SUBMISSION IS OCTOBER 15, 2007

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THE HISTORY OF NEUROSURGERY AT THE HOSPITAL FOR SICK CHILDREN IN TORONTO

THE TRADITION OF selfless charity for children in Toronto was established by Elizabeth McMaster, founder of the Hospital for Sick Children, or "Sick Kids," in 1875. The tradition of fortitude and perseverance in trying to cure children who were deemed incurable by others was sealed into the history of the Hospital by early pioneering surgeons, including Drs. Clarence Starr, A.W. Farmer, and William Gallie. Dr. William Gallie recognized the importance of neurosurgery for the future of the Hospital and encouraged Dr. William Keith to acquire training in pediatric neurosurgery in Chicago and London. Dr. Keith began the practice of pediatric neurosurgery at Sick Kids in 1935 and worked in the primordial phase of the subspecialty for the next 20 years until he was joined by Dr. E. Bruce Hendrick in 1955. In time, Dr. Hendrick was joined by Drs. Harold Hoffman and Robin Humphreys who led a decidedly strong pediatric neurosurgery unit between 1975 and 1995. During this epoch, the pediatric neurosurgery service grew to become one of the busiest and most progressive units in the world. Over the years, numerous neurosurgery fellows and faculty from all over the world have trained at or have visited Sick Kids to learn how pediatric neurosurgery is practiced in Toronto. The purpose of this article is to review the history of the individuals who founded the Hospital for Sick Children and its Division of Neurosurgery.

KEY WORDS: Hospital for Sick Children, Medical history, Neurosurgery, Pediatric neurosurgery

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The pediatric neurosurgery service at the Hospital for Sick Children ("Sick Kids") has had a rich tradition of excellence devoted to children with neurosurgical disorders. Although the first neurosurgeon to perform surgery at Sick Kids was Dr. William Keith in 1933, it was not until the arrival of Dr. E. Bruce Hendrick, Canada's first fully trained pediatric neurosurgeon, who had trained under Dr. Donald Matson in 1952, that a full-time pediatric neurosurgeon was devoted to the care of children. Dr. Hendrick was subsequently joined by Dr. Harold Hoffman in the 1960s and Dr. Robin Humphreys in the 1970s at a time when pediatric neurosurgery was developing as a bona fide subspecialty in neurosurgery. Other centers that were developing pediatric neurosurgery services at this time were located in Boston, Chicago, Philadelphia, and New York.

The following is an account of the history of the Hospital for Sick Children, a haven where pediatric neurosurgery has grown and flourished and where numerous fellows and faculty from all corners of the globe have come to seek specialty training in the field.

ELIZABETH MCMASTER AND MAGGIE: THE HISTORY OF THE HOSPITAL FOR SICK CHILDREN

Elizabeth Janet Wyllie, the daughter of Scottish immigrants, George Black Wyllie and Mary Ann Reid, was born on December 27, 1847, in Toronto. She married Samuel Fenton McMaster on June 1, 1865, when she was not yet 18 years of age. Samuel F. McMaster was a successful businessman in the dry goods importing industry. He was the nephew of Senator William McMaster, founder of McMaster University in Hamilton, Ontario. By 1874, Elizabeth McMaster had already borne three children.

During that time, the population of the city of Toronto was 68,000. For the most part, it was a wealthy, bustling city enjoying its eighth year

as the capital of Ontario. However, the streets were also filled with Torontonians who were desperately poor. There were no welfare, family allowance, health plan, unemployment insurance, or pension plans to help them. Children suffered the most, coughing from bronchopneumonia; hobbling from tuberculosis osteomyelitis; and dying from diphtheria, scarlet fever, typhoid fever, and septicemia (4). Elizabeth McMaster believed that general hospitals did not provide the special care children needed (4). Childrens' hospitals had already been established in 17 major European cities, but the only childrens' hospital in the British Empire was at Great Ormond Street in London. Elizabeth McMaster was determined to establish the second one in Toronto (*Fig. 1*) (4).



FIGURE 1. *A portrait of Elizabeth McMaster, founder of the Hospital for Sick Children, still hangs in the main corridor of the hospital today.*

In 1874, a group of deeply religious women who possessed a strong social conscience and cared a great deal for the condition of the poor met in the home of Mrs. Elizabeth McMaster to consider how they could help sick children. They decided to establish a hospital to help the poor and sick children of Toronto. The hospital they founded was opened on March 1, 1875. The group of women rented an 11-room house in downtown Toronto, where the Toronto General Hospital now stands, for $320 a year. There, they set up six iron cots and declared the hospital open "for the admission and treatment of all sick children" (4). One month later, on April 3, 1875, Maggie, a victim of a scalding burn, became the first patient of the Hospital for Sick Children in Toronto.

The first Annual Report of the Hospital (4), dated July 1, 1876, stated that in the first year, the Hospital treated 111 patients. Forty-four children were inpatients; 67 were treated as outpatients. Of the inpatients, 21 were surgical patients and 23 were medical patients. Interestingly, this ratio between surgical and medical patients seen in the Hospital has been maintained to the present time (17).

The demand for services was so great that the hospital had to move to a larger building in 1876, another rented house at 206 Seaton Street. This house could accommodate 16 patients at one time. In 1891, under the leadership of John Ross Robertson, publisher of the *Evening Telegram* and chairman of the Hospital's Board of Trustees, the Hospital for Sick Children moved to a new four-story, 320-bed facility at the corner of Elizabeth and College Streets (*Fig. 2*). The Toronto city council asked that it be named "Victoria Hospital for Sick Children," but the new name was never officially adopted. Instead, the Hospital for Sick Children became known as "Sick Kids."



FIGURE 2. *This building housed the third Hospital for Sick Children in Toronto in 1891. The hospital was to be named the "Victoria Hospital for Sick Children," but that name was never officially adopted. Today, the hospital is nicknamed "Sick Kids."*



FIGURE 3. *The Hospital for Sick Children as it stands today at 555 University Avenue. With the addition of the Atrium in 1993, the hospital occupies one entire city block.*

On February 4, 1951, the hospital moved to its current location at 555 University Avenue (*Fig. 3*), occupying the grounds where the childhood home of actress Mary Pickford once stood. At the same time, there was a switch in emphasis from nutritional research to the repair of congenital defects. Three years later, the Research Institute was established.



FIGURE 4. *A view from inside the Atrium. The Atrium allows natural light into the hospital. Each patient room has exposure to natural sunlight, a great healing effect for the children.*

In January 1993, a new inpatient facility was built, complete with an expansive Atrium just behind the 555 University Avenue site (*Fig. 4*). The Atrium was designed by Eberhard Zeidler of the Zeidler-Roberts Partnership. Believing that light is important to healing, Zeidler designed the building around a nine-story, glass-roofed atrium. Most patients now have their own room with natural sunlight, a washroom, storage, and a day bed so that a parent can stay overnight. With the addition of the new wing, the hospital now occupies an entire city block. The Atrium houses facilities to help provide enhanced care and improve the treatment and diagnosis of childhood disease. The critical care unit, where children with life-threatening illness and injury receive care, almost doubled in size to 36 beds. The emergency department has two trauma rooms and a six-bed observation room. The operating room now houses 15 operating rooms, each fully equipped to perform modern surgical practices across six different divisions. Most recently, on May 25, 2001, the imaging guided therapy department opened, enabling surgeons to perform interventional radiological and minimally invasive neurosurgical procedures under image guidance.

THE KEITH YEARS: THE BIRTH OF THE DIVISION OF NEUROSURGERY

Dr. William S. Keith, the second of four children, was born in Toronto on June 20, 1902. He was educated in Toronto and completed medical school at the University of Toronto in 1927. After graduation, he performed his internship at the Toronto General Hospital and had the opportunity to work with Dr. Kenneth McKenzie, Canada's first neurosurgeon (1, 69). It was this early experience working with Dr. McKenzie that inspired Dr. Keith to pursue a career in neurosurgery (12, 13, 26).

In 1929, Dr. Gallie, Surgeon-in-Chief at the Hospital for Sick Children, encouraged Dr. Keith to become a neurosurgeon and to work at the Hospital for Sick Children (14). He secured a Douglas Smith Fellowship for Dr. Keith, which allowed him to study at the University of Chicago with Dr. Roy Grinker, Professor of Neurology, and Dr. Percival Bailey, Professor of

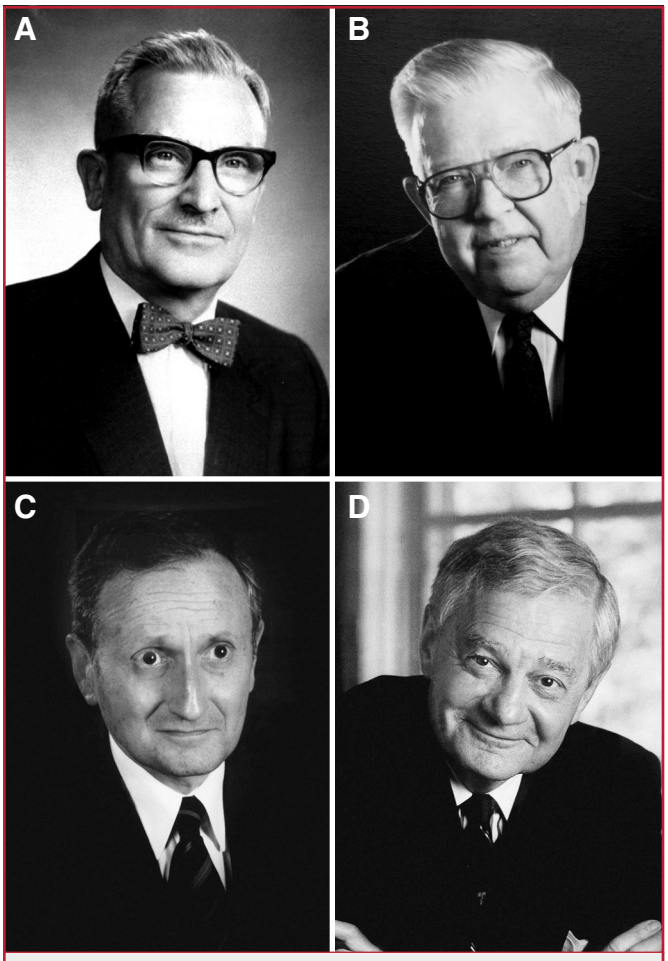


FIGURE 5. *Portraits of the fathers of neurosurgery at the Hospital for Sick Children: Dr. William Keith (**A**), Dr. E. Bruce Hendrick (**B**), Dr. Harold Hoffman (**C**), and Dr. Robin Humphreys (**D**).*

Neurosurgery (26). Dr. Keith also had an opportunity to work with Dr. Paul Bucy who was finishing his residency as Dr. Bailey's Chief Resident.

Dr. Keith returned to Toronto in 1930 to work with Dr. McKenzie (1, 12, 13, 69). One year later, in 1931, the Hospital for Sick Children sponsored his studies at the National Hospital for Neurological Disorders at Queen's Square in London, England, as a Clinical Clerk to the Neurology Service (26). While in England, on April 2, 1931, he married Eleanor, a nurse who worked at the Hospital for Sick Children in Toronto.

He returned to the Hospital for Sick Children to become Chief Resident in Surgery. In 1933, he joined the staff at the Hospital for Sick Children with a primary interest in neurosurgery. At the time, neurosurgery was a fledgling specialty, and Dr. Keith was required to take call for general surgery and orthopedic surgery (14). In 1936, he organized an adult neurosurgical service at the Toronto Western Hospital. He continued to serve as Chief of Neurosurgery at both the Hospital for Sick Children and the Toronto Western Hospital until his retirement in 1964 (*Fig. 5A*).

TABLE 1. Major contributions to neurosurgery and Pediatric neurosurgery by Dr. William S. Keith and the "3 Hs"

Subspecialty	Contribution	References
Hydrocephalus	Management of shunt infections	93
	Experience with ventriculopleural shunts	39
	Lumboperitoneal shunt for hydrocephalus	37
	Percutaneous third ventriculostomy	31
	Slit ventricle syndrome	50
	Normal pressure hydrocephalus	61
Epilepsy	Lesional temporal lobe epilepsy	9
	Rasmussen's encephalitis	77
	Hemispherectomy	23, 33
	Posttraumatic epilepsy	21
Cerebrovascular	Moyamoya disease	28
	Management of arteriovenous malformations	57, 60, 63
	Pediatric hemorrhagic strokes	52
	Vein of Galen malformations	29
	Pediatric intracranial aneurysms	88
Neuro-oncology	Craniopharyngiomas	30, 42, 59
	Gangliogliomas	15, 72
	Low-grade astrocytomas	47
	Optic pathway/hypothalamic gliomas	43
	Dorsally exophytic brainstem gliomas	78, 89, 90
	Intracranial germ cell tumors	46
	Infratentorial ependymomas	71
	Thalamic tumors	3
	Congenital neoplasms	2
	Medulloblastoma	36, 40, 76
	Pineal region tumors	49
	Tectal gliomas	67
Spine	Tethered cord syndrome	24, 38
	Lumbar disc disease in children	16
	Hydrosyringomyelia	45
	Traumatic spinal cord infarction	5, 61
	Whiplash injury	62
	Occipital neuralgia	62
Congenital abnormalities of development	Separation of craniopagus twins	83
	Encephaloceles	66
	Colloid cysts	65
	Lipomyelomeningoceles	48
	Surgical management of Chiari I malformations	35, 75
	Surgical management of Chiari II malformations	92
	Dermoid cysts of the anterior fontanelle	74
	Suprasellar arachnoid cysts	41
Neurotrauma	Complications of pediatric head trauma	22, 53, 58
	Significance of skull fractures	18
	Therapeutic benefit of hypothermia in severe head trauma	19
Craniofacial abnormalities	Lambdoid synostosis	70
	Early repair of craniofacial dysmorphism	32
	Management of unilateral and bilateral coronal craniosynostosis	44, 68
Infection	Subdural empyema and epidural abscess	87
	Cerebral abscesses in infants	34
Surgical technology	Frameless stereotaxy	11, 25, 73

In May 1942, Dr. Keith volunteered to serve in the Canadian Armed Forces and organized a mobile neurosurgical unit. He returned to Toronto in May 1945 to resume his neurosurgical practice and his duties at the University of Toronto. He was a founding member of the Canadian Neurological Society and served as President from 1964 to 1965.

At the Hospital for Sick Children, he pioneered pediatric neurosurgery *(Table 1)*. He was one of the early proponents of lumboperitoneal shunting for hydrocephalus, which he introduced to the Hospital for Sick Children in 1948. During these early years of pediatric neurosurgery in Toronto, Dr. Keith developed significant experience treating children with head trauma, craniofacial disorders, spina bifida, hydrocephalus, and stroke. He trained many young, aspiring pediatric neurosurgeons, including Dr. Harold J. Hoffman (26).

For almost 20 years, Dr. Keith maintained a hurried pace as the sole neurosurgeon for both the Hospital for Sick Children and the Toronto Western Hospital. He was joined by Dr. Ross Fleming at the Toronto Western Hospital and by Dr. E. Bruce Hendrick at the Hospital for Sick Children in 1954 and 1955, respectively.

Dr. Keith had a long-term friendship with Dr. Frank Mayfield, dating back to 1938, and the two were among several neurosurgeons who founded the American Academy of Neurological Surgery (26).

In 1964, he retired from the University of Toronto staff and from his position as Chief of Neurosurgery at both the Toronto Western Hospital and the Hospital for Sick Children. Dr. Keith continued general practice in aboriginal communities in Ontario, British Columbia, and Newfoundland, and as a camp doctor in northern Ontario for children with medical disorders (14) for many years. On December 27, 1987, at the age of 85, Dr. Keith died of Hodgkin's disease at his home in Toronto surrounded by his family. In his name, the annual William Keith Lectureship has been established at the Toronto Western Hospital in the Division of Neurosurgery. A listing of past Keith Visiting Professors in Toronto is shown in *Table 2*.

HISTORY IN THE MAKING: THE ERA OF "THE 3 H's"

E. Bruce Hendrick

Dr. E. Bruce Hendrick, a native Torontonian who was born, lived, practiced, retired, and died in the city (27). Apart from a brief absence during his residency, his unflagging loyalty to Canada had been sustained through his high school and University of Toronto education, the postgraduate surgical training (the famed Gallie Course) at that university, and a brief military career. He traveled to Boston in 1952 to begin a 2-year fellowship at the Children's Hospital and Peter Bent Brigham Hospital, where he studied under Drs. Franc Ingraham and Donald Matson.

The Hendrick aphorisms, of which there are many, such as the time he asked Dr. Matson's patient with a spinal cord tumor

TABLE 2. Past William S. Keith visiting professors

Year	Lecturer	City of residence
1976	Prof. Gilles Bertrand	Montreal, Canada
1977	Prof. Douglas Miller	Edinburgh, Scotland
1978	Dr. Robert Ojemann	Boston, MA
1979	Prof. Bryce K.A. Weir	Edmonton, Canada
1980	Prof. Lindsay Symon	London, England
1981	Dr. Blaine Nashold	Durham, NC
1982	Prof. Charles Drake	London, Canada
1983	Prof. Graham Teasdale	Glasgow, Scotland
1984	Dr. Douglas Long	Baltimore, MD
1985	Prof. Patrick Derome	Paris, France
1986	Dr. Charles Wilson	San Francisco, CA
1987	Prof. Kenichiro Sugita	Matsumoto, Japan
1988	Prof. Madjid Samii	Hannover, Germany
1989	Dr. Toralf M. Sundt	Rochester, MN
1990	Prof. Tyrone Hardy	Montreal, Canada
1991	Dr. George Ojemann	Seattle, WA
1992	Dr. Laligam N. Sekhar	Pittsburgh, PA
1993	Prof. Andrè Olivier	Montreal, Canada
1994	Dr. Robert Martuza	Washington, D.C.
1995	Dr. Volker K.H. Sonntag	Phoenix, AZ
1996	Dr. Roberto C. Heros	Miami, FL
1997	Prof. Alim-Louis Benabid	Grenoble, France
1999	Dr. Edward Oldfield	Bethesda, MD
2000	Dr. Arnold Menezes	Iowa City, IA
2001	Dr. David Piepgras	Rochester, MN
2002	Dr. Mitchel Berger	San Francisco, CA
2003	Dr. Edward Benzel	Cleveland, OH
2004	Dr. David Roberts	Lebanon, NH
2005	Dr. Richard Fessler	Chicago, IL
2006	Dr. Webster H. Pilcher	Rochester, NY

and associated paresthesias if "[his] legs feel like ginger ale looks" (55, p 100) will remain with students and residents alike for generations to come.

Having completed his training in pediatric neurosurgery in Boston, Dr. Hendrick returned to Toronto in 1954 to begin neurosurgical practice at the Hospital for Sick Children. Although he also held responsibilities at the Toronto Western Hospital, his joy came from caring for children with neurosurgical disorders. Dr. Hendrick became Neurosurgeon-in-Chief at the Hospital for Sick Children in 1964 (*Fig. 5B*).

Dr. Derek Harwood-Nash, a young South African newly graduated from medical school, obtained a neurosurgical fellowship at the Hospital for Sick Children to work on a pediatric head injury project under the mentorship of Dr. Hendrick (51). From that time, he remained in Canada to complete a residency in radiology at the University of Toronto and, after a fellowship, he joined the Sick Kids staff and dedicated himself to the emerging specialty of pediatric neuroradiology. After morning sessions performing ventriculograms, myelograms, and arteriography, Dr. Harwood-Nash would hold court in his tiny office cluttered with viewing boxes and bags of films. Without the benefit of modern neuroimaging techniques, he had to interpret inferential data, such as obscured air shadows and suspended droplets of contrast, and provide a learned opinion on the structural disorder in the child's nervous system. Eventually, he championed the Hospital for Sick Children's acquisition of computed tomographic and magnetic resonance imaging scanners, which are now ubiquitous in all pediatric hospitals. He was responsible for the training of more than 70 fellows in pediatric neuroradiology, many of whom were internationals (6, 51). Dr. Harwood-Nash, regarded by some as the "4th H" in the "3 H" era because of his major impact on the neurosciences at the time, died suddenly and unexpectedly from a basilar artery dissection on October 18, 1996 (6, 51).

Over the years, the relationship between Dr. Hendrick and his resident staff evolved into something truly unique. Eschewing complete reliance on gadgetry for clinical decisions, he taught residents to adhere to fundamental Oslerian principles of history gathering and physical examination or, as he said in a 1993 editorial, "Whatever mother says!" (20, p 193). He advised residents to be prepared to defend their own conclusions and not to be influenced by the "reckless courage of the noncombatant" (55).

Dr. Hendrick had been part of the nascence and maturation of the specialty of pediatric neurosurgery *(Table 1)* (80). He was on the founding committees of the International Society of Pediatric Neurosurgery and the American Society of Pediatric Neurosurgeons. He was President of the Canadian Neurosurgical Society and was a Board Member of the American Association of Neurological Surgeons, which honored him in 1998 as the first recipient of the Franc D. Ingraham Lifetime Achievement Award.

Dr. Hendrick's most enduring contribution to pediatric neurosurgery was his devotion to his patients (27). He brought joy to the children for whom he cared. In return, they showered him with crayon drawings, stuffed toys, small soldiers, and large cigars. The Friday afternoon water gun fights (55) were serious business. Nurses, parents, and child life therapists joined patients to develop strategies on how to outdo "Uncle Bruce" in the water gun fights. Syringe barrels worked for patients who did not have their own water pistols. The children wore green garbage bags while Uncle Bruce took the soaking in his scrub suit.

A familiar sight late at night in the Hospital would be Dr. Hendrick sitting in his office with arms folded across numerous open books on his desktop, providing fatherly counsel to young parents seeking hope and reassurance concerning their child's illness. Occasionally, at times when he had to disappoint and break bad news to parents, Dr. Hendrick, in expressing his own frustration, could be heard saying, "If I had distilled essence of moonbeams to give, I would" (55, p 101).

TABLE 3. Past E. Bruce Hendrick professors of pediatric neurosurgery

Year	Visiting professor	Institution
1986	Dr. Fred J. Epstein	New York University, New York, New York
1987	Dr. Luis Schut	University of Pennsylvania, Philadelphia, Pennsylvania
1988	Dr. Marion L. Walker	University of Utah, Salt Lake City, Utah
1989	Professor Maurice Choux	l'Hôpital des Enfants de la Timone, Marseille, France
1990	Dr. Michael S.B. Edwards	University of California San Francisco, San Francisco, California
1991	Dr. David G. McLone	Northwestern University, Chicago, Illinois
1992	Dr. R. Michael Scott	Harvard University, Boston, Massachusetts
1993	Professor Kiyoshi Sato	Juntendo University School of Medicine, Tokyo, Japan
1994	Dr. Warwick J. Peacock	University of California Los Angeles, Los Angeles, California
1995	Dr. J. Gordon McComb	University of Southern California, Los Angeles, California
1996	Professor Christian Sainte-Rose	University of Paris, Paris, France
1997	Dr. Derek A. Bruce	University of Texas Southwestern Medical Center, Dallas, Texas
1998	Professor Concezio Di Rocco	Catolica University Medical School, Rome, Italy
1999	Dr. Harold L. Rekate	University of Arizona School of Medicine, Phoenix, Arizona
2000	Dr. Tae Sung Park	Washington University, St. Louis, Missouri
2001	Professor D. Douglas Cochrane	University of British Columbia, Vancouver, British Columbia, Canada
2002	Professor Dominique Renier	University of Paris, Paris, France
2003	Professor Anthony D. Hockley	Diana, Princess of Wales Children's Hospital, Birmingham, UK
2004	Dr. W. Jerry Oakes	University of Alabama, Birmingham, Alabama
2005	Professor Alain Pierre-Khan	l'Hôpital Necker-Enfants Malades, Paris, France
2006	Dr. Robert A. Sanford	St. Jude Children's Research Hospital, Memphis, Tennessee

Throughout his professional career, Dr. Hendrick enjoyed the tremendous support of his wife, Gloria, to whom he had been married for 54 years, and his children, Michael and Sheelagh, who he described as always being there for him (55). Sadly, Dr. Hendrick died in 2001 from complications related to ruptured diverticulitis. The annual E. Bruce Hendrick Lectureship has been established in his honor at the Hospital for Sick Children in the Division of Neurosurgery. A listing of past Hendrick Lecturers at Sick Kids is shown in *Table 3*.

Harold J. Hoffman

Dr. Harold J. Hoffman was arguably the most famous pediatric neurosurgeon of his day (82). He set the standard for the treatment of many pediatric neurosurgical disorders by virtue of his understanding of the diseases that afflicted children, his unparalleled surgical skills, and his numerous publications in the scientific literature.

Dr. Hoffman graduated from the University of Toronto Faculty of Medicine in 1956. In 1957, he married JoAnn Shulman and became the loving father of Richard, Andrew, and Katie soon thereafter (82). Dr. Hoffman traveled to London in 1963 to complete a McLaughlin Fellowship before returning to Toronto.

He joined the Neurosurgical Staff at the Hospital for Sick Children in 1964. At that time, the neurosurgeon's day was occupied with the management and treatment of head trauma and brain tumors. Therefore, the major focus of Dr. Hoffman's practice was the treatment of pediatric brain tumors. His major publications in the neurosurgical literature began to appear around 1976, after approximately 12 years of working diligently in the field. By that time, he had amassed a huge clinical experience at Sick Kids, which enabled him to become an authority on virtually every topic in pediatric neurosurgery (82). He was tireless in his documentation of clinical case materials, amassing thousands of slides and photographs of cases that chronicled the state-of-the-art treatment of children with neurosurgical disease at the time. Many of his slides and case materials have been preserved for posterity on the Division of Neurosurgery web site (www.surg.med.utoronto.ca/neuro/slides.html). By the time he retired from neurosurgical practice, he had published more than 200 peer-reviewed articles on pediatric neurosurgery topics on which he had become an authority such as craniopharyngioma, tethered cord, spina bifida, Chiari malformation, moyamoya disease, and epilepsy surgery (*Table 1*) (9, 25, 28, 30, 38, 42, 73, 77, 91). Dr. Hoffman's final major scientific contribution to pediatric neurosurgery was acknowledged in the August 2004 issue of Child's Nervous System (83), in which he pioneered the use of interventional neuroradiological and neuronavigation techniques to separate craniopagus twins in 1995.

Dr. Hoffman quickly demonstrated his inquisitive enthusiasm for the investigation and treatment of a child's nerv-

ous system disorder; he left no stone unturned in his quest for clinical solutions. He put in very long days, often joining the residents side-by-side in their ward and emergency room duties. He initiated a laboratory project to study the value of dexamethasone treatment for focal brain edema. Early in his career, when he was not in the laboratory, operating room, radiology, or his Monday morning clinics, he would be off to Sunnybrook Hospital for his once-weekly commitment there. For all of his tireless and inspirational confidence and enthusiasm, Dr. Hoffman was not without his foibles and eccentricities. For example, he was perhaps the only neurosurgeon who wore a monacle and, on formal occasions, pince-nez (82).

Another one of Dr. Hoffman's most notable characteristics was his desire to stay current with or, at times, ahead of the latest neurosurgical technologies. He had a passion for understanding mechanical gadgets that ranged from wristwatches to automobiles (56). It is no small wonder that he insisted that the Hospital for Sick Children would be at the forefront of acquiring cutting-edge technologies such as mouth-driven microscopes, lasers, ultrasonic tumor aspirators, and image-guided therapy. Regarding the latter, Dr. Hoffman secured the ISG-viewing wand (SNS, Inc., Toronto, Canada) in 1992, making Sick Kids the first pediatric neurosurgery service in the world to use neuronavigation in the resection of complex pediatric brain tumors (11). Dr. Hoffman's ingenuity also led to the design of new equipment for pediatric neurosurgery cases. He invented two types of shunt devices for hydrocephalus: the lumboperitoneal shunt, the so-called Hoffman T-tube shunt, and one of the world's first "uni-shunts," designed with his colleague and friend, Dr. Fred Epstein, to avoid problems of shunt disconnections and breakages.

During his career in pediatric neurosurgery, Dr. Hoffman received numerous honors, including the Lister Prize in the Department of Surgery at the University of Toronto and the Donald Matson Memorial lecture given by the American Association of Neurological Surgeons in 1996. He held several major offices in organized neurosurgery during his career. He was President of the American Society of Pediatric Neurosurgery from 1980 to 1982, President of the International Society of Pediatric Neurosurgery in 1983 and 1984, Chairman of the Pediatric Section of the American Association of Neurological Surgeons/Congress of Neurological Surgeons in 1983, and President of the Canadian Neurosurgical Society and Vice President for North America of the World Federation of Neurosurgical Societies from 1993 to 1996. In 1986, he was appointed Neurosurgeon-in-Chief at the Hospital for Sick Children (*Fig. 5C*) for a term that would span 10 years. In 1998, after his retirement, the Harold J. Hoffman/Shoppers Drug Mart Chair in Pediatric Neurosurgery was established at Sick Kids.

Dr. Hoffman died in 2004 from complications related to frontal lobe atrophy. In 2006, the Hoffman family established the Harold and JoAnn Hoffman lectureship in Pediatric Neurosurgery, which is delivered annually on the occasion of the annual meeting of the American Society of Pediatric Neurosurgery.

Robin P. Humphreys

Dr. Robin Humphreys received all of his formal education in Toronto, where he graduated from the University of Toronto Faculty of Medicine in 1962. He began his internship in Toronto at St. Michael's Hospital in orthopedics but was captivated by a rotation in neurosurgery (81). After much soul searching, he made the fateful decision to change career paths and entered the neurosurgery training program at the University of Toronto. He became a Fellow of the Royal College of Surgeons in Neurosurgery in 1970 and a staff surgeon at the Hospital for Sick Children on the recommendation of the Neurosurgeon-in-Chief, Dr. E. Bruce Hendrick. Dr. Hendrick's plan for Dr. Humphreys to complete a 1-year fellowship with Dr. Donald Matson in Boston and then Mr. Kenneth Till in London, England went awry when Dr. Matson succumbed to a serious illness and Mr. Till organized his own retirement just before Dr. Humphreys' departure for his fellowship. Instead, Dr. Hendrick announced to Dr. Humphreys, "You might as well learn on the job" (55, p 100).

In the years that followed Dr. Humphreys' addition to the neurosurgical staff, the case volume accelerated exponentially (81). He initiated the Craniofacial Program at the Hospital for Sick Children along with Dr. Ian Munro and became an expert in the care of children with spina bifida and vascular malformations. He established a structured teaching program to help residents and fellows learn the nuances of pediatric neurosurgery. He continues to personally meet with the fellows and residents in monthly teaching sessions as an Emeritus Professor.

Dr. Humphreys was president of the American Society of Pediatric Neurosurgery in 1992 and 1993 and the International Society for Pediatric Neurosurgery from 1993 to 1994. He has been on the editorial boards for *Pediatric Neurosurgery* and **NEUROSURGERY**. He was awarded the Donald Matson Lectureship by the American Association of Neurological Surgeons/Congress of Neurological Surgeons Section on Pediatric Neurosurgery in 2003 and the Hospital for Sick Children Foundation Claus Wirsig Humanitarian Award in 2003 (79). He was Neurosurgeon-in-Chief at the Hospital for Sick Children from 1996 to 2003 and the Chairholder of the Harold J. Hoffman/Shoppers Drug Mart chair in pediatric neurosurgery at that time (*Fig. 5D*).

Dr. Humphreys retired after 33 years of devoted service to the Pediatric Neurosurgery Program at the Hospital for Sick Children, completing a glorious chapter in the history of pediatric neurosurgery at the Hospital for Sick Children that began with the "3 Hs" (81). Working with Dr. Hoffman, Dr. Humphreys helped to write the next chapter in the history of pediatric neurosurgery with the recruitment of Drs. James Drake and James Rutka (the "2 Jims") to the service (*Fig. 6*) (81).

It is almost impossible to describe the impact of the dynasty created at the Hospital for Sick Children by the union of the first three full-time pediatric neurosurgeons (82).



FIGURE 6. *Historic photograph capturing "3 Hs" and "2 Jims." From left to right: Dr. James Rutka, Dr. Harold Hoffman, Dr. James Drake, Dr. Bruce Hendrick, and Dr. Robin Humphreys.*

The moniker, the "3 Hs" (82), short for Drs. Hendrick, Hoffman, and Humphreys, was actually coined by Mr. Kenneth Till (RP Humphreys, personal communication, September 7, 2006). Collectively, they coauthored some of the most important works published on pediatric neurosurgery topics in the literature *(Table 1*). Their worldwide visibility in pediatric neurosurgery placed the Hospital for Sick Children on the map for being one of the busiest services in the world. Accordingly, during their administration, the Sick Kids service in neurosurgery attracted fellows and faculty from all corners of the globe, a practice that has continued to this day (*Appendix 1*).

THE NEXT GENERATION: A FOCUS ON THE SURGEON-SCIENTIST

James M. Drake

Dr. James Drake (*Fig. 6*) attended Princeton University from 1969 to 1974, receiving a degree in aerospace and mechanical engineering. He then received his medical education at the Royal College of Surgeons in Ireland, graduating in 1979. In 1982, Dr. Drake entered the Neurosurgery Training Program at the University of Toronto. He received his Master's degree in magnetic resonance imaging of hydrocephalus in 1987 at the University of Toronto. In the same year, he became a Fellow of the Royal College of Surgeons of Canada. After a Clinical Fellowship in Pediatric Neurosurgery at l'Hôpital Necker-Enfants Malades in Paris, Dr. Drake joined the neurosurgical staff at the Hospital for Sick Children in 1988. He promptly established the Hydrocephalus Research Laboratory and began working on the application of robotics to the resection of pediatric brain tumors (10). He is an author of more than 150 peer-reviewed publications, including the definitive textbook on cerebrospinal fluid shunts, *The Shunt Book,* which he coauthored with Professor Christian Sainte-Rose of Paris. He is currently a Full Professor in the Department of Surgery and succeeded Dr. Robin Humphreys as the Division's fifth Neurosurgeon-in-Chief on Dr. Humphreys' retirement in 2003. He is the current Harold J. Hoffman/Shopper's Drug Mart Chair in Pediatric Neurosurgery. His clinical practice focuses on hydrocephalus, spasticity, neuroendoscopic procedures, the pediatric spine, and peripheral nerve surgery. His research is devoted to engineering a better cerebrospinal fluid shunt design system and mathematical models of hydrocephalus.

James T. Rutka

Dr. James Rutka (*Fig. 6*) was educated at Princeton University from 1975 to 1977 and Queen's University Medical School from 1977 to 1981. He entered the Neurosurgery Training Program at the University of Toronto in 1982. He undertook basic science research studies in Experimental Neuro-oncology at the Brain Tumor Research Center at the University of California, San Francisco, from 1984 to 1987 where he also received his Ph.D. in Experimental Pathology before returning to Toronto to complete his neurosurgery residency. He became a Fellow of the Royal College of Surgeons in Canada in 1989.

After a Clinical-Research Fellowship in Japan as a Kenichiro Sugita Fellow, Dr. Rutka joined the Neurosurgical Staff at the Hospital for Sick Children in 1990. His clinical practice is devoted to the care of children with epilepsy and brain tumors. In 1997, he helped to establish the first brain tumor research center in Canada with the generous gift of business magnate, Arthur Labatt, and his wife, Sonia. He is currently codirector of the Labatt Brain Tumor Research Center (www.sickkids.ca/BTRC/), which houses eight principal investigators and more than 50 research associates, graduate students, and fellows. Dr. Rutka became Chairman of the Division of Neurosurgery at the University of Toronto in 1999, a position he will hold for 10 years.

Peter B. Dirks

Dr. Peter Dirks (*Fig. 7A*) is a 1989 graduate of Queen's University Medical School. He entered the Neurosurgery Training Program at the University of Toronto in 1990. During his neurosurgical training, he undertook research studies as a graduate student in experimental neuro-oncology in Dr. Rutka's laboratory. He received a Ph.D. in Cellular and Molecular Pathology in 1998. Dr. Dirks became a Fellow of the Royal College of Physicians and Surgeons of Canada in 1998.

After a clinical fellowship in pediatric neurosurgery at l'Hôpital Necker-Enfants Malades in Paris in 1998, he began his neurosurgical staff appointment at the Hospital for Sick Children in 1998. He is currently an associate professor in the Department of Surgery at the University of Toronto.

His clinical practice is devoted to children with vascular, head injuries, spinal dysraphism, and neoplastic diseases of the nervous system. His research laboratory is within the Arthur and Sonia Labatt Brain Tumor Research Center at the Hospital for Sick Children where he is currently conducting

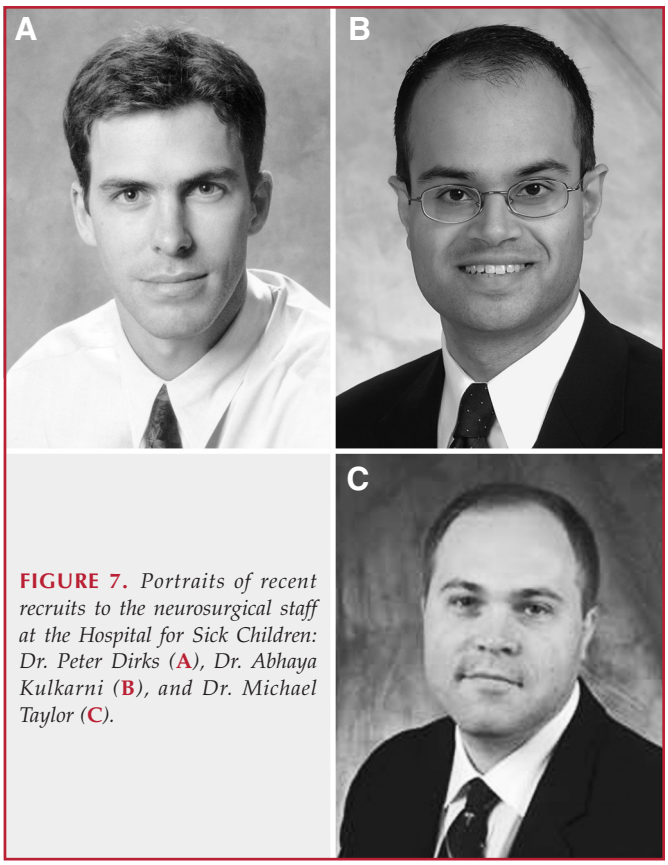


FIGURE 7. *Portraits of recent recruits to the neurosurgical staff at the Hospital for Sick Children: Dr. Peter Dirks (**A**), Dr. Abhaya Kulkarni (**B**), and Dr. Michael Taylor (**C**).*

research in stem cells and cell cycle pathways as a principal investigator (7, 8, 85, 86).

Abhaya V. Kulkarni

Dr. Abhaya Kulkarni (*Fig. 7B*) completed his residency in the Neurosurgery Training Program at the University of Toronto in 2002. During his training, Dr. Kulkarni published several peer-reviewed articles and was awarded numerous citations, including the Congress of Neurological Surgeons Resident Award and the McKenzie Prize in Clinical Neurosciences. He received specialized training as a clinical fellow at l'Hôpital Necker-Enfants Malades in pediatric neurosurgery. In Paris, Dr. Kulkarni completed and published a widely quoted study on the conservative management of children with spinal lipomas (64).

Dr. Kulkarni joined the neurosurgical staff at the Hospital for Sick Children in 2003. He successfully completed his graduate studies and has received a Ph.D. in Clinical Epidemiology from McMaster University. Dr. Kulkarni brings his expertise on evidence-based medicine and clinical epidemiology to the Hospital for Sick Children, where he continues his role in organizing and conducting clinical trials in neurosurgery. He also holds an appointment in the Hospital for Sick Children Research Institute in Population Health Sciences.

Michael D. Taylor

Dr. Michael Taylor (*Fig. 7C*) is a 2003 graduate of the University of Toronto Neurosurgery Training Program. He received his Ph.D. in Dr. Rutka's laboratory in the Labatt Brain Tumor Research Centre in Laboratory Medicine and Pathobiology in 2002. He completed a clinical fellowship in pediatric neurosurgery at Le Bonheur Hospital for Children in Memphis, Tennessee, under the auspices of Drs. Robert Sanford and Frederick Boop. That same year, he spent time as a postdoctoral fellow in the Department of Developmental Neurobiology at St. Jude's Children's Research Hospital.

Dr. Taylor joined the staff at the Hospital for Sick Children in 2004 as a faculty neurosurgeon in the Department of Surgery and as a principal investigator in the Labatt Brain Tumor Research Center where he is studying the molecular genetic underpinnings of medulloblastoma and ependymoma.

The Division of Neurosurgery at the Hospital for Sick Children today receives approximately $2 million annually of peer-reviewed funding from various sources, including the National Cancer Institute of Canada, the Canadian Institutes of Health Research, the Ontario Cancer Research Network, the Pediatric Brain Tumor Foundation, and the Natural Sciences and Engineering Research Council of Canada (JT Rutka, personal communication, March 10, 2007).

THE TRAINEES: FROM FAR AND WIDE

In April 1988, more than 100 past residents and fellows gathered in Toronto at the King Edward Hotel for a Hospital for Sick Children neurosurgical reunion dinner (28). The men and women who have rotated through the Hospital for Sick Children as pediatric neurosurgical residents or fellows have brought their skills and knowledge to the Hospital. They have shared this knowledge with the medical students, other residents and fellows, and the staff. Their talents have been noted in the emergency room, operating room, intensive care unit, outpatient clinics, and inpatient wards. They have all added to the fabric of the institution by their interactions with the neurosurgical staff. A review of the locations of the trainees from Sick Kids reveals their positions in five provinces in Canada, 28 states in the United States, and 16 other countries around the world, including Argentina, Australia, Brazil, Great Britain, Ireland, Germany, Israel, Japan, Thailand, Taiwan, South Korea, the Philippines, Saudi Arabia, France, Italy, and South Africa.

In the Neurosurgery Office at Sick Kids, the portraits of former fellows and trainees are proudly displayed. The purpose of the fellowship program is to train, foster, and nurture tomorrow's leadership of pediatric neurosurgery. Some of the leaders of modern-day pediatric neurosurgery who have graced Sick Kids as fellows and residents are listed in *Appendices 1* and *2*.

CONCLUSION

Nine years after Dr. Kenneth G. McKenzie established neurosurgery in Canada at the Toronto General Hospital, Dr.

William S. Keith was appointed to the Hospital for Sick Children in 1933. He was the first neurosurgeon in the Hospital's 58-year history. Although his appointment was only part-time, he nevertheless began a tradition of pediatric neurosurgery that has flourished for seven decades at the Hospital for Sick Children in Toronto.

The future goals of the Division of Neurosurgery at the Hospital for Sick Children in Toronto are to maintain its position as an outstanding unit for the care of children with neurosurgical disorders and to continue research in the fields of hydrocephalus, congenital malformations, brain tumors, clinical epidemiology, and clinical trials design. It is expected that the neurosurgical service will continue to train the best and brightest for future careers in pediatric neurosurgery. It is hoped that the mandate for dedication to the academic mission will be maintained through the establishment of future endowed chairs to commemorate and honor the founding fathers who gave rise to the neurosurgery service. The final and perhaps most important mandate of the Division is to continue providing leading-edge clinical care to the youngest of patients and education for the next generation of pediatric neurosurgeons.

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APPENDIX 1. Chief fellows and visiting fellows trained at the Hospital for Sick Children in pediatric neurosurgery

Term of service	Fellows
July 1, 1969–June 30, 1970	Dr. J. Gary Ashby
July 1–December 15, 1970	Dr. Robin P. Humphreys
July 1, 1970–June 30, 1971	Dr. Miguel S. Garrote
January 1–December 31, 1972	Dr. Andrew J. Joaquin
January 1–June 30, 1973	Dr. John M. Crouch
July 1–December 31, 1976	Dr. Renn O. Holness
January 1–March 30, 1977	Dr. Edward Garrido
January 1–June 30, 1977	Dr. Michael Feely
July 1–December 31, 1978	Dr. Dachling Pang
July 1–December 31, 1979	Dr. Warren S. Ishida
April 1–December 31, 1980	Dr. Toru Shirouzu
January 1, 1980–February 28, 1981	Dr. Tai-Tong Wong
January 1–March 31, 1981	Dr. Toru Shirouzu
January 1–December 31, 1981	Dr. Diogenes A. Harris
April 1, 1981–March 31, 1982	Dr. Tae Sung Park
August 1, 1981–August 31, 1982	Dr. Shigetake Anegawa
January 1–December 31, 1982	Dr. Masafumi Yoshida
January 15–June 30, 1983	Dr. Akira Ishibashi
August 9, 1982–December 31, 1983	Dr. Chopeow Taecholarn
January 1–June 30, 1984	Dr. David S. Knierim
July 1–December 31, 1984	Dr. Beverly C. Walters
September 25–December 31, 1984	Dr. Shigeru Nemoto
October 1984–September 30, 1985	Dr. Joong Uhn Choi
January 1–June 30, 1985	Dr. Ann R. Stroink
July 1, 1985–June 30, 1986	Dr. Robert W. Griebel
January 1–June 30, 1986	Dr. Mitchel S. Berger
January 1–June 30, 1986	Dr. John Johnson
July 1–December 31, 1986	Dr. Corey Raffel
January 1–July 30, 1987	Dr. Robert J. Backer
January 1–March 31, 1987	Dr. Denis Ladoucer
January 1–July 30, 1987	Dr. Padraic O'Neill
July 1, 1987–June 30, 1988	Dr. Liliana Goumnerova
September 1, 1987–August 31, 1988	Dr. Akio Asai
July 1–December 31, 1988	Dr. Tai Ngar Lui
October 1–December 31, 1988	Dr. Carolyn Wright
July 1, 1988–June 30, 1989	Dr. Semion Rochkind
July 1, 1988–June 30, 1989	Dr. Richard E. George
July 1, 1988–June 30, 1989	Dr. Benicio Oton de Lima
April 1, 1988–December 31, 1989	Dr. Hiroshi Otsubo
January 23–July 31, 1989	Dr. Judith A. Murovic
July 1–December 31, 1989	Dr. Dong Won Kim
September 11–October 11, 1989	Dr. Anita North
July 1, 1988–June 30, 1990	Dr. Marcia da Silva
July 1, 1989–June 30, 1990	Dr. Antonio R. Mock
July 1, 1989–June 30, 1990	Dr. Samuel Keith St. Clair
January 1–June 30, 1990	Dr. Hiroshi Otsubo
January 1–June 30, 1990	Dr. Donald S. Soloniuk
July 1, 1989–June 30, 1991	Dr. Shalom D. Michowiz
July 1, 1990–June 30, 1991	Dr. Lewis W. Harris
July 1, 1990–June 30, 1991	Dr. Rosemaria Gennuso
July 1–September 30, 1991	Dr. Ian F. Pollock
July 1–October 31, 1991	Dr. Premkumar Pillay

APPENDIX 1. *(continued)*

Term of service	Fellows
July 1, 1991–June 30, 1992	Dr. John R.W. Kestle
May 1–August 15, 1992	Dr. Paul D. Chumas
July 1, 1991–June 30, 1993	Dr. Abraham Cohen
July 1, 1992–June 30, 1993	Dr. John A. Duncan III
September 1, 1992–June 30, 1993	Dr. Marcia da Silva
September 1, 1992–October 31, 1993	Dr. Mehdi Abdolahzadeh
July 1, 1993–June 30, 1994	Dr. Andre Turmel
July 1, 1993–June 30, 1994	Dr. Daniela Stritt
July 1, 1993–October 31, 1994	Dr. Hanoch Elran
July 1, 1994–June 30, 1995	Dr. Mark Souweidane
November 23, 1994–August 15, 1995	Dr. Young Shin Ra
July 1, 1995–February 15, 1996	Dr. Maria Varela-Stavrinou
July 1, 1995–June 30, 1997	Dr. Essam Al-Shail
October 15, 1995–June 30, 1997	Dr. Kahil Salame
July 1, 1996–June 30, 1997	Dr. John Myseros
February 1–May 31, 1997	Dr. Franck-Emmauel Roux
May 1, 1997–June 30, 1998	Dr. Awni Musharbash
July 1, 1997–June 30, 1998	Dr. Nalin Gupta
September 1, 1997–February 28, 1998	Dr. Anantha Kishan
July 1, 1998–June 30, 1999	Dr. Mark Iantosca
July 1, 1998–December 18, 1999	Dr. Lynn Myles
February 1, 1999–January 31, 2000	Dr. Teresa K. Withers
July 1, 1999–June 30, 2000	Dr. Jeffrey P. Blount
July 1, 1999–April 3, 2000	Dr. Dwight Webster
February 1, 2000–January 31, 2001	Dr. Patrick Lo
July 1, 2000–June 30, 2001	Dr. Walter Hader
July 1, 2000–June 30, 2001	Dr. Hussam Kutub
January 1- June 30, 2001	Dr. Wilson Ho
February 1–December 31, 2001	Dr. Torben Hansen
July l–December 31, 2001	Dr. Carl Bruce
July 1, 2001–June 30, 2002	Dr. Stephen Santorenos
July l, 2001–June 30, 2002	Dr. Patrick McDonald
January 1–June 30, 2002	Dr. Mamoud Rashidi
November 1, 2001–February 28, 2003	Dr. Hisashi Hatano
July 1, 2002–June 30, 2003	Dr. William Whitehead
July 1, 2002–June 30, 2003	Dr. Michael Carter
July 1, 2002–June 30, 2003	Dr. Aurelia Peraud
July 1, 2002–June 30, 2003	Dr. Raafat Yahya
July 1, 2003–June 30, 2004	Dr. John Jane, Jr.
March 1, 2003–December 31, 2004	Dr. Takashi Araki
July 1, 2003–June 30, 2004	Dr. Jayaratnam Jayamohan
September 1, 2003–September 30, 2004	Dr. Francesco Sala
June 1–November 30, 2004	Dr. Amit Ray
January 1–June 30, 2005	Dr. Takashi Araki
July 1, 2004–June 30, 2005	Dr. Sami Khoshyomn
July 1, 2004–June 30, 2006	Dr. Mony Benifla
July 1–October 15, 2005	Dr. Neermala Dasi
July 1, 2005–June 30, 2006	Dr. Jay Riva-Cambrin
July 1, 2005–June 30, 2006	Dr. Richard Edwards
August 30, 2005–January 3, 2006	Dr. Bart Depreitere
January 1–December 30, 2006	Dr. Zulma Tovar-Spinoza
July 1, 2006–June 30, 2007	Dr. Andrew Jea
July 1, 2006–June 30, 2007	Dr. Sandrine de Ribaupierre

APPENDIX 2. Selected residents rotated through the Hospital for Sick Chldren in pediatric neurosurgery

Residency term	Residents
July 1–December 31, 1970	Dr. William Shucart
July 1–December 31, 1971	Dr. Paul Chapman
July 1, 1972–June 30, 1973	Dr. Marion L. Walker
January 1–June 30, 1975	Dr. Anthony D. Hockley
July 1–December 31, 1975	Dr. W. Jerry Oakes
July 1–December 31, 1976	Dr. Haring Nauta
July 1–December 31, 1976	Dr. Guy Sava
January 1–June 30, 1977	Dr. Kotoo Meguro
July 1–December 31, 1978	Dr. Warwick J. Peacock
January 1–June 30, 1979	Dr. Michael Besser
July 1–December 31, 1980	Dr. Bruce B. Storrs
January 1–June 30, 1981	Dr. Harold P. Smith
July 1–December 31, 1982	Dr. Patricia A. Aronin
July 1, 1982–December 31, 1983	Dr. Jonathon Punt
October 1–December 31, 1982	Dr. Kamel Muakkassa
January 1–June 30, 1984	Dr. Nasri J. S. Khoury
January 1–June 30, 1984	Dr. Bruce Tranmer
January 1–June 30, 1985	Dr. Beverly C. Walters
July 1–December 31, 1985	Dr. Kerry R. Crone
July 1–December 31, 1985	Dr. Kim H. Manwaring
January 1–June 30, 1986	Dr. Fred A. Lenz
July 1, 1986–June 30, 1987	Dr. Joseph H. Piatt
August 1–September 30, 1987	Dr. Frederick A. Boop
January 1–June 30, 1989	Dr. Douglas Kondziolka
July 1–September 30, 1989	Dr. Allan Levi
July 1–December 31, 1994	Dr. Hal Meltzer
April 1–May 31, 2000	Dr. David Sandberg

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COMMENTS

The esteemed reputation of Sick Kids is shadowed only by the personnel that have passed through her doors, most notably those who have spent their careers enriching our understanding of the field of pediatric neurosurgery. This treatise documenting the historical and contemporary era of that venerated hospital is long overdue and greatly appreciated. I have dedicated my career to caring for children with ailments of the central nervous system, and seldom does a day go by when I do not incorporate some "trick of the trade" inherited from Drs. Hoffman, Humphreys, Drake, or Rutka. Although the technical merit is the most immediate benefit acquired during my year at Sick Kids, I must recount two anecdotes that furthers the characterization of two individuals who manned the helm at various times.

The first of these accounts took place 1 month after my arrival in Toronto. I was invited to dine with Dr. Bruce Hendrick, a person I knew by name only, but nevertheless respected. His purpose was simple, to introduce himself, recount the history of Sick Kids, and engender a philosophical perspective on the profession that I chose to pursue. Before departing that afternoon, he generously presented a token of remembrance. He joyfully handed me a sculptured stone facsimile of the Country's national bird, a loon, which continues to rest on a bookcase in my office. Generous, thoughtful, and nostalgic were my first and lasting impressions of Dr. Hendrick.

The second narrative describes an event that left me with an eternal impression of the personal nature of Harold J. Hoffman. After 10 or so months that elapsed in my year-long adventure at Sick Kids, I was kindly invited to the home of Robin Humphreys for a backyard barbecue. I had shared many occasions with Dr. Hoffman and was well aware of the deserved respect that he held in the hallways and operating room theaters of the Hospital. On this wonderful spring evening, while listening to one of Dr. Humprey's expertly presented tales in his backyard, Dr. Hoffman entered through the front door, thus requiring a long walk through the living room and across the back porch. It was not his normal gallant manner of walking that immediately furthered my admiration for him; instead it was the fact that he was carrying his wife, JoAnn, in his arms because of her incapacity stemming from a disabling ailment. From that time forward, I was never to listen or recount a story of Dr. Hoffman without interjecting some element of his enormous humanity and caring.

I will bookmark this article with many of my other favorites that define the practice and character of pediatric neurosurgery. This history offers the reader who has never visited Sick Kids a great insight into a remarkable place and provides the person familiar with the hospital a stimulus for sentimental memories. My many thanks to Jea et al. for their splendid contribution.

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I can write this publication comment on a purely objective basis and without a single prejudice. I unabashedly admit that I have never trained at The Hospital of Sick Children in Toronto, nor have I had the opportunity to visit this renowned institution. However, its influence has made a significant impact on me. I dare say the neurosurgical advances which have emanated from Sick Kids have reached nearly every neurosurgeon who has operated upon a child. So what is the magic of this place? It appears it is a very simple concoction of the following principals: altruism, fortitude, dedication, talent, wise resource management, effective regionalization, internationalism, and formidable but benevolent leadership. More specifically, a group of altruistic women in Toronto had the vision and fortitude to set up a Children's Hospital to serve the children of Canada at a time when none existed. They found ambitious, talented faculty to move their respective practices and dedicate their lives to this vision. The effective political and medical leaders wisely decided to regionalize pediatric care and preserve their precious resources, thus creating a unique regional referral system that attracted the brightest and most gifted surgeons to serve an enormous population of children in need. This atmosphere made the chances for discovery and innovation that much more likely. International colleagues and ideas were imported and generously welcomed to ensure that there was a steady export of ideas, good will, and Sick Kids' selfless culture. The institution retained the native, creative, and colorful surgeons by wisely providing them with cutting edge resources and robust leadership that was renewed from a deep pool of rising stars every 10 years. The authors are to be congratulated for recounting a compelling model of neurosurgical success that has benefited patients worldwide, and is worthy of emulation.

Richard G. Ellenbogen
Seattle, Washington

Einstein said, "If I have seen a little farther than others it is because I have stood on the shoulders of giants." Pediatric neurosurgery is a recent enough specialty that many of us now in practice have had the privilege of knowing and learning from the founding giants of our field. Bruce Hendricks, Harold Hoffman, and Robin Humphreys of the "3 H" era are among these. Although they have moved from the scene, they live on in what they have passed on to others. The great medical institutions such as Toronto Sick Kids have encouraged and fostered the creativity of such individuals.

Leslie N. Sutton
Philadelphia, Pennsylvania

Writing the history of the Department of Pediatric Neurosurgery at the Sick Children's Hospital in Toronto is somehow writing the history of pediatric neurosurgery. After the pioneering years of Dr. Keith, the impressive influence that Bruce Hendricks had over his generation of colleagues is still remembered today. I first met Harold Hoffman at the International Society for Pediatric Neurosurgery meeting in Rome in 1988, during my second year of residency. It was my first international meeting of neurosurgery, and I remained fascinated by the continuous, vivid, and endless discussions between Drs. Hoffman, Epstein, Schut, Hirsch, and Lapras during the sessions. It was impossible not to note Harold Hoffman, always in the first or second row, apparently not paying too much attention to the speaker but ready to stare at him and let the eyeglass fall whenever he heard something he disagreed with, filling his comments with humor and intelligence. He was part of a generation of neurosurgeons who had to struggle to find a place and identity for pediatric neurosurgery in the larger and more powerful world of general neurosurgery, and he did this very well with personality and intelligence, and even fighting when necessary.

The staff at Sick Kids is a tremendous blend of gentlemen, scientists, and surgeons, each one well aware of the high reputation of the institution and of the scientific group they represent. They are all committed to excellence in order to produce scientific work that will be considered a scientific standard in that specific field around the world. The Shunt Design Trial, designed and completed in the 1990s was a very important turning point for both Sick Kids and the whole community of pediatric neurosurgeons and was a wonderful and enriching experience for all participants. That work has set the standard for much future clinical research, not only in the field of pediatric hydrocephalus but for all of pediatric neurosurgery.

The long tradition and the recent work on hydrocephalus, epilepsy surgery, brain tumor biology, and outcome evaluation are there to witness the commitment of a very productive and dedicated group. For all those who had the pleasure of meeting the staff of Sick Kids, the quality appreciated most remains their ease and kindness in any circumstance, as well as the value they place on friendship and personal relationships, which they keep preciously separated from the scientific and academic process. This article reflects this style very nicely and is certainly very useful for future generations as an example of how an academic, surgical, and scientific group should be.

Giuseppe Cinalli
Naples, Italy

INTERNATIONAL TRAVELING FELLOWSHIP IN PEDIATRIC NEUROSURGERY

The Joint Pediatric Neurosurgery Section of the ***American Association of Neurological Surgeons*** and the ***Congress of Neurological Surgeons*** has established an international traveling fellowship for neurosurgeons who at the time of their application are either training in a residency program outside the United States and Canada, or who have completed residency training outside the United States and Canada within the past five years. The fellowship will cover the traveling and living expenses for a three month period to be spent observing the activities of an established Pediatric Neurosurgical service in the United States or Canada. The fellowship can be spent in any activity on such a service which broadens the individual's exposure to Pediatric Neurosurgery, and can include observation at a clinical or research center, or any other relevant activity which the committee finds acceptable. One fellowship per year will be awarded on the basis of the recommendation of a committee of the Pediatric Section. The maximum fellowship stipend is $5000.

The application must include:

1) A statement defining the purpose of the proposed fellowship and an estimate of expenses for the period of the fellowship.

2) A letter of recommendation from the applicant's current Neurosurgical program director.

3) A letter of acceptance from the institution where the applicant will seek the fellowship confirming the description of the fellow's activities during the period of the award.

4) The applicant's current Curriculum Vitae.

The completed application should be sent to:

R. Michael Scott, M.D.
Department of Neurosurgery, The Children's Hospital
300 Longwood Avenue, Bader 319
Boston, Massachusetts 02115

or via e-mail to:
michael.scott@childrens.harvard.edu

THE ABSOLUTE DEADLINE FOR APPLICATION SUBMISSION IS NOVEMBER 15, 2007

The Madness of Dionysus: A Neurosurgical Perspective on Friedrich Nietzsche

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OBJECTIVE: To examine the possibility that an intracranial mass may have been the etiology of the headaches and neurological findings of the philosopher Friedrich Nietzsche (1844–1900) and the cause of his ultimate mental collapse in 1889.

METHODS: The authors conducted a comprehensive English and German language literature search on the topic of Nietzsche's health and illness, examining Nietzsche's own writings, medical notes from his physicians, contemporary medical literature, biographical texts, and past attempts at pathography. We also examined archived portraits and engravings of the philosopher from 1864 onward. An English language search in the modern literature on the topic of psychiatric presentations of intracranial mass lesions was also conducted.

RESULTS: From his late 20s onward, Nietzsche experienced severe, generally right-sided headaches. He concurrently suffered a progressive loss of vision in his right eye and developed cranial nerve findings that were documented on neurological examinations in addition to a disconjugate gaze evident in photographs. His neurological findings are consistent with a right-sided frontotemporal mass. In 1889, Nietzsche also developed a new-onset mania which was followed by a dense abulia, also consistent with a large frontal tumor.

CONCLUSION: A close examination of Nietzsche's symptomatic progression and neurological signs reveals a clinical course consistent with a large, slow growing, right-sided cranial base lesion, such as a medial sphenoid wing meningioma. Aspects of his presentation seem to directly contradict the diagnosis of syphilis, which has been the standard explanation of Nietzsche's madness. The meningioma hypothesis is difficult, though not impossible, to prove; imaging studies of Nietzsche's remains could reveal the bony sequelae of such a lesion.

KEY WORDS: Abulia, Mania, Meningioma, Nietzsche, Pathography, Syphilis

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A casual stroll through the lunatic asylum shows that faith does not prove anything.

—Friedrich Nietzsche, *The Antichrist*, sec. 51

In the writings of the famous German philosopher Friedrich Nietzsche (1844–1900), one sees the marks of ill health that plagued him throughout his adult life. Indeed, by his own account, the entire body of his later work was in no small part a product of his debilitating afflictions. Severe headaches, protracted vomiting, and visual disturbances had a marked effect on the course of his philosophy and his life. His central principle of *amor fati*, embracing the totality of one's fate, including suffering, and his attacks upon Christianity as a manifestation of *resentiment*, an ideological symptom of physical and psychological weakness, were both conceived primarily from his attempts to cope with, understand, and overcome his own painful illness (12). Ultimately, Nietzsche utterly succumbed to progressive disease. Insane at the age of 44, the philosopher who proclaimed "Above all, die at the right time!" (11, p 71), spent the last 10 years of his life as an invalid. However, more than a century after his death, the etiology of his illness remains poorly understood.

Nietzsche's Development and Deterioration

Friedrich Wilhelm Nietzsche (*Fig. 1*) was born in a small village of Prussian Saxony in 1844. The son of a Lutheran minister, he displayed precocious aptitudes for letters and music. He studied theology and classical language at Bonn and later at Leipzig, earning academic distinction and the respect of his professors. He accepted an offer of professorship in classical philology at the University of Basel when he was only

24 years old (9). In the ensuing 10 years, he was plagued by progressively severe headaches, typically frontal, generally on the right side, and accompanied by visual disturbances, eye pain, nausea, and vomiting (6). Although Nietzsche had always been myopic (6, 17), during his tenure at Basel, his right eye underwent a progressive loss of visual acuity. By the age of 30, he was essentially blind in his right eye (3, 16). The precise etiology of this asymmetric visual loss is unknown, although one ophthalmologist in 1877 attributed it to a "retinal exudate" (3), which would be more suggestive of an intraocular inflammatory process.



FIGURE 1. *Friedrich Wilhelm Nietzsche (1844–1900).*

These afflictions forced Nietzsche to take at least two extended sick leaves until he resigned his post and left Basel in 1879, 10 years after he was made the youngest professor in the history of the institution. He would return 10 years later, escorted by his closest friends, to be committed to a lunatic asylum. During those intervening years, Nietzsche remained productive, despite the headaches that continued to interrupt his work. His headaches were episodic and typically rendered him incapacitated for periods of 4 to 9 days (6). In 1876, he was diagnosed with neuralgia after he expressed to a physician that he was worried he had a brain tumor (6). Even after his mental breakdown in early 1889, records from his doctors note that he "often complains of supra-orbital neuralgia on the right side" (15, p 193).

Examination of Nietzsche's work (*Table 1*) suggests a progression of psychiatric symptoms superimposed upon his physical suffering. This has led some authors to assert that Nietzsche's ultimate breakdown was purely the result of psychiatric disease, the intimations of which are found throughout his life and work (17). His first book, *The Birth of Tragedy from the Spirit of Music* (1872), is a rich yet restrained dialectic. Nietzsche's middle works, typified in his *Thus Spoke Zarathustra* (1884), have an exuberant and overwhelming style, yet can hardly be considered evidence of psychopathology. By the time he wrote his autobiography, *Ecce Homo* (1888), however, his voice had become manifestly grandiose. Coherent and deeply insightful, this book nonetheless bore the chapter titles "Why I am So Wise," "Why I am So Clever," "Why I Write Such Good Books," and, lastly, "Why I am a Destiny." In it, he called his *Thus Spoke Zarathustra* "The greatest gift that could ever have been given to mankind" (12, p 675). *Ecce Homo* was finished in 1888, a year which saw Nietzsche complete four other major works in a furious streak of creative activity. *Twilight of the Idols* was written in a mere 10 days. Another, *The Antichrist*, was the first in a planned series of four volumes that was to set forth nothing less than the "revaluation of all values."

The philosophical worth of these works is beyond question (9). However, between December 1888 and January 1889, while still revising the proof of his autobiography, Nietzsche became overtly manic. His friend Jacob Burkhardt received a letter dated January 5, 1889, which convinced him at once that his friend was no longer sane (15). In it, Nietzsche says that he would rather have remained a Basel professor than become God, but his ego was not so large. One of the five postscripts to that letter reads: "I go everywhere in my student's jacket, and here and there slap people on the back and ask 'Are we content? I am the god who has created this farce!'" (13, p 348)

At the same time, Nietzsche's old friend and colleague Franz Overbeck received a postcard signed "Dionysus," in which Nietzsche claimed that he was "just having all anti-Semites shot"(13, p 347). He also posted a letter to King Umberto of Italy, whom he addressed as his son, announcing that he would arrive in Rome on Tuesday and looked forward to his audience with the Pope (9). Nietzsche never regained his sanity.

The Nature of Nietzsche's Pathology

The precise nature of Nietzsche's pathology has been inconsistently and inadequately described, despite rampant conjecture on the subject. Syphilis, schizophrenia, bipolar disorder (17), frontotemporal dementia (14), and brain tumor (7, 16) have all been proposed, but evidence tends to be only partially convincing in each case. The suggestion has even been made that Nietzsche was driven mad by the idiocy of his contemporaries (9). Nietzsche himself blamed his afflictions on listening to too much Wagner, asking, "Has not this nerve shattering music ruined my health?" (13, p 180). Wagner, meanwhile,

TABLE 1. Major works of Friedrich Nietzsche (1844–1900)

Year[a]	Work
1872	*The Birth of Tragedy from the Spirit of Music*
1873–1876	*Untimely Meditations* (Vols. I–IV)
1878	*Human, All Too Human*
1882	*The Gay Science*
1884	*Thus Spoke Zarathustra (A Book for All and None)*
1886	*Beyond Good and Evil (Prelude to a Philosophy of the Future)*
1887	*On the Genealogy of Morals*
1888	*The Case of Wagner (A Musician's Problem)*
1888	*Twilight of the Idols, or How to Philosophize with a Hammer* (published 1889)
1888	*Nietzsche Contra Wagner* (published 1889)
1888	*The Antichrist* (published 1894)
1888	*Ecce Homo (How One Becomes What One Is)* (published 1908)

[a] Works were published in the year of completion unless otherwise noted.

opined that "excessive masturbation" was at the root of Nietzsche's troubles (6, p 203).

Nietzsche's own physicians agreed on the etiology of some of his major symptoms. Their contemporary descriptions have persisted throughout most subsequent accounts of his life and illness. His chronic headaches, nausea, and visual disturbances were taken to be migraines. Elsewhere his dyspepsia is ascribed to his abuse of chloral hydrate, prescribed as a sleep aid (15). His progressive visual loss was considered simple myopia, although at least one account suggests that he had retinitis in his right eye (3). As for his madness and subsequent collapse, syphilis was certainly the most likely etiology of dementia in a middle-aged man in 1889 (5), and has been the standard explanation of Nietzsche's ultimate decline.

Given the severity and multitude of Nietzsche's symptoms viewed in aggregate, it is decidedly non-Oslerian to posit migraines, myopia, retinitis, and a psychiatric disorder collectively as causative in Nietzsche's case. Diagnostic confusion is perhaps hardly surprising as Nietzsche consulted with many physicians and yet prided himself on "…the insistence on not allowing myself any longer to be cared for, waited on, and *doctored*…I took *myself* in hand, I made *myself* healthy again" (12, p 680). It is, therefore, reasonable to propose that he was not entirely forthcoming with his physicians regarding the totality of his medical history.

The Syphilis Hypothesis

To explain Nietzsche's constellation of symptoms, many authors have implicated syphilis, the "Great Imitator" (5). However, Sax (16) and Schain (17) make powerful arguments that Nietzsche did not have syphilis at all, citing his protracted life of 10 years after the onset of paretic symptoms and the fact that he never developed the characteristic syphilitic tremor. Indeed, late in 1890, nearly 2 years after his mental breakdown, Nietzsche's friend and disciple Peter Gast still took delight as Nietzsche improvised on the piano at the asylum: "Oh if you had been listening! Not one wrong note! Interwoven tones of Tristan like sensitiveness…Beethoven like profundity… it beggars description. Oh, for a phonograph!" (15, p 216). Such virtuosity would be unexpected in a patient experiencing advanced neurosyphilis.

Casting further doubt on the syphilis diagnosis, the actual event of Nietzsche's presumed infection is known only through third-hand accounts at best. There is an oft-recounted tale of Nietzsche's visit to a brothel in Cologne in 1865, which was romanticized by Thomas Mann in *Dr. Faustus*; however, this is not taken seriously even by authors who maintain that Nietzsche did indeed have syphilis (5, p 185). Nietzsche himself wrote that he was put off by those "apparitions in tinsel and gauze," (6, p 64) and on the evening in question, he confined himself to playing on the piano in the brothel's parlor. Interestingly, the psychiatrist Carl Jung (1875–1961) had a considerable role in popularizing the notion that Nietzsche had syphilis (5, p 186). His chief evidence for this, however, was based on rumors that Nietzsche had been infected with an unspecified venereal disease in 1867 and on a recurring dream of Nietzsche's involving a toad (8, p 193). Jung interpreted Nietzsche's toad dream as evidence for the subconscious apprehension that he had been infected with syphilis. Jung also hypothesized that Nietzsche was actually infected at a homosexual brothel, although his evidence for this is scarcely more compelling (5, p 189). Even assuming that Nietzsche was infected during his college years, this would mean he suffered a 23-year latency period during which he was often ill, followed by a 10-year survival after the onset of fulminant neurological symptoms. Although not unheard of, this would place Nietzsche at the extreme of longevity for cases of tertiary syphilis (16).

Potential Evidence for an Intracranial Mass Lesion

As early as 1926, the suggestion was made that Nietzsche's symptoms could have been caused by a brain tumor (7, p 151). Sax (16) also offers alternate explanations for Nietzsche's constellation of symptoms, including optic nerve meningioma. He bases this surmise on the picture reproduced in *Figure 2*, circa 1874, which supposedly demonstrates evi-



FIGURE 2. *Photographs and an engraving of Nietzsche revealing the development and progression of a right Cranial Nerve VI palsy between 1874 and 1882. A dilated right pupil is also discernible in the 1875 photograph.*

dence of proptosis: "Note the prominence of the right eye, which almost appears to bulge out of the head…" (16, 51). To our scrutiny, this claim is tenuous at best. The left eye, however, is clearly adducted toward the camera, and the right appears to be gazing straight ahead, suggesting a right abducens palsy. This is clearly not the case in the 1865 photograph, in which the right eye is obviously abducted past midline (*Fig. 2*). The 1875 photograph shows a dilated right pupil and disconjugate gaze, albeit more subtly. We found no photographs taken after 1874 in which Nietzsche can be seen to abduct his right eye past midline (*Fig. 2*). Although we found no evidence that Nietzsche or his physicians ever mention double vision, if the vision of his right eye had deteriorated to the extent suggested (3), one would not expect him to have noticed a horizontal diplopia.

Nietzsche's Physical Findings

In January 1889, Nietzsche was brought to the asylum at Basel by his friends Jacob Burkhardt and Franz Overbeck after they received disturbing letters posted from Turin. Upon arrival there, he was frankly manic, complaining of the bad weather and promising that "for you good people, I shall prepare the loveliest weather tomorrow" (15, p 170). He was coherent enough though to relate a recent history of severe headaches and nausea to his examining physician. His neurological examination was described as follows:

> Pupillary disparity, right larger than left, reaction sluggish. Convergent strabismus-acute myopia. Tongue heavily furred, no deviation, no tremor! Facial nerve almost normal; right nasolabial fold slightly contracted. Exaggerated patellar reflex; plantar reflexes normal…(15, p 170).

Along with the strabismus, right Cranial Nerve III palsy and hyper-reflexia, the exclamation point after "no tremor" is notable, as the presence of tremor would be an expected finding in tertiary syphilis (5, 16).

Nietzsche remained at Basel for 1 week before his mother requested that he be moved closer to her home in Germany. Nietzsche was transferred to the Psychiatric Clinic at the University of Jena, then under the direction of noted neuropsychiatrist Otto Binswanger (1852–1929) (*Fig. 3*). A description of Nietzsche's arrival there indicates that, "Looking up at the ceiling he enters the room with majestic strides and gives thanks for the 'magnificent reception'" (15, p 183). His physical examination upon arrival at Jena is documented as follows:



FIGURE 3. *Otto Binswanger (1852–1929), Director of the Jena Asylum. He described encephalitis subcorticalis chronica progressiva, later known as Binswanger's disease.*

> Pupils right wide, left rather narrower, left contracted with slight irregularity, all reactions normal on left, on right only reaction to convergence, consensual reactions only on left…symmetrical smile, tongue non tremulous with deviations to right…Romberg negative…screws left shoulder up spasmodically when walking…slight ankle clonus on left…head percussion not sensitive, facial nerves sensitive (15, p 183).

Although this examination appears to document an Argyll-Robertson pupil, it should be noted that "the Jena records were made by persons who had paralysis (i.e., syphilis) in mind all the time," and that a subsequent review of cases from Basel diagnosed as syphilis around the same time were in fact schizophrenia (15, p 236).

Whereas Dr. Binswanger's colleagues, most likely students given that Nietzsche's limited finances meant he was a second-class patient at Jena, seemed satisfied with paralytic syphilis as a diagnosis, at least one of them subsequently questioned this:

> In Jena the diagnosis had been made: 'Progressive paralysis on a syphilitic basis.'…But he did live on for almost a dozen years in a tolerable physical condition. Was he really syphilitic? I began to doubt it more and more as time went on…(18, p 225).

Nietzsche's longstanding history of lateralized headaches, associated cranial nerve palsies, and contralateral hyperreflexia are more suggestive of an intracranial mass lesion, specifically a mass in the vicinity of the optic canal, superior orbital fissure, cavernous sinus, and medial portion of the sphenoid wing. In 1889, however, the art of neurological localization was still in its infancy, and the potential significance of many of Nietzsche's presenting signs was only beginning to be appreciated. The routine use of reflex examination was only instituted in 1886 by S. Weir Mitchell in Philadelphia. Before the 1890s, neurological texts did not contain descriptions of detailed cranial nerve examinations. It was only after the first successful surgical resections of intracranial lesions in Queen's Square and Glasgow in the 1880s that discrete localization began to have any widespread importance for practicing neurologists (4).

Perhaps even more intriguingly, an enlarging intracranial mass fits Nietzsche's psychiatric progression as well. Although psychiatric manifestations of frontal tumors are more typically in the form of negative symptoms, there are well documented series of frontal and frontotemporal mass lesions presenting as mania (1, 2, 10, 19). Manic presentation has particularly been described in tumors that interrupt the frontolimbic pathways (19), and right-sided pathology has been shown to correlate with positive psychiatric symptoms. Indeed, an intracranial mass lesion, particularly in frontotemporal locations, is an

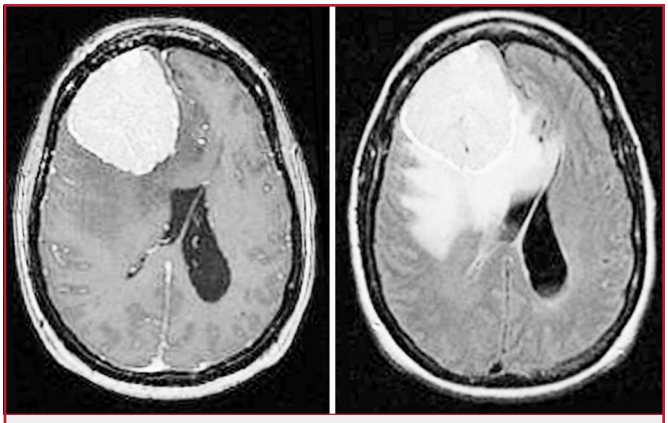


FIGURE 4. *Magnetic resonance imaging scans of a right-sided meningioma demonstrating mass effect, midline shift and bifrontal edema (**A**, post-gadolinium axial T1-weighted scan; **B**, axial fluid-attenuated inversion recovery image). Such a lesion arising in the cranial base could have been responsible for Nietzsche's cranial neuropathies, and continued expansion could have caused his psychiatric symptoms.*

important consideration on the list of differential diagnoses in the evaluation of secondary mania (1, 19).

After spending 1 year as an inpatient in Jena, Nietzsche was released to the care of his mother. He stayed at her home in the small resort city of Naumburg until her death in 1897, at which time his sister, Elisabeth, took over his care and moved him to her home in Weimar. After his release from Jena, his manic symptoms gradually gave way to a dense abulia (17). He became passive, docile, and emotionally labile. By 1893, he was mute and akinetic, although he is rumored to have spoken once subsequently. He said only "I believe I have written some good books" (6, p 349) before lapsing back into a silence that would persist until his death in 1900. His cause of death has been variously reported as stroke (5) or pneumonia (15). At the behest of his sister, no autopsy was performed.



FIGURE 5. *Nietzsche's gravesite at Röcken, Germany.*

Perspective

Although many authors have assumed that Nietzsche's neurological and psychiatric deterioration was largely or entirely the result of neurosyphilis, it is clear that the diagnosis itself is in doubt and alternative possibilities should be considered. A large, slow-growing, frontal cranial base tumor such as a meningioma (*Fig. 4*) could explain Nietzsche's documented signs and symptoms, including right-sided frontal headaches, an afferent pupillary defect and loss of visual acuity in the right eye (although some evidence suggests an intraocular etiology for this); a right Cranial Nerve III palsy, a right Cranial Nerve VI palsy (either via mass effect or direct involvement), contralateral long tract signs (left ankle clonus and patellar hyperreflexia); and particularly the "supraorbital neuralgia" noted at Jena via involvement of the right V1 at the cavernous sinus or superior orbital fissure. It is not unexpected that the localizing significance of these findings was not appreciated at the time of Nietzsche's acute presentation in 1889. A cranial base tumor could grow large enough to cause psychiatric symptoms, including mania, and could also account for the emotional lability, depression, and abulia that Nietzsche developed two years after his manic presentation and maintained until his death in 1900 (2).

This hypothesis is also unique among other attempts to explain Nietzsche's pathology in that it is conceivably testable. A meningioma large enough to account for Nietzsche's presentation and progression should have left an enduring mark upon his relic. Radiographic studies could reveal hyperostosis, erosions, or calcifications along the base of Nietzsche's cranium. His body lies in rest at his family's plot in Röcken, in the modern German state of Saxony-Anhalt between Leipzig and Weißenfels (*Fig. 5*).

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Acknowledgments

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COMMENTS

One of the first courses I took as an undergraduate was in philosophy and was taught by a professor who was totally enamored of Friedrich Nietzsche. His history, his contributions, and, of course, his demise were discussed in more detail than I thought necessary at the time; so much for youth. At the time, I found him to be a boring and somewhat monomaniacal person: brooding, manic, and thought to have suffered the ravages of syphilis. His writings covered a very wide spectrum, including critiques of philosophy, science, morality, and religion, among other topics. At the incredible young age of 24, he became a Professor of Classical Philology at the University of Basel and was clearly a giant early on. Having said that, it was most interesting to go from a young undergraduate to a practicing neurosurgeon, and then to read this article in which the authors argue that, rather than syphilis, the patient was suffering from a brain tumor. With careful research of contemporary materials, some most interesting ocular findings, and several contemporary neurological examinations, the authors have come up with some very real observations. Rather than syphilis, a manic Nietzsche clearly could have had a frontal brain tumor. The authors have done some very methodical documentation and have certainly convinced me that a frontal brain tumor, most likely a meningioma, could have caused Nietzsche's underlying disorder. I found this a most fascinating article and consider it a wonderful addition to the Legacy section.

James T. Goodrich
Bronx, New York

Nietzsche's importance in *Geistesgeschichte,* or intellectual history, is indisputable. However, some of his writings, or at least their interpretation, are much more controversial. In his work, *Beyond Good and Evil* (1886), for instance, he exhorts individuals to make decisions and lead their lives without regard for the artificially and arbitrarily created labels, "good" and "evil." Concomitantly, he assails his contemporary philosophers and their predecessors for their blind acceptance of prevailing morality and values as the basis for all intellectual thought. Not surprisingly, this work was met with widespread condemnation and ultimately led to accusations that Nietzsche was championing immorality. To this day, many contend that *Beyond Good and Evil* provided the intellectual foundation and impetus for the perceived unraveling of contemporary society's moral fabric. A closer read, however, reveals something quite to the contrary. Instead of condoning "immoral" decision making, Nietzsche implores individuals to chart out and execute well-formulated courses of action without being burdened by dogmatic adherence to artificially created concepts such as "good" or "evil." In the end, he concludes that this would lead to the creation of superior, stronger, and more independent individuals.

Nietzsche's basic concept has obvious applications in contemporary neurosurgery, science, and beyond. When individuals are not restricted by certain thought paradigms, innovation and creativity are permitted to flourish, and major breakthroughs can occur. Stated in a more colloquial way, encouraging people to "think outside the box" facilitates progress.

In this article, Owen et al. provide an interesting and potentially verifiable hypothesis of Nietzsche's medical condition just before his death. Consistent with the spirit of the writings of the subject which it describes, this well-referenced article asks the reader to at least entertain the possibility that conventional wisdom about a historical event may not be accurate. With the synthesis of their research, Owen et al. raise the possibility that an important 19th century historical figure could have succumbed to a neurological lesion. But, more importantly, the authors do the Journal's readership a service by highlighting the life of an individual who, although controversial, trumpeted the importance of expanding the frontiers of thought beyond traditional boundaries.

Bryan C. Oh
Los Angeles, California

This article presents a very intriguing story presented logically such that the authors' conclusion is not only probable but also welcome.

Lycurgus M. Davey
New Haven, Connecticut

It is appropriate that generalists in the modern field of comparative literature concern themselves with new medical hypotheses about the physical and mental traits of one of the most famous philosophers of the late 19th century. Nietzsche's story strikes many writers and artists as paradigmatic of a massive crisis afflicting European civilization, and his views, including his obsession with questions of health and decadence in society, have enormous currency (1). Nietzsche emerged on the scene as the interest of the naturalists, such as the novelist Emile Zola, in biological, psychological, and social pathologies was reaching its climax. His death occurred in the same year as the publication of Sigmund Freud's *Interpretation of Dreams.* Thus, it is hardly surprising that Freud's younger contemporary, Thomas Mann, used Nietzsche as a model for Adrian Leverkuhn, a character who exemplifies the tragic position of the creative artist in a time when his world is going mad, in his novel, *Doktor Faustus.* Mann drew on the legend and gave it a specific nonhistorical symbolic twist by having Leverkuhn contract syphilis in a Hungarian border town by adding a dangerous cross from Apollonian into Dionysian territory and into imbalance. The self-inflicted disease replicates the collapse of the "Western" Apollonian by the "Eastern" Dionysian principle, which figured importantly in Nietzsche's psychohistorical meditations.

The International Comparative Literature Association was born of discussions at the sixth congress of the International Federation for Modern Languages and Literatures at Oxford in 1954 when interest in the relation between literary history and the history of science was strong and psychology and psychoanalysis enjoyed special prominence (2). In a classical essay of 1961, a pioneer of the postwar restart of international comparative studies, Henry Remak, explained why "comparative literature" would develop as the pre-eminent cluster for interdisciplinary work. With the waning of the Freudian direction, it was virtually inevitable that "comparatists" would rekindle interest in neuroscience. But the main emphases of this attraction for literary scholars have been in the fields of "memory" and "identity," which correlate very readily with traditional literary areas of analysis: patterns of narration and portrayals of character. A good example of this scholarly orientation is Suzanne Nalbantian's *Memory in Literature: From Rousseau to Neuroscience* (4). In *I Am Charlotte Simmons* (2006), the contemporary novelist Tom Wolfe has raised awareness that neuroscience can have a bearing on our understanding of identity.

That Nietzsche remains an attractive legend around which to spin new fabulations is evident in books such as *When Nietzsche Wept* (6) by the prominent psychiatrist Irvin Yalom. Out of actual elements of Nietzsche's biography, Yalom invents a nonhistorical relationship for the philosopher with Josef Breuer, a pioneer in the founding of modern psychoanalysis, during the difficult period of Nietzsche's chaste romance with bewitching Lou Salome (approximately 1882), who herself later became a practicing psychoanalyst. Because the events of the novel predate Nietzsche's sensational breakdown in Turin during his Zarathrustra phase, Yalom can concentrate on the existential issues that Nietzsche's own philosophy and attempt at living raise. Thus, through Nietzsche's troubled symbiosis with physician and friend Breuer (as invented by Yalom), the book can strive tacitly to offer its own cultural commentary on the role of psychotherapy under the modern condition. Yalom wisely sounds a note of skepticism over the thesis of syphilis when Breuer performs a thorough, and, of course, fictitious, clinical evaluation of his patient.

The 375-page book, *Nietzsche: A Novel* (3), by the Nietzsche expert and historian David Farrell Krell surely counts as one of the more radical engagements with the philosopher. It sets in directly with the crisis in Turin and the worried intervention of Nietzsche's Basel colleagues. Krell not only follows the case chronologically in meticulous detail all the way to Nietzsche's death, but he also intermingles historical facts and pieces of Nietzsche's writings and utterances with invented reconstructions of the probable experiences, memories, feelings, and thoughts of all the parties involved, including Nietzsche himself. The daring expansive "inner" portrait increasingly seeks to imitate Nietzsche's rhapsodic or frenzied state. As Krell shuttles among minds and levels of reality, clearly influenced by Joyce's *Ulysses* and *Finnegans Wake,* he aims to impart more than a deep wonder over the existential mysteries probed by Nietzsche. The reader is induced to slip over into a Dionysiac communion with the now effectively undead incarnation of "Zarathustra." The total complex of the Nietzschean "sickness" (medical, social, and metaphysical) is elevated to vatic status.

Hardly any other thinker or artist at the dawn of high modernism has benefited from being so frequently mentioned in memoirs by contemporaries or studied biographically in retrospect as Nietzsche. The centenary of his death saw a flood of monographs and articles, among which was an important book by Richard Schain (5) that directly tackled the legend of Nietzsche's syphilis. Schain very competently draws together the main documented details of the philosopher's life from childhood up to his mental collapse in Turin and devotes much of his work to describing him as an asylum inmate and his descent into apathy. Shain also rehearses the possible type of dementia and the many controversies over diagnosis that started during Nietzsche's lifetime and have continued to the present. In a chapter titled "Nietzsche's Legacy," Schain essays an appreciation of the unparalleled appeal of his thought and life story for our age.

Clearly, Schain's book is a platform for Owen et al., a foundational synthesis of the "story" gathered one century later that includes the irritation and incitement of the syphilis thesis. Schain pleads in his penultimate chapter for a more rigorous application of advances in science in view of the unsatisfactory suggestions to date and because no postmortem was performed in 1900 despite Nietzsche's international stature. Owen et al.'s article offers a specific, concrete reply to this need, and can serve more broadly as an example of the value of neuroscientific approaches in forensic medicine and forensic anthropology. The reviewer is not qualified to pass judgment on the probable "correctness" of the meticulously argued case for an intracranial mass lesion as explanatory of Nietzsche's final breakdown and of many of his earlier symptoms and patterns of behavior. The key point here is that Owen et al. justifiably call for a new attempt to analyze the remains. This would involve a combination of physical visualization using our latest technology and application of more recently accrued knowledge in the field of neuroscience.

There is a more perplexing dimension buried in the call to reassess the reasons for Nietzsche's breakdown. If, as Owen et al. assert, neuroscience can at last reach a convincing "verdict" for a particular medical problem other than syphilis, we will still face the dilemma that bothers writers like Tom Wolfe. The dilemma is also fundamental to the legal system of the culture that Nietzsche affected: To "whom" do we attribute "identity" and concomitant "responsibility" and "where" along the line of a particular life does "mental illness" intrude in a manner that legitimately alters the status or authority of any individual (let alone possibly altering the status of the inspiration of a great philosopher!), and just how do we determine these things? It has taken many centuries to accrue standards in judicial proceedings through trial and error. Psychoanalysis deeply affected our social and legal institutions during the 20th century, sometimes for the worse, many argue. Neuroscience is now provoking, and must provoke, a renewed philosophical discussion of the nature of mental life. It is a good guess that this kind of discussion will be as intense as was that between "materialists" and more traditional thinkers in the Enlightenment. The debate requires the participation of neuroscientists of philosophical bent in order to fend off, to the extent possible, popularist oversimplifications of the knowledge base and its possible implications.

Owen et al. suggest a forensic method of testing in an instance in which we have a mountain of other evidence of varying reliability. This is a worthwhile proposal in basic terms of "pure" science; it is an exciting proposal because it can spark renewed controversy over a major figure in cultural history. Because of the forensic thrust, I see this article as being a contribution not so much to medical history, but more suited to Clio Medica. However, being from the scientific perspective, this is a contribution to the junction in interdisciplinary studies where science, literature, and philosophy meet.

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Sir Robert Boyle and His Unique Case Report on Depressed Cranial Fracture

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SIR ROBERT BOYLE is one of the foremost English scientists in history. He received his inspiration from the scientific approaches initiated by Galileo and his disciple, Torricelli. Through rigorous experimentation, Boyle established the fundamental gas laws as we know them today. Although not a physician himself, he contributed enormously to the practice of medical sciences. His voluminous observations and writings represent a landmark in the history of human thought. This article summarizes the scientific contributions of Robert Boyle, with particular emphasis on his contributions to medicine. Boyle wrote a unique case report describing in detail a patient with depressed cranial fracture who underwent successful surgery. Although on only a single case report, it provides us with a unique and rare opportunity to look at the practice of neurosurgery in the mid-17th century. Also presented in this article is Boyle's accurate description of a horse with holoprosencephaly, which was perhaps the first in history. The oft-quoted axiom in clinical medicine "First, do no harm *(primum non nocere)*" attributed to Sydenham, may be partially credited to Robert Boyle as well.

KEY WORDS: 17th-century neurosurgery, Depressed cranial fractures, Gas law, Holoprosencephaly, Iatrochemistry, *Primum non nocere*, Robert Boyle, Royal Society

Neurosurgery 61:633–640, 2007 DOI: 10.1227/01.NEU.0000280052.78028.33 www.neurosurgery-online.com

Although attempts at surgery on the brain and the spine have been made since prehistoric times, neurosurgery as a specialty is deemed to have started on a firm scientific basis in the late 19th and early 20th century with pioneers such as William MacEwen, Victor Horsley, Harvey Cushing, and Walter Dandy (4, 25). Today, few written documents which detail neurosurgical procedures attempted in earlier centuries still exist (17). The authors have located a detailed case report of a patient with depressed cranial fracture written by Sir Robert Boyle (1627–1691), considered to be a foremost scientist, who described the fundamental gas laws now named after him (23). A detailed analysis of this case report, along with a summary of Boyle's life history and accomplishments, provides a good view into medicine in general, and neurosurgery in particular, as this surgery was practiced in the mid-17th century, nearly two centuries before the establishment of neurosurgery as a formal subspecialty.

Personal Biography

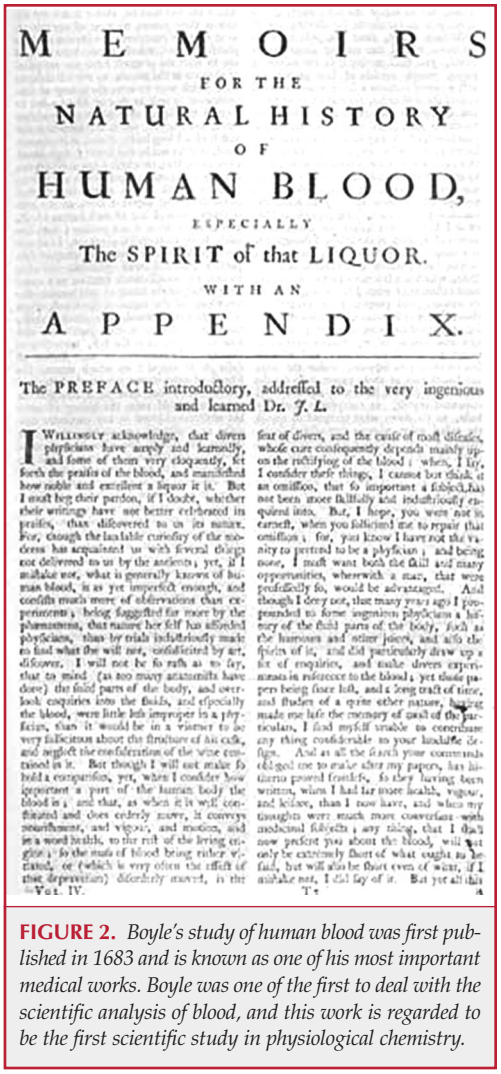
A brief review of Boyle's life history is essential in understanding his contributions to science and medicine. Robert Boyle (*Fig. 1*) was born into a Protestant family in 1627 in Ireland; he was the 14th of 15 children. His father, Richard Boyle (1566–1643), Earl of Cork, was then the wealthiest man in all of England through acquisitions of vast tracts of land and estates. This wealth would help Boyle later in life, as it allowed him to concentrate all of his efforts on intellectual pursuits and scientific experimentation without need for personal remuneration or monetary support for research.



FIGURE 1. *Portrait of Sir Robert Boyle (1627–1691).* From, *the Chemical Heritage Foundation Collections, by Johann Kerseboom, 1689. Photograph by Will Brown.*

Raised by a countryside nurse until the age of 4 years, Boyle was sent to Eton College along with his brother at the age of 8 years. At Eton, Boyle received an excellent liberal education from his headmaster, John Harrison, with whom he lived while at school. When Harrison retired, his replacement was an authoritarian who believed that memorization and recitation of Latin texts were crucial for learning; however, Boyle's pleasant days at Eton were numbered (12). The Earl of Cork, realizing that his sons were not receiving a proper education, pulled them out of Eton in 1638 and sent them on an educational tour of Europe.

In Geneva, Boyle studied French, Latin, rhetoric, religion, and mathematics under the tutelage of Isaac Marcombes. In



M E M O I R S
FOR THE
NATURAL HISTORY
OF
HUMAN BLOOD,
ESPECIALLY
The SPIRIT of that LIQUOR.
WITH AN
A P P E N D I X.

The PREFACE introductory, addressed to the very ingenious and learned Dr. J. L.

I Willingly acknowledge, that divers physicians have amply and learnedly, and some of them very eloquently, set forth the praises of the blood, and manifested how noble and excellent a liquor it is. But I must beg their pardon, if I doubt, whether their writings have not better celebrated its praises, than discovered to us its nature. For, though the laudable curiosity of the modern has acquainted us with several things not delivered to us by the ancients; yet, if I mistake not, what is generally known of human blood, is as yet imperfect enough, and consists much more of observations than experiments; being suggested far more by the phænomena, that nature her self has afforded physicians, than by trials industriously made to find what she will not, conducted by art, discover. I will not be so rash as to say, that to mind (as too many anatomists have done) the fluid parts of the body, and overlook enquiries into the fluids, and especially the blood, were little less improper in a physician, than it would be in a vintner to be very fastidious about the structure of his cask, and neglect the consideration of the wine contained in it. But though I will not make so bold a comparison, yet, when I consider how important a part of the human body the blood is; and that, as when it is well constituted and does orderly move, it conveys nourishment, and vigour, and motion, and in a word health, to the rest of the living engine; so the seats of blood being either wounded, or (which is very often the effect of that depravation) disorderly moved, in the fear of divers, and the cause of most diseases, whose cure consequently depends mainly upon the rectifying of the blood: when, I say, I consider these things, I cannot but think it an omission, that so important a subject has not been more skilfully and industriously enquired into. But, I hope, you were not in earnest, when you solicited me to repair that omission; for, you know I have not the vanity to pretend to be a physician; and being none, I must want both the skill and many opportunities, wherewith a man, that were professedly so, would be advantaged. And though I deny not, that many years ago I proceeded to some inquiries physicians a history of the fluid parts of the body, such as the humours and other juices, and also the spirits of it, and did particularly draw up a list of enquiries, and make divers experiments in reference to the blood; yet those papers being since lost, and a long train of time, and flutter of a quite other nature, having made me lose the memory of most of the particulars, I find myself unable to contribute any thing considerable to your laudable design. And as all the search your commands obliged me to make after my papers, has hitherto proved fruitless, so they having been written, when I had far more health, vigour, and leisure, than I now have, and when my thoughts were much more conversant with medicinal subjects; any thing, that I shall now perform you about the blood, will but only be extremely short of what ought to be said, but will also be short even of what, if I mistake not, I did say of it. But yet all this

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FIGURE 2. *Boyle's study of human blood was first published in 1683 and is known as one of his most important medical works. Boyle was one of the first to deal with the scientific analysis of blood, and this work is regarded to be the first scientific study in physiological chemistry.*

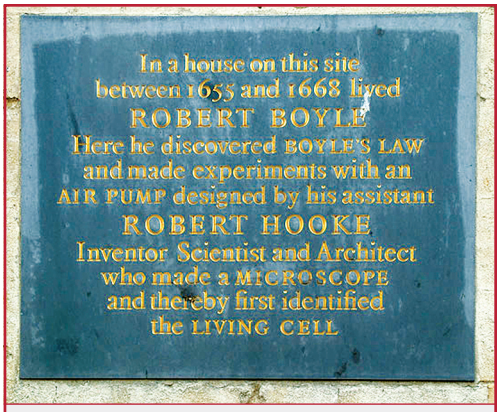


FIGURE 3. *An inscription found on the wall of University College, Oxford, in the High Street at Oxford marking the spot where Cross Hall (Boyle's residence) stood until the early 1800s. It is here that Boyle, along with Robert Hooke, devised his famous air pump.*

1641, he traveled with his Swiss tutor to Florence, Italy. At this time, he learned Italian, which later enabled him to study the works of Galileo (16). This was probably the single most influential event in directing Boyle toward science and scientific methodology. It is also possible that Boyle felt a connection with Galileo (1564–1642), with his own inherent fear of Jesuits spurred by a Protestant upbringing and Galileo's famous persecution by the Roman Catholic Church. Boyle embraced Galileo's philosophy and started to believe that most natural phenomena may be explained through mathematics and mechanics.

He eventually returned to his family estate in Stalbridge, Dorset. He began conducting anatomic dissections on living animals under the direction of William Petty (1623–1687) and Nathaniel Highmore (1613–1685), famous anatomists of the time. Concurrently, he was introduced to several scientists from the nearby Oxford University, which resulted in his frequent visits to Oxford to meet these faculty members. Among them were Thomas Willis (1621–1675, physician of the circle of Willis fame), Christopher Wren (1632–1723, architect), John Wilkins (1614–1672, physician and one of the founders of the Royal Society), Richard Lower (1631–1691, physician with whom Boyle conducted experiments on blood transfusion in animals) (*Fig. 2*), Ralph Bathurst (1620–1704, physician), John Wallis (1616–1703, mathematician), and Seth Ward (1617–1689, mathematician).

Boyle eventually decided to move to Oxford in 1655 with plans to vigorously continue his scientific efforts (6). Early work at this institution along with his technical associate Robert Hooke (1635–1703) resulted in the discovery of the classical gas law (Boyle's law) (*Fig. 3*). This was an offshoot of the discovery and demonstration of atmospheric pressure through the "J-tube" filled with mercury by Torricelli (1608–1647). Boyle immensely enjoyed the intellectual climate at Oxford, and his association with the "natural philosophers" at Oxford soon became known as an "Invisible College." This group was the forerunner of the Royal Society, one of the oldest established scientific societies in the world, of which Boyle was a founding member (21).

When King Charles II (1630–1685) rose to power, Boyle was at the peak of his career and fame. The King awarded him with new lands in Ireland to propagate the Protestant doctrine through Ireland and North America. In turn, Boyle left a part of his estate to the Harvard College and William and Mary College in North America in his will to spread Christianity among the Native Americans (2, 12). He was appointed a member of the Board of Directors of the East India Company (*Fig. 4*) and took this opportunity to spread Protestantism in India, as well as to gather information regarding exotic plants and animals of the subcontinent. He strongly felt that being a pious Christian did not prevent one from being a good scientist (7), as the title of one of his paper's suggests: "The Christian Virtuoso: Shewing, That by Being Addicted to Experimental Philosophy, a Man is Rather Assisted Than Indisposed to be a Good Christian (1690)" (*Fig. 5*)

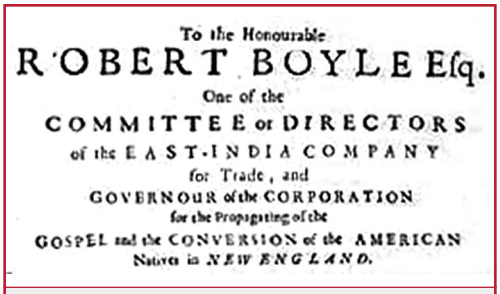

To the Honourable
ROBERT BOYLE Esq.
One of the
COMMITTEE or DIRECTORS
of the EAST-INDIA COMPANY
for Trade, and
GOVERNOUR of the CORPORATION
for the Propagating of the
GOSPEL and the CONVERSION of the AMERICAN
Natives in NEW ENGLAND.

FIGURE 4. *Boyle, as the Director of the East India Company, saw it as the primary channel for promoting the Protestant doctrine. He provided funds for the sponsorship of missionaries to the East Indies or for the production of the translation of scripture into the language of that area. This is an advertisement of a book produced through his monetary support and dedicated to him.*

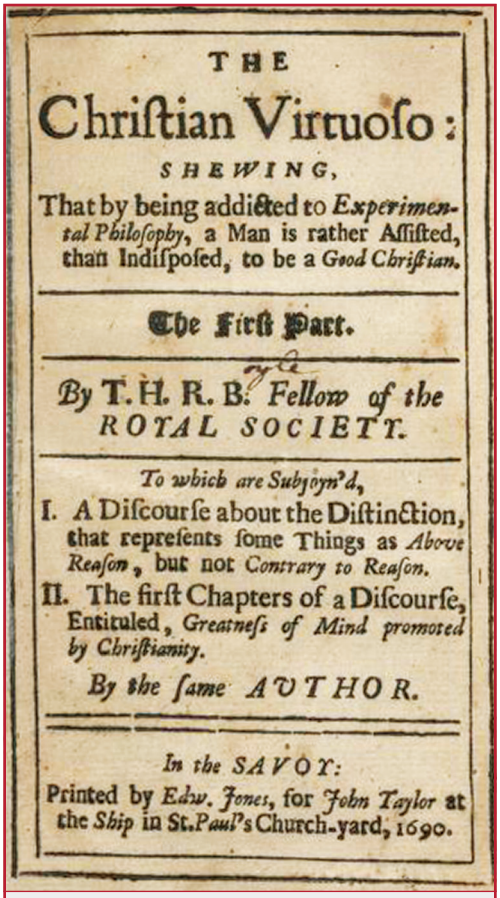

THE
Christian Virtuoso:
SHEWING,
That by being addicted to Experimental Philosophy, a Man is rather Assisted, than Indispos'd, to be a Good Christian.
The First Part.
By T. H. R. B. Fellow of the ROYAL SOCIETY.
To which are Subjoyn'd,
I. A Discourse about the Distinction, that represents some Things as Above Reason, but not Contrary to Reason.
II. The first Chapters of a Discourse, Entituled, Greatness of Mind promoted by Christianity.
By the same AUTHOR.
In the SAVOY:
Printed by Edw. Jones, for John Taylor at the Ship in St. Paul's Church-yard, 1690.

FIGURE 5. *The title page from one of Boyle's most famous works, "The Christian Virtuoso."*

(10). Boyle was a prolific writer and composed 40 books and numerous articles during his career. To this day, he is recognized as one of the foremost scientists the world has produced. A crater on the surface of the moon bears the name of Robert Boyle.

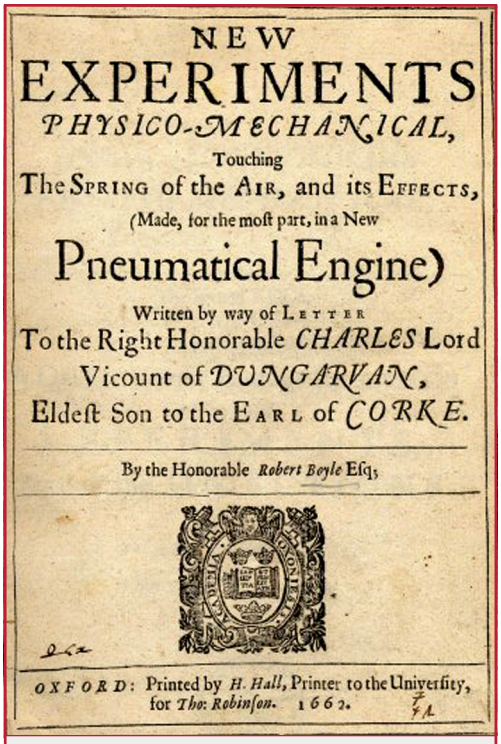

NEW
EXPERIMENTS
PHYSICO-MECHANICAL,
Touching
The SPRING of the AIR, and its EFFECTS,
(Made, for the most part, in a New
Pneumatical Engine)
Written by way of LETTER
To the Right Honorable CHARLES Lord
Vicount of DUNGARVAN,
Eldest Son to the EARL of CORKE.
By the Honorable Robert Boyle Esq;
OXFORD: Printed by H. Hall, Printer to the University, for Tho: Robinson. 1662.

FIGURE 6. *Boyle's paper, "New Experiments, Physico-Mechanical," in which he discusses an account of the work he did with the air pump, leading to the formulation of Boyle's law, published in 1660.*

Boyle's Contributions to Science

Boyle's exposure to the work of Galileo and his student, Torricelli, steered him into the field of science at a crucial point in his life. He conditioned himself to think scientifically for the rest of his career, which explains his lifetime academic output. Boyle reported his scientific methods and findings in a detailed manner that enabled others to reproduce his experiments, and he was not hesitant to report negative results. In a major landmark in the history of human and scientific thought, Boyle practiced the idea of presenting a hypothesis and testing it inductively by scientific experimentation, forming the modern scientific process just as his contemporary scholar Galileo did.

Although Boyle is known for his famous gas law (*Fig. 6*), he has made contributions bridging the various disciplines of science (22). Aristotle (384–322 BC) preached that a vacuum cannot exist in nature; his teachings were followed for 19 centuries after his death, until Otto Van Guericke (1602–1686) from Germany and Sir Robert Boyle from England conclusively and scientifically proved that a vacuum can be created through sound experimental techniques. A unique experimental device, a vacuum pump (*Fig. 7*) built with the assistance of Robert Hooke, was a milestone in Boyle's research career. His many seminal contributions may be traced back to this experimental device or modifications thereof.

First and foremost, he established Boyle's law, describing the reciprocal relationship between volume and pressure at a constant temperature of a given gas, which is a commendable extension of the observations of Torricelli and Pascal (1623–1662) on atmospheric pressure. Using the same system, he cleverly identified that sound waves propagate only in the presence of air and that sound transmission does not occur in a vacuum (3) (*Fig. 8*). He recognized that living creatures required air for their survival, that an animal stands in need of almost incessantly drawing in fresh air (11). He also realized that air is a prerequisite for combustion. It is also fascinating to note that Boyle recognized light's ability to travel through a vacuum, stating: "If I thought your Lordship could seriously imagine that light could be conveyed without, at least, having (if I may so speak) a body for its vehicle" (3). He proved experimentally that falling objects, regardless of their mass, fall at the same velocity in a vacuum. In addition, he discovered that electric force is not affected in a vacuum.

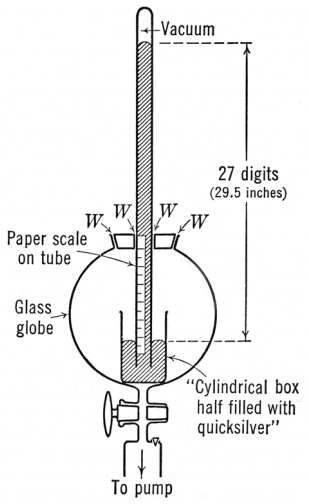


FIGURE 7. *Diagram of Robert Boyle's first air pump in which he conducted several experiments, which led to explanations of various phenomena related to vacuum.*

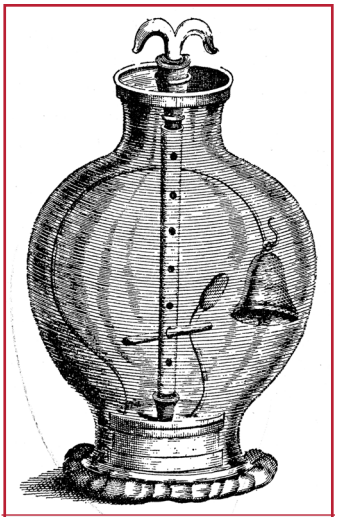


FIGURE 8. *Diagram of the apparatus in which the difference in the propagation of sound through a vacuum and air was tested by Boyle.*

Although not his original idea, Boyle believed all matter was composed of small particles (9), a forerunner of modern atomic theory. However, the technology at hand was insufficient to prove this theory. Enumeration of Boyle's contributions to science is incomplete without mention of his contributions to the science of chemistry. He was instrumental in differentiating acids from bases and formulated the concept of indicators. Although he had some belief in alchemy and transmutation of metals (18), he was unable to conclusively prove it in his lifetime.

Boyle's Contributions to Medicine

Although a natural philosopher for the majority of his scientific career, Boyle also had a keen interest in medicine. It appears to have stemmed from two factors, his health and his connection to many prominent physicians of the era. First, Boyle had a frail constitution and was prone to repeated illnesses that kept him away from work. Boyle also had an unfortunate episode during his Eton days. He was treated for a minor illness and became deathly ill from the treatment he received. This experience undoubtedly left an indelible mark in his mind. He felt throughout the rest of his life that medications used by physicians of the time caused more harm than good to the patients.

Therefore, in subsequent years, he did not consult physicians when he was ill, but rather tried simple medications on his own, constantly striving to invent simpler pharmacological agents with fewer side effects and more efficacy. Being a chemist himself, he strongly believed in research into the chemistry of drugs to improve the quality of life. Not wishing to have these maladies impede his career or his life, Boyle decided to try to develop his own cures for various diseases. He asserted his conviction that the trained chemist can provide significant insight into the medical art (11), which can be considered a forerunner to modern day clinical pharmacology, referred to as iatrochemistry in the past. Boyle, as noted, preferred working with simple medications, rather than complex mixtures for two reasons. First, he felt that simpler agents are easier to target to specific disease entities. Second, being a champion of the experimental method, Boyle believed in conducting clinical trials to test the efficacy of drugs, and simple drugs were easier to analyze and provided more precise information regarding their effectiveness. Most historians consider Boyle's use of specific gravity to determine purity of a chemical substance, a test that is still used today, as his paramount contribution to the field of pharmacology.

Boyle's interest in medicine led him towards clinical observation, in which he fervently believed. He often accompanied Thomas Sydenham (1624–1689) on his visits to the sick (8). It is possible that his relationship with Sydenham could have had some considerable influence on the concept of one of medicine's most well-known aphorisms, that which states "First do no harm."

Primum Non Nocere: First Do No Harm or Above All, Do No Harm

The meaning of this aphorism is now well understood, but its origin is controversial. It is often mistakenly attributed to Hippocrates (460–370 BC) or part of the Hippocratic Oath. However, Hippocratic writings were in Greek, not in Latin. *Of the Epidemics, Book I, Section II, Part 5*, states that "the physician…must…have two special objects in view with regard to diseases, namely, to do good or to do no harm" (13). Clearly, this is not the exact aphorism we use today and, on this ground, most historians do not credit Hippocrates for this aphorism. Others have variously attributed this aphorism to

Galen (129–200 AD), Ambroise Pare (1510–1590), Florence Nightingale (1820–1910), Worthington Hooker (1806–1867), Francois Chomel (1788–1858), Oliver Wendell Holmes (1809–1894), and William Osler (1849–1919), but there is no evidence to support these assertions (20). The definitive reference for the first time in the English medical literature is in a textbook by Thomas Inman, who attributes the aphorism to Thomas Sydenham, referred to by some as the "English Hippocrates" for his work in internal medicine (14). It has not escaped our attention that Sir Robert Boyle was a close associate of Thomas Sydenham; in fact, he was his next-door neighbor. There is historical proof that Boyle accompanied Sydenham on his rounds and, in most matters, they shared similar views, although they did disagree in certain instances. If this attribution of aphorism to Thomas Sydenham is indeed true, the personal unfortunate experience of Boyle at Eton and his personal convictions might have been shared with Sydenham. Biographers of Sir Robert Boyle repeatedly emphasize Boyle's notion that the treatment was much worse for the patient than the disease.

The second reason Boyle may have had interest in the realm of medicine was his close affiliation with the prominent physicians of his time, including Thomas Sydenham, Thomas Willis, John Wilkins, William Petty, and Nathaniel Highmore. It is probable that his conversations and interactions with these physicians aroused a curiosity in biological sciences that could possibly have rivaled his passion for the physical fields. Boyle also met William Harvey (1578–1657) on at least one occasion to discuss circulation of blood; in fact, Boyle used injections of colored fluid and molten wax to trace capillaries joining arteries to veins in support of Harvey's hypothesis on the subject (11). Boyle even engaged himself with prevalent beliefs regarding digestion, which attributed the digestion of food to the heat imparted by the stomach. On the contrary, Boyle believed that gastric juices had some components that solubilized the food, the details of which he was uncertain. In certain physiological essays, Boyle claimed to have prepared a substance in his laboratory that resembled digestive juice and asserted that the stomach was "endowed with a subtile dissolvent (whence soever hath it) by which it may perform divers things, not to be done by…languid…heat" (11).

Regardless of his level of interest or from whence it came, Boyle obviously had some medical knowledge. Because of his knowledge of iatrochemistry, his detailed knowledge of anatomy, his inquisitive nature towards physiological phenomena, and the creation of the aforementioned circulation model that reinforced Harvey's theory, Boyle was awarded an honorary Doctor of Physick degree from Oxford in 1665. Boyle also performed anatomic dissections under the guidance of Petty and Highmore, reputed anatomists of his time, and used his background in chemistry to devise preservative fluid for biological specimens (1, 11). As noted previously, he made rounds with Thomas Sydenham and saw patients. It is also apparent that he talked to these patients himself. It is perhaps through these experiences that Boyle gained his understanding of manifestations of neurological disorders noted in the case report described in this article, which is very unique for a scientist of his time.

Boyle perhaps gave the earliest description of holoprosencephaly with associated facial anomalies in a colt ("a single eyed monster") in *Figure 9*. He mentioned the absence of nose, except perhaps in a rudimentary form, and the fusion of two eyes into a single form placed just in the middle of the brow, as well as the presence of a single orbital cavity into which a large, single, thick optic nerve entered. Boyle used alcohol ("Spirit of Wine") to preserve the tissue so later anatomists could examine the deformities in detail (1) (*Fig. 10*).



FIGURE 9. *Picture of a colt, as printed in the Philosophical Transactions, with a severe case of holoprosencephaly. Note the absence of the nose and a single eye placed where the nose is normally present.*

The following is the case report by Boyle on a patient with a depressed cranial fracture, reproduced from *Experimentae et Observaciones Physicae*, *The Works of Robert Boyle*, Vol. 11:

Observables upon a Monſtrous Head.

This was the Head of a *Colt*, repreſented in the annexed *Figure* 4. firſt viewed by Mr. *Boyle*, who went into the Stable where the *Colt* lay, and got the Head haſtily and rudely cut off, the *Body* thereof appearing to his Eye compleatly formed, without any *Monſtroſity* to be taken notice of in it. Afterwards he cauſed it to be put into a Veſſel, and covered with *Spirit of Wine*, thereby chiefly intending, to give good example, together with a proof, that by the help of the ſaid *Spirit*, (which he hath recommended for ſuch Properties in one of his *Eſſays* of the *Uſefulneſs* of *Natural Philoſophy*) the parts of *Animals*, and even *Monſters*, may in *Summer* it ſelf be preſerved long enough, to afford *Anatomiſts* the opportunities of examining them.

The Head being opened, and examined, it was found,

Firſt, That it had no ſign of any *Noſe* in the uſual place, nor had it any, in any other place of the Head, unleſs the double Bagg CC, that grew out of the midſt of the forehead, were ſome rudiment of it.

Next, That the *two Eyes* were united into one *Double Eye*, which was placed juſt in the middle of the Brow, the Noſe being wanting, which ſhould have ſeparated them, whereby the two Eye-holes in the Scull were united into one very large round hole, into the midſt of which, from the Brain, entred one prety large *Optick Nerve*, at the end of which grew a great *Double Eye*, that is, that *Membrane*, called *Sclerotis*, which contained both, was one and the ſame, but ſeemed to have a *Seam*, by

FIGURE 10. *A reprint of "Observables upon a Monstrous Head," published in the Philosophical Transactions of the Royal Society of England, Vol. 1 (1655–1656 A.D) detailing the description holoprosencephaly in a colt.*

THE I. PENTADE. EXPERIMENT I.

A very Tall and well Set Gentleman, Aged about 24 years, by a Fall from his Horse, had / his Skull broken in several places, and being a Person of good Estate, had several Chirurgeons to attend him in the course of his Sickness; during which he was divers times Trepan'd, and had several pieces of his Skull taken off, which left Great Chasms (that I have seen and felt) between the remaining Parts. Within about three days after his Fall, this Knight (for so he now is) was taken with a Dead Palsey on his Right Side, which did not equally affect his Arm and his Leg: The use of the latter being somtimes suddenly Restor'd to him in some measure, and (tho seldom) after a while almost as suddenly Lost: But his Arm and Head were constantly Paralytical, being wholly depriv'd of Motion; and having so little Sense, that it would sometimes lye under his Body without his Feeling it. But if his Hand were prick't with a Pin, he could take notice of it. This Palsey continu'd / during almost the whole time of the Cure, which lasted 23 or 24 Weeks. And when the Chirurgeons were going to close up his Head, as having no more to do; one of them who was an Ingenious Man, and Tenant to this Gentleman oppos'd all the rest, alledging, that, if they did no more, the Gentleman would lead an Useless and very Melancholy Life; and that he was confident, the Palsey was some way or other occasion'd by the Fall, which had left something in the Head they had not yet discover'd. And the Knight himself agreeing to this Man's motion, his Head was further laid open; and at length, under a piece of proud Flesh, they found, with much ado, a Splinter, or rather Flake, of a Bone, that bore hard upon the *dura mater*, and was not pull'd out without a great Hemmorhage, and such a stretch of the Parts, as made the Patient think his Brain it self / was tearing out. But this Mischief was soon Remedy'd, and his Hurts securely Heal'd up; and he is now a Strong Healthy Man, and finds no Inconvenience by having so broad and various a *Callus* instead of the Skull; save that he is a little obnoxious to take Cold in his Head. But the memorable Circumstances, for whose sake I mention this Narrative, were these: When I ask'd him how big the Bone was, that was last taken out? He told me, that it was less than half the Nail of one of his Fingers (not his Thumb) and that it was almost as thin, being in size and shape like the Scale of a Fish: But that it did not in his Head lye flat, but bore hard upon the *dura mater.* When I ask'd him how long after it was taken out, he began to feel some Relief, as to his Paralytic Distemper? He reply'd, That in less than five hours he found himself, to his great / joy, able to move his little Finger;and (tho this happen'd in the Evening) he was the next morning able to move all his Fingers, and within 2 or 3 days after to lift up his Arm: By which it seem'd manifest, that so little a Body as the Splinter lately mention'd, produc'd in so robust a Person, a Palsey of the whole side it lay on. For when I particularly ask't him, Whether, after the taking away of the proud Flesh that encompass'd the little Bone, he did not find, if he found none before, some Relief as to his Palsey? He answer'd, that he found none at all, till the Bone had been pull'd out, which was not till a good while after the Chirurgeon had been by degrees eating off the proud Flesh that grew about it. But there was in this case another *Phaenomenon* that I thought little less considerable than the former. For, remembring the important controversie, that is agitated among / modern Physicians and Anatomists, about Nutrition by the Nerves, and having thereupon ask'd this Knight, whether he did not find any Atrophy in the Limbs of his Body that were affected? He told me, that when he began to be Paralytic on that side, it by degrees much wasted, and the Paralytic Leg was very much Extenuated: But the Arm and Hand much more, seeming nothing but a System of Bones, with the Skin pasted on them. And when I further ask'd, if upon the removal of the Bony Splinter above-mentioned, the Atrophy of the Parts did not also begin to lessen; he answered affirmatively, and told me, that in no very long time his Leg and Arm recover'd their wonted Dimensions; and in effect I (some d since) saw the restor'd Arm well plump'd up with musculous Flesh, tho the Weather were exceeding Cold. And he further told me, that he found / no difference between the Limbs that had been Paralytic, and the others, except that they would grow sooner and more sensibly cold in Sharp or Frosty Weather.

This Gentleman answer'd me, to add that upon the by, that, during course of his Cure, he was very frequently (almost every s d) let Blood; that he wanted not Appetite to his Meat; that for the most part he slept indifferent well; and, which was more remarkable, upon so great a Hurt of the Head he did not Vomit, nor had afterwards any Convulsions (1).

DISCUSSION

The favorable surgical outcome in this patient presented by Boyle might be related in part to him being a robust, young, and otherwise healthy adult. Unquestionably, the diagnosis of multiple cranial fractures after a fall from a horse was made entirely based on clinical observations because the incident predated the discovery and use of x-rays by Roentgen by at least 250 years.

The patient in this case report was described as a knight, but the term "knight" was used in three different contexts in this period, meaning a person with excellent horsemanship, a male advancing from childhood to adulthood through adolescence, or a non-heritable title bestowed by the king to a chosen few; we do not know in which of these categories Boyle's patient

falls. However, it is clear that he had substantial wealth and social status that allowed him access to several talented surgeons. Ironically, the differential access to health care based on financial stratification in the 1600s is no different than the current structure in the United States or even the "Hammurabi Code," the earliest documented decree (circa 1760 BC) regarding fee structure for physicians (15): "If a physician makes a wound and cures a free man, he shall receive ten pieces of silver, but only five if the patient is the son of plebeian or two if he is a slave" (5).

It is striking that even though the surgical procedures were done in multiple sittings and within a short time frame (24 wk), there was no mention of fever, infection, or purulent drainage from the wound. As it follows, it is also somewhat enigmatic as to what anesthesia or sedation was used for the procedure. It was customary to give liquor for sedation (24), but Boyle's case report makes no mention of it.

It is apparent from the description that Boyle himself was not a physician, although he had personally visited and seen the patient on many occasions with Sydenham, had made many astute personal observations, and perhaps observed most surgical procedures, except the last procedure in which the depressed bone fragment was removed. Neither the patient nor the surgeons who treated him were identified by Boyle. We also do not know the hospital at which the surgery was performed. Even though Boyle was a basic scientist and not a trained neurologist, he made many astute bedside observations. He noted that the arm was more paralyzed than the leg and that a differential sensory loss with preserved sensation of pinprick but loss of touch and joint sense had occurred. However, he was not cognizant of the fact that the motor cortex controls the opposite limbs, as noted by the statement: "so little a Body as the Splinter. . . . .produc'd . . . a Palsey of the whole side it lay on" (10, pp 72–73).

This is the first well documented case of an awake craniotomy during which the patient was alert, was able to participate in the decision making process when an alternative strategy to the original plan was suggested, and was able to relate the details of the operations after the procedure.

It is evident that there was significant bleeding when the depressed bone fragment was removed (the author uses a double negative), presumably from the middle meningeal arteries; however, the author did not indicate how it was controlled. It is commendable that the surgeons recognized that the depressed cranial fragment was responsible for neurological deficit and not the swollen muscle ("proud flesh"). It is clear that the surgeons were aware of the sensitivity of the dura to pain because "such a stretch of the Part as made the patient think his Brain it self, was tearing out" (10, pp 72–73).

Boyle mistakenly attributes the atrophy of the muscle to impairment of "nutrition by the nerve," implying a lower motor neuron lesion when, in fact, the atrophy seems to be the result of disease from an upper motor neuron lesion. It is interesting to note that through the short period of observation, the patient had no seizures.

The sophistication, technical complexity, and outcome of the surgical procedure undertaken in this case report is unprecedented for its time. This case has provided the authors of this article and its readers with a remarkable opportunity to further investigate the procedures of brain surgery before the 19th century, which is formally referred to as the era establishing the practice of neurosurgery.

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COMMENTS

This article on Sir Robert Boyle, a leading scientist and natural philosopher of the 17th century, nicely reviews the biographical history of this man along with a number of his contributions to medicine and science. The authors point out that Boyle is remembered mostly for contributions to the field of chemistry and that most modern readers would not necessarily identify his contributions to medicine, much less neurosurgery. Having said that, the authors proceed to detail a number of very interesting contributions Boyle made to medicine and, in one particular case, to neurosurgery; the authors have detailed Boyle's observations on an early case of a treating a depressed cranial fracture. Reading the report on the depressed fracture clearly revealed how enlightened Boyle was for his time. Using initially visual observations, which are then documented with a clinical examination, Boyle described the skull fracture, surgical treatment, and clinical outcome, especially the need for a second surgical elevation. Boyle then chronicled the patient's clinical recovery after the second surgery to remove a bone fragment. This article is a most remarkable case history and provides a remarkable commentary on 17th century neurosurgery.

James T. Goodrich
Bronx, New York

A "Renaissance man" is defined by Webster as a person who has a wide range of interests and is an expert in several areas. The term is often applied too liberally, but Sir Robert Boyle is a quintessential example of this species. In addition to writing a vast array of scientific and religious tracts, Boyle was the author of two works of romantic fiction: *Seraphick Love* and *The Martyrdom of Theodora.* Boyle's description of the clinical features of a patient being treated for a depressed cranial fracture reveals his profound powers of observation. A treasure trove of information about Sir Robert Boyle's writings is contained in John Fulton's bibliography of Robert Boyle (1), which lists nearly 200 separate publications plus 37 articles published in *The Philosophical Transactions of the Royal Society.* Addressing Boyle's position in the history of science, Fulton observed that: "There is little that he did not touch; and almost every branch of modern science can trace phases of its origin in his writings. It is probable that in the broad field of science Boyle made a greater number and variety of discoveries than one man is ever likely to make again. Weighing the air, the thermometer, the barometer, freezing mixtures, the gas laws, phosphorus and phosphorescence, electricity—- all these things are associated with his name."

Norman H. Horwitz
Washington, District of Columbia

1. Fulton JF: *A Bibliography of the Right Honourable Robert Boyle. Fellow of the Royal Society.* Oxford, Clarendon Press, 1961, ed 2.

The life and considerable scientific works of Sir Robert Boyle are very interestingly presented in this scholarly researched and written article. The report of the surgical treatment of a depressed cranial fracture in the mid-17th century is remarkably detailed. Boyle's non-physician scientific observations are, for the most part, quite impressive. It is obviously a curiosity, however, why there was such a rapid and dramatic recovery from a profound, 6-month-old neurological deficit on removal of one last remaining fragment of bone, irrespective of its apparently insignificant size. The authors are to be congratulated for enlightening us on this non-physician scientist's contributions to our neurosurgical heritage.

Jack E. Wilberger
Pittsburgh, Pennsylvania

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MELVILLE, *MOBY-DICK*, AND THE PURSUIT OF THE INSCRUTABLE WHALE

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KEY WORDS: 19th century American literature, Herman Melville, *Moby-Dick*, Whaling

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The name of Melville's notorious whale was suggested to derive from the name of a real-life sperm whale, Mocha Dick. The first part of the name is after the island of Mocha, located off Chile's southern coast; the second part is a generic name often used to call deadly whales, as cited by Melville in Chapter 45 of Moby-Dick. *Like the fictional whale, Mocha Dick escaped capture several times and ferociously attacked whaler ships and their crews (8).*

Herman Melville's *Moby-Dick* holds a distinctive position in the American literary tradition that no other work can match. Andrew Delbanco, a Melville biographer, points out, "[Other] writers were kept alive mainly as classroom assignments; but Melville is different: he is a living presence in the larger culture" (1, p 12). Who has not heard of *Moby-Dick*'s infamous opening line, "Call me Ishmael"? From political satire to the name of seaside restaurants, *Moby-Dick* references are ubiquitous. Yet despite *Moby-Dick*'s current, solid position in the American canon and culture, during the book's early publication in 1851, it was in danger of being lost to obscurity. The book was received, at best, by mixed reviews (7, 8). Melville's 19th century readers found it a disappointing follow-up to his earlier works, *Typee* and *Omoo*, light-hearted accounts of young Melville's adventures to the tropical Marquesas and Polynesian Islands. *Moby-Dick*'s experimental, digressive composition, which combined cetological learning, philosophy, poetry, bawdy humor, and Shakespearean soliloquies, was lost on the 19th century audience, who was accustomed to a unified narrative.

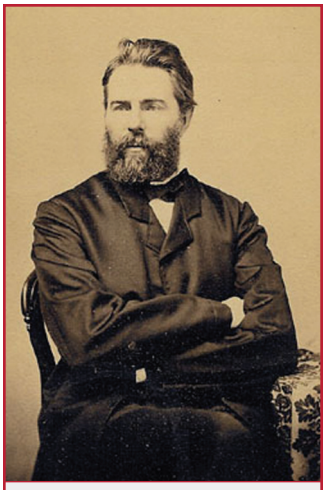


FIGURE 1. *Photograph of Herman Melville, 1861.* Courtesy of, *the Berkshire Athenaeum, Pittsfield, MA.*

In writing *Moby-Dick*, Melville attempted a narrative altogether different than what he had written before and he was aware of the possible consequences. In a letter written to his friend and contemporary, Richard Henry Dana, dated May 1850, he expressed some doubts:

> It will be a strange book, tho', I fear; blubber is blubber you know; tho' you may get oil out of it, the poetry runs as hard as sap from a maple tree;—& to cook the thing up, one must needs throw in a little fancy, which from the nature of the thing must be as ungainly as the gambols of the whales themselves (4, p. xiv).

He feared his experiment to combine a factual discourse on cetology with philosophical speculations on humanity was in danger of becoming an "ungainly" catastrophe. Later, in June 1851, he expressed in a letter to his friend, Nathaniel Hawthorne, "What I most feel moved to write, that is banned,—it will not pay. Yet, altogether, write the other way I cannot" (4, xi). Melville knew that his writing about whaling would go against 19th century sensibilities. It was assumed that readers were mainly modest young ladies, who were unaccustomed to sailors' vulgarity (1). He faced the dilemma of writing to please his audience or writing for the sake of writing. This could not have been an easy decision as Melville's life was burdened with financial

woes. As expressed in his letter, ultimately, Melville bravely chose to write what he felt "moved to write," despite its potential financial consequence. Unfortunately, the book's reception turned out as Melville feared: parts of the book were indeed banned and it was unprofitable. *Moby-Dick*'s first printed version was subjected to further revisions and censorship by the publisher, who expurgated certain passages without Melville's consent. In Melville's lifetime, *Moby-Dick*'s total sales reached only $556.37 and it was last reprinted in 1876 (1, 8).

Moby-Dick marked a decline in Melville's career as a writer, though he continued to write short-stories, poems, and novels until his death. In 1891, he passed away without ever knowing of his eventual fame. The novel was not widely appreciated until a revival of 19th century writings in the 1920s. *Moby-Dick* finally took its place in the canon in the 1940s, nearly a century after its first publication.



FIGURE 2. *A rendering of Moby-Dick resisting the attacks of Captain Ahab and the Pequod's crew, painted by notable book illustrator and artist, Kinuko Y. Craft.*

Many critics attribute the book's initial failure and late success to Melville's "precocious modernity" (1, p 10). In the words of Delbanco, "*Moby-Dick* was a work of a twentieth-century imagination" (1, p 175). Had Melville been born a hundred years later, he would have enjoyed the book's tremendous success. Recognizing Melville as a man far ahead of his time, D.H. Lawrence called him "a futurist long before futurism" and E.M. Forster described Melville's *Moby-Dick* as a "prophetic song" (1, p 11). His experiment with mixed forms and stream of consciousness narration, more similar to the mode of James Joyce or Virginia Woolf, predated the 20th century period of experimentation known as Modernism (2). He was a century ahead of his time, distinctively different from the writers of his era, the likes of Nathaniel Hawthorne, Henry David Thoreau, and Ralph Waldo Emerson, whose styles were more closely aligned with 19th century Romanticism.

What makes Melville so different from his colleagues? One theory purports that Melville's writing reflects his eclectic background and influences (3). He came from a genteel family, but his father squandered the family's fortune and passed away early, leaving his mother as the sole provider for eight children. As a result, their family was in constant debt and Melville was deprived of his class' upbringing. At the age of 19, Melville took to exploring the seas as a cabin boy and later boarded a whaling ship. In *Moby-Dick*, Ishmael claims, "a whale-ship was my Yale College and my Harvard" (4, p 93), a point that is also applicable to Melville. Without a formal education, Melville gained his general education from the seas and his literary knowledge from being a voracious reader and essentially becoming an autodidact. One critic contends that when Melville wrote *Moby-Dick*, he was in a state of "intellectual frenzy" that was inspired by his readings: "the more Melville read the more he wanted to find a way of writing that would enable him to meld together all that he found valuable in other works" (4, xi). *Moby-Dick* was partly a melding of Melville's extensive reading list, which included the Bible, Plutarch, Montaigne, Shakespeare, Sir Thomas Browne, Milton, Pope, Goldsmith, Jefferson, Rabelais, and many others, partly drawn from his experiences at sea, and partly a daring experiment to "look for philosophy in whales [and] poetry in blubber" (6, 8).

The result of Melville's aspirations is the emblematic tale of Captain Ahab's monomaniacal hunt of Moby-Dick. The qualities of the story, which had captured the 20th century audience (and perhaps what had turned away the 19th century audience), were its immense scope and complexity. Captain Ahab is not an ordinary captain, this is not an ordinary chase, and Moby-Dick is not an ordinary whale. The hunt for Moby-Dick, who Ahab repeatedly refers to as "the inscrutable thing" who is simultaneously a simple animal and a complex representation of an equivocal force, reflects our own collective human search for elusive meaning (5). Unlike a typical man, who, for the most part, is content with the vagaries of the universe and humbly accepts his powerlessness and insignificant role in the grander scheme of things, Ahab contemptuously defies higher forces with the audacity of mythical figures like Prometheus and Oedipus. He claims, "I'd strike the sun if it insulted me" (4, p 136). Whether such

brazenness is heroic or absurd, Ahab's hubris is a hyperbolic reminder of the indignant part of our nature. Whether we approve of or reject him, Ahab "is more a part of us than apart from us" (1, p 12).

Melville once fondly said of Shakespeare that through his dark characters, Shakespeare could "insinuate the things, which we feel to be so terrifically true" (1, p 131). With Ahab, Melville achieved such a character. Through Ahab's exasperations and bitterness towards the whale for destroying his ship and maiming him, Melville examines our own indignation towards our futile suffering and our incapacity to understand the meaning of life's afflictions. In a speech persuading his crew to join his obsessive chase, Ahab argues:

> All visible objects, man, are but as pasteboard masks. But in each event—in the living act, the undoubted deed—there, some unknown but still reasoning thing puts forth the moldings of its features from behind the unreasoning mask. If man will strike, strike through the mask! How can the prisoner reach outside except thrusting through the wall? To me, the white whale is that wall, shoved near to me (4, p 174).

Ahab uses the metaphors of the mask and the wall to represent barriers preventing us from crossing the threshold of meaning. Then, drawing a connection between what the whale represents to him and the impenetrable mask which covers all visible objects, Ahab appeals to the human impulse to struggle to understand things beyond our understanding. He urges his shipmates to act on that impulse by forcibly breaking through the threshold. For Ahab, the threshold is embodied in Moby-Dick. Ishmael, the narrator, explains, "All that most maddens and torments; all that stirs up the lees of things; all truth with malice in it; all that cracks the sinews and cakes the brain; all the subtle demonisms of life and thought; all evil, to crazy Ahab, were visibly personified and made practically assailable in Moby-Dick" (4, p 174). As Ishmael points out, Ahab not only sees the whale as a metaphorical representation of the barrier between the known and unknown, he believes it to literally be the barrier. To Ishmael, Ahab's view seems absurd. Although Ahab's madness is hyperbolic, it strikes a note that resonates a certain truth, the understanding of which is dependent upon each person's experience and the degree of our personal imperative to assail the barrier we face. Doubtlessly, it is this ability to resonate truth that preserved *Moby-Dick* from the obscurity of time.

Each has his own Moby-Dick, his own "wall" to assail. For Melville, the novel itself was his Moby-Dick. Though Melville originally intended to write another short account of his seafaring experiences in the same fashion of his previous, well-received works, he instead labored much more intensively over *Moby-Dick*. His preoccupation with writing bordered on obsession at times. He often shut himself up in his room for days, calling the book "my 'Whale'" (4, xvi), and working well past the manuscript's intended deadline even at high financial costs. In an encounter with Melville in 1856, Hawthorne said of his friend,

> Melville has not been well, of late; . . . and no doubt has suffered from too constant literary occupation, pursued without much success . . . It is strange how he persists—and has persisted ever since I knew him, and probably long before—in wondering to-and-fro over these deserts, as dismal and monotonous as the sand hills amid which we were sitting. He can neither believe, nor be comfortable in his unbelief (8).

As evident in Hawthorne's observation, Melville approached writing with untiring intellectual zeal. In the middle of writing *Moby-Dick*, Melville commented on the frustrating endeavor of "taking a book off the brain": "it is akin to the ticklish & dangerous business of taking an old painting off a panel—you have to scrape off the whole brain in order to get at it with due safety" (1, p 145). Having to search for the right words within one's mind while they slip and slide from conscious grasp is no doubt difficult, but having to scrape off the whole brain to produce a book makes writing seem an impossible task. In addition, Melville had to worry about money, publisher's approval, and public reception. Against these seemingly insurmountable odds and with Ahab-like ambition, Melville created *Moby-Dick*, a tour de force encompassing in one novel both the common experience of being a sailor on a whaling ship and the metaphysical reflection on the "voids and immensities of the universe" (4, p 162). The product of Melville's ambition and genius proved not only to be ahead of its time, but also time enduring. Moby-Dick is an impenetrable mystery that haunts not only Ahab, but also generations of readership. Ahab's obstinate pursuit of Moby-Dick is paralleled by the continual attempts of multitudes of critics, artists, filmmakers, musicians, writers, readers, and various other enthusiasts to dissect and capture the meaning of this great literary work more than a century after it was written.

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WINGSPAN IN-STENT RESTENOSIS AND THROMBOSIS: INCIDENCE, CLINICAL PRESENTATION, AND MANAGEMENT

OBJECTIVE: Wingspan (Boston Scientific, Fremont, CA) is a self-expanding stent designed specifically for the treatment of symptomatic intracranial atheromatous disease. The current series reports the observed incidence of in-stent restenosis (ISR) and thrombosis on angiographic follow-up.

METHODS: A prospective, intent-to-treat registry of patients in whom the Wingspan stent system was used to treat symptomatic intracranial atheromatous disease was maintained at five participating institutions. Clinical and angiographic follow-up results were recorded. ISR was defined as stenosis greater than 50% within or immediately adjacent (within 5 mm) to the implanted stents and absolute luminal loss greater than 20%.

RESULTS: To date, follow-up imaging (average duration, 5.9 mo; range, 1.5–15.5 mo) is available for 84 lesions treated with the Wingspan stent (78 patients). Follow-up examinations consisted of 65 conventional angiograms, 17 computed tomographic angiograms, and two magnetic resonance angiograms. Of these lesions with follow-up, ISR was documented in 25 and complete thrombosis in four. Two of the 4 patients with stent thrombosis had lengthy lesions requiring more than one stent to bridge the diseased segment. ISR was more frequent (odds ratio, 4.7; 95% confidence intervals, 1.4–15.5) within the anterior circulation (42%) than the posterior circulation (13%). Of the 29 patients with ISR or thrombosis, eight were symptomatic (four with stroke, four with transient ischemic attack) and 15 were retreated. Of the retreatments, four were complicated by clinically silent in-stent dissections, two of which required the placement of a second stent. One was complicated by a postprocedural reperfusion hemorrhage.

CONCLUSION: The ISR rate with the Wingspan stent is higher in our series than previously reported, occurring in 29.7% of patients. ISR was more frequent within the anterior circulation than the posterior circulation. Although typically asymptomatic (76% of patients in our series), ISR can cause neurological symptoms and may require target vessel revascularization.

KEY WORDS: Angioplasty, In-stent restenosis, Intracranial atheromatous disease, Stenting, Thrombosis, Wingspan stent

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The Wingspan stent system (Boston Scientific, Fremont, CA) was approved for use in patients with symptomatic intracranial atheromatous disease (ICAD) in the United States under a Humanitarian Device Exemption (HDE) in 2005. Approval was granted on the basis of a 45-patient single-arm, multicenter safety study conducted in Europe and Asia (2). This study demonstrated a favorable periprocedural safety profile with a complication rate of only 4.5% at 30 days. Moreover, at the time of a 6-month angiographic and clinical follow-up evaluation, very low rates of in-stent stenosis (ISR; 7.5%, 3 out of 40 patients) and ipsilateral stroke or death (7%) were observed (2).

ISR typically reaches peak severity between 3 and 6 months after treatment and has been attributed to the proliferation of vascular smooth muscle cells within the stented seg-

ment (7). Late luminal loss related to ISR represents a major limitation of percutaneous transluminal angioplasty and stenting (PTAS) for atheromatous disease. This process is observed in 25 to 35% of coronary stents (6), 40 to 45% of vertebral artery origin stents (1), and 32% of intracranial stents (8).

Our multicenter registry was constructed to perform a prospective, "real-world," post-market assessment of the performance, safety, and efficacy of the Wingspan device. We report our observed rate of Wingspan ISR and thrombosis in a series of 84 lesions in 79 patients for whom follow-up imaging is available.

PATIENTS AND METHODS

Patient and Institutional Enrollment

All patients with ICAD undergoing attempted treatment with the Wingspan system were prospectively enrolled into a multicenter intention-to-treat registry that included the Barrow Neurological Institute, Cleveland Clinic, State University of New York at Buffalo, University of Texas Southwestern, and University of Wisconsin. The institutional review board at each institution approved the use of Wingspan as an HDE device, as well as the collection and sharing of registry data among the participating centers.

Patient and Lesion Accounting

Patients who underwent stenting of the target lesion before Wingspan stent implantation and those treated in the setting of acute thrombotic or thromboembolic occlusion of the targeted vessel were excluded from the present analysis. If multiple contiguous stents were required to cover a single diseased segment, this stent construct was counted as one lesion treated. If discrete lesions were treated in the same vascular distribution, this was counted as one patient with two treated lesions, and the stents were evaluated independently for ISR. If lesions were treated in two separate vascular distributions in the same patient, that patient was counted twice and each stent was independently evaluated for ISR.

Data Collection

Clinical and angiographic data were typically collected at the time of the initial procedure, then at 3 to 6 months and 12 to 15 months thereafter according to a standardized follow-up protocol. Clinical data were also collected at the time of discharge and between 2 and 6 weeks after the original procedure.

The average time between the procedure and the follow-up imaging study was 5.9 months, with a range of 1.5 to 15.5 months. In the present series, seven of the 79 patients underwent follow-up imaging at time points less than 3 months after stenting. Early imaging was typically performed to assess recurrent or new neurological symptoms.

Stenting Technique

PTAS was performed using the Wingspan system as described previously (5). Access was typically achieved through the common femoral artery. In rare instances, radial, brachial, and direct carotid access was required. All cases were performed through a 6-French system. The targeted parent vessel was accessed with either a 6-French guiding catheter (Envoy or Envoy XB; Cordis, Miami Lakes, FL) or a 6-French KSAW Shuttle-Select sheath system (Cook, Bloomington, IN). Heparinization was instituted to a targeted activated coagulation time of 250 to 300 seconds. In most cases, after conventional catheter-based angiography, an SL-10 (Boston Scientific, Natick, MA), Prowler-10 (Cordis), or Eschelon-10 (Microtherapeutics, Irvine, CA) microcatheter was manipulated across the target lesion using a 0.014-inch Synchro (Boston Scientific) or Transcend EX Soft Tip (Boston Scientific) microwire. The microcatheter was then exchanged over a 0.014-inch Transcend Floppy (Boston Scientific), Luge (Boston Scientific), or Pversus (Boston Scientific) exchange microwire for a Gateway angioplasty balloon. The remaining lesions were primarily crossed with the Gateway angioplasty balloon and a Transcend 300 cm exchange length 0.014-inch microwire (Boston Scientific). In each case, the balloon diameter was sized to 80% of the "normal" parent vessel diameter. The balloon length was selected to match the length of the lesion. Angioplasty was typically performed with a slow, graded inflation of the balloon to a pressure of between 6 and 12 atm for approximately 120 seconds. After angioplasty, the balloon was removed and conventional angiography was repeated.

Next, the Wingspan delivery system was prepared and advanced over the exchange wire across the target lesion. The stent diameter was sized to exceed the diameter of the normal parent vessel by 0.5 to 1.0 mm. The stent length was selected to equal or exceed the length of the angioplasty balloon. In addition, the stent length was selected both to completely cover the entire diseased segment and to allow positioning of the proximal end of the stent so as not to preclude future endovascular access into the stented segment. The diameter of the stenotic lesion was measured using biplane angiography and compared with a reference diameter of the normal vessel, usually proximal to the lesion, per the technique used in the Warfarin-Aspirin Symptomatic Intracranial Disease study (3). All patients were pretreated with antiplatelet agents (aspirin and clopidogrel) and were discharged on both aspirin (325 mg daily) and clopidogrel (75 mg daily). The dual antiplatelet regimen was usually maintained until follow-up angiography was performed (3–6 mo). Provided that no in-stent restenosis had developed, clopidogrel was usually discontinued after follow-up angiography. All patients remained on aspirin therapy (325 mg daily) indefinitely after treatment.

Follow-up Imaging

The majority of lesions were evaluated at the time of the follow-up evaluation by means of conventional catheter-based angiography. In some cases, patients were evaluated with computed tomographic angiography. If the entire stented segment and the proximal and distal parent vessel were well visualized (*Fig. 1*), these stents were designated as demonstrating "no ISR." If a region of the stented segment or adjacent parent vessel could not be well visualized, catheter angiography was performed. In cases in which non-invasive imaging findings were ambiguous or suggested ISR, conventional angiography was performed. In two cases, only follow-up magnetic resonance angiography is available.

As mentioned, all lesions were measured using the Warfarin-Aspirin Symptomatic Intracranial Disease study technique (3) to determine the initial stenosis severity. On angiographic follow-up, the minimum luminal diameter was identified and measured. The percentage of residual or recurrent stenosis was again calculated using the Warfarin-Aspirin Symptomatic Intracranial Disease study technique. ISR was defined as a lesion demonstrating stenosis greater than 50% adjacent to the stent (i.e., within, or immediately [5 mm]) and absolute luminal loss greater than 20% on follow-up imaging. This second criterion was added because some lesions were left with residual stenoses measuring between 30 and 50% after the initial treatment. In these cases, a relatively small degree of luminal loss (i.e., $<$20%) could result in "ISR" if

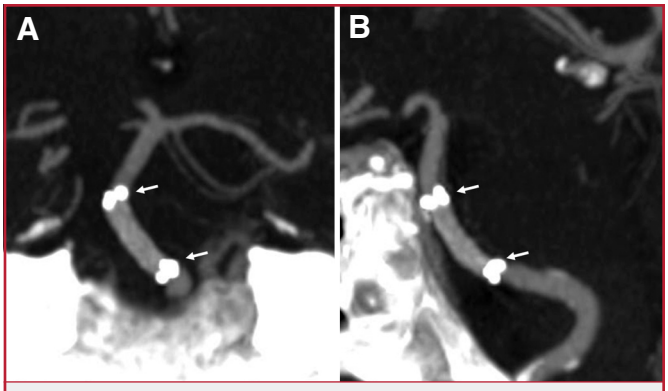


FIGURE 1. *Coronal (**A**) and sagittal (**B**) multiplanar reformations of computed tomograpgic angiography source data depict a basilar Wingspan stent with no evidence of ISR at the time of the 1-year follow-up evaluation. The entire length of the stented segment is well visualized. Streak artifact and blooming from the radio-opaque stent end-markers (*arrows*) obscure a very short segment of the adjacent parent vessel. The remainder of the parent vessel is normal in appearance and the stent is widely patent.*

a binary criterion of greater than 50% stenosis at the time of follow-up was utilized. The measurements were made by the authors at each institution and then adjudicated by one investigator (DF). Lesion retreatment was performed at the discretion of the primary operator.

RESULTS

To date, 129 patients with 137 lesions have been treated with the Wingspan stent system. Follow-up imaging is available for 84 stented lesions in 78 patients, including 65 with conventional angiography, 17 with only computed tomographic angiography, and two with only magnetic resonance angiography. In one patient, complete stent thrombosis was diagnosed by magnetic resonance imaging and magnetic resonance angiography (*Fig. 2, A–E*). A second patient with a basilar stent underwent only magnetic resonance angiography, which demonstrated flow-related enhancement throughout the stented segment. This was adjudicated as "no ISR." The average interval between lesion treatment and the most recent follow-up evaluation is 5.9 months.

Of those patients with follow-up, 25 have demonstrated ISR (29.7%) and an additional four have demonstrated complete thrombosis (4.8%). Two of the four patients with delayed (>30 d) stent thrombosis had lengthy lesions requiring more than one stent to bridge the diseased segment. In one other patient, antiplatelet medications had been interrupted because of gastrointestinal bleeding before stent thrombosis. In the fourth patient, the stent was placed within the A1 segment of the anterior cerebral artery, a vessel measuring only 1.5 mm in diameter. This is the only anterior cerebral artery stent placed in our series. Two of the four patients with stent thrombosis were symptomatic with stroke. Of these, one patient with a basilar stent thrombosis who presented initially with stroke, subsequently died (*Fig. 2, A–E*).

ISR was more frequent (odds ratio, 4.7; 95% confidence intervals, 1.4–15.5) within the anterior circulation (42% overall; 44.8% internal carotid artery, 38.1% middle cerebral artery) than the posterior circulation (13.3% overall; 13.3% basilar artery, 13.3% vertebral artery) (*Fig. 3*). A history of smoking or current tobacco use was slightly more common in patients with ISR (72%) than in those who had no ISR (54%); however, this trend did not reach statistical significance (odds ratio, 2.2; 95% confidence interval, 0.76–6.2). An evaluation of other medical risk factors for vascular disease (*Table 1*) did not reveal any predisposing trends toward ISR. There was no trend towards a difference in the severity of the initial stenosis, the post-PTAS or post-stenting residual stenosis, or the incidence of post-stenting angioplasty (i.e., post-dilation) between the ISR and no ISR groups (*Table 2*).

Of the 29 patients with ISR or thrombosis, eight were symptomatic. Four were symptomatic with stroke, including two with ISR (both minor strokes) and two with thrombosis (one minor stroke and one major stroke with subsequent death). The other four patients experienced transient ischemic attacks. Fifteen restenoses have been retreated (*Fig. 4*); 13 patients were treated with angioplasty alone, two of whom required angioplasty and placement of a second stent.

Of the patients requiring retreatment, four were complicated by clinically silent in-stent dissections (*Fig. 4*), two of whom required the placement of a second stent. One was complicated by a postprocedural reperfusion hemorrhage (*Fig. 5, A–D*).

DISCUSSION

We present the interim angiographic follow-up results from our prospective multicenter Wingspan registry. The most important findings from our registry include the following: 1) the observed rate of ISR in our series is higher than that reported in the initial HDE Wingspan study (2); 2) the majority of patients with ISR are asymptomatic; 3) the rate of ISR is higher for stents placed within the anterior circulation compared to the posterior circulation; and 4) retreatment of these lesions can be performed safely; however, the appropriate threshold for the retreatment of asymptomatic lesions remains unclear.

Rate of ISR

In our series, the rate of ISR was substantially higher than that reported in the HDE study (29.7 versus 7.5%). There were no significant differences between the patient populations in terms of demographic characteristics or risk factors. The average pretreatment stenosis, post-PTAS, and post-stenting stenosis were similar in both studies. In our registry, 60.6% of lesions treated and 61.9% of lesions with angiographic follow-up were within the anterior circulation versus 48.9% in the HDE study (2). Given that the rate of ISR observed for anterior circulation lesions was approximately three times greater than that of posterior circulation lesions, this difference in lesion distribution may have influenced the observed ISR rates to some degree.

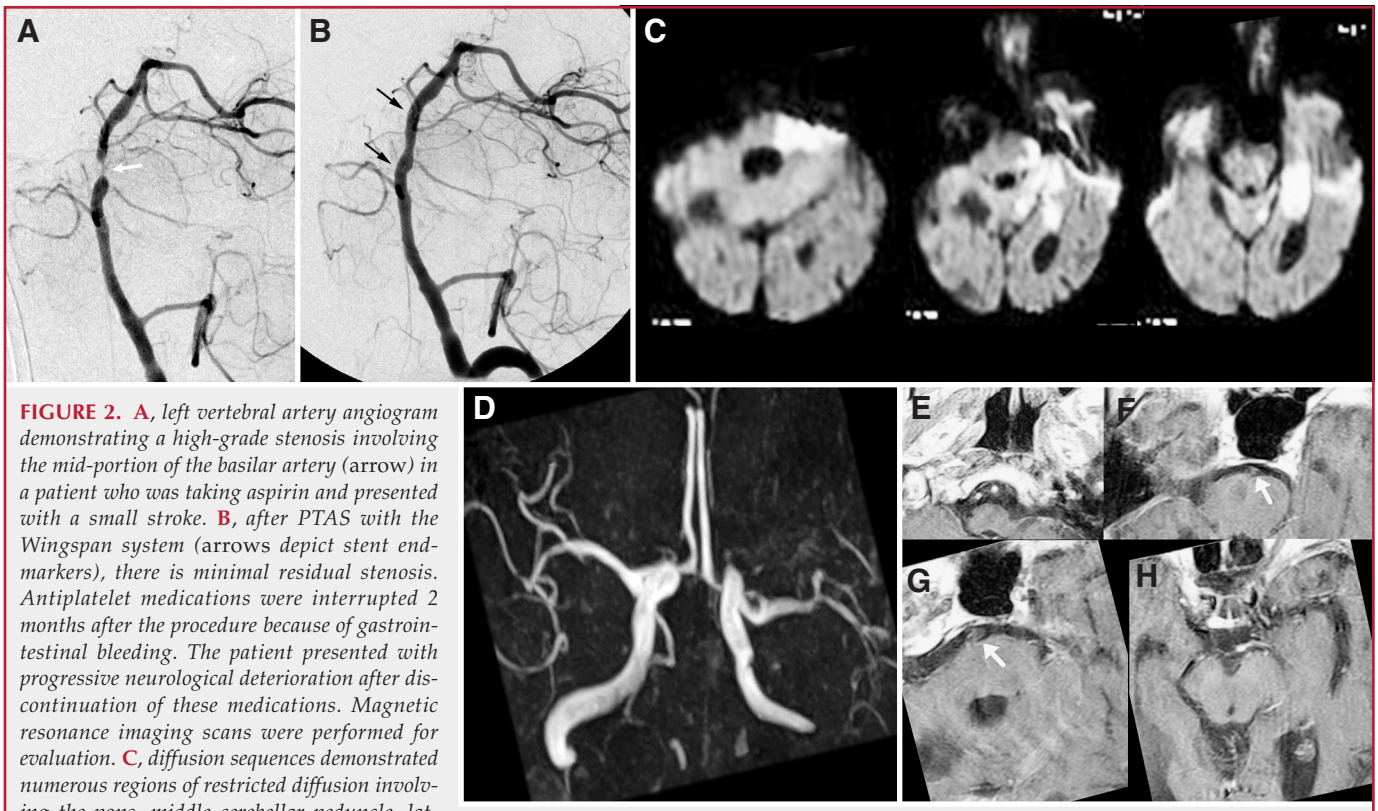


FIGURE 2. **A**, *left vertebral artery angiogram demonstrating a high-grade stenosis involving the mid-portion of the basilar artery* (arrow) *in a patient who was taking aspirin and presented with a small stroke.* **B**, *after PTAS with the Wingspan system* (arrows *depict stent end-markers), there is minimal residual stenosis. Antiplatelet medications were interrupted 2 months after the procedure because of gastrointestinal bleeding. The patient presented with progressive neurological deterioration after discontinuation of these medications. Magnetic resonance imaging scans were performed for evaluation.* **C**, *diffusion sequences demonstrated numerous regions of restricted diffusion involving the pons, middle cerebellar peduncle, lateral cerebellum, and left medial temporal lobe.* **D**, *maximum-intensity projections from a 3-dimensional time-of-flight magnetic resonance angiographic image showing no flow-related enhancement within the posterior circulation.* **E–H**, *axial T1-weighted postcontrast sequence showing contrast enhancement within the vertebral arteries and basilar apex (from posterior communicating artery collaterals), consistent with slow flow. The mid-portion of the basilar artery* (arrows) *is filled with intermediate signal, consistent with thrombosis.*

Significance of ISR

Most (76%) patients with ISR in our series were asymptomatic at the time of diagnosis. Those patients with symptomatic ISR presented primarily with transient ischemic attacks (n = 4) that resolved after successful treatment. The two patients with ISR who presented with stroke had relatively minor events, consisting of multiple small, subcortical infarcts on diffusion-weighted imaging.

Symptomatic patients with ISR in our series underwent retreatment. The clinical implications of asymptomatic ISR, particularly over the long term, are unknown. The optimal medical management of asymptomatic patients with ISR is unclear. There are also no established "threshold levels" of restenosis or other imaging criteria (e.g., perfusion imaging parameters) to guide the retreatment of asymptomatic ISR.

Given the current absence of data regarding the long-term prognosis of asymptomatic Wingspan ISR, it is difficult to provide a strong recommendation, either for or against, serial follow-up imaging in asymptomatic patients. We continue to perform a protocol-based follow-up imaging regimen, typically with conventional catheter-based angiography and sometimes with computed tomographic angiography. Patients are maintained on dual antiplatelet therapy until the 3- to 6-month follow-up examination is completed. If follow-up imaging shows no ISR, one of the agents is discontinued. When asymptomatic ISR is identified, patients are typically either retreated with angioplasty or maintained on dual antiplatelet medications at the discretion of the managing physicians. In all patients, maximal statin therapy is instituted and risk factor management is aggressively pursued from the time of treatment.

Predictors of ISR

Of all the findings in the current series, the discrepancy between the distribution of ISR within the anterior and posterior circulation was the most striking. To our knowledge, this phenomenon has not been previously observed. However, the preexisting balloon-mounted coronary stents could not be easily delivered into the anterior circulation, particularly the middle cerebral artery. For this reason, many previous studies of intracranial PTAS have been weighted toward posterior circulation lesions (4, 9).

With respect to risk factors, only tobacco use was associated with a weak trend towards a higher level of ISR. Although nearly three-quarters of the patients with ISR were current

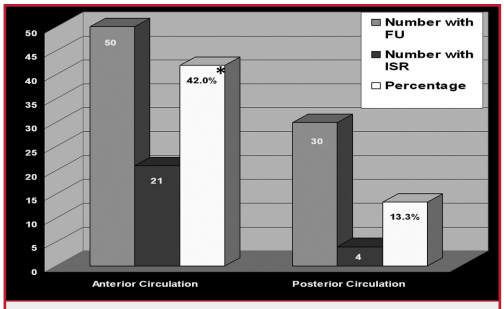


FIGURE 3. *Bar graph showing the distribution and Incidence of ISR by vascular distribution (anterior versus posterior circulation). The* gray bars *represent the number of Wingspan stent-treated lesions with follow-up imaging. The four patients with complete thrombosis were not included in this analysis. The* black bars *represent the number of lesions demonstrating ISR at follow up. The* white bars *represent the percentage of lesions demonstrating ISR at the time of follow up in each group. The rate of ISR observed within the anterior circulation is significantly greater than that observed within the posterior circulation.* Asterisk, *odds ratio, 4.7; 95% confidence intervals, 1.4–15.5.*

TABLE 1. Clinical characteristics and in-stent restenosis

	In-stent restenosis	No in-stent restenosis
Age (yr)	59.9	63.5
Qualifying event (no. of patients)		
Stroke	17	27
Transient ischemic attack	7	21
Other	1	1
Risk factors (% of patients)		
Hypertension	88%	88%
Hyperlipidemia	36%	37.5%
Hypercholesterolemia	52%	43.8%
Diabetes	48%	45.8%
Coronary artery disease	36%	39.6%
Peripheral artery disease	16%	20.8%
Smoking (% of patients)		
Any	72%	54%
Current	28%	32.6%
Former	44%	21.7%
Never	28%	46%

tobacco users or had a history of tobacco use, only approximately half of patients without ISR fell into this category. Other risk factors did not seem to be important. Balloon diameter was, on average, slightly (approximately 0.3 mm) smaller in patients with ISR. The angioplasty balloon was selected on the basis of the diameter of the normal parent vessel, thus providing a surrogate indicator of vessel size. This observation suggests that the smaller vessels treated in our series were more susceptible to ISR. No other specific characteristics of the procedure seemed to have a significant influence either, including postdilation or stent sizing.

TABLE 2. Lesion characteristics[a]

	In-stent restenosis (25 lesions)	No in-stent restenosis (55 lesions)
Stenosis		
Pretreatment stenosis	77.1%	73.8%
Post-PTA stenosis	46.2%	44.9%
Post-Wingspan stenosis	29.3%	29.4%
Technique		
Post-dilation	2/25 (8%)	3/55 (5.5%)
Balloon diameter (mm)	2.29[b]	2.64
Stent diameter (mm)	3.66	3.88
Stent-to-balloon diameter ratio	1.65	1.52

[a] PTA, percutaneous transluminal angioplasty. Four lesions with stent thrombosis are not included here.
[b] $P < 0.05$.

Retreatment

In our series, retreatment of both symptomatic and asymptomatic lesions was typically achieved without clinically evident complications. However, reangioplasty was not always technically straightforward. The open-cell design of the stent and its relatively low metal surface area coverage often allow passage of the microwire between the stent tines and vessel wall (i.e., outside of the "true lumen" of the stent) during attempted catheterization. This is frequently encountered as the stent courses around vascular curves. Even months after the stents are placed, passing through them with a microwire and subsequently an angioplasty balloon catheter can be challenging. In-stent dissections, with discrete, angiographically visible, in-stent dissection flaps, seem to be a unique technical complication of re-angioplasty within the Wingspan stent. The open-cell design and relatively low metal surface area coverage of the Wingspan may account for this phenomenon in which the hyperplastic in-stent tissue is more easily disrupted during angioplasty. In those cases in which the dissection was felt to compromise flow, the flaps were easily secured with the placement of a second Wingspan device. In all cases, these in-stent dissections were clinically silent.

Stent Thrombosis

More concerning from a clinical standpoint than ISR is the delayed occurrence of stent thrombosis, which was observed in four cases. In each of these cases, deviations from the typical application of the device or posttreatment management strat-

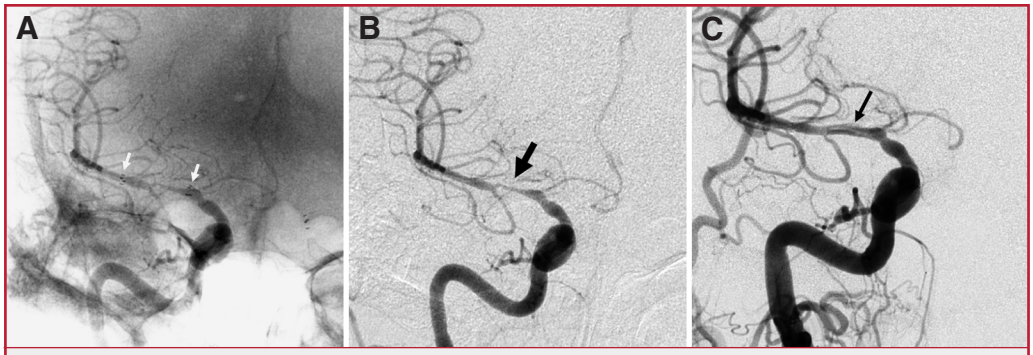


FIGURE 4. **A** and **B**, *follow-up angiograms obtained 5 months after successful Wingspan PTAS demonstrating a long segment of high-grade ISR involving the proximal half of the stented M1 segment of the MCA (***A****, native image,* arrows *denote stent markers;* **B****, subtracted image,* arrow *denotes high-grade ISR).* **C****, after retreatment with angioplasty, an in-stent dissection flap (*arrow*) is apparent. This dissection did not result in flow limitation; for this reason, an additional stent was not placed. The patient emerged from the procedure neurologically intact and remained so at the time of follow-up.*

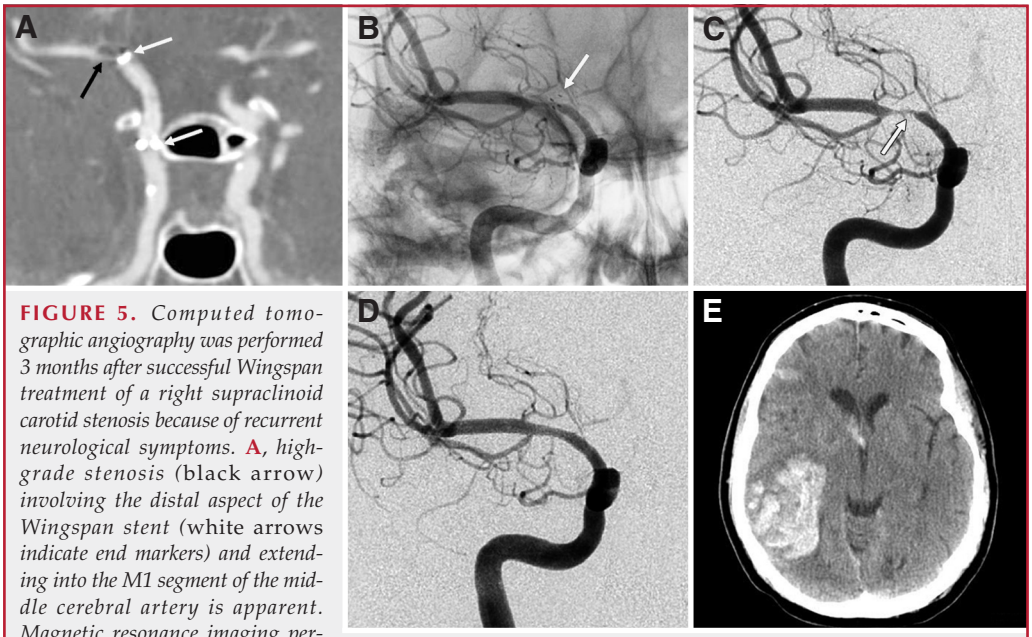


FIGURE 5. *Computed tomographic angiography was performed 3 months after successful Wingspan treatment of a right supraclinoid carotid stenosis because of recurrent neurological symptoms.* **A****, high-grade stenosis (*black arrow*) involving the distal aspect of the Wingspan stent (*white arrows *indicate end markers) and extending into the M1 segment of the middle cerebral artery is apparent. Magnetic resonance imaging performed at this time demonstrated multiple small diffusion-positive lesions within the ipsilateral hemisphere in an MCA distribution.* **B** and **C****, angiography confirmed this stenosis extending from the end-markers (*arrows*) of the stent distally into the proximal M1 segment of the MCA (***B****, native image;* **C****, subtracted image).* **D****, after retreatment with angioplasty, the stenosis is resolved. Although the patient emerged from anesthesia neurologically intact, a neurological decline occurred several hours after the procedure and prompted the performance of a cranial computed tomographic scan (***E****), which demonstrated a large reperfusion hemorrhage.*

egy occurred. In two cases, the lesions treated involved a long segment of the target vessel and multiple serial stents were required to achieve adequate lesion coverage. In one case, the patient was taken off antiplatelet medications because of gastrointestinal bleeding. In the final case, a very small vessel, the A1 segment of the anterior cerebral artery, was stented. Each of these scenarios, particularly the application of multiple contiguous serial stents to treat a single diseased vascular segment and the premature discontinuation of antiplatelet medications, should be avoided whenever possible.

CONCLUSION

Wingspan ISR occurred in our "real-world" registry at a rate that was significantly higher than that reported in the European HDE trial. However, the majority of patients were asymptomatic, and symptomatic patients usually presented with either transient ischemic attack or minor stroke. Stents placed within the anterior circulation developed ISR at a higher rate than those placed within the posterior circulation. No other significant risk factors for, or predictors of, ISR were identified. The retreatment of ISR has been relatively safe; however, the criteria for the retreatment of asymptomatic lesions remain unclear. Stent thrombosis has been observed in four cases, and, although cause for concern, this has typically been attributable to specific circumstances.

Disclosures

Felipe C. Albuquerque, M.D., serves as a consultant and on the Advisory Boards of Boston Scientific, Cordis, and Micrus. David J. Fiorella, M.D., Ph.D., has received grant support from and serves on the Speaker's Bureau and as Honoraria for Boston Scientific and as a consultant for Cordis Neurovascular. L. Nelson Hopkins, M.D., has received industry grant support and consultant fees from Boston Scientific, Cordis, EndoTex, and Micrus; is a stock- or shareholder for EndoTex and Micrus; serves as Honoraria-Bard for Boston Scientific, Cordis, and Medsn; and serves as a boardmember, trustee, or officer for Access Closure, marketRx, and Micrus. Elad I. Levy, M.D., has received industry grant support from Boston Scientific and Cordis; serves as Honoraria for Boston Scientific and Cordis; and receives patent royalties from Zimmer Spine. Cameron G. McDougall, M.D., serves as Honoraria for Boston Scientific. David B. Niemann, M.D., serves as a consultant or on the advisory board for Boston Scientific, Cordis, ev3, and Micrus; serves on the Speakers Bureau and as Honoraria for Cordis, ev3, and Micrus; and has received research grants from

Cordis, ev3, and Micrus. Lee Pride serves as Proctor for ev3 and Cordis. Phil Purdy serves as a consultant for Cordis. Peter A. Rasmussen, M.D., serves on the Speakers Bureau and as Honoraria for Boston Scientific. Aquila S. Turk, D.O., has received research support from Boston Scientific, GE Healthcare, and Biomerix Corp., and serves as a consultant for Boston Scientific. Babu Welch serves as a consultant for Medtronic. Henry Woo, M.D., has ownership interest in ev3 for consulting services and serves as a consultant and on the Advisory Board for ev3.

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COMMENTS

The authors report on their experience treating 84 lesions in 79 patients with the Wingspan (Boston Scientific/Target, Freemont, CA) stent design for atherosclerotic intracranial occlusive disease. It is important to note that the rate of intrastent stenosis was documented in 25 patients with complete thrombosis in four patients for an overall incidence of 29.7%. This is certainly quite concerning and something that I think is important to have when discussing this potential treatment with patients. Unfortunately, the investigators were not able to determine specific epidemiology of technical risk factors. Tobacco use was only associated with a weak trend towards a higher level of intrastent stenosis, which may, perhaps, pan out when the cohort is larger. There were no specific characteristics of the procedure appearing to have a significant influence in terms of postdilatation or stent sizing. Although retreatment of symptomatic and asymptomatic lesions was reportedly relatively safe, it was technically difficult in terms of advancing a wire across the lesion to avoid the creation of a dissection or a false lumen.

The other point to which the authors alluded was the incidence of delayed intrastent thrombosis. In two of the cases, the lesions were long; in one case, the patient had been taken off of antiplatelet therapy because of gastrointestinal bleeding. Clearly, this new treatment is an advance considering the data and the natural history of this pathology. I am certain that, as the technology improves, this will be less of an issue. Be that as it may, this is important information to have at hand when discussing these procedures with patients and families.

Robert H. Rosenwasser
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The authors have reported on the rate of in-stent stenosis after placement of a Wingspan stent. The data was obtained from a prospective intent-to-treat multicenter registry compiled at well known institutions with large cerebrovascular practices. Their data has demonstrated much higher than expected rates of in-stent stenosis and complications and readdresses the question of whether or not the placement of an intracranial stent is good clinical practice for patients with intracranial stenosis compared with the best medical therapy. This is a very interesting and important article that is needed in the literature. From a scientific viewpoint, the real question that needs to be answered is: Why is the rate of in-stent stenosis is higher for atherosclerotic lesions compared with nonatherosclerotic lesions (e.g., Neuroform [Boston Scientific] for aneurysms)? Is it because predilatation with a balloon injures the endothelium? Is oversizing the stent injuring the endothelium or vascular smooth muscle? Or, is it because the pre-existing atherosclerotic lesions set up the restenosis pathway? The latter has to be dissected in the laboratory, but this clinical report is important as it will provide the evidence for the need for the basic science research in addition to questioning the indications for stenting of intracranial stenosis.

Gavin W. Britz
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The data presented in this article is of great value as it reassesses the incidence of Wingspan in-stent restenosis and thrombosis in a patient cohort approximately double that of the joint European-Asian Humanitarian Device Exemption study conducted earlier (2). The results of this series suggest a higher in-stent restenosis rate than previously reported, 29.7 versus 7.5%, respectively. When compared with this previous study, a higher proportion of anterior circulation lesions were treated (61 versus 49%, respectively). Interestingly, in-stent stenosis was more likely in the anterior circulation, a finding not previously reported. Nonetheless, the majority of restenoses in this study remained asymptomatic. Complete thrombosis occurred in 4.8% of the patients, which led to fatality in 1.2% of the patients. Tobacco use proved to be the only risk factor positively related to restenosis rate.

Although a comparison of the current series with the Humanitarian Device Exemption study is appropriate, several limitations exist when making this comparison. Stent length, parent vessel size, lesion length, and lesion type are among the important variables that can impact outcomes and may confound comparisons with previous cohorts. It is possible that factors that are not evident may explain the higher in-stent stenosis rate seen in this study when compared with previous data.

It is our sense that intracranial atherosclerosis is a highly heterogeneous disease with regards to response and complications related to endovascular intervention. This issue was clearly illustrated by Mori et al. (9) in a study that assessed outcomes after angioplasty for intracranial stenotic lesions. In this study, lesions were classified into three groups based on certain angiographic characteristics. Type A included short (length ≤ 5 mm), concentric or moderately eccentric

lesions not completely occlusive; Type B included tubular (5–10 mm), extremely eccentric or totally occluded lesions less than 3 months old; and Type C included diffuse (>10 mm), extremely angulated (>90°) lesions with excessive tortuosity of the proximal segment, or completely occluded lesions 3 or more months old. The results showed an overall risk of fatal or nonfatal ipsilateral ischemic stroke and ipsilateral bypass surgery of 8, 26, and 87% in Types A, B, and C lesions, respectively, at 1 and 2 years. It is likely that such heterogeneity will affect stenting results.

The natural history of intracranial stenoses after medical treatment has recently been reviewed in the Study Group on Survival of Heart Failure in Argentina study and showed a recurrent ischemic event rate of 38.2% in the territory of the stenotic artery at the time of the 2-year follow-up evaluation, as well as a mortality rate of 8.8% (8). The study further supports the consideration of endovascular modalities as part of the armamentarium to treat these lesions.

There is no doubt that studies aiming at evaluating in-stent restenosis are invaluable, as the risks associated with such recurrent stenoses are yet to be clearly defined. In the Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries trial, all ipsilateral strokes were associated with in-stent restenosis (11). Moreover, stenting encompasses other inherent risks and some authors have evaluated the use of angioplasty alone for the treatment of symptomatic intracranial stenoses. In two different studies, Marks et al. (6, 7) reported high procedural success rates and low complication rates with annual ipsilateral stroke rates of approximately 3%. They concluded that angioplasty alone was safe and efficacious in preventing future stroke in patients with symptomatic intracranial stenoses. Another alternative that might be considered in the management paradigm of these lesions is an approach using drug coated stents (10). Levy et al. (4, 5) have published studies on the use of drug eluting stents in canine models and have found them to be safe in the cerebral vasculature, because they do not hamper the endothelialization process while maintaining vascular patency. Another therapeutic variant that might be advocated in certain challenging cases is a staged stent-assisted angioplasty technique. This method may reduce the procedure-related morbidity in symptomatic intracranial vertebrobasilar artery stenoses that are of high grade, increased length, recently symptomatic, or related to a tortuous vasculature. Previous angioplasty would allow for a larger luminal diameter that could safely accommodate bulkier devices such as stents. Furthermore, it would allow for scar tissue formation and lesion stabilization, thus constituting a safer milieu for stent deployment (3). We have favored this approach for complex lesions, especially in perforator rich zones.

For the above reasons, we agree with the authors that a randomized trial to evaluate medical management versus stenting for intracranial atherosclerosis is premature. More experience is needed by practitioners before a plateau is reached in comfort with the technique and approach to this disease. Failure to account for the heterogeneity of these diseases was also noted in the EC/IC Bypass Study Group trial published in the *New England Journal of Medicine* in the mid 1980s (1).

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INTRANEURAL PERINEURIOMA OF THE VIIITH CRANIAL NERVE: CASE REPORT

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OBJECTIVE: The authors describe the clinical and pathological features of the second reported case of an intraneural perineurioma involving a major intracranial nerve and the first case of this entity involving the VIIIth cranial nerve.

CLINICAL PRESENTATION: A 59-year-old woman presented with a long history of dizziness, tinnitus, hearing loss, and unstable gait. A magnetic resonance imaging scan revealed a small intrameatal lesion, which showed no clear progression from 2000 to 2006.

INTERVENTION: As a result of worsening symptoms and a suspected vestibular schwannoma, an attempt of tumor resection through a retrosigmoid approach was performed. This revealed diffusely infiltrated and fusiform enlarged vestibular and cochlear nerves, with no identifiable border between the main tumor mass and normal nerve. An *en bloc* nerve-tumor mass excision was performed. The pathological findings confirmed the diagnosis of an intraneuronal perineurioma.

CONCLUSION: The experience with this unique case and the experience of others with the management of extracranial intraneural perineuriomas lead the authors to conclude that the most reasonable surgical management of this tumor at this location is a nerve-tumor cross-section resection.

KEY WORDS: Cranial nerve tumor, Intracranial intraneural perineurioma, Vestibular schwannoma

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Perineuriomas are uncommon, mostly benign, nerve sheath neoplasms that arise from perineurial cells and are classified into two general types: intraneural and soft tissue perineuriomas, with the latter apparently not associated with nerves (1, 6, 8, 9, 13). Recently, three subvarieties of the soft tissue perineurioma have been recognized, including the fibrous, sclerosing, and reticular types (8, 13). Malignant proliferation of perineural cells has recently gained acceptance as a concept, and malignant perineurioma has increasingly been recognized as a discrete entity (12, 23). However, given the limited number of cases that have been reported, a consensus has yet to be reached involving the exact classification and the biological behavior of the more recently recognized variants.

Intraneural perineuromas (INP) are extremely rare tumors composed exclusively of perineural cells and involve mainly peripheral nerves (6, 9, 10, 11). They are composed of perineurial cells, which penetrate the endoneurium and form concentric layers around nerve fibers in characteristic pseudo-onion bulb formations, which demonstrate immunoreactivity for epithelial membrane antigene (EMA) but not for S100 protein. This feature distinguishes the perineuriomas from a Schwann cell process, which contains true onion-bulbs and is EMA-negative and S100-positive. Historically referred to as localized hypertrophic neuropathy (9), it is now believed that INP is a true tumor. Emory et al. (6) demonstrated the true neoplasmic nature of the lesion, which is associated with the loss of a gene on chromosome 22. All reported cases of INP have been benign tumors that have not displayed metastasis.

An extensive literature review by Al-Mefty et al. (1) showed that only three cranium-related INPs have been reported. Two lesions involved cranial nerves at their extracranial course, the facial nerve in the mastoid segment in one and the mandibular nerve in the other (16, 18). In the third case, the tumor, arising in

the choroid plexus of the third venrticle, was apparently not associated with a nerve, but the authors speculated on a possible origin from minor nerve twigs within the choroid plexus because sympathetic nerves are known to be present in the normal choroid plexus (7). In some other reports of cranial nerve neoplasms with onion-bulb formation, of which three occurred in the trigeminal nerve (2, 4, 17), four occurred in the VIIIth cranial nerve (20, 21), and one occurred in the facial nerve (14), the Schwann cell was acknowledged as the origin of the tumors. In our literature review, we detected one report of a process with onion bulbs involving the VIIIth cranial nerve recognized as interstitial hypertrophic neuritis (3). Because of the lesion's similarity to a schwannoma and because of different classifications in the past, it is difficult to determine how many cases of cranium-related INP have been reported previously. Here, we present the clinical and pathological features of the first reported INP of the VIIIth cranial nerve.

Case Report

History

A 59-year-old Greek woman presented to our institution in 2006 with a long history of slow progressive dizziness, hearing loss, tinnitus, and unstable gait since 1999. A magnetic resonance imaging (MRI) scan performed in 2000 revealed a small left intrameatal lesion (*Fig. 1*). Over the course of the following years, worsening of symptoms occurred. Since 2001, she was not able to use her left ear for telephoning. The most recent MRI scan, obtained in 2006, showed no clear progression of the tumor (*Fig. 1*). Because her symptoms progressed, we decided to operate on the tumor.

Examination

On physical examination, the patient exhibited some minor gait instability and pathological Romberg and Unterberger signs. Preoperative audiograms revealed a hearing loss of 60 dB at 1 KHz. MRI scans revealed a small intrameatal mass with imaging characteristics mimicking a vestibular schwannoma (*Fig. 1*).

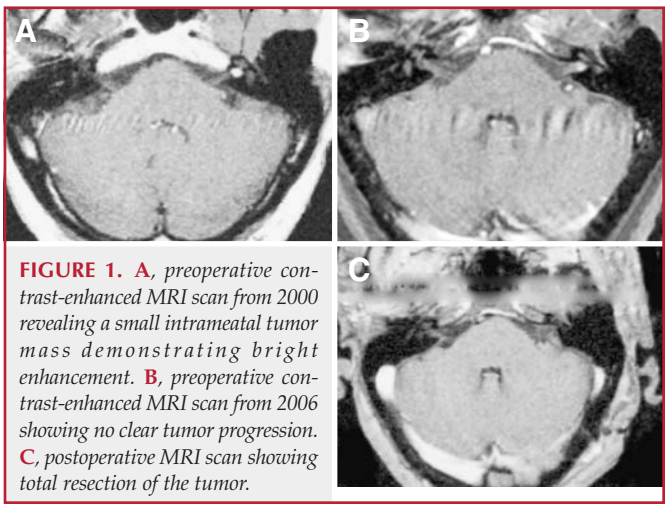


FIGURE 1. A, *preoperative contrast-enhanced MRI scan from 2000 revealing a small intrameatal tumor mass demonstrating bright enhancement.* **B**, *preoperative contrast-enhanced MRI scan from 2006 showing no clear tumor progression.* **C**, *postoperative MRI scan showing total resection of the tumor.*

Operation and Postoperative Course

The patient underwent a standard suboccipittal retrosigmoid approach. Intraoperatively, all three parts of the VIIIth nerve (superior and inferior vestibular as well as cochlear) were infiltrated with tumor masses. The main lesion was found to arise from the cochlear nerve, making us doubt that it was a typical schwannoma. The nerve was sacrificed in order to extirpate the tumor. No infiltration of the facial nerve was observed, and the nerve was preserved. Postoperative MRI scans revealed no tumor remnant (*Fig. 1*). The patient recovered well in the postoperative course, having some exaggeration of tinnitus and moderate gait instability at the time of discharge. At her 4-month follow-up examination, a satisfactory improvement of the gait disturbance was observed. Tinnitus and exaggerated gait instability in darkness remain the patient's major complaints.

Neuropathological Findings

Histological evaluation revealed a neoplasm with moderate cellularity. The tumor cells were spindle-shaped with elongated nuclei and bipolar cytoplasmic processes (*Fig. 2*). A diffuse infiltration of the nerve was noted. There were many concentric whorls of cells. Mitoses or necroses were not observed. Immunohistochemistry showed strong positivity for EMA but negativity for S100 protein (*Fig. 2*). The Ki67/MIB1-proliferation index was below 1%. These pathological findings were consistent with a benign tumor of perineural origin; thus, the diagnosis of benign intraneural perineurioma of the VIIIth cranial nerve was made.

DISCUSSION

Because this is the second reported case of an intraneuronal perineurioma involving a major intracranial nerve, no general suggestions can be made regarding the optimal management of these tumors. The natural history of our patient was that of slow worsening symptoms, probably caused by a very slow growing tumor. The effect of radiotherapy is also unknown because, to our knowledge, no attempt has been made until now to radiate the peripheral INP.

From the surgical perspective, the growth pattern of the tumor is completely different from that of a schwannoma. As in the case reported by Al-Mefty et al. (1) and other cases of extracranial INPs, the tumor intraneurally and diffusely infiltrates the nerve fascicles, embedding the nerve fibers into whorls of neoplasmic perineural cells. It spreads intraneuronally and grows along the nerve. Usually, no discreet fascicles can be identified within the mass (5, 10). No exophytic component unassociated with nerve fibers has been reported. This growth pattern gives the macroscopic and radiographic appearance of an enlarged fusiform nerve without a defined mass (24). Another important issue is that the tumorous process exceeds the macroscopic identifiable main tumor mass and diffusely infiltrates the part of the nerve that appears to be uninvolved. Considering these two issues, it seems impossible to shell out such lesions as can be done

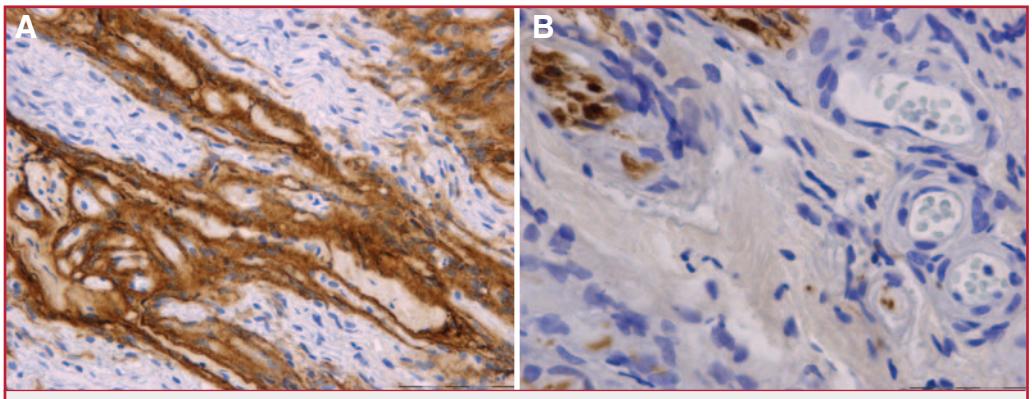


FIGURE 2. A, *EMA-positive* (brown) *spindle-shaped tumor cells infiltrate between and within nerve fascicles, the latter being negative for EMA.* **B**, *in contrast, tumor cells are negative for S100-protein, while positivity is restricted to Schwann cells of nerve fascicles. Note the whorls of tumor cells in* **B**.

with a schwannoma or a neurofibroma and have long-term maintenance or recovery of function. However, because the cranial nerve fascicles are sometimes not as tight to each other as the fascicles of a peripheral nerve, it would be possible, especially in early stages of the disease, that the tumor leaves some parts of a nerve uninvolved, allowing for the preservation of some parts of the nerve.

In our case, we found an enlarged cochlear and vestibular nerve with no identifiable border between the tumor and normally appearing nerve. This was also in agreement with the microscopic examination, which showed an enlarged nerve segment diffusely infiltrated by tumor. Thus, the only option left in order to excise the tumor was to resect the nerve-tumor mass *en bloc*.

There are different opinions regarding the optimal management of peripheral INPs. To our knowledge, there is only one report of a peripheral INP in which a clear border between tumor and normal uninvolved nerve fascicles could be identified and the tumor could be shelled out, preserving normal appearing fascicles (11). Although no neurological improvement was seen in this case after 2 and 5 years, the authors state that it is possible to excise the tumor without graft placement and observe some improvement of function in some cases. In their comment on this opinion, Kline et al. (15) state, "often what appear to be uninvolved fascicles in this disease are actually fascicles with some degree of change, but less severe than the more involved portion of the nerve" and "over time those changes usually progress and become more severe." They recommend resection of the involved nerve and graft repair (9, 15, p 238). Cortes et al. (5) also propose an algorithm for the surgical management of focal intraneural tumors, whereby failing to identify a tumor-fascicles border indicates the presence of an INP and should be managed with excision and graft repair. Their suggestion "reflects the identification of INP as a benign, progressive neoplastic entity." Thus, it seems that the most favorable approach for peripheral INPs is a total cross-section resection of the nerve and replacement with autologous graft.

One more interesting issue in our case is that the tumor, which apparently originated from the cochlear nerve, invaded the vestibular nerve as well, which was also macroscopically enlarged. Because INP spread intraneuronally, this observation could be the result of interconnections between the cochlear and vestibular nerves. Previous studies have detected such interconnections between the cochlear, vestibular, and facial nerves (19, 22). Peripheral INP usually affects only one nerve in a given individual, but it can affect multiple plexus elements, which are usually interconnected (15, 24).

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COMMENTS

Intraneural perineuriomas are benign intraneural neoplasms composed mainly of perineurial cells that lead to fusiform nerve enlargement. Despite the identical clinical and radiological characteristics with vestibular schwannomas, they are a separate pathological entity and have typical immunohistochemical characteristics.

The authors describe the first reported case of an intraneural perineurioma involving the VIIIth cranial nerve. At the time of surgery, the cochlear, superior, and inferior vestibular nerves were found to be infiltrated by the tumor that originated from the cochlear nerve. It is thought that it invaded the vestibular nerves secondarily via the interconnections between these nerves.

En block nerve-tumor mass excision was performed. In view of the fact that the patient had profound hearing loss and the facial nerve was not infiltrated, this surgical strategy seems quite reasonable.

Venelin Gerganov
Madjid Samii
Hannover, Germany

This is a well-documented report of a very rare and interesting case. In patients with tumors of the cerebellopontine angle or the internal auditory canal who present with significant vestibular dysfunction, it has been our experience that sectioning the vestibular nerve proximal to the pathology, rather than preserving it, provides improved vestibular function in the long term, although the symptoms may worsen in the early postoperative period. Therefore, the surgical treatment would have been the same whether the tumor was found to be extrinsic (i.e., vestibular schwannoma) or intrinsic to the cranial nerves (as in this particular case), i.e. total removal of the pathology accompanied by complete sectioning of the involved nerves intraoperatively. We congratulate the authors for their well-written presentation.

Burak Sade
Joung H. Lee
Cleveland, Ohio

The authors present the second reported case of an intraneural perineurioma involving a major intracranial nerve and the first case of this entity involving the VIIIth cranial nerve.

The authors did an excellent job describing the clinical and pathological features of this extremely rare entity. They also described the features that distinguish these tumors of perineural origin from more common Schwann cell tumors.

Jose N. Fayad
Derald E. Brackmann
Neuro-otologists
Los Angeles, California

The authors have described what is probably the first case of an intraneural perineurioma involving the VIIIth cranial nerve. The intraoperative findings were interesting in that the superior vestibular, inferior vestibular, and cochlear nerves were all infiltrated with the tumor mass, although the facial nerve was preserved. The origin of the tumor seems uncertain in view of the involvement of all three nerves, although it is evident that this type of tumor does infiltrate diffusely. This case report is an important addition to the literature regarding the rare tumors that may be found in this region.

Andrew H. Kaye
Melbourne, Australia

CAVERNOUS HEMANGIOMA OF THE THIRD CRANIAL NERVE: CASE REPORT

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OBJECTIVE: The authors report a rare case of a cavernous hemangioma (CH) involving the third cranial nerve.

CLINICAL PRESENTATION: A 25-year-old Caucasian woman presented with neuralgic facial pain that responded to pharmacological management. She had no neurological deficit. Magnetic resonance imaging scans revealed a space-occupying lesion in the interpeduncular cistern with no evidence of hemorrhagic event. Preoperative cerebrospinal fluid and blood samples were negative for cytology and tumor markers.

INTERVENTION: The patient underwent craniotomy and exploration of the interpeduncular cistern. A lesion with the raspberry-like appearance characteristic of a CH was found emerging from between the fibers and completely encircling Cranial Nerve III. The surgeon decided to leave the lesion in place to avoid creation of a new neurological deficit in the young patient. The patient is asymptomatic with a stable radiological picture 18 months after surgery.

CONCLUSION: CH should be considered as a possible differential diagnosis of extra-axial space-occupying lesions along the course of the cranial nerves. Resection with resulting deficit may not be indicated in patients presenting with normal neurological function. Further research and longer follow-up periods are required to better understand the natural history of CH involving the cranial nerves.

KEY WORDS: Brain neoplasm, Cavernous hemangioma, Cranial nerves, Oculomotor, Surgical treatment

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A 25-year-old woman with an unremarkable medical history presented with a 3-month history of pain in the right occipital and hemifacial regions. The pain was stronger at night and did not respond to conventional analgesia, but resolved when carbamazapine was administered. Physical examination was normal, and the patient had no neurological deficit.

Computed tomographic scans of her head revealed an isodense mass without bony involvement in the right prepontine area just adjacent to the clivus. No enhancement was seen after administration of contrast material. T1-weighted magnetic resonance imaging (MRI) scans revealed a lesion with mixed high and low signal intensities, with only very subtle enhancement when gadolinium was administered (*Fig. 1, A* and *B*). On T2-weighted MRI scans, the lesion had mixed signal intensity with low intensity predominance. The lesion was situated at the level of the oculomotor nerve and in close proximity to the dura of the cavernous sinus and tentorial edge.

The patient was admitted to the neurosurgery department for further investigation. When cerebrospinal fluid cytology and tumor markers in the blood and cerebrospinal fluid were negative, a decision was made to proceed with surgery.

Intervention

The patient underwent a right pterional craniotomy. As the medial portion of the sylvian fissure was opened and the basal arachnoid cisterns were dissected, a red, multiloculated lesion with the raspberry-like appearance typical of a cavernous hemangioma (CH) came into view. The lesion was situated in the interpeduncular cistern ventral to the brainstem, between the tentorial edge, the right internal carotid artery, and the basilar artery. The CH was arising from among the fibers of the oculomotor nerve and completely encircled

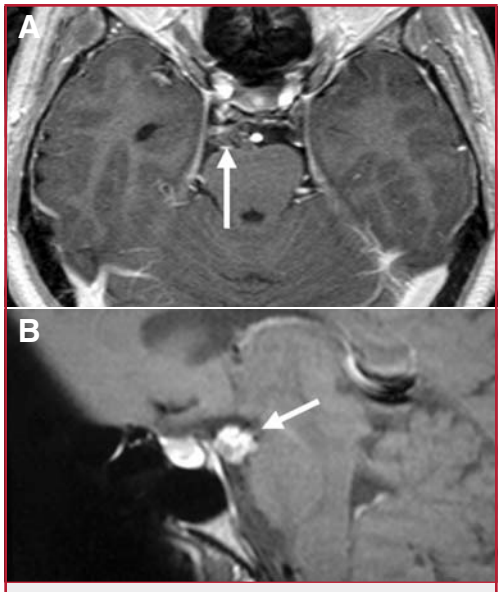


FIGURE 1. *T1-weighted axial (A) and sagittal (B) MRI scans after gadolinium injection demonstrating a lesion with irregular enhancement, located in the interpendicular cistern, ventral to the brainstem (arrows). The sagittal image clearly demonstrates flow voids in the posterior cerebral and superior cerebellar arteries. The lesion is located on the anatomic location of the oculomotor nerve.*

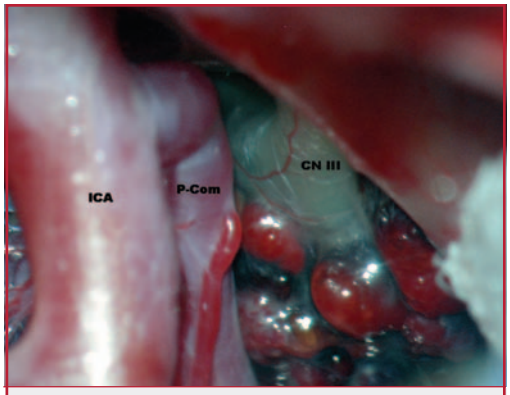


FIGURE 2. *Intraoperative microscopic photograph viewing a red multiloculated lesion with the raspberry-like appearance typical of a CH. The internal carotid artery (ICA) and posterior communicating artery (P-Com) are visible on the left. The lesion is seen arising from between the fibers and adherent to the third cranial nerve (CN III) in the interpeduncular cistern.*

it (*Fig. 2*). The surgeon decided not to resect the lesion to avoid postoperative oculomotor palsy.

The postoperative course was benign. The patient is followed with routine neurological examinations and periodic MRI scans. Eighteen months after surgery, she remains asymptomatic with a stable radiological picture.

DISCUSSION

Cavernomas are angiographically occult vascular malformations with an incidence of 0.3 to 0.5% and comprise 10 to 20% of all vascular malformations (6, 8). They are composed of large, sinusoidal, thin-walled capillary spaces that do not invade surrounding neural tissue (2, 3). They may appear sporadically or in a familial pattern (8). Most are intracerebral, although they have also been reported in the peripheral nervous system (2–4). CH rarely involve the cranial nerves; space-occupying lesions along the course of the cranial nerves are generally schwannomas. The differential diagnosis can be problematic.

Deshmukh et al. (1) described six cases and reviewed 44 previously reported cases of CH involving the cranial nerves. In 23 (46%) of these cases, the CH arose from the optic pathways. Twenty-two patients (44%) had a CH in the cerebellopontine angle involving the seventh and eighth cranial nerves; among these patients were four with concomitant vestibular schwannomas. The article also described one case of a CH involving the hypoglossal nerve in a patient with a 4-year history of weakness of the tongue.

Only four cases of CH arising from the third cranial nerve have been described in the literature (5, 7, 9, 10). Three of these patients presented with a hemorrhagic event resulting in oculomotor paresis that rapidly progressed to complete palsy (7, 9, 10). These patients where treated surgically, with transection of the oculomotor nerve in order to achieve total removal of the CH. The fourth patient with CH was a 36-year-old woman with a history of galactorrhea, amenorrhea, headache, and quadrant anopia. She presented with a large CH, mainly in the region of the cavernous sinus. The patient was treated surgically with partial resection of the lesion, resulting in oculomotor palsy (5).

The clinical course of the first three oculomotor CHs eased the surgeons' decisions. Because these patients presented with third cranial nerve palsy, radical resection of the lesion with sacrifice of the oculomotor nerve was a curative procedure that did not create new neurological deficit. In the fourth patient, subtotal resection as the result of cavernous sinus proximity nevertheless led to new oculomotor paralysis.

We describe CH in a young female patient who presented with fifth cranial nerve symptoms that led to radiological investigation. Computed tomographic and MRI studies showed a lesion on the oculomotor nerve bordering the dura of the cavernous sinus and touching the fifth cranial nerve. The patient's pain most likely originated from dural irritation. There was no clinical or radiological evidence of a hemorrhagic event before surgery and no oculomotor deficit.

At the time of surgery, we found an extracerebral CH arising among the nerve fibers and encircling the oculomotor nerve. Radical resection would result in complete oculomotor palsy because even slight damage to the third cranial nerve is associated with significant neurological deficit. The natural history

of CH involving the cranial nerves is unclear, and the patient had no history of hemorrhagic events. Should the cavernoma bleed, a subarachnoid hemorrhage would result, probably with less serious consequences than those expected from intracerebral hemorrhage. Review of the very limited relevant literature suggests the patient would likely experience oculomotor palsy after resection. We decided in favor of oculomotor nerve preservation based on the relatively low risk of hemorrhage from cavernoma left in situ. The patient remains asymptomatic and radiologically stable 18 months after surgery. We assume that our decision to preserve neurological function was correct in this young female patient.

CONCLUSION

CH should be considered as a possible differential diagnosis of extra-axial space-occupying lesions along the course of the cranial nerves. Conservative management and follow-up evaluation, with the goal of preserving neurological function, may be appropriate in patients with no history of hemorrhage and no existing deficit. Further research and longer follow-up periods are required to better understand the natural history of CHs involving the cranial nerves.

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We thank Shifra Fraifeld, M.B.A., for her editorial contribution to the preparation of this article.

COMMENTS

The authors describe a rare case of a cavernoma of the interpeduncular cistern, which involved the oculomotor nerve intimately. The authors made a wise decision to leave the tumor alone. Of course, the lesion may grow or hemorrhage, resulting in third nerve paresis, which may then necessitate an operation. The preoperative images and the intraoperative pictures are a very nice addition to this case report.

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The authors describe a very rare and interesting case of a cavernous hemangioma of the oculomotor nerve. The clinical presentation and management of the patient are presented briefly but accurately. The images are of high quality and supplement accordingly the text.

The lesion was located in the interpeduncular cistern, and the pterional approach with dissection of the medial part of the Sylvian fissure was used. Although a red, multiloculated lesion with the raspberry-like appearance is definitely typical of a cavernous hemangioma, the authors decided not to resect the lesion and the diagnosis was not proven histologically. We commend the authors for this decision: functional preservation should have a priority in benign lesions if the risk of neurological deterioration during their natural evolution is not higher than the surgery-related risk of morbidity.

The possibility of removing cranial nerve cavernous hemangiomas and avoiding postoperative deficit is debatable, and factors such as clinical presentation, previous bleeding, and degree of adhesion to the nerves should be taken into account. Cavernous hemangiomas arise within the cranial nerves or from adjacent vessels and compress the nerve secondarily (1). Because the presented patient did not have even a slight oculomotor deficit at the time of presentation, a secondary compression of the nerve could be assumed and its operative removal could be an alternative option. In a series of seven patients with cavernous hemangiomas within the internal auditory canal, we were able to dissect them away from the facial nerve in five cases. In two cases, the cavernomas involved the nerve so that the nerve had to be sectioned and repaired with a sural nerve graft. The outcome was good in all cases, and improvement was observed in each of them. The main difference with the presented case, however, was that all cases were symptomatic because of either bleeding or nerve compression.

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A Form of Dysplasia or a Fortuitous Association? A Cerebral Aneurysm Inside an Arachnoid Cyst: Case Report

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OBJECTIVE: Although arachnoid cysts and intracranial aneurysms are very common lesions, their association in the same patient is rare. We present a case of a middle cerebral artery aneurysm ruptured into an arachnoid cyst. We found only six cases with intracystic hemorrhage reported in the literature. The presence of an arachnoid cyst can mislead clinical presentation. The patient presented a paradoxically small temporal fossa and thickening of the temporal and sphenoid bone. The authors suggest that this uncommon association (arachnoid cyst, atypical cranial vault, and "mirror-like" cerebral aneurysm) could represent a form of dysplasia.

CLINICAL PRESENTATION: A 46-year-old patient presented with a 3-week history of slight headaches, which had worsened in the last 3 days before presentation. Computed tomographic scans showed a cystic lesion located in the middle cranial fossa and sylvian fissure with suspected aneurysm dilation inside. Magnetic resonance imaging scans showed an intracystic hemorrhage but not subarachnoid hemorrhage. Paradoxically, changes in the cranial vault around the cyst were noted. Digital subtraction angiography showed bilateral "mirror" middle cerebral artery aneurysms.

INTERVENTION: A large right pterional craniotomy was performed with full microsurgical removal of the arachnoid cyst walls and aneurysm clipping. The aneurysm was in the medial wall of the arachnoid cyst with its dome inside the cyst. The contralateral aneurysm was clipped 2 weeks later. The follow-up period was uneventful, and the patient returned to normal life.

CONCLUSION: Rupture of a cerebral aneurysm into an arachnoid cyst is rare. Clinical presentation may be unusual because the cyst can prevent subarachnoid hemorrhage. A middle fossa cranial arachnoid cyst in the presence of temporal bone depression, small middle fossa, and thickness of squamous temporal bone and the lesser wing of sphenoid is rare and suggests that congenital factors may play an important role in their development. The exceptional association between "mirror" aneurysms and arachnoid cyst with bone changes suggests a possible congenital form of dysplasia.

KEYWORDS: Arachnoid cyst, Cerebral aneurysm, Cranial vault, Dysplasia, Intracystic hemorrhage

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Intracranial aneurysms and arachnoid cysts are common pathologies whose etiologies have not been completely resolved. Rupture of an aneurysm causes classical sudden and intense headache, motivating the patient to seek medical attention. Bleeding of a cerebral aneurysm inside an arachnoid cyst has rarely been described. In a search of the literature, we found only six previously published cases (2, 5, 9, 10, 12, 31). We present another case of a bilateral middle cerebral artery (MCA) aneurysm that ruptured into a sylvian fissure arachnoid cyst. The clinical presentation in this case was unusual, leading to a delay in medical attention. The patient also presented with a history of temporal region cranial vault change since an early age. Apparent paradoxical vault changes in patients with arachnoid cysts have been described previously (19). To our knowledge,

no relationship between these findings has yet been discussed in the literature.

Case Report

A 46-year-old woman was admitted to our neurosurgical service in March 2002 with a 3-week history of sporadic headaches without vomiting that resolved with analgesia. She did not seek medical attention because she considered her symptoms unimportant. Three days before admission, she presented a new sudden headache associated with vomiting. There was no history of trauma or nervous system infection. Morbid antecedents were arterial hypertension, smoking, and a chronic polyradiculopathy. Her neurological examination was normal, without meningial signs. Since infancy, she had noted a cranial deformity with depression (atrophy) in the right temporal bone (*Fig. 1*). Computed tomographic (CT) scans showed a right cystic lesion located in the right middle fossa and sylvian fissure with intracystic hemorrhage. CT scans showed an increased thickness in the squamous temporal bone and lesser sphenoidal wing, with slight depression on convexity and small middle fossa. Contrast CT scans showed saccular dilation of the MCA suggesting an aneurysm (*Fig. 2, A–C*). Magnetic resonance imaging scans showed a cystic lesion in the right middle fossa and sylvian fissure with a slightly increased signal on T1-weighted and proton density images, isointense in fluid-attenuated inversion recovery images, and high in T2-weighted images, suggesting an intracystic hemorrhage. There were also signs of hemosiderin in the cyst boundaries and a void signal in the right MCA (*Fig. 2, D–F*). These clinical and image findings suggested a ruptured aneurysm into cystic lesion, which led us to perform digital subtraction angiography. A superiorly projecting ruptured right MCA bifurcation saccular aneurysm was identified along with a smaller unruptured left MCA bifurcation aneurysm in the mirror position (*Fig. 3*). There was no vasospasm. The patient underwent a large right pterional craniotomy for cyst evacuation and aneurysm clipping (*Fig. 4*). During surgery, the duramater was bulging and in tension. After opening the dura, the arachnoid cyst appeared to be bulging in the sylvian fissure. The cyst appeared blood-tinged and its boundaries were impregnated with hemosiderin. The wall was opened and fully removed. The cyst contained hemorrhagic, xantochromic fluid under pressure. The pathologist confirmed arachnoid cyst. The base of aneurysm was firmly adhered to the medial wall of the cyst, which was dissected, and the aneurysm was clipped. Two weeks later, the left aneurysm was clipped. The patient was discharged after another 5 days without deficits and returned to her normal activites.

DISCUSSION

An association between a ruptured aneurysm and an arachnoid cyst is rare. Only six have been previously reported with intracystic hemorrhage (ICyH) (*Table 1*) (2, 5, 9, 10, 12, 31). Jinkins et al. (12) were the first to describe a ruptured MCA aneurysm with subarachnoid hemorrhage (SAH) discharging within convexity arachnoid cyst. Hirose et al. (9) described a carotid artery bifurcation aneurysm into a media fossa arachnoid cyst without SAH. Barker et al. (2) described the rupture of an internal carotid-posterior communicating artery aneurysm with SAH and ICyH. Huang et al. (10) described an ICyH and subdural hematoma caused by MCA aneurysm rupture. Zanini et al. (31) described an ICyH with SAH caused by a carotid artery bifurcation aneurysm and discussed the etiopathogenetic mechanisms. Berhouma et al. (5) recently reported bilateral "mirror" MCA aneurysms with ICyH, SDH, and SAH. There are other reported cases of associated aneurysms and arachnoid cysts; however, all are without ICyH (3, 15, 24). Recent descriptions of parenchymal cysts around cerebral aneurysms (4, 22) and spontaneous intracystic hemorrhages without aneurysms (11) are not related to our subject.



FIGURE 1. *Cranial vault deformity in the temporal region* (black arrow).

Clinical Presentation

This is the second case in our department in which an aneurysm ruptured into an arachnoid cyst. As in the previous case (31), this patient presented with slight to moderate headache, without vomiting or compromising consciousness. The symptoms did not motivate the patient to seek medical help because the headaches were slight and transient. Only when symptoms worsened, days after the first onset, did the patient seek medical attention at the hospital. Other unusual manifestations from ruptured aneurysms are the absence of meningeal signs (5, 9) and transient motor deficits (5, 31). The presence of the arachnoid cyst probably prevented the spread of blood into the arachnoid space. Nevertheless, some blood can spread to the subarachnoid (2, 12, 31) or subdural (5, 10) space causing typical SAH symptoms.

Arachnoid Cyst Etiopathogenesis

Arachnoid cysts are cavities filled by cerebrospinal fluid-like fluid. They occur inside the arachnoid membranes and are, in fact, intra-arachnoid. They make up 1% of all intracranial mass lesions and are found in 0.1% of autopsies (21). The most frequent location, nearly half of all cases, is the middle fossa. They are considered the result of abnormal arachnoid layer development during the embryo stage of life. However their precise pathogenesis remains unclear. There are three popular theories: dysembryogenesis of the arachnoid membrane related to a primary disturbance of the primitive mesenchyma adjacent to the neural tube; lobe agenesia resulting in secondary expansion of the cerebrospinal fluid space; and acquired process resulting from infectious, inflammatory, traumatic, or hemorrhagic events in the fetus or early life (16, 21). The arachnoid cyst may

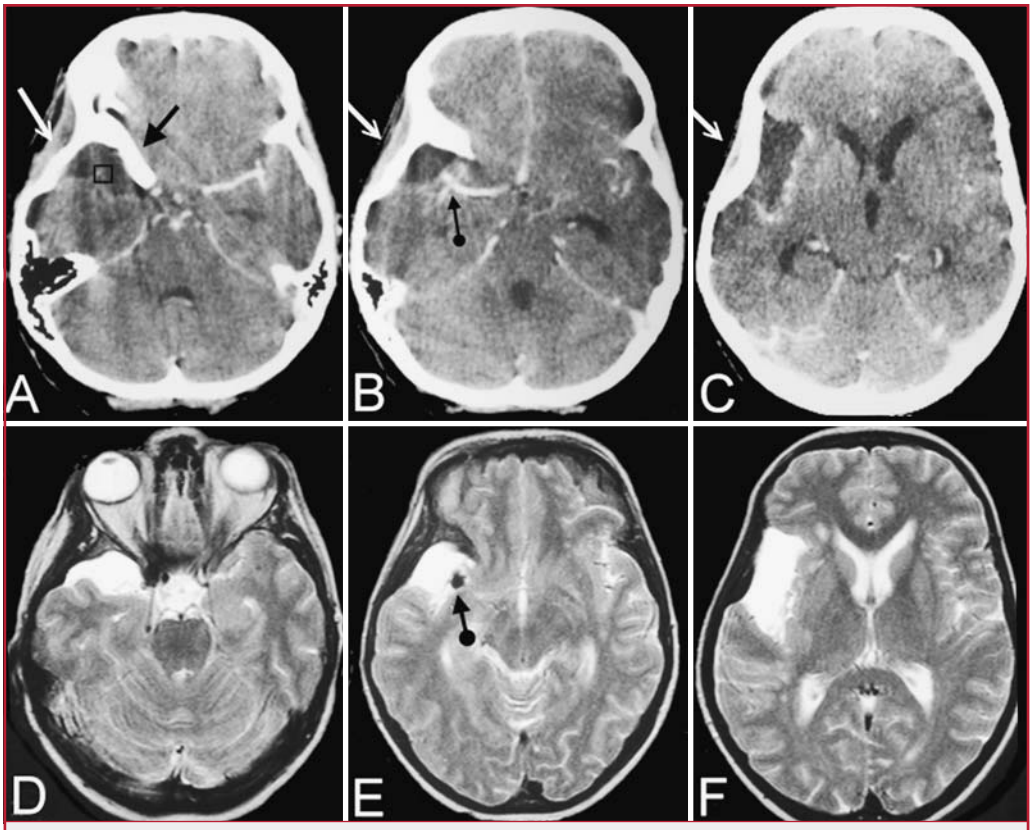


FIGURE 2. **A–C**, *contrasted CT scans showing a depression in the squamous temporal bone* (white arrow), *small middle fossa* (black square), *thickness of squamous temporal bone and lesser wing of the sphenoid* (black arrow), *and middle cerebral artery dilation suggesting aneurysm.* **D–F**, *axial T2-weighted magnetic resonance imaging scans showing an arachnoid cyst in the small middle cranial fossa and sylvian fissure. Note the presence of flow void at the medial wall of the cyst* (black arrow).



FIGURE 3. *Digital subtraction angiography showing a bilateral "mirror-like" aneurysm* (arrows) *at MCA bifurcation.*

be a manifestation of an underlying extracellular matrix defect in polycystic kidney disease (PKD) (24). The frequent association between arachnoid cysts and other malformations, such as Type I neurofibromatosis, Marfan syndrome, PKD, and callosum agenesis, supports a congenital or genetically related pathogenesis (24, 26). It is frequently associated with the thinning and expansion (bulging) of the adjacent bones (temporal bone and the lesser sphenoidal wing), causing a larger than normal middle fossa. However, an apparently paradoxical vault change related to arachnoid cyst has been described by Redla et al. (19). They reported three cases of arachnoid cysts in which the middle cranial fossa was paradoxically small and had thickening of the squamous temporal bone and lesser sphenoidal wing. They reinforce the temporal lobe hypoplasia theory as the initial event followed by compensatory bone changes, before the appearance of the arachnoid cyst. In our patient, the arachnoid cyst was asymptomatic and became symptomatic only after ICyH caused by aneurysm rupture. The cranial vault alterations were probably congenital. In the presence of an arachnoid cyst, it presented a paradoxically small middle fossa, depression of the temporal region, and thickening of the squamous temporal bone and the lesser wing of the sphenoid.

Aneurysm Etiopathogenesis

Sacular aneurysms in the cerebral circulation are relatively common. The lifetime prevalence of these aneurysms ranges from 2 to 5.5% (29, 30). The precise development, growth, and rupture mechanisms of intracranial aneurysms are still to be discovered (7, 13, 30). The effects of hemodynamic stress causing degenerative vascular diseases and known risk factors such as smoking, contraceptives, and hypertension provide evidence favoring an acquired etiopathogenesis (28, 30). Several recent studies on aneurysm wall biology have highlighted the importance of inflammatory response in ruptured cerebral aneurysms (7, 8, 13, 29). A disruption of the arterial wall extracellular matrix, compromising the strength and elasticity of the intracranial arteries is a likely predisposing factor in aneurysm formation. Even so, genetic factors could also play an important role in their formation (17, 23, 30) in some cases. Family predisposition and an association with other inheritable disorders of connective diseases, such as PKD, Ehlers-Danlos disease Type IV, and Marfan's syndrome, and the extracellular matrix support this (6, 27, 30). A congenital decrease in extracellular matrix structural proteins has been

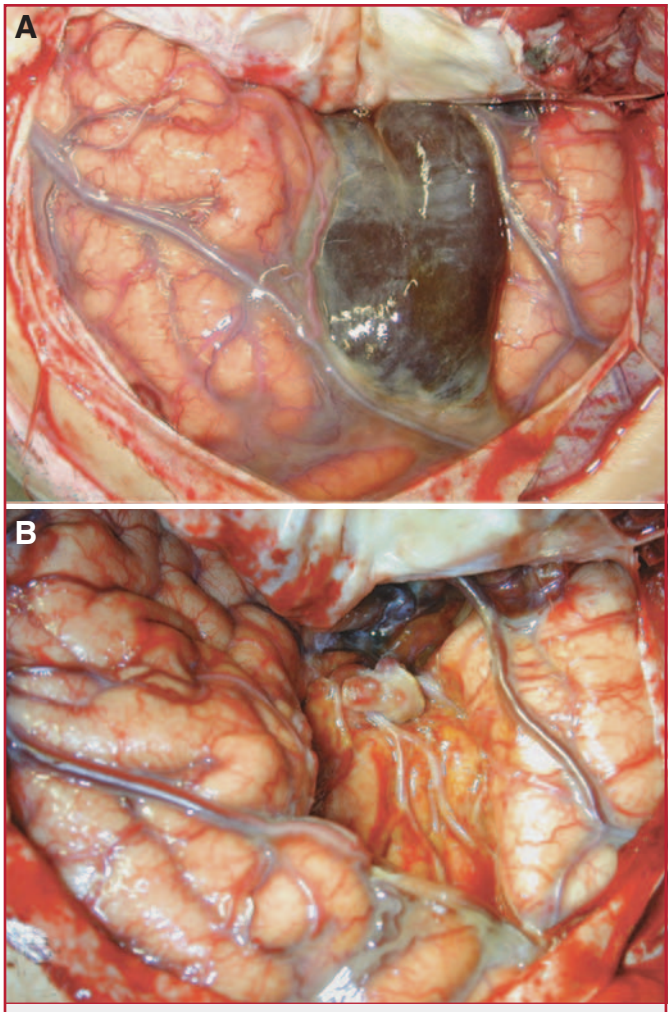


FIGURE 4. **A**, *intraoperative photograph showing the bulging sylvian fissure arachnoid cyst with intracystic hemorrhage.* **B**, *intraoperative photograph showing the cavity after removal of the full arachnoid cyst walls showing the aneurysm. Note the presence of hemosiderin in the cavity boundaries.*

seen in aneurysms (20). Collagen deficiency has also been proposed (14, 17, 20). Recently, Baccin et al. (1) reported a case of multiple mirror aneurysms associated with familial aneurysmal disease and, thus, suggested that an earlier defect in embryogenesis may be involved in multiple and mirror aneurysms (1). Multiple aneurysms are encountered in a variety of disorders such as PKD, fibromuscular dysplasia, Marfan syndrome, and Type I neurofibromatosis, which may result from defects in the mesodermal-neural crest or focal endothelial cell during embryonic stages.

Arachnoid Cyst and Aneurysm Association

There are few reports of an association between unruptured aneurysms and arachnoid cysts (3, 15, 24), and the prevalence of this association in the normal population is unknown. However, some embryological aspects of both pathologies and reports of unusual malformations might lead to speculation on a common pathophysiological pathway. There is controversy concerning the histogenesis of the arachnoid layer and the arterial layer involved in aneurysm formation. However, both apparently originate from the mesoderm, the primitive mesenchyme that surrounds the neural tube (16, 21), which is also involved in producing collagen for the extracellular matrix in the cerebral vessels. Schievink et al. (24) reported a case with generalized connective diseases and presented an association between cardiovascular disturbance (carotid-jugular fistulae, arterial dissection, arterial wall irregularities), skin (facial hemiatrophy), and multiple arachnoid cysts. In another report, Schievink et al. (25) described a child with progressive hemifacial atrophy (Parry-Romberg syndrome) and intracranial aneurysm disease. Another communication reports the same association (18). They suggest a malformation hypothesis in which both vascular and mesenchymal structures with common progenitors, derived from neural crest cells, are involved at the same time. The presence of the arachnoid cyst and an intracranial aneurysm in inheritable connective tissue disorders are higher than in the normal population. Analyzing 247 patients with PKD, Schievink et al. (26) detected 20 (8.1%) harboring arachnoid cysts and 27 (10.8%) with intracranial aneurysms. However, they did not find any correlation

TABLE 1. Reports of ruptured intracranial aneurysm and arachnoid cyst hemorrhage[a]

Series (ref. no.)	Age (yr)/sex	Aneurysm location	Cyst location	Presentation
Jinkins et al., 1987 (12)	40/M	MCA	Right convexity	IcyH, SAH
Hirose et al., 1995 (9)	45/M	BifCA	Left middle fossa	IcyH
Barker et al., 1998 (2)	29/F	PCoA	Left middle fossa	IcyH, SAH
Huang et al., 1999 (10)	61/F	MCA	Left middle fossa	IcyH, SDH
Zanini et al., 2000 (31)	35/M	BifCA	Left sylvian fissure	IcyH, SAH
Berhouma et al., 2006 (5)	37/F	Bilateral "mirror" MCA	Left middle fossa and sylvian fissure	IcyH, SAH, SDH
Current study	46/F	Bilateral "mirror" MCA	Right middle fossa and sylvian fissure	IcyH

[a] MCA, middle cerebral artery; IcyH, intracystic hemorrhage; SAH, subarachnoid hemorrhage; BifCA, bifurcation carotid artery; PCoA, posterior communicating artery; SDH, subdural hematoma.

between arachnoid cysts and intracranial aneurysms and, because of the relatively small number of aneurysm patients in the study, they could not draw a definitive conclusion. Perhaps the arachnoid cyst and intracranial aneurysm represent a distinct epiphenomenon of a single dysembryogenesis in some specific cases. Notwithstanding the fact that no concrete evidence of connective disease, PKD, or Parry-Romberg disease was found in our patient, the cranial vault changes and arachnoid cyst could represent a localized dysembryogenesis or a mild form of extracellular matrix disturbance.

Lack of supportive tissue surrounding the vessels, which occurs inside of the cyst, may contribute to the development, increase, and rupture of an aneurysm. In this and our previous case report, there were close relationships between both lesions, with the aneurysm inside the arachnoid cyst suggesting a basic underlying cause. However, as both pathologies are very common and no molecular data were provided, their association can only be fortuitous and many more cases studying molecular alterations of extracellular matrix would be needed to support this suggested underlying association. Reports of positive associations between, at first, unrelated lesions can induce erroneous conclusions. However, careful analysis of uncommon cases such as this one may contribute to an understanding of the still unresolved questions surrounding these common pathologies.

CONCLUSION

The rupture of a cerebral aneurysm into an arachnoid cyst has rarely been described in the literature. The clinical presentation may be unusual because the cyst can prevent subarachnoid hemorrhage. Atypical cranial vault changes can occur in the presence of an arachnoid cyst. In our opinion, this uncommon association, an arachnoid cyst, cranial vault deformity, and bilateral "mirror" cerebral aneurysm, strongly suggests a mild form of a dysplasia.

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COMMENTS

Arachnoid cysts or aneurysms are different lesions that are usually treated in neurosurgical practice. Both isolated lesions have a high incidence, but the presence of aneurysms and arachnoid cysts in different locations in the cranial vault within the same patient seems to be rare. Small arachnoid cysts are often found incidentally in association with different brain pathologies, such as tumors, arteriovenous malformations, and others around or at some distance from the former. Indeed, the suggested mild forms of connective diseases could also be a reasonable explanation for the isolated aneurysms or arachnoid cysts that are not associated with familial disorders or known connective disorders.

The angiogram shows a mirror-like middle cerebral artery bifurcation aneurysm with its usual configuration in both sides. Despite the bigger size of the intra-arachnoid cyst aneurysm, the direction of the bleeding was very similar to the usual place from which those aneurysms bleed, the sylvian fissure or temporal lobe, where the arachnoid cyst is located.

For all of these reasons, we agree with the authors that the common disorder can be found in both pathologies. However, we also think that the number of variables is stronger to support the idea of fortuitous finding until more cases can be studied and some evidence of dysplasia can be demonstrated.

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The authors present an interesting observation on the common occurrence of an arachnoid cyst and intracranial aneurysm formation. Six cases have been published in the literature so far. A mild form of dysplasia is suggested. The etiopathogenesis of aneurysms comprises not only the effects of hemodynamic stress, risk factors, e.g., smoking, contraceptives, hypertension, or inflammations, but also genetic factors. Some hereditary diseases are known to be associated with aneurysm formation (e.g., polycystic kidney disease, Ehlers Danlos syndrome, and Marfan syndrome). Gene coding for structural proteins of the extracellular matrix are also associated with aneurysm formation and are the focus of molecular investigations. If the authors' hypothesis that an arachnoid cyst and intracranial aneurysms are a mild form of dysplasia is true, molecular investigations should follow in order to elucidate a common molecular pathway.

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Cerebral aneurysms are more common than arachnoid cysts in most autopsy studies. On the other hand, some of the cysts, especially those that are small in size, may be missed during autopsies. The authors have described a very rare event of a middle cerebral artery bifurcation aneurysm that ruptured into an arachnoid cyst without more widespread subarachnoid hemorrhage. However, having these two lesions together seems to be more of a coincidence than a mutual pathobiology, as we should still see it happen more often in clinical practice. One must still remember that a patient with a sudden headache has an aneurysm rupture until proven otherwise and, with modern computed tomographic angiography, this can very easily and noninvasively be ruled out (1).

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Intercostal Arteriovenous Fistula Associated with Neurofibromatosis Manifesting as Congestive Myelopathy: Case Report

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OBJECTIVE: Vascular abnormalities associated with neurofibromatosis Type 1 (NF-1) are well known, but arteriovenous fistulae (AVF) are rare and usually involve vertebral AVF. A case of intercostal AVF associated with NF-1 and manifesting as congestive myelopathy is described.

CLINICAL PRESENTATION: A 62-year-old woman with a medical history of NF-1 experienced gradually worsening gait disturbance. Neurological examination at the time of admission found spastic paraparesis, decrease of sensation in the bilateral lower extremities, and vesicorectal disturbance. Magnetic resonance imaging scans revealed flow void sign and a congestive lesion of the thoracolumbar spinal cord, as well as a huge mass in the paravertebral region at T10–T12. Spinal angiography revealed an intercostal AVF with a large paravertebral varix, which drained to the spinal medullary vein and caused dilation of the intradural venous plexus of the spinal cord resulting in congestive myelopathy.

INTERVENTION: Direct surgery was selected for the occlusion of the draining point of the medullary vein, located in the entry of the dura. The patient underwent hemilaminectomy at T10–T12, and the dural entry of the draining vein was occluded. Postoperative angiography revealed no dilated venous plexus of the spinal cord and reduced paravertebral varix. The symptoms were gradually relieved after the surgery.

CONCLUSION: The present case of a very rare intercostal AVF with an unusual manifestation of congestive myelopathy occurred in a relatively rare association with NF-1. Accurate evaluation of the vascular anomaly allowed selection of the appropriate surgical method.

KEY WORDS: Arteriovenous fistula, Congestive myelopathy, Neurofibromatosis

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Neurofibromatosis Type 1 (NF-1) is a well-known autosomal dominant inheritant disease caused by an abnormality on chromosome 17q11.2 and manifesting as characteristic clinical features such as café-au-lait spots, neurofibroma, freckling, and Lisch nodules (2, 6, 12, 14). NF-1 is often associated with mesodermal and ectodermal abnormalities; vascular abnormalities are also well known (2, 6, 21). Other associations include systemic vascular diseases, such as occlusive or stenotic diseases, aneurysms, arteriovenous malformations, and arteriovenous fistulae (AVF) (3, 6, 11, 14). Vascular lesions associated with NF-1 often occur in the abdominal aorta and its branches (2, 6, 15, 16). These lesions result from neurofibroma or proliferative changes in smooth muscles; thus, obstructive vascular lesions are common (2, 6, 18). In contrast, AVFs in the nervous system are rarely associated with NF-1 (2, 6, 18). Moreover, to our knowledge, there have been no reports of patients who presented with spinal congestion by AVF associated with NF-1.

We treated a female patient with NF-1 associated with an intercostal AVF manifesting as congestive myelopathy. Direct occlusion of the draining vein after partial laminectomy was successful in completely obliterating the AVF with neurological improvement.

Case Report

A 62-year-old woman presented with paraparesis in July 2004. She visited our department in August 2004 because of deterioration in gait and urinary function within the course of a few weeks. Neurological examination found the spastic paraparesis of the lower limbs at 4/5 of manual muscle testing, decrease of sensation in the bilateral lower extremities, and vesicorectal disturbance. A diagnosis of NF-1 was based on multiple café-au-lait spots and neurofibromas, as well as a familial history of NF-1. Sagittal T2-weighted magnetic resonance imaging (MRI) scans revealed a congestive lesion of the thoracolumbar spinal cord and flow void sign on the dorsal surface of the spine. Axial T2-weighted MRI scans revealed a paravertebral giant varix as a low signal mass at the left T10–T11 level (*Fig. 1, A* and *B*). The mass lesion located at the dorsal portion of the thoracic vertebrae and its lateral side was a capsulated thin wall. Spinal angiography revealed an intercostal AVF fed from the intercostal artery of T10 associated with a large paravertebral varix, which drained to the intradural medullary vein and dilated posterior spinal vein (*Fig. 1C*). No draining was observed through the azygous or hemiazygous veins. The Adamkiewicz artery was also not observed. The draining vein from intercostal AVF was considered to cause venous hypertension of the intradural venous plexus of the spinal cord resulting in congestive myelopathy.

Direct surgery was selected to occlude the draining point of the intradural medullary vein, which was located in the entry of the dura. The patient underwent hemilaminectomy at T10–T12. The dilated spinal vein and the draining point of the intradural medullary vein could be directly observed (*Fig. 2A*). Temporary clipping of this draining point reduced the venous dilation and dramatically decreased the entry flow. Clipping and electrical coagulation were applied to completely occlude the dural entry of this draining point (*Fig. 2B*). There were no other feeding arteries or draining points into the medullary vein around this dural entry area.

Postoperative T2-weighted MRI scans revealed that the high intensity lesion of the spinal cord was remarkably diminished and no dilated venous flow void was observed (*Fig. 3A*). Postoperative angiography revealed the disappearance of the venous plexus of the spinal cord and diminished paravertebral giant varix (*Fig. 3B*). The Adamkiewicz artery was recognized at the same level as the segmental artery. The symptoms of gait disturbance and viscorectal disorder were gradually relieved after the surgery. Her paraparesis of the lower limbs relieved the spasticity and improved up to 5 to 4/5 of manual muscle testing. She was ambulating when discharged 3 weeks after the surgery, and no recurrence of neurological deficits was observed 3 years after the treatment.



FIGURE 1. *Preoperative MRI scans and angiogram of the thoracic spine.* **A**, *sagittal T2-weighted MRI scan showing a flow void sign on the dorsal surface of the spine and high signal intensity and edematous swelling of the spinal cord.* **B**, *axial T2-weighted MRI scan revealing the paravertebral giant varix as a low signal mass at the left T10–T11 level.* **C**, *angiogram of the intercostal artery of T-10 showing the AVF with giant varix, the draining vein flowing into the intradural medullary vein* (arrowhead)*, and dilation of the spinal veins.*

DISCUSSION

Intercostal AVFs are very rare with only 17 reported cases since 1933 (1, 4–6, 10, 13, 17). Nine of these 17 cases resulted from thoracic trauma or interventions such as biopsy and transthoracic surgical treatment (1, 4–6, 10, 13, 17). Only seven cases were angiographically proven as congenital intercostal AVF, all of whose fistulas drained to the azygous or hemiazygous venous systems (1, 4–6, 10, 13, 17). Patients with a large malformation may present early in life with congestive heart failure or embolic phenomena and abnormal bruit (4). Intercostal AVFs manifesting as myelopathy resulting from congestion of the spinal cord were unknown (1, 4, 5, 7, 8, 13, 17).

In our present case, the intercostal AVF formed a giant varix after venous shunting and the arterial blood passed into the medullary vein. This arterial shunting flow might disturb the normal spinal venous circulation, resulting in progressive congestive myelopathy. Our case was characterized by a long abnormal venous system, with the arteriovenous shunting from the intercostal artery associated with a varix and draining into the medullary venous system. There was no characteristic finding of the spinal dural AVF because we could not observe arterial supplies along the spinal dura in the operative finding.

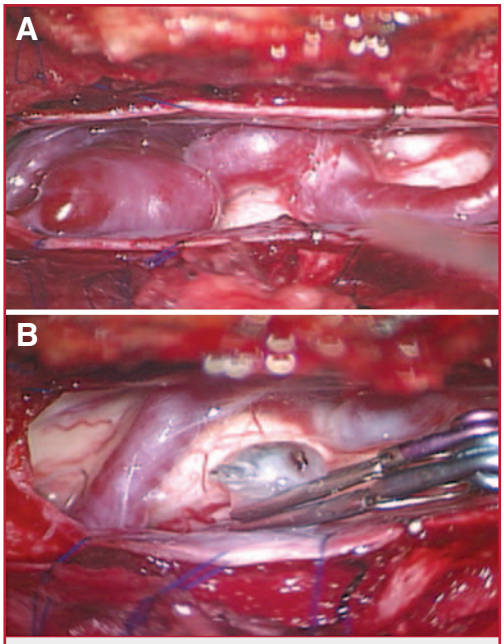


FIGURE 2. **A**, *intradural operative photograph showing that arterial blood passed into the medullary vein and apparent dilation of the spinal veins at the intradural draining entry zone.* **B**, *intradural operative photograph after obliteration of the draining point showing that clipping and electrical coagulation had thrombosed and reduced the dilated spinal veins.*

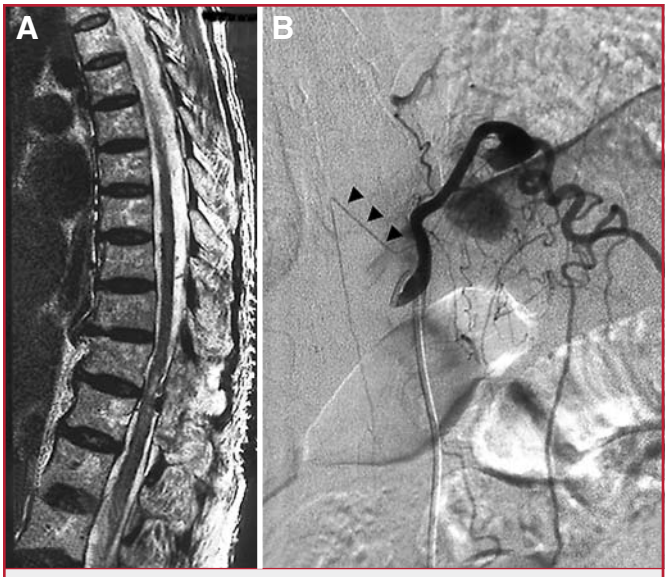


FIGURE 3. *Postoperative MRI scan and angiogram of the thoracic spine.* **A**, *sagittal T2-weighted MRI scan showing a reduction of the flow void sign on the dorsal surface of spine and high signal intensity and edematous swelling of the spinal cord.* **B**, *angiogram of the intercostal artery of T-10 revealing no AVF draining into the medullary vein, no dilation of the spinal veins, and the partially thrombosed varix. The Adamkiewicz artery was recognized at the same level as the segmental artery* (arrowheads).

The arterial blood pressure might be directly transmitted into this long abnormal venous system. Such internal high pressure could affect the abnormal venous wall and eventually result in the giant varix after the shunt. The abnormal medullary venous system directly penetrated into the intradural venous system at the dural entry zone and caused the dilation of the spinal venous plexus. Therefore, the mechanism of spinal congestion in our case might resemble that of spinal dural AVF characterized by dilation of the spinal venous plexus due to abnormal medullary venous shunting flow at the dural entry level. A postoperative angiogram demonstrated that the fistula did not completely disappear. There is the possibility that shunting of blood from the artery of Adamkiewicz into the fistula is at least partially responsible for her problem. We need further follow-up of her symptoms.

Only 28 cases (6 males and 22 females) of AVF associated with NF-1 have been reported in the literature (2, 6, 9, 10, 16, 19, 20, 22, 23). The age of onset of AVF ranged from 0 to 62 years (mean, 39.1 yr) and most cases were vertebral AVFs (2, 6, 9, 10, 16, 19, 20). Only seven were supplied by the external carotid artery or, in extracranial locations, supplied by the occipital artery (16, 19, 22, 23). Extracranial AVFs all manifested initially as bruit (2, 6, 9, 10, 16, 19, 20, 22, 23).

The pathogenesis of AVFs associated with NF-1 has not been determined, but cell proliferation originating from Schwann cells, hypertrophy of the vascular intimal layer, reduction of the vascular medial layer, or thinning of the elastic fibrous layer may be involved (2, 6, 21). The chief pathological finding is the proliferation of neurofibroma or ganglioneuroma in the outer membrane of large vessels, such as the aorta and carotid artery, and proliferation of smooth muscle in small vessels (2, 6, 21). The vascular wall of some AVFs associated with NF-1 showed destruction of elastic fiber, which might be the primary reason for the hemorrhagic onset (2, 6, 21). Otherwise, microarterial aneurysms, which are often associated with NF-1, might rupture into the venous plexus resulting in shunting into a venous fistula, based on the hemorrhagic change of vascular lesions associated with NF-1 (20, 21). In our present case, only the draining vein was removed and no particular pathological finding was observed.

Ten previous cases of AVFs associated with NF-1 were treated by surgery such as ligation or resection of a feeding artery (2, 3, 6, 9, 12, 14, 15, 22, 23). Successful obliteration was achieved in only four patients, but the symptoms improved in all 10 as a result of shrinkage of the AVF or varices causing compression. Surgery and embolization were performed in six patients (2, 3, 6, 9, 12, 14, 15, 22, 23). Successful obliteration was achieved in four, and symptoms improved in all six. Embolization was performed in eight patients by using balloons in three and coils in five (1, 3, 6, 10). Successful obliteration was achieved in seven, three of whom were treated with balloons and four with coils. Thus, there was no difference in outcome between the two treatment methods, and symptoms improved in all patients. Treatment plans should be formu-

lated individually; however, the outcomes of endovascular surgery have been favorable because of the low surgical invasiveness (2, 3, 6, 9, 12).

The surgical strategy in our case aimed at complete occlusion of the draining point of the spinal dural AVF. Endovascular treatment was not possible, although the occlusion point could be approached because preoperative angiography did not show the branched portion of the Adamkiewicz artery. The endovascular procedure might be considered if the detail of the preoperative vascular anatomy was thoroughly studied. Spinal congestion might affect the spinal arterial circulation and the artery of Adamkiewicz was not clearly observed before the treatment. The dural entry zone of the medullary vein at the intradural level was selected as the appropriate draining point based on the angiographical findings. At this point, we could obliterate the arterial high blood flow into the spinal venous system and induce thrombosis of the long abnormal venous system with the varix. Postoperative examinations showed the dilation of the spinal venous plexus and the extradural abnormal venous system were successfully reduced, and the congestive myelopathy was also dramatically improved.

CONCLUSION

The present case of a very rare intercostal AVF with an unusual manifestation of congestive myelopathy occurred in a relatively rare association with NF-1. Accurate evaluation of the vascular anomaly allowed selection of the appropriate surgical method.

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COMMENTS

The authors present a case of a 62-year-old woman with neurofibromatosis-1 (NF-1) and progressive myelopathy. Magnetic resonance imaging scans of the thoracic spine suggested a vascular lesion with an associated paravertebral mass. Angiography revealed an intercostal arteriovenous fistula (AVF) with a large associated paravertebral varix. There was retrograde drainage into the medullary venous system and venous congestion. The vascular lesion was addressed surgically with obliteration of the medullary draining vein. Spinal cord vascular congestion was relieved immediately after division of the vein. The patient improved clinically after surgery.

Spinal AVFs are extraordinarily rare in pateints with NF-1, although they often have vascular fistulea noted elsewhere, such as the abdominal aorta. Moreover, intercostal AVFs are also rare, with only a few cases reported in the literature. Congestive myelopathy has not been reported in these cases. This report is, therefore, a valuable contribution to the literature. The lesion presented was confirmed on angiography; interestingly, the artery of Adamkiewicz could not be characterized. Congestive myelopathy in this patient could be treated effectively as if this were a Type I spinal arteriovenous malformation (dural AVF), i.e., obliteration of the draining vein without direct treatment of the fistula itself. Options

include direct surgical or endovascular obliteration of the vein. It is our opinion that surgery is the most effective form of therapy with few complications, based on the treatment of spinal dural AVFs. Endovascular therapy may be considered but only in appropriate cases. In the case presented, the arterial anatomy could not be clearly delineated (location of the artery of Adamkiewicz) and endovascular therapy could, therefore, not be performed safely. Although the patient's myelopathy improved after surgery, she will continue to need to be followed clinically for some time. The fistula and varix remained patent after surgery and venous congestion of the spinal cord could recur in the future. This report is an important contribution to the literature. Vascular lesions should be considered as causes of myelopathy in patients with NF-1. Careful evaluation of the vascular anatomy of the lesion will permit selection of the appropriate treatment strategy.

Michael P. Steinmetz
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Saito et al. describe the treatment of a 62-year-old woman with NF-1 and an intercostal fistula. She presented with a progressive myelopathy and was found to have a marked intramedullary venous dilatation due to her fistula. Before treatment, the artery of Adamkiewicz was not well visualized; for that reason, the patient underwent an open surgical procedure in which the venous connection between the fistula and the intradural venous system was eliminated. The patient improved, but a postoperative angiogram demonstrated a persistent fistula. The authors report that the patient was doing well 3 years after surgery.

This report details an exceedingly rare situation in which a patient with NF-1 also had an intercostal AVF. Although the patient has done well after treatment, it is possible that her symptoms may recur. Although the fistula may go on to completely thrombose, a relatively early study demonstrated persistent venous flow. Ultimately, a connection to the medullary venous system may mature and result in a recurrent case of myelopathy due to venous hypertension.

Vincent C. Traynelis
Iowa City, Iowa

The authors present an interesting case of an AVF in a patient with NF-1. The case was well worked up, and it is to the authors' credit that they made an accurate diagnosis. Having meticulously examined the case and made this diagnosis, the authors were then able to develop a sound treatment plan. The ultimate outcome was favorable for the patient. The authors present a good review of the literature on this topic. This case report offers information which will enhance the current body of information regarding the treatment of neurosurgical spinal disorders.

Robert F. Heary
Newark, New Jersey

The authors present an interesting discussion of the association of NF-1 with systemic vascular lesions, especially in the abdomen. This case report seems to be the first report of an association of NF-1 with an intercostal AVF and a paravertebral varix that drained into a spinal medullary vein. Whether or not there is a causal relationship between NF-1 and the vascular malformation is speculative, but the report is useful in heightening awareness of the possibility of systemic vascular lesions in patients with NF-1.

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Pseudotumoral Presentation of a Cervical Extracranial Vertebral Artery Aneurysm in Neurofibromatosis Type 1: Case Report

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OBJECTIVE: Neurofibromatosis Type 1 (NF1) is known to be associated with vascular lesions. Association with an extracranial vertebral artery aneurysm is very rare. We report the case of such an aneurysm mimicking a cervical neurofibroma in NF1.

CLINICAL PRESENTATION: An 18-year-old woman with previously diagnosed NF1 presented with a C6 radiculopathy. There were no clinical features suggesting a vascular origin for the lesion. The computed tomographic and standard magnetic resonance imaging scans showed a C5–C6 contrast-enhancing lesion responsible for bony erosion. Subsequent, magnetic resonance angiography and digital subtraction angiography diagnosed the lesion as a C5–C6 vertebral artery aneurysm.

INTERVENTION: The lesion was treated by endovascular occlusion of both the aneurysm and the parent vertebral artery with an initial immediate disappearance of the pain.

CONCLUSION: This case serves as a reminder of the importance of ruling out a vertebral artery aneurysm with angiography when managing cervical lesions in patients with NF1.

KEY WORDS: Neurofibromatosis Type 1, Vertebral artery aneurysm

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Neurofibromatosis Type 1 (NF1) is a genetic disease with simple autosomal inheritance and variable expressivity but a 100% penetrance in individuals who have reached adulthood (7). Its incidence is approximately one in every 3000 to one in every 4000 births, depending on the study. Vascular lesions in NF1 occur most often in the abdominal aorta and the renal arteries (3).

Extracranial vertebral artery aneurysms are rare (1) and, in the general population, are usually consequences of trauma. Non-traumatic vertebral artery aneurysms have been described in association with hypertension, infection, inflammatory disease, and inherited disorders such as Marfan's syndrome, Ehlers-Danlos syndrome, and neurofibromatosis. We report a new case of presumed nontraumatic extracranial giant aneurysm of the right vertebral artery in a young patient with NF1.

CASE REPORT

The patient was diagnosed with NF1 at the age of 6 years after developing "café-au-lait" spots on her trunk and limbs and ptosis in the left eye secondary to a neurofibroma. After several years of surveillance with only cutaneous manifestations of the disease, the patient presented to our department at the age of 18 years with new onset of increasing right arm pain. The pain followed a C6 dermatomal pattern commencing at the elbow and then radiating along the outside of the arm. Neurological examination at this stage revealed no concomitant motor or sensory loss. There was no evidence of a pulsatile mass or bruit on general examination of the upper limbs and neck. Despite 2 months of conservative management with analgesics, the pain continued to worsen and repeat neurological examination revealed a motor deficit of the right deltoid, the right common extensor of the fingers, and the wrist extensor associated with paresthesiae of all the fingers.

Radiological Findings

The main diagnosis based on the clinical context and neurological examination was a neurofibroma of the sixth cervical nerve. Plain



FIGURE 1. *Axial computed tomographic scan at the C5–C6 level showing enlargement of the right transverse foramen.*



FIGURE 2. *Sagittal T2-weighted MRI scan showing an aneurysm with flow void visible as a hyposignal.*

x-rays showed enlargement of the C5–C6 exit foramen compatible with this diagnosis. A cervical computed tomographic scan (Fig. 1), however, demonstrated a lesion expanding the transverse foramen rather than the neural foramen with scalloping of the adjacent vertebral body. This raised the possibility of a vascular lesion. A cervical magnetic resonance imaging (MRI) scan revealed a round contrast-enhancing mass in the transverse foramen outside the vertebral canal. The flow void inside the lesion on sagittal T2-weighted sequences (*Fig. 2*) also suggested a vascular lesion. Magnetic resonance angiography confirmed the diagnosis of a vertebral artery aneurysm with a diameter of 25 mm (*Fig. 3*). There was no evidence of intraluminal thrombus. Digital subtraction angiography demonstrated a large fusiform aneurysm at the C6 level and a normal and functional left vertebral artery, filling the controlateral cerebellar arteries, thus allowing consideration of treatment by occlusion and sacrifice of the right vertebral artery.

Treatment

The procedure was conducted under general anesthesia. A standard femoral approach was performed and a 5-French sheath was introduced and connected to a flushing system. During attempted balloon occlusion, spasm of the ostium of the vertebral artery occurred on introduction of the guide catheter. As a result, utilization of a gold valve balloon to occlude the vertebral artery distal and proximal to the aneurysm was not possible. Instead, proximal occlusion (13) of the vertebral artery was performed using a Guglielmi detachable coil 18 (Boston Scientific/Target, Fremont, CA) deployed in the proximal segment of the vertebral artery, with the distal portion of the coil floating into the aneurysm itself. After establishing the stability of the system, the occlusion of the vertebral artery and the absence of revascularization by anastomosis, the coil was detached. A follow-up MRI scan performed 2 days later showed complete thrombosis of the aneurysm.

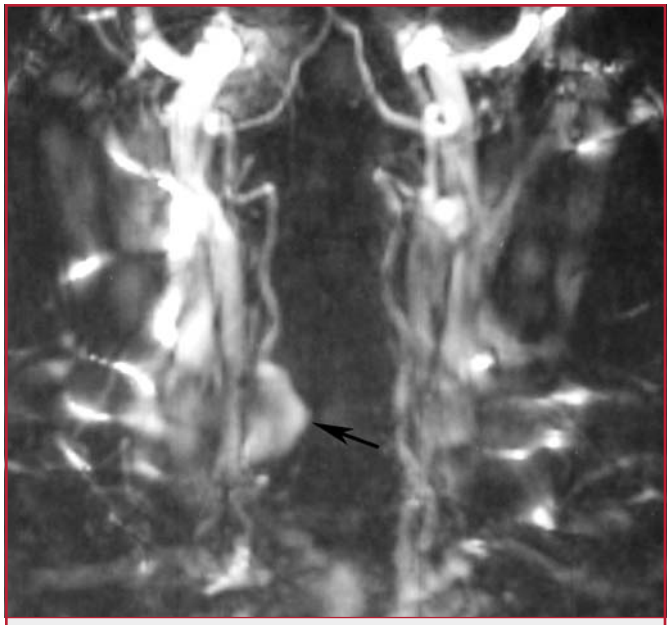


FIGURE 3. *Magnetic resonance angiogram showing the aneurysm* (arrow).

Clinical Outcome

Immediately after the embolization, the patient had complete cessation of the radiculopathy. Unfortunately, the pain recurred a few months later in the same C6 distribution with a fluctuating intensity, being eased a little by the use of standard analgesics. Follow-up magnetic resonance angiography and digital subtraction angiography confirmed stability of the coil and occlusion of the aneurysm. Surveillance imaging obtained 6 years later (*Fig. 4*) showed continued occlusion of the vertebral artery and associated aneurysm.

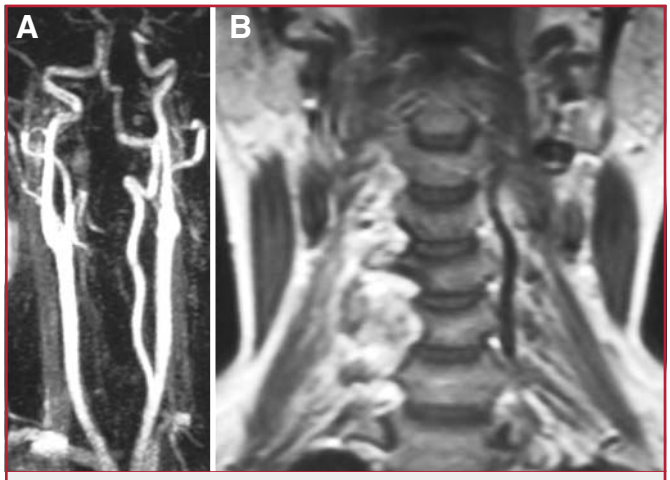


FIGURE 4. *Follow-up MRI (**A**) and magnetic resonance angiogram (**B**) showing the thrombosed aneurysm.*

TABLE 1. Summary of 13 reported cases of extracranial vertebral artery aneurysms associated with neurofibromatosis I and their symptoms at presentation[a]

Series (ref. no.)	Age (yr)/sex	Side	Level	Symptoms	Non-ruptured		Ruptured	Treatment	Outcome
					Pseudotumoral presentation	Others			
Schubiger and Yaşargil, 1978 (19)	50/M	Left	C2–C6	Cervical bruit		+		Surgical removal	Full recovery
Pentecost et al., 1981 (12)	1/F	Left	T1	Limited neck movement and weakness of the left arm leading to diagnosis of NF1 + associated aneurysms	+			None	Progression of symptoms, increase of the size of aneurysm
Detwiler et al., 1987 (2)	52/F	Left	C2	Enlarging neck mass with bruit		+		Proximal occlusion by DB	Symptoms disappeared, size of aneurysm decreased
Negoro et al., 1990 (10)	47/M	Left	C1	Sudden neck pain and subcutaneous hemorrhage			+	Proximal occlusion by DB	Decrease of symptoms, aneurysm totally obliterated
Muhonen et al., 1991 (9)	52/F	Left	C2	Acute presentation with neck mass and pain		+		Occlusion by DB	Not known
Schievink and Piepgras, 1991 (18)	43/F	Left	C7	Rupture of a left subclavian artery aneurysm		+		None	No change for 2 years
Okhata et al., 1994 (11)	48/F	Left	C4–C6	Weakness and numbness of the left upper extremity + C5–C6 radiculopathy	+			Surgical trapping	Full recovery
Uranishi et al., 1995 (20)	60/F	Left	–	Radiculopathy, cerebellar infarction		+		None	Death
Horsley et al., 1997 (5)	56/F	Left	C5–C7	Swelling of the left side of the neck and respiratory distress after traction			+	Occlusion by DB	Full recovery at 2 years
Hoffmann et al., 1998 (4)	59/M	Right	C6	Systolic bruit along the course of the carotid artery		+		None	Not known
Ushikoshi et al., 1999 (21)	40/F	Left	C1	Occipitalgia and subcutaneous neck haematoma			+	Proximal occlusion by DB	Secondary arteriovenous fistula at the same site
Miyazaki et al., 2004 (8)	52/F	Left	C5–C7	Rupture into the thoracic cavity, sudden decrease of blood pressure			+	Proximal occlusion after the rupture	Death
Current series	18/F	Right	C6	Radiculopathy	+			Proximal occlusion by coils	Increase of symptoms, aneurysm totally obliterated

[a] NF1, neurofibromatosis type 1; DB, detachable balloon. Plus signs indicate the type of aneurysm.

DISCUSSION

Although vascular lesions have already been described in NF1 patients, including those lesions affecting the renal, aortic, and intra- and extracranial cerebral vessels, their physiopathology remains unclear. In the first article published on the subject in 1944, Reubi (14) studied vessels of 1 mm or less in kidneys of NF1 patients and described three types of lesions: intimal proliferation, thinning of the tunica media with fragmentation of the limitant elastic membrane, and proliferation of the adventia. These three forms can be combined together. Further studies reported by Salyer and Salyer (17) in 1974 and Greene et al. (3) in 1976 helped enlarge this classification to lesions involving larger vessels such as the aorta and carotid arteries. Greene et al. showed that the proliferation in the vessel wall is related to smooth muscle cells.

NF1 is caused by mutations of the gene *NF1* localized to chromosome 17q11.2 (22). The NF1 gene product is neurofibromin. This raises the possibility of a link between neurofibromin deficiency and the NF1 vasculopathy. The main hypothesis proposed by Riccardi (15, 16) is that the vasculopathy is caused by the alteration of the normal process of vascular maintenance and repair regulated by neurofibromin. Considering this, the goal of treatment is to sacrifice the diseased vessel surgically or with endovascular techniques.

With particular regard to the cervical region, vertebral artery aneurysms have already been reported. It is important to note, however, that they are very rare. A total of 13 cases of aneurysms have been described in the literature (*Table 1*). The mean age at the time of diagnosis is 44 years, and the aneurysms tend to occur lower down in the neck and more commonly on the left side. Among the thirteen reported cases of extradural vertebral aneurysms, including the case reported here, nine were intact on presentation (2, 4, 9, 11, 12, 18, 19, 20) versus four presenting with symptoms resulting from rupture (5, 8, 10, 21). This is the third case to present with symptoms resulting from compression of adjacent structures, a radiculopathy in this case. The six other unruptured vertebral aneurysms presented with cervical bruit (2, 4, 19), on angiography after rupture of an aneurysm elsewhere on the vascular tree (18), or after ischemic stroke (20). Most of the ruptured vertebral aneurysms presented with cervical hematoma (10) or hemothorax (8), and only one case gave rise to a vertebrovertebral arteriovenous fistula (21).

In this case, the absence of clinical signs pointing towards the vascular nature of the lesion could have led to unnecessary and possibly dangerous surgery. The plain x-ray findings demonstrating bony erosion of the C6 exit foramen rather than erosion of the transverse foramen supported this erroneous diagnosis. A careful analysis of the computed tomographic, MRI, and angiographic findings led to an alternative and correct diagnosis. Both the expansion of the transverse foramen and the flow void seen on the T2 sequences supported the diagnosis of a vascular lesion, which was confirmed by angiography. Although it is correct to say that the mass did not have the dumbbell shape classically associated with a neurofibroma, this argument alone cannot be used to rule out a tumor because purely extradural neurofibromas have been well reported (6).

Therefore, although neurofibromas are more common lesions, the possibility of an extracranial vertebral aneurysm should always be considered in the differential diagnosis of a neck mass in such cases. Because of this possibility, investigations aimed at specifically excluding an aneurysm should be performed before any surgery on a presumed cervical neurofibroma in patients with NF1.

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COMMENTS

Peyre et al. have presented a case report that should serve as a reminder to us all that many pitfalls and potential disasters await the unwary. Bony erosions, as presented by the authors, should serve as warning signs for such. Such erosions in neurofibromatosis (NF) patients can result from tumor, dural ectasia, or vascular pathology. One should not make assumptions and proceed with definitive workup before surgical intervention. Peyre et al.'s case is timely in this regard. For this, the authors are to be congratulated.

Edward C. Benzel
Cleveland, Ohio

The authors studied an 18-year-old woman with NF who presented with a C6 radiculopathy. Computed tomographic and standard magnetic resonance imaging (MRI) scans showed a C5–C6 contrast-enhancing lesion with enlargement of the vertebral foramen. Magnetic resonance angiography demonstrated this lesion to be a vertebral artery aneurysm. Follow-up angiography was performed with endovascular sacrifice of the parent vessel. This case reminds us that patients with NF Type 1 can develop aneurysms of the vertebral artery. The unique feature of this case and those reviewed by the authors is the potential to mimic a more benign tumor. I agree with the authors that all patients with NF should have some type of radiological study that evaluates the potential for vascularity of a lesion before contemplating any surgical attack on the lesion.

Christopher S. Ogilvy
Boston, Massachusetts

This article reminds us of the importance of reviewing some modality of angiographic study in NF patients presenting with a cervical lesion. Although the authors note only nine cases of vertebral artery aneurysms reported in the literature, other case reports are available covering this type of pathology. However, their treatment of only partial occlusion of only the proximal segment of the aneurysm using Guglielmi detachable coiling has not been previously reported in this patient population.

The authors felt that the imaging studies originally obtained demonstrated a lesion not in continuity with the vertebral artery. Instead, they initially felt that the vertebral artery was displaced in the vertebral foramen; however, the source imaging suggests that the vertebral artery is, indeed, involved in the pathology. Without the advantage of serial axial images, the reader is unable to follow the logic in separating this lesion from the vertebral artery. Should serial axial images be presented, one might be able to follow the central area of the lesion to determine if it is a flow void associated directly with the course of the vertebral artery. When examining the single axial slice presented, the reader is unable to appreciate widening of the neuroforamina or mass effect on the spinal cord. These two findings would be consistent with a neurofibroma and would be more fitting with the classically described dumbbell shaped lesion. In addition, inclusion of at least one computed tomographic reference image obtained would give the reader a better understanding of the bony erosion associated with this lesion. From the MRI scans presented, the expected finding would be that the foramen transversarium is eroded, not the neuroforamina. One would question the practice of obtaining the standard MRI scans separately from angio-MRI scans when the lesion is thought to be so intimately involved with the vascular structures, as appears to be the case here.

The authors state that balloon occlusion was not possible in this case, secondary to spasm of the vertebral artery at the ostium. It is presumed but unclear as to whether or not this was a direct affect of the test occlusion. At this point, the authors describe the use of 18 Guglielmi detachable coils to occlude the proximal portion of the aneurysm with the distal portion of the coil free floating in the aneurysm. The standard reported techniques involve balloon occlusion or distal and proximal occlusion of the aneurysm. The technique of using only proximal occlusion is widely known, but no data is referenced as to the safety or long-term viability of this method.

Overall, this case report was very interesting in reminding us of the importance of angiographic studies when a (NF) patient presents with a cervical lesion. This concept was originally put forward by Schubiger and Yaşargil (1) in 1978 after their intraoperative finding of an aneurysm. The literature documents well the presence of arteriovenous fistulae involving the vertebral arteries as a more common vascular lesion in NF Type I patients. A further question would arise regarding the incidence of vertebral artery aneurysms in this patient population. Vertebral artery aneurysms are thought to comprise fewer than 5% of aneurysms, and no incidence is referenced or recorded for the NF1 population.

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New Orleans, Louisiana

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The authors describe a case of a vertebral artery aneurysm in a patient with NF Type 1. The interesting aspect of this case, in contrast to most of the literature reviewed, is that this patient presented with a radiculopathy which could have easily been mistaken for a disc herniation based on the history and physical examination alone. Fortunately, modern radiological techniques have now made both the diagnosis and treatment of this patient more straightforward.

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This article describes an atypical cause of radiculopathy in a young patient with NF Type 1. The authors performed appropriate preoperative imaging studies and were able to avoid a potentially catastrophic intraoperative misadventure. The aneurysm was managed endovascularly; however, the patient continues to have symptoms. This case illustrates the need to have a high level of suspicion regarding lesions in the region of the vertebral foramen and also illustrates the types of multimodality treatments available. Finally, it illustrates the fact that, despite optimal treatment, not all patients improve symptomatically.

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Delayed Fibrotic Obliteration of the Spinal Subarachnoid Space after Cerebral Aneurysmal Subarachnoid Hemorrhage: Case Report

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OBJECTIVE: Widespread fibrotic obliteration of the spinal subarachnoid space after cerebral aneurysmal subarachnoid hemorrhage (SAH) is rare.

CLINICAL PRESENTATION: A 57-year-old woman presented with the gradual development of a spastic paraparesis. Two years earlier, she experienced a cerebral aneurysmal SAH that was successfully managed with endovascular coiling. However, the SAH was complicated by transient aseptic meningitis and hydrocephalus. Magnetic resonance imaging and computed tomographic myelography at the time of admission 2 years after SAH revealed widespread cystic obliteration of the thoracic subarachnoid space.

INTERVENTION: Through an extensive laminoplasty, multiple non-communicating fibrotic cysts, intimately adherent to the pia, were found to have obliterated the spinal subarachnoid space. A full communication between all cysts and the subarachnoid space was ultimately established using a Fogarty catheter. The cerebrospinal fluid was clear and colorless, with normal microscopy. Histopathological examination revealed non-specific fibrosis with scattered lymphocytes and uniform hemosiderosis.

CONCLUSION: In addition to precipitating leptomeningeal fibrosis within the convexity subarachnoid space and/or arachnoid granulations (causing delayed hydrocephalus), cerebral aneurysmal SAH may also rarely elicit widespread symptomatic fibrotic obliteration of the spinal subarachnoid space. Such cases seem to be characterized by a posterior circulation, Fisher Grade 3 to 4, aneurysmal SAH, and, when circumscribed and cystic, seem amenable to surgical decompression.

KEY WORDS: Posterior fossa, Spinal subarachnoid fibrosis, Subarachnoid hemorrhage

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CASE REPORT

A 57-year-old woman presented with a 4-month history of increasing painless numbness, as well as weakness and clumsiness of both legs with frequent falls and urge incontinence. She was a school teacher who smoked 10 cigarettes per day.

Medical History

The patient was hypertensive and took 7.5 mg of bisoprolol per day. Two years earlier, she exerienced a non-coma-producing subarachnoid hemorrhage (SAH) from a left posterior inferior cerebellar aneurysm (PICA) (World Federation of Neurological Societies Grade 2). Computed tomographic scans obtained at that time demonstrated significant basal cistern and posterior fossa SAH without hydrocephalus (Fisher Grade 4). After successful endovascular coiling with Gugliemi Detachable Coils (GDC; Boston Scientific/Target, Fremont, CA) (GDC [r]-10-SOFT-3 mm × 10 cm; GDC [r]-10-SOFT-3 mm × 8 cm; GDC [r]-10-SOFT-2 mm × 8 cm), she insidiously developed increasing headache, pyrexia and meningism. Computed tomographic scans demonstrated a left PICA infarct and mild non-communicating hydrocephalus. Lumbar punctures repeatedly revealed normal cerebrospinal fluid (CSF) pressures. The CSF was turbid and xanthochromatous with a white cell count of 126/mm^3 (70% lymphocytes), a red cell count of 520/mm^3, a glucose level of 4.5 mmol/L, and a protein concentration of 0.9 g/l. No organisms were seen or cultured at any stage,

and symptomatology rapidly resolved with repeated lumbar punctures. She was discharged 5 days later without neurological deficit and without hydrocephalus. Follow-up cerebral angiography at 6 months confirmed complete aneurysmal obliteration. She remained asymptomatic until her subsequent admission 2 years later.

Examination at Admission 2 Years after SAH

The patient's general examination and temperature were normal, her Glasgow Coma Scale score was 15, and her cranial nerve and upper limb examination were normal. Her tandem gait was poor with circumduction of the left leg and Romberg's test was positive. Her coordination was poor in both legs, with Grade 4 power for extensors and Grade 3 for flexors. Tone was markedly increased in both legs with sustained clonus, hyper-reflexia and upgoing plantars. Sensation was decreased to light touch and pin prick to T_4 on the right and L_3 on the left. Sacral sensation (S_3–S_5) was preserved, and anal tone was normal. Vibration sense and joint position sense were normal in both legs.

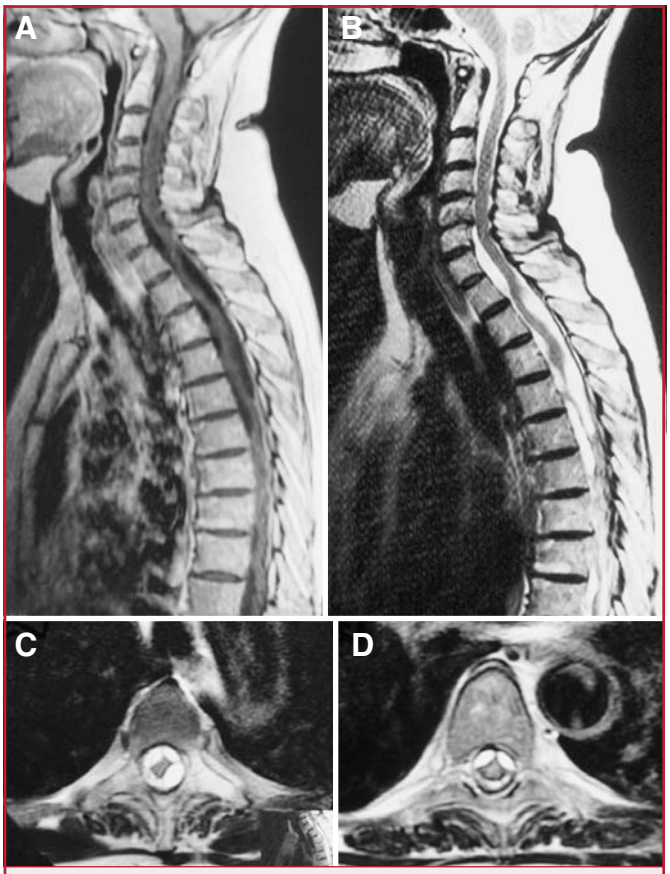


FIGURE 1. *MRI scans obtained at the time of presentation 2 years after cerebral aneurysmal subarachnoid hemorrhage. Sagittal T1-weighted contrasted image (**A**) and sagittal T2-weighted image (**B**) showing the thoracic spinal cord compressed, deviated, and distorted from T1 to T10. The cyst fluid is hypointense to CSF on the T2-weighted images. **C** and **D**, axial T2-weighted images showing that the thoracic cord is grossly distorted and compressed. Septae pass from pia to dura in stellate fashion, and contain loculated CSF found to be under pressure at the time of surgery.*

Investigations

Full blood count, urea and electrolytes, serum glucose, liver function tests, calcium and phosphate, C-reactive protein, erythrocyte sedimentation rate, chest x-ray, serum folate, serum B12 were all normal.



FIGURE 2. *Myelogram obtained at the time of presentation 2 years after cerebral aneurysmal subarachnoid hemorrhage. Blockage to contrast flow is demonstrated from T1 (not shown) to T7–T8.*

Radiological Examination

Magnetic resonance imaging (MRI) scans revealed a multiloculated cystic lesion from T1 to T10 (*Fig. 1, A* and *B*). The cyst fluid signal was hypointense to CSF on T2-weighted images and compressed and distorted the thoracic cord (*Fig. 1, B–D*). Myelography (*Fig. 2*), performed by C1–C2 puncture, demonstrated a block to contrast flow from T2 to T8, with minimal CSF egress and an unrecordable opening pressure. The CSF was clear and colorless with a white cell count of less than $1/mm^3$, a red cell count of $2/mm^3$, a glucose concentration of 4.5 mmol/L, and a protein concentration of 3.73 g/L. No organisms were seen or cultured.

Operation

Through a T3–T7 laminoplasty, multiple non-communicating pressurized fibrotic cysts were found within the subarachnoid space. The intervening subarachnoid space was completely obliterated with thickened fibrous tissue densely adherent to the pia. A full communication between all cysts was established using a Fogarty catheter. The CSF was clear and colorless, with normal microscopy. Histopathological examination revealed nonspecific fibrosis with scattered lymphocytes and uniform hemosiderin staining.

Postoperative Progress

Sensation was improved, and the patient was discharged 1 week later with a significantly improved gait. Unfortunately, readmission was required 3 weeks after the time of discharge because of drowsiness, decreased cognition, and a Glasgow Coma Scale score of 14. Computed tomographic scans revealed communicating hydrocephalus without periventricular lucency. CSF examination was normal. External ventricular drainage, with subsequent conversion to a ventriculoperitoneal shunt, restored normal cerebral functioning. Repeat MRI scans (*Fig. 3*) revealed a significantly restored spinal subarachnoid space. After 1 year of follow up, she remains independent with a steady gait, normal continence, and restored trunk and leg sensation.

DISCUSSION



FIGURE 3. *Postoperative MRI scan demonstrating improved appearances after laminoplasty and decompression of the spinal subarachnoid space.*

Hammes (3) described the inflammatory reaction of the meninges to ectopic blood in 1944, whereas Jackson (4) later used the phrase "aseptic hemogenic meningitis." Bagley (1) first demonstrated that autologous blood injected into the subarachnoid space could elicit hydrocephalus, whereas Kibler and Crompton (5) correlated this with leptomeningeal fibrosis. Suzuki et al. (12, 13) experimentally produced widespread fibrotic obliteration of the subarachnoid space after SAH. Motohashi et al. (7) later correlated such post-SAH fibrosis with widespread leptomeningeal proliferation, induced by thrombin and tumor necrosis factor-β, within both the subarachnoid space and arachnoid granulations. Such fibrosis potentially explained delayed post-SAH hydrocephalus.

A significant proportion of the extracellular matrix of both the dura and arachnoid is ordinarily composed of an array of different collagens, each synthesized by leptomeningeal cells and/or dural fibroblasts (9). Sajanti et al. (10, 11) demonstrated that collagen synthetic activity increases in a time-dependent manner after SAH and that such activity may be maintained for several months (10, 11). Sajanti and Majamaak (9) and Sajanti et al. (10, 11) also demonstrated that the extent of such fibroproliferation could be monitored by radioimmunoassay of CSF carboxyterminal propeptide procollagen I and aminoterminal propeptide procollagen III.

In our patient, leptomeningeal fibrosis appeared overtly restricted to the thoracic subarachnoid space (*Fig. 1*). Nevertheless, the convexity subarachnoid space and/or arachnoid granulations were also implicated because communicating hydrocephalus subsequently developed, with exacerbation possibly emanating from arachnoiditis consequent upon interim spinal surgery. After SAH, clots may form heterogeneously throughout the subarachnoid space, without strict localization to the site of rupture. Nevertheless, a concentration of fibrosis within the thoracic subarachnoid space would seem to be rare given the scarcity of such reports in comparison to the frequency of post-SAH communicating hydrocephalus. Such rare spinal cases as the one presented here appear to have invariably followed a posterior circulation, Fisher Grade 3 to 4, aneurysmal SAH (15).

It is unlikely that bacterial meningitis caused subarachnoid fibrosis in our case because the SAH experienced 2 years earlier had been managed endovascularly and because CSF analysis at that juncture had repeatedly demonstrated "aseptic" meningitis. Moreover, hemosiderin staining was uniformly present throughout the fibrotic specimen obtained from surgery. It is also unlikely that any fibrosis had predated SAH because lumbar punctures had been repeatedly unimpeded immediately after SAH, yet were impossible during the admission 2 years later. We, therefore, believe that leptomeningeal fibrosis developed insidiously in our patient as a direct consequence of SAH-induced "aseptic meningitis" (3, 4) with its subsequent stimulatory effect upon subarachnoid collagen synthetic activity (9–11). This caused both delayed post-SAH hydrocephalus (10) as well as delayed obliteration of the thoracic spinal subarachnoid space.

Most authors have concluded that operative intervention procures little benefit over conservative management for spinal arachnoiditis per se (14). However, operative management would seem to be indicated where spinal arachnoiditis is circumscribed (16), particularly when also associated with arachnoid cyst formation, as in the case presented here. In this case, treatment was successfully achieved with an extensive laminoplasty, with cyst-subarachnoid space communication successfully established using a Fogarty catheter. Notwithstanding, a similar result could have been achieved through a smaller opening using neuroendoscopy. Although Wilkinson et al. (17) found that, experimentally, systemic corticosteroids ameliorated communicating hydrocephalus after SAH, potentially by ameliorating "aseptic meningitis" and stimulated collagen synthesis (8), such a result has not been widely replicated clinically. Interestingly, urokinase has been shown to prevent leptomeningeal fibrosis in experimental Phase I studies (2). Unfortunately, however, no study has demonstrated urokinase-mediated reversal of established subarachnoid fibrosis.

Although the cyst fluid was hypointense to CSF on T2-weighted imaging in our case (*Fig. 1B*), insufficient T1-weighted and T1-weighted contrast image resolution (*Fig. 1A*) obviated any further analysis. Fluid appearances, therefore, could have related to lysis-derived blood products or, instead, to normal phase-encoding flow artifacts related to intracystic fibrotic bands.

CONCLUSION

In addition to precipitating leptomeningeal fibrosis within the convexity subarachnoid space and/or arachnoid granulations, causing delayed hydrocephalus, cerebral aneurysmal SAH may also rarely elicit widespread symptomatic fibrotic obliteration of the spinal subarachnoid space. Such cases seem to be characterized by a posterior circulation, Fisher Grade 3 to 4, aneurysmal SAH and, where circumscribed and cystic, seem amenable to surgical decompression.

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COMMENTS

Marshman et al. present an uncommon but recognized occurrence of delayed severe spinal adhesive arachnoiditis after aneurysmal subarachnoid hemorrhage (SAH). Previously reported manifestations have ranged from small acquired spinal arachnoid cysts to near-complete obliteration of the subarachnoid space, with time of onset ranging from days or weeks to months or years. This case represents close to the extreme end of the spectrum, both in terms of extent of the lesion and timing. It is self-evident that this is an entity to be aware of, particularly when SAH arises within the posterior circulation, with Fisher Grade 3 or 4, as the authors note.

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This well-written case report describes a rare complication of SAH to be remembered by clinicians. Hydrocephalus 2 to 3 months after the ictus necessitating a shunt in 5 to 10% of SAH patients is a complication caused by scarring of the arachnoid villi and obliteration of the subarachnoid space. Naturally, scarring may cause more widespread obliteration, also extending the spinal subarachnoid space. It may be there in mild form in many but very rarely to the extent described by the authors. The patient probably had a very strong inflammatory reaction towards the initial blood showing later as an aseptic meningitis and cyst formation with severe symptoms. Inflammation has a role in not only the rupture of cerebral aneurysms (1), but it also plays a major role after the rupture. As knowledge of these mechanisms becomes more profound, we may find prognostic factors for inflammation to be measured in the cerebrospinal fluid, perhaps indicating an increased risk for scarring of the leptomeninges and/or a worse prognosis in general. Further studies are needed to develop specific anti-inflammatories to avoid these complications.

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The authors present a single, yet interesting and important, case report of a patient experiencing what I would describe as extensive spinal arachnoiditis 2 years after aneurysmal SAH treated with coiling and complicated by hydrocephalus and meningitis. The authors also report improvement after subsequent surgical treatment.

In my experience, this is not a unique phenomenon but it is rare; it occurs when there has been very significant blood load in poor-grade patients, usually with posterior circulation aneurysms. I would agree with the authors that surgery is often helpful, though rarely curative, in these circumstances. The lesson of this case report is that long-term follow-up of SAH patients needs to be assiduous. Such delayed phenomena include not only rare occurrences such as spinal arachnoiditis but also communicating hydrocephalus, psychometric delay, and other psychosocial sequalae. We as neurosurgeons need to continue active follow-up of all of our patients with SAH, whether treated with coils, operative clipping, or conservatively. I commend the authors for bringing this rare delayed complication to the readerships' attention.

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CONGENITAL PTERIONAL DERMAL SINUS IN AN 18-MONTH-OLD CHILD: CASE REPORT

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OBJECTIVE: Congenital dermal sinus tracts most frequently occur in the midline and are often associated with dermoid or epidermoid inclusion cysts. A lateral cranial origin is extremely rare and anatomically inconsistent with an etiology involving closure of the rostral neural tube during embryogenesis.

CLINICAL PRESENTATION: We describe the first case of a pterional cranial dermal sinus tract associated with a small epidermoid, with extension to the dura of the anterior cranial fossa.

INTERVENTION: The extra- and intracranial portions of the tract were visualized and resected with the use of an operating microscope. Pathological diagnosis confirmed dermal sinus tract.

CONCLUSION: We review the existing literature and address the developmental and clinical features pertinent to the management of cranial dermal sinus tracts, emphasizing the need for exploration of these potentially harmful lesions.

KEY WORDS: Dermal sinus, Epidermoid, Lateral

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A cranial dermal sinus is an elongated epithelial-lined conduit that originates from the skin and exhibits variable intracranial extension. It is thought to result from a focal segmental adhesion or disordered separation between the cutaneous and neural layers of the ectoderm during the fourth week of gestation (2, 6). Nearly all reported cases occur in the midline and involve the external occipital protuberance (85%), nasion (10%), or the posterior parietal area (5%) (9). Inclusion cysts (dermoid, epidermoid, and teratoma) are often associated with these lesions and may exist at any point along the tract.



FIGURE 1. *Photograph of the child demonstrating a left pterional dermal sinus tract.*

Nonmidline dermal sinuses are exceedingly rare. A literature review disclosed six previously published case reports, five of which involved the skin of the anterior temporal region with variable termini (3, 4, 5, 7, 8, 9). These tracts traversed the temporalis muscle and terminated as dermoid tumors within the pterional diploe, sphenoid bone, middle fossa dura, or brain parenchyma. We describe an additional case of a lateral dermal sinus associated with a small epidermoid with extension to, but not through, the dura of the anterior cranial fossa.

Case Report

History and Examination

The patient is an 18-month-old girl with a left temporal "dimple" discovered shortly after birth (*Fig. 1*). The mother noticed spontaneous intermittent clear drainage from the site over the course of several months. The child was the product of an uncomplicated pregnancy and had no history of mass, pain, erythema, or fullness in the temporal region and no midline lesions. She had no fevers or other infectious symptoms and was neurologically intact with normal developmental milestones. Palpation and expression yielded 1 ml of clear fluid. Magnetic resonance imaging (MRI) scans demonstrated a high T2 signal tract in the left temporalis region, which appeared to extend from the skin surface to the anterior cranial fossa (*Fig. 2*).

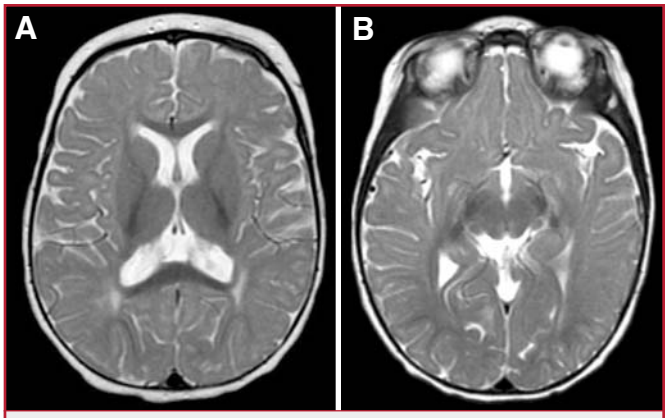


FIGURE 2. **A** *and* **B**, *axial T2-weighted MRI scans demonstrating a high signal tract in the left temporalis region which appears to communicate medially with the middle cranial fossa and laterally with the skin surface.*

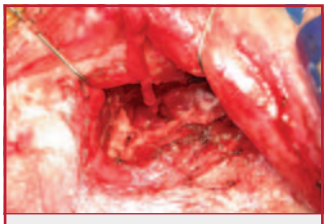


FIGURE 3. *Intraoperative view showing the elliptical incision made around the skin dimple and a dermal sinus tract penetrating the sphenoid wing.*

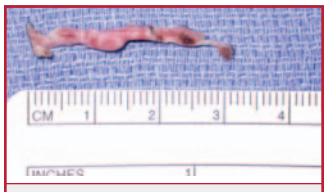


FIGURE 4. *Photograph showing the gross pathological specimen (dermal sinus tract). The sebaceous material that was encountered distally changed to a fibrovascular consistency without sebum proximally.*

Operation and Postoperative Course

An elliptical incision was fashioned around the skin dimple and a dermal sinus was identified. It extended from the skin surface, though the soft tissue, down to the bone of the sphenoid wing (*Fig. 3*). An operating microscope was used to visualize and dissect the transcranial and intracranial component of the tract. The sebaceous material that was encountered more distally changed to a fibrovascular consistency without sebum (*Fig. 4*). The tract was firmly attached to the dura of the anterior cranial fossa over the orbitofrontal cortex. As the dissection progressed, it became clear that the tract invested itself in the leaves of the dura and dissipated. Pathological diagnosis confirmed dermal sinus. A primary closure was achieved. Recovery was uneventful, and the patient was discharged home 1 day after surgery. She is currently asymptomatic and is developing normally after 12 months of follow-up.

DISCUSSION

To date, six cases of laterally positioned cranial dermal sinuses have been reported in the neurosurgery, otolaryngology, and plastic surgery literature (*Table 1*). Clinical presentations were varied and diagnostic evaluations assessed by a diverse group of surgical specialists (neurosurgeons, plastic surgeons, head and neck surgeons, and oral maxillofacial surgeons). Neblett et al. (5) described the first such case in 1970. A 20-month-old boy presented with a small cutaneous dimple and frontotemporal dermal sinus associated with an intradiploic dermoid tumor. Diagnosis was confirmed by a lateral cranial x-ray, and the lesion was excised through a curvilinear skin incision with a temporal base, centered on the soft tissue mass. In 1973, Green (3) documented the case of a 6-year-old boy with an infected dermal sinus coupled with a dermoid cyst, also in the frontotemporal region (3). X-rays and computed tomographic scans of the cranium reportedly showed no underlying abnormality. The purulent lesion was excised in three stages. The operations all employed elliptical skin incisions and occurred over the course of a year. In 1998, Hong (4) presented a case of a girl with a dimple present since birth that began to discharge when she was 2 years old. An operative exploration was performed without diagnostic imaging. Through a small elliptical

TABLE 1. Catalog of nonmidline dermal sinus tract cases reported in the literature[a]

Series (ref. no.)	Location	Radiographic diagnosis	Termination, associated tumor/cyst	Operative incision
Neblett et al., 1970 (5)	Right frontotemporal	Cranial x-ray	Intradiploic dermoid cyst	Curvilinear incision
Green, 1973 (3)	Right frontotemporal	Cranial x-ray, CT scan	Intradiploic dermoid cyst	Two-staged/elliptical incisions
Hong, 1998 (4)	Right frontotemporal	None	Dermoid cyst adherent to middle fossa dura	Elliptical incision
Parag et al., 2001 (7)	Left temporal	CT scan	Dermoid cyst	Hemicoronal incision
Scolozzi et al., 2005 (8)	Right frontotemporal	None, postoperative CT and MRI scans	Subcutaneous/intracranial dermoid cyst	Two-staged/elliptical and coronal incisions
Nejat et al., 2003 (6)	Bilateral retroauricular	MRI scan	Subdural/intracranial	Bilateral retromastoid elliptical incision

[a]CT, computed tomographic; MRI, magnetic resonance imaging.

incision, the surgeon excised a tract that terminated on a dermoid cyst adherent to the dura of the middle cranial fossa.

In 2001, Parag et al. (7) described a case of a 14-month-old girl who presented with a left temporal mass with three tracts that had been discharging over the cheek, lower eyelid, and temporal region. Computed tomographic scans demonstrated a mass in the left temporal region with extension into the orbit and dura mater below the temporal bone. A dermoid cyst and associated sinus tract were removed through a hemicoronal incision extending to the preauricular area. In 2004, Scolozzi et al. (8) presented a case of a girl with a right frontotemporal sinus diagnosed at 1 year of age. The tract was removed without preoperative imaging. At the time of operation, a subcutaneous dermoid cyst was found to be eroding the orbital wall and extending intracranially. Postoperative computed tomographic and MRI scans revealed a stalk extending to the dura of the middle cranial fossa. A second operation was performed through a coronal approach and a lateral orbitotomy was used to excise an extradural dermoid cyst. In 2003, Nejat et al. (6) published an article describing a patient with bilateral retroauricular dermal sinuses confirmed on MRI scans. These lesions involved the asterion with extension into the dura and cerebellar parenchyma and were excised through bilateral retromastoid elliptical incisions. The case presented in our report is unique in that the pterional location of the dimple gave way to a tract with extension through the temporalis and sphenoid bone, as in other reports, but with termination in the anterior cranial fossa. These findings emphasize an inability to predict the terminus of any dermal sinus, and the need for complete surgical resection and meticulous inspection.

Unlike midline dermal sinuses, the embryogenesis of these lateral lesions has not been adequately characterized. In their case with intradural extension, Nejat et al. proposed that the developmental anomaly leading to bilateral retroauricular tracts involved the early development of the otic placode. They believe that abnormal invagination and separation of the otic vesicle from the overlying cutaneous ectoderm led to a persistent tract of tissue between the vesicle and the retroauricular skin (6). Of note, however, six of the seven reported cases of nonmidline cranial dermal sinuses have involved the frontotemporal region. In contrast to the aforementioned retroauricular tracts, the pathogenesis of these lesions is unlikely to be related to "non-disjunction," placode migration, or disordered branchial arch development. Instead, we propose the following embryogenic etiology.

During cranial bone development, the embryonic ectoderm and the periosteum are apposed at the suture lines (4). As embryogenesis and growth occur, the ectoderm may pinch off between the two disarticulated bone edges at the suture lines. Complete amputation of the migrating tissue might result in the ectopic epithelium that forms an encapsulated tumor or cyst, a commonly accepted theory concerning the formation of scalp or intradiploic dermoid/epidermoid cysts (4). Incomplete or partial retardation of normal migration, however, may produce a rest of cells that remain connected to the ectoderm/skin. This could lead to the formation of a sinus with or without a dermoid or epidermoid tumor at the point of initiation. The upper quadrant of the orbit or the frontotemporal region would be a logical location for ectopic dermal rests or tract development as the sphenofrontal suture resides at the confluence of the frontal, sphenoid, and zygomatic bones and the squamous suture continues posteriorly. Bartlett et al. (1) reported 84 cases of orbitofacial dermoid cysts in the absence of associated dermal sinuses, noting that 64% resided in the frontotemporal region, whereas 25% were orbital and 11% nasoglabelar. Furthermore, the frontotemporal group was characteristically slow growing without intradural extension, as in the case presented here.

The presence of a cutaneous dimple on the forehead indicates the potential for an underlying dermal sinus. Although rare, lateral tracts present a risk for intracranial infection and must be carefully evaluated. MRI scans often assist in determining the depth and extension of the sinus and can document the presence of an underlying tumor or cyst. However, tract diameters can be small enough to be missed or incompletely visualized. If a dermal sinus is suspected, surgical exploration with microdissection is indicated. Operative repair allows for rigorous visual inspection and eliminates the persistent risk of meningitis and abscess formation. To this end, the entire tract must be excised along with any associated dermoid or epidermoid tumor. Given the epidural terminus of the tract in this case, however, the likelihood of meningitis and intradural abscess is remote.

CONCLUSION

This report describes a frontotemporal dermal sinus associated with a small epidermoid with intracranial extension to the dura of the anterior fossa floor. We review the existing literature regarding these extremely rare lateral cranial dermal sinus tracts and discuss the developmental and clinical features pertinent to the diagnosis and management of these lesions.

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COMMENTS

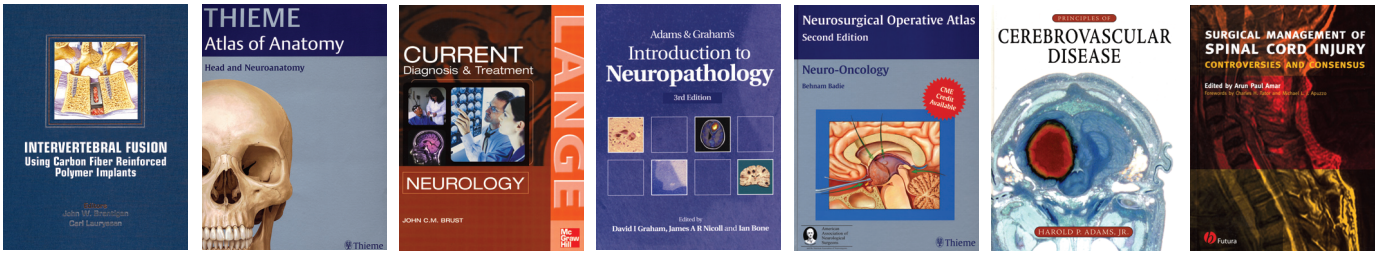
The authors present an unusual case of a non-midline congenital dermal sinus (CDS) and associated dermoid cyst that extended to the external surface of the dura mater in the pterional region of the anterior fossa in an infant. As the authors note, it is but with very rare exception that CDSs are located in the midline. Is the embryogenesis of these non-midline CDS any different from those that are midline? Dermoid inclusion cysts anywhere around the cranium often extend to the external surface of the dura mater. Is the embryogenesis of dermal inclusion cysts any different from those that have a tract?

As has been previously noted, only those midline CDS that extend through the foramen cecum or enter the calvarial vault inferiorly to the torcula are found to penetrate through the dura mater and enter the subarachnoid space on some occasions. Thus, the superior sagittal sinus provides a barrier to prevent a CDS from becoming intradural and being a portal of entry for bacteria to cause meningitis or an abscess. A CDS needs to be explored operatively to its terminus and excised, even if a magnetic resonance imaging scan does not show intracranial extension as the tract, and especially if a dermoid cyst is not present and it may not be imaged easily.

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This is a single case report of a temporal congenital sinus tract. The authors note the rarity of these CDSs and emphasize the importance of removal of the entire tract. I have seen one of these, referrred by a plastic surgeon who had only removed the superficial portion, resulting in a chronic infection. Because the tract traverses the sphenoid wing, it is helpful to drill the bone circumferentially around the sinus and follow it to the dura.

Leslie N. Sutton
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Intervertebral Fusion Using Carbon Fiber Reinforced Polymer Implants

Editors: John W. Brantigan
653 pages
Quality Medical Publishing, St. Louis, MO (2006)

The use of manufactured spinal interbody fusion devices has been a recent development, a fact that is frequently taken for granted by surgeons trained in the modern era of spinal neurological or orthopedic surgery. One of the pioneers in this field, John Brantigan, was instrumental in the development of the first such devices, carbon fiber cages, in the 1980s. This text outlines the full spectrum of topics concerning these implants, including their history, indications, biomechanics, and surgical application.

The text is well-written, accessible to surgeons at all levels of training, and is filled with beautiful color photos and figures. Several chapters in the book are particularly noteworthy. Chapter 2, contributed by Wolfgang Rauschling, is filled with fantastic color sections of the human spinal column that brilliantly illustrate both the normal and pathological anatomy. Chapter 8, "Transfusion Management," is a highly detailed and informative discourse with information that is vital for all surgeons but seldom found in neurosurgical texts. It outlines pre-, intra-, and postoperative strategies for avoiding and administering blood product replenishment. Chapter 22, by Boriani et al., is a wonderfully illustrated and comprehensive discussion of vertebrectomy reconstruction for tumor removal and describes techniques for en bloc tumor removal. There are four excellent subsequent chapters on "Patient Education" and six on "Surgical Techniques."

Also included in the book are two DVDs containing narrated surgical videos from Drs. Brantigan, Taneichi, Lauryssen, and Fraser, which make for an excellent review of nuances for various interbody techniques in the cervical and lumbar spine, particularly for surgeons who are not familiar with the precise techniques for proper carpentry of interbody devices.

One obvious drawback of this text is that it focuses on only a single product line of spinal implants: carbon reinforced interbody implants. These devices are essentially exclusively manufactured, marketed, and sold by Depuy Spine, Inc. (Raynham, MA), a subsidiary of Johnson and Johnson. Furthermore, the senior author, John Brantigan, has been intimately involved in the design, manufacture, and Food and Drug Administration approval of these devices; he also has financial interests in the product. Despite these concerns, all of these potential conflicts of interest are fully disclosed in the Preface, and the authors seem to maintain a respectable level of objectivity throughout most of the text.

Overall, this is a highly readable and informative text written by well-respected authorities in spinal surgery. Although the meticulous attention to detail may be excessive for neurosurgeons-in-training, this text will serve as a valuable reference and a delightful read for those with a special interest in spinal column reconstruction.

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THIEME Atlas of Anatomy Series: Volume 3: Head and Neuroanatomy

Authors: Michael Schuenke, Erik Schulte, Udo Schumacher, Lawrence Ross, Edward Lamperti, Markus M. Voll, Karl H. Wesker
412 pages
Thieme Medical Publishers, New York, NY (2007)

Thieme Medical Publishers recently published the "Thieme Atlas of Anatomy" series. *Head and Neuroanatomy* is a revised translation of the German edition authored by Michael Schuenke, M.D., Ph.D., Erik Schulte, M.D., and Udo Schumacher, M.D. This atlas contains 1182 illustrations and 72 tables among its more than 400 pages. The remaining anatomy books in the series are *General Anatomy and Musculoskeletal System* and *Neck and Internal Organs*.

The objective of the authors and publisher is to create an atlas suitable for the needs of students and lecturers. Specifically, the atlas is designed to facilitate mastery of the extensive information presented in the text amidst the rigors of a busy academic schedule. The information is considered accurate and up-to-date. This atlas is designed to be unique in that topics are presented in a comprehensive manner. Illustrations and legends, which comprise the majority of most atlases, are accompanied by explanatory text and summarizing tables. Additionally, clinical scenarios assist with integration and correlation of anatomic information.

Presenting illustrations with text allows for in-depth explanations and descriptions of anatomic structures, but the resulting book is large, heavy, and, therefore, minimally portable. One advantage of a large book is that its sizeable pages allow for small details to be illustrated at a scale that remains easy to visu-

alize. Structures of disparate sizes can be easily distinguished and represented in a single drawing. Thus, their functional and structural relationship to each other can be depicted at the same time as their difference in scale can be appreciated.

The table of contents is clear and concise, bringing ease to the initial search for a specific neuroanatomy topic. The text is much more abundant than typical anatomy atlases and is presented in an enticing format that is easy to read. The translation from German to English shows no major or consistent flaws in grammar or flow, and maintains faith to the authors' original insights and intentions.

Central to a review of an atlas of neuroanatomy is an evaluation of the illustrations and figures. The cross-sectional and three-dimensional anatomic renderings are crisp and colorful. The anatomic relationship of structures within individual figures appears accurate in terms of scale and positional relationship. Labels for the figures are clear and well-planned. Additional information, such as physical examination findings in oculomotor palsies, is thoroughly depicted by both tables and illustrations. Each neuroanatomy topic receives adequate attention throughout the text, making the atlas a complete source for anatomic illustrations of the head and cranial central nervous system.

Head and Neuroanatomy supplements large, clear illustrations with detailed explanations and clinical correlations. This provides the reader with amounts of information beyond what is normally found in an atlas of anatomy. Although the text throughout the atlas is rich with detail, the index is difficult to navigate. Some subjects are found in unexpected places within the index, requiring a prolonged search, and subtopics are organized in a confusing method involving varying numbers of dashed lines. This may limit ease of use for those intending it as an occasional reference. However, students of anatomy courses and frequent readers of the atlas will certainly become familiar with the book and will benefit greatly from its abundance of information. The reference section lists mostly foreign titles, which will be of little use to the majority of English-speaking readers. Although this may not be significant to most students of neuroanatomy, other readers, such as basic scientists and clinical neuroscientists, who wish to review a specific topic further may be disappointed.

Overall, *Head and Neuroanatomy* offers a unique and thoughtful approach to the subject of human neuroanatomy. The authors intended the atlas to serve as the "ideal" atlas of anatomy for students who are required to master massive amounts of information while balancing a busy course schedule. I consider this goal to be met by the authors and recommend the book as a primary source of learning for students whose coursework requires significant knowledge of neuroanatomy. For the purposes of a student of neuroanatomy, this atlas is a superior source of learning compared with those that offer only illustrations and labels. Other readers interested in anatomic explanations and detail, with supplemental clinical correlations, may also benefit from this atlas. The drawback of the text is that its abundance of information mandated a larger, more cumbersome book. Those searching for a portable text or intending to use the atlas as an infrequent reference should probably consider other selections.

James B. Elder, M.D.
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Current Diagnosis & Treatment in Neurology

Editor: John C.M. Brust
601 pages
McGraw-Hill, New York, NY (2007)

The successful practice of neurosurgery rests upon a thorough understanding of neurology. This is especially true today, as advances in neurosurgery have enabled surgeons to effectively treat a growing spectrum of neurological conditions, such as Parkinson's disease, epilepsy, and dystonia. To that end, this concise, comprehensive, and practical neurology text will prove very useful.

Current Diagnosis & Treatment in Neurology is a first edition, multi-author text edited by John C.M. Brust, M.D. Dr. Brust, a professor of neurology at Columbia University College of Physicians & Surgeons and the director of the Department of Neurology at Harlem Hospital Center in New York, has assembled a stellar group of writers from across the United States, particularly Columbia University College of Physicians & Surgeons, to create this work. To review the scope of neurology is a sizable task, albeit one that Dr. Brust has admirably accomplished.

The text is divided into two sections: "Neurologic Investigations," which reviews electroencephalography, electromyography, nerve conduction studies, evoked potentials, and neuroradiology, and "Neurologic Disorders," which encompasses the spectrum of pathologic conditions faced by the neurologist, such as epilepsy, stroke, movement disorders, headache, dementia, multiple sclerosis, motor neuron diseases, and sleep disorders.

The chapters are nicely integrated and almost never redundant despite this being a multi-author text. A summary of key diagnostic elements usually introduces the specific topics each chapter encompasses. The text is usable and management-oriented. Numerous tables beautifully highlight the main points, while black and white photographs clearly illustrate classic radiographic findings. To enhance readability, the more esoteric information is also relegated to the tables. The voluminous, cross-referenced index allows rapid access to the topic of interest. The key to Dr. Brust's success is that he doesn't stray from the goal of creating a concise yet comprehensive review of neurology.

In summary, *Current Diagnosis & Treatment in Neurology* is a well-written text covering the many facets of neurology in a detailed, yet succinct and digestible, format. Although primarily written for generalists, I strongly recommend this thoughtfully designed book to any student or physician caring for patients with neurological disorders.

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Adams and Graham's Introduction to Neuropathology

Editors: David I. Graham, James A.R. Nicoll, Ian Bone
464 pages
Hodder Education, London, United Kingdom (2006)

Adams and Graham's Introduction to Neuropathology, published by Hodder Arnold in 2006, is the third published edition of this book. The first two versions were published in 1988 and 1994, respectively. This third edition is a comprehensive rewrite of the book, which was deemed necessary due to the lengthy time interval between the second edition and the present text.

The primary goal of this introduction to neuropathology, as outlined in the edition's preface, is to provide information regarding common and important central nervous system diseases. The target audience is clinicians in training, as well as basic scientists whose research may benefit from a reference containing human clinical and pathological correlations. The material is organized into pathological categories such as bacterial infections, intoxications, tumors, and paraneoplastic syndromes, each of which comprises a separate chapter.

One difference between this and the second edition is the expansion from 18 to 21 chapters, reflecting recent advances in the field of neuropathology. New chapters include "Peroxisomal and Mitochondrial Disorders," "Lysosomal Diseases and the Leukodystrophies," "Disorders of the Bony Coverings of the Brain and Spine," and "The Law and Forensic Neuropathology."

The table of contents lists only the chapter titles and authors, in contrast to the index, which offers detail adequately organized for finding a topic of interest. The black and white illustrations, including radiology images and transmission electron micrographs, are sharp and detailed, and are framed in a manner that allows adequate context for the evaluation of the images. Extraneous information, such as dates or time stamps, often found in x-rays is absent. Schematic representations, such as a drawing of a cross-section of the brainstem showing cranial nerve nuclei, are often presented and correlate well with their partner images. The color images are also clear and sharp, with distinct colors and obvious labels, and the method of tissue preparation is indicated for each figure. Moreover, the descriptions of a specific neuropathology finding presented in the figure legends and subject of the text are well-represented by the images. The examples that the images are intended to illustrate are easy to visualize, although the level of magnification of the micrographs is not always clearly indicated.

Each chapter is well organized and contains sufficient detail to provide a comprehensive introduction to the topic reviewed. The text is well-written and easy to read, and the tables clarify subtopics by condensing vital information in a well-organized format. Each chapter devotes adequate length and a sufficient number of images, including supplemental illustrations and tables, to the neuropathological category being discussed. The bibliography is referenced only infrequently throughout the book, with references listed alphabetically as suggestions for further reading.

Overall, this is a very practical text offering an introduction to pathological findings of the central nervous system organized by category of disease. The book provides relevant clinical and radiological information, as well as guidance in the differential diagnosis of neurological diseases. The book itself is light, thin, and portable, and the text is very readable.

I highly recommend this book to physicians and scientists desiring a handy neuropathology reference which, at the very least, can be used to guide further reading on a specific central nervous disease. Clinical trainees in specific fields, including pathology, neurology, forensic medicine, psychiatry, and neurosurgery, are likely to benefit most from using this book as a reference or to study for their respective written boards.

The editors stress that this book is an introduction to neuropathology intended to promote a closer working relationship between physicians and basic scientists from different specialties. They also intend the information to serve as a basis for clinicians and pathologists to work towards maximizing the potential of surgical specimens for diagnostic or research purposes. Toward these ends, the authors should consider their efforts a success.

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Neurosurgical Operative Atlas: Neuro-Oncology

Editor: Behnam Badie
337 pages
Thieme Medical Publishers, New York, NY (2006)

Despite its title, this volume is not a true atlas but rather a multiauthor, edited volume that covers a number of neurosurgical techniques relevant to the operative treatment of brain tumors. Those looking for an illustrated guide to surgery are likely to be disappointed. This volume is perhaps more comparable to a technique book, such as the venerable *Rand's Microneurosurgery* or the work of Schmidek and Sweet, rather than a traditional surgical atlas.

Aimed at residents in training, this book totals 337 pages divided among 36 chapters organized into seven sections covering sellar and parasellar tumors, intraventricular tumors, spinal and peripheral nerve tumors, malignant brain tumors, surgical management of meningiomas, posterior fossa tumors, and skull base approaches. Each chapter is generally divided into sections covering patient selection, preoperative management, operative technique, and postoperative management. The authors are, with a few exceptions, recognized leaders in their field.

A number of weaknesses are evident in this book. The figures are taken from a variety of different sources and artists; as such, there is no unifying graphic theme. That being said, the quality of the illustrations is generally high. The most glaring omission, however, is the lack of footnotes or references, which are essential to the serious study of the field, especially for those who are beginning their surgical training.

Some topics are unevenly covered or covered in a redundant fashion. A few rather large gaps in presentation are made, particularly on the topic of primary brain tumors in which there is no serious treatment of selection of operative corridors for deep-seated primary tumors. In addition, there is no mention of modern techniques such as diffusion-tensor fiber tracking, functional magnetic resonance imaging, superselective Wada testing, etc., as guides to the surgical approach. The stereotactic biopsy is not covered, and only a rudimentary discussion of radiosurgery is presented.

Fortunately, this book is strongest in its discussion of technically demanding methods for operative resection of cranial base tumors and meningiomas. These approaches comprise more than half the length of the book, and there are a number of chapters that are well suited for this book's approach. In particular, chapters authored by Drs. Al-Mefty, Samii, Day, Spetzler, and Robertson are well constructed and contain particularly relevant details. Residents preparing for these complex cranial operative cases would be well served by reviewing these chapters.

At a cost of $250, this book is likely to be too expensive for its intended audience of residents in training. For institutional libraries, however, it is a worthwhile purchase to complement other treatments of neuro-oncology.

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Principles of Cerebrovascular Disease

Author: Harold P. Adams, Jr.
564 pages
McGraw-Hill Professional, New York, NY (2006)

This is a single-author volume dedicated to cerebrovascular diseases from a recognized leader in neurology and cerebrovascular diseases. As listed in the acknowledgements, however, the author has enlisted help and contributions from numerous people, including neurosurgeons, neurologists, pathologists, and radiologists. There is no question about the clinical and economic impact of cerebrovascular diseases world-wide. Rather than being a neuroscience text, the purpose of this volume is to provide clinical insight and utility to practicing physicians. Therefore, details of basic science are included in a clinical context rather than being comprehensively considered. The author has organized the volume similar to the course and evaluation of a hypothetical patient with cerebrovascular diseases. There are 564 total pages organized into 25 chapters. The volume begins with three chapters on the classification, terminology, and pathophysiology of stroke, epidemiology of stroke, and organizing resources for stroke management. It is followed by a chapter on carotid disease and transient ischemic attacks. Chapters 6 and 7 consider the clinical manifestation of ischemic and hemorrhagic stroke, respectively, and are followed by a chapter on the diagnostic studies for evaluating patients with cerebrovascular disease. The next six chapters deal with atherosclerotic disease, no inflammatory arteriopathies, infectious and inflammatory causes of strokes, genetic considerations, cardiogenic embolism, and coagulation disorders that cause stroke. Chapter 15 deals with neurosurgical lesions such as aneurysms and arteriovenous malformations. Chapter 16 considers causes of intracranial hemorrhage, followed by a chapter on strokes in children and young adults. Chapter 18 treats a heterogeneous group of diseases, including venous thrombosis, pituitary apoplexy, and spinal cord vascular diseases. The remaining chapters deal with treatment options, including antithrombotic medications, surgical interventions, emergency management of suspected stroke patients, treatment of acute ischemic stroke, treatment of hemorrhagic stroke, and management of patients with recent stroke. The volume concludes with a final chapter dealing with the rehabilitation and return of stroke patients to society. The chapters are well illustrated, with color figures included before the first chapter. Each chapter is also referenced with a bibliography included with each chapter. In addition, there is a comprehensive index included at the end of the volume. The volume is easy to read and clinically relevant, and the subject matter is well organized. This volume should be a welcome addition to the libraries of both practicing clinical neuroscientists and those at various stages in their training.

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Surgical Management of Spinal Cord Injury: Controversies and Consensus

Editor: Arun P. Amar
256 pages
Blackwell Publishing Limited, Oxford, United Kingdom (2007)

This text summarizes and discusses the major issues surrounding the management of patients with spinal cord injury. A particular emphasis is placed on using scientific data to support the opinions expressed in the various chapters. The text consists of 14 chapters, each of which was contributed by very well known spinal surgeons, general surgeons, emergency room physicians, and neurologists. The target audience appears to be residents and practicing surgeons faced with managing patients with spinal cord injury, and many of the chapters provide practical advice based on either scientific evidence or the author's experience. The book is very well illustrated and attractively packaged.

Overall, the quality of the chapters is excellent. The discussions of the pathophysiology of spinal cord injury, pharmacotherapy, and radiographic workup are thorough and easily read, even if they do not provide much in the way of novel content. There are two chapters dealing with biomechanical considerations of spinal injury and stabilization, a critical topic for the practitioner. Dr. Watkins' chapter on decision making is an excellent treatise that is particularly recommended for residents and fellows interested in spinal surgery. Other excellent reviews are provided dealing with pediatric patients and those with penetrating injuries. Much of the practical advice provided in these chapters represents recommendations based on literature review, and most of the rec-

ommendations are consistent with other published guidelines and treatment strategies. Excellent reviews of the literature regarding the radiographic workup, timing of decompression, and role of delayed surgery for patients with persistent deficits will aid in surgical decision making.

I found two chapters to be problematic. The authors of the chapter dealing with vascular injury were very dogmatic in recommending aggressive diagnostic workup of vascular injuries in patients with cervical spine fractures, stating that such a workup and consequent treatment with anticoagulation represent the "standard" treatment. This statement is offered despite the acknowledged lack of evidence supporting the practice and despite very different recommendations from other evidence-based reviews. Similarly, strong recommendations for the use of multimodality electrophysiological monitoring are made in the following chapter, again without any evidence presented to indicate that outcomes are improved through the use of monitoring. The author of the monitoring chapter recommends a wake-up test or aborting surgery as a reasonable response to alterations in electrophysiological response. Given the potential morbidity of either of these interventions, more evidence to suggest that this response is warranted is needed to convince readers that there is utility in electrophysiological monitoring during decompression and stabilization of the spinal cord injured patient.

Despite these two caveats, I believe this book would be a valued addition to the library of residency training programs and for those training to become spinal surgeons. The use of literature review, description of important basic principles, and inclusion of practical advice from established practitioners will make this text useful as a teaching tool. The vast majority of the chapters provide balanced and comprehensive reviews of relevant topics for the surgical care of patients with spinal cord injury.

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NEUROSURGERY'S Science Times

CHRONICLING THE TIMES IN THE INFORMATION AGE

Science Times and a Discourse on Innovation in Neurosurgery

Science Times Editorial

Five years ago, through a charge by Editor Michael L.J. Apuzzo, a team was assembled to survey the world's literature for articles in science and engineering relevant to Neurosurgery. A panel of neurosurgeons was recruited, representing a broad diversity of interests and expertise, from basic neuroscience, to epilepsy research, spinal research, stem cells, translational science, and outcomes and population science. Others contributed information on funding and grant opportunities, and legislative and regulatory issues affecting neurosurgical research. Every two months or so, since the fall of 2002, the smart and creative minds of NEUROSURGERY delivered dozens of crisp summaries of novel concepts and discoveries, enhancing our collective literacy on ideas and techniques likely to shape the future of our field. The goal was to cast as broad a net as possible, and assemble as much diverse and potentially useful information as possible, knowledge that otherwise would not make its way to the neurosurgeon's lexicon.

In these Science Times columns, the concept of interference ribonucleic acid (iRNA) was first presented upon its publication in the literature and several subsequent potential applications, including in this issue, a coupling with rabies virus for neurotherapeutic delivery. The concepts of mapping disease genes, and their evolution from candidate gene research to genome wide explorations and "snips," with specific and potentially useful applications to common neurosurgical problems were presented. Several articles presented much on stem cell biology, bringing its concept into common neurosurgical discourse, with regenerative, developmental and oncogenesis implications. The applied and translational neurosciences were always represented, including novel analyses of spinal and epilepsy systems. Regeneration biology was well covered, as was computer science, brain-machine interface, and neurosurgery-bioengineering initiatives. And the regulatory and legislative processes affecting neuroscience and practical neurosurgery applications were explored from different angles, including the science, and lack thereof, in the approval of surgical devices. Science Times articles summarized the legislative agendas and budgetary implications affecting research, including the ongoing stem cell research controversy, National Institutes of Health budgets, and novel concepts on surgical econometrics. Regular contributions highlighted new funding mechanisms and other opportunities for neurosurgical research endeavors.

Another dimension of Science Times presented scientific and contextual analyses of recently published clinical trials and new technology, often brutally critical, and at times purposely controversial. These included subjects as varied as clipping versus coiling of aneurysms, angioplasty and stent versus endarterectomy for carotid disease, surgery versus conservative therapies for herniated disc, and antibiotics for neurosurgical disease. In this issue, for example, a review of Information Technology in Medicine is presented. It challenges prevailing adoptive trends regarding this technology, urging closer scientific question-driven assessment. The incisive review exposes several very different systems of information technology, each with a discrete vocabulary, objectives and outcomes parameters, and each with discrete obstacles and potential drawbacks. Questions about applicability to small physician practices, still dominating the American medical landscape, are thought provoking. Although such discussion will make us wonder and debate how long any physician can remain (or whether they should) outside the information technology nets of insurance companies, hospitals, healthcare networks, or government payers. A rigorous scientific discourse will help us not only define, but refine these applications and deploy them in arenas where effectiveness and potential impact are greatest, while learning to minimize their burdens and drawbacks. And we will learn to evaluate their impact on quality and cost, hence their true value. As with many basic and applied scientific concepts presented in these columns, and as our society has learned with computer technology in general, these innovations will have an unavoidable impact on our lives and practices. We should embrace them with literacy, objectivity, and a critical mind. If applied properly, they can improve our lives.

The Science Times contributions are now indexed and archived, and each is accessible for direct PDF download through Neurosurgery Online. This will enhance their educational and scholarly impact. Ultimately, this effort remains a tool to enhance the breadth and depth of neurosurgical science, and hence a link in the complex chain that tows us toward progress. As we celebrate another Annual Meeting of the Congress of Neurological Surgeons, with a theme of innovation, the Science Times team salutes the Journal and its parent organization leadership for their continued progressive ambitions on behalf of neurosurgical education.

ISSAM A. AWAD, MD, MSC
ASSOCIATE EDITOR
RICHARD G. ELLENBOGEN, MD
SCIENCE TIMES PRINCIPAL

More on Gene Therapy for Parkinson's Disease: An Open Label, Phase I Trial

The treatment of Parkinson's Disease has been greatly improved by the development of dopaminergic-based medical therapies, and more recently, by the use of deep brain stimulation surgical strategies. However, despite these advances, Parkinson's remains a chronic and progressive condition. Transplantation strategies offer the hope and potential of halting and possibly even reversing the inexorable progression of this condition. As the circuitry in Parkinson's becomes progressively well understood, the targets for Parkinson's transplantation become clearer.

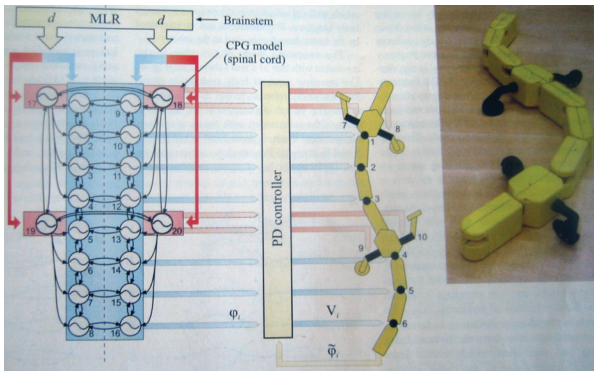
Most experimental Parkinson's transplantation work has focused on either improving the survival and function of existing dopaminergic neurons or providing a cellular source of dopamine replacement. However, a recent preliminary study by Kaplitt et al. published in **The Lancet (369:2097–2105, 2007)** has taken another route to treat Parkinson's disease. Rather than attempting to impact dopaminergic neurons directly, the multidisciplinary, multi-institutional team centered at Cornell University chose to use a viral vector gene transfer based approach to modify the local circuitry in Parkinson's patients. Taking advantage of the now well established finding of subthalamic nucleus (STN) hyperactivity in Parkinson's Disease, Kaplitt et al. designed an adeno-associated virus (AAV) vector to transfer glutamic acid decarboxylase (GAD) to glutamatergic STN neurons, in hopes of converting them from an excitatory glutamatergic to an inhibitory γ-amniobutyric phenotype.

Please see GENE THERAPY, next page

Robotics Discerning the Primordial Origins of the Spinal Cord Central Pattern Generator

One potential therapeutic avenue for restoring ambulation to paraplegic patients involves external control of the central pattern generator (CPG) of the spinal cord, which is able to create rhythmic locomotion in vertebrates without higher order input. To date, little information has been available on the CPG in humans, but even less is understood about the evolutionary origins of this neural system.

Recent progress in this area has been made by Ijspeert et al. from Lausanne, Switzerland and Bordeaux, France (**Science 315: 1416–1419, 2007**). The researchers were interested in the vertebrate transition from swimming to locomotion controlled by the CPG. Using the salamander as their model, they studied the CPG in the lamprey, a primitive vertebrate that swims in a mechanical pattern similar to the salamander. They then created a model which consisted of a series of coupled motor units responsible for limb actions along the length of the "spinal cord." This is similar to primitive vertebrates, where an initiation drive from the mesencephalon results in sequential stimulation from cranial to caudal, resulting in a rhythmic pattern of movement for locomotion.



Configuration of the CPG model and salamander robot. Courtesy of ***Science (315:1416–1420, 2007)****.*

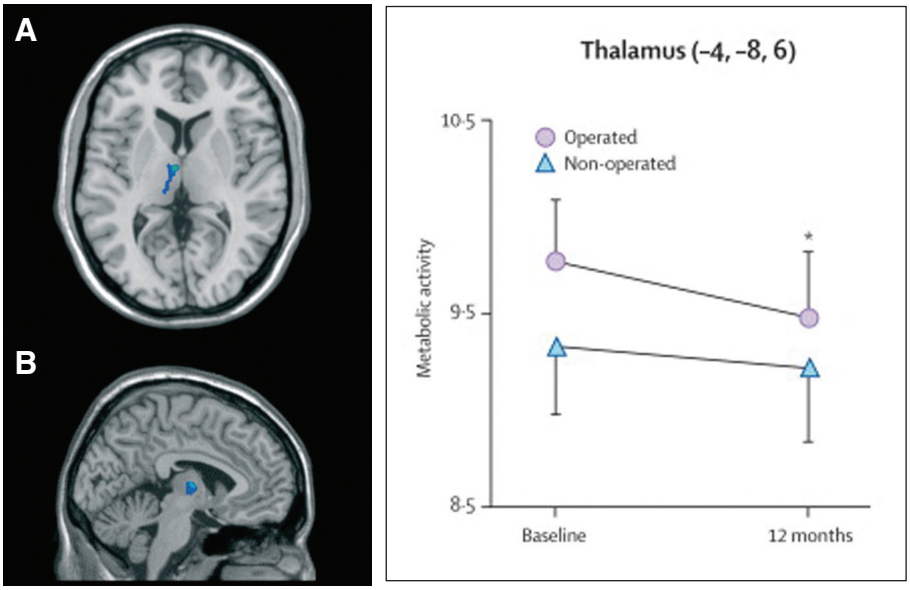
Previous work had demonstrated that gentle stimulation of the most proximal portion of the CPG resulted in a cascade of rhythmic activity causing limb motions consistent with salamander walking. However, as the amplitude of stimulation increased, limb motion decreased and the axial undulating "S-shaped" motion of swimming in lampreys and salamanders predominated. The researchers then created an electrically-based model of the system where the CPG was composed of a series of coupled oscillators somatotopically representing the vertebral segments (Figure). Their postulation that at low stimulation modes the CPG components responsible for limb motion interfered with the swimming undulations, allowing the slower body motions necessary for walking on land, whereas at high stimulation modes the axial undulations predominated for swimming proved to be correct.

They then manufactured a robotic salamander based upon this model and were able to effectively demonstrate that this relatively simple alteration in the degree of stimulation at the level of the brainstem resulted in two distinct, but effective means for motion. From an evolutionary standpoint, this suggests that early vertebrates did not have to innovate entirely new neural circuitry when transitioning from an aquatic to a terrestrial environment.

While this work does little to elucidate the evolutionary development or physiologic basis for the CPG in humans or terrestrial mammals, the innovative work provides some insight into how the CPG is similar across very different vertebrates (the lamprey and salamander). In addition, this work in modeling animal behavior with robotics may eventually lead to alternative means for mechanical re-animation and functional restoration.

MICHAEL Y. WANG, MD
SPINAL RESEARCH

GENE THERAPY (continued)



*Reduction of thalamic metabolic activity after gene therapy of the subthalamic nucleus. (***A***) Representative axial (top) and sagittal (bottom) slices at 12 months after gene therapy. (***B***) Metabolic activity in this region was plotted for the operated and non-operated hemispheres at baseline and 12 months. *p < 0.02. Courtesy of* ***The Lancet (69:2097–2105, 2007)****.*

This 12 patient study was a preliminary safety study, as mandated by the government regulatory authorities prior to a definitive clinical trial. As such, it was nonrandomized, without a sham surgery control arm, and without blinded neurologist follow-up evaluation of the treatment. Nevertheless, the study was carefully designed and executed. Three months following AAV-GAD vector implantation, the study patients demonstrated modest benefit in the Unified Parkinson's Disease Rating Scale (UPDRS), accompanied by PET imaging demonstration of decreased thalamic metabolism on the appropriate side of treatment (Figure). Most importantly, the treatment was safe, with no unanticipated side effects or complications.

If confirmed effective in follow-up investigation, the genetic approach utilized in this study is potentially in competition with STN DBS. STN DBS acts to normalize the same symptomatic hyperactivity in Parkinson's. Neither DBS nor AAV-GAD therapy directly treats the underlying neurodegenerative defect in Parkinson's Disease. DBS is now well established in the movement disorder world as an appropriate treatment for medication refractory Parkinson's Disease. Whether the disadvantages of DBS such as mechanical implant, risk of infection, need for pulse generator replacement, need of fine tuning of device programming, and stimulation side effects can be improved by a strategy such as that employed in this study remains to be seen. A definitive clinical trial of efficacy is planned by the authors. If positive, this will hopefully be followed by a direct comparison trial of DBS versus AAV-GAD therapy.

This study is most significant in its demonstration of the safety of an AAV-based approach to modulate local basal ganglionic circuitry. The potential exists to not just fine-tune this type of treatment for Parkinson's Disease but also to apply a similar methodology to other neurodegenerative conditions.

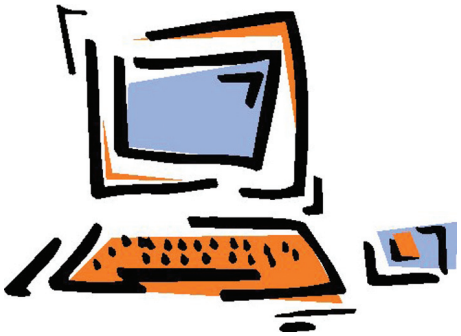
GUY M. MCKHANN II, MD
EPILEPSY AND NEUROTRANSPLANTATION RESEARCH

Continues ⇨ N7

Information Technology in Medicine: The Good, the Bad, and the Future

The effects of Health Information Technology (HIT) on the United States health care system are difficult to predict. Some view HIT as simply one more in a list of technologies that medicine has accommodated without great disruption. Others view HIT as something that is fundamentally different, a transforming force that will produce radical changes in the practice of medicine. A recent scholarly review by Blumenthal and Glaser (**N Engl J Med 356:2527–2534, 2007**) addresses five questions: What is HIT? What do we know of its benefits and risks? How prevalent is its use? What are policymakers doing to encourage or manage its dissemination? And what does the future hold for HIT in U.S. medicine? It is a balanced and thoughtful survey of a topic notorious for generating articles and discussions that yield more heat than light. All practicing United States neurosurgeons will be affected by the push to adopt HIT in the near future and the paper serves as an excellent introduction to many of the issues surrounding HIT.

HIT consists of a diverse set of technologies for manipulating health information by consumers, providers, payers, insurers, and all the other groups with an interest in health care. The focus of this review is on technologies relevant to storing and processing data about patients and providers. These range from the mundane, widely disseminated applications such as computerized storage and reporting of laboratory results to newly developing systems that permit physicians and patients to share information across institutional and geographic boundaries. Three types of HIT receive particular attention in this review: the electronic health record (EHR), the personal health record (PHR), and clinical data exchanges.



In the near future, the EHR is likely to have the greatest effect on the daily work of neurosurgeons and other health care providers. The core functions of an EHR include the ability to collect and store data about patients, supply that information to providers on request, permit physicians to enter patient care orders (computerized order entry) and provide advice for making health care decisions (computerized decision support).

A related technology, the Personal Health Record (PHR) is being developed in an attempt to involve patients more actively in managing their health care. At present, PHRs most commonly consist of systems that give patients access to EHRs maintained by health care institutions. Such "patient portals" permit patients to go online to view (and sometimes modify) data in their EHR, e-mail their health care providers, obtain referrals, schedule appointments and obtain medication refills. Some insurers offer their own PHRs with online access to reports derived from claims data that include lists of medical problems and medications and reminders about pending services.

Clinical data exchange systems are the most abstract of the three forms of HIT discussed in this review. In most cases, clinical data exchanges are established and managed by a regional health information organization (RHIO). These organizations consist of hospitals, insurance companies, employers, pharmacies, consumer groups, and government officials collaborating to interconnect HIT systems maintained by separate entities in the region. Very few functioning RHIOs exist but more than 100 are in the planning stage. If successful, RHIOs will allow all regional health care providers to share information about common patients.

Advocates of rapid adoption of HIT view it as a needed catalyst for sweeping changes in the practice of medicine. They believe that HIT will give health care providers the right information at the right time and place to allow them to make the best health care decisions. Computerized decision support will ensure that these providers use the information supplied to them wisely. In this view, missed diagnoses, poor clinical choices and the use of unnecessary tests and procedures will be dramatically reduced with the adoption of HIT. Patients, using their PHRs, will become active partners in maintaining their health and treating their own illnesses. These empowered and enlightened patients will monitor their health status and, using decision support software, will make informed decisions about management of their health problems without needing to contact a doctor or a nurse. Quality and efficiency will soar.

It should be obvious that to achieve such dramatic change it will be necessary for clinicians to change the way their offices are organized, the processes by which they make medical decisions, and how they relate to and interact with their patients. Furthermore, patients will need to understand huge amounts of health care information and be able to use this information in a beneficial way. The true believers in HIT rarely recognize how gargantuan these issues are. In my experience, there is an inverse relationship between the number of patients seen by the authors of HIT papers and the enthusiasm of these authors for the transformative power of HIT.

Whether HIT can deliver on its promise of great benefits is difficult to evaluate. At present, it is only possible to begin to assess the benefits and risks associated with some types of HIT, primarily EHRs. The data on EHRs is decidedly mixed. Some, but not all, studies have found evidence that EHRs enhance the capacity of providers to monitor care delivery, reduce rates of medication errors and deliver care that adheres to guidelines and protocols. Whether or not adhering to guidelines actually improves patient outcomes is, of course, another question. It should be noted that most of the studies documenting a benefit of EHRs originated at a small number of institutions that pioneered the use of HIT and developed their own EHRs incrementally over an extended period of time. It is not clear that the same benefits would accrue to providers who purchase off-the-shelf EHRs for use in their practices or hospitals. There is also evidence of adverse effects associated with the institution of EHRs, including an increase in certain types of medication errors for hospital patients and an increase in mortality in a pediatric intensive care unit. There are also indications that the transition to the use of EHRs adds to physician time burdens and may result in a 10 to 20% reduction in physician productivity for extended periods of time.

Evaluating the available evidence on EHRs raises a question that plagues the whole area of evidence-based medicine: does evidence of efficacy in a well controlled environment translate into increased effectiveness when applied in a real world setting? As noted above, in some settings in which EHRs have been evaluated, evidence of efficacy seems clear. I believe these studies are analogous to the data generated from randomized controlled trials and, as for clinical trial data, when EHR data from a controlled environment are applied in a real world setting, much of the expected benefit evaporates and unanticipated problems occur.

Adoption of HIT has been slower than the advocates of this technology desired and expected. This raises the question of why EHRs have not spread more rapidly in the U.S. health care system. Although the expense of adopting HIT is often cited as the prime reason, a lack of capital cannot be the sole reason. For example, hospital expenditures on HIT systems are a small fraction of hospital spending on new physical plants. This suggests that, even when capital is available, hospital administrators favor investment in projects they believe will offer better returns than investment in HIT. In short, the primary reason for

Please see INFORMATION TECHNOLOGY, next page

INFORMATION TECHNOLOGY (continued)

the relatively slow pace of adoption of HIT is that such technology can be viewed as costly and disruptive, with a questionable return on investment, at least in the short term.

Although the benefits of HIT are uncertain, belief in its potential is sufficiently compelling to have generated a great deal of activity among public and private health care groups aimed at promoting it. The Bush administration has made promotion of HIT one of its highest health care priorities with the goal that most physicians should be using an EHR system by 2014. To achieve this, the Office of the National Coordinator of Health Information Technology, in the Department of Health and Human Services was created. Thankfully or regretfully, depending on your point of view, federal authorities have operated on a very modest budget and have focused on strengthening private markets for HIT adoption. The federal government has also removed an important legal barrier to hospital–physician cooperation in the adoption of EHRs. Until recently, federal regulations made it illegal for hospitals to give doctors they did not employ any assistance in acquiring HIT because it was feared that such assistance would induce physicians to make referrals to particular hospitals. The secretary of Health and Human Services recently issued regulations easing these restrictions. President Bush has also issued an executive order requiring that providers doing business with the federal government, including Medicare, make certain cost and quality data publicly available, a requirement that is likely to encourage the adoption of HIT.

State governments and private sector health care stakeholders such as health insurers, have also been strong advocates for adopting HIT. Such vocal support for HIT throughout government and the private sector health care system creates the impression that widespread adoption of HIT is inevitable. Is this really the case? I doubt that many of the vocal advocates of HIT have a good understanding of the issues involved in its adoption. HIT has a wide spectrum of support because many of the supporters (a diverse group that includes Hillary Clinton and Newt Gingrich) view it as an ideologically neutral way to reform a health care system that is trying to simultaneously improve quality and reduce costs. Such support is likely to be a mile wide and an inch deep, with many defectors when the real costs of implementation are known.

Furthermore, many questions persist in regard to how HIT can be introduced into the U.S. healthcare system and whether its widespread adoption will perpetuate and possibly exacerbate disparities in care among different population groups. In a health care system like that of the United States, where 75% of physicians practice alone or in groups of five or less, it is not clear how practices will function effectively within the HIT network or how to defray the costs of acquiring, installing, and maintaining EHRs and other forms of HIT.

HIT enthusiasts seem to believe that this technology has miraculous powers. In their view, HIT will bring us health care of almost unimaginable quality and efficiency where medical errors are eliminated and health care guidelines and protocols determine the treatment of joyful, enlightened clients who actively cooperate with their providers and their computers to improve their health and prevent disease. HIT detractors, including many practicing physicians, believe that the more accurate vision of the HIT future is a blighted landscape, where ever more time is taken from patient care so doctors and nurses can attend to the needs of the computer terminals. They see overworked professionals and dying patients at the mercy of the IT consultant in Bangladesh. As the review by Blumenthal and Glaser points out, the reality of HIT is likely to be somewhere between these Panglossian and apocalyptic visions.

ROBERT E. HARBAUGH, MD
OUTCOMES AND POPULATION SCIENCE

Funding Opportunities for Neurotrauma and Neurocritical Care

Perhaps one of the most important impacts that neurosurgeons have on the public health relates to the care of the neurotrauma patient. This endeavor is an important element of the practice and activity of the neurosurgeons around the world, irrespective of socioeconomic and geographic circumstance. Indeed, there are parts of the world where neurotrauma is the principal focus of neurosurgery in general, with 21st century technology being almost irrelevant in terms of daily practice. As was eloquently presented in a review article by Valadka and Robertson (**Neurosurgery 61: SHC-203-SHC-220, 2007**), published as part of the 30th Year Anniversary Supplement, Surgery of the Human Cerebrum, surgery of cerebral trauma and associated critical care has evolved considerably over the course of the past decades. Many new advances in understanding the pathophysiology and biology of nervous system injury have come to fruition in the greater context of the neurosurgical or polytrauma critical care patient. However, as the article concludes, translation of this knowledge to improved care and outcomes of neurotrauma patients remains few and less evident.



Courtesy of www.ucsfhealth.org.

The National Institutes of Health (NIH) have recognized this need and the potential impact of interdisciplinary translational research to improve the treatment, diagnosis, and outcome of the critically ill patient across all age groups. To support this, the NIH initiated a new Program Announcement (PA) in 2007 that is relevant to all neurosurgeons involved in neurotrauma and neurovascular research. The PA (07–233) aims to encourage interdisciplinary, investigator-initiated translational research in the science of critical care. It requires that investigators represent at least two different disciplines of medicine or research, collaborating on a common critical care question or theme. This PA will utilize the NIH Research Project Grant (R01) award mechanism, and expires in February 6, 2010. More information about this program can be found online at http://grants.nih.gov/grants/guide/pa-files/PA07–233.html.

CHARLES Y. LIU, MD, PHD
RESEARCH TRAINING AND FUNDING

Continues ⇨ N9

Update: Randomized Clinical Trials of Surgery versus Prolonged Non-operative Management of Herniated Lumbar Discs

Lumbar spine disorders are among the leading causes of morbidity in the United States (1, 3). One of the challenges of managing and treating patients with symptomatic lumbar disk herniation is determining when and in whom surgery is a better option than non-operative treatment. To this end, Peul et al. recently published results of a clinical trial comparing surgery after 6 to 12 weeks of non-operative management with that of continued non-operative management in the treatment of sciatica **(N Engl J Med 356:2245–2256, 2007)**. A total of 283 patients suffering from sciatica for a period of 6 to 12 weeks were randomly assigned to receive either operative or continued non-operative treatment. Of the 141 patients that were designated for early surgery, 125 (89%) of them received the surgery within an average of two weeks, while the remaining 16 were either lost to follow-up or had resolution of their symptoms before their scheduled procedure. A total of 142 patients were assigned to non-operative treatment, with 55 (39%) electing to undergo surgery after a mean time of 18.7 weeks. Surgery was only offered to this group if sciatica persisted for longer than 6 months, or, in cases of increasing pain that were unresponsive to medication, or progressive neurological deficits **(N Engl J Med 356:2245–2256, 2007)**.

The results demonstrated a statistically significant difference in the timing of relief from leg pain, with the group assigned to early surgery finding relief sooner after randomization than those who were assigned to non-operative treatment (P<0.001). No statistically significant difference in disability scores was found, however, between the two groups after the first year (P=0.13); approximately 95% of each group reported recovery by that time **(N Engl J Med 356:2245–2256, 2007)**.

The results of this intention-to-treat analysis should be interpreted with caution in light of a thirty-nine percent crossover from the non-operative treatment group to eventual surgery. This crossover reduces the differences in treatment received between groups, thereby attenuating effect size. As-treated analysis, although potentially subject to significant bias, may more accurately estimate the difference in effectiveness of treatment received. It is also important to note that the non-operative therapy in this study was administered by skilled nursing, a level of care that is not available to most people suffering from sciatica **(N Engl J Med 356:2245–2256, 2007)**.

The SPORT randomized clinical trial, which compared operative and non-operative treatment for lumbar disk herniation, had similar problems with adherence to the randomly assigned treatment groups. In that study, bidirectional crossover was prevalent, as 30% and 50% of patients in the non-operative and operative groups, respectively, did not undergo assigned treatment within the first 3 months. The intent-to-treat analysis demonstrated that differences in changes from baseline between treatment groups at all measured time points favored surgery for the primary outcomes but were not statistically significant. As-treated analysis, however, demonstrated a statistically significant advantage that was seen for surgery at all time points through 2 years **(JAMA 296:2441–2450, 2006)**.

Although both of these studies address the effectiveness of surgery versus non-operative treatment little is likely to change in the treatment of symptomatic herniated lumbar disk as a result of these reports. Physicians will continue to inform patients regarding the pros and cons of treatment options, and patients will make educated treatment decisions based on that information. Except for select patients, such as those with progressive neurological deficits or cauda equina syndrome, non-operative treatment will remain the first-line treatment for symptomatic lumbar herniated disc. Those who fail to improve with non-operative treatment, or those with more severe pain, will tend to elect surgery, as demonstrated by the SPORT studies **(JAMA 296: 2441–2450, 2006 and JAMA 296: 2451–2459, 2006)**.

In conclusion, Peul et al. confirmed that operative intervention confers rapid pain relief in select patients with herniated lumbar disk disease, while SPORT showed that despite worse initial symptoms, patients that underwent operative intervention for herniated lumbar disk disease receive significant symptomatic benefit. Further randomized clinical trials regarding this condition are likely to be compromised by high crossover, limiting the value of these involved and resource-intensive studies.

RICARDO J. KOMOTAR, MD
ERIC J. ARIAS, BS
E. SANDER CONNOLLY, JR., MD
PETER D. ANGEVINE, MD, MPH
TECHNICAL AND CLINICAL RESEARCH

Rabies and siRNA Team up to Treat Neurologic Diseases

Small interfering RNAs (siRNA) are small RNA molecules that regulate expression levels of specific RNA species and therefore regulate the amount of proteins within the cell. siRNAs hold significant promise as tools to treat neurologic diseases. For example, siRNAs could be used to reduce the levels of specific oncogenes in a brain tumor, to reduce the levels of mutant huntingtin, which causes Huntington's disease, or of any other protein whose presence is detrimental to the cell.

A major impediment for the therapeutic use of siRNAs in the brain is just getting there. Systemic delivery has to manage the challenge of crossing the blood-brain barrier to reach the intended target in a specific and bioactive manner. Even direct delivery into the central nervous system is faced with multiple challenges including drug distribution, technical device malfunction, and surgical complications.

To penetrate the blood-brain barrier, Kumar et al. from the Center for Blood Research Institute for Biomedical Institute at Harvard Medical School report in recent issue of **Nature (448:39–43, 2007)** an ingenious strategy that makes use of the natural abilities of the rabies virus. The authors demonstrate that a 29 amino-acid peptide derived from the rabies virus glycoprotein (RVG) provides siRNA the ability of penetrating into the brain following vascular delivery. The core of the strategy takes advantage of the natural ability of the RVG to specifically enter the central nervous system through the brain vasculature. Not only does RVG cross the blood-brain barrier, but also it can also specifically gain access into neurons, in theory transporting a molecule bound to it from the blood, through the blood-brain barrier and specifically into neurons. This hypothesis was put to the test. The authors of this elegant work demonstrate that a specifically engineered RVG was able to cross from the vasculature into the brain and specifically enter neurons in vivo. Additionally, by engineering specific modifications, the resultant protein (RVG-9R) was able to bind siRNA molecules, and also was able to protect the siRNA from serum nucleases.

As final proof of principle, mice infected with the Japanese Encephalitis Virus (JEV) were treated using a systemic RVG-9R siRNA strategy. The siRNA in this case targeted a key protein in the life cycle of this virus. All the control mice infected with the JEV died within 10 days. Remarkably, 80% of the mice treated with intravenous injection of the specific RVG-9R siRNA construct were alive at 30 days.

The results described in this report are very important and exciting. Although clearly much work remains, this could represent a novel strategy and an important step towards realizing the therapeutic potential of siRNA for the treatment of a variety of neurologic diseases.

ROBERT M. FRIEDLANDER, MD, MA
BASIC SCIENCE RESEARCH

Bumpy Road Ahead As Democrats Clash with President Over Health Care Legislation

As the 110th Congress moves into full speed, the Bush Administration is clashing with the new Congress over some of the most important health care legislation being considered this year. The battle lines have been drawn on such issues as the State Children's Health Insurance Program (SCHIP), stem cell research, fixing the Medicare physician payment system, and funding for the National Institutes of Health and other discretionary health programs.

Health and Human Services Appropriations

Health program appropriations continue to face an uphill battle to recoup funds that were lost in fiscal year 2006 (FY06), when the Labor, Health and Human Services, and Education (L-HHS-Ed) appropriations bill was cut by $1.6 billion. Congress worked to restore some of those cuts in the FY07 Joint Funding Resolution, which was signed by the President five months into the current fiscal year. The Joint Funding Resolution included a $2.3 billion increase over the previous year's funding level for health and education programs, an impressive amount considering over 60 programs received less than FY06 levels, some unobligated balances were rescinded, and the President's FY07 budget proposed cutting health and education programs by about $5 billion. The National Institutes of Health (NIH) received a $620 million (2.2%) increase in funding over FY06, also a large amount considering the NIH appropriation has shifted from marked growth to low or no increases over the past few years. Despite this accomplishment, the funding increase only brought the L-HHS-Ed appropriation back to FY05 levels, which many research advocates say is far too low to adequately fund most, if not all, of the departments' programs.

FY08 Budget

Despite these modest gains, the FY08 appropriations process has gotten off to a rocky start. In February 2007, the President released his budget proposal to Congress for FY08 spending. The proposed budget would increase discretionary spending by $57 billion, but $53.5 billion of that total increase would go to security programs—defense, homeland security, and international affairs. Domestic discretionary programs, such as social programs, would grow by only 1%, or $3.5 billion, under the President's budget. The budget would actually cut labor, health and education programs by $3 billion in FY08 and cut NIH funding by over $500 million for FY08, thus reducing it to its FY05 funding level. Although the President's budget has no legal force, it tends to shape the Congressional debate on key issues.

For the past three years, the President has submitted budget proposals which flat-lined NIH funding, and the Republican Congress, in essence, rubber stamped the President's recommendations. However, this year, Democrats, who are now in control of both the House of Representatives and the Senate, have rejected the President's plan to



freeze overall non-defense discretionary spending. On May 16, House and Senate Conferees agreed on a Budget Resolution to provide an additional $21 billion for non-defense domestic discretionary programs in the FY08 Budget Resolution. The $21 billion is significant and a victory for the programs, including the NIH, that are funded out of the discretionary part of the federal budget. Although this budget blueprint is not signed by the President and is not law, it sets an overall discretionary spending cap for the Appropriations Committee.

President Bush Issues Veto Threat

As the House and Senate were voting to add the additional money for domestic programs, the White House threatened to veto any domestic appropriations bill that exceeds the President's proposed budget. Based on the allocations that each of the House Appropriations Subcommittees received, this would result in the President vetoing eight of the twelve appropriations bills, including the L-HHS-Ed appropriations. However, it has also become evident that sustaining a veto on some of these bills, including the L-HHS-Education Appropriations bill, will be no easy task given that they include numerous popular programs. Many Congressional Democrats and Republicans have remarked that these programs, such as research at the NIH and the Centers for Disease Control and Prevention (CDC), have been squeezed in the past few years, and that there is pent-up demand for spending on these critical programs.

Appropriators Complete Work on Health Spending

With the Congressional Budget Resolution passed, the House and Senate Appropriations Subcommittees began working on the FY08 bills in late spring. The passage of the Budget Resolution paved the way for the first Democratic party-controlled appropriations process in twelve years, which many in the research community believe represents an opportunity to change the dimensions of the debate for increasing the NIH's budget. However, as is usually the case, both chambers got bogged down in complexities as they worked under what is still considered tight budgetary constraints.

Senate Bill—On June 21, the Senate Appropriations Committee unanimously approved its FY08 L-HHS-Ed appropriations bill, which included $152 billion in discretionary funding. This amount exceeds FY07 discretionary spending by about $7 billion and exceeds the President's request by almost $10 billion. The bill also includes a $1 billion increase (3.5%) in NIH funding over FY07 levels, which is more than $1.2 billion over the President's NIH budget request. However, because the Senate has agreed with the President's proposal to increase the amount that the NIH is required to transfer to the Global HIV/AIDS program, the NIH funding increase is actually closer to $799 million (2.8%). Although this represents the largest increase (in dollar terms) that the agency would receive in four years, it is still less than the biomedical inflation rate of 3.7% for FY08. It also falls significantly short of the 6.7% increase recommended by the broader medical research community, which if implemented over the next three years, would have erased the inflationary losses suffered by the NIH since 2003.

House Bill—On July 11, 2007, the House Appropriations Committee approved its FY08 Labor-HHS-Ed spending bill, which includes $151.5 billion in discretionary spending. The bill also provides a $750 million increase (2.6%) for the NIH for FY08. Due to the Global HIV/AIDS program transfer, the NIH increase under this bill is actually closer to $549 million (1.9%) for FY08.

There are many steps left in the appropriations process before final funding levels are enacted. The House and Senate bills will be brought to the floor for consideration, after which a conference committee will meet to reconcile the differences. The schedule for Senate floor consideration of the bill is uncertain, while the House plans to consider the bill in mid-July. Finally, the House and Senate must pass an identical bill before it can be sent to the President for his signature. The goal is to finish this work by October 1, the start of the next fiscal year. But if last year is any indicator—when nine appropriation bills were still pending at the start of the fiscal year—Congress has a long road ahead.

Embryonic Stem Cell Research

Legislation to provide federal funding for embryonic stem cell research was reintroduced at the start of the new Congress after it was defeated in the previous Congress by the President's first and only veto. The Stem Cell Research Enhancement Act (H.R.3/S.5) would lift the current ban on the use of federal funds for research using embryos created after Aug. 9, 2001, if they came from embryos to be discarded from in vitro fertilization clinics. Most importantly, the legislation would have ensured that such research was safe, regulated, and conducted under certain ethical requirements.

House and Senate Pass Stem Cell Bills

On January 11, 2007, the House of Representatives passed H.R. 3, gaining 15 more votes compared to the previous Congress. Despite these gains, the margin still fell short of the two-thirds majority needed in each chamber to override an expected Presidential veto. On April 11, 2007, the Senate also passed its version of the bill, but the vote also fell short of the margin necessary to override a veto. The 63 votes in favor of S.5 were

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HEALTH CARE LEGISLATION (continued)

the same as last year's vote on the bill, although there were three fewer votes against the measure.

Since S.5 included additional language directing the NIH to research alternative ways of procuring stem cells that have the same qualities as embryonic cells, but do not destroy an embryo, it was returned to the House for reconsideration, which, on June 7, joined the Senate in passing S.5. This marked the second time in less than a year that Congress sent a bill to the President to increase the number of embryonic stem cell lines eligible for federally funded research.

President Uses Veto Pen Once Again

Unfortunately, however, on June 20 the President vetoed the legislation. On the same day, however, the President did issue an executive order that would implement the second part of S.5, which directs the NIH to study alternative ways of procuring stem cells that have the same qualities as embryonic cells, but do not destroy an embryo.

The House and Senate are still exploring ways of attaching the same provisions to must-pass legislation, but have not specified the bills that might be involved. The Senate Appropriations Committee took another tack in expanding stem cell research by attaching an amendment to the recently passed L-HHS-Ed Appropriations bill that would allow federal funding for embryonic stem cell research under ethical guidelines if the embryos were derived before June 15, 2007. However, House Appropriations Chair David Obey (D-WI) has indicated that the stem cell language added by the Senate Appropriations Committee would not be added to the House bill.

STOP Stroke Act of 2007

On March 27, 2007, the Stroke Treatment and Ongoing Prevention Act of 2007 (STOP Stroke Act, H.R. 477), sponsored by Lois Capps (D-CA) and Chip Pickering (R-MS), was passed by the House of Representatives by voice vote. The legislation would help educate the public about the need to treat stroke as a medical emergency and establish coordinated statewide systems of care so that all stroke patients have access to the latest and most effective treatments and therapies.

Similar legislation, S.999, was introduced in the Senate by Senators Thad Cochran (R-MS) and Ted Kennedy (D-MA) and currently has 29 cosponsors. The Chairman of the Health, Education, Labor and Pensions Committee, Senator Ted Kennedy (D-MA) has expressed his intention to "mark up" this bill later this year. Since this legislation has passed the Senate in the past by unanimous consent, there is hope this long delayed legislation will finally be enacted once "marked up" by the committee.

RACHEL GROMAN
KATIE ORRICO, JD
LEGISLATIVE AND REGULATORY NEWS

The Origins of Brain Tumor Stem Cells

CD133 has emerged as a crucial marker in neural stem cell research after initially being identified as an antigen on human fetal and adult hematopoietic stem and progenitor cells. Recently, CD133 has gained increased attention as a surface marker to isolate a subpopulation of cells from glioblastoma, medulloblastoma and ependymoma, which initiates and sustains tumor growth. The presence of CD133 on fetal neural stem cells and the enrichment of brain tumor stem cells in the CD133-positive fraction has led investigators to postulate a stem cell origin of brain tumor stem cells. Because of this CD133 has sometimes been referred to as a neural stem cell marker. Better understanding the crucial (and still debated) connection between CD133 expression during development and its expression on brain tumor cells was the source of the study published this past June in **Cancer Research (67: 5727–5736, 2007)**. In this report, the group from Lund University in Sweden studied the localization of CD133 cells in mouse brain at different developmental stages, as well as in the adult ventricular wall. They also isolated CD133-positive and negative cells and tested their proliferative and differentiation capacity.

The results of their studies indicate that CD133 is not present on neurogenic astrocytes in the adult subventricular zone, but on embryonic neural stem cells, ependymal cells, and glioblastoma cells. Specifically, CD133 is present on the multiciliated ependymal cells in the adult mouse and human brains. This same antibody recognized cells within human glioblastoma conforming shared epitopes between these normal and malignant cell types. Interestingly, they showed a paucity of neurospheres could be formed from the CD133-positive cells isolated from adult lateral ventricular wall whereas CD133-negative cells could be derived and passaged easily into neurospheres. This is a novel finding and implies that in the adult brain, neural stem cells are contained within the CD133-negative fraction. If brain tumor stem cells in GBM, medulloblastoma or ependymoma are indeed derived from a CD133-positive cell in the ventricular wall, these results imply neuroepithelial cells, radial glial cells and ependymal cells as possible sources.

Although a direct lineage relationship between CD133-enriched brain tumor stem cells and CD133-positive cells of the normal brain is intriguing, it is also possible that CD133 could simply be produced by tumor cells. The exact cellular origin of stem cells in brain tumors and the role that CD133 has in normal neural development and tumor intiation obviously remains to be determined, but this study provides an important clue in sorting out this highly relevant puzzle.

JEFFREY P. GREENFIELD, MD, PHD
JOHN BOOCKVAR, MD
STEM CELL RESEARCH

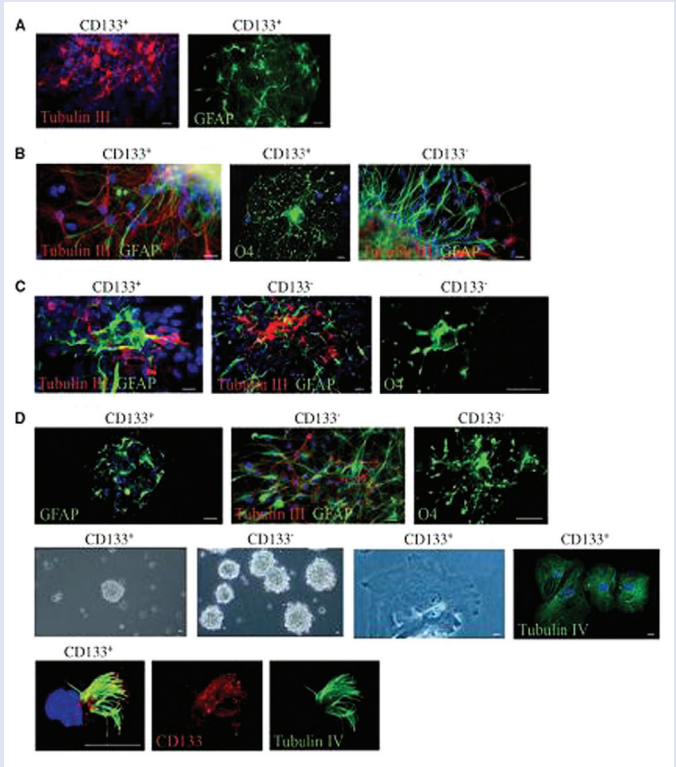


*Figure. Immunofluorescence microscopy of cultured and uncultured cells from murine CD133-positive and CD133-negative populations. Neurospheres are derived from CD133-sorted cells of E9.5 forebrain (**A**), E14.5 forebrain (**B**), P4 LVW (**C**), and adult LVW (**D**, top). The vast majority of neurospheres derived from the adult LVW were formed by the CD133-negative fraction (**D**,* middle*). A low number of small spheres was found in the CD133-positive fraction, but the majority of cells attached to the cell culture dish and synthesized tubulin-h-IV (**D**,* middle*). **D**, bottom, CD133-positive uncultured cell isolated from the adult LVW, attached to coverslips with a cytospin centrifuge directly after sorting, showing multiple cilia, stained with antibodies against CD133 (*red*) and tubulin-h-IV (*green*). Courtesy of **Cancer Research (67:5727–5736, 2007)**.*

CALENDAR OF EVENTS

Full contact information is available online only

Listings for this section need to be submitted at least 3 months in advance. Please include a telephone number and/or a fax number.

SUBMIT LISTINGS TO
Joel D. MacDonald, M.D.
University of Utah
Department of Neurosurgery
30 North 1900 East, 3B-409 SOM
Salt Lake City, UT 84132-2303
TEL: 801/581-6908
FAX: 801/581-4138
EMAIL: vasospaz@aol.com

INTERNATIONAL / GENERAL NEUROSURGERY

SEPTEMBER 9–13, 2007	**35th Annual Meeting of the International Society for Paediatric Neurosurgery**	Liverpool, England	**CONTACT:** Jaime Bennett **EMAIL:** jaime@happen.co.uk **WEB SITE:** www.happen.co.uk/ispn2007
SEPTEMBER 10–11, 2007	**8th Workshop in Endoscopic Pituitary Surgery**	Bologna, Italy	**CONTACT:** Elisa Marzaloni **TEL:** 39/051-765357 **FAX:** 39/051-765195 **EMAIL:** emarzaloni@csrcongressi.com **WEB SITE:** www.csrcongressi.com
SEPTEMBER 14–16, 2007	**14th Convention of Academia Eurasiana Neurochirurgica**	Tianjin, China	**CONTACT:** Shu-yuan Yang, M.D. **TEL:** 86/22 60362621 **FAX:** 86/22 60362621 **EMAIL:** eans2007@eans2007.org **WEB SITE:** www.eans2006.org
SEPTEMBER 15–20, 2007	**57th Annual Meeting of the Congress of Neurological Surgeons**	San Diego, CA	**WEB SITE:** www.neurosurgeon.com
SEPTEMBER 26, 2007	**12th French Course of Neurosurgery in Romania**	Bucharest, Romania	**CONTACT:** Prof. A.V. Ciurea **TEL:** 40/21-3347388 **FAX:** 40/21-3347388 **EMAIL:** rsn@bagdasar-arseni.ro **WEB SITE:** www.rsn.ro
SEPTEMBER 27–29, 2007	**Romanian Congress of Neurosurgery**	Bucharest, Romania	**CONTACT:** Prof. A.V. Ciurea **TEL:** 40/21-3347388 **FAX:** 40/21-3347388 **EMAIL:** rsn@bagdasar-arseni.ro **WEB SITE:** www.rsn.ro
SEPTEMBER 30– OCTOBER 3, 2007	**Neurosurgical Society of Australasia Annual Scientific Meeting**	Gold Coast, Australia	**CONTACT:** Stacie Gull **TEL:** 61/3-9249-1294 **FAX:** 61/3-9249-1293 **EMAIL:**stacie.gull@surgeons.org **WEB SITE:** www.nsa.org.au
NOVEMBER 15–17, 2007	**First Congress of the International Society for Intraoperative Neurophysiology**	Lucerne, Switzerland	**CONTACT:** Dr. Karl F. Kothbauer **EMAIL:** karl.kothbauer@ksl.ch **WEB SITE:** http://www.imk.ch/ION2007
NOVEMBER 18–22, 2007	**12th AACNS/13th WFNS Interim Meeting**	Nagoya, Japan	**CONTACT:** Tetsuo Kanno **EMAIL:** kanno@kojima-kai.or.jp **WEB SITE:** www.aacns07.umin.ne.jp
JANUARY 17–19, 2008	**Euroneuro 2008**	Maastricht, The Netherlands	**TEL:** 31/411 61 1199 **FAX:** 31/411 63 3805 **EMAIL:** info@euroneuro.eu **WEB SITE:** www.euroneuro.edu
APRIL 26–MAY 1, 2008	**2008 American Association of Neurological Surgeons Annual Meeting**	Chicago, IL	**CONTACT:** Patty Anderson **TEL:** 847/378-0500 **EMAIL:** meetings@aans.org **WEB SITE**: www.aans.org
SEPTEMBER 4–7, 2008	**6th International Congress on Meningiomas and Cerebral Venous System**	Boston, MA	**CONTACT:** AANS **TEL:** 847/378-0500 **EMAIL:** meetings@aans.org **WEB SITE:** www.themeningiomaconference 2008.org
SEPTEMBER 8–11, 2007	**Western Neurosurgical Society Annual Meeting**	Kohala Coast, HI	**CONTACT:** Jeffery L. Rush **TEL:** 970/453-5631 **FAX:** 970/453-8093 **EMAIL:** jefferyleerush@msn.com **WEB SITE:** www.westnsurg.org

OCTOBER 31– NOVEMBER 4, 2007	**American Academy of Neurological Surgery Annual Meeting**	Henderson, NV	**CONTACT:** Dr. Henry Brem **TEL:** 410/614-0477 **FAX:** 410/614-0478
NOVEMBER 15–18, 2007	**Society for Neuro-oncology 12th Annual Scientific Meeting**	Dallas, TX	**CONTACT:** Society for Neuro-Oncology **TEL:** 713/349-0952 **FAX:** 832/201-8129 **WEB SITE:** www.soc-neuro-onc.org
JANUARY 18–20, 2008	**2008 AAN Winter Conference**	Miami, FL	**CONTACT:** Lori Strachota **TEL:** 651/695-2706 **EMAIL:** lstrachota@aan.com **WEB SITE:** www.aan.com/winter08
MARCH 13–15, 2008	**34th Annual Barrow Symposium: Advancements in Neuroscience for the Practicing Neurosurgeon and Neurologist**	Phoenix, AZ	**CONTACT:** Barrow Neurological Institute **TEL:** 602/406-3067 **WEB SITE:** www.thebarrow.org/conferences

SPINE / PERIPHERAL NERVE

SEPTEMBER 27–29, 2007	**Spine Tumor Symposium**	Vancouver, Canada	**CONTACT:** AO North America **TEL:** 800/769-1391 **FAX:** 610/695-2420 **WEB SITE:** www.aona.org
SEPTEMBER 28–29, 2007	**Complex Surgical Techniques for Treating Cervical Spine Pathology: Advanced Two-Day Program**	Denver, CO	**CONTACT:** Rose McCusker **TEL:** 800/253-7657 **EMAIL:** rmccusker@cine-med.net **WEB SITE:** www.cervicalspineeducation.com
OCTOBER 23–26, 2007	**Syringomyelia 2007**	Rugby, England	**CONTACT:** Graham Flint **TEL:** 44-121/697-8224 **FAX:** 44-121/697-8246 **EMAIL:** graham.flint@uhb.nhs.uk **WEB SITE:** www.syringomyelia2007.org
NOVEMBER 2–4, 2007	**Principles and Treatment of Spinal Disorders for Residents and Fellows Course**	Las Vegas, NV	**CONTACT:** AO North America **TEL:** 800/769-1391 **FAX:** 610/695-2420 **WEB SITE:** www.aona.org
NOVEMBER 28– DECEMBER 1, 2007	**Cervical Spine Research Society 12th Instructional Course and 35th Annual Meeting**	San Francisco, CA	**CONTACT:** Cervical Spine Research **WEB SITE:** www.csrs.org/research/applications.htm
JANUARY 19–23, 2008	**University of South Florida, College of Medicine 20th Annual Disorders of the Spine: A Contemporary Update**	Whistler, Canada	**CONTACT:** Connie Kenyon **TEL:** 813/974-1414 **FAX:** 813/974-3217 **WEB SITE:** www.whistlerspine.org
JANUARY 26– FEBRUARY 1, 2008	**3rd Mayo Clinic International Spine Symposium 2008**	Koloa, HI	**CONTACT:** Mayo Clinic **WEB SITE:** www.mayo.edu/cme/spine
FEBRUARY 27– MARCH 1, 2008	**AANS/CNS Section on Disorders of the Spine and Peripheral Nerves**	Buena Vista, FL	**CONTACT:** Nathalie Johnson **TEL:** 847/378-0500 **EMAIL:** meetings@aans.org **WEB SITE:** www.aans.org
SEPTEMBER 24–28, 2007	**Principles and Practice of Gamma Knife Radiosurgery**	Pittsburgh, PA	**CONTACT:** Charlene Baker **TEL:** 412/647-7744 **EMAIL:** bakerch@upmc.edu **WEB SITE:** www.neurosurgery.pitt.edu
OCTOBER 3–5, 2007	**University of Virginia Advanced Gamma Knife Course**	Charlottesville, VA	**CONTACT:** Jason Sheehan **TEL:** 866/244-4040 **EMAIL:** jps2f@hscmail.mcc.virginia.edu **WEB SITE:** www.healthsystem.virginia.edu/internet/neurosurgery/gkcourse/home.cfm
OCTOBER 9–10, 2007	**UCLA Shaped Beam Radiosurgery Tutorial Course (Basic)**	Los Angeles, CA	**TEL:** 310/267-5217 **FAX:** 310/794-1848 **EMAIL:** emitchell@mednet.ucla.edu **WEB SITE:** http://neurosurgery.ucla.edu/conference

OCTOBER 14–16, 2007	**University of Virginia Lars Leksell Symposium**	Charlottesville, VA	**CONTACT:** Sophie Lee Yu **TEL:** 434/924-2336 **FAX:** 434/977-6279
OCTOBER 22–26, 2007	**Gamma Knife Radiosurgery Training Program**	Cleveland, OH	**CONTACT:** Rosemary Vernick **TEL:** 216/444-7591 **FAX:** 216/445-9999 **WEB SITE:** http://cms.clevelandclinic.org/neuroscience/body.cfm?id=727
NOVEMBER 12–16, 2007	**Principles and Practice of Gamma Knife Radiosurgery**	Pittsburgh, PA	**CONTACT:** Charlene Baker **TEL:** 412/647-7744 **EMAIL:** bakerch@upmc.edu **WEB SITE:** www.neurosurgery.pitt.edu
DECEMBER 3–7, 2007	**Gamma Knife Radiosurgery Training Program**	Cleveland, OH	**CONTACT:** Rosemary Vernick **TEL:** 216/444-7591 **FAX:** 216/445-9999 **WEB SITE:** http://cms.clevelandclinic.org/neuroscience/body.cfm?id=727
DECEMBER 4–5, 2007	**UCLA Shaped Beam Radiosurgery Tutorial Course (Advanced)**	Los Angeles, CA	**TEL:** 310/267-5217 **FAX:** 310/794-1848 **EMAIL:** emitchell@mednet.ucla.edu **WEB SITE:** http://neurosurgery.ucla.edu/conferences

TUMOR

SEPTEMBER 6–8, 2007	**Pediatric Brain Tumors: Advances in Molecular Biology, Therapies, and Outcomes Conference**	Columbus, OH	**CONTACT:** Conference Coordinator **FAX:** 614/722-3864 **WEB SITE:** www.columbuschildrens.com/braintumors
OCTOBER 10–13, 2007	**2007 International Conference on Glioma Research and Therapy**	Boston, MA	**CONTACT:** Tammy Gilson-Hodge **TEL:** 617/355-8719 **FAX:** 617/713-3050 **WEB SITE:** www.glioma2007.org

CEREBROVASCULAR

SEPTEMBER 9–13, 2007	**9th Congress of World Federation of Interventional and Therapeutic Neuroradiology**	Beijing, China	**CONTACT:** Organizing Secretariat **FAX:** 8610/6566 7304 **EMAIL:** registration@wfitn2007.org **WEB SITE:** www.wfitn2007.org
SEPTEMBER 26–29, 2007	**3rd European Cerebral Revascularization Course: Hands-on Microsurgical and Endovascular Training**	Bern, Switzerland	**TEL:** 41582585073 **FAX:** 0319616973 **EMAIL:** cornelia.kost-fuchs@aesculap-akademie.ch **WEB SITE:** www.aesculap-akademie.ch
FEBRUARY 20–22, 2008	**AANS/CNS Cerebrovascular Section and American Society of Interventional and Therapeutic Neuroradiology**	New Orleans, LA	**CONTACT:** Nathalie Johnson **TEL:** 847/378-0500 **EMAIL:** meetings@aans.org **WEB SITE:** www.aans.org
NOVEMBER 15, 2007	**Pediatric Developmental/Behavioral Pre-Symposium**	Phoenix, AZ	**CONTACT:** Barrow Neurological Institute **TEL:** 602/406-3067 **WEB SITE:** www.thebarrow.org/conferences
NOVEMBER 16–17, 2007	**12th Annual Pediatric Neurosciences Symposium**	Phoenix, AZ	**CONTACT:** Barrow Neurological Institute **TEL:** 602/406-3067 **WEB SITE:** www.thebarrow.org/conferences
NOVEMBER 27–DECEMBER 1, 2007	**AANS/CNS Section on Pediatric Neurological Surgery**	South Beach, FL	**CONTACT:** Nathalie Johnson **TEL:** 847/378-0500 **EMAIL:** meetings@aans.org **WEB SITE:** www.aans.org

TRAUMA / CRITICAL CARE

SEPTEMBER 19–22, 2007	**International Conference on Recent Advances in Neurotraumatology**	Tianjin, China	**CONTACT:** Kui Lui, M.D., Ph.D. **TEL:** 86/22-23359875 **FAX:** 86/22-23359858 **EMAIL:** kuiliu@hotmail.com
OCTOBER 6–7, 2007	**Principles of Operative Treatment of Craniomaxillofacial Trauma and Reconstruction**	Charlotte, NC	**CONTACT:** AO North America **TEL:** 800/769-1391 **FAX:** 610/695-2420 **WEB SITE:** www.aona.org
OCTOBER 20–21, 2007	**Principles of Operative Treatment of Craniomaxillofacial Trauma and Reconstruction**	Dallas, TX	**CONTACT:** AO North America **TEL:** 800/769-1391 **FAX:** 610/695-2420 **WEB SITE:** www.aona.org
NOVEMBER 3–4, 2007	**Principles of Operative Treatment of Craniomaxillofacial Trauma and Reconstruction**	Miami, FL	**CONTACT:** AO North America **TEL:** 800/769-1391 **FAX:** 610/695-2420 **WEB SITE:** www.aona.org
DECEMBER 1–2, 2007	**Principles of Operative Treatment of Craniomaxillofacial Trauma and Reconstruction**	New York, NY	**CONTACT:** AO North America **TEL:** 800/769-1391 **FAX:** 610/695-2420 **WEB SITE:** www.aona.org
JANUARY 17, 2008	**2nd Annual Neurotrauma Symposium**	Phoenix, AZ	**CONTACT:** Barrow Neurological Institute **TEL:** 602/406-3067 **WEB SITE:** www.thebarrow.org/conferences

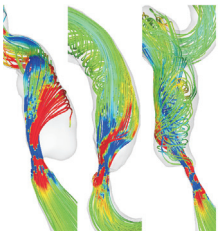
CRANIAL BASE

DECEMBER 1–2, 2007	**Craniofacial Surgery and Transfacial Approaches to the Skull Base**	St. Louis, MO	**CONTACT:** Karen M. Hutsel **TEL:** 314/977-7400 **FAX:** 314/977-7345 **EMAIL:** hutselkm@slu.edu **WEB SITE:** http://pa.slu.edu
APRIL 24–26, 2008	**Advances in Minimally Invasive Endoscopic Skull Base Surgery**	Pittsburgh, PA	**CONTACT:** Continuing Medical Education **TEL:** 412/359-4952 **FAX:** 412/359-8218 **EMAIL:** cjackel@spahs.org
OCTOBER 3–4, 2007	**Endoscopic Endonasal Skull Base Surgery: International Hands-on Workshop**	Naples, Italy	**CONTACT:** Dr. Paolo Cappabianca **TEL:** +39 081 746.2582 **FAX:** +39 081 746.2497 **EMAIL:** paolo.cappabianca@unina.it **WEB SITE:** www.neurosurgery.unina.it
JUNE 4–7, 2008	**World Congress of Minimally Invasive Spine Surgery and Techniques**	Honolulu, HI	**CONTACT:** James Lee, Jason Lee **TEL:** +82-2-513-8157 **FAX:** +82-2-513-8386 **EMAIL:** wcmisst@wooridul.co.kr **WEB SITE:** http://www.wcmisst.org
SEPTEMBER 14–16, 2007	**SVU Vascular Ultrasound Advanced Interpretation Course**	Scottsdale, AZ	**CONTACT:** SVU **FAX:** 301/459-5651 **WEB SITE:** www.svunet.org
SEPTEMBER 14–16, 2007	**Transcranial Doppler and Imaging Course**	Bothell, WA	**TEL:** 425/398-7772 **EMAIL:** dfields@pacificvascular.com **WEB SITE:** www.pvicme.com
SEPTEMBER 19–21, 2007	**4th ICCM, 4th International Conference on Clinical Microdialysis**	Cambridge, England	**CONTACT:** Ulla Ungerstedt **TEL:** +468 4701047 **FAX:** +468 4701050 **EMAIL:** ulla.ungerstedt@microdialysis.se **WEB SITE:** www.iccm4.com

Calendar of Events

SEPTEMBER 24–27, 2007	**Neuroradiology: Clinical Functional MRI and Spectroscopy**	Cambridge, MA	**Contact:** Harvard Medical School **Tel:** 617/384-8600 **Fax:** 617/384-8686 **Email:** hms-cme@hms.harvard.edu **Web Site:** www.cme.hms.harvard.edu
SEPTEMBER 28, 2007	**Medical Center of Plano Neuroscience Conference**	Plano, TX	**Contact:** Maria Bradberry **Tel:** 972/596-6800 **Web Site:** www.medicalcenterofplano.com
OCTOBER 10–13, 2007	**American Academy for Cerebral Palsy and Developmental Medicine**	Vancouver, Canada	**Contact:** American Academy for Cerebral Palsy & Developmental Medicine **Tel:** 414/918-3014 **Fax:** 414/276-2146 **Email:** info@aacpdm.org **Web Site:** www.aacpdm.org
OCTOBER 12–13, 2007	**Festschrift to Honor Peter J. Jannetta, M.D.**	Pittsburgh, PA	**Contact:** Julie Young **Email:** jyoung1@wpahs.org **Web Site:** www.wpahs.org
OCTOBER 19–20, 2007	**2007 Barrow Stroke Update**	Phoenix, AZ	**Contact:** Barrow Neurological Institute **Tel:** 602/406-3067 **Web Site:** www.thebarrow.org/conferences
OCTOBER 31– NOVEMBER 1, 2007	**NCS Pre-Meeting UCNS Certification for Neurocritical Care Review Course**	Las Vegas, NV	**Contact:** Neurocritical Care Society **Web Site:** www.neurocriticalcare.org
NOVEMBER 2–3, 2007	**5th Annual Neurocritical Care Society Meeting**	Las Vegas, NV	**Contact:** Neurocritical Care Society **Web Site:** www.neurocriticalcare.org
NOVEMBER 4–6, 2007	**Neurosurgery Review by Case Management: Oral Board Preparation**	Houston, TX	**Contact:** Vanessa Garlisch **Tel:** 847/378-0500 **Email:** epm@aans.org **Web Site:** www.aans.org
NOVEMBER 5–9, 2007	**Neuroradiology: Practice to Innovation**	Scottsdale, AZ	**Contact:** Department of Radiology CME Office **Tel:** 866/246-1581 **Fax:** 507/266-3061 **Web Site:** www.mayo.edu/cme
NOVEMBER 6–9, 2007	**ABNS Oral Board Exam**	Houston, TX	**Tel:** 713/441-6015 **Fax:** 713/794-0207 **Email:** abns@tmh.tmc.edu **Web Site:** www.abns.org
NOVEMBER 8–10, 2007	**Mayo Clinic 2007: Parkinson's Disease and Other Movement Disorders for the Practitioner**	Loloa Kauiai, HI	**Contact:** Mayo Clinic **Tel:** 480/301-4580 **Fax:** 480/301-8323 **Email:** mcs.cme@mayo.edu **Web Site:** www.mayo.edu/cme/sct.courses.html
NOVEMBER 9–13, 2007	**Written Exam Review**	New York, NY	**Contact:** Center for Continuing Medical Education **Tel:** 1-800/575-4431 **Fax:** 718/798-2336 **Web Site:** www.medme.org
DECEMBER 1–2, 2007	**Principles of Operative Treatment of Craniomaxillofacial Trauma and Reconstruction**	NJ or NY	**Contact:** AO North America **Tel:** 800/769-1391 **Fax:** 610/695-2420 **Web Site:** www.aona.org
JANUARY 24–25, 2008	**6th Biennial Balance Center Symposium**	Phoenix, AZ	**Contact:** Barrow Neurological Institute **Tel:** 602/406-3067 **Web Site:** www.thebarrow.org/conferences
JANUARY 24– FEBRUARY 3, 2008	**Chicago Review Course in Neurosurgery**	Chicago, IL	**Contact:** Maria Pena **Tel:** 773/296-6666 **Fax:** 773/296-9999 **Email:** chicagoreviewcourse@yahoo.com **Web Site:** www.chicagoreviewcourse.com
APRIL 25, 2008	**AANS/CNS 2008 Biennial Pain Meeting**	Chicago, IL	**Contact:** Paula Flynn **Tel:** 847/378-0500 **Email:** meetings@aans.org **Web Site:** www.aans.org

MAY 25–27, 2008	**Goodman Oral Board Preparation Neurosurgery Review by Case Management**	Houston, TX	**CONTACT:** Vanessa Garlisch **TEL:** 847/378-0500 **EMAIL:** epm@aans.org **WEB SITE:** www.aans.org



Coming in the October Issue of...

NEUROSURGERY

OFFICIAL JOURNAL OF THE CONGRESS OF NEUROLOGICAL SURGEONS

OCTOBER 2007 VOLUME 61 NUMBER 4

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Bottleneck Factor and Height-width Ratio: Association with Ruptured Aneurysms in Patients with Multiple Cerebral Aneurysms
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Clinical Utility and Safety of Routine Intraoperative Angiography for Patients and Personnel
Lopez/Connolly

Association of Tumor Necrosis Factor-α-238GA and Apolipoprotein E2 Polymorphisms with Intracranial Hemorrhage after Brain Arteriovenous Malformation Treatment
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Bendok

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Wall Shear Stress Gradient Analysis within an Idealized Stenosis Using Non-Newtonian Flow
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