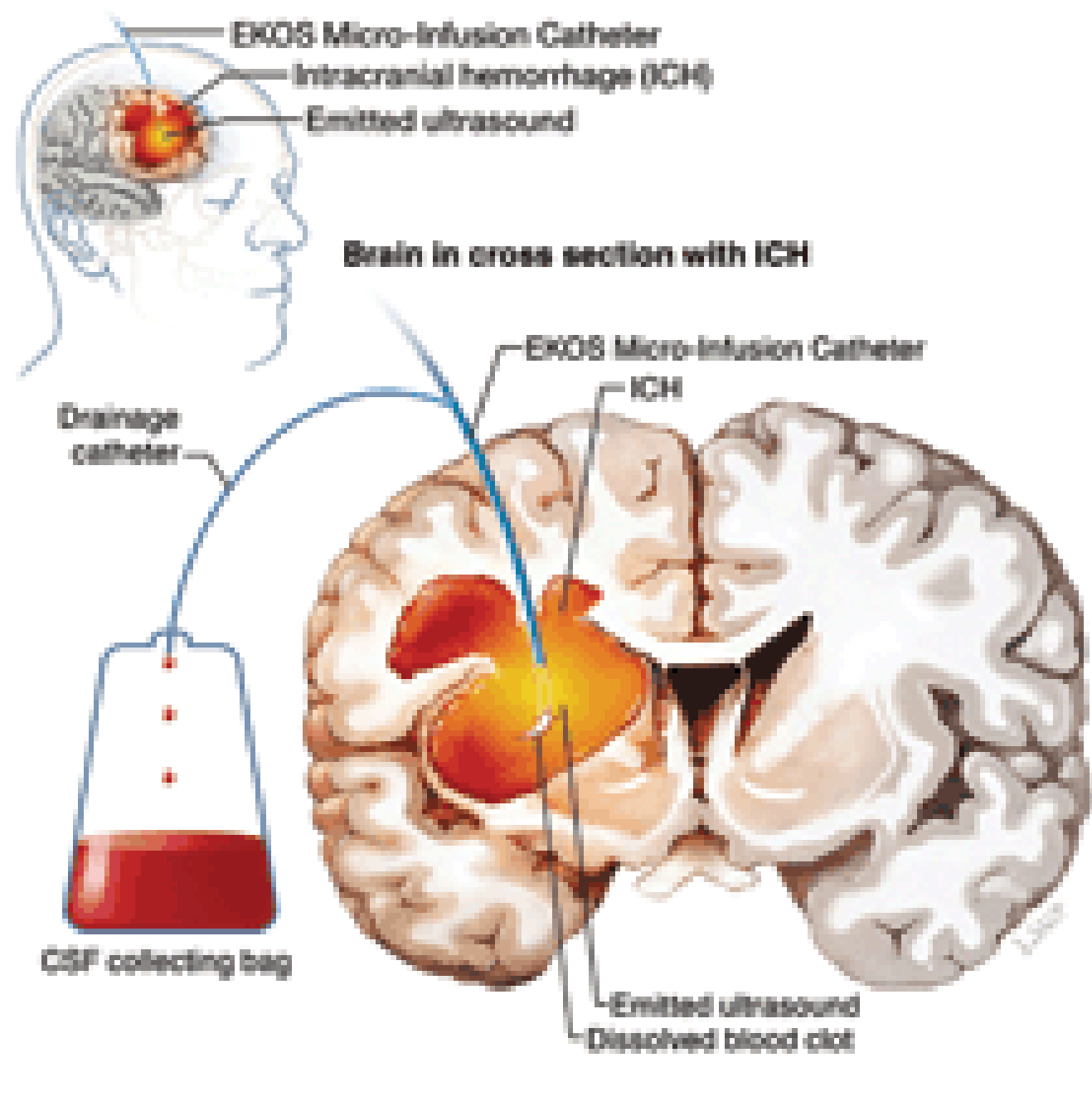
EKOS Micro-Infusion Catheter
Intracranial hemorrhage (ICH)
Emitted ultrasound
Brain in cross section with ICH
EKOS Micro-Infusion Catheter
ICH
Drainage catheter
CSF collecting bag
Emitted ultrasound
Dissolved blood clot

Introduction

Intracerebral hemorrhage

Marc R. Mayberg, M.D.,[1] and Arthur L. Day, M.D.[2]

[1]Department of Neurosurgery, Swedish Neuroscience Institute, Seattle, Washington; and [2]Mischer Neuroscience Institute, The University of Texas Medical School at Houston, Texas

Nontraumatic intracerebral hemorrhage (ICH) remains a common management dilemma for neurosurgeons. Intracerebral hemorrhage represents approximately 15% of all strokes and the 30-day mortality rate ranges from 40% to 50%, with significant disability in survivors.[1] Despite advances in the rapid diagnosis of the disorder, few effective treatments for ICH have been realized. There is increasing evidence that initial ICHs progress in the first few hours,[2] and pharmacological therapy to prevent rehemorrhage has been only equivocally effective.[3] It appears logical that surgical removal of the mass and potential toxic constituents of the hematoma with coagulation of the bleeding site should be an effective therapy. Nevertheless, multiple surgical trials have shown limited or no benefit to surgery, including a large international multicenter randomized trial.[4] The advent of minimally invasive techniques and use of thrombolytic agents to facilitate clot removal are exciting new adjuncts to therapy, but remain unproven.

The current issue of *Neurosurgical Focus* explores a number of topics related to existing and future treatments for ICH, prognostic factors that determine outcome, and features related to the pathophysiology of brain damage. Dr. Amar summarizes ongoing neurosurgical controversies in the management of ICH and its consequences. Levy et al. explore the increasingly frequent occurrence of ICH associated with cerebral revascularization treatments and thrombolysis. Abdu and colleagues present a new technology that may enable the rapid and minimally invasive removal of an ICH and intraventricular hemorrhage. Basaldella et al. examine the effect of endoscopic surgery on subsequent shunt dependence for intraventricular hemorrhage. Zacharia and associates describe factors that predict hydrocephalus following ventriculostomy associated with ICH. Conti et al. relate their experience with a telenetwork triage system for ICH, and Selman et al. review the literature pertinent to ICH associated with cerebral amyloid angiopathy. Finally, Adamson and colleagues review the mechanisms of brain injury directly referable to the thrombus constituents.

It is hoped that this collection of topics related to ICH will provide a better understanding of this common and devastating disorder, and potentially lead to new research regarding effective therapies.

(http://thejns.org/doi/abs/10.3171/2012.2.FOCUS1279)

Disclosure

The authors report no conflict of interest.

References

1. Broderick J, Connolly S, Feldmann E, Hanley D, Kase C, Krieger D, et al: Guidelines for the management of spontaneous intracerebral hemorrhage in adults: 2007 update: a guideline from the American Heart Association/American Stroke Association Stroke Council, High Blood Pressure Research Council, and the Quality of Care and Outcomes in Research Interdisciplinary Working Group. **Circulation 116:**e391–e413, 2007
2. Brott T, Broderick J, Kothari R, Barsan W, Tomsick T, Sauerbeck L, et al: Early hemorrhage growth in patients with intracerebral hemorrhage. **Stroke 28:**1–5, 1997
3. Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringer MN, et al: Recombinant activated factor VII for acute intracerebral hemorrhage. **N Engl J Med 352:**777–785, 2005
4. Mendelow AD, Gregson BA, Fernandes HM, Murray GD, Teasdale GM, Hope DT, et al: Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomised trial. **Lancet 365:**387–397, 2005

Please include this information when citing this paper: DOI: 10.3171/2012.2.FOCUS1279.

Neurosurg Focus 32 (4):E1, 2012

Controversies in the neurosurgical management of cerebellar hemorrhage and infarction

Arun Paul Amar, M.D.

Department of Neurological Surgery, Keck School of Medicine, University of Southern California, Los Angeles, California

Evidence-based guidelines for the management of hemorrhagic and ischemic cerebellar stroke are sparse, and most available data come from Class III studies. As a result, opinions and practices regarding the nature and role of neurosurgical intervention vary widely. A comprehensive literature review was conducted to adjudicate several contentious issues, such as the difference in the management of cerebellar hemorrhage versus infarction, criteria for imaging to exclude an underlying structural lesion, the value of MRI for patient selection, the role of external ventricular drainage, the indications for operative management, the timing of surgical intervention, and various options of surgical technique, among others. Treatment algorithms proposed in several different studies are compared and contrasted. This analysis is concluded by a summary of the recommendations from the American Stroke Association, which advises that patients with cerebellar hemorrhage who experience neurological deterioration or who have brainstem compression and/or hydrocephalus due to ventricular obstruction should undergo surgical evacuation of the hemorrhage as soon as possible, and that initial treatment of such patients with ventricular drainage alone rather than surgical removal of the hemorrhage is not recommended.
(http://thejns.org/doi/abs/10.3171/2012.2.FOCUS11369)

Key Words • **cerebellar hemorrhage** • **cerebellar infarction** • **management** • **review** • **stroke** • **surgery**

The management of cerebellar hemorrhage has endured controversy ever since Sir Charles Ballance reported the first successful surgical evacuation in 1906.[2] Institutional and individual variations abound in the management of cerebellar hemorrhage. To a degree, this debate is due to the relatively flimsy quality of the medical literature in support of different practices. For instance, in advocating against external ventricular drainage alone in the treatment of patients with cerebellar hemorrhage who are deteriorating neurologically or who have brainstem compression and/or hydrocephalus from ventricular obstruction, the American Stroke Association relies on evidence rated as Level C, the weakest category in effect at the time (consensus opinion of experts, case studies, or standard of care).[24] Similarly, their prior recommendation that angiography is not required for older, hypertensive patients with cerebellar hemorrhage in whom CT findings do not suggest a structural lesion is based upon Level V evidence, the weakest category in effect at the time (data from anecdotal case series only).[4]

Several randomized trials comparing early surgery with initial conservative management for ICH have been conducted, including the recent Surgical Trial in Intracerebral Hemorrhage (STICH).[23] Overall, these studies have largely shown no benefit to surgery, although post hoc subgroup analysis reveals some exceptions. Patients with cerebellar ICH have been excluded from all these randomized trials, because clinical equipoise was not believed to be present.[24] As one expert commented about the related condition of cerebellar infarction, "the results of surgery have been so consistently favorable in patients who clearly were progressively deteriorating that it seems fair to say that this is one surgical indication that does not need the scrutiny of a randomized study."[12]

As a result of these biases, data principally consist of uncontrolled, single institution retrospective case series (Class III evidence). Collectively, however, these reports suggest that the benefit of surgery is not so straightforward. Donauer et al.[7] reviewed 21 papers from 1958 to 1993 and performed a meta-analysis comparing medical versus operative treatment of cerebellar ICH. In the cohort of 357 patients who underwent surgery, the mortality rate was 49%, while that in the 269 patients treated conservatively was 50%. Similarly, Hankey and Hon[10] reviewed 8 prior series of surgery for infratentorial hemorrhage comprising a total of 405 patients. One study suggested overall benefit, while 2 studies reported benefit only in certain subgroups (conscious or drowsy but deteriorating patients), and the remaining 5 studies were either inconclusive or showed no benefit of surgery.

Abbreviations used in this paper: AVM = arteriovenous malformation; GCS = Glascow Coma Scale; ICH = intracerebral hemorrhage.

In an effort to provide more concreteness to this issue and to elucidate related concepts in the management of cerebellar hemorrhage and infarction, this article reviews relevant studies from the past century. It begins with an overview of the pathogenesis and natural history, which form the foundation and rationale for all treatment. Next, 9 separate areas of controversy are explored in detail. The review concludes with a summary of the recommendations from the American Stroke Association, whose position statements have evolved considerably from their first publication in 1999 to 2010.[3,4,24]

Pathophysiology and Natural History

Spontaneous cerebellar hematomas represent approximately 10%–15% of all ICH.[11,18,35] As with cerebellar infarction, cerebellar hemorrhage occurs most frequently in the 5th through the 8th decades of life and with greater frequency in males than in females.[11,18] Between 60% and 90% of all spontaneous cerebellar hemorrhages occur in hypertensive patients. Vascular malformations, coagulopathies (including the use of anticoagulants), neoplasms, aneurysms, cerebral amyloid angiopathy, and trauma account for the remainder.[11,17] In younger patients, underlying structural conditions are the prevailing causes.

Cerebellar infarctions, on the other hand, may result from cardiac emboli, traumatic injury to the vertebral arteries, and other causes.[11,14,26] The majority of patients also have hypertension.[13,26] The infarction most frequently occurs in the vascular distribution of the posterior inferior cerebellar artery, but the anterior inferior cerebellar artery and/ or superior cerebellar artery territories can also be involved.[14,26] Cerebellar infarctions are approximately two-thirds as common as cerebellar hemorrhage.[11]

In hypertensive patients, cerebellar hematoma is believed to result from rupture of microaneurysms, as first proposed by Charcot and Bouchard, and recently confirmed.[31] Typically, these hemorrhages begin in the area of the dentate nucleus and then spread throughout the ipsilateral hemisphere.[15] They may also extend across the vermis to the contralateral side. Although they commonly spread into the cerebellar peduncles or rupture into the fourth ventricle, only rarely do they directly involve the brainstem.[11] Dizziness, headache, nausea, vomiting, loss of balance, and difficulty walking are the most common presenting symptoms of both cerebellar hemorrhage and infarction.[1,11,14,26,30]

Clinical deterioration befalls up to 50% of patients with cerebellar ICH.[25] In its mild form, deterioration manifests as irritability, confusion, or somnolence, while the more severe form presents as coma, stupor, posturing, and hemodynamic or respiratory instability due to loss of brainstem regulation.[13] The peak incidence of deterioration is 3 days after onset, although it may occur within hours or even weeks later. When deterioration occurs, mortality has been reported to be high (25%–100%), regardless of treatment.[1,7,17,18,30] Deterioration can occur unpredictably, even in patients who appear to have reached a clinical plateau.[11,17] Ott et al.[25] reported that 50% of patients who remained alert and relatively stable for 2 days degenerated into coma over the course of the next several days, and a disconcerting 25% of patients who remained awake for 7 days subsequently deteriorated.

The causes of deterioration are protean and include increased mass effect from surrounding edema or expansion of the hematoma from repeat bleeding. Either mechanism can cause direct brainstem compression, which leads to upwards herniation through the tentorial incisura or downward tonsillar herniation through the foramen magnum. Obstructive hydrocephalus, caused by intraventricular extension of the hemorrhage or by compression of the fourth ventricle, is another mechanism of clinical decline.

In cerebellar infarction, brain swelling results from both cytotoxic and vasogenic edema. Initially, brain ischemia disrupts cell membrane integrity, which causes the accumulation of intracellular fluid. Later, vasogenic edema results from the diffusion of protein-bound fluid across a damaged blood-brain barrier.[5,19] With progressive mass effect caused by the infarct and surrounding edema, brainstem compression and/or fourth ventricle compression can result. The range of time that can elapse between symptom onset and further neurological deterioration is typically 1–7 days, with a median and mode of 3 days.[5,13,14] However, the likelihood of deterioration has been reported to be lower in cerebellar infarct (7%–32%) than in hemorrhage.[1,14]

Whereas hydrocephalus and brainstem compression can both cause decreased level of consciousness, the latter is alleged to have associated focal neurological signs.[11,13,29] Early compression of the dorsal pons results in ipsilateral sixth nerve paresis of voluntary lateral gaze that can be overcome with caloric stimulation. Later, as the compression progresses, conjugate gaze paresis that is unresponsive to caloric stimulation occurs from pressure upon the horizontal gaze center. At this stage, ipsilateral peripheral-type facial paresis is usually present due to concomitant compression of the facial colliculus. Babinski signs, Horner syndrome, and hemiparesis are all late signs of brainstem compression.[11,13,29] Recognition of these findings, along with neuroimaging, can help distinguish between altered level of consciousness due to hydrocephalus versus that due to direct brainstem compression. Appropriate therapy (for example, ventricular drainage versus surgical decompression) can then be targeted to the underlying mechanism.

The tenets of medical management of cerebellar hemorrhage are similar to those of supratentorial ICH.[24] Patients are generally monitored in a critical care setting, with frequent neurological assessment. Those with severe coagulation factor deficiency or thrombocytopenia should receive transfusion of appropriate blood products to correct the disorder. Patients whose hemorrhage is caused by oral anticoagulation therapy should receive intravenous vitamin K as well as therapy to replace the vitamin K–dependent factors. Prothrombin complex concentrates have not been proven to improve outcome compared with fresh-frozen plasma, but may have fewer complications.[24] Recombinant factor VIIa is not routinely recommended as the sole agent for reversal of oral anticoagulation therapy.[24] All patients should undergo intermittent pneumatic compression for prevention of venous thromboembolism in addition to elastic stockings. After documentation of

cessation of bleeding, low-dose subcutaneous heparin formulations may be considered as well.[24] Glucose should be monitored closely, and normoglycemica is recommended. The management of blood pressure remains disputed, without clear guidelines or target parameters, but in patients presenting with systolic blood pressure of 150 to 220 mm Hg, acute lowering to 140 mm Hg is probably safe.[24] Therapeutic cooling has not been adequately studied in cerebellar ICH, although most practitioners favor avoidance of hyperthermia.

Hemorrhagic Versus Ischemic Cerebellar Stroke

Since the first reports of decompressive surgery performed by Fairburn and Oliver[8] and by Lindgren,[20] both in 1956, the potential value of suboccipital craniectomy and resection of necrotic tissue in cerebellar infarction has been recognized. However, cerebellar hemorrhage and infarction are distinct entities, which calls into question whether the same management principles should apply to each.

Mathew et al.[21] compared the neurosurgical management of 48 patients with cerebellar ICH to that of 71 patients with cerebellar infarction. They found that patients with hematoma were more likely to be in a coma and more likely to have brainstem compression upon presentation than those with infarction. This explains why 75% of their patients with ICH required surgery, while it was necessary in only 24% for infarction.

In both cerebellar hemorrhage and infarction, perilesional edema can aggravate the space-occupying effect within the confines of the posterior fossa. However, a condition unique to ICH is the toxic effects of blood products and associated inflammation, which might provide impetus for its removal regardless of the mechanical compression of adjacent tissue. Furthermore, cerebellar hemorrhage may extend into the ventricle system, thus providing an additional mechanism of hydrocephalus besides fourth ventricle effacement. Conversely, cerebellar ICH only rarely extends directly into the brainstem.[17]

By comparison, cerebellar infarction does not lead to intraventricular hemorrhage and is thus less likely to cause hydrocephalus than cerebellar hematoma. In the patient series of Auer et al.,[1] occlusive hydrocephalus developed in 75% of patients with cerebellar hemorrhage but only 23% of those with cerebellar infarction. Patients with cerebellar ICH also had a higher incidence of hydrocephalus than those with cerebellar infarct in the series by Mathew et al.[21] However, cerebellar infarction is more likely to directly involve the brainstem than cerebellar ICH due to shared vascular territory; this occurred in 2 of 40 patients in the series of Auer et al.[1]

Emerging data suggest that in some circumstances, the area of restricted diffusion apparent on MRI, once believed to represent permanent damage, may be reversible.[16] Therefore, it is conceivable that resection of this presumed necrotic tissue in cerebellar infarction may actually compromise recovery.

In light of these considerations, a policy that limits the extent of resection of apparent necrotic tissue to the mininum needed to achieve adequate decompression appears reasonable, although the data in support of this practice are not robust.

Criteria for CT Angiogram or Catheter Angiogram

Although most cases of spontaneous cerebellar hemorrhage are the result of hypertension, some are caused by underlying lesions. In Kobayashi et al.'s series of 110 patients,[18] for example, 5 hemorrhages resulted from a cerebellar AVM, 2 resulted from a cerebellar tumor, and the remaining 103 were believed to be caused by hypertension on the basis of prior history and/or negative angiographic studies.

Even in the presence of preexisting hypertension, however, as many as 36% of all ICH cases are associated with secondary causes.[35] The indications, nature, and diagnostic accuracy of imaging for an underlying structural lesion in spontaneous cerebellar hemorrhage remains controversial. The presence of subarachnoid blood, calcification, prominent vascular structures, or edema out of proportion to the size and age of the hemorrhage might suggest the presence of an underlying lesion. Similarly, a hemorrhage that has an unusual (geographic or noncircular) shape or is located in an unusual location, such as an epicenter remote from the dentate nucleus, might prompt further study (Fig. 1). However, features of CT in isolation had a sensitivity of only 77% and specificity of only 84% in 1 study.[9] Clinical features such as age and history of preexisting hypertension also affect the decision to pursue advanced imaging.

Halpin et al.[9] performed a prospective evaluation of catheter cerebral angiography in the workup of 102 patients with spontaneous cerebral hematoma. Both supratentorial and cerebellar hemorrhages were included in the analysis. Overall, an aneurysm or AVM was the cause of the hemorrhage in 12.8% of hypertensive patients and in 18.2% of those with posterior fossa hemorrhage. The authors prospectively stratified the patients into 2 groups: those suspected to have a high likelihood of an underlying structural lesion based on CT features (Group 1) and those without such findings (Group 2). Catheter angiography was positive for AVM or aneurysm in 84% of the high-suspicion cohort and 24% in the low-suspicion one.

In another study, Zhu et al.[35] reviewed 206 consecutive patients with spontaneous ICH to determine the diagnostic yield of cerebral angiography. Both supra- and infratentorial hemorrhages were included. Patients in whom severe coagulopathy accounted for the ICH, those with bleeding into tumor, or those with predominant subarachnoid hemorrhage were excluded. Overall, the angiographic yield was significantly higher in patients less than the median age of 45 years and those without prior hypertension. In 15 patients with posterior fossa hemorrhage, 5 (33%) were found to have an underlying AVM. All 5 were normotensive, and the oldest patient in this group was 39. Another 6 patients had preexisting hypertension, the youngest of whom was 48. None of those 6 patients had positive angiography. The authors amalgamated hemorrhages in the putamen, thalamus, or posterior fossa into a single group for analysis. In this collective, the angiographic yield in patients with younger age and without preexisting hypertension was 48%, while in hypertensive patients the yield was 0%. They concluded that diagnostic angiography should not be routinely performed in patients with cerebellar hemorrhage over 45 years old with preexisting hypertension.

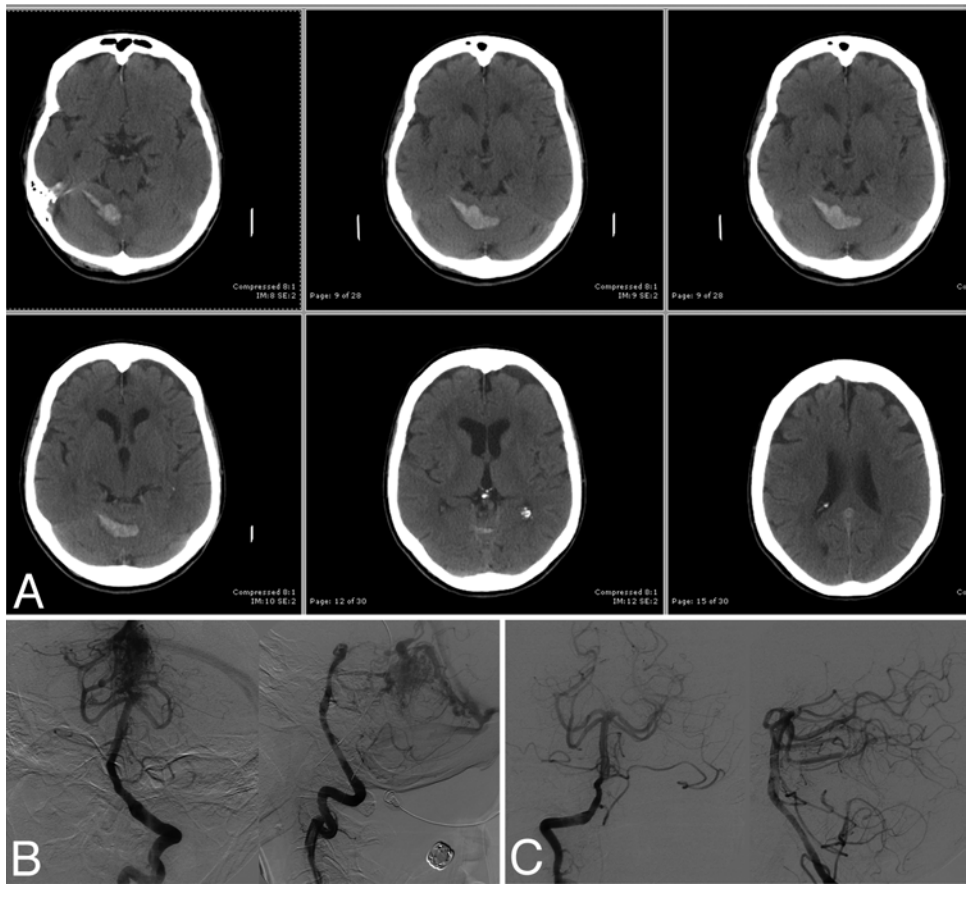

Fig. 1. Images obtained in a 77-year-old woman with a medical history significant for hypertension, heart murmur, and Crohn disease requiring large doses of aspirin. She awoke with headache, dizziness, and incoordination of the right arm. **A:** Unenhanced axial CT scans of her brain reveal acute hemorrhage of the right cerebellum extending to the tentorial surface and across the vermis to the left hemisphere. **B:** Although she had multiple risk factors for spontaneous intracerebral hemorrhage (such as hypertension, possible cardiac embolism related to the cause of her heart murmur, aspirin use, and possible age-related amyloid angiopathy), the unusual location of the hemorrhage and questionable prominence of vessels near the vein of Galen prompted further imaging. This frontal view of a left vertebral catheter angiogram reveals an AVM of the cerebellar vermis supplied primarily by branches of the bilateral superior cerebellar arteries. High risk features include feeding artery aneurysms bilaterally and venous outflow restriction of the draining vein coursing to the straight sinus. **C:** The patient underwent a series of staged liquid adhesive embolization sessions to protect against rehemorrhage. This frontal view of left vertebral catheter angiography after embolization reveals elimination of the feeding artery aneurysms and significantly reduced flow through the nidus.

Although CT angiography and catheter angiography are potentially useful in the workup of spontaneous cerebellar ICH, neither is completely reliable. In some cases, compression of adjacent vessels by the hematoma can give the false appearance of a vascular malformation, thus reducing the specificity of these tests (Fig. 2). Conversely, the mass effect can conceal an underlying lesion, thus reducing the sensitivity of vascular studies performed acutely. In the series of Halpin et al.,[9] for example, follow-up angiography at 3 months showed an AVM in 1 of 7 patients in the high-suspicion group, even though the original study results were normal. Thus, when clinically warranted, vascular studies should be repeated in a delayed fashion even if the initial workup is negative.

Role of External Ventricular Drainage

The indications for ventricular drainage in cerebellar hemorrhage and infarction remain contested. Many propose that hydrocephalus resulting from fourth ventricle obstruction should be treated with surgical decompression rather than CSF diversion.[5,17,33] Among this group, some advocate for pre- or intraoperative placement of a ventricular catheter, in case the decompression fails to achieve reconstitution of CSF pathways, while others renounce ventricular drainage altogether. One argument in favor of this approach is that decompressive surgery can shorten the duration of CSF diversion and reduce the need for a permanent shunt.[5] In many cases, the catheter can be removed within 72 hours after surgery.[5] In the series of Mathew et al.,[21] no patient required external ventricular drainage or delayed shunt placement after initial treatment with craniectomy.

Conversely, others argue that the effects of hydrocephalus can be falsely interpreted as resulting from brainstem compression. They advocate liberal use of CT imaging to distinguish between the two and institution of ventricular drainage if hydrocephalus is present and there is any clinical sign of elevated intracranial pres-

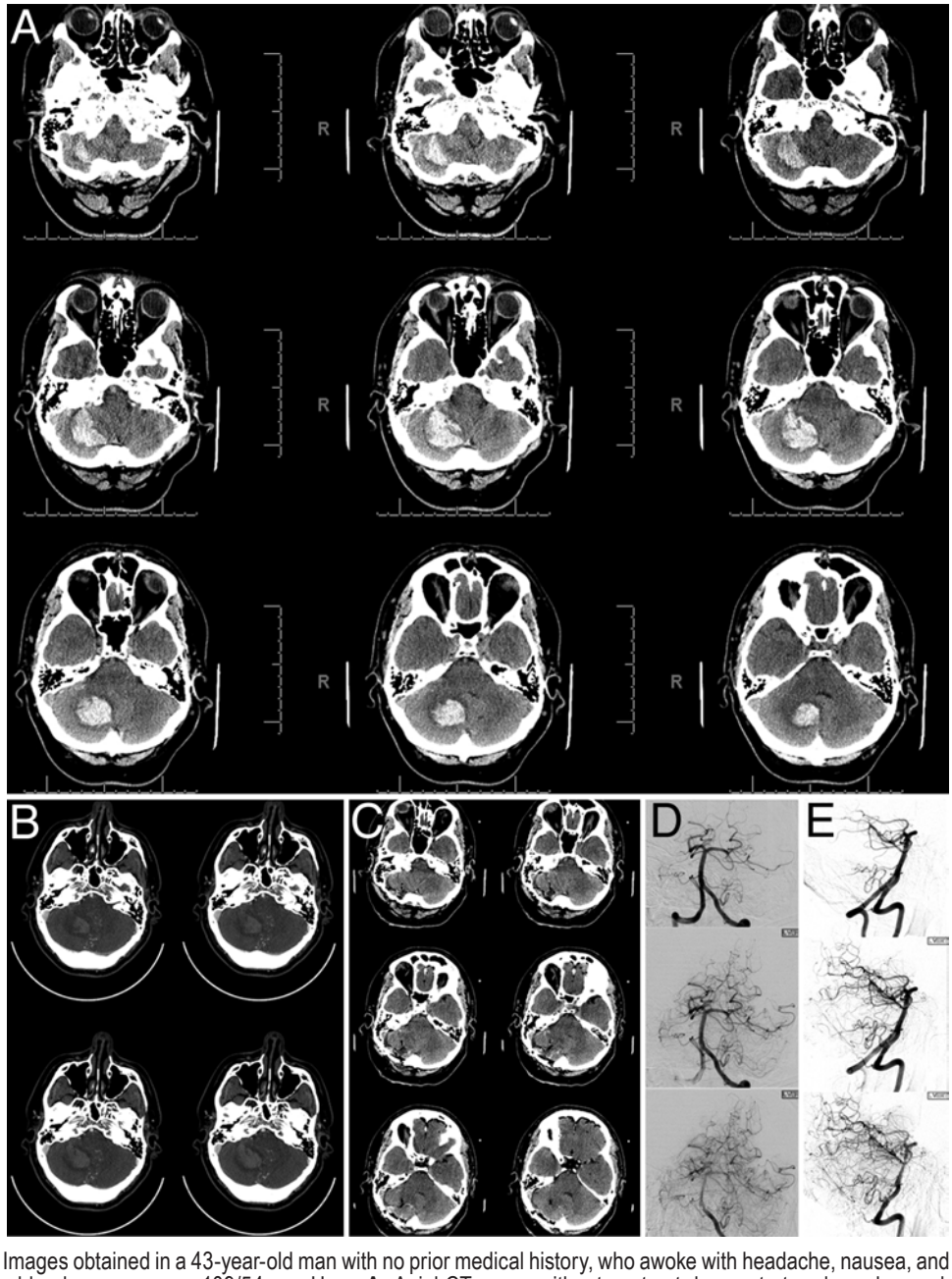

Fig. 2. Images obtained in a 43-year-old man with no prior medical history, who awoke with headache, nausea, and dizziness, and whose blood pressure was 109/54 mm Hg. **A:** Axial CT scans without contrast demonstrate a large hemorrhage of the right cerebellar hemisphere. **B:** Because of the patient's young age and lack of hypertension, a high suspicion for an underlying structural lesion led to the performance of a CT angiogram, which demonstrates an abundantly prominent collection of vessels suggesting a possible AVM. In retrospect, however, this finding was found to merely represent compression of normal vessels by the mass effect of the bleed. **C:** Axial CT scan after surgical evacuation of the hemorrhage reveals no further mass effect. **D:** Frontal view of a vertebral artery catheter angiogram confirms the absence of an underlying AVM. **E:** Lateral view of a vertebral artery catheter angiogram confirms the absence of an underlying AVM.

sure.[7,17,18,26,29] In this algorithm, decompression of the brainstem follows only if the patient does not improve with relief of the hydrocephalus.

The threshold of drainage is another debated issue, due to the risk of upward herniation caused by altering the pressure gradient across the tentorium. This phenomenon is purported to have occurred in 2 of 30 patients in the series of van Loon et al.,[30] although others believe that concern for this event is overstated.[4,26,29] Conventional neurosurgical training advises drainage at no less than 15–20 mm Hg above the level of the third ventricle.[7]

These debates began in the pre-CT era, when attribution of the underlying cause of clinical deterioration (hydrocephalus vs brainstem compression) was left to clinical examination alone. In 1960, McKissock et al.[22] reported 34 cases of cerebellar hemorrhage. Nine patients were treated with ventricular drainage, and all of them died. In some of these patients, sudden decline after

ventricular deterioration was hypothesized to be due to upward herniation, although this was not confirmed. Conversely, of the 14 patients treated with craniectomy and hematoma resection, 9 survived.

In more recent series, however, the potential value of ventricular drainage has been affirmed. In 2003, Raco et al.[26] reviewed 44 patients with cerebellar infarction. Of 17 patients who deteriorated clinically and required intervention, 13 patients with hydrocephalus underwent treatment with ventricular drainage, while the remaining 4 without hydrocephalus underwent craniectomy. Of the 13 initially managed using CSF diversion, 5 required subsequent craniectomy, while 8 were able to be treated with ventricular drainage alone. Similarly, in the series of Hornig et al.,[13] of 10 patients with cerebellar infarction and clinical deterioration initially treated with ventriculostomy, only 4 required secondary craniectomy because of continued decline. Outcome concerning mortality and functional status was not different when results of external ventricular drainage and suboccipital craniectomy were compared in this study.[13] In the series of van Loon et al.,[30] secondary craniectomy was necessary in only 6 (20%) of 30 patients with cerebellar ICH, while in other series the percentage of patients requiring craniectomy because of deterioration or failure to improve after ventricular drainage ranges from 25% to 80%.[1,13,16,30] Mathew et al.[21] found that more than half of their patients with cerebellar ICH who were initially treated with ventricular drainage subsequently required craniectomy, in contrast to only 2 (18%) of 11 patients with cerebellar infarction.

In summary, while some patients with cerebellar ICH and stroke who deteriorate neurologically and develop hydrocephalus have been successfully managed with external ventricular drainage alone, others still require surgery. As discussed below, the American Stroke Association favors operative resection of the ICH in this scenario.

Indications for Craniotomy

In the management of cerebellar ICH and infarction, the indications for operative intervention remain the supreme controversy. Some authors invoke a size threshold, typically 3 or 4 cm, above which they recommend surgical evacuation of the hemorrhage regardless of clinical status. Others use the criteria of radiographic evidence of brainstem compression or cisternal effacement, which accounts for surrounding edema in addition to the size of the ICH or infarct in determining overall mass effect. For instance, Taneda et al.[28] reported 75 cases of spontaneous cerebellar ICH and classified the appearance of the quadrigeminal cistern into 3 groups: Grade I (normal), Grade II (compressed), and Grade III (absent). Good outcomes were reported in 88%, 69%, and 0% of Grade I, II, and III cases, respectively. However, they noted that the size of the hematoma was unrelated to the degree of cisternal compression, pointing out the influence of edema or hydrocephalus on overall mass effect. The predictive value of quadrigeminal cistern compression was confirmed in the series of van Loon et al.,[30] and patients with totally obliterated cisterns had poor outcomes regardless of treatment.

Still others discount these radiographic features and emphasize the neurological examination, including level of consciousness and brainstem reflexes, in determining criteria for surgery. Kobayashi et al.[18] performed a retrospective review of 52 patients with hypertensive cerebellar ICH. On the basis of this analysis, they proposed new criteria for intervention that were prospectively applied to the next 49 patients for validation and confirmation. Patients with GCS scores of 14 or 15 and with hematoma sizes less than 4 cm in maximal diameter were treated conservatively, while patients with GCS scores of 13 or less at admission or with a hematoma measuring greater than 4 cm underwent surgical evacuation. For patients with flaccid tetraplegia and absent brainstem reflexes, intensive therapy was not rendered.

Kirollos et al.[17] developed a different protocol, based on compression of the fourth ventricle as a measure of mass effect, which they applied prospectively in the management of 50 consecutive patients with cerebellar ICH. The appearance of the fourth ventricle was divided into 3 groups: Grade I (normal size and configuration), Grade II (partially compressed and shifted), and Grade III (completely obliterated). The ICH was evacuated for all patients with Grade III compression and for patients with Grade II compression when the GCS score deteriorated in the absence of untreated hydrocephalus. Patients with Grade I or II compression were initially treated using only ventricular drainage if they developed hydrocephalus and clinical deterioration. Stable Grade I and II patients were managed conservatively. Acute deterioration to comatose state occurred in 6 (43%) of the 14 patients with Grade III compression who were conscious at presentation; none of them experienced good outcomes. However, 15 (60%) of 25 patients with hematomas greater than 3 cm and Grade I or II compression did not require clot evacuation.

In summary, clinical considerations should complement radiographic appearance in the management algorithm, and decisions for surgical intervention should rarely be made on the basis of imaging findings alone.

Timing of Surgical Intervention

Evidence consistently shows that postoperative outcomes generally correlate with preoperative status.[6,17] For instance, in the series of Ott et al.,[25] the mortality rate was 17% for patients who were conscious at the time of surgery and 75% for those who were unconscious. Similarly, in the series of Donauer et al.,[7] patients presenting with GCS scores less than 6 had a 60% mortality rate and Karnofsky Outcome Index total of 26, while those with GCS scores greater than 10 had only a 20% mortality rate and a Karnofsky Outcome Index total of 66. In the series of Kobayashi et al.,[18] of the 5 patients with GCS scores of 4, 3 died and 2 remained vegetative despite surgery. In the series of van Loon et al.,[30] patients with total obliteration of the quadrigeminal cistern had a poor outcome irrespective of treatment.

Furthermore, many patients who experience clinical deterioration improve significantly after surgery. Some have even been restored to functional capacity. On this basis, it is natural to question whether patients who remain dependent after surgery would have fared better if intervention had been performed earlier in their course.[12,19]

For these reasons, many recommend surgery prior to clinical deterioration.[12] Yoshida et al.[34] emphasize the importance of surgical therapy even for alert patients if the hematoma is larger than 3 cm to avoid delayed deterioration. Similarly, in the series of Kirollos et al.,[17] no patient with Grade III compression of the fourth ventricle who was conscious at the outset but then developed a GCS score less than 8 experienced a good outcome. These authors thus advocate aggressive early surgical evacuation of the hematoma for all Grade III patients, regardless of initial examination results, before deterioration occurs.

Conversely, Dammann et al.[6] reviewed their series of 57 patients who underwent surgical evacuation of spontaneous cerebellar ICH. The initial neurological condition proved to be highly predictive of outcome. Based on the excellent results in patients with good initial clinical condition who underwent surgery due to secondary deterioration, this group advises against the preventive evacuation of cerebellar hemorrhage. Similarly, in the German Austrian Cerebellar Infarction Study, 84 patients with massive cerebellar infarction were prospectively observed after assignment to 1 of 3 groups: craniotomy and evacuation, ventriculostomy, or medical therapy alone. Treatment was left to the discretion of the provider in this unrandomized trial. In a logistic regression model, there was found to be no benefit to performing surgery in patients who had not yet deteriorated to coma.[14]

Despite the focus on early evacuation of cerebellar ICH, even delayed removal might have benefit. Auer et al.[1] reported 2 patients with cerebellar hemorrhage and focal signs of a posterior fossa lesion. Because they had no impairment of consciousness, they were initially managed conservatively. Because their symptoms had not shown a tendency to improve, however, they underwent evacuation of the hematoma performed on Days 23 and 54, respectively. Both patients then recovered fully without neurological deficit.

What Constitutes Futility?

As stated, evidence consistently shows that postoperative outcomes generally correlate with preoperative status. However, there are numerous anecdotal accounts of good postoperative outcome among comatose patients.[11,12] In some cases, even patients with fixed and dilated pupils or other absent brainstem reflexes have recovered.[32] In the series of Hornig et al.,[13] 38% of comatose patients achieved a good recovery (nondisabled at hospital discharge) after decompressive surgery. In the German -Austrian Cerebellar Infarction Study, half of all patients who deteriorated into coma and were treated with ventricular drainage or decompressive craniotomy experienced a meaningful recovery (modified Rankin score of 2 or less).[14] Similarly, Kobayashi et al.[18] reported 2 patients with ruptured cerebellar AVMs who had flaccid tetraplegia and apnea at admission. After emergency surgery, both recovered to enjoy "a useful life."[18]

Furthermore, pathoanatomical studies reveal surprisingly few structural changes due to brainstem compression in patients with fatal space-occupying cerebellar infarcts.[27] Similarly, there is no intrinsic damage to supratentorial telencephalic structures in cerebellar ICH and infarct, which suggests the possibility of full intellectual and cognitive recovery in some cases.[7,12] In light of these considerations, it is reasonable to question whether any patient's condition is "too poor" to forego surgical intervention and what constitutes futile treatment. From a practical standpoint, surgery might be considered, even if the situation appears "hopeless."

Value of Preoperative MRI

Yanaka et al.[33] studied the prognostic value of postoperative MRI in 31 patients, all with GCS scores of 8 or less, who underwent surgical evacuation of cerebellar ICH. The patients were divided into 2 groups based on outcome. Good recovery or only moderate disability was achieved in 8 patients, while the remaining 23 died or became severely disabled/vegetative. There were no significant differences between the 2 groups in preoperative CT findings such as hematoma size, presence of hydrocephalus, fourth ventricular compression, or obliteration of the perimesencephalic cistern. However, the incidence of high signal intensity in the pons and midbrain on T2-weighted MRI, indicating brainstem damage, was significantly higher in the poor outcome group. These intriguing results raise the question of whether preoperative MRI can be used as a predictive tool to screen patients for brainstem injury, thus improving patient selection for aggressive therapy. However, no study has yet addressed this issue, possibly because of logistical impediments to performing MRI scans acutely in critically ill patients. The absence of brainstem injury, confirmed by preoperative MRI, might provide impetus for surgical intervention in patients who otherwise might have been considered "hopeless."

Technical Aspects of Surgery

Numerous technical considerations in the operative management of cerebellar hemorrhage and infarction remain in the realm of individual preference. These include the size of the suboccipital bone removed and whether to fixate the bone flap (craniotomy) or float it or abandon it (cranieCtomy) at the end of the procedure. Other adjuncts such as the removal of the arch of the first cervical vertebra remain optional. In the German Austrian Cerebellar Infarction Study, for instance, decompressive surgery consisted of a large craniotomy, duraplasty, and resection of the posterior atlas arch if tonsillar herniation was apparent, but resection of necrotic tissue was not mandatory.[14] In other series, however, craniectomy with resection of the infarcted tissue was applied, including possible resection of cerebellar tonsils.[13,25] One risk of too large a craniectomy is subsequent sagging of the cerebellar hemispheres. Conversely, a bone flap that is too small and then replaced may fail to achieve adequate decompression (Fig. 3). Because the degree of mass effect is different in each patient, intraoperative judgement must be exercised in determining the extent of bone removal necessary to achieve decompression, and no rigid guidelines can be offered about a prespecified size threshold.

Role of Other Interventions

In lieu of suboccipital craniectomy and evacuation of

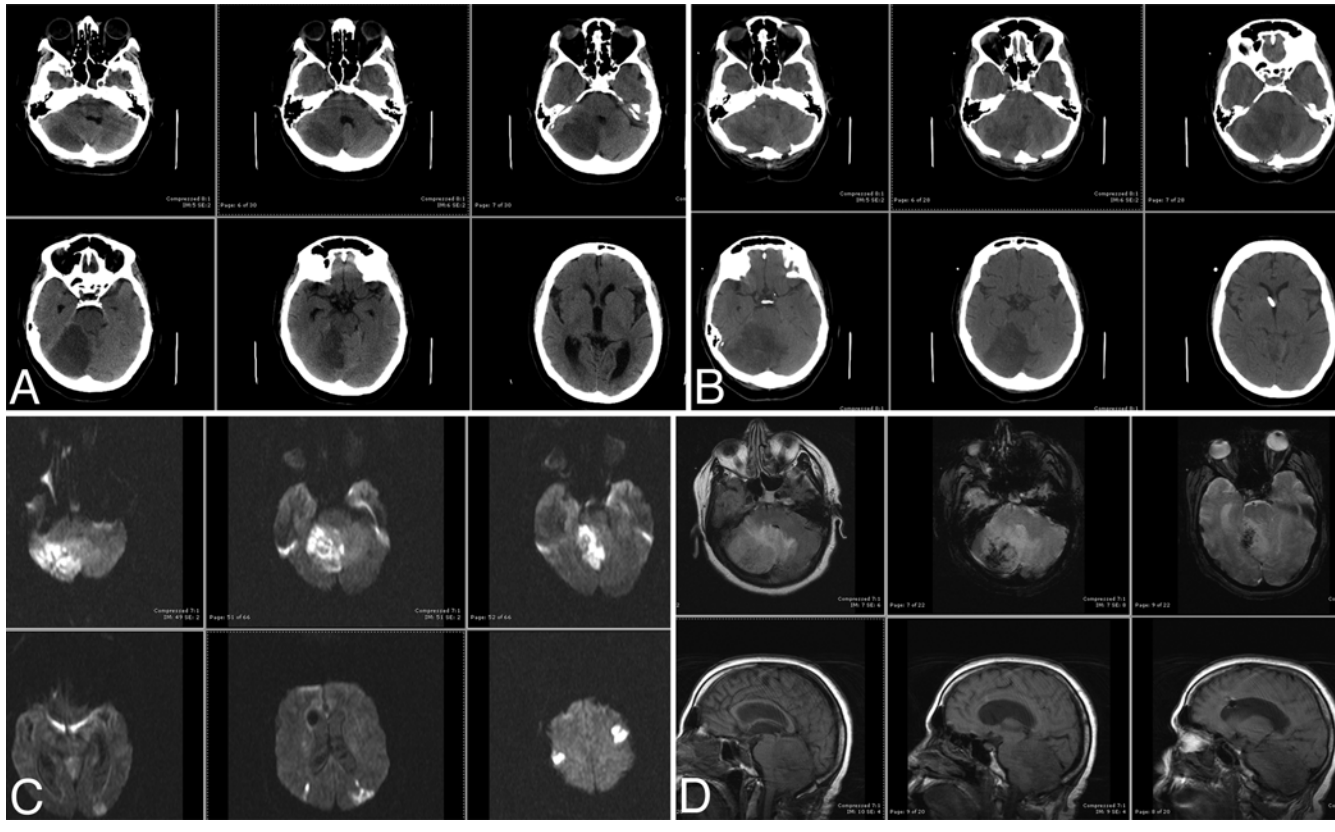

Fig. 3. Images obtained in a 56-year-old woman with mitral regurgitation, who underwent cardiac surgery and developed decreased consciousness 1 day later. **A:** Axial CT scans of the brain without contrast demonstrate a large infarction of the right cerebellar hemisphere with mass effect and hydrocephalus. **B:** Due to progressive obtundation, the patient underwent suboccipital craniotomy and partial removal of infarcted tissue. The bone flap was replaced and left floating. These postoperative axial CT scans reveal persistent mass effect. **C:** Postoperative diffusion-weighted axial MR images demonstrate persistent, widespread infarcted tissue and mass effect. **D:** Magnetic resonance imaging performed on postoperative Day 3. Axial FLAIR sequence *(upper left)* shows persistent edema and mass effect. Axial gradient echo sequence *(upper center and right)* shows hemorrhagic transformation. Sagittal T1-weighted images *(lower row)* show ascending transtentorial herniation and tonsillar herniation through the foramen magnum. The patient remained symptomatic for the next 2 weeks, suggesting that the bone decompression and/or removal of infarcted tissue was insufficient.

the hemorrhage, several other surgical approaches have been proposed for the management of cerebellar ICH, including stereotactic aspiration, endoscopic bur hole evacuation, and local infusion of a thrombolytic agent such as tissue plasminogen activator.[1] Data regarding the safety and efficacy of these procedures are lacking, and they are currently not considered mainstream therapy.

American Stroke Association Guidelines

Recognizing that the management of ICH by neurologists and neurosurgeons throughout the world varies greatly, the Stroke Council of the American Heart Association formed a task force to develop practice guidelines and to suggest areas where further research was needed. In 1999, the first guidelines were published, although the authors acknowledged that the strength of their recommendations was limited by the quality of the medical literature, which consists more of anecdotal case series than well-designed clinical trials.[4] Since then, the guidelines have undergone updates in 2007 and 2010.[3,24] Besides the evolution of the position statements, these updates reclassified the level of certainty of the treatment effect and recategorized the class of evidence from which they are derived.

Regarding the indications for vascular imaging to search for an underlying structural cause of the ICH, the 1999 Council wrote, "Angiography should be considered for all patients without a clear cause of hemorrhage who are surgical candidates, particularly young, normotensive patients who are clinically stable (level of evidence V, grade C recommendation)."[4] Additionally, they wrote, "Angiography is not required for older hypertensive patients who have a hemorrhage in the basal ganglia, thalamus, cerebellum, or brain stem and in whom CT findings do not suggest a structural lesion ….(level of evidence V, grade C recommendation)."[4] Under the definitions in effect at that time, these were the weakest possible recommendations and based on the lowest quality data. In 2010, the guidelines state that, "…CT angiography, CT venography, contrast-enhanced CT, contrast-enhanced MRI, magnetic resonance angiography, and magnetic resonance venography can be useful to evaluate for underlying structural lesions, including vascular malforma-

tions and tumors when there is clinical or radiological suspicion (*Class IIa; Level of Evidence: B*)."[24]

Regarding the indications for surgical removal of ICH, the 1999 council wrote:[4]

> Patients with cerebellar hemorrhage > 3 cm who are neurologically deteriorating or who have brain stem compression and hydrocephalus from ventricular obstruction should have surgical removal of the hemorrhage as soon as possible (levels of evidence III through V, grade C recommendation)… Stereotactic aspiration may be associated with better outcomes than standard craniotomy for moderate-sized cerebellar hemorrhages, but this hypothesis has yet to be tested in a randomized study (no recommendation).

In 2007, there was no change to this recommendation, although the authors revised the categorization of its strength as "Class 1, Level of Evidence B," which is an intermediate grade.[3] In 2010, the qualification of the 3-cm-size threshold was abandoned, and a new recommendation concerning ventricular drainage was offered:[24]

> Patients with cerebellar hemorrhage who are deteriorating neurologically or who have brainstem compression and/or hydrocephalus from ventricular obstruction should undergo surgical removal of the hemorrhage as soon as possible (*Class 1; Level of Evidence: B*). (Revised from the previous guideline). Initial treatment of these patients with ventricular drainage alone rather than surgical evacuation is not recommended (*Class III; Level of Evidence: C*) . (New recommendation).

Conclusions

The management of cerebellar hemorrhagic and ischemic stroke is controversial. Issues such as the difference in the treatment algorithm of cerebellar ICH versus infarction, criteria for imaging to exclude an underlying structural lesion, the value of MRI for patient selection, the role of external ventricular drainage, the indications for operative management, the timing of surgical intervention, and various options of surgical technique remain unresolved. Professional society guidelines for these considerations are sparse and based on relatively poor quality data. Nonetheless, the potential value of neurosurgical intervention remains well established.

Disclosure

The author reports no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

References

1. Auer LM, Auer T, Sayama I: Indications for surgical treatment of cerebellar haemorrhage and infarction. **Acta Neurochir (Wien) 79:**74–79, 1986
2. Ballance HA: Case of traumatic haemorrhage into the left lateral lobe of the cerebellum, treated by operation, with recovery. **Surg Gynecol Obstet 3:**223–225, 1906
3. Broderick J, Connolly S, Feldmann E, Hanley D, Kase C, Krieger D, et al: Guidelines for the management of spontaneous intracerebral hemorrhage in adults: 2007 update: a guideline from the American Heart Association/American Stroke Association Stroke Council, High Blood Pressure Research Council, and the Quality of Care and Outcomes in Research Interdisciplinary Working Group. **Circulation 116:**e391–e413, 2007
4. Broderick JP, Adams HP Jr, Barsan W, Feinberg W, Feldmann E, Grotta J, et al: Guidelines for the management of spontaneous intracerebral hemorrhage: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. **Stroke 30:**905–915, 1999
5. Chen HJ, Lee TC, Wei CP: Treatment of cerebellar infarction by decompressive suboccipital craniectomy. **Stroke 23:**957–961, 1992
6. Dammann P, Asgari S, Bassiouni H, Gasser T, Panagiotopoulos V, Gizewski ER, et al: Spontaneous cerebellar hemorrhage—experience with 57 surgically treated patients and review of the literature. **Neurosurg Rev 34:**77–86, 2011
7. Donauer E, Loew F, Faubert C, Alesch F, Schaan M: Prognostic factors in the treatment of cerebellar haemorrhage. **Acta Neurochir (Wien) 131:**59–66, 1994
8. Fairburn B, Oliver LC: Cerebellar softening; a surgical emergency. **BMJ 1:**1335–1336, 1956
9. Halpin SF, Britton JA, Byrne JV, Clifton A, Hart G, Moore A: Prospective evaluation of cerebral angiography and computed tomography in cerebral haematoma. **J Neurol Neurosurg Psychiatry 57:**1180–1186, 1994
10. Hankey GJ, Hon C: Surgery for primary intracerebral hemorrhage: is it safe and effective? A systematic review of case series and randomized trials. **Stroke 28:**2126–2132, 1997
11. Heros RC: Cerebellar hemorrhage and infarction. **Stroke 13:** 106–109, 1982
12. Heros RC: Surgical treatment of cerebellar infarction. **Stroke 23:**937–938, 1992
13. Hornig CR, Rust DS, Busse O, Jauss M, Laun A: Space-occupying cerebellar infarction. Clinical course and prognosis. **Stroke 25:**372–374, 1994
14. Jauss M, Krieger D, Hornig C, Schramm J, Busse O: Surgical and medical management of patients with massive cerebellar infarctions: results of the German-Austrian Cerebellar Infarction Study. **J Neurol 246:**257–264, 1999
15. Kanno T, Sano H, Shinomiya Y, Katada K, Nagata J, Hoshino M, et al: Role of surgery in hypertensive intracerebral hematoma. A comparative study of 305 nonsurgical and 154 surgical cases. **J Neurosurg 61:**1091–1099, 1984
16. Kidwell CS, Alger JR, Saver JL: Beyond mismatch: evolving paradigms in imaging the ischemic penumbra with multimodal magnetic resonance imaging. **Stroke 34:**2729–2735, 2003
17. Kirollos RW, Tyagi AK, Ross SA, van Hille PT, Marks PV: Management of spontaneous cerebellar hematomas: a prospective treatment protocol. **Neurosurgery 49:**1378–1387, 2001
18. Kobayashi S, Sato A, Kageyama Y, Nakamura H, Watanabe Y, Yamaura A: Treatment of hypertensive cerebellar hemorrhage—surgical or conservative management? **Neurosurgery 34:**246–251, 1994
19. Koh MS, Goh KY, Tung MY, Chan C: Is decompressive craniectomy for acute cerebral infarction of any benefit? **Surg Neurol 53:**225–230, 2000
20. Lindgren SO: Infarctions simulating brain tumours in the posterior fossa. **J Neurosurg 13:**575–581, 1956
21. Mathew P, Teasdale G, Bannan A, Oluoch-Olunya D: Neurosurgical management of cerebellar haematoma and infarct. **J Neurol Neurosurg Psychiatry 59:**287–292, 1995
22. McKissock W, Richardson A, Walsh L: Spontaneous cerebellar haemorrhage: a study of 34 consecutive cases treated surgically. **Brain 83:**1–9, 1960
23. Mendelow AD, Gregson BA, Fernandes HM, Murray GD, Teasdale GM, Hope DT, et al: Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomised trial. **Lancet 365:**387–397, 2005
24. Morgenstern LB, Hemphill JC III, Anderson C, Becker K, Broderick JP, Connolly ES Jr, et al: Guidelines for the management of spontaneous intracerebral hemorrhage: a guide-

line for healthcare professionals from the American Heart Association/American Stroke Association. **Stroke 41:**2108–2129, 2010
25. Ott KH, Kase CS, Ojemann RG, Mohr JP: Cerebellar hemorrhage: diagnosis and treatment. A review of 56 cases. **Arch Neurol 31:**160–167, 1974
26. Raco A, Caroli E, Isidori A, Salvati M: Management of acute cerebellar infarction: one institution's experience. **Neurosurgery 53:**1061–1066, 2003
27. Sypert GW, Alvord EC Jr: Cerebellar infarction. A clinicopathological study. **Arch Neurol 32:**357–363, 1975
28. Taneda M, Hayakawa T, Mogami H: Primary cerebellar hemorrhage. Quadrigeminal cistern obliteration on CT scans as a predictor of outcome. **J Neurosurg 67:**545–552, 1987
29. Tulyapronchote R, Malkoff MD, Selhorst JB, Gomez CR: Treatment of cerebellar infarction by decompression suboccipital craniectomy. **Stroke 24:**478–480, 1993 (Letter)
30. van Loon J, Van Calenbergh F, Goffin J, Plets C: Controversies in the management of spontaneous cerebellar haemorrhage. A consecutive series of 49 cases and review of the literature. **Acta Neurochir (Wien) 122:**187–193, 1993
31. Wakai S, Nagai M: Histological verification of microaneurysms as a cause of cerebral haemorrhage in surgical specimens. **J Neurol Neurosurg Psychiatry 52:**595–599, 1989
32. Yanaka K, Meguro K, Fujita K, Narushima K, Nose T: Immediate surgery reduces mortality in deeply comatose patients with spontaneous cerebellar hemorrhage. **Neurol Med Chir (Tokyo) 40:**295–300, 2000
33. Yanaka K, Meguro K, Fujita K, Narushima K, Nose T: Postoperative brainstem high intensity is correlated with poor outcomes for patients with spontaneous cerebellar hemorrhage. **Neurosurgery 45:**1323–1328, 1999
34. Yoshida S, Sasaki M, Oka H, Gotoh O, Yamada R: [Hypertensive cerebellar hemorrhage with signs of lower brainstem compression—a case report (author's transl).] **No Shinkei Geka 6:**379–383, 1978 (Jpn)
35. Zhu XL, Chan MS, Poon WS: Spontaneous intracranial hemorrhage: which patients need diagnostic cerebral angiography? A prospective study of 206 cases and review of the literature. **Stroke 28:**1406–1409, 1997

Manuscript submitted December 16, 2011.
Accepted February 3, 2012.
Portions of this work were previously presented in oral form on October 2, 2010, at the 36th Annual Kaiser Neurology and Neurosurgery Symposium in Newport Beach, California, as well as the University of Southern California Department of Neurosurgery Grand Rounds in January 2011.
Please include this information when citing this paper: DOI: 10.3171/2012.2.FOCUS11369.
Address correspondence to: Arun Paul Amar, M.D., 1520 San Pablo Street, Suite 3800, Los Angeles, California 90033. email: amar@aya.yale.edu.

Neurosurg Focus 32 (4):E2, 2012

Intracerebral hemorrhage secondary to intravenous and endovascular intraarterial revascularization therapies in acute ischemic stroke: an update on risk factors, predictors, and management

Maxim Mokin, M.D., Ph.D.,[1,2] Peter Kan, M.D., M.P.H.,[3,4] Tareq Kass-Hout, M.D.,[1,2] Adib A. Abla, M.D.,[3,4] Travis M. Dumont, M.D.,[3,4] Kenneth V. Snyder, M.D., Ph.D.,[3–6] L. Nelson Hopkins, M.D.,[3–6] Adnan H. Siddiqui, M.D., Ph.D.,[3–6] and Elad I. Levy, M.D.[3–6]

Departments of [1]Neurology, [3]Neurosurgery, and [5]Radiology, and [6]Toshiba Stroke Research Center, School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York; and Departments of [2]Neurology and [4]Neurosurgery, Millard Fillmore Gates Circle Hospital, Kaleida Health, Buffalo, New York

Intracerebral hemorrhage (ICH) secondary to intravenous and intraarterial revascularization strategies for emergent treatment of acute ischemic stroke is associated with high mortality. ICH from systemic thrombolysis typically occurs within the first 24–36 hours of treatment initiation and is characterized by rapid hematoma development and growth. Pathophysiological mechanisms of revascularization therapy-induced ICH are complex and involve a combination of several distinct processes, including the direct effect of thrombolytic agents, disruption of the blood-brain barrier secondary to ischemia, and direct vessel damage from wire and microcatheter manipulations during endovascular procedures. Several definitions of ICH secondary to thrombolysis currently exist, depending on clinical or radiological characteristics used. Multiple studies have investigated clinical and laboratory risk factors associated with higher rates of ICH in this setting. Early ischemic changes seen on noncontrast CT scanning are strongly associated with higher rates of hemorrhage. Modern imaging techniques, particularly CT perfusion, provide rapid assessment of hemodynamic parameters of the brain. Specific patterns of CT perfusion maps can help identify patients who are likely to benefit from revascularization or to develop hemorrhagic complications. There are no established guidelines that describe management of revascularization therapy–induced ICH, and great variability in treatment protocols currently exist. General principles that apply to the management of spontaneous ICH might not be as effective for revascularization therapy–induced ICH. In this article, the authors review current knowledge of risk factors and radiological predictors of ICH secondary to stroke revascularization techniques and analyze medical and surgical management strategies for ICH in this setting.
(http://thejns.org/doi/abs/10.3171/2012.1.FOCUS11352)

Key Words • **acute ischemic stroke** • **intracerebral hemorrhage** • **intravenous thrombolysis** • **endovascular intervention** • **computed tomography** • **blood pressure**

According to the most recent report from the American Heart Association, 795,000 people in the US experience a new or recurrent stroke each year, and 87% of these strokes are ischemic.[42] Despite advances in treatment and rehabilitation strategies, stroke remains the leading cause of long-term disability in adults. A short time window for treatment (within the first 4.5 hours of stroke onset) and late arrival to the hospital are major barriers preventing many patients from receiving IV thrombolysis. Careful analysis of acute stroke care provided at multiple hospitals in the US shows that even some patients with no absolute contraindications for thrombolysis who present to the emergency department within the "therapeutic window" do not receive recommended thrombolytic therapy.[7,21] Intracerebral hemorrhage secondary to thrombolysis is associated with high mortality and remains the most feared complication of acute stroke treatment. In fact, it is often cited as a primary reason preventing patients from receiving fibrinolytic agents to restore blood flow to the brain.[50]

Endovascular interventions with IA thrombolytic

Abbreviations used in this paper: ASPECTS = Alberta Stroke Programme Early CT Score; CBF = cerebral blood flow; CBV = cerebral blood volume; ECASS = European Cooperative Acute Stroke Study; HI-1 = hemorrhagic infarction Type 1; HI-2 = hemorrhagic infarction Type 2; IA = intraarterial; ICH = intracerebral hemorrhage; IMS = Interventional Management of Stroke; IV = intravenous; MCA = middle cerebral artery; MERCI = Mechanical Embolus Removal in Cerebral Ischemia; MTT = mean transit time; NIHSS = National Institutes of Health Stroke Scale; NINDS = National Institute of Neurological Disorders and Stroke; PH-1 = parenchymal hematoma Type 1; PH-2 = parenchymal hematoma Type 2; PROACT = Prolyse in Acute Cerebral Thromboembolism; sICH = symptomatic ICH; SITS-MOST = Safe Implementation of Thrombolysis in Stroke–Monitoring Study; tPA = tissue plasminogen activator.

agents or by means of mechanical revascularization strategies demonstrate high recanalization rates in strokes with large artery occlusion and can be performed with an extended time window[36] or when contraindications for IV thrombolysis are present. Theoretical models have projected that IA therapies for acute stroke secondary to large-vessel occlusion will be used in up to 10,400–41,500 cases per year in the US.[22] However, similar to IV thrombolysis, endovascular interventions carry a risk of ICH. Recent advances in stroke imaging allow selection of patients who can benefit the most from revascularization and prediction of which patients are at higher risk for hemorrhagic complications.

In this article, we review the current literature on clinical and laboratory risk factors and radiological predictors of ICH secondary to IV and IA revascularization therapies in patients presenting with acute ischemic stroke, as well as analyzing strategies for managing this iatrogenic complication.

Frequency and Definition

Intracerebral hemorrhage after systemic thrombolysis typically occurs within the first 24–36 hours after initiation of treatment. In the landmark NINDS tPA Stroke Trial,[38] most hemorrhages occurred within the first 6 hours from tPA infusion. Several definitions of thrombolysis-induced symptomatic ICH (sICH) currently exist, depending on the clinical or radiological characteristics considered. According to the NINDS definition, a hemorrhage is considered symptomatic if it is associated with any decline in neurological status.[37] An alternative definition of sICH frequently used in many clinical trials is deterioration of 4 or more points in the NIHSS score.[15,20] When comparing the frequency of sICH among trials evaluating different revascularization strategies, it should be taken into account that the rates can vary significantly, depending on the definition chosen. For example, in a recent study of 985 ischemic strokes, the frequency of sICH ranged from 2.1% to 9.4% when different definitions of sICH were applied.[45] Likewise, the ECASS III trial,[18] which tested IV tPA administered between 3 and 4.5 hours after stroke onset, demonstrated a wide range of sICH rates (2.4%–7.9%), depending on specific criteria used to define sICH.

Table 1 summarizes the rates of sICH and sICH-related mortality in major international stroke trials conducted during the last 2 decades.[8,14,18–20,23,24,37,43,44] The rate of sICH following administration of IV tPA within the first 3 hours of acute stroke was 6.4% in the original NINDS tPA trial.[37] The SITS-MOST[49] provided valuable information about the safety of administering IV tPA within 0–3 hours in routine clinical practice. In this large observational study, a total of 6483 patients were enrolled from 285 centers in the European Union (of which half had little previous experience with stroke thrombolysis).

TABLE 1: Rate and definition of sICH in major international stroke trials*

Authors & Year	Study	Protocol	Rate of sICH	Definition of sICH	Mortality Due to sICH
NINDS rt-PA Stroke Study Group, 1995	NINDS tPA	IV tPA (0.9 mg/kg) w/in 3 hrs of stroke onset	6.4%	any decline in neurol status	47%
Hacke et al., 1995	ECASS I	IV tPA (1.1 mg/kg) w/in 6 hrs of stroke onset	10.7%	24-hr deterioration	53%
Hacke et al., 1998	ECASS II	IV tPA (0.9 mg/kg) w/in 6 hrs of stroke onset	8.8%	clinical worsening (e.g., drowsiness) or worsening in NIHSS score by ≥4 points	44% "at 7 days"
Hacke et al., 2008	ECASS III	IV tPA (0.9 mg/kg) btwn 3 & 4.5 hrs after stroke onset	2.4%	worsening in NIHSS score by ≥4 points	9.4%
del Zoppo et al., 1998	PROACT I	IA pro-UK (6 mg) w/in 6 hrs of stroke onset in pts w/ MCA occlusion	15.4%	neurol deterioration w/in 24 hrs of treatment	25%
Furlan et al., 1999	PROACT II	IA pro-UK (9 mg) w/in 6 hrs of stroke onset in pts w/ MCA occlusion	10.2%	neurol deterioration w/in 24 hrs of treatment	NR
Smith et al., 2005	MERCI	mechanical embolectomy w/in 8 hrs of stroke onset in pts ineligible for IV tPA	7.8%	worsening in NIHSS score by ≥4 points or any subarachnoid blood on CT scan	NR
Smith et al., 2008	Multi MERCI	mechanical embolectomy w/in 8 hrs of stroke onset in pts w/ persistent large-vessel occlusion after IV tPA	9.8%	worsening in NIHSS score by ≥4 points	NR
IMS Study Investigators, 2004	IMS I	0.6 mg/kg IV tPA started w/in 3 hrs of stroke onset followed by IA tPA	6.3%	any decline in neurol status w/in 36 hours of treatment	28% "at 7 days"
IMS II Trial Investigators, 2007	IMS II	0.6 mg/kg IV tPA started w/in 3 hrs of stroke onset followed by IA tPA using small-vessel US infusion system	9.9%	any decline in neurol status w/in 36 hrs of treatment	NR

* neurol = neurological; NR = not reported; pro-UK = pro-urokinase; pts = patients; US = ultrasound.

The rate of sICH (according to the NINDS definition) was 7.3%, indicating that systemic thrombolysis administered outside a clinical trial was associated with a similar complication rate.

Accurate comparison of sICH rates for different IA revascularization approaches is complicated because often more than one treatment modality is used to achieve successful revascularization. In many large prospective studies, the trial design allows patient enrollment after "failure" of systemic thrombolysis, whereas other patients can be taken directly for intervention because of ineligibility for systemic IV tPA administration. Trials of IA pharmacological thrombolysis (PROACT I and II and IMS I and II) demonstrated a rate of sICH in the range of 6.3%–15.4%.[8,14,23,24] When mechanical thrombectomy with the Merci retriever device (Concentric Medical) was tested for acute stroke treatment in the MERCI[44] and Multi-MERCI[43] trials, sICH occurred in 7.8% and 9.8% of patients, respectively. Aspiration thrombectomy with the Penumbra system (Penumbra, Inc.) utilizes continuous aspiration together with mechanical fragmentation of the clot. In the Penumbra Pivotal Stroke trial,[41] which was designed to assess safety of the Penumbra system for treatment of acute stroke due to large-vessel occlusion within the first 8 hours of symptom onset, sICH occurred in 11.2% of patients. Although the overall rates of sICH following pharmacological and mechanical endovascular approaches to acute stroke treatment are higher compared with IV thrombolysis with tPA alone, these results should be interpreted with caution. Endovascular therapy is typically reserved for strokes in patients with higher NIHSS scores (scores of 8–10 and above, depending on the trial design) and within a more extended time window (up to 6–8 hours of stroke onset). Both severity of baseline NIHSS score and extended treatment window are well-known risk factors for sICH (which we discuss in further detail later in this article), raising an argument that patients eligible for endovascular treatment are more prone to develop sICH due to the natural history of these strokes.

Intracerebral hemorrhage as a result of acute stroke treatment (either with IV or IA approaches) should be distinguished from ICH that can occur from a hyperperfusion syndrome following endarterectomy or carotid artery stenting in patients with carotid artery stenosis. This syndrome is thought to be caused by impaired cerebral autoregulatory mechanisms and usually occurs a few days after the surgery, although delayed presentations for up to several weeks have been described.[39,48] The most catastrophic presentation associated with this syndrome—ICH—occurs in up to 1%–2% of patients who undergo carotid artery interventions, according to previously published retrospective studies of case series summarized in a review article by Moulakakis et al.[34]

Radiographically, ICH can be classified on the basis of size of hemorrhage, as well as extent of ischemic infarct. This principle is applied in the ECASS classification scheme, in which hemorrhagic transformation after IV thrombolysis can be divided into 4 categories.[13] Examples of these categories are shown in Fig. 1. Hemorrhagic infarction types 1 and 2 (HI-1 and HI-2) are defined as small petechiae along the margins of the infarct and larger more confluent petechiae without a space-occupying effect, respectively. Parenchymal hematoma Type 1 (PH-1) is defined as hemorrhage in less than 30% of the infarcted area, with some mild space-occupying effect. In parenchymal hematoma Type 2 (PH-2), hemorrhage is seen in more than 30% of the infarcted area, and there is significant space-occupying effect. Analysis of neurological outcomes in patients with each subtype of hemorrhagic transformation shows that PH-2 is associated with a poor chance for neurological recovery and a high rate of death at 3 months, whereas other subtypes do not have a significant effect on clinical outcomes following IV thrombolysis.[13]

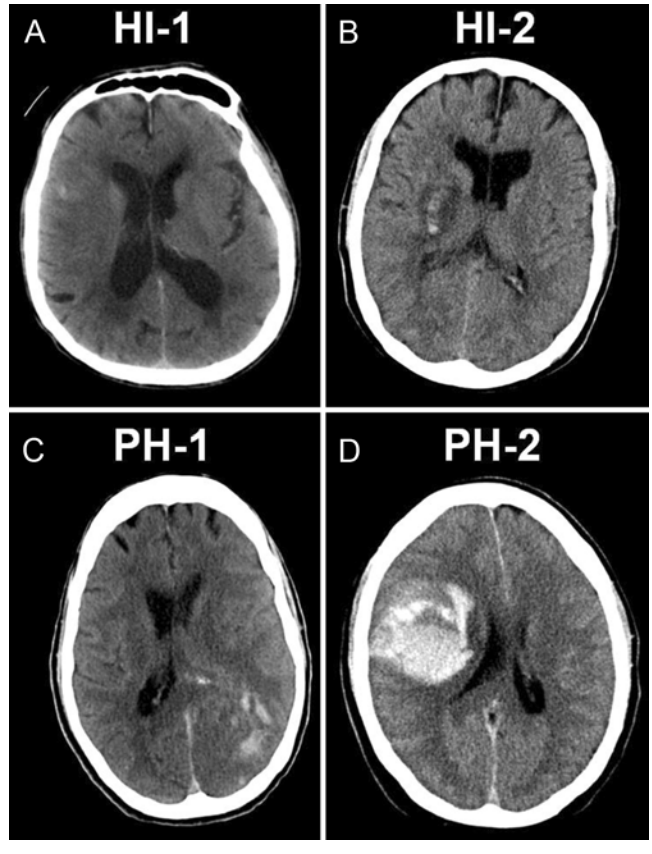

Fig. 1. Noncontrast CT scans showing examples of radiographic types of revascularization-induced ICH, according to the ECASS classification. **A:** Right MCA stroke with small petechial hemorrhage representing hemorrhagic infarction Type 1 (HI-1). **B:** Right internal capsule stroke with larger confluent petechial hemorrhages within the infarct core representing HI-2. **C:** Left parietooccipital stroke with hemorrhage in less than 30% of the infarcted area and some mild space-occupying effect representing parenchymal hematoma Type 1 (PH-1) hemorrhage. **D:** A large hematoma with significant space-occupying effect is characteristic of PH-2 hemorrhage.

Mechanisms

Pathophysiological mechanisms of revascularization therapy–induced ICH are complex and include a combination of several distinct processes. Direct thrombolytic effects of pharmacological agents can occur parallel to

blood-brain-barrier alteration, which is triggered by ischemia. Spontaneous hemorrhagic transformation and edema formation are frequently observed in large strokes due to major artery occlusion.[2] When occurring at the same time, these processes potentiate hematoma formation, causing rapid growth of intraparenchymal hematomas. Recanalization strategies introduce the risk of reperfusion hemorrhage, and wire and catheter manipulation in cases of IA interventions can cause direct damage to the endothelial wall. A combined analysis of the IMS I and II trials, as well as local registries of IA cases, showed that microcatheter contrast injections during IA thrombolysis also increase hemorrhagic risk, potentially due to degradation of the basal lamina.[25,26]

Clinical and Laboratory Predictors

Many studies have addressed various clinical and laboratory risk factors associated with higher rates of ICH, predominantly in patients who received IV thrombolysis with tPA. In general, these factors can be divided into modifiable types (such as baseline blood pressure, serum glucose level, or lytic dose) and nonmodifiable types (such as admission NIHSS score, age, and comorbid conditions). Here, we will review only those factors that are of greatest importance in clinical practice when evaluating potential candidates for revascularization approaches.

Severity of NIHSS score and its correlation with higher rates of ICH has been a subject of multiple study analyses since the NINDS tPA trial investigators showed that patients with higher admission NIHSS scores were at greater risk for development of sICH.[37,38] In patients with NIHSS scores lower than 10, the rate of sICH was 3%, compared with 17% in patients with an NIHSS scores of 20 or greater. This relationship between severity of stroke symptoms and increased risk of hemorrhage was later confirmed by studying a large number of patients receiving IV tPA for acute ischemic stroke treatment in routine clinical practice.[46] The higher baseline NIHSS scores of patients enrolled in IA revascularization trials is one potential explanation for the higher rates of ICH in these trials than in IV thrombolysis trials.

Elevated systemic blood pressure is frequently observed in patients who present with acute ischemic stroke. This is thought to represent a physiological response to brain ischemia, causing an increase in cerebral blood perfusion to maintain adequate oxygenation of brain "penumbra" (that is, brain tissue at risk). For patients to be eligible for IV thrombolysis with tPA, blood pressure should not exceed 185/110 mm Hg, according to the acute stroke management guidelines of the American Heart Association's Stroke Council.[1] During and within the first 24 hours following IV thrombolysis, blood pressure should be maintained at a level below 180/105 mm Hg. The guidelines indicate that similar blood pressure parameters should be applied to stroke patients treated with other acute reperfusion interventions, but no data currently exist to support this principle. In clinical practice, however, more conservative blood pressure parameters are often used for endovascular interventions, on the basis of evidence that higher NIHSS scores (an endovascular approach is typically reserved for patients with an NIHSS score ≥ 8) and frequent concurrent use of systemic anticoagulation further increase the risk for ICH.[8,38,46]

Another important modifiable risk factor is glucose control.[9,35] Hyperglycemia is responsible for blood-brain barrier damage through increased production of lactic acid and free radicals, as well as direct damage to the lipid-rich neuronal membrane.[30] The desired range of blood glucose values is 80–140 mg/dl.[1] To avoid causing hypoglycemia, treatment is often not recommended unless glucose values exceed 200 mg/dl.

Radiographic Predictors

When evaluating patients with suspected acute stroke, a noncontrast cranial CT scan is always part of the initial diagnostic algorithm, allowing rapid and accurate differentiation between ischemic and hemorrhagic strokes. Patients who are candidates for an endovascular approach often undergo a CT angiogram. This study allows direct visualization of vascular anatomy and identification of potential sites of vessel occlusion. Although CT perfusion imaging is not (yet) a component of clinical trials or standard evaluation protocols, its utilization has markedly increased at stroke centers. For example, in the ongoing IMS III trial, the investigators noticed more frequent use of CT angiograms and perfusion studies for assessment of patients with acute stroke during the past 5 years, both at academic centers and at community hospitals.[32] With rapid advancement in imaging technologies, radiographic findings are becoming a promising tool in predicting risk of hemorrhagic complications due to stroke revascularization therapies.

Noncontrast CT Scanning. Multiple studies have demonstrated that early ischemic changes, especially hypodensity on a noncontrast CT scan, are strongly associated with higher rates of thrombolysis-induced hemorrhage.[10,28,38] Unfortunately, during the first few hours of stroke symptom onset, these findings can be rather subtle and thus are interpreted with great variability, even by experienced clinicians. Current recommendations for imaging of acute ischemic stroke state that frank hypodensity on noncontrast CT scans, particularly if occupying more than one-third of the MCA territory, is a strong contraindication to treatment with IV thrombolytics owing to a high chance of hemorrhagic complication.[29]

Several scoring scales have been proposed in an attempt to simplify evaluation of noncontrast images when estimating risk of hemorrhagic transformation. The most commonly used scale, the ASPECTS, is a 10-point grading system that divides the MCA territory into 10 regions of interest.[5] Subcortical structures are allotted 3 points; MCA cortex is allotted 7 points; and 1 point is subtracted for each area displaying early ischemic change. Patients with ASPECTS below 8 are at substantially higher risk of thrombolysis-related ICH.[11]

Intracerebral hematomas in the setting of endovascular interventions can sometimes be mistaken for contrast medium. Hyperdense lesions of various degrees of intensity can be found in up to 50% of interventional cases, and some of these do not represent hemorrhage and are

benign. Early differentiation is clinically important when deciding whether to continue systemic anticoagulation therapy or treatment with antiplatelet agents. Yoon et al.[52] described 2 distinct imaging features of contrast medium in an attempt to differentiate it from hemorrhage. First is contrast enhancement, which shows rapid clearance of a hyperdense lesion on follow-up CT scans and does not produce any mass effect. Second is contrast extravasation, which is characterized by a mixture of blood and contrast material. It typically exhibits extremely high density on CT studies and, unlike contrast enhancement, is associated with poor neurological outcomes. Two illustrative cases of hyperdense signal due to contrast medium and ICH following interventional procedures are shown in Fig. 2. Disruption of the blood-brain barrier, especially at the core of the cerebral infarct, is believed to be the underlying mechanism of extensive contrast extravasation. An iodine-induced signal can be subtracted from the brain CT scan using dual-energy CT technology and virtual imaging, allowing accurate differentiation between ICH and iodinated contrast medium staining.[17] Although this technique does not require extra doses of radiation and appears to have great potential for clinical practice, its use at the present time is limited to major clinical research centers.

Computed Tomography Perfusion Imaging. The use of CT perfusion provides rapid assessment of hemodynamic parameters of the brain. With the introduction of 320–detector row CT perfusion scanners, perfusion maps of the whole brain (including posterior fossa structures) can now be rapidly obtained in minutes.[40] Two illustrative cases of CT perfusion findings in patients with ischemic stroke who received emergent endovascular interventions are shown in Figs. 3 and 4. Matched areas of decreased CBV, CBF, and MTT represent areas of the brain with irreversible ischemic damage.[31] When only CBF or MTT is compromised but CBV is preserved, indicating salvageable tissue known as "penumbra," recanalization techniques can reverse ischemic damage to the brain tissue. Identification of brain regions with decreased CBV, especially when combined with the ASPECTS grading system, can help identify patients who are at higher risk for hemorrhagic complications from both IV and IA therapies.[4,15] Larger infarct core size, which is characterized by significant loss of CBV, is a strong predictor of hemorrhage and poor outcomes. Given the wide availability of CT perfusion scanners and short imaging protocol times, CT perfusion is becoming more commonly used in evaluating patients with acute stroke.

The endovascular approach to acute stroke allows

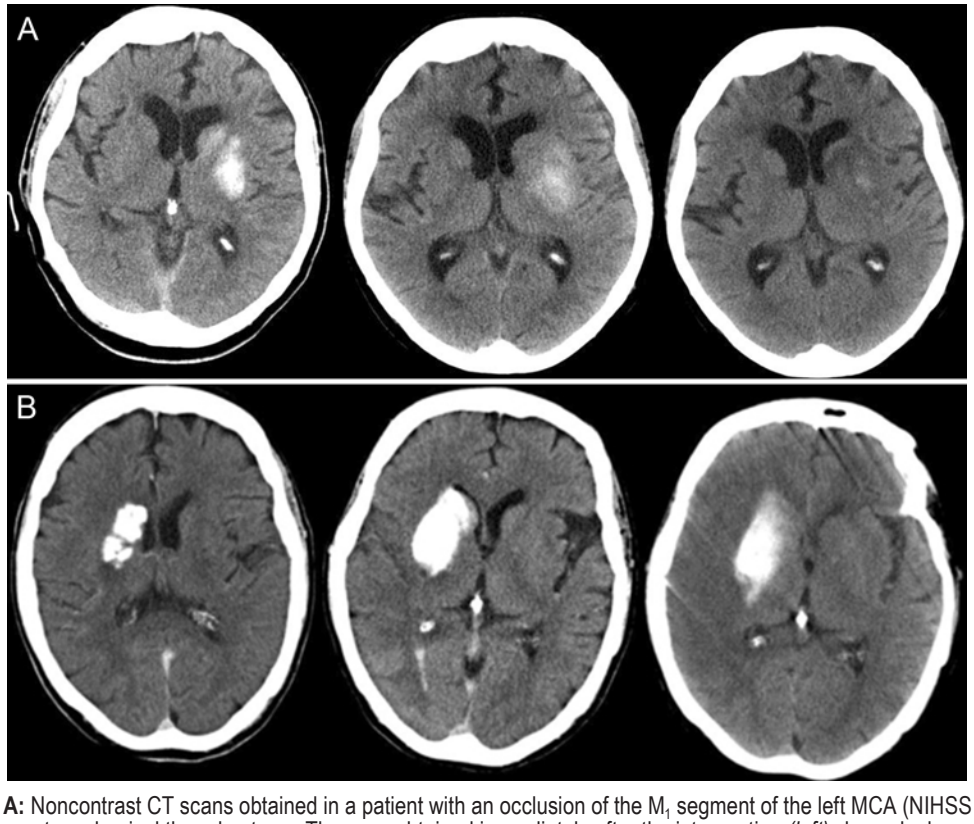

Fig. 2. **A:** Noncontrast CT scans obtained in a patient with an occlusion of the M_1 segment of the left MCA (NIHSS score 23) who underwent mechanical thrombectomy. The scan obtained immediately after the intervention *(left)* showed a hyperdense lesion in the left basal ganglia. The follow-up serial studies *(middle and right)* showed gradual resolution of the hyperdense signal, indicating that it represented contrast medium. **B:** Noncontrast CT scans obtained in a patient with a right M_1 occlusion (NIHSS score 14) who underwent mechanical thrombectomy. A bright hyperdense signal was seen on the study performed immediately after the procedure *(left)*. Extremely high signal intensity was suggestive of contrast medium. However, follow-up studies showed continuous growth of the lesion with significant mass effect indicative of newly developed parenchymal hemorrhage mixed with contrast material *(middle and right)*.

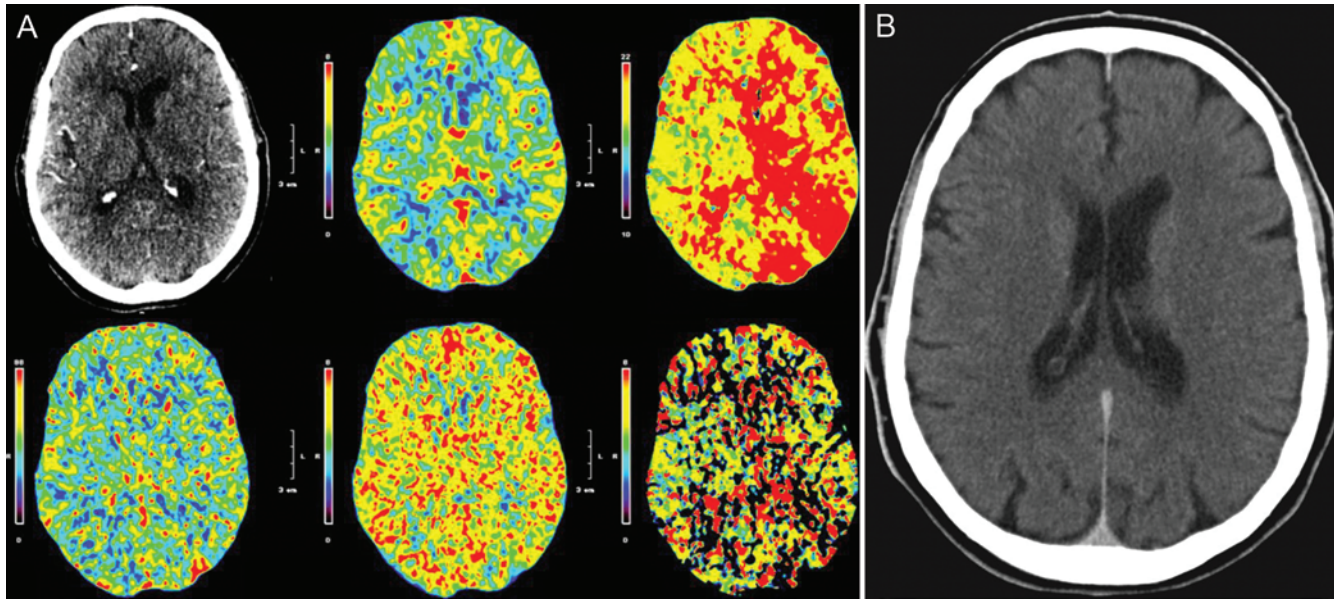

Fig. 3. **A:** Noncontrast CT scan and perfusion maps obtained in a patient with acute stroke from a left internal carotid artery occlusion (NIHSS score 12). The perfusion maps demonstrate markedly increased time-to-peak *(upper right)* in the left hemisphere but preserved CBV *(upper middle),* indicating a significant amount of brain tissue at risk (penumbra). The patient subsequently underwent mechanical thrombectomy. **B:** Follow-up CT scan showing no postintervention hemorrhage.

extension of the treatment window compared with IV thrombolysis. A real-world experience with patient selection for endovascular therapy on the basis of CT perfusion findings shows a similar rate of ICH in those who had favorable CT perfusion findings irrespective of time constraints and those who had time-guided selection (0–6 hours from symptom onset to endovascular procedure).[47] This suggests that in properly selected patients, ischemic stroke can be safely treated beyond the current recommended time intervals without significantly increasing the rate of hemorrhagic complications.

Management

In contrast to several existing reports of well-defined clinical, laboratory, and radiographic risk factors and predictors, few studies have addressed efficacy of management strategies in ICH secondary to revascularization therapies in acute ischemic stroke. Therefore, general principles that apply to management of spontaneous ICH might not be as effective for thrombolysis-induced ICH.

Medical Management

According to the American Heart Association guidelines, infusion of platelets and cryoprecipitate is recommended to reverse coagulopathy secondary to systemic administration of tPA.[6] Intraarterial stroke interventions often include use of heparin infusion; in these cases, protamine sulfate can be used to reverse the systemic effect of heparin. However, the guidelines do not address the optimal range of blood pressure parameters. Large parenchymal hemorrhages (PH-2 according to the ECASS classification) strongly correlate with poor neurological outcome and high mortality rate, whereas petechial hemorrhages do not seem to affect long-term outcomes.[13] Therefore, more aggressive blood pressure management might be justified in cases of thrombolysis complicated by large parenchymal hematomas. On the other hand, patients with strokes with smaller petechial hemorrhages might benefit from a less aggressive approach allowing higher blood pressure to preserve blood perfusion to the "penumbra." A quantitative analysis of hematoma volumes and blood pressure measurements during and immediately after IV tPA administration showed that early blood pressure reduction can have a significant effect on hematoma expansion.[33] The majority of patients included in this study had at least one blood pressure reading above the American Heart Association's recommended 180/105 mm Hg parameters, demonstrating that deviations from treatment protocols are associated with higher rates of ICH.[1] Blood pressure variability—not just an increase in absolute blood pressure parameters—might also contribute to hemorrhagic transformation. Patients with higher variability of both systolic and diastolic blood pressure measurements showed increased rates of hemorrhagic transformation, possibly due to rupture of vessels within the ischemic core as a result of sudden rises in blood pressure.[27]

In a retrospective analysis of data from patients with ICH secondary to IV and IA thrombolysis, Goldstein at al.[16] found great variability in treatment protocols, including use of fresh frozen plasma, platelets, cryoprecipitate, phytonadione, and aminocaproic acid. Analysis of treatment records showed that very few patients received the same treatment regimen. The small number of patients with data available for analysis and the wide range of treatment strategies precluded the determination of whether any specific therapy was associated with improved clinical outcomes. Forty percent of patients showed a significant increase in hematoma size, despite

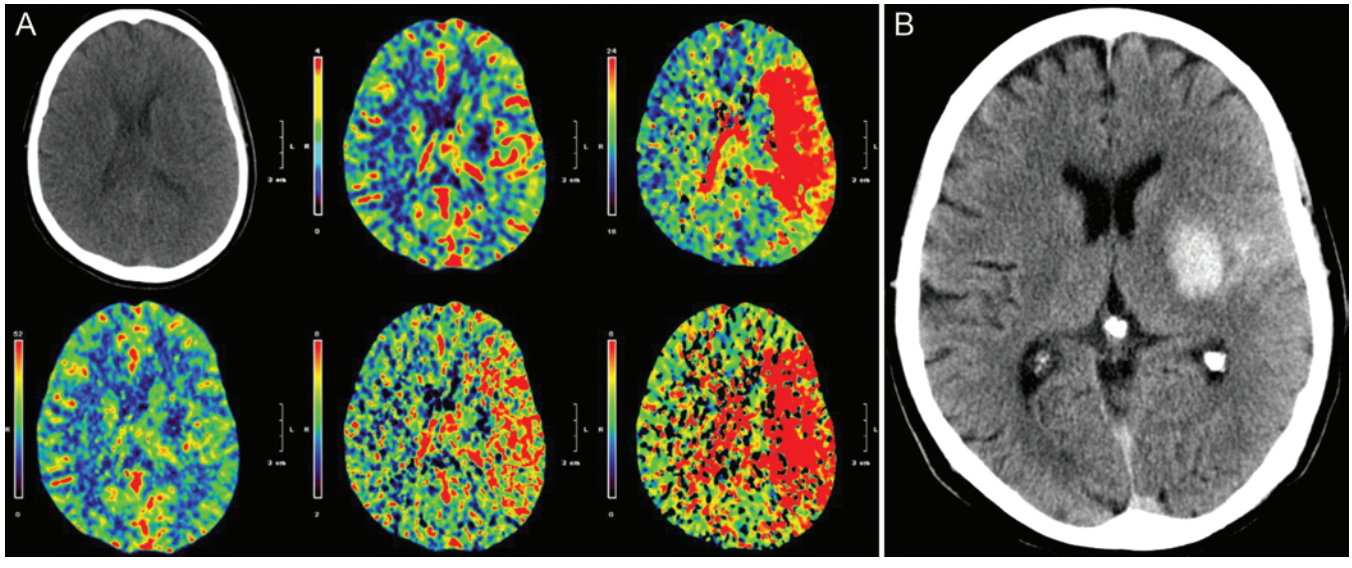

Fig. 4. **A:** Noncontrast CT scan and perfusion maps obtained in a patient with a left M_2 superior trunk occlusion (NIHSS score 12), showing a large area of increased MTT and time-to-peak penumbra, indicating potentially salvageable brain (*upper middle* and *bottom middle*, respectively). However, the perfusion mapping shows significant signal loss in the left basal ganglia *(upper middle)*. **B:** Noncontrast CT scan obtained following mechanical thrombectomy and angioplasty, showing a parenchymal hematoma in the left basal ganglia.

reversal of coagulopathy. Rapid hematoma expansion due to IV thrombolysis with tPA was confirmed by another recent study that reported an even more dramatic 74% increase in the size of the ICH, as demonstrated by 2 serial CT scans performed only 9 hours apart.[33] These 2 studies clearly show that more effective treatment strategies are needed to achieve better control of hematoma expansion.

Surgical Management

To date, the effect of decompressive surgery in patients with revascularization therapy–induced ICH has not been studied in a randomized trial. In patients with malignant MCA strokes, 3 randomized clinical trials (Decompressive Craniectomy in Malignant Middle Cerebral Artery Infarcts [DECIMAL], Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery [DESTINY], and Hemicraniectomy After Middle Cerebral Artery Infarction with Life-threatening Edema Trial [HAMLET]) showed that hemicraniectomy performed within the first 48 hours of stroke onset leads to reduction of mortality and improvement of functional outcomes compared with medical therapy alone.[24,27,47] However, patients who received IV thrombolysis or had hemorrhagic transformation resulting in a large parenchymal hematoma were excluded from enrollment in all three trials.

Williams et al.[51] reported 2 cases of patients who underwent decompressive hemicraniectomy postthrombolysis. No significant intraprocedural complications related to thrombolysis were noted, and both patients had favorable outcomes. In neither case was there any hemorrhagic component to the initial stroke. Opposite results were demonstrated in a study investigating in-hospital mortality in a large cohort of patients from multiple hospitals in the US who underwent hemicraniectomy for large ischemic strokes.[3] Mortality rates were significantly higher in patients who were treated with thrombolysis and subsequently underwent hemicraniectomy for life-threatening brain edema than in patients who were treated with thrombolysis and did not undergo hemicraniectomy. No information was provided whether any patients in the hemicraniectomy group had thrombolysis-related ICH.

In one case report, a young patient with a left MCA stroke who was treated with a combination of IV thrombolysis and IA thromboaspiration developed a large insular hematoma immediate after the intervention and underwent emergent craniectomy and hematoma evacuation.[12] Despite a high initial NIHSS score of 24, the patient made a significant recovery. In the study by Mokin et al.[33] cited above, 3 patients with thrombolysis-induced ICH were treated surgically. One patient had PH-1; 2 patients had PH-2. Details of the surgical procedures were not provided.

The limited number of publications suggests that surgical evacuation of ICH after tPA or endovascular stroke intervention is uncommon. More research is required to determine which patients with ICH secondary to IV or IA revascularization therapy can benefit from a surgical approach. Given the relatively low number of such cases, however, it is unlikely that a randomized trial addressing this subject will be conducted in the near future.

Conclusions

A review of the literature demonstrates that the occurrence of ICH after IV tPA thrombolysis or endovascular stroke intervention is multifactorial. Variability in the definition of ICH associated with either treatment approach provides some limitations in the ability to draw definitive conclusions from pooling the several large studies described in this report. Prevention of ICH in this setting involves careful patient selection using pre-

viously described clinical and radiographic predictors of ICH and conscientious management of blood pressure and glucose values during and following IV thrombolysis and IA interventions. Management of revascularization therapy–induced ICH (by comparison with hemorrhage outside the ischemic realm) focuses on reversal of anticoagulation and/or antiplatelet effects of medications while instituting a tempered antihypertensive strategy without inducing hypotension. Surgical evacuation of ICH after tPA or endovascular stroke intervention is uncommon, and further studies are needed to determine which patients can benefit from such an approach.

Disclosure

Drs. Abla, Dumont, Kan, and Mokin report no financial relationships. Dr. Hopkins receives grant/research support from Toshiba; serves as a consultant to Abbott Vascular, Boston Scientific, Cordis, Micrus, and W.L. Gore; holds a financial interest in AccessClosure, Augmenix, Boston Scientific, Claret Medical Inc., Micrus, and Valor Medical; has (or had) a board/trustee/officer position with AccessClosure, Claret Medical Inc., and Micrus (until September 2010); belongs to the Abbott Vascular speakers' bureau; and receives honoraria from Bard, Boston Scientific, Cordis, Memorial Healthcare System, Complete Conference Management, SCAI, and Cleveland Clinic. Dr. Kass-Hout has received a research grant from Genentech. Dr. Levy receives research grant support (principal investigator: Stent-Assisted Recanalization in acute Ischemic Stroke, SARIS), other research support (devices), and honoraria from Boston Scientific and research support from Codman & Shurtleff, Inc. and ev3/Covidien Vascular Therapies; has ownership interests in Intratech Medical Ltd. and Mynx/Access Closure; serves as a consultant on the board of scientific advisors to Codman & Shurtleff, Inc.; serves as a consultant per project and/or per hour for Codman & Shurtleff, Inc., ev3/Covidien Vascular Therapies, and TheraSyn Sensors, Inc.; and receives fees for carotid stent training from Abbott Vascular and ev3/Covidien Vascular Therapies. Dr. Levy receives no consulting salary arrangements. All consulting is per project and/or per hour. (Note regarding the previously listed relationships with Boston Scientific: Boston Scientific's neurovascular business has been acquired by Stryker.) Dr. Siddiqui has received research grants from the National Institutes of Health (coinvestigator: NINDS 1R01NS064592-01A1, Hemodynamic induction of pathologic remodeling leading to intracranial aneurysms; not related to present manuscript) and the University at Buffalo (research development award); holds financial interests in Hotspur, Intratech Medical, StimSox, and Valor Medical; serves as a consultant to Codman & Shurtleff, Inc., Concentric Medical, ev3/Covidien Vascular Therapies, GuidePoint Global Consulting, and Penumbra; belongs to the speakers' bureaus of Codman & Shurtleff, Inc. and Genentech; serves on an advisory board for Codman & Shurtleff; and has received honoraria from Abbott Vascular, the AANS (for courses), Genentech, Neocure Group LLC, an emergency medicine conference, and from Abbott Vascular and Codman & Shurtleff, Inc. for training other neurointerventionists in carotid stent placement and for training physicians in endovascular stent placement for aneurysm treatment. Dr. Siddiqui has no consulting salary arrangements; all consulting is per project and/or per hour. Dr. Snyder serves as a consultant to, serves as a member of the speakers' bureau of, and has received honoraria from Toshiba. He serves as a member of the speakers' bureau for ev3 and The Stroke Group (consultants to the healthcare industry) and has received honoraria from these entities.

Author contributions to the study and manuscript preparation include the following. Conception and design: Levy, Mokin, Siddiqui. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting the article: Mokin. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors.

Acknowledgments

The authors thank Paul H. Dressel, B.F.A., for assistance with preparation of the illustrations and Debra J. Zimmer, A.A.S., C.M.A.-A., for editorial assistance.

References

1. Adams HP Jr, del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, et al: Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. **Stroke 38:**1655–1711, 2007
2. Alexandrov AV, Black SE, Ehrlich LE, Caldwell CB, Norris JW: Predictors of hemorrhagic transformation occurring spontaneously and on anticoagulants in patients with acute ischemic stroke. **Stroke 28:**1198–1202, 1997
3. Alshekhlee A, Horn C, Jung R, Alawi AA, Cruz-Flores S: In-hospital mortality in acute ischemic stroke treated with hemicraniectomy in US hospitals. **J Stroke Cerebrovasc Dis 20:**196–201, 2011
4. Aviv RI, Mandelcorn J, Chakraborty S, Gladstone D, Malham S, Tomlinson G, et al: Alberta Stroke Program Early CT Scoring of CT perfusion in early stroke visualization and assessment. **AJNR Am J Neuroradiol 28:**1975–1980, 2007
5. Barber PA, Demchuk AM, Zhang J, Buchan AM: Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT Score. **Lancet 355:**1670–1674, 2000
6. Broderick J, Connolly S, Feldmann E, Hanley D, Kase C, Krieger D, et al: Guidelines for the management of spontaneous intracerebral hemorrhage in adults: 2007 update: a guideline from the American Heart Association/American Stroke Association Stroke Council, High Blood Pressure Research Council, and the Quality of Care and Outcomes in Research Interdisciplinary Working Group. **Stroke 38:**2001–2023, 2007
7. Cocho D, Belvís R, Martí-Fàbregas J, Molina-Porcel L, Díaz-Manera J, Aleu A, et al: Reasons for exclusion from thrombolytic therapy following acute ischemic stroke. **Neurology 64:** 719–720, 2005
8. del Zoppo GJ, Higashida RT, Furlan AJ, Pessin MS, Rowley HA, Gent M: PROACT: a phase II randomized trial of recombinant pro-urokinase by direct arterial delivery in acute middle cerebral artery stroke. PROACT Investigators. Prolyse in Acute Cerebral Thromboembolism. **Stroke 29:**4–11, 1998
9. Demchuk AM, Morgenstern LB, Krieger DW, Linda Chi T, Hu W, Wein TH, et al: Serum glucose level and diabetes predict tissue plasminogen activator-related intracerebral hemorrhage in acute ischemic stroke. **Stroke 30:**34–39, 1999
10. Dubey N, Bakshi R, Wasay M, Dmochowski J: Early computed tomography hypodensity predicts hemorrhage after intravenous tissue plasminogen activator in acute ischemic stroke. **J Neuroimaging 11:**184–188, 2001
11. Dzialowski I, Hill MD, Coutts SB, Demchuk AM, Kent DM, Wunderlich O, et al: Extent of early ischemic changes on computed tomography (CT) before thrombolysis: prognostic value of the Alberta Stroke Program Early CT Score in ECASS II. **Stroke 37:**973–978, 2006
12. Fargen KM, Hoh BL, Fautheree GL, Morgan WR, Velat GJ, Waters MF, et al: Aggressive intervention to treat a young woman with intracranial hemorrhage following unsuccessful intravenous thrombolysis for left middle cerebral artery occlusion. Case report. **J Neurosurg 115:**359–363, 2011
13. Fiorelli M, Bastianello S, von Kummer R, del Zoppo GJ, Lar-

rue V, Lesaffre E, et al: Hemorrhagic transformation within 36 hours of a cerebral infarct: relationships with early clinical deterioration and 3-month outcome in the European Cooperative Acute Stroke Study I (ECASS I) cohort. **Stroke 30:**2280–2284, 1999
14. Furlan A, Higashida R, Wechsler L, Gent M, Rowley H, Kase C, et al: Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. Prolyse in Acute Cerebral Thromboembolism. **JAMA 282:**2003–2011, 1999
15. Gasparotti R, Grassi M, Mardighian D, Frigerio M, Pavia M, Liserre R, et al: Perfusion CT in patients with acute ischemic stroke treated with intra-arterial thrombolysis: predictive value of infarct core size on clinical outcome. **AJNR Am J Neuroradiol 30:**722–727, 2009
16. Goldstein JN, Marrero M, Masrur S, Pervez M, Barrocas AM, Abdullah A, et al: Management of thrombolysis-associated symptomatic intracerebral hemorrhage. **Arch Neurol 67:**965–969, 2010
17. Gupta R, Phan CM, Leidecker C, Brady TJ, Hirsch JA, Nogueira RG, et al: Evaluation of dual-energy CT for differentiating intracerebral hemorrhage from iodinated contrast material staining. **Radiology 257:**205–211, 2010
18. Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, et al: Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. **N Engl J Med 359:**1317–1329, 2008
19. Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, von Kummer R, et al: Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. **JAMA 274:**1017–1025, 1995
20. Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, et al: Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). **Lancet 352:**1245–1251, 1998
21. Hills NK, Johnston SC: Why are eligible thrombolysis candidates left untreated? **Am J Prev Med 31 (6 Suppl 2):**S210–S216, 2006
22. Hirsch JA, Yoo AJ, Nogueira RG, Verduzco LA, Schwamm LH, Pryor JC, et al: Case volumes of intra-arterial and intravenous treatment of ischemic stroke in the USA. **J Neurointerv Surg 1:**27–31, 2009
23. IMS II Trial Investigators: The Interventional Management of Stroke (IMS) II Study. **Stroke 38:**2127–2135, 2007
24. IMS Study Investigators: Combined intravenous and intra-arterial recanalization for acute ischemic stroke: the Interventional Management of Stroke Study. **Stroke 35:**904–911, 2004
25. Khatri P, Broderick JP, Khoury JC, Carrozzella JA, Tomsick TA: Microcatheter contrast injections during intra-arterial thrombolysis may increase intracranial hemorrhage risk. **Stroke 39:**3283–3287, 2008
26. Khatri R, Khatri P, Khoury J, Broderick J, Carrozzella J, Tomsick T: Microcatheter contrast injections during intra-arterial thrombolysis increase intracranial hemorrhage risk. **J Neurointerv Surg 2:**115–119, 2010
27. Ko Y, Park JH, Yang MH, Ko SB, Han MK, Oh CW, et al: The significance of blood pressure variability for the development of hemorrhagic transformation in acute ischemic stroke. **Stroke 41:**2512–2518, 2010
28. Larrue V, von Kummer R, Müller A, Bluhmki E: Risk factors for severe hemorrhagic transformation in ischemic stroke patients treated with recombinant tissue plasminogen activator: a secondary analysis of the European-Australasian Acute Stroke Study (ECASS II). **Stroke 32:**438–441, 2001
29. Latchaw RE, Alberts MJ, Lev MH, Connors JJ, Harbaugh RE, Higashida RT, et al: Recommendations for imaging of acute ischemic stroke: a scientific statement from the American Heart Association. **Stroke 40:**3646–3678, 2009
30. Lindsberg PJ, Roine RO: Hyperglycemia in acute stroke. **Stroke 35:**363–364, 2004
31. Lui YW, Tang ER, Allmendinger AM, Spektor V: Evaluation of CT perfusion in the setting of cerebral ischemia: patterns and pitfalls. **AJNR Am J Neuroradiol 31:**1552–1563, 2010
32. Mackey J, Khatri P, Broderick JP: Increasing use of CT angiography in interventional study sites: the IMS III experience. **AJNR Am J Neuroradiol 31:**E34, 2010 (Letter)
33. Mokin M, Kass-Hout T, Kass-Hout O, Zivadinov R, Mehta B: Blood pressure management and evolution of thrombolysis-associated intracerebral hemorrhage in acute ischemic stroke. **J Stroke Cerebrovasc Dis** [epub ahead of print], 2011
34. Moulakakis KG, Mylonas SN, Sfyroeras GS, Andrikopoulos V: Hyperperfusion syndrome after carotid revascularization. **J Vasc Surg 49:**1060–1068, 2009
35. Natarajan SK, Dandona P, Karmon Y, Yoo AJ, Kalia JS, Hao Q, et al: Prediction of adverse outcomes by blood glucose level after endovascular therapy for acute ischemic stroke. Clinical article. **J Neurosurg 114:**1785–1799, 2011
36. Natarajan SK, Snyder KV, Siddiqui AH, Ionita CC, Hopkins LN, Levy EI: Safety and effectiveness of endovascular therapy after 8 hours of acute ischemic stroke onset and wake-up strokes. **Stroke 40:**3269–3274, 2009
37. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group: Tissue plasminogen activator for acute ischemic stroke. **N Engl J Med 333:**1581–1587, 1995
38. NINDS t-PA Stroke Study Group: Intracerebral hemorrhage after intravenous t-PA therapy for ischemic stroke. **Stroke 28:**2109–2118, 1997
39. Ogasawara K, Sakai N, Kuroiwa T, Hosoda K, Iihara K, Toyoda K, et al: Intracranial hemorrhage associated with cerebral hyperperfusion syndrome following carotid endarterectomy and carotid artery stenting: retrospective review of 4494 patients. **J Neurosurg 107:**1130–1136, 2007
40. Orrison WW Jr, Snyder KV, Hopkins LN, Roach CJ, Ringdahl EN, Nazir R, et al: Whole-brain dynamic CT angiography and perfusion imaging. **Clin Radiol 66:**566–574, 2011
41. Penumbra Pivotal Stroke Trial Investigators: The penumbra pivotal stroke trial: safety and effectiveness of a new generation of mechanical devices for clot removal in intracranial large vessel occlusive disease. **Stroke 40:**2761–2768, 2009
42. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, et al: Heart disease and stroke statistics—2011 update: a report from the American Heart Association. **Circulation 123:**e18–e209, 2011
43. Smith WS, Sung G, Saver J, Budzik R, Duckwiler G, Liebeskind DS, et al: Mechanical thrombectomy for acute ischemic stroke: final results of the Multi MERCI trial. **Stroke 39:**1205–1212, 2008
44. Smith WS, Sung G, Starkman S, Saver JL, Kidwell CS, Gobin YP, et al: Safety and efficacy of mechanical embolectomy in acute ischemic stroke: results of the MERCI trial. **Stroke 36:**1432–1438, 2005
45. Strbian D, Sairanen T, Meretoja A, Pitkäniemi J, Putaala J, Salonen O, et al: Patient outcomes from symptomatic intracerebral hemorrhage after stroke thrombolysis. **Neurology 77:** 341–348, 2011
46. Tanne D, Kasner SE, Demchuk AM, Koren-Morag N, Hanson S, Grond M, et al: Markers of increased risk of intracerebral hemorrhage after intravenous recombinant tissue plasminogen activator therapy for acute ischemic stroke in clinical practice: the Multicenter rt-PA Stroke Survey. **Circulation 105:**1679–1685, 2002
47. Turk A, Magarik JA, Chaudry I, Turner RD, Nicholas J, Holmstedt CA, et al: CT perfusion-guided patient selection for endovascular treatment of acute ischemic stroke is safe and effective. **J Neurointerv Surg** [epub ahead of print], 2011
48. van Mook WN, Rennenberg RJ, Schurink GW, van Oostenbrugge RJ, Mess WH, Hofman PA, et al: Cerebral hyperperfusion syndrome. **Lancet Neurol 4:**877–888, 2005
49. Wahlgren N, Ahmed N, Dávalos A, Ford GA, Grond M, Hacke

W, et al: Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. **Lancet 369:**275–282, 2007
50. Weintraub MI: Thrombolysis (tissue plasminogen activator) in stroke: a medicolegal quagmire. **Stroke 37:**1917–1922, 2006
51. Williams A, Sittampalam M, Barua N, Mohd Nor A: Case series of post-thrombolysis patients undergoing hemicraniectomy for malignant anterior circulation ischaemic stroke. **Cardiovasc Psychiatry Neurol 2011:**254569, 2011
52. Yoon W, Seo JJ, Kim JK, Cho KH, Park JG, Kang HK: Contrast enhancement and contrast extravasation on computed tomography after intra-arterial thrombolysis in patients with acute ischemic stroke. **Stroke 35:**876–881, 2004

Manuscript submitted December 7, 2011.
Accepted January 27, 2012.
Please include this information when citing this paper: DOI: 10.3171/2012.1.FOCUS11352.
Address correspondence to: Elad I. Levy, M.D., University at Buffalo Neurosurgery, 100 High Street, Suite B4, Buffalo, New York 14203. email: elevy@ubns.com.

Neurosurg Focus 32 (4):E3, 2012

Minimally invasive treatment for intracerebral hemorrhage

Emun Abdu, M.D.,[1] Daniel F. Hanley, M.D.,[2] and David W. Newell, M.D.[1]

[1]Department of Neurosurgery, Swedish Neuroscience Institute, Seattle, Washington; and [2]Brain Injury Outcomes Center, The Johns Hopkins University School of Medicine, Baltimore, Maryland

Spontaneous intracerebral hemorrhage is a serious public health problem and is fatal in 30%–50% of all occurrences. The role of open surgical management of supratentorial intracerebral hemorrhage is still unresolved. A recent consensus conference sponsored by the National Institutes of Health suggests that minimally invasive techniques to evacuate clots appear to be a promising area and warrant further investigation. In this paper the authors review past, current, and potential future methods of treating intraparenchymal hemorrhages with minimally invasive techniques and review new data regarding the role of stereotactically placed catheters and thrombolytics.
(http://thejns.org/doi/abs/10.3171/2012.1.FOCUS11362)

Key Words • **intracerebral hemorrhage** • **sonothrombolysis** • **tissue plasminogen activator** • **intraventricular hemorrhage**

Spontaneous ICH is a serious public health problem accounting for 10%–15% of strokes.[34] In the United States, 60,000–120,000 patients suffer from hemorrhagic strokes each year, and the incidence has been increasing due to an aging population in addition to an increased use of anticoagulation and antiplatelet agents for thromboembolic diseases. On average, only 20%–40% of those who suffer an ICH are expected to have functional outcomes at 6 months.[9] Moreover, the cost of care for patients with ICH is among the highest of all brain disorders.[39] Half of the patients with ICH will die in the hospital after requiring expensive ICU care, and an additional 30% will survive as dependents requiring long-term care and rehabilitation.

Common causes of spontaneous ICH include hypertension, anticoagulation, and amyloid angiopathy. The presenting neurological signs and symptoms are dependent on the size, location, and degree of mass effect of the clot. In an autopsy study of hypertensive hemorrhages, the common locations were external capsule in 42%, pons in 16%, thalamus in 15%, cerebellum in 12%, and white matter in 10%.[12] The 1-year mortality rates for ICH vary depending on location: 65% for brainstem, 57% for lobar, 51% for deep, and 42% for cerebellar.[11] Frequently, ICH is complicated by IVH, which can lead to obstructive hydrocephalus, thereby independently increasing the mortality rate to as high as 80%.[14,30,41]

Unlike cerebellar hemorrhages in which there are more defined medical and surgical management pathways, surgical treatment of supratentorial ICH, specifically deep subcortical and basal ganglia hemorrhages, is controversial. The principal aims of treatment are preventing further hemorrhage, reducing ICP, controlling cerebral perfusion pressure, and reducing mass effect when possible.

Deep lesions (that is, those in the basal ganglia or brainstem) have a dismal prognosis, and open surgical evacuation does not appear to improve the patient's outcome compared with medical management. Historically, there has been no role for open surgery in such cases.[32] Surgery is believed to save lives by decreasing ICP in select patients, but it does not necessarily result in restoration of meaningful functional status. In cases in which supratentorial ICH is surgically treated, removal of the ICH reduces mass effect, and it also removes the neurotoxic blood products, helping to prevent edema and secondary brain injury.[34]

Abbreviations used in this paper: CLEAR = Clot lysis: Evaluating accelerated resolution of intraventricular hemorrhage; EVD = external ventricular drainage; GCS = Glasgow Coma Scale; ICH = intracerebral hemorrhage; ICP = intracranial pressure; IVH = intraventricular hemorrhage; MIS = minimally invasive surgery; MISTIE = Minimally Invasive Surgery plus T-PA for Intracerebral Hemorrhage Evacuation; mRS = modified Rankin Scale; NIH = National Institutes of Health; NIHSS = NIH Stroke Scale; rt-PA = recombinant tissue plasminogen activator; SLEUTH = Safety of Lysis with EKOS Ultrasound in the Treatment of Intracerebral and Intraventricular Hemorrhage; STICH = Surgical Trial in Traumatic intraCerebral Haemorrhage.

Open surgery is relatively contraindicated due to the frequent medical comorbidities that these patients have. Moreover, surgeons are often reluctant to make an extensive corticotomy through uninjured brain to evacuate deep ICHs. An ideal technique for ICH evacuation would be one that minimizes brain manipulation and one that could also be performed under minimal anesthesia, preferably at the bedside. This approach may offset the added morbidity of surgery, especially for deep lesions and those that are too unstable to undergo any major operative intervention.

Current NIH Consensus

In 2007, a consensus conference was sponsored by the NIH to try to establish priorities for further investigation into the most promising therapies for the management of spontaneous ICH. A number of different medical and surgical therapies were examined. The mainstay of medical management for intracranial hemorrhage includes reversal of anticoagulation (international normalized ratio < 1.4), treatment of hypertension, treatment of increased ICP with osmotic diuretics or hypertonic saline, and placement of an EVD catheter for IVH.[6] The primary goal of lowering blood pressure is to prevent continued hemorrhage and rehemorrhage without drastically lowering cerebral perfusion pressure in those patients who have high ICP. There is incomplete evidence to support specific blood pressure parameters; therefore, until such randomized studies exist to suggest a specific goal, the American Stroke Association guidelines recommend maintaining blood pressure lower than 180 mm Hg in the acute period with short-acting antihypertensive agents while concurrently paying attention to cerebral perfusion pressure in patients in whom clear signs of increased ICP are shown both clinically and on images.[30,33] Furthermore, for those without clear clinical signs of increased ICP, aggressive lowering of blood pressure is recommended.

Treatment with procoagulants, such as factor VIIa, were thought to be theoretically beneficial by promoting hemostasis at sites of vascular injury and by limiting further enlargement of hemorrhage.[20] The FAST (Factor VIIa for Acute Hemorrhagic Stroke) study was a Phase III prospective randomized trial to determine the efficacy of factor VIIa in patients with ICH who presented within 3 hours of symptoms onset. Although this was a promising theory, this large multicenter study did not confirm better functional outcomes despite producing significant reduction in the rate of hematoma expansion.[19] Therefore, the use of factor VIIa is currently not recommended in the treatment of patients with ICH.

Surgical Therapy

Evaluation of outcomes in most large studies of open surgery can be difficult because of the lack of subcategorization of patients depending on location, size, degree of brain destruction, and comorbidity, as well as other factors. Evacuation of ICH via craniotomy is the most commonly used surgical treatment for ICH. However, its benefits are marginal at best, and its uses remain controversial.[32,36] A meta-analysis of multiple prior surgical trials has not shown benefit for ICH evacuation over nonsurgical treatment. The largest among these, the STICH trial, was a prospective study of 1033 patients from 107 centers over an 8-year period in which patients were randomized to surgery or best medical management.[21] Its results indicated that surgical evacuation did not appear to be helpful in treating supratentorial ICH.[21] However, in a subset of patients presenting with superficial hematomas without IVHs, 49% of patients achieved favorable outcomes compared with 37% of those treated conservatively.[22] Since the initial trial was not sufficiently powered to examine this subgroup, the STICH II study is now ongoing to further determine whether open surgical evacuation is beneficial in cases of superficially located ICH.

Despite the fact that surgical studies to date have shown that craniotomy is not the mainstay of treating unselected cases, the current nonsurgical management is insufficient, especially in cases with mass effect and secondary deterioration. There is growing evidence that there is value in evacuating the clot and decreasing mass effect, subsequently reducing a further cascade of injury due to the presence of hemorrhage (edema, apoptosis, necrosis, and inflammation).[34,35] Hence, one of the outcomes from the 2007 NIH consensus statement was that minimally invasive techniques to evacuate clots seemed to be a promising area for further investigation based on favorable results in various studies and case series.[6] Minimally invasive therapeutic modalities have become more attractive in treating ICH over craniotomy for various reasons, including short operative time, the potential for performing them at the bedside, and minimizing the potential exacerbation of secondary brain trauma through the avoidance of larger corticotomies and brain retraction.

Minimally Invasive Therapy: Mechanical and Pharmacological Approaches

The earliest work on mechanical thrombectomy was conducted using a stereotactic approach to drain clots via a cannula.[5] This was done prior to the CT era, and localization was based on the clinical examination and evaluation of vessel displacement on cerebral angiography.[5] Knowing that the lateral lenticulostriate arteries were responsible for most hypertensive ICHs, the authors aimed a rigid cannula to the lateral lenticulostriate arteries using plain skull radiographs and a stereotactic apparatus. Although the clinical outcome was poor, the authors were able to localize the ICH and perform drainage in 12 of 13 patients.

This minimally invasive technique has been further developed since the advent of CT scanning. The introduction of stereotactic systems such as the Leksell frame further improved accuracy of localizing the clot. However, because most acute hematomas are solid, clots clogging the drainage system were noted to be a problem. Several modifications of clot-evacuating instruments have been made to overcome this issue. Backlund and von Host[4] used CT scanning for the stereotactic localization of hematomas and used a device that evacuated the clot by the Archimedes

principle, in which an outer cannula is attached to suction and an inner screw is rotated to mechanically break the clot. This was a novel technique that facilitated mechanical clot lysis, and since the advent of this device, others have reported larger case series showing that mechanical lysis facilitates clot removal.[16,17] Hondo et al.[15] tried to overcome this using an ultrasound aspirator to facilitate mechanical clot lysis. Nizzuma and Suzuki[28,29] left a drain in the cavity after the aspiration of a hematoma and injected urokinase to facilitate pharmacological lysis. They reported promising outcomes at 6 months.

Endoscopy-guided aspiration has also been investigated with use of a single bur hole and endoscope. In 1989, Auer et al.[3] reported the first randomized controlled trial comparing the difference between endoscopically assisted aspirations and pure medical management. At 6 months, there was decreased mortality and a trend toward better outcomes in the surgical group, but these benefits were limited to lobar hematomas and to patients younger than 60 years.

Urokinase[26] and streptokinase were the initial common agents for thrombolysis, but recently the use of rt-PA has become more prevalent. Rohde et al.[38] reported that IVH cleared earlier with rt-PA than urokinase by 5 days. Hanley and colleagues have extensively studied the role of rt-PA in ICH and IVH (unpublished data). These authors performed multiple prospective studies to assess safety, optimum dose, and interval for treatment using rt-PA for IVH (CLEAR studies) and ICH (MISTIE studies).

These studies laid out the principles for successful minimally invasive operative intervention, which included subtotal evacuation to relieve mass effect but enough to tamponade and prevent rehemorrhage, avoid injury to normal brain, provide accurate localization using stereotaxy, and facilitate lysis of clot either mechanically, via thrombolytics, or both. Table 1 outlines these initial case reports and series depicting the method of clot evacuation and outcomes.

Intraventricular Hemorrhage Trials

The CLEAR study is a multicenter blinded prospective safety trial comparing best medical/ICU care with aggressive ventricular drainage with rt-PA injected into ventricular catheters at a dose of 3 mg every 12 hours.[25] The study enrolled 48 patients. Symptomatic bleeding was noted in 23% of the rt-PA group and in 5% in the placebo group ($p = 0.1$). Mortality was 19% in the rt-PA group and 23% in the placebo group. The clot resolution rate was significantly increased in the rt-PA group (18% vs 8%, $p < 0.001$). The rt-PA group also underwent earlier removal of the EVD catheter and relied less on exchanging EVD catheters due to clot obstruction of catheters. They also noted clinical improvement by an increase in GCS scores at 4 days within the rt-PA group.

This initial safety study was not designed to assess long-term functional outcome. Patients with significant impairment at presentation could take more than 30 days to recover consciousness; therefore, functional outcomes are better studied at longer time intervals.[24,42] The CLEAR III trial is a current ongoing trial that will assess functional performance in a 90- to 180-day time frame.

Intraparenchymal Hemorrhage Trials

Lippitz[18] and Schaller[40] and their colleagues conducted a study for thrombolytic treatment of ICH by injecting rt-PA every 12–24 hours via a drain stereotactically placed in the hematoma cavity. Lippitz et al. used 3 mg rt-PA delivered through a stereotactically placed catheter; depending on residual ICH on CT at 24 hours, rt-PA treatment was repeated for 1–3 days. Schaller et al. further calculated the dose of rt-PA relative to the maximum hematoma diameter of 1 cm for 1 mg rt-PA. Doses were repeated every 24 hours for a total of 3 days of treatment if necessary. Morgan et al.[23] conducted a prospective study consisting of ICH aspiration via a stereotactically placed catheter and rt-PA injection starting 12 hours after onset of symptoms in patients with supratentorial ICH regardless of the depth of ICH. Aspiration was repeated after 24 hours. If subsequent CT scanning showed significant hematoma, the procedure was repeated for up to 3 days or until the hematoma was smaller than 15 cm^3.

The MISTIE trial was a Phase II study for ICH treatment.[13] The trial evaluated the safety, efficacy, and surgical performance, including accuracy of catheter placement and volume of ICH reduction at the end of treatment. Forty patients were randomized to MIS plus rt-PA or medical therapy. The rt-PA dose used was 0.3, 1, or 3 mg. The patients' profiles included a mean age of 62 ± 11 years, location in the basal ganglia (in 58%) and lobar area (in 42%), GCS score lower than 14, NIHSS score greater than 6, and an ICH larger than 25 cm^3 on CT scanning. Patients who were excluded from the study were those with infratentorial hemorrhage, IVH, coagulopathy, and an underlying vascular lesion. The group randomized to surgery had a 14-Fr cannula placed stereotactically into the center of the clot. Using a 10-ml syringe, the surgeon first aspirated the clot until resistance was met. Then a soft ventricular catheter was placed, and accurate placement was confirmed using CT scanning. Thrombolytics were given, and the catheter was initially closed, but it was later opened to allow for drainage. This was done every 8 hours for up to 9 doses or until the clinical end point was reached. Clinical end points were reduction of clot by 80% of the original size, clot size reduction to 15 cm^3 or smaller, or new hemorrhage.

Mortality rates at 7 and 30 days were 0% and 10.5%, respectively. Rebleeding was observed in 10.5% of patients (in the MIS group), and there were no instances of brain infection. Clot removal rates were significantly higher in the treatment group than in the medically treated patients (19%/day for patients receiving 0.3 mg and 16%/day for those receiving 1.0 mg). The amount of residual volume correlated strongly with the accuracy of catheter placement, but patient demographics, clot location, and duration of treatment did not appear to be associated. Baseline factors (GCS and NIHSS scores) and ICH/IVH clot volumes at presentation and at the end of end of treatment were predictors of good functional outcome (mRS Score 0–3) at 180 days. Surgical extraction of the clot was associated with an mRS score of 0–3. These authors concluded that a minimally invasive approach appears to be safe compared with medical therapy and can

TABLE 1: Table outlining select case reports, case series, and a randomized trial on minimally invasive approach to treat ICH spanning from the pre-CT and MRI eras to a current ongoing randomized multicenter trial*

Authors & Year	Study Type	No. of Pts	Method	Vol (cm^3)	FU Duration	Location	Outcome	Re-hemorrhage
Benes et al., 1965	case series	13	stereotactic apparatus w/ clinical exam & cerebral angiographic signs of shift	unk	NS	basal ganglia	localized & drained in 12/13 pts	NR
Backlund & von Holst, 1978	case report	1	CT-guided stereotactic device w/ Archimedes screw principle; novel device	~100	NS	NS	drained 70 ml from estimated 100 ml clot	NR
Niizuma & Suzuki, 1987	case series	145	CT-guided w/ Leksell stereotactic system for 1st evacuation followed by urokinase infusion via cath placed in ICH	NS	6 mos	basal ganglia, thalamus, lobar	8% full recovery, 29% independent, 43% dependent, 13% poor	NR
Auer et al., 1989	randomized control trial	100	endoscopic evacuation of ICH vs best medical management	>10	6 mos	basal ganglia, thalamus, lobar	lobar hemorrhage w/ minimal initial neurological deficits, <50-cm^3 clot, <60 yrs old had favorable outcome compared w/ medically managed pts; no difference in functional outcome in basal ganglia or thalamic hemorrhages	NR
Kandel & Peresedov, 1990	case series	74	CT-guided stereotactic device w/ Archimedes screw principle	24–115	9 yrs	basal ganglia, thalamus, lobar	9 (12%) had recurrent clots; 48 (64%) had complete recovery; 36 (49%) had residual hemiparesis	12%
Hondo et al., 1990	case series	437	CT-guided stereotactic device w/ US aspirator followed by urokinase infusion via cath placed in ICH	NS	NS	basal ganglia, thalamus, lobar	mortality 26% thalamic, 23% lobar, 27% cerebellar, 33% pontine	NR
Lippitz et al., 1994	case series	10	CT-guided stereotactic insertion of cath into hematoma followed by scheduled rt-PA infusion & closed system drainage	30–100	4–17 mos	basal ganglia, thalamus, lobar	84% of hematoma removed; 6/10 pts independent at FU	0%
Schaller et al., 1995	case series	14	CT-guided stereotactic insertion of cath into hematoma followed by scheduled rt-PA infusion & closed system drainage	36–196	3–13 mos	basal ganglia, thalamus, lobar	fast improvement in level of consciousness in 5 pts who presented w/ poor GCS scores	0%
Newell et al., 2011	case series	9	CT guided insertion of cath & US microcatheter into hematoma followed by tPA infusion & closed drainage system	>25	3 mos	basal ganglia, thalamus, lobar	45% vol reduction of ICH in 24 hrs; clinical improvement in NIHSS in 8/9 pts; faster rate of clot lysis compared w/ current MISTIE trial pts	0%
Hanley et al., ongoing	MISTIE: randomized control trial Phases I & II	40	CT or MRI guided insertion of cath into hematoma followed by scheduled t-PA infusion & closed system drainage	>25	6 mos	basal ganglia, thalamus, lobar	10.5% mortality at 30 days in MIS group; 46% clot resolution in acute phase in the rt-PA group vs 4% in medical group	10%

* cath = catheter; FU = follow-up; NR = not reported; NS = not specified; pts = patients; unk = unknown; US = ultrasound.

accomplish clot evacuation without craniotomy and that catheter localization is critical to optimizing hematoma resolution.[13]

Carhuapoma et al.[7] also studied the effect of stereotactic aspiration and rt-PA on perihematomal edema. Perihematomal edema is thought to occur from local mass effect of the clot and secondary injury from blood degradation products. The impact of perihematomal edema on neurological function of patients who survive the acute phase is unknown.[7] Some studies have reported a reduction in perihematomal edema with clot removal regardless of the surgical approach.[20,31] However, there are also reports suggesting that while thrombolytic agents administered within clots accelerate the rate of lysis, they can also potentially worsen associated edema.[10,37] To test whether thrombolytics exacerbate perihematomal edema, Carhuapoma et al. investigated 15 patients with ICH who underwent frameless stereotactic aspiration of the clot followed by insertion of a catheter into the hematoma. Recombinant tissue plasminogen activator was given every 12 hours until clot resolution or until the catheter fenestrations were no longer in the clot. The rate of ICH and perihematomal edema volume resolution was determined using CT findings. The authors observed a significant rate of hematoma resolution (9.65%/day) and perihematomal edema resolution (4%/day) with in the first 8 days of treatment.[7]

Combined Mechanical and Pharmaceutical Approach

As mentioned above, mechanical devices and thrombolytics have achieved positive effects on clot lysis. It would therefore make sense to have a device that can incorporate both modalities to safely augment the rate of lysis. The efficacy of thrombolytics has been shown to be augmented by the adjunct use of ultrasound in both in vivo and in vitro studies.[1,2,8] The mechanism by which ultrasound enhances thrombolysis is believed to be the result of acoustical streaming where ultrasound facilitates delivery of drug through the clot structure. Newell et al.[27] first reported the use of locally delivered ultrasound and thrombolytics to sites of hematoma by stereotactic insertion of microcatheters with ultrasound-emitting elements in the SLEUTH study.

The inclusion criteria for this study were ICH larger than 25 cm^3, IVH producing obstructive hydrocephalus, treatment within 72 hours of initial CT, blood pressure lower than 200 mm Hg, mRS Score 0 or 1, and age 18–85 years. Nine patients (6 females and 3 males) who met the criteria entered the trial. A microcatheter emitting ultrasound waves as well as a drainage catheter was placed stereotactically into an ICH or IVH (Fig. 1). The rt-PA protocol was identical to that in the MISTIE II trial. The distal catheter tip emitted ultrasound at a frequency of 2 MHz and 0.45 W. This was delivered for 24 hours. The hemorrhages were predominately IVHs in 3 patients and ICHs in 6 patients. Compared with the MISTIE and CLEAR studies, a faster rate of clot lysis was observed. This approach seems to be very promising, but the study was conducted in only 9 patients. Larger study groups are needed to confirm these findings. Furthermore, the ultrasound-emitting catheter was designed for intraarterial placement and clot lysis for the treatment of ischemic strokes. Catheters specifically devised for intracranial use may provide better clot lysis, and they are currently in development by the EKOS Corp. (Fig. 2).

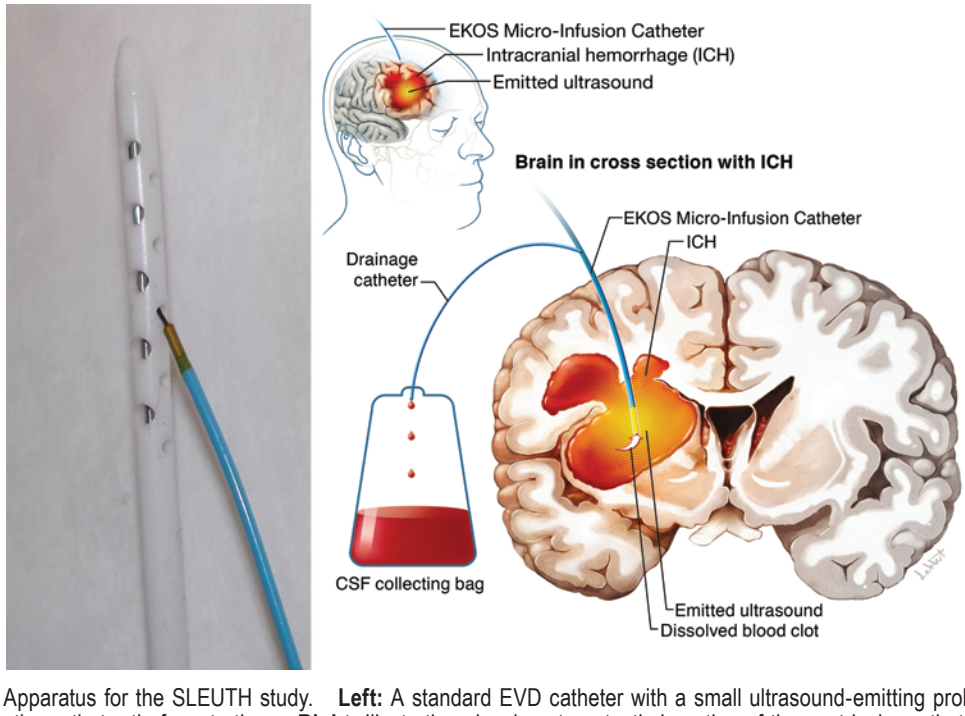

Fig. 1. Apparatus for the SLEUTH study. **Left:** A standard EVD catheter with a small ultrasound-emitting probe (EKOS) inserted in the catheter tip fenestration. **Right:** Illustration showing stereotactic insertion of the ventricular catheter with the EKOS US microcatheter *(upper)*. The tip of the catheter assembly is seen within the intraparenchymal clot *(lower)*. Printed with permission from the Swedish Neuroscience Institute.

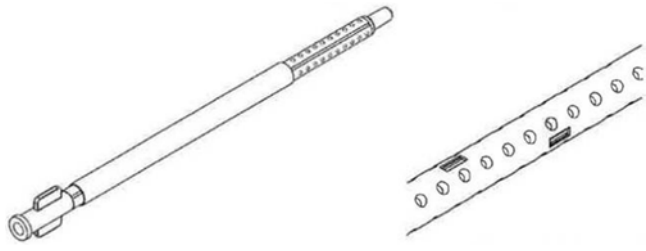

Fig. 2. New design of an ultrasound-emitting drainage catheter designed to deliver ultrasound directly into the center of an ICH and allow continuous drainage of the liquefied clot. Reprinted from EKOS Corp., internal document.

Conclusions

A minimally invasive approach to evacuate ICH has been well documented to be a safe practice. Thus far, the CLEAR and MISTIE studies have supported this assertion. An increased rate of clot lysis could potentially be achieved with a combination of mechanical and pharmaceutical approaches. However, more extensive studies need to be conducted to determine whether the additional mechanical effects via ultrasound further yield beneficial long-term outcome versus pharmacological lysis alone. Currently, catheters are being redesigned for this purpose and will be evaluated in additional future clinical trials.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Hanley, Newell. Acquisition of data: Hanley, Newell. Analysis and interpretation of data: all authors. Drafting the article: Newell. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Abdu. Statistical analysis: Hanley, Newell. Administrative/technical/material support: Abdu, Newell.

References

1. Alexandrov AV: Ultrasound enhancement of fibrinolysis. **Stroke 40 (3 Suppl):**S107–S110, 2009
2. Alexandrov AV, Demchuk AM, Burgin WS, Robinson DJ, Grotta JC: Ultrasound-enhanced thrombolysis for acute ischemic stroke: phase I. Findings of the CLOTBUST trial. **J Neuroimaging 14:**113–117, 2004
3. Auer LM, Deinsberger W, Niederkorn K, Gell G, Kleinert R, Schneider G, et al: Endoscopic surgery versus medical treatment for spontaneous intracerebral hematoma: a randomized study. **J Neurosurg 70:**530–535, 1989
4. Backlund EO, von Holst H: Controlled subtotal evacuation of intracerebral haematomas by stereotactic technique. **Surg Neurol 9:**99–101, 1978
5. Benes V, Vladyka V, Zvěrina E: Stereotaxic evacuation of typical brain haemorrhage. **Acta Neuurochir (Wien) 13:**419–426, 1965
6. Broderick J, Connolly S, Feldmann E, Hanley D, Kase C, Krieger D, et al: Guidelines for the management of spontaneous intracerebral hemorrhage in adults: 2007 update: a guideline from the American Heart Association/American Stroke Association Stroke Council, High Blood Pressure Research Council, and the Quality of Care and Outcomes in Research Interdisciplinary Working Group. **Stroke 38:**2001–2023, 2007
7. Carhuapoma JR, Barrett RJ, Keyl PM, Hanley DF, Johnson RR: Stereotactic aspiration-thrombolysis of intracerebral hemorrhage and its impact on perihematoma brain edema. **Neurocrit Care 8:**322–329, 2008
8. Cintas P, Nguyen F, Boneu B, Larrue V: Enhancement of enzymatic fibrinolysis with 2-MHz ultrasound and microbubbles. **J Thromb Haemost 2:**1163–1166, 2004
9. Daverat P, Castel JP, Dartigues JF, Orgogozo JM: Death and functional outcome after spontaneous intracerebral hemorrhage. A prospective study of 166 cases using multivariate analysis. **Stroke 22:**1–6, 1991
10. Figueroa BEKR, Keep RF, Betz AL, Hoff JT: Plasminogen activators potentiate thrombin-induced brain injury. **Stroke 29:**1202–1208, 1998
11. Flaherty ML, Woo D, Broderick J: The incidence of deep and lobar intracerebral hemorrhage in whites, blacks, and Hispanics. **Neurology 66:**956–957, 2006 (Letter)
12. Freytag E: Fatal hypertensive intracerebral haematomas: a survey of the pathological anatomy of 393 cases. **J Neurol Neurosurg Psychiatry 31:**616–620, 1968
13. Hanley D, Li M, Chong X, Ullman N, Lane K, Aldrich F, et al: The MISTIE trial: surgical performance results from Tier I and Tier II. Presented at the **2011 European Stroke Conference**, Hamburg, Germany (Abstract) (http://www.esc-archive.eu/20.%20ESC%20Hamburg,%20Germany%20E-Book/20._ESC_Hamburg_Germany_2011_Abstract_E_Book/index.html#/1240/) [Accessed February 27, 2012]
14. Hanley DF: Intraventricular hemorrhage: severity factor and treatment target in spontaneous intracerebral hemorrhage. **Stroke 40:**1533–1538, 2009
15. Hondo H, Uno M, Sasaki K, Ebisudani D, Shichijo F, Tóth Z, et al: Computed tomography controlled aspiration surgery for hypertensive intracerebral hemorrhage. Experience of more than 400 cases. **Stereotact Funct Neurosurg 54-55:**432–437, 1990
16. Kandel EI, Peresedov VV: Stereotactic evacuation of spontaneous intracerebral hematomas. **Stereotact Funct Neurosurg 54-55:**427–431, 1990
17. Kandel EI, Peresedov VV: Stereotaxic evacuation of spontaneous intracerebral hematomas. **J Neurosurg 62:**206–213, 1985
18. Lippitz BE, Mayfrank L, Spetzger U, Warnke JP, Bertalanffy H, Gilsbach JM: Lysis of basal ganglia haematoma with recombinant tissue plasminogen activator (rtPA) after stereotactic aspiration: initial results. **Acta Neurochir (Wien) 127:** 157–160, 1994
19. Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringer MN, et al: Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. **N Engl J Med 358:**2127–2137, 2008
20. Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringer MN, et al: Recombinant activated factor VII for acute intracerebral hemorrhage. **N Engl J Med 352:**777–785, 2005
21. Mendelow AD, Gregson BA, Fernandes HM, Murray GD, Teasdale GM, Hope DT, et al: Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomised trial. **Lancet 365:**387–397, 2005
22. Mendelow AD, Unterberg A: Surgical treatment of intracerebral haemorrhage. **Curr Opin Crit Care 13:**169–174, 2007
23. Morgan T, Zuccarello M, Narayan R, Keyl P, Lane K, Hanley D: Preliminary findings of the minimally-invasive surgery plus rtPA for intracerebral hemorrhage evacuation (MISTIE) clinical trial. **Acta Neurochir Suppl 105:**147–151, 2008
24. Morgenstern LB, Frankowski RF, Shedden P, Pasteur W, Grotta JC: Surgical treatment for intracerebral hemorrhage (STICH): a single-center, randomized clinical trial. **Neurology 51:**1359–1363, 1998
25. Naff N, Williams MA, Keyl PM, Tuhrim S, Bullock MR, Mayer SA, et al: Low-dose recombinant tissue-type plasmin-

ogen activator enhances clot resolution in brain hemorrhage: the intraventricular hemorrhage thrombolysis trial. **Stroke 42:**3009–3016, 2011
26. Narayan RK, Narayan TM, Katz DA, Kornblith PL, Murano G: Lysis of intracranial hematomas with urokinase in a rabbit model. **J Neurosurg 62:**580–586, 1985
27. Newell DW, Shah MM, Wilcox R, Hansmann DR, Melnychuk E, Muschelli J, et al: Minimally invasive evacuation of spontaneous intracerebral hemorrhage using sonothrombolysis. Clinical article. **J Neurosurg 115:**592–601, 2011
28. Niizuma H, Suzuki J: Computed tomography-guided stereotactic aspiration of posterior fossa hematomas: a supine lateral retromastoid approach. **Neurosurgery 21:**422–427, 1987
29. Niizuma H, Suzuki J: Stereotactic aspiration of putaminal hemorrhage using a double track aspiration technique. **Neurosurgery 22:**432–436, 1988
30. Nyquist P, Hanley DF: The use of intraventricular thrombolytics in intraventricular hemorrhage. **J Neurol Sci 261:**84–88, 2007
31. Okuda M, Suzuki R, Moriya M, Fujimoto M, Chang CW, Fujimoto T: The effect of hematoma removal for reducing the development of brain edema in cases of putaminal hemorrhage. **Acta Neurochir Suppl 96:**74–77, 2006
32. Paillas JE, Alliez B: Surgical treatment of spontaneous intracerebral hemorrhage. Immediate and long-term results in 250 cases. **J Neurosurg 39:**145–151, 1973
33. Qureshi AI: Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH): rationale and design. **Neurocrit Care 6:**56–66, 2007
34. Qureshi AI, Mendelow AD, Hanley DF: Intracerebral haemorrhage. **Lancet 373:**1632–1644, 2009
35. Qureshi AI, Suri MF, Ostrow PT, Kim SH, Ali Z, Shatla AA, et al: Apoptosis as a form of cell death in intracerebral hemorrhage. **Neurosurgery 52:**1041–1048, 2003
36. Ransohoff J, Derby B, Kricheff I: Spontaneous intracerebral hemorrhage. **Clin Neurosurg 18:**247–266, 1971
37. Rohde V, Rohde I, Thiex R, Ince A, Jung A, Dückers G, et al: Fibrinolysis therapy achieved with tissue plasminogen activator and aspiration of the liquefied clot after experimental intracerebral hemorrhage: rapid reduction in hematoma volume but intensification of delayed edema formation. **J Neurosurg 97:**954–962, 2002
38. Rohde V, Schaller C, Hassler WE: Intraventricular recombinant tissue plasminogen activator for lysis of intraventricular haemorrhage. **J Neurol Neurosurg Psychiatry 58:**447–451, 1995
39. Russell MW, Boulanger L, Joshi AV, Neumann PJ, Menzin J: The economic burden of intracerebral hemorrhage: evidence from managed care. **Manag Care Interface 19:**24–28, 34, 2006
40. Schaller C, Rohde V, Meyer B, Hassler W: Stereotactic puncture and lysis of spontaneous intracerebral hemorrhage using recombinant tissue-plasminogen activator. **Neurosurgery 36:** 328–335, 1995
41. Tuhrim S, Horowitz DR, Sacher M, Godbold JH: Volume of ventricular blood is an important determinant of outcome in supratentorial intracerebral hemorrhage. **Crit Care Med 27:**617–621, 1999
42. Zuccarello M, Brott T, Derex L, Kothari R, Sauerbeck L, Tew J, et al: Early surgical treatment for supratentorial intracerebral hemorrhage: a randomized feasibility study. **Stroke 30:**1833–1839, 1999

Manuscript submitted December 13, 2011.
Accepted January 30, 2012.
Please include this information when citing this paper: DOI: 10.3171/2012.1.FOCUS11362.

Address correspondence to: Emun Abdu, M.D., Swedish Neuroscience Institute, 550 Seventeenth Avenue, Suite 500, Seattle, Washington 98122. email: emun.abdu@swedish.org.

Neurosurg Focus 32 (4):E4, 2012

External ventricular drainage alone versus endoscopic surgery for severe intraventricular hemorrhage: a comparative retrospective analysis on outcome and shunt dependency

Luca Basaldella, M.D.,[1] Elisabetta Marton, M.D.,[1] Alessandro Fiorindi, M.D., Ph.D.,[1] Bruno Scarpa, Ph.D.,[2] Hadi Badreddine, M.D.,[1] and Pierluigi Longatti, M.D.[1]

[1]Department of Neurosurgery, Treviso Regional Hospital, University of Padova, Treviso; and [2]Department of Statistical Sciences, University of Padova, Italy

Object. Massive intraventricular hemorrhages (IVHs) require aggressive and rapid management to decrease intracranial hypertension, because the amount of intraventricular blood is a strong negative prognostic predictor on outcome. Neuroendoscopy may offer some advantages over more traditional surgical approaches on outcome and may decrease the number of shunt procedures that need to be performed.

Methods. The authors retrospectively reviewed the clinical and radiological data in 96 patients treated for massive IVH who were admitted between January 1996 and June 2008 to the neurosurgery unit after undergoing emergency CT scanning. Forty-eight patients (Group A) were treated with endoscopic aspiration surgery using a flexible endoscope with a "freehand" technique. A historical group of 48 patients (Group B) treated using external ventricular drain (EVD) placement alone was used as a comparison. The authors compared the radiological results with the clinical outcomes at 1 year according to the modified Rankin Scale and the need for internal CSF shunt treatment in the 2 groups.

Results. Endoscopic aspiration did not significantly affect the outcome at 1 year as determined using the modified Rankin Scale. Patients who underwent endoscopy had an EVD in place for 0.18 days fewer than patients treated with an EVD alone. Patients undergoing external ventricular drainage alone had a 5 times greater chance of requiring a shunting procedure than those treated using neuroendoscopy and external ventricular drainage. Neuroendoscopy plus external drainage reduces shunting rates by 34% when compared with external drainage alone.

Conclusions. The reduction in internal shunt surgery encourages the adoption of neuroendoscopic aspiration of severe IVH as a therapeutic tool to decrease shunt dependency.
(http://thejns.org/doi/abs/10.3171/2012.1.FOCUS11349)

Key Words • **intraventricular hemorrhage** • **neuroendoscopy** • **ventriculoperitoneal shunt** • **external ventricular drainage**

During the past decade, there has been a considerable and increasing interest in the medical and surgical management of massive IVHs.[4,8,16,20,26,36,37,51] Intraventricular blood brings about multiple noxious effects[10,13] on the brain causing impairment of CSF circulation,[29] intracranial hypertension,[19] and acute[14] or delayed hydrocephalus.[15]

Mortality estimates for IVH range from 50% to 80%. The most common cause of IVH is spontaneous ICH,[6,18] followed by SAH.[40] The incidence of IVH in intracerebral hemorrhage is roughly twice that in SAH.[18] Approximately 10% of patients suffering aneurysmal SAH and 40% of those suffering primary ICH experience IVH.[6,18,40] At present, medical management of ICH and IVH revolves around the control of ICP. Despite medical management, mortality remains high, with only 38% of patients surviving the 1st year.[6] Even with the best medical management, mortality rates have been reported to be as high as 50%. These studies suggest that measures to control ICP through control of factors such as hydrocephalus have little effect.[33] Massive IVH requires aggressive and rapid management to decrease intracranial hypertension. The amount of intraventricular blood is a strong prognostic factor,[3,44] and its fast removal should be considered a priority. The immediate control of ICP by external ventricular drainage is a res-

Abbreviations used in this paper: AVM = arteriovenous malformation; EVD = external ventricular drain; GCS = Glasgow Coma Scale; ICH = intracranial hemorrhage; ICP = intracranial pressure; IVH = intraventricular hemorrhage; LOS = length of stay; mRS = modified Rankin Scale; SAH = subarachnoid hemorrhage; VP = ventriculoperitoneal.

cue surgical action,[21] but tetraventricular blood inundation should be managed using bilateral ventricular catheters, which frequently become obstructed by blood clots and need to stay in place for a longer period for blood washout. Naff et al.[31] clearly demonstrated that the percentage of clot resolution is 10.8% per day and is independent from the initial clot volume, patient age and sex, type of underlying hemorrhage, and use of external ventricular drainage.[24]

The fibrinolytic system of CSF is limited.[24] Blood may remain for weeks after hemorrhage; acute clots obstruct ventricular CSF pathways, and clot degradation products obstruct extraventricular CSF pathways. When present, blood degradation products continue to contribute to patients' poor clinical statuses[5,6,9–11] and are responsible for chronic shunt–dependent hydrocephalus in more than 30% of them.[15–17,30] At present, reduction in the ventricular clot size seems to be the only method for reducing mortality rates after the ICH has stabilized. Many studies have demonstrated the independent effect of IVH on mortality.[16–20] Neuroendoscopy may offer some advantages over more traditional surgical approaches such as EVD placement and intraventricular fibrinolysis and should be considered the gold-standard approach, especially when dealing with elderly patients in poor general health.

Methods

Patient Population

We retrospectively reviewed the demographic, clinical, and outcome data of a series of 96 patients treated for massive IVH between January 1996 and June 2008 (Table 1). All patients presented with spontaneous primary or secondary tetraventricular inundation, acute hydrocephalus, progressive worsening of neurological conditions, and/or coma. A CT scan was obtained within 3 hours of hospital admission, and the blood amount was quantified according to the Graeb score.[14] Angiography was performed when a vascular malformation was suspected. Surgery was always performed in emergency conditions. Forty-eight patients underwent neuroendoscopic surgery (Group A), and the remaining 48 patients underwent EVD placement alone (control Group B). No fibrinolytic agents were used in either group. In patients with a vascular malformation as the likely cause of bleeding, the endoscopic procedure or the EVD placement was performed in close association with endovascular or surgical treatment. In all patients, clinical follow-up was assessed at 1 year according to the mRS score (see Fig. 3).[7]

TABLE 1: Demographic and clinical characteristics

Variable	Group A	Group B
sex		
male	28	23
female	20	25
M/F ratio	1.4	0.92
age (yrs)		
mean	57.8	56.4
range	7–80	14–78
etiology distribution (%)		
ICH	39	36
ruptured aneurysm	29	50
pure IVH	17	10
AVM	8	4
posterior fossa hemorrhage	6	0
mean admission Graeb score	9.75	8.5
mean admission GCS score	6.6	7.2
mean duration of EVD placement (days)	12.1	13.9
mean ICU LOS (days)	13	19

Group A. Forty-eight patients (28 male and 20 female; male/female ratio 1.4) with a mean age of 57.8 years (range 7–80 years) were treated with endoscopic aspiration of intraventricular blood. All patients exhibited acute hydrocephalus on the initial CT scan as well as blood clots obstructing the third and fourth ventricles.

The IVH was a result of ICH in 39% of patients, a ruptured aneurysm in 29%, primary IVH in 17%, an AVM in 8%, and a posterior fossa hematoma in 6% (Fig. 1). The severity of IVH was graded according to the Graeb scoring system: 65% of patients had a Graeb scale score greater than 10 and tetraventricular clots. The mean Graeb score was 9.75 ± 2.7 (± SD). The mean GCS score at the time of admission was 6.6.[45] Sixty-three percent of patients were treated on the day of admission (within 24 hours from the onset of hemorrhage). The remaining 37% were treated in a delayed fashion (between 48 and 72 hours after onset). Especially in the initial period of training of the last author (P.L.), some of those patients who were admitted overnight were initially managed conservatively with an EVD if the surgeon was not available. Since that time, a second surgeon (A.F.) mastered the technique, and in the past 8 years we have been able to guarantee emergency treatment (within 24 hours) for all patients suitable for undergoing endoscopic aspiration of ventricular clots.

Group B. The records of 48 patients (23 male and 25 female; male/female ratio 0.92) with a mean age of 56.4 years (range 14–78 years) treated with external ventricular drainage for intraventricular blood removal were retrieved and matched from our institutional database as a historical

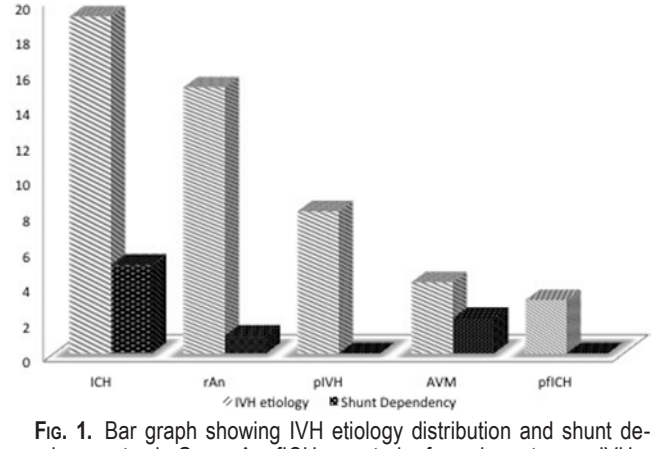

Fig. 1. Bar graph showing IVH etiology distribution and shunt dependency rates in Group A. pfICH = posterior fossa hematoma; pIVH = primary IVH; rAn = ruptured aneurysm.

control group. All patients exhibited acute hydrocephalus on the initial CT scan.

The IVH was a result of ICH in 36% of patients, a ruptured aneurysm in 50%, primary IVH in 10%, and an AVM in 4% (Fig. 2). The severity of IVH was graded according to the Graeb scoring system. In 70% of patients the Graeb score was greater than 8 and tetraventricular clots were present; the mean Graeb score was 8.5 ± 1.8. The mean GCS score at admission was 7.2.

Surgical Procedure

Group A. Despite their clinical condition, all patients with IVH immediately underwent CT scanning, CT angiography, and digital subtraction angiography or MRI when deemed appropriate. Urgent blood work was obtained with special focus on prothrombin time and liver and kidney function. Preoperative management included identification and correction of coagulation disorders, administration of prophylactic anticonvulsants, controlling body temperature, and glycemia correction. The mean arterial pressure should be kept lower than 110 mm Hg and systolic pressure lower than 150 mm Hg. For the endoscopic procedure, 2 types of flexible endoscopes were used with an external diameter of either 2.5 mm (Karl Storz) or 3.9 mm (Codman) and an operative length of 53 cm. The internal diameter of the working channel was 1.2 mm. For aspiration procedures, the entire working channel was used as a sucking device. The access was precoronal, 2 cm from lateral to the midline, through a 12-mm bur hole (Figs. 4 and 5). The access side was chosen as the side of the lateral ventricle containing the largest amount of blood or the largest dilation. In cases with bilateral massive inundation, the access was bilateral. In the presence of a ventricular vascular malformation or aneurysm, an approach from that side was avoided. Lateral ventricle cannulation was achieved using a semirigid peel-away catheter, and systolic blood pressure was maintained at 120 mm Hg. An energetic intermittent manual aspiration was started using a rigid syringe connected to the operating channel of the endoscope. This action breaks down the clot and allows initial visualization in the ventricle. Once the choroidal plexus and Monro foramen were identified, the endoscope was advanced into the third ventricle, preferably into the right-sided bur hole,

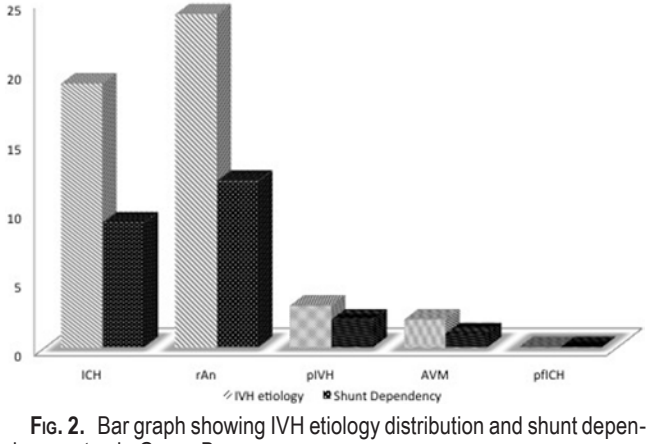

Fig. 2. Bar graph showing IVH etiology distribution and shunt dependency rates in Group B.

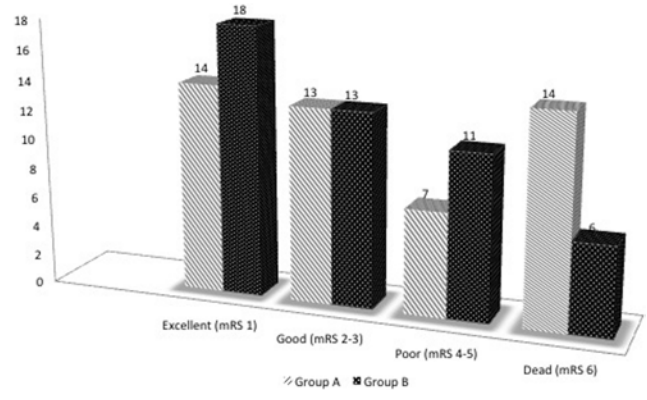

Fig. 3. Comparison of the 1-year mRS scores in Groups A and B.

and the procedure was repeated. Evacuation of the third ventricle paved the way to the aqueduct and to the fourth ventricle, where the aspiration-irrigation procedures were carefully performed, since the endoscope fills the entire diameter of the aqueduct and potentially dangerous local hypertension might easily be caused by excessive irrigation with Ringer solution. At the end of the procedure, an EVD was left in all patients for ICP monitoring and drainage (with a constant gradient of 15 mm Hg). The mean ICU LOS after the operation was 13 days. Endoscopy was successfully completed in all cases, and each patient received an EVD. There were no intraoperative deaths. The EVD was removed on the same day as the endoscopy procedure in 12 patients and after 1–25 days in the other patients (median 10 days).

Group B. An EVD was positioned in all patients on the 1st day. Bilateral EVDs were positioned in 35 of the 48 patients. The EVD was removed after 8–32 days (median 13.99 days), and all patients underwent catheter substitution 1 or more times during the ICU LOS. In this group, no thrombolysis with rtPA was performed to maintain homogeneity between the 2 groups. The mean ICU LOS after the operation was 19 days.

Statistical Analysis

Statistical models have been fitted to data to describe the specific effect of endoscopy once the effects of sex, age, and admission GCS score were eliminated. We fit a logistic model to measure the effects of available variables on the insertion of a VP shunt, where significant variables were selected by a backward stepwise procedure based on the Akaike information criterion.

Proportional odds models have been fitted to describe a connection between endoscopy and mRS score, which is a scoring variable that is ordinal in that its value increases when outcome is worse. Also in this case we selected significant variables by backward stepwise selection based on the Akaike information criterion. We also considered, as secondary outcomes of interest, the number of days that the EVD was required and the number of days spent in the neuro-ICU. Both these variables are quantitative, nonnegative, and right skew. We used the Box-Cox transformation to select the best function of these outcomes. In both cases the square root transform was chosen. Here too, in both cases, we implemented a backward stepwise procedure

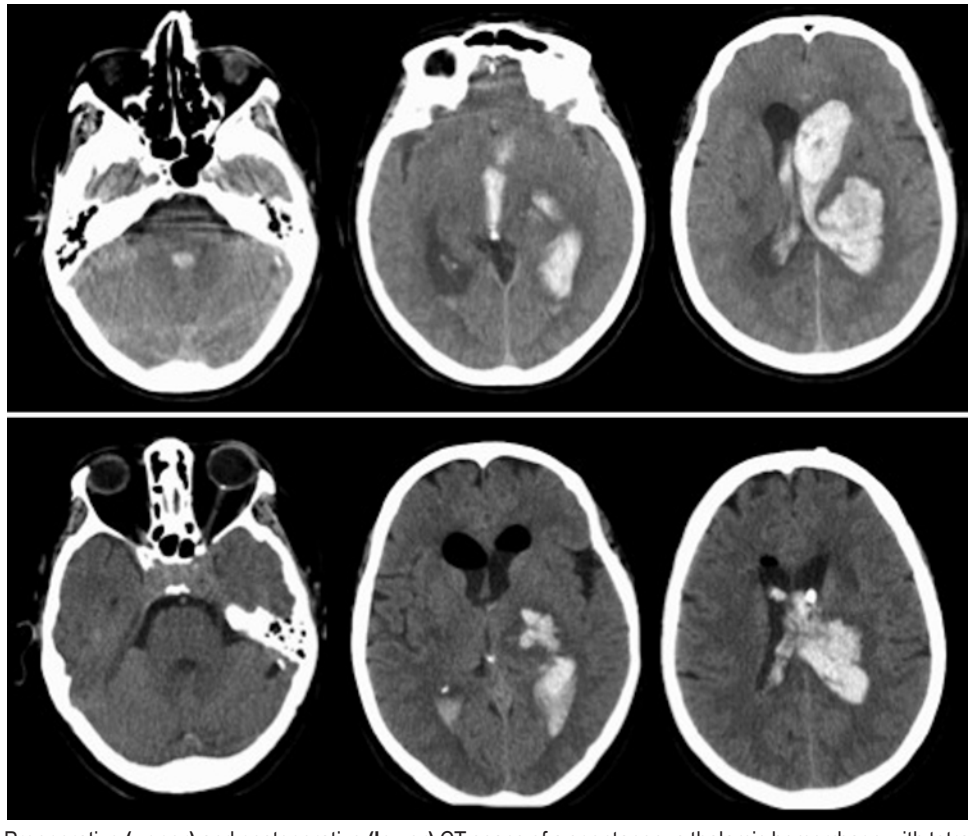

Fig. 4. Preoperative **(upper)** and postoperative **(lower)** CT scans of a spontaneous thalamic hemorrhage with tetraventricular clots.

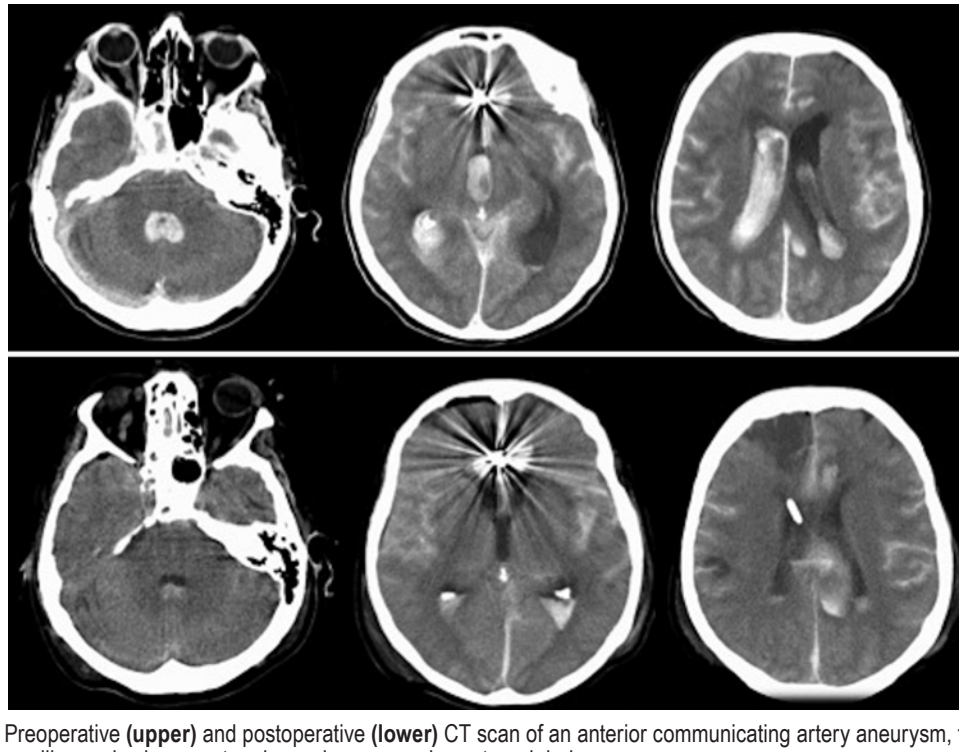

Fig. 5. Preoperative **(upper)** and postoperative **(lower)** CT scan of an anterior communicating artery aneurysm, treated with emergency coiling and subsequent endoscopic surgery plus external drainage.

based on the Akaike information criterion to select the significant variables.

Results

A VP shunt was required by 17% of patients in Group A and by 50% of patients in Group B. The 1-year follow-up was recorded according to the mRS. Excellent outcome (mRS Score 0 or 1) was achieved in 29% of patients in Group A and in 37% of patients in Group B. A good outcome (mRS Score 2 or 3) was seen in 27% of patients in both groups. A poor outcome (mRS Score 4 or 5) was recorded in 14% and 23% of patients, and death (mRS Score 6) occurred in 29% and in 13% in Groups A and B, respectively (Table 2). The mRS results in an independent variable when compared with each group (Group A vs Group B, $p = 0.2$; chi-square test).

Backward selection of the logistic model to estimate the effect of endoscopy on the need for a VP shunt revealed that age and admission GCS score were not significant when sex and endoscopy are included in the model. As shown in Table 3, patients who did not undergo endoscopy had an almost 5 times greater probability of requiring a shunt procedure than those who did.

The model describing the effects of endoscopy on mRS score provides different results. Here, only age and admission GCS score result were significant in describing the outcome; the fact that endoscopy was performed did not add any relevant information in predicting the mRS score. The same result of no effect of endoscopy on mRS score was obtained if this variable is recoded in the 4 classes scoring as in Table 2. We also did not find any effect of endoscopy when we relaxed the proportional odds hypothesis by fitting a multinomial model, by not considering the ordinal characteristic of the mRS score. We therefore conclude that there is not a specific effect of endoscopy once age and admission GCS score are considered in predicting the mRS score.

A significant effect of endoscopy is, instead, observed in both models predicting the number of days of external ventricular drainage and neuro-ICU LOS. The presence of endoscopy is significant ($p = 0.038$) regardless of whether the other insignificant variables (sex, age, and admission GCS score) are included. Patients who underwent endoscopy spent about 0.18 days fewer in the ICU than those who underwent EVD placement alone (Table 4).

Similar results were obtained using the model when predicting the LOS in the neuro-ICU. In this case, only age and sex were not significant, whereas admission GCS score had a significant negative effect on this parameter. Patients who underwent endoscopy had about half a day (0.504) longer stay in the neurological ICU than the others (Table 4).

TABLE 2: Modified Rankin Scale score distribution

mRS Outcome	No. of Patients (%)	
	Group A	Group B
excellent (score 1)	14 (29)	18 (37)
good (score 2 or 3)	13 (27)	13 (27)
poor (score 4 or 5)	7 (14)	11 (23)
dead (score 6)	14 (29)	6 (13)

Discussion

The prognosis of IVH is affected by several factors, including age, sex, GCS score, presence of acute hydrocephalus, coagulopathy, origin of the bleeding, and tetraventricular inundation. These factors all play a critical role, but in the first hours after IVH, the sudden increase in ICP associated with initial bleeding may cause a significant reduction in cerebral blood flow, potentially leading to ischemia.[28] The obstruction of CSF pathways and the mass effect associated with clots in the satellite hematoma and within the ventricles cause further damage. The fibrinolytic system of the CSF is limited,[32] and blood may remain for weeks after hemorrhage.[6,15,18] Delay of clot resolution leads to obstruction of extraventricular CSF pathways, contributing to the patient's poor clinical status. In the late stage, biochemical changes and blood degradation products are responsible for secondary damage to neurons and white matter.[41,49] Hematoma and perihematoma regions after intracerebral hemorrhage are biochemically active environments known to undergo potent oxidizing reactions.[9,11] After ICH, amounts of unconjugated bilirubin in the hematoma can be substantial, as can levels of iron and hemoglobin.[11] Oxidation of unconjugated bilirubin to yield bioactive molecules, such as BOXes (bilirubin oxidation products), is an important discovery, expanding the role of bilirubin in pathological processes seen after ICH. Blood degradation products are responsible for oxidative stress in brain surrounding the hematoma, and the spreading through the CSF may be responsible for late damage to the ventricle-facing structures. Thus, the primary goal of acute management for IVH should be the fast removal of intraventricular blood, rapid reversal of ventricular dilation, and normalization of ICP. All of these goals can be achieved immediately using the neuroendoscopic procedure,[16,25,26,36,37,51] while complications often observed with other traditional approaches are minimized.[33]

External Ventricular Drainage

The initial management of IVH has included the placement of 1 EVD or more to allow the egress of blood and CSF from the ventricle system and decrease ICP. However, this approach alone is often not sufficiently effective in improving the poor prognosis of patients with severe IVH.[4,15,21] Patency of the EVD is frequently difficult to maintain due to occlusion of the catheter by coagulated blood. Optimal treatment should also include removal and dissolution of the intraventricular hematoma itself. This would be expected to decrease ICP, increase cerebral perfusion, and minimize the chance of IVH-induced hydrocephalus resulting from obstruction of CSF drainage from the ventricular system. In selected cases, surgical evacuation of intraparenchymal and intraventricular hematomas has resulted in decreases in mortality rates and disability.[12] However, surgery is invasive and is not always feasible. Survival after primary IVH is common,[27] but it is accompanied by considerable morbidity. In general, patients with

TABLE 3: Estimates of the parameters for the final logistic model connecting endoscopy and VP shunt

Parameter	Estimate	exp(estimate)	SE	z Value	p Value
base level (female of Group A)	–1.2284	0.293	0.4424	–2.777	0.005
additional effect for male	–0.7626	0.466	0.4725	–1.614	0.106
additional effect for Group B	1.5771	4.841	0.4894	3.223	0.001

secondary IVH fare worse than those with primary IVH.[47] When an intracerebral hematoma extends into a portion of the ventricular system, mortality has been reported to be 32%–44%.[14,22] When IVH extends into all 4 ventricles, mortality has been reported as 60%–91%.[4,6,12,18,40] With respect to the location of the hematoma causing the IVH, the worst prognosis is found with hematomas located in the thalamus.[18] Predictors of poor outcome are GCS score on presentation and the volume of blood in the ventricle system.[47,50] The degree of ventricular dilation, independent of the obstruction of CSF flow, has also been found to be a strong indicator for poor outcome.[39]

Fibrinolytic Agents

Investigators have sought to develop improved methods of treating patients with IVH, trying to expedite the resolution of the ventricular blood clots and improve morbidity and mortality in these patients by administering fibrinolytic agents directly into the ventricular system. The basic rationale for this treatment is to dissolve the blood clot within the ventricular system, since it continues to exert a deleterious effect on the brain. A major reason to consider the use of a fibrinolytic agent is to keep the EVD open so that blood and spinal fluid can continue to drain freely from the ventricular system. In 1990, Shen et al.[43] reported on 4 patients with IVH who received [urokinase] u-PA either as an intermittent infusion (n = 2) or continuous infusion (n = 2), into the lateral ventricles through an EVD. All patients underwent bilateral EVD placement. Two patients had a good recovery, 1 had a severe disability, and 1 persisted in a vegetative state. All patients developed meningitis that was likely related to the continuous manipulation of the ventricular catheters. Rainov and Burkert[39] reported results of u-PA treatment that were found to be favorable. In their treatment and control groups, respectively, 15 (94%) and 2 (40%) patients had excellent or good outcomes (that is, no deficits or minor neurological deficits), and 1 (6%) and 2 (40%) patients had poor outcomes (that is, permanent vegetative state). No patient in the treatment group died, and 1 patient (20%) in the control group died. Tush et al.[48] have been the only authors to report complications encountered with intraventricular u-PA, including 1 case of rebleeding and 2 cases of ventriculitis (in a series of 5 patients). Coplin et al.[11] conducted a retrospective cohort study in 1998, which included the largest number of patients thus far treated with intraventricular u-PA under a given protocol. Similar to other reports, the median time for clearance of blood from the third ventricle was 7.0 days and that from the lateral ventricles was 16.0 days. Thrombolytic therapy was found to result in significantly lower mortality (31.8% vs 66.7%; p = 0.03). Previous reports that have included a control group[11] or comparison group[39,43,48] in their analysis have similarly reported that treatment with intraventricular u-PA in patients with IVH reduces mortality by 30%–35%. What is not clear from the literature, however, is whether such treatment results in an improved neurological outcome of the survivors. Shen et al.,[43] Akdemir et al.,[1] and Todo et al.[46] reported good recovery with or without moderate disability in 50%–83% of the patients who received this treatment. However, 1 cohort study found that a larger proportion of the survivors remained in a vegetative state (31.8% treatment group vs 11.1% control group).[11] Andrews et al.[2] concluded that clinical studies of fibrinolytic therapy for IVH have found a 30%–35% reduction in mortality with treatment, but, to date, they have not clearly documented improved neurological outcome of the survivors. Nieuwkamp et al.[35] conducted a systematic review to compare conservative treatment, extraventricular drainage alone, and extraventricular drainage combined with fibrinolysis. They reported a poor outcome rate for conservative treatment of 90%; that for extraventricular drainage was 89% (relative risk 0.98 [95% CI 0.75–1.30]) and that for extraventricular drainage with fibrinolytic agents was 34% (relative risk 0.38 [95% CI 0.21–0.68]). In 2002 Lapointe and Haines[23] concluded that there was suggestive and anecdotal evidence that the intraventricular administration of fibrinolytic agents in cases of IVH might be safe and of therapeutic value.

TABLE 4: Summary of the estimates for the final models relating endoscopy to square root of EVD placement and of neuro-ICU LOS

Model	Estimate	SE	t Value	p Value
square root of EVD				
Group A	3.2564	0.1426	22.841	<0.0001
additional effect for Group B	0.4244	0.2016	2.105	0.038
square root of neuro-ICU stay				
base level (Group A)	5.28544	0.50770	10.411	<0.0001
additional effect for each single GCS point at admission	0.16497	0.07093	2.326	0.0222
additional effect for Group B	0.16497	0.27319	2.628	0.0100

Endoscopic Aspiration

Neuroendoscopic approaches have been reported to produce positive outcomes in patients with IVH.[8,16,25,36,37,51] In all cases, efficient removal of intraventricular clots was rapidly achieved. However, in 2 of these reports, use of a rigid endoscope required either a cumbersome biportal approach[17] or an ultrasonic aspirator,[38] with a high risk (20%) of postoperative rebleeding. The use of a flexible instrument and the freehand technique, albeit offering a narrower operating channel, allows more complete cleansing of the third ventricle and navigation down to the fourth ventricle through the aqueduct. Persistence of blood in the fourth ventricle is related to poor outcomes in patients with IVH.[42] Complete clearing of the aqueduct and the fourth ventricle is thus an important feature of this treatment because it rapidly establishes the physiological CSF dynamics.

Our experience with flexible endoscopic treatment of severe primary and secondary IVH did not demonstrate any infective complications or rebleeding, showing that this approach can be safe and effective and may favorably compare with more established approaches.[34]

Conclusions

Our experience with flexible endoscopic treatment of severe primary and secondary IVH shows that once certain measures are taken to minimize the risk of bleeding resulting from ruptured vascular malformations, this approach can be safe and effective and may compare favorably with more established approaches. Similar to other ventricular diseases, IVH can be treated successfully with flexible endoscopes, which may result in a very satisfactory, albeit challenging, approach for experienced neuroendoscopists. Flexible neuroendoscopy in our series was not associated with complications or rebleeding. Neuroendoscopy plus external ventricular drainage reduces shunting rates by 34% when compared with external ventricular drainage alone. Patients who undergo EVD placement have a 5 times higher probability of requiring an internal shunt than those treated with neuroendoscopy plus EVD placement. Neuroendoscopy plus EVD placement together do not significantly improve the 1-year mRS scores when compared with EVD placement alone. Neuroendoscopy plus EVD placement significantly reduces the need for postoperative external ventricular drainage days after surgery, potentially reducing infective complications. The limitation of this study lies in its retrospective nature. However, being aware of the selection biases in determining the treatment group due to differences in time epoch for the 2 treatments, we still think that the data from this study are lacking in the contemporary literature and may prompt a cooperative randomized trial to acquire Level A evidence data that may be adopted as guidelines in the management of an unsolved clinical problem. Reduction of the need for VP shunt procedures encourages the adoption of neuroendoscopic aspiration as a therapeutic tool in cases of massive IVH.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Basaldella, Longatti. Acquisition of data: Basaldella, Marton, Fiorindi, Badreddine. Analysis and interpretation of data: Basaldella. Drafting the article: Basaldella, Marton, Scarpa. Critically revising the article: Basaldella, Marton, Longatti. Reviewed submitted version of manuscript: Basaldella. Approved the final version of the manuscript on behalf of all authors: Basaldella. Statistical analysis: Scarpa. Study supervision: Basaldella, Fiorindi, Longatti.

References

1. Akdemir H, Selçuklu A, Paşaoğlu A, Oktem IS, Kavuncu I: Treatment of severe intraventricular hemorrhage by intraventricular infusion of urokinase. **Neurosurg Rev 18:**95–100, 1995
2. Andrews CO, Engelhard HH: Fibrinolytic therapy in intraventricular hemorrhage. **Ann Pharmacother 35:**1435–1448, 2001
3. Angelopoulos M, Gupta SR, Azat Kia B: Primary intraventricular hemorrhage in adults: clinical features, risk factors, and outcome. **Surg Neurol 44:**433–437, 1995
4. Aoki N: Treatment for intraventricular hemorrhage. **J Neurosurg 75:**494–495, 1991
5. Bakshi R, Kamran S, Kinkel PR, Bates VE, Mechtler LL, Belani SL, et al: MRI in cerebral intraventricular hemorrhage: analysis of 50 consecutive cases. **Neuroradiology 41:**401–409, 1999
6. Bhattathiri PS, Gregson B, Prasad KS, Mendelow AD: Intraventricular hemorrhage and hydrocephalus after spontaneous intracerebral hemorrhage: results from the STICH trial. **Acta Neurochir Suppl 96:**65–68, 2006
7. Bonita R, Beaglehole R: Recovery of motor function after stroke. **Stroke 19:**1497–1500, 1988
8. Chen CC, Liu CL, Tung YN, Lee HC, Chuang HC, Lin SZ, et al: Endoscopic surgery for intraventricular hemorrhage (IVH) caused by thalamic hemorrhage: comparisons of endoscopic surgery and external ventricular drainage (EVD) surgery. **World Neurosurg 75:**264–268, 2011
9. Chen M, Regan RF: Time course of increased heme oxygenase activity and expression after experimental intracerebral hemorrhage: correlation with oxidative injury. **J Neurochem 103:**2015–2021, 2007
10. Clark JF, Loftspring M, Wurster WL, Beiler S, Beiler C, Wagner KR, et al: Bilirubin oxidation products, oxidative stress, and intracerebral hemorrhage. **Acta Neurochir Suppl 105:**7–12, 2008
11. Coplin WM, Vinas FC, Agris JM, Buciuc R, Michael DB, Diaz FG, et al: A cohort study of the safety and feasibility of intraventricular urokinase for nonaneurysmal spontaneous intraventricular hemorrhage. **Stroke 29:**1573–1579, 1998
12. de Weerd AW: The prognosis of intraventricular hemorrhage. **J Neurol 222:**46–51, 1979
13. Dull C, Torbey MT: Cerebral vasospasm associated with intraventricular hemorrhage. **Neurocrit Care 3:**150–152, 2005
14. Graeb DA, Robertson WD, Lapointe JS, Nugent RA, Harrison PB: Computed tomographic diagnosis of intraventricular hemorrhage. Etiology and prognosis. **Radiology 143:**91–96, 1982
15. Gross WP, Hesselmann V, Wedekind C: Development of chronic hydrocephalus and early cranial CT findings in spontaneous intracerebral/intraventricular hemorrhage. **Zentralbl Neurochir 67:**21–25, 2006
16. Hamada H, Hayashi N, Kurimoto M, Umemura K, Nagai S, Kurosaki K, et al: Neuroendoscopic removal of intraventricular hemorrhage combined with hydrocephalus. **Minim Invasive Neurosurg 51:**345–349, 2008
17. Horváth Z, Veto F, Balás I, Kövér F, Dóczi T: Biportal endoscopic removal of a primary intraventricular hematoma: case report. **Minim Invasive Neurosurg 43:**4–8, 2000
18. Huttner HB, Köhrmann M, Berger C, Georgiadis D, Schwab

S: Influence of intraventricular hemorrhage and occlusive hydrocephalus on the long-term outcome of treated patients with basal ganglia hemorrhage: a case-control study. **J Neurosurg 105:**412–417, 2006
19. Huttner HB, Staykov D, Bardutzky J, Nimsky C, Richter G, Doerfler A, et al: [Treatment of intraventricular hemorrhage and hydrocephalus.] **Nervenarzt 79:**1369–1370, 1372–1374, 1376, 2008 (Ger)
20. Huttner HB, Tognoni E, Bardutzky J, Hartmann M, Köhrmann M, Kanter IC, et al: Influence of intraventricular fibrinolytic therapy with rt-PA on the long-term outcome of treated patients with spontaneous basal ganglia hemorrhage: a case-control study. **Eur J Neurol 15:**342–349, 2008
21. Kiymaz N, Demir O, Cirak B: Is external ventricular drainage useful in primary intraventricular hemorrhages? **Adv Ther 22:**447–452, 2005
22. Lagares A, Putman CM, Ogilvy CS: Posterior fossa decompression and clot evacuation for fourth ventricle hemorrhage after aneurysmal rupture: case report. **Neurosurgery 49:**208–211, 2001
23. Lapointe M, Haines S: Fibrinolytic therapy for intraventricular hemorrhage in adults. **Cochrane Database Syst Rev 3:** CD003692, 2002
24. Lodhia KR, Shakui P, Keep RF: Hydrocephalus in a rat model of intraventricular hemorrhage. **Acta Neurochir Suppl 96:** 207–211, 2006
25. Longatti P, Fiorindi A, Martinuzzi A: Neuroendoscopic aspiration of hematocephalus totalis: technical note. **Neurosurgery 57 (4 Suppl):**E409, 2005
26. Longatti PL, Martinuzzi A, Fiorindi A, Maistrello L, Carteri A: Neuroendoscopic management of intraventricular hemorrhage. **Stroke 35:**e35–e38, 2004
27. Martí-Fàbregas J, Piles S, Guardia E, Martí-Vilalta JL: Spontaneous primary intraventricular hemorrhage: clinical data, etiology and outcome. **J Neurol 246:**287–291, 1999
28. Mayer SA, Kessler DB, Van Hurtum RL, Thomas CE, Fink ME, Brannigan T: Effect of intraventricular blood on global cortical perfusion in acute intracerebral hemorrhage: a single-photon emission computed tomographic study. **Ann Neurol 38:**288, 1995 (Abstract)
29. Mayfrank L, Kissler J, Raoofi R, Delsing P, Weis J, Küker W, et al: Ventricular dilatation in experimental intraventricular hemorrhage in pigs. Characterization of cerebrospinal fluid dynamics and the effects of fibrinolytic treatment. **Stroke 28:**141–148, 1997
30. Morgan T, Awad I, Keyl P, Lane K, Hanley D: Preliminary report of the clot lysis evaluating accelerated resolution of intraventricular hemorrhage (CLEAR-IVH) clinical trial. **Acta Neurochir Suppl 105:**217–220, 2008
31. Naff NJ, Carhuapoma JR, Williams MA, Bhardwaj A, Ulatowski JA, Bederson J, et al: Treatment of intraventricular hemorrhage with urokinase: effects on 30-day survival. **Stroke 31:**841–847, 2000
32. Naff NJ, Williams MA, Rigamonti D, Keyl PM, Hanley DF: Blood clot resolution in human cerebrospinal fluid: evidence of first-order kinetics. **Neurosurgery 49:**614–621, 2001
33. Nakagawa T, Suga S, Mayanagi K, Akaji K, Inamasu J, Kawase T: Predicting the overall management outcome in patients with a subarachnoid hemorrhage accompanied by a massive intracerebral or full-packed intraventricular hemorrhage: a 15-year retrospective study. **Surg Neurol 63:**329–335, 2005
34. Nakano T, Ohkuma H, Ebina K, Suzuki S: Neuroendoscopic surgery for intracerebral haemorrhage—comparison with traditional therapies. **Minim Invasive Neurosurg 46:**278–283, 2003
35. Nieuwkamp DJ, de Gans K, Rinkel GJ, Algra A: Treatment and outcome of severe intraventricular extension in patients with subarachnoid or intracerebral hemorrhage: a systematic review of the literature. **J Neurol 247:**117–121, 2000
36. Nishikawa T, Takehira N, Matsumoto A, Kanemoto M, Kang Y, Waga S: Delayed endoscopic intraventricular hemorrhage (IVH) removal and endoscopic third ventriculostomy may not prevent consecutive communicating hydrocephalus if IVH removal was insufficient. **Minim Invasive Neurosurg 50:** 209–211, 2007
37. Nishikawa T, Ueba T, Kajiwara M, Iwata R, Yamashita K: Combined treatment of ruptured aneurysm accompanied by intraventricular hemorrhage; neuroendoscopy and coiling: case report. **Minim Invasive Neurosurg 51:**354–357, 2008
38. Oka K, Go Y, Yamamoto M, Kumate S, Tomonaga M: Experience with an ultrasonic aspirator in neuroendoscopy. **Minim Invasive Neurosurg 42:**32–34, 1999
39. Rainov NG, Burkert WL: Urokinase infusion for severe intraventricular haemorrhage. **Acta Neurochir (Wien) 134:**55–59, 1995
40. Rosen DS, Macdonald RL, Huo D, Goldenberg FD, Novakovic RL, Frank JI, et al: Intraventricular hemorrhage from ruptured aneurysm: clinical characteristics, complications, and outcomes in a large, prospective, multicenter study population. **J Neurosurg 107:**261–265, 2007
41. Rosenberg GA, Saland L, Kyner WT: Pathophysiology of periventricular tissue changes with raised CSF pressure in cats. **J Neurosurg 59:**606–611, 1983
42. Shapiro SA, Campbell RL, Scully T: Hemorrhagic dilation of the fourth ventricle: an ominous predictor. **J Neurosurg 80:**805–809, 1994
43. Shen PH, Matsuoka Y, Kawajiri K, Kanai M, Hoda K, Yamamoto S, et al: Treatment of intraventricular hemorrhage using urokinase. **Neurol Med Chir (Tokyo) 30:**329–333, 1990
44. Song Z, Yang QD, Zi XH, Fan X: Modified Graeb criteria for predicting the post-hemorrhagic hydrocephalus in intraventricular hemorrhage. **Chin Med Sci J 19:**138–141, 2004
45. Teasdale G, Jennett B: Assessment of coma and impaired consciousness. A practical scale. **Lancet 2:**81–84, 1974
46. Todo T, Usui M, Takakura K: Treatment of severe intraventricular hemorrhage by intraventricular infusion of urokinase. **J Neurosurg 74:**81–86, 1991
47. Tuhrim S, Horowitz DR, Sacher M, Godbold JH: Volume of ventricular blood is an important determinant of outcome in supratentorial intracerebral hemorrhage. **Crit Care Med 27:** 617–621, 1999
48. Tush GM, Tesoro EP, Prabhu S, Brown K, Bullock MR: Intraventricular urokinase for the treatment of intraventricular hemorrhage. **Crit Care Med 27 (Suppl 1):**79A, 1999 (Abstract)
49. Wasserman JK, Schlichter LC: White matter injury in young and aged rats after intracerebral hemorrhage. **Exp Neurol 214:**266–275, 2008
50. Young WB, Lee KP, Pessin MS, Kwan ES, Rand WM, Caplan LR: Prognostic significance of ventricular blood in supratentorial hemorrhage: a volumetric study. **Neurology 40:**616–619, 1990
51. Zhang Z, Li X, Liu Y, Shao Y, Xu S, Yang Y: Application of neuroendoscopy in the treatment of intraventricular hemorrhage. **Cerebrovasc Dis 24:**91–96, 2007

Manuscript submitted December 6, 2011.
Accepted January 16, 2012.
Please include this information when citing this paper: DOI: 10.3171/2012.1.FOCUS11349.

Address correspondence to: Luca Basaldella, M.D., Department of Neurosurgery, Treviso Regional Hospital, University of Padova, Piazzale Ospedale Civile 1, 31100 Treviso, Italy. email: lbasaldella@ulss.tv.

Neurosurg Focus 32 (4):E5, 2012

Predictors of long-term shunt-dependent hydrocephalus in patients with intracerebral hemorrhage requiring emergency cerebrospinal fluid diversion

Brad E. Zacharia, M.D.,[1] Kerry A. Vaughan, B.A.,[1] Zachary L. Hickman, M.D.,[1] Samuel S. Bruce, B.A.,[1] Amanda M. Carpenter, B.A.,[1] Nils H. Petersen, M.D.,[2] Stacie Deiner, M.D.,[3] Neeraj Badjatia, M.D.,[2] and E. Sander Connolly Jr., M.D.[1]

Departments of [1]Neurological Surgery and [2]Neurology, Columbia University; and [3]Departments of Anesthesiology, Neurosurgery, Geriatrics, and Palliative Care, Mount Sinai Hospital, New York, New York

Object. Intracerebral hemorrhage (ICH) is frequently complicated by acute hydrocephalus, necessitating emergency CSF diversion with a subset of patients, ultimately requiring long-term treatment via placement of permanent ventricular shunts. It is unclear what factors may predict the need for ventricular shunt placement in this patient population.

Methods. The authors performed a retrospective analysis of a prospective database (ICH Outcomes Project) containing patients with nontraumatic ICH admitted to the neurological ICU at Columbia University Medical Center between January 2009 and September 2011. A multiple logistic regression model was developed to identify independent predictors of shunt-dependent hydrocephalus after ICH. The following variables were included: patient age, admission Glasgow Coma Scale score, temporal horn diameter on admission CT imaging, bicaudate index, admission ICH volume and location, intraventricular hemorrhage volume, Graeb score, LeRoux score, third or fourth ventricle hemorrhage, and intracranial pressure (ICP) and ventriculitis during hospital stay.

Results. Of 210 patients prospectively enrolled in the ICH Outcomes Project, 64 required emergency CSF diversion via placement of an external ventricular drain and were included in the final cohort. Thirteen of these patients underwent permanent ventricular CSF shunting prior to discharge. In univariate analysis, only thalamic hemorrhage and elevated ICP were significantly associated with the requirement for permanent CSF diversion, with p values of 0.008 and 0.033, respectively. Each remained significant in a multiple logistic regression model in which both variables were present.

Conclusions. Of patients with ICH requiring emergency CSF diversion, those with persistently elevated ICP and thalamic location of their hemorrhage are at increased odds of developing persistent hydrocephalus, necessitating permanent ventricular shunt placement. These factors may assist in predicting which patients will require permanent CSF diversion and could ultimately lead to improvements in the management of this disorder and the outcome in patients with ICH.

(http://thejns.org/doi/abs/10.3171/2012.2.FOCUS11372)

Key Words • intracerebral hemorrhage • hydrocephalus • external ventricular drain • ventriculoperitoneal shunt

Acute hydrocephalus is a common complication of ICH, with an incidence of 40%–50%, and is an independent predictor of poor outcome in this population.[3,6,28] In patients with ICH, acute hydrocephalus generally develops as a consequence of intraventricular extension of the hematoma, resulting in IVH and impairment of CSF drainage and reabsorption.[20] Intraventricular hemorrhage is observed in 45% of patients with ICH, which in and of itself also independently predicts poor outcome.[11,13] Standard treatment of acute hydrocephalus in patients with ICH in whom IVH is present typically involves emergency CSF diversion via placement of an EVD.

Placement of an EVD also affords the opportunity for intraventricular thrombolysis through the administration of compounds such as rtPA into the CSF, which may accelerate clot resolution and decrease the risk of chronic hydrocephalus.[12] In fact, patients with significant IVH, defined as a Graeb score of ≥ 6, have 24 times the odds of developing acute hydrocephalus compared with patients who have minimal or no IVH.[17] This acute CSF flow obstruction can evolve into persistent communicating hydrocephalus despite intraventricular clot resolution, and may necessitate the placement of a VP shunt for permanent CSF diversion.

Little is known about the progression from acute to chronic hydrocephalus and what factors are involved in the process. Few studies have focused specifically on hydrocephalus following ICH; one prior study at a tertiary

Abbreviations used in this paper: CUMC = Columbia University Medical Center; EVD = external ventricular drain; GCS = Glasgow Coma Scale; ICH = intracerebral hemorrhage; ICP = intracranial pressure; IVH = intraventricular hemorrhage; NICU = neurological ICU; rtPA = recombinant tissue plasminogen activator; SAH = subarachnoid hemorrhage; VP = ventriculoperitoneal.

care center identified thalamic location and elevated ICP as independent predictors of the need for VP shunt placement in patients with ICH admitted for acute hydrocephalus.[14] We sought to identify early predictors of long-term shunt dependency in a prospectively studied cohort of patients with ICH who had undergone EVD placement for emergency CSF diversion.

Methods

Patient Selection and Data Collection

All patients with primary spontaneous ICH admitted to the NICU within 7 days of ICH onset at CUMC between January 2009 and August 2011 were screened for enrollment in our prospective ICH Outcomes Project. All patients opted to participate and were entered into the database. The protocol was approved by the CUMC institutional review board, and written consent was obtained from the patient or a designated surrogate. Admission head CT imaging was used to establish the diagnosis of ICH. Patients with ICH secondary to trauma or underlying vascular abnormalities such as arteriovenous malformations were excluded from our analysis. Patients were followed throughout their hospital course, and their disorder was managed according to current ICH guidelines set forth by the American Heart Association and the American Stroke Association.[15]

Clinical Variables

Demographic information collected at admission included age, ethnicity, and sex. Neurological and general medical evaluations, including determination of disease severity according to the ICH score, were performed by neurointensive care physicians on admission.[8] Clinical variables were recorded at admission and subsequently examined for potential associations with shunt-dependent hydrocephalus. Treatment modalities and complications were recorded, including placement of an EVD, number of days with an EVD in place, maximum ICP during the index ICU stay, and development of ventriculitis. Ventriculitis was defined as fever with CSF pleocytosis, with or without positive CSF cultures, and without other identifiable sources of fever. Maximum ICP was analyzed as 2 dichotomous variables (any ICP ≥ 25 mm Hg and/or a recorded ICP ≥ 20 mm Hg on ≥ 2 consecutive days) based on criteria used in a previous study by Miller et al.[14]

Radiographic Variables

Admission head CT imaging was used for independent assessment of radiographic characteristics including ICH location, ICH volume, presence of IVH, the IVH volume, presence of third ventricular blood, presence of fourth ventricular blood, temporal horn diameter, and bicaudate index.[2] The LeRoux score was calculated from radiographic measurements.[10] Location was classified into the following categories: thalamic, basal ganglia, cortical, cerebellar, brainstem, or subcortical white matter. Hydrocephalus was dichotomized as present or absent on the admission CT scan, based on temporal horn diameter and bicaudate index. Both the Graeb and LeRoux scores were calculated for each scan. The volume of ICH and IVH was quantified using MIPAV software (version 4.3, National Institutes of Health).

Placement and Management of the EVD

The neurological status of all patients admitted with spontaneous ICH was assessed at least hourly by qualified staff while the patients remained in the NICU. Any clinical evidence of hydrocephalus (for example, severe headache or decrement of GCS) during this period prompted evaluation for acute CSF diversion via EVD placement. Subsequent radiographic assessment for hydrocephalus was then performed in all cases using head CT imaging, with comparison of temporal horn diameter, bicaudate index, and shape of the third ventricle to any available prior imaging. The presence of clinical and radiographic hydrocephalus was ultimately determined based on the clinical judgment of the NICU team. The EVD insertion was preferentially performed on the right (generally nondominant) side unless there were relative radiographic contraindications as determined by the attending neurosurgeon, such as hematoma in the planned path of the EVD, difficulty in accessing the right lateral ventricle, a completely blood-filled right lateral ventricle, or a concern for worsened left-to-right midline shift. The site of EVD insertion was at the Kocher point in all cases and was performed in routine fashion. Following placement and confirmation at the bedside of a working drain, an immediate postprocedure CT scan was obtained to document the location of the proximal EVD tip. All patients received a preprocedure dose of prophylactic antibiotics (cefazolin, or vancomycin if the patient was allergic to penicillins or cephalosporins). Appropriate prophylactic antibiotics were continued for the time that the EVD remained in place and were discontinued thereafter.

Random CSF sampling from the EVD collection system was performed routinely 3 times per week and when clinically indicated. If patients were deemed by the NICU team to have ventriculitis, either due to a persistently worrisome CSF profile or to positive CSF cultures, patients were treated with a course of appropriate antibiotics (generally vancomycin and cefepime). The EVDs were not prophylactically exchanged for fresh catheters, nor were prophylactic intraventricular antibiotics routinely administered, given a lack of evidence for these practices.[22] In patients with significant IVH, intraventricular thrombolysis with rtPA was administered per the Clot Lysis: Evaluating Accelerated Resolution of IVH (CLEAR IVH) protocol to facilitate clot resolution.[7,9,24]

Intracranial pressure was recorded at least hourly in all patients with EVDs. Drain height was adjusted as needed based on the patient's neurological status and to maintain a goal ICP between 0 and 20 mm Hg. Any recorded ICP ≥ 25 or ≥ 20 mm Hg for > 10 consecutive minutes was considered to be elevated ICP and was treated with additional CSF drainage and/or standard medical therapy.

Weaning from the EVD was performed based on the patient's neurological status, radiographic criteria (such as ventricular size and resolution of IVH), and hourly CSF output. When deemed appropriate by the NICU team and

attending neurosurgeon, daily EVD clamp trials were initiated. During periods when an EVD was clamped, ICP was continuously transduced. Clinical criteria for aborting an EVD clamp trial included the following: 1) decline in neurological status or significant worsening of symptoms, such as persistent severe headache; and 2) sustained ICP ≥ 20 mm Hg for > 10 minutes. When possible, a repeat head CT would be obtained without contrast to assess radiographic appearance of the ventricular system prior to reopening of the EVD. Patients successfully completing a 24-hour clamp trial would have their EVD removed at the bedside. For those patients in whom repeated EVD clamp trials failed, a VP shunt was placed as definitive treatment for persistent hydrocephalus.

Definition of Outcome

Shunt-dependent hydrocephalus was defined as symptoms of hydrocephalus (decreased mental status) with persistent elevated ICP as measured via a transduced EVD, or radiographic evidence of enlarged ventricles, necessitating the placement of a VP shunt for permanent CSF diversion prior to hospital discharge. No patients with ventriculoatrial shunts were included in this analysis, because these types of shunts have not been placed as a first-line permanent diversion system for any patients with ICH at our center.

Statistical Analysis

Univariate analyses were performed using the Student t-test for continuous variables, the Wilcoxon rank-sum test for ordinal variables, and the Fisher exact and Pearson chi-square tests for categorical variables. Location was assessed by comparing each group individually to the remaining locations as an aggregate. A multiple logistic regression model was constructed with significant variables from the univariate analyses to identify predictors of VP shunt placement. All statistical analyses were performed using the R environment for statistical computing (R Development Core Team, 2008).

Results

During the study period, 66 of 210 patients enrolled in our ICH Outcomes Project required emergency CSF diversion via EVD placement on admission. We excluded 2 of these 66 patients from our analysis due to incomplete data, resulting in a final cohort of 64 patients. Of these, 13 patients (20%) developed shunt-dependent hydrocephalus, necessitating VP shunt placement prior to discharge. The mean age was similar, 60.1 versus 61.5 years for those without and with VP shunt placement, respectively, and the admission GCS score was identical in both groups. There was a greater proportion of patients diagnosed with ventriculitis in the VP shunt group, although the difference was not statistically significant. Demographic data and baseline characteristics of the patients included in our analysis are provided in Table 1.

The admission characteristics and radiographic variables significantly associated with shunt dependency in the univariate analysis included maximum ICP ($p = 0.013$), ICP ≥ 25 mm Hg ($p = 0.030$), ICP ≥ 20 mm Hg on ≥ 2 consecutive days ($p = 0.033$), thalamic location ($p = 0.008$), and number of days with EVD in place ($p < 0.001$). Of the 23 patients with a thalamic lesion who required placement of an EVD, only 3 also had persistently elevated ICP; 1 of these patients ultimately required VP shunt placement.

Two multiple logistic regression models were then constructed, the first including thalamic location and ICP ≥ 25 mm Hg and the second with thalamic location and ICP ≥ 20 mm Hg on ≥ 2 consecutive days (Table 2). The number of days that an EVD was in place was not included as a variable in our final models because it is probably an index of disease severity rather than a predictive factor for persistent hydrocephalus. Because age, admission neurological status, and IVH volume were not associated with VP shunt placement in our univariate analysis, nor have they been shown to be significant in prior studies of shunt-dependent hydrocephalus after ICH and SAH, they were not included in our multiple logistic regression models.[14,23]

Discussion

In a cohort of 210 patients admitted to the NICU at CUMC with spontaneous ICH, 64 patients required placement of an EVD for the management of acute hydrocephalus. Within this group, we identified 2 independent predictors of shunt-dependent hydrocephalus: 1) patients with a thalamic ICH, and 2) those demonstrating persistently elevated ICP during their ICU stay. The effect of these factors on the odds of requiring permanent CSF diversion was independent of age, admission neurological status, or IVH volume. Miller and colleagues[14] previously identified similar predictors in a comparable cohort of patients following ICH. The results of our analysis confirm the results of this prior study, suggesting that these factors are robust predictors of shunt dependency in patients with acute hydrocephalus from ICH. Furthermore, the rates of emergency CSF diversion via EVD placement and eventual VP shunt placement in these 2 series may serve as a reliable benchmark for future investigations into the clinical course of hydrocephalus. Unlike in SAH, there has been no association reported between hydrocephalus and age, sex, or ethnicity in patients with ICH.[5] A prior investigation found no association between shunt-dependent hydrocephalus and admission neurological status in patients with SAH, in agreement with previous ICH cohort data as well as results from our univariate analysis.[23]

Interestingly, development of shunt-dependent hydrocephalus was more likely in those patients with a thalamic hemorrhage, but independent of other hemorrhage locations or IVH volume, despite the fact that IVH is known to predict worse outcomes in patients with ICH in a volume-dependent manner.[18,25] Given the anatomical relationship of thalamic hemorrhages to the third ventricle and the foramen of Monro, it is intuitive that hematoma formation in this location more easily results in obstruction of CSF flow independent of IVH volume than in hemorrhages occurring in other locations. Reports of thalamic cavernomas and hemorrhages without intraventricular extension have documented the development of

TABLE 1: Demographic, clinical, and radiographic characteristics in 64 patients with ICH treated with and without VP shunts*

Variable	No VP Shunt	VP Shunt	p Value
no. of patients	51	13	
age in yrs	60.1 ± 16.1	61.46 ± 10.1	0.707
admission GCS score	7 (IQR 5–13)	7 (IQR 5–9)	0.663
ventriculitis	7 (13.7%)	3 (23.1%)	0.411
lat ventricular blood	46 (90.2%)	12 (92.3%)	1.000
3rd ventricle >50%†	33 (64.7%)	7 (53.8%)	0.688
4th ventricle >50%†	31 (60.8%)	8 (61.5%)	0.788
multiple ventricles >50%	32 (62.7%)	7 (53.8%)	0.788
max ICP	22 (IQR 18–28)	30 (IQR 27–33)	0.013
max ICP ≥25 mm Hg	21 (41.2%)	10 (76.9%)	0.030
ICP ≥20 mm Hg on ≥2 days	26 (51.0%)	11 (84.6%)	0.033
ICH location			
thalamic	14 (27.5%)	9 (69.2%)	0.008
basal ganglia	11 (21.6%)	2 (15.4%)	1.000
cortical	15 (29.4%)	1 (7.7%)	0.157
cerebellum	9 (17.6%)	1 (7.7%)	0.672
brainstem	1 (2.0%)	0 (0%)	1.000
subcortical white matter	1 (2.0%)	0 (0%)	1.000
ICH score	3 (IQR 2–3)	2 (IQR 2–3)	0.302
Graeb score	7 (IQR 4–8.5)	6 (IQR 5–7)	0.769
LeRoux score	10 (IQR 5–11)	9 (IQR 6–10)	0.688
hydrocephalus	37 (72.5%)	11 (84.6%)	0.489
bicaudate index	0.18 ± 0.07	0.21 ± 0.06	0.290
ICH vol in cm^3	11.6 (IQR 3.4–30.5)	13.7 (IQR 6.2–17.0)	0.854
rtPA	9 (17.6%)	1 (7.7%)	0.672
days w/ EVD	8 (IQR 5–11)	14 (IQR 12–15)	<0.001

* Data are presented as the mean ± SD; median (IQR); or number (%). Abbreviations: IQR = interquartile range; max = maximum.
† The entries "3rd ventricle >50%" and "4th ventricle >50%" refer to hemorrhage obstructing > 50% of the volume of the respective ventricles on admission CT scans.

hydrocephalus.[4,16,19,26,27] The pathophysiological mechanisms predisposing thalamic lesions to hydrocephalus remain unclear and are worthy of further investigation.

It remains unclear precisely how IVH contributes to the development of persistent hydrocephalus, although one hypothesis is that obstruction of the arachnoid villi by blood, a known factor in the development of acute hydrocephalus after IVH, may also contribute to the development of chronic hydrocephalus.[5] In our cohort, however, we found no association between IVH volume and the development of shunt-dependent hydrocephalus. It is interesting to note the very high percentage of patients (> 90% for both those requiring VP shunt placement and those who did not) who had any amount of IVH on admission CT imaging. This tends to argue that, although IVH may be important in the development of acute hydrocephalus, continued obstruction of the arachnoid villi by blood products or subsequent scarring may be rare phenomena.

Persistently elevated ICP was also associated with an increased risk of shunt-dependent hydrocephalus in our cohort. Although increased ICP is generally accepted to be a predictor of poor outcome following ICH, controlling ICP via medical and surgical means may not necessarily improve outcomes or reduce the risk for chronic hydrocephalus.[1,21] More specifically, our final model supports an association between elevated ICP, despite continued CSF diversion with an EVD, and an increased risk of progressing to shunt-dependent hydrocephalus. One explanation may be that following the onset of acute hydrocephalus, a subset of patients are prone to developing decreased ventricular compliance, poor CSF flow dynamics and reabsorption, or both, resulting in a continued need for CSF diversion. Given that the age range of our cohort is limited, the pathophysiological implications of age-related cerebral volume loss on the development of elevated ICP and shunt dependency are unclear. However, within the typical age range of most patients with ICH, there appears to be no association between age and the development of shunt-dependent hydrocephalus, as evidenced by our results.

Although our study includes a reasonably large co-

TABLE 2: Final multiple logistic regression models*

Variable	OR	95% CI	p Value
Model 1			
max ICP ≥25 mm Hg	1.264	1.056–1.513	0.013
thalamic location	1.344	1.115–1.621	0.003
Model 2			
ICP ≥20 mm Hg on ≥2 days†	1.214	1.007–1.462	0.046
thalamic location	1.312	1.083–1.589	0.007

* The final models both include thalamic location and elevated ICP; however, each uses a different dichotomized measurement for presence of elevated ICP. The 2 forms of increased ICP both remain significant in their respective models.

† The term "ICP ≥20 mm Hg on ≥2 days" refers to ICP ≥ 20 mm Hg on ≥ 2 consecutive days.

hort of patients with primary ICH in whom adjudicated prospectively collected data were available, it has several limitations. First, there were relatively few patients (13 [20.3%] of 64) who reached the study end point of long-term shunt dependency requiring permanent CSF diversion. Second, our study is also potentially subject to survivor bias, in that within our cohort there was a subset of patients in whom care was ultimately withdrawn due to the patient's or family's wishes following EVD placement, but prior to establishing a requirement for permanent CSF diversion. It is possible that several of these patients may have eventually required VP shunt placement. Ultimately, additional tertiary care center studies may strengthen our benchmark data and elucidate other risk factors for persistent posthemorrhagic hydrocephalus. Future investigations using data from multimodality intracranial monitoring may provide greater insight into the pathophysiological mechanisms that underlie the development of shunt dependency.

Conclusions

The development of shunt-dependent hydrocephalus after ICH was associated in our cohort with thalamic location of the hemorrhage and persistently elevated ICP. This is in agreement with a prior study, and our results may therefore serve as a baseline epidemiological reference in future investigations for both the incidence of acute hydrocephalus requiring emergency CSF diversion via EVD and the need for eventual VP shunt placement. Thalamic location of an ICH and continually elevated ICP may alert physicians early during ICH recovery that a patient may be more likely to require permanent CSF diversion. This may promote more aggressive monitoring and earlier interventions for continually elevated ICP in patients at risk. However, the pathophysiological mechanisms underlying progression of acute to shunt-dependent hydrocephalus remain poorly understood. Our results, in conjunction with those from other groups, provide a reference point on which to base further inquiries and to gauge the potential benefits of more aggressive management for this disorder in at-risk patients with ICH.

Disclosure

Sources of funding were as follows: Department of Neurological Surgery, Columbia University, New York, New York (B.E.Z., K.A.V., Z.L.H., S.S.B., A.M.C., E.S.C.), and Doris Duke Clinical Foundation Research Fellowship, Hillsborough, New Jersey (K.A.V.). The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Zacharia, Vaughan. Acquisition of data: Vaughan, Carpenter. Analysis and interpretation of data: Zacharia, Vaughan, Bruce, Petersen, Deiner. Drafting the article: Vaughan. Critically revising the article: Zacharia, Hickman, Petersen, Deiner, Badjatia, Connolly. Reviewed submitted version of manuscript: Zacharia, Badjatia, Connolly. Approved the final version of the manuscript on behalf of all authors: Zacharia. Statistical analysis: Bruce, Petersen, Deiner. Administrative/technical/material support: Carpenter, Badjatia, Connolly. Study supervision: Zacharia, Hickman, Carpenter, Connolly.

References

1. Adams RE, Diringer MN: Response to external ventricular drainage in spontaneous intracerebral hemorrhage with hydrocephalus. **Neurology 50:**519–523, 1998
2. Barr AN, Heinze WJ, Dobben GD, Valvassori GE, Sugar O: Bicaudate index in computerized tomography of Huntington disease and cerebral atrophy. **Neurology 28:**1196–1200, 1978
3. Bhattathiri PS, Gregson B, Prasad KSM, Mendelow AD: Intraventricular hemorrhage and hydrocephalus after spontaneous intracerebral hemorrhage: results from the STICH trial. **Acta Neurochir Suppl 96:**65–68, 2006
4. Cartmill M, Vloeberghs M: The fate of the cerebrospinal fluid after neuroendoscopic third ventriculostomy. **Childs Nerv Syst 16:**879–881, 2000
5. Dey M, Jaffe J, Stadnik A, Awad IA: External ventricular drainage for intraventricular hemorrhage. **Curr Neurol Neurosci Rep 12:**24–33, 2012
6. Diringer MN, Edwards DF, Zazulia AR: Hydrocephalus: a previously unrecognized predictor of poor outcome from supratentorial intracerebral hemorrhage. **Stroke 29:**1352–1357, 1998
7. Gaberel T, Magheru C, Parienti J-J, Huttner HB, Vivien D, Emery E: Intraventricular fibrinolysis versus external ventricular drainage alone in intraventricular hemorrhage: a meta-analysis. **Stroke 42:**2776–2781, 2011
8. Hemphill JC III, Bonovich DC, Besmertis L, Manley GT, Johnston SC: The ICH score: a simple, reliable grading scale for intracerebral hemorrhage. **Stroke 32:**891–897, 2001
9. Herrick DB, Ziai WC, Thompson CB, Lane K, McBee NA, Hanley DF: Systemic hematologic status following intraventricular recombinant tissue-type plasminogen activator for intraventricular hemorrhage: the CLEAR IVH Study Group. **Stroke 42:**3631–3633, 2011
10. LeRoux PD, Haglund MM, Newell DW, Grady MS, Winn HR: Intraventricular hemorrhage in blunt head trauma: an analysis of 43 cases. **Neurosurgery 31:**678–685, 1992
11. Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringer MN, et al: Recombinant activated factor VII for acute intracerebral hemorrhage. **N Engl J Med 352:**777–785, 2005
12. Mayer SA, Rincon F: Treatment of intracerebral haemorrhage. **Lancet Neurol 4:**662–672, 2005
13. Mendelow AD, Gregson BA, Fernandes HM, Murray GD, Teasdale GM, Hope DT, et al: Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomised trial. **Lancet 365:**387–397, 2005

14. Miller C, Tsivgoulis G, Nakaji P: Predictors of ventriculoperitoneal shunting after spontaneous intraparenchymal hemorrhage. **Neurocrit Care 8:**235–240, 2008
15. Morgenstern LB, Hemphill JC III, Anderson C, Becker K, Broderick JP, Connolly ES Jr, et al: Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. **Stroke 41:**2108–2129, 2010
16. Ng LK, Schwarz G, Mishkin MM: Hematoma from arteriovenous malformation producing hydrocephalus and simulating a thalamic tumor. Report of two cases. **J Neurosurg 34:**229–235, 1971
17. Nishikawa T, Ueba T, Kajiwara M, Miyamatsu N, Yamashita K: A priority treatment of the intraventricular hemorrhage (IVH) should be performed in the patients suffering intracerebral hemorrhage with large IVH. **Clin Neurol Neurosurg 111:**450–453, 2009
18. Ozdemir O, Calisaneller T, Hastürk A, Aydemir F, Caner H, Altinors N: Prognostic significance of third ventricle dilation in spontaneous intracerebral hemorrhage: a preliminary clinical study. **Neurol Res 30:**406–410, 2008
19. Pozzati E: Thalamic cavernous malformations. **Surg Neurol 53:**30–40, 2000
20. Qureshi AI, Mendelow AD, Hanley DF: Intracerebral haemorrhage. **Lancet 373:**1632–1644, 2009
21. Qureshi AI, Wilson DA, Traystman RJ: Treatment of elevated intracranial pressure in experimental intracerebral hemorrhage: comparison between mannitol and hypertonic saline. **Neurosurgery 44:**1055–1064, 1999
22. Ratilal B, Costa J, Sampaio C: Antibiotic prophylaxis for surgical introduction of intracranial ventricular shunts. **Cochrane Database Syst Rev 3:**CD005365, 2006
23. Rincon F, Gordon E, Starke RM, Buitrago MM, Fernandez A, Schmidt JM, et al: Predictors of long-term shunt-dependent hydrocephalus after aneurysmal subarachnoid hemorrhage. Clinical article. **J Neurosurg 113:**774–780, 2010
24. Staykov D, Huttner HB, Struffert T, Ganslandt O, Doerfler A, Schwab S, et al: Intraventricular fibrinolysis and lumbar drainage for ventricular hemorrhage. **Stroke 40:**3275–3280, 2009
25. Staykov D, Wagner I, Volbers B, Hauer EM, Doerfler A, Schwab S, et al: Natural course of perihemorrhagic edema after intracerebral hemorrhage. **Stroke 42:**2625–2629, 2011
26. Tokumitsu N, Sako K, Kunimoto M, Nakai H, Yonemasu Y: Glial cyst in the thalamus with intracystic hemorrhage—case report. **Neurol Med Chir (Tokyo) 37:**284–287, 1997
27. Waga S, Okada M, Yamamoto Y: Reversibility of Parinaud syndrome in thalamic hemorrhage. **Neurology 29:**407–409, 1979
28. Zazulia AR: Hydrocephalus in ICH: what do we really know? **Neurocrit Care 8:**233–234, 2008

Manuscript submitted December 21, 2011.
Accepted February 6, 2012.
Please include this information when citing this paper: DOI: 10.3171/2012.2.FOCUS11372.

Address correspondence to: Brad E. Zacharia, M.D., Department of Neurological Surgery, Columbia University, 630 West 168th Street, Room 5-454, New York, New York 10032. email: bez2103@columbia.edu.

Neurosurg Focus 32 (4):E6, 2012

Telemedicine-assisted treatment of patients with intracerebral hemorrhage

Filippo F. Angileri, M.D., Ph.D., Salvatore Cardali, M.D., Ph.D., Alfredo Conti, M.D., Ph.D., Giovanni Raffa, M.D., and Francesco Tomasello, M.D.

Department of Neurosurgery, University of Messina, Italy

Object. Telemedicine provides a new approach to improve stroke care in community settings, delivering acute stroke expertise to hospitals in rural areas. Given the controversies in many aspects of the treatment of intracerebral hemorrhage (ICH) and the lack of guidelines, a prompt neurosurgical second opinion may facilitate the treatment of patients with ICH. Here, the authors' 8-year experience with the use of telemedicine in the management of ICH is reported.

Methods. The medical records of patients with ICH treated through a telemedicine system in the district of Messina, Italy, between June 2003 and June 2011 were retrospectively reviewed. Neuroradiological and clinical data for patients were transmitted through a high-technology "hub-and-spoke" telemedicine network. Neurosurgical teleconsulting (at the hub) was available for 7 peripheral hospitals (spokes) serving about 700,000 people. The authors analyzed 1) the time between peripheral hospital admission and the specialized second opinion consultation, 2) primary and secondary transfers to the authors' neurosurgery department, and 3) the treatments (surgical or medical) of patients transferred to the hub.

Results. The telemedicine network was used to treat more than 2800 patients, 733 with ICH. A neurosurgical consultation was provided in 38 minutes versus 160 minutes for a consultation without telemedicine. One hundred seventy-six (24%) of 733 patients were primarily transferred to the hub. Ninety-five patients (13%) underwent surgical treatment. The remaining 81 patients (11%) underwent neurointensive care. Eight (1.4%) of 557 patients treated at the spokes needed a secondary transfer for surgical treatment because of a worsening clinical condition and/or CT findings. Considering secondary and inappropriate transfers, the interpretation of data was correct in 96.5% of cases.

Conclusions. Telemedicine allowed rapid visualization of neuroradiological and clinical data, providing neurosurgical expertise to community hospitals on demand and within minutes. It allowed the treatment of patients at peripheral hospitals and optimized resources. A small percentage of patients treated at the peripheral hospitals had secondary deterioration. Telemedicine allowed fast patient transfer when necessary and provided improved accuracy in patient care.

(http://thejns.org/doi/abs/10.3171/2012.1.FOCUS11356)

Key Words • **intracerebral hemorrhage** • **telemedicine** • **telestroke**

Intracerebral hemorrhage accounts for 15%–30% of all acute strokes, with an incidence of approximately 12–15 cases/100,000 persons/year.[5,10] Overall mortality from ICH is worse than that from ischemic stroke, approaching 50% at 30 days after hemorrhage,[6,9] and patients who survive are independent at 6 months after ICH in less than 20% of cases.[5] Because of its frequency and dramatic impact on the neurological status of patients, ICH is one of the most frequent clinical conditions for which an emergency neurosurgical consultation is required. An expert opinion is needed to coordinate the best patient care, because there are no guidelines for the management of many aspects of ICH, including the choice of medical versus surgical treatment. Telemedicine is the ideal means of immediately providing this consultation for patients admitted to peripheral hospitals.[12]

"Telemedicine," a term coined in the 1970s,[25] is the use of information and communication technology to improve patient outcomes by increasing access to care, medical information, and evidence-based clinical practice. It includes consultative, diagnostic, and treatment services with the aim of improving patient care and the efficacy of the diagnostic and therapeutic strategies at the peripheral hospitals.

Abbreviations used in this paper: CTA = CT angiography; GCS = Glasgow Coma Scale; ICH = intracerebral hemorrhage; ICP = intracranial pressure; IVH = intraventricular hemorrhage; MRA = MR angiography; PACS = picture archiving and communication system; ROI = region of interest.

Many studies have shown that telemedicine improves the care of patients with ischemic stroke who have been admitted to peripheral hospitals,[12–14,22,27] allowing for the quick selection of candidates for thrombolytic therapy[7] and eventually improving the long-term neurological outcome.[3,18] However, studies focused on the role of telemedicine in the treatment of patients with ICH in an acute setting are missing. The aim of the present study was to analyze the role of a telemedicine network in the treatment of patients with spontaneous ICH in terms of a faster neurosurgical evaluation and selection of patients who are the best candidates for direct neurosurgical or neurointensive care.

Methods

A telemedicine network project named RESPECT, from the Italian "REte SPECialistica per il Trauma," meaning specialized network for trauma, was set up in 2003 and co-financed by the Italian Ministry of Education, University and Research. The telemedicine system is coordinated by the Department of Neurosurgery at the University of Messina. Seven peripheral hospitals are connected to this neurosurgical department. The system serves a population of 684,703 people living in the area of Messina, whose extra-urban territory is mainly composed of a rural territory and 7 small islands. We retrospectively reviewed all medical records of patients with spontaneous ICH who had been admitted to the peripheral hospitals of the Messina district between June 2003 and June 2011 and for whom an urgent neurosurgical consultation had been requested.

Teleconsultation System and Procedures

Neuroradiological data on patients were transmitted from the peripheral hospitals to our department through a high-technology "hub-and-spoke" telemedicine network implemented in the territory of the Messina province. The radiology departments of the connected hospitals (the "spokes") used PACS (picture archiving and communication system) technology for archiving the images. The images were reviewed at the Department of Neurosurgery at the University of Messina (the "hub").

The transmission of information was performed using a pixels-on-demand technology provided by Telbios S.p.A. In brief, the system encodes only the pixels relevant for presenting the required image view, namely a ROI requested by the user and not the full image file, by connecting to the original archived images. The ROI is streamed to the client location from the original PACS in lossless quality and in real time. Once the hub user selects a remote image from the archive, the system performs a fast preprocessing step in near real time. From then on, the system is able to respond to any request in real time. When a ROI request arrives at the server, progressive image encoding is performed only for the ROI and not for the full image. Similarly, on the client side, decoding and rendering is only performed for the ROI. When a user pans, zooms, or scrolls to the next slices, the server encodes the missing parts of the new ROI "on the fly" and sends them to the client.

The system is connected to the DICOM (Digital Imaging and Communications in Medicine) archive via a fast LAN (local area network) connection, and a further integrated services delivery network line is provided in case of malfunctioning. Images are taken via DICOM protocol or from direct file system access (read-only input/output).

When a patient with ICH was admitted to the spoke hospital, he or she underwent CT scanning. The radiologist on duty interpreted the CT images. A neurosurgical consultation was requested through the telemedicine system. The neurosurgeon on duty at the academic hub analyzed the neuroradiological images along with the radiology report, as well as anamnestic and clinical data. Clinical information included age, sex, GCS score, pupillary status, respiratory status, complete blood count, coagulation status, and use of anticoagulants, heparin, or antiplatelet drugs. Any information concerning clinical onset and evolution of symptoms or previous relevant pathological events were communicated and recorded as well.

After neurosurgical consultation, patients were treated at the peripheral hospitals or transferred to the hub for the best treatment (medical or surgical), depending on the case. Patients were treated at the peripheral hospital through clinical observation, neuroradiological monitoring, and medical therapy or were transferred to our department for clinical/neuroradiological monitoring and medical/surgical treatment.

We analyzed the 1) time between peripheral hospital admission and the second opinion specialist consultation, 2) primary and secondary transfers to our neurosurgical department, and 3) treatment (surgical or medical) of patients transferred to the hub. Through the analysis of the aforementioned parameters, we sought to investigate the utility of our telemedicine network in terms of faster transfer to a specialized hospital, better management at the peripheral hospitals, and improved medical and/or surgical treatment of patients with hemorrhagic stroke.

Results

Seven hundred thirty-three patients with ICH received neurosurgical consultation through the Telbios telemedicine system at the neurosurgical clinic of the University of Messina between June 2003 and June 2011. These patients with ICH represented 26% of all patients who needed an urgent neurosurgical consultation through telemedicine during the selected period (2819 patients).

The first end point of this study was the analysis of the time frame needed to provide a neurosurgical second opinion consultation. Analyzing the CT scanning records and the relevant neurosurgical opinion, we recorded a mean of 38 minutes (range 23–109 minutes) between hospital admission at the spoke and neurosurgical consultation at the hub. The mean time was 160 minutes (range 68–204 minutes) for a second opinion consultation obtained through patient transportation, before the introduction of the telemedicine system. The time needed to obtain neurosurgical teleconsultation at the periphery was not dissimilar to that in Messina's urban area, which was estimated at an average of 26 minutes (range 0–37 minutes).

The second study end point was the analysis of primary and secondary transfers to our neurosurgical department and neurointensive care. Data are summarized in Fig. 1. During the evaluation period, 176 (24%) of 733 patients needed a primary transfer to the academic hub for the management of ICH. Selecting patients for transfer was based on a combination of clinical, demographic, and radiological characteristics. Hematoma location, CT features, and size were the radiological characteristics considered in combination with the age of, relevant clinical data on, and neurological status of the patient. In cases of controversial interpretation, the neuroradiological team at the hub reevaluated the images.

On the basis of hematoma location, capsular, thalamic, or posterior fossa ICH in patients older than 45 years and with a history of systemic hypertension was presumptively judged as primary hypertensive ICH, without the need for further diagnostic workup. Transfer to the hub of patients with ICHs in the aforementioned locations was done on the basis of hematoma size and patient clinical status (Fig. 1). Patients with capsular or thalamic ICHs with volumes ranging between 30 and 70

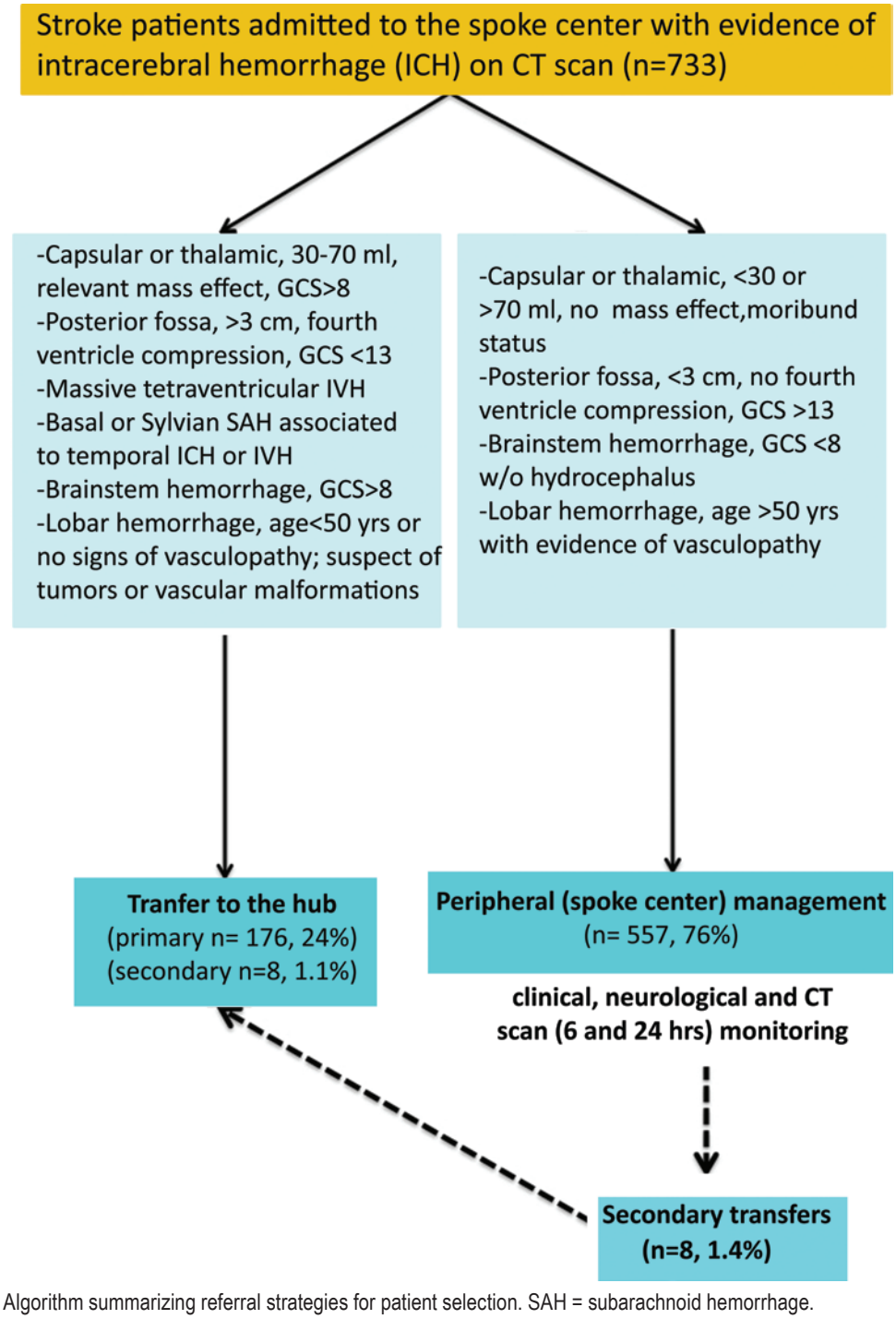

Fig. 1. Algorithm summarizing referral strategies for patient selection. SAH = subarachnoid hemorrhage.

ml—that is, with evidence of relevant mass effect—and a GCS score > 8 were transferred to the hub and underwent surgical treatment (Fig. 2). With regard to posterior fossa ICHs, compression of the fourth ventricle and/or a clot size > 3 cm were considered criteria for transfer to our neurosurgical unit. Patients underwent surgical treatment if they had a GCS score < 13 or evidence of neurological deterioration.

Patients with blood in the entire ventricular system were considered at risk for hydrocephalus and were centralized, whereas patients with only a minimal amount of blood in 1 lateral ventricle were left at the peripheral hospital and observed. All patients with a subarachnoid clot in the basal or sylvian cisterns associated with temporal or IVH were admitted to the central hospital for further studies. Patients with brainstem hemorrhage were admitted only if the GCS score was > 8 to treat or prevent deterioration as a result of acute hydrocephalus. Patients in a deep coma because of large brainstem injuries were treated only with supportive care.

With regard to lobar hemorrhages, patients younger than 50 years of age were admitted to the central hospital (Fig. 3). Older patients with evidence of vasculopathy remained at the peripheral hospital with the indication for performing MRI and MRA.

In general, other CT features were considered, including marks suggestive of vascular abnormalities, tumors, sinus thrombosis, or hemorrhagic transformation of ischemic stroke, and were evaluated on an individual basis. When a secondary ICH was suspected, the patient was admitted to the neurosurgical department to complete our institutional diagnostic workup protocol consisting of CTA, MRI, MRA, SPECT, and eventually angiography.[20]

The 557 patients who remained at a peripheral hospital had neuroradiological images and clinical/neurological conditions that did not require direct neurosurgical or neurointensive care management. They were treated through clinical, neurological, and neuroradiological monitoring, according to the neurosurgical consultation and indications. In particular, the neurosurgeon recommended a control CT scan 6 hours later and a second control scan 24 hours after stroke onset. This practice was different for patients directly admitted to the central hospital, who did not undergo the 6-hour CT control study unless their condition clinically deteriorated.

Eight (1.4%) of 557 patients needed a secondary transfer to our department for a worsening of clinical conditions and/or deterioration of neuroradiological findings. Five of these 8 patients were on anticoagulation drugs for other diseases. Patients in a deep coma or with a moribund status were not transferred, however, and were given only supportive care.

Of the 176 patients who were centralized, 95 (13% of the overall group) underwent surgical evacuation of an ICH. Surgical indication was individualized and based on the patient's age and neurological status, hematoma size and location, and related mass effect (Fig. 4). The remaining 81 patients (11%) underwent clinical, neurological, and neuroradiological monitoring and received only medical therapy. Thirty-nine of these patients underwent

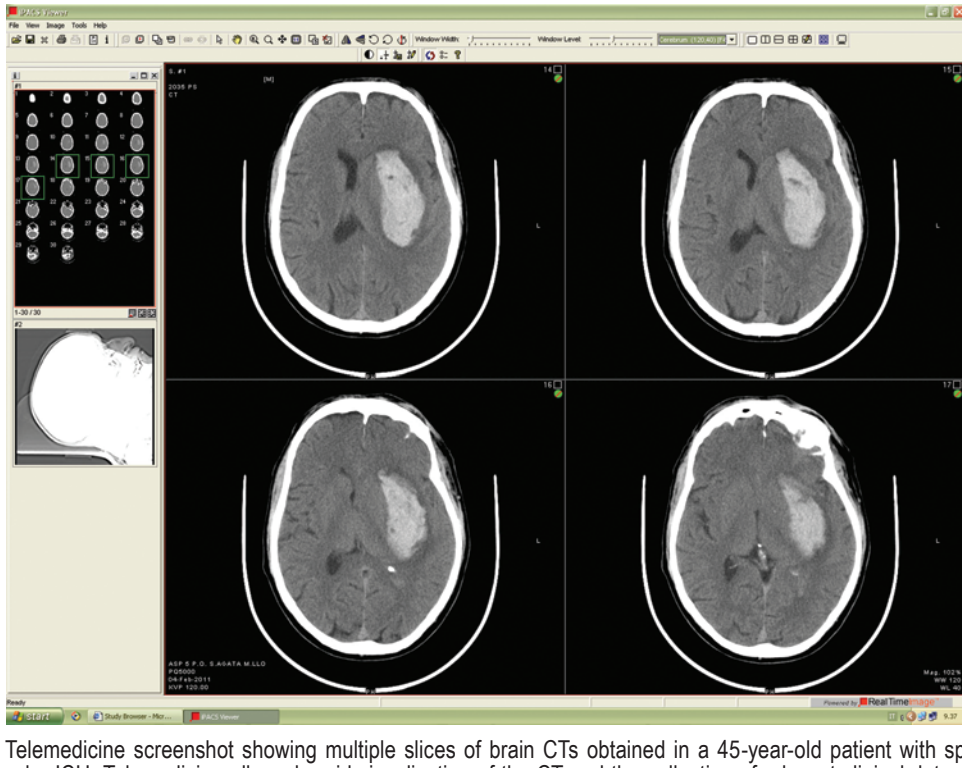

Fig. 2. Telemedicine screenshot showing multiple slices of brain CTs obtained in a 45-year-old patient with spontaneous nucleocapsular ICH. Telemedicine allowed rapid visualization of the CT and the collection of relevant clinical data. In general, nucleocapsular hematoma was not managed by central transfer, unless there was evidence of relevant mass effect with possible deterioration requiring neurointensive care or surgical control of ICP. Cautious conservative management led to a good outcome in this case.

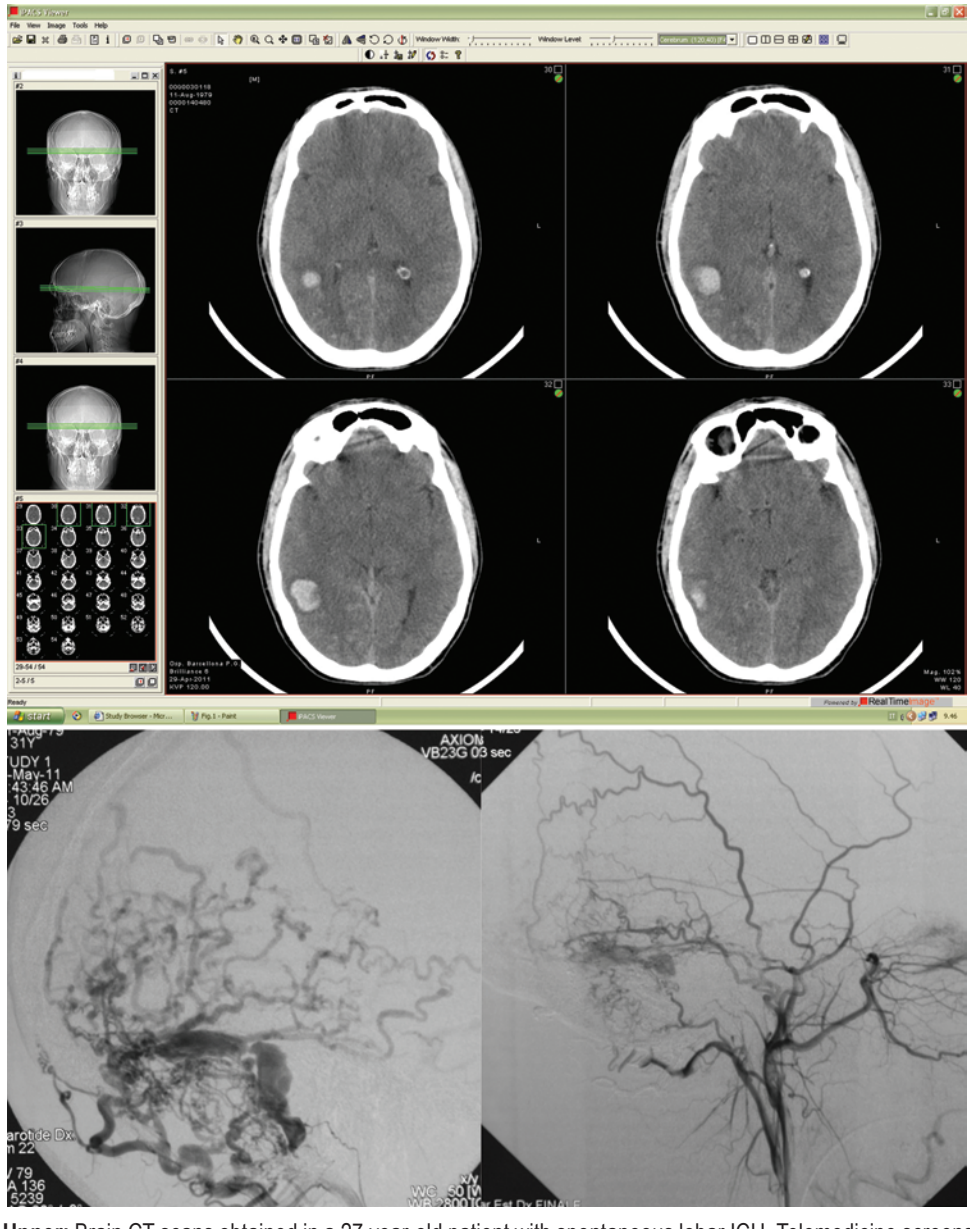

Fig. 3. Upper: Brain CT scans obtained in a 27-year-old patient with spontaneous lobar ICH. Telemedicine screenshot reproduces the CT console of the peripheral hospital with visualization of the scouts, multiple slices of the examination, and tools for image management. In general, hematoma without evidence of mass effect was managed at the peripheral hospital, unless one suspected vascular malformations, tumors, or sinus thrombosis, requiring urgent management. In such cases, clinical data collection is fundamental to avoid disastrous delay of diagnosis and treatment. **Lower:** Angiograms showing evidence of a dural arteriovenous fistula *(left)*, which was promptly managed with embolization *(right)*.

further studies for suspected vascular malformations, tumors, or sinus thrombosis. Suspicion was confirmed in 21 patients. In terms of efficacy of interpretation, clinical and radiological data were misinterpreted in 26 cases, including 8 cases of secondary centralization and 18 cases of inappropriate centralization, corresponding to 3.5% of the whole series.

Discussion

Results suggested that the care of patients with ICH through a telemedicine system is safe and effective. The telemedicine network allowed prompt selection of a subgroup of patients who were the best candidates for direct neurosurgical or neurointensive care. This group consisted of 24% of all patients with ICH who had been admitted to the peripheral hospitals and included those (13%) in whom the surgical control of ICP was readily necessary or decidedly predictable and those (11%) in whom bleeding due to vascular malformations, tumors, or sinus thrombosis had to be ruled out in the acute setting. The interpretation of images and clinical data was correct in 96.5% of cases.

The selection of patients as candidates for direct

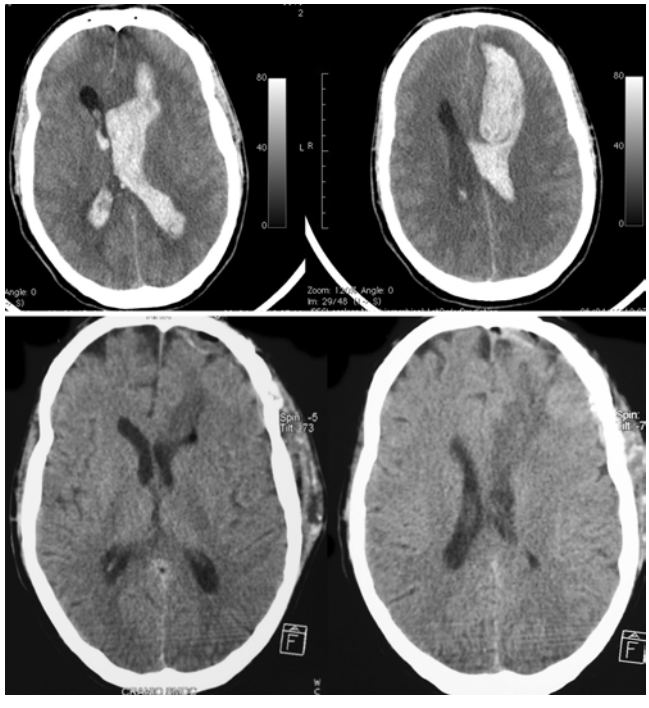

Fig. 4. Upper: Computed tomography scans obtained with the telemedicine system, showing ICH and IVH in a 24-year-old patient. Cases of large lobar hemorrhage in young patients were centralized to undergo emergency CTA and surgical treatment. **Lower:** Computed tomography scans obtained after emergency surgical treatment.

neurosurgical care is controversial, and the practice in ICH care continues to be arbitrary.[8,11,16,21] This attitude is in part a consequence of the misinterpretation of the results of the largest trial on spontaneous ICH management, the International Surgical Trial in Intracerebral Haemorrhage (STICH).[15] Evidence of the poor efficacy of surgical management for spontaneous ICH persuaded many surgeons that there is no need to perform surgery in patients with ICH. However, it is evident that early relief of elevated ICP is effective in all other clinical settings. Furthermore, a detailed post hoc analysis of the data in the STICH showed that 42% of patients had an associated IVH, and the prognosis in most of these cases is dismal. Removing these patients from the analysis and focusing on superficial ICHs, the data presented a more encouraging picture for surgery, with 49% of patients gaining a favorable outcome versus 37% of the conservatively treated patients ($p = 0.080$).[16]

Beyond the data mentioned above, there are specific categories of patients with spontaneous ICH who remain reasonably suitable candidates for surgery, such as those with acute hydrocephalus due to intraventricular bleeding and those with a large (> 3 cm) cerebellar hemorrhage who are neurologically deteriorating or have brainstem compression and/or hydrocephalus.[5] Furthermore, seemingly spontaneous ICHs may hide vascular abnormalities (aneurysm, arteriovenous malformation, dural arteriovenous fistula, and cavernous malformation), tumors, or venous thrombosis, which require specific surgical treatments, or vasculitis and coagulopathy, which require specific medical treatments. A qualified judgment of the combined clinical status of the patients and the neuroradiological picture is therefore essential to avoid inappropriate management.

Telemedicine networks represent a new approach to improve stroke care in community settings. Since the first 1999 description by Levine and Gorman[14] of a telemedicine network for the treatment of patients with ischemic stroke (Telestroke), several studies have been conducted to demonstrate the efficacy of telemedicine in providing specialist care to patients with ischemic stroke in rural communities. Telemedicine clearly showed its efficacy in providing hospitals in rural communities with the expertise of established stroke centers on demand and within minutes.[14,17,19] Moreover, it has been demonstrated that, embedded in a comprehensive stroke network, the teletransfer of clinical information and brain images yields medical results similar to those following treatment at experienced stroke centers.[2,23]

In particular, it has been shown that Telestroke improves the care of patients with ischemic stroke by limiting the number of interhospital referrals,[3] allowing one to choose or exclude candidates for thrombolytic therapy with intravenous tissue plasminogen activator[7] and eventually improve neurological outcome in these patients.[3,18] Actually, using the Telestroke approach, intravenous thrombolysis with tissue plasminogen activator has been shown to be safe and has been applied more frequently than without teleneurological consultation.[1,2,4,24] Nonetheless, studies focused on the role of telemedicine in the treatment of patients with ICH in acute settings are lacking. Only 1 study demonstrated that telemedicine might enhance enrollment of patients with ICH into time-sensitive stroke trials, such as FAST (Factor Seven for Acute Hemorrhagic Stroke), a multicenter randomized trial to study the role of recombinant factor VIIa in ICH.[26]

Our telemedicine network (RESPECT) considerably improved the rapidity of a second opinion consultation, making it more efficient in acute settings. The possibility of directly viewing neuroradiological images and doing postprocessing analysis made neurosurgical consultation easier and faster, allowing us to choose patients who needed transfer to the academic hub and making their transfer more rapid. Indeed, our data confirm that telemedicine allows one to effectively organize selected and timely interhospital transfers to specialized institutions.[1]

As a second step, we evaluated the role of telemedicine in optimizing the care of patients with ICH at peripheral hospitals in the acute setting. Five hundred forty-nine patients (74.9%) could be directly treated at the spoke hospitals. They underwent clinical, neurological, and neuroradiological monitoring based on neurosurgical indications; they also underwent more CT studies than the patients admitted to the hub, despite similar clinical conditions. We did not address the safety and efficacy of the procedure by measuring the long-term outcome. Actually, in general it is possible that patients treated at the peripheral hospitals received different levels of care. Nevertheless, our experience suggests that in the acute and subacute settings, telemedicine allows the treatment of patients with ICH directly at the peripheral hospitals with the opportunity for online neurosurgical evaluation. This

may contribute to increase competence in ICH management among health system professionals and optimization of resources, avoiding unnecessary transfers. Patients treated at the spokes were those who needed standard care or those in whom supportive care was indicated. Nonetheless, 8 patients (1.4%) treated at the spoke hospitals presented with a rapid and unpredicted worsening of neurological status and/or a neuroradiological picture that made secondary transfer to the referring neurosurgical department necessary. In 5 of 8 patients, the worsening was a result of treatment with oral anticoagulants. As demonstrated already, the use of such drugs can increase the risk of spontaneous ICH or hemorrhagic evolution in patients with ICH. There are lessons to be learned from these cases. To avoid secondary transfer, history and clinical/neurological examination by emergency physicians at the peripheral hospitals should be as accurate as possible to make neurosurgical consultation easier and more precise. Moreover, one must strictly follow neurosurgical indications, respecting time intervals between radiological examinations and repeatedly using the telemedicine system for a second opinion. Even if those needing secondary transfer were a small proportion, the patients in a deep coma or moribund status were not centralized and were only given supportive care. Thus, the rate of secondary transfer may underestimate the patient deterioration that occurred at the spoke hospitals.

Conclusions

Telemedicine may represent a new approach for the treatment of patients with ICH in the acute and subacute settings. Allowing rapid visualization and interpretation of neuroradiological data, telemedicine brought to rural community hospitals the expertise of established stroke centers on demand and within minutes. When necessary, patient referrals via telemedicine were faster. In the remaining cases, the treatment of patients with ICH at the peripheral hospitals was possible, avoiding unnecessary and costly transfers. This in some way contributed to increased competence among health system professionals, showing a significant educational impact. Nevertheless, the interpretation of data was inaccurate in 3.5% of the cases, with a small percentage of patients treated at the peripheral hospitals who had a secondary deterioration in their neurological status or neuroradiological picture and a group of patients who were inappropriately transferred to the hub. Secondary referrals can be avoided by implementing the transfer of clinical data to make neurosurgical consultation easier and more precise.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Angileri. Acquisition of data: Raffa. Drafting the article: Conti, Cardali. Approved the final version of the manuscript on behalf of all authors: Conti. Study supervision: Tomasello.

References

1. Audebert HJ, Kukla C, Clarmann von Claranau S, Kühn J, Vatankhah B, Schenkel J, et al: Telemedicine for safe and extended use of thrombolysis in stroke: the Telemedic Pilot Project for Integrative Stroke Care (TEMPiS) in Bavaria. **Stroke 36:**287–291, 2005
2. Audebert HJ, Kukla C, Vatankhah B, Gotzler B, Schenkel J, Hofer S, et al: Comparison of tissue plasminogen activator administration management between Telestroke Network hospitals and academic stroke centers: the Telemedical Pilot Project for Integrative Stroke Care in Bavaria/Germany. **Stroke 37:**1822–1827, 2006
3. Audebert HJ, Moulin T: Telestroke: the use of telemedicine in stroke care. Preface. **Cerebrovasc Dis 27 (Suppl 4):**V–VI, 2009
4. Audebert HJ, Schwamm L: Telestroke: scientific results. **Cerebrovasc Dis 27 (Suppl 4):**15–20, 2009
5. Broderick J, Connolly S, Feldmann E, Hanley D, Kase C, Krieger D, et al: Guidelines for the management of spontaneous intracerebral hemorrhage in adults: 2007 update: a guideline from the American Heart Association/American Stroke Association Stroke Council, High Blood Pressure Research Council, and the Quality of Care and Outcomes in Research Interdisciplinary Working Group. **Stroke 38:**2001–2023, 2007
6. Broderick JP, Brott TG, Duldner JE, Tomsick T, Huster G: Volume of intracerebral hemorrhage. A powerful and easy-to-use predictor of 30-day mortality. **Stroke 24:**987–993, 1993
7. Demaerschalk BM, Hwang HM, Leung G: Cost analysis review of stroke centers, telestroke, and rt-PA. **Am J Manag Care 16:**537–544, 2010
8. Dubourg J, Messerer M: State of the art in managing nontraumatic intracerebral hemorrhage. **Neurosurg Focus 30(6):**E22, 2011
9. Fogelholm R, Murros K, Rissanen A, Avikainen S: Long term survival after primary intracerebral haemorrhage: a retrospective population based study. **J Neurol Neurosurg Psychiatry 76:**1534–1538, 2005
10. Gebel JM, Broderick JP: Intracerebral hemorrhage. **Neurol Clin 18:**419–438, 2000
11. Gregson BA, Mendelow AD: International variations in surgical practice for spontaneous intracerebral hemorrhage. **Stroke 34:**2593–2597, 2003
12. Hess DC, Wang S, Gross H, Nichols FT, Hall CE, Adams RJ: Telestroke: extending stroke expertise into underserved areas. **Lancet Neurol 5:**275–278, 2006
13. Hess DC, Wang S, Hamilton W, Lee S, Pardue C, Waller JL, et al: REACH: clinical feasibility of a rural telestroke network. **Stroke 36:**2018–2020, 2005
14. Levine SR, Gorman M: "Telestroke:" the application of telemedicine for stroke. **Stroke 30:**464–469, 1999
15. Mendelow AD, Gregson BA, Fernandes HM, Murray GD, Teasdale GM, Hope DT, et al: Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomised trial. **Lancet 365:**387–397, 2005
16. Mendelow AD, Gregson BA, Mitchell PM, Murray GD, Rowan EN, Gholkar AR: Surgical trial in lobar intracerebral haemorrhage (STICH II) protocol. **Trials 12:**124, 2011
17. Meyer BC, Raman R, Chacon MR, Jensen M, Werner JD: Reliability of site-independent telemedicine when assessed by telemedicine-naive stroke practitioners. **J Stroke Cerebrovasc Dis 17:**181–186, 2008
18. Meyer BC, Raman R, Ernstrom K, Tafreshi GM, Huisa B, Stemer AB, et al: Assessment of long-term outcomes for the STRokE DOC Telemedicine Trial. **J Stroke Cerebrovasc Dis** [epub ahead of print], 2010
19. Meyer BC, Raman R, Hemmen T, Obler R, Zivin JA, Rao R, et

al: Efficacy of site-independent telemedicine in the STRokE DOC trial: a randomised, blinded, prospective study. **Lancet Neurol 7:**787–795, 2008
20. Minutoli F, Angileri FF, Conti A, Herberg A, Aricò D, Baldari S, et al: Timing of examination affects reliability of 99mTc-methoxyisobutylisonitrile SPECT in distinguishing neoplastic from nonneoplastic brain hematomas. **J Nucl Med 46:** 574–579, 2005
21. Pouratian N, Kassell NF, Dumont AS: Update on management of intracerebral hemorrhage. **Neurosurg Focus 15(4):**E2, 2003
22. Sairanen T, Soinila S, Nikkanen M, Rantanen K, Mustanoja S, Färkkilä M, et al: Two years of Finnish Telestroke: thrombolysis at spokes equal to that at the hub. **Neurology 76:**1145–1152, 2011
23. Schwab S, Vatankhah B, Kukla C, Hauchwitz M, Bogdahn U, Fürst A, et al: Long-term outcome after thrombolysis in telemedical stroke care. **Neurology 69:**898–903, 2007
24. Schwamm LH, Rosenthal ES, Hirshberg A, Schaefer PW, Little EA, Kvedar JC, et al: Virtual TeleStroke support for the emergency department evaluation of acute stroke. **Acad Emerg Med 11:**1193–1197, 2004
25. Strehle EM, Shabde N: One hundred years of telemedicine: does this new technology have a place in paediatrics? **Arch Dis Child 91:**956–959, 2006
26. Switzer JA, Hall CE, Close B, Nichols FT, Gross H, Bruno A, et al: A telestroke network enhances recruitment into acute stroke clinical trials. **Stroke 41:**566–569, 2010
27. Wang S, Lee SB, Pardue C, Ramsingh D, Waller J, Gross H, et al: Remote evaluation of acute ischemic stroke: reliability of National Institutes of Health Stroke Scale via telestroke. **Stroke 34:**e188–e191, 2003

Manuscript submitted December 14, 2011.
Accepted January 27, 2012.
Please include this information when citing this paper: DOI: 10.3171/2012.1.FOCUS11356.
Address correspondence to: Alfredo Conti, M.D., Ph.D., Department of Neurosurgery, University of Messina, Via Consolare Valeria, 1, 98125 Messina, Italy. email: alfredo.conti@unime.it.

Neurosurg Focus 32 (4):E7, 2012

Cerebral amyloid angiopathy–associated intracerebral hemorrhage: pathology and management

Prachi Mehndiratta, M.D.,[1] Sunil Manjila, M.D.,[2] Thomas Ostergard, M.S.,[2] Sylvia Eisele,[1] Mark L. Cohen, M.D.,[3] Cathy Sila, M.D.,[1] and Warren R. Selman, M.D.[2]

Departments of [1]Neurology, [2]Neurological Surgery, and [3]Pathology, The Neurological Institute, University Hospitals Case Medical Center, Cleveland, Ohio

Amyloid angiopathy–associated intracerebral hemorrhage (ICH) comprises 12%–15% of lobar ICH in the elderly. This growing population has an increasing incidence of thrombolysis-related hemorrhages, causing the management of hemorrhages associated with cerebral amyloid angiopathy (CAA) to take center stage. A concise reference assimilating the pathology and management of this clinical entity does not exist. Amyloid angiopathy–associated hemorrhages are most often solitary, but the natural history often progresses to include multifocal and recurrent hemorrhages. Compared with other causes of ICH, patients with CAA-associated hemorrhages have a lower mortality rate but an increased risk of recurrence. Unlike hypertensive arteriolar hemorrhages that occur in penetrating subcortical vessels, CAA-associated hemorrhages are superficial in location due to preferential involvement of vessels in the cerebral cortex and meninges. This feature makes CAA-associated hemorrhages easier to access surgically. In this paper, the authors discuss 3 postulates regarding the pathogenesis of amyloid hemorrhages, as well as the established clinicopathological classification of amyloid angiopathy and CAA-associated ICH. Common inheritance patterns of familial CAA with hemorrhagic strokes are discussed along with the role of genetic screening in relatives of patients with CAA. The radiological characteristics of CAA are described with specific attention to CAA-associated microhemorrhages. The detection of these microhemorrhages may have important clinical implications on the administration of anticoagulation and antiplatelet therapy in patients with probable CAA. Poor patient outcome in CAA-associated ICH is associated with dementia, increasing age, hematoma volume and location, initial Glasgow Coma Scale score, and intraventricular extension. The surgical management strategies for amyloid hemorrhages are discussed with a review of published surgical case series and their outcomes with a special attention to postoperative hemorrhage.
(http://thejns.org/doi/abs/10.3171/2012.1.FOCUS11370)

Key Words • **diagnostic criteria** • **cerebral amyloid angiopathy** • **lobar intracerebral hemorrhage** • **Alzheimer dementia** • **neuroimaging** • **dot burden**

The deposition of a "peculiar and difficult to stain" substance in intracranial vessels was first described by Alois Alzheimer in 1907.[37] Gustav Oppenheim[83] subsequently recognized this substance as amyloid in 1909 when he discovered foci of necrosis in areas adjacent to hyalinized capillaries in patients with cognitive decline. This pathology later became popularly known as cerebral amyloid angiopathy or angiopathy dysphorique. Stefanos Pantelakis[85] made several of the pertinent pathological observations in 1954, including predilection for posterior brain regions, involvement of small arteries, and an association with increasing age.

Abbreviations used in this paper: ABRA = amyloid beta–related angiitis; CAA = cerebral amyloid angiopathy; GOS = Glasgow Outcome Scale; ICH = intracerebral hemorrhage; IVH = intraventricular hemorrhage; PACNS = primary angiitis of the CNS; STICH = International Surgical Trial in Intracerebral Haemorrhage; tPA = tissue plasminogen activator.

In 1960, Neumann[72] reported the occurrence of symptomatic lobar as well as asymptomatic petechial hemorrhages in a 45-year-old woman. He hypothesized that CAA likely weakens the vessel wall, resulting in hemorrhage, but he was unclear as to the cause of the petechiae. Cerebral amyloid angiopathy has increasingly gained clinical importance over the past few decades due to its association with lobar hemorrhage and dementia, highlighted by an influential article in 1979 by Okazaki and colleagues.[79]

Intracerebral hemorrhage currently accounts for about 15% of acute strokes and has an incidence of 10–30 cases per 100,000.[30,47,92] Studies have shown that CAA is relatively common, especially in the elderly. In a review of 2060 autopsies of elderly patients,[7] CAA was diagnosed in 21% of those 61–70 years old, 42.2% of those 71–80 years old, 56.8% of those 81–90 years old, and 68.5% of those 91–100 years old. In the same study, CAA was pres-

ent in more than 98.5% of all patients with Alzheimer disease. The majority of cases of CAA-associated ICH are thought to be due to sporadic disease; however, the increased use of anticoagulant, antiplatelet, and thrombolytic therapies has brought attention to iatrogenic CAA-associated ICH. It has been postulated that patients with cerebral vasculopathies have an increased risk of iatrogenic ICH, particularly with the administration of thrombolytics.[57,60]

There is a strong association between CAA and dementia, and increasing age is a risk factor for both Alzheimer disease and CAA.[89,93] Up to one-third of patients with pathologically confirmed CAA had previous onset of dementia. Due to continued improvements in molecular techniques, familial forms of Alzheimer disease are being recognized with increasing frequency. However, familial forms of CAA and their potential role in ICH are frequently not addressed in neurosurgical practice. This review describes the familial forms of CAA with hemorrhages, highlighting the importance of screening family members of affected patients with inherited CAAs (Table 1).

The more common forms of familial CAA are further detailed below. Although sporadic CAA is the most common cause of nonhypertensive lobar ICH,[89,93] it is commonly found in elderly patients with or without Alzheimer disease.[93] The familial forms of CAA present with hemorrhagic strokes and occur at a much younger age.[32,108]

Pathogenesis of CAA and Related Hemorrhages

In CAA, there is a predilection for deposition of Aβ protein in the cortical vessels compared with the brain parenchyma. Three hypotheses have been postulated to account for this selective vascular amyloid deposition. The neuronal or "drainage hypothesis" suggests that the underlying cause of amyloid deposition is due to poor drainage of amyloid protein along the perivascular spaces, eventually causing subsequent deposition along this path. This hypothesis is supported by studies on transgenic mice and is based on the derivation of amyloid precursor protein from neurons.[9,43]

The second hypothesis, the so-called "systemic hypothesis," proposes that receptor-mediated transport of systemic Aβ protein across the blood-brain barrier results in amyloid deposition. Several receptors such as the receptor for advanced glycation end-products, low-density lipoprotein receptor, and scavenger receptors have been implicated in the luminal to abluminal transport of Aβ protein. However, this concept is controversial and disputed due to preferential involvement of arteries rather than veins and the selective involvement of smaller rather than large vessels. It is intriguing that studies in transgenic mice have demonstrated, even with systemic overproduction of amyloid precursor protein, that selective deposition in intracranial vessels is a less likely occurrence when studied up to 29 months of age.[9,43] Furthermore, Aβ protein is first detected in the abluminal basement membrane, arguing against a systemic origin.[118]

The third hypothesis, or "vessel wall hypothesis," supports the notion that Aβ protein is produced by smooth muscle cells in the tunica media of cerebral arteries. Prior studies have shown that these myocytes are capable of producing Aβ.[21,89] Larger arteries have multiple layers of smooth muscle cells and should therefore contain significantly more amyloid deposits than smaller arteries. However, CAA-associated ICH preferentially involves smaller superficial arteries. This finding casts some doubt on the accuracy of the "vessel wall hypothesis."

Approximately 12%–15% of lobar ICH in the elderly is associated with CAA,[94] and the risk increases in carriers of the *APOE-ε2* or *APOE-ε4* allele.[117] Familial forms of Alzheimer disease are now recognized with identification of the *APOE-ε2* and *APOE-ε4* alleles in patients

TABLE 1: Amyloid peptides related to familial CAA-associated ICHs*

Amyloid Peptide & APP	Chromosome No.	Disease Type	Identified Mutation (codon)	AA Substitution	Clinical Features†	Index Cases
Aβ/APP	21	HCHWA-Dutch type	G to C (693)	Glu22Gln	age 50 yrs; lobar ICH, focal neurological deficits, dementia, & leukoencephalopathy	2 Dutch families
		HCHWA-Italian type	G to A (693)	Glu22Lys	lobar ICH & dementia	3 Italian families
		HCHWA-Flemish type	C to G (692)	Ala21Gly	age 45 yrs; progressive dementia, lobar ICH	1 Dutch/British family
		HCHWA-Iowa type	G to A (694)	Asp23Asn	age 50–66 yrs; memory impairment, expressive dysphasia, personality changes, myoclonic jerks, lobar ICH	1 American & 1 Spanish family
		HCHWA-Piedmont type	G to C (705)	Leu34Val	recurrent lobar ICH & cognitive decline	1 Italian family
ACys/Cystatin C	20	HCHWA-Icelandic type	A to T (68)	Leu68Gln	recurrent lobar ICH	9 Icelandic families

* A = adenine; AA = amino acid; Ala = alanine; APP = amyloid precursor protein; Asn = asparagine; Asp = aspartate; C = cytosine; G = guanine; Gln = glutamine; Glu = glutamate; Gly = glycine; HCHWA = hereditary cerebral hemorrhage with amyloidosis; Leu = leucine; Lys = lysine; T = thymine; Val = valine.

† Age refers to the mean age at onset of symptoms.

with CAA.[26,57,60,74] In patients with Alzheimer dementia, the presence of the *APOE-ε4* allele appears to accelerate formation and deposition of Aβ fibrils in the blood vessel wall.[80,91] Possession of both alleles (ε2/ε4 genotype) is associated with early-onset CAA with recurrent lobar hemorrhages.[76] McCarron and colleagues[61] offered evidence that the presence of *APOE-ε2* might convey additional surgical risk. In their series, 2 of the 3 patients with postoperative hemorrhage were found to have *APOE-ε2*.

When hemorrhages occur in the setting of CAA, they are most often solitary but can also be multifocal and recurrent.[58,67] In an acute CAA-associated ICH, the area around the hematoma is typically surrounded by edema and necrosis with infiltration of inflammatory cells (Fig. 1). A secondary cascade of injury is produced by a combination of vasogenic edema from blood-brain barrier breakdown, mitochondrial dysfunction, and the products of hemoglobin breakdown. Hemostasis is eventually achieved by activation of the coagulation cascade along with mechanical tamponade.[34] In rare occasions, surgical specimens are found to have areas of both hemorrhagic and ischemic foci (Fig. 1). Extension into the subarachnoid space or the ventricles is possible, as well as secondary subdural hematomas.[87,101,115] These hemorrhages most frequently occur in the parietooccipital region with frontal hemorrhages being the next most common.[5,55,105]

Pathological Findings in CAA-Associated Hemorrhages

Cerebral amyloid angiopathy is a vasculopathy characterized by the deposition of amyloid fibrils in the arteries and arterioles of the cerebral cortex and meninges. Hematoxylin and eosin staining of affected tissues shows hyaline thickening in vessel walls with luminal narrowing. The presence of amyloid protein can be confirmed by multiple techniques but has traditionally been diagnosed by staining with Congo red.[51] In the presence of polarized light, Congo red binds to amyloid fibrils and causes the classic finding of apple-green birefringence (Fig. 2). Alternative methods to confirm the presence of amyloid fibrils include thioflavin T/S and immunohistochemistry with anti-Aβ antibodies, the latter technique being frequently used in the diagnosis of CAA.[82]

Cerebral amyloid angiopathy can also present subacutely with progressive dementia over the course of weeks to months. Pathologically, the dementia associated with CAA is characterized by severe vascular amyloid deposition, cortical hemorrhages and/or infarctions, white matter destruction, or leukoencephalopathy. In Alzheimer disease, the deposited amyloid is primarily located in the parenchyma and leads to neuritic dystrophy and loss of synapses.[28] Despite some similarities in pathological findings,

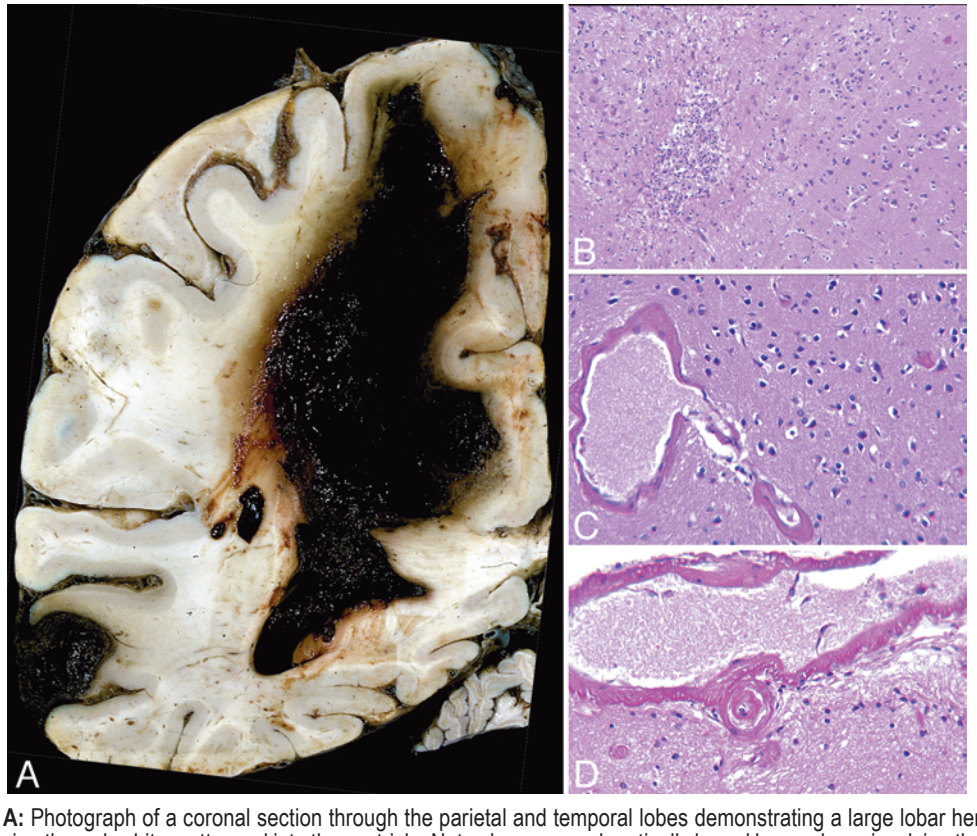

Fig. 1. A: Photograph of a coronal section through the parietal and temporal lobes demonstrating a large lobar hemorrhage with extension through white matter and into the ventricle. Note also a second cortically based hemorrhage involving the cerebral cortex of the middle temporal gyrus. **B:** Photomicrograph showing the organizing microinfarct within the cerebral cortex of the patient with severe amyloid angiopathy. **C and D:** Photomicrographs demonstrating amyloid-laden blood vessels showing pseudoaneurysm formation (C) and "double-barreling" (D). H & E, original magnification × 100 (B) and × 200 (C and D).

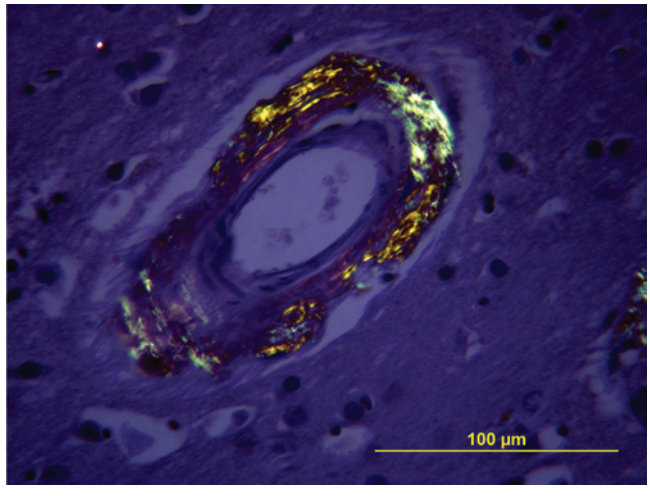

Fig. 2. Amyloid-laden cortical arteriole photographed with polarization microscopy, demonstrating apple-green birefringence characteristic of amyloid. Original magnification × 400.

the rapidity of symptom progression in CAA distinguishes it from Alzheimer disease.

Cerebral amyloid angiopathy is characterized by Aβ fibril deposition into the vessel wall, preferentially at vascular bifurcations and distal to these bifurcations,[44,114] causing subsequent degeneration of leptomeningeal and cortical arteries.[93] Amyloid beta protein is primarily deposited in the abluminal portion of the tunica media and adventitia of the blood vessel in close proximity of smooth muscle cells.[116] As the disease progresses, all parts of the vessel wall are affected, leading to the pathological hallmarks of obliterative intimal thickening ("onion skin" appearance), fibrinoid necrosis, hyalinoid degeneration of the media, and subsequent new media formation,[81,110] which can lead to "vessel-within-a-vessel" formation or the so-called "double-barrel" appearance. Aneurysm formation and microhemorrhages within the vessel wall have also been described and can be seen in Fig. 1.[39,53] The aforementioned *APOE-ε2* allele has been associated with fibrinoid necrosis, as well as the double-barrel appearance of blood vessels.[26,62]

These spontaneous hemorrhages are a result of vessel wall degeneration due to deposition of Aβ protein. In vitro and in vivo experiments in animal models suggest that Aβ deposition leads to degeneration of smooth muscle cells in the tunica media and creates an anticoagulative microenvironment by mimicking inhibitors of the coagulation cascade or by inducing and activating important tissue proteinases, for example, MMP-2 and MMP-9,[40,50] which may add to the fragility of affected cerebral blood vessels.

Pathological grading systems have been established to characterize CAA based on autopsy findings. Olichney and colleagues[81] classified amyloid angiopathy based on Aβ positivity in leptomeningeal and cortical blood vessels (Table 2). Vonsattel and colleagues[112] graded the severity of CAA by the degree of amyloid infiltration into the vessel wall. Both grading systems can be used in a complimentary manner; the former localizes the disease process while the latter ascertains the severity of disease.

Clinical Presentation of CAA and CAA-Associated ICH

Clinically, patients with CAA-related ICH present with a focal neurological deficit and/or symptoms of increased intracranial pressure. Alterations in consciousness might be seen with large parenchymal hematomas. There are also reports of CAA presenting with a mass lesion[11] or transient neurological symptoms,[28,79] leukoencephalopathy,[77] and seizures.[31,89] Transient neurological symptoms are likely caused by vessel obliteration due to intimal thickening.[53,112] These symptoms may last from minutes to hours. Seizures have also been reported and are possibly caused by microhemorrhages irritating the cortex.[28]

Rosand and colleagues[98] used MRI to describe the spatial clustering in probable CAA-associated ICH. The absolute number of total hemorrhages is greatest in the frontal lobes. However, after taking into account the volume of each cerebral lobe using an atlas,[45] they found that CAA-associated ICH has a significant predilection for the temporal and occipital lobes. Recurrent hemorrhages are more likely to occur in the same lobe as prior hemorrhages; however, this scenario only occurs in 29% of recurrent hemorrhages.[98] This finding agrees with autopsy studies that have shown a predilection for the temporal and occipital lobes.[6]

TABLE 2: Pathological grading systems for CAA

Grading System	Definition
Olichney et al., 1995	
0	no Aβ-positive blood vessels
1	scattered Aβ positivity in leptomeningeal or intracortical blood vessels
2	strong, circumferential Aβ positivity in some leptomeningeal or intracortical blood vessels
3	widespread, strong, circumferential, Aβ positivity in leptomeningeal & intracortical blood vessels
4	same as Grade 3, w/ additional dysphoric changes
Vonsattel et al., 1991	
mild	amyloid is restricted to the tunica media without significant destruction of smooth muscle cells
moderate	the tunica media is replaced by amyloid & is thicker than normal
severe	extensive amyloid deposition w/ focal wall fragmentation or even double barreling of the vessel wall, microaneurysm formation, fibrinoid necrosis, & leakage of blood through the blood vessel wall

Originally proposed by Greenberg and colleagues,[26] the Boston Criteria guides clinical diagnosis of CAA in the setting of ICH. All of the diagnostic categories require the absence of other conditions that could cause lobar ICH, such as coagulopathy, antecedent trauma or ischemic stroke, CNS neoplasm, vascular malformation, and vasculitis. A diagnosis of definite CAA-associated hemorrhage requires a full pathological examination that demonstrates the following: lobar, cortical, or subcortical hemorrhage; severe CAA with vasculopathy; and the absence of an alternate diagnostic lesion. Probable CAA-associated hemorrhage requires an age older than 55 years and MRI or CT findings that demonstrate multiple hemorrhages restricted to lobar, cortical, subcortical, or cerebellar hemorrhage. Probable CAA-associated hemorrhage with supporting pathology requires the previous clinical data with the addition of some degree of CAA seen in pathological specimens. Possible CAA-associated hemorrhage requires age greater than 55 years with a solitary lobar, cortical, or subcortical hemorrhage.

A study by Knudsen and colleagues[46] demonstrated that the Boston Criteria can be effectively used to predict the presence of underlying CAA in lobar hemorrhages. The accuracy of the criteria was compared against pathological specimens obtained from hematoma evacuation or brain biopsy, as well as autopsy findings. All 13 patients classified as having probable CAA were pathologically diagnosed with CAA. The other 26 patients were classified as having possible CAA, and 62% of them were ultimately pathologically diagnosed with CAA. Given the apparent accuracy of this classification scheme, clinicians should strongly consider incorporating the Boston criteria into the management of CAA-associated ICH.

When patients present with lobar ICH of unknown cause, age is a good predictor of the most likely underlying cause. A study by Wakai and colleagues[113] reviewed 29 patients who presented with lobar ICH and underwent surgical biopsy. Listed by increasing mean age, the cause of ICH was cavernous malformation (27.0 years), arteriovenous malformation (45.8 years), tumor apoplexy (47.5 years), microaneurysm (59.8 years), and CAA-associated ICH (70.0 years). The difference in age was statistically significant when comparing arteriovenous malformation or microaneurysm with CAA-associated ICH, although no formal regression model was reported. These data support the use of increasing age to assist in clinical diagnosis of CAA-associated ICH.

Thrombolysis-Related Hemorrhages in Patients With CAA

Intracranial hemorrhage is an uncommon but devastating complication after thrombolytic therapy.[64] In patients receiving thrombolysis for acute ischemic stroke, it was recognized that up to 20% of hemorrhages occur outside of the ischemic penumbra.[75] This finding provides some evidence that these patients might have an underlying vasculopathy. In a situation in which an elderly patient receives thrombolysis, it is most likely that CAA is the underlying vasculopathy.

Thrombolysis-associated ICH is seen in 0.6% of patients treated for acute myocardial infarction, 3% of patients treated for pulmonary embolism, 6% of patients receiving intravenous tPA for ischemic stroke, and 11% of patients receiving intraarterial tPA for ischemic stroke. Thrombolysis-related ICHs are usually solitary, large, and lobar in location.[23] Clinical risk factors such as age, hypertension, low body weight, and the type of thrombolytic agent appear to increase the risk for ICH after thrombolytic therapy.[42] Therefore, pathological conditions other than ischemic brain tissue, such as hypertensive vascular disease and CAA, are suspected to predispose to hemorrhage after thrombolysis.[23,101,113]

Amyloid Beta–Related Angiitis

Amyloid beta–related angiitis (ABRA) is a unique presentation of CAA that is not commonly encountered. It is closely related to primary angiitis of the central nervous system (PACNS), and 20% of patients present with ICH. It must be noted that patients with ABRA also can present with acute changes in mental status, altered consciousness, confusion, and memory loss. Thus, PACNS and CAA are among the mimickers of ABRA. These acute symptoms are often superimposed on a subacute course of headaches, dementia, seizures, and focal neurological deficits. Approximately 20% of patients with ABRA present with ICH.[100] The distinction between these pathologies is clinically important, as the prognosis and treatments vary significantly between these entities (Table 3).[20,54,100,103] Amyloid beta–related angiitis is a frequently fatal condition that must be suspected in patients with serial focal neurological deficits of unknown origin. Brain biopsy is the gold standard for diagnosis, and some benefit has been reported with use of steroids and cyclophosphamide.[95,99]

Eng and colleagues[17] described cerebrovascular pathology in a subset of 7 patients who presented with headaches, seizures, and rapidly progressive cognitive decline over several months. Cerebral histopathology was characterized by perivascular inflammation with multinucleated giant cells. Figure 3 demonstrates these same classic pathological findings in one of our own patients diagnosed with ABRA.

Imaging Characteristics of CAA-Associated ICH and Microhemorrhages

Currently available literature on CAA imaging defines microhemorrhages as foci of smaller than 5 mm that are hypointense on T2-weighted MR sequences.[18,27] Microhemorrhages likely result from the rupture of small blood vessels that are smaller than 200 μm in diameter. The microhemorrhages associated with CAA are best visualized on gradient echo sequences. These T2-weighted sequences are highly sensitive to the field inhomogeneity that results from hemosiderin deposition in macrophages after the breakdown of blood products.[4,96] Hemosiderin remains in macrophages for many years after hemorrhage, allowing for determination of the total microhemorrhage burden.[28] Autopsy studies have shown that microhemorrhages appear larger on MR images, which is attributed

TABLE 3: Differences among ABRA, CAA, and PACNS*

Parameter	ABRA	CAA	PACNS
typical age (yrs) at onset	65–70	75–80	40–50
sex predilection	none	none	none
clinical features	TIA, ICH, dementia	ICH, dementia	focal neurological deficits, TIA, seizures, SAH
type of vessel involvement	severe leptomeningeal & parenchymal amyloid angiopathy	leptomeningeal & superficial cortical vessels	small leptomeningeal & parenchymal vessels
pathology	angiocentric lymphocytic inflammation, perivascular multinucleated giant cells around amyloid-laden blood vessels, Aβ deposition in blood vessel walls	Aβ deposition in superficial cortical & meningeal arteries; evidence of neurofibrillary tangles & neuropil threads; occasional splitting of vessel walls w/ double-barrel appearance	segmental/circumferential involvement of blood vessels; inflammation may be lymphocytic, granulomatous, or mixed; presence of fibrinoid necrosis
MRI findings	focal patchy nonspecific white matter hyperintensities on T2WI	nonspecific white matter hyperintensities on T2WI; microhemorrhages on gradient echo	subcortical nonspecific white matter hyperintensities on T2WI
treatment	no RCTs; trial of steroids & immunosuppressive agents as described in historical case reports	withhold anti-PLT or anticoagulants if at high risk for hemorrhage; no use of steroids	no RCTs; use of steroids & steroid-sparing agents, such as cyclophosphamide, is indicated
complications & prognosis	poor prognosis; most patients develop ICH	unclear; dementia & ICH often result	fair prognosis w/ use of immunosuppressants

* anti-PLT = anti-platelet therapy; RCT = randomized control trial; SAH = subarachnoid hemorrhage; T2WI = T2-weighted MRI; TIA = transient ischemic attack.

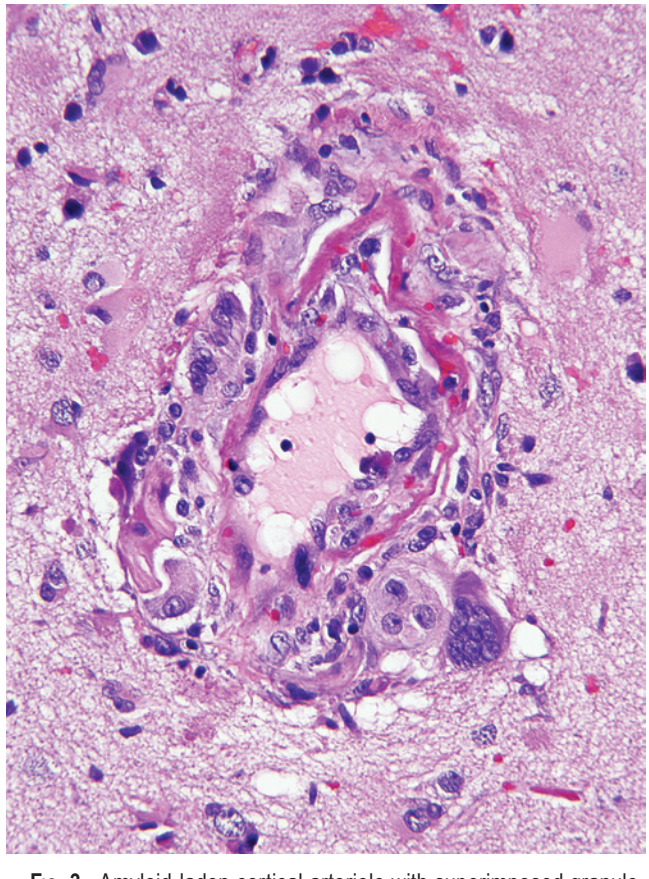

Fig. 3. Amyloid-laden cortical arteriole with superimposed granulomatous inflammation. H & E, original magnification × 400.

to the so-called "blooming" that is seen on susceptibility-weighted imaging. The interface between the hematoma and surrounding tissues provides susceptibility artifact that increases the apparent size of the hematoma.[2]

Asymptomatic microhemorrhages are the most common radiological findings in CAA.[18] The differential diagnosis of this appearance includes cavernous malformations, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), ABRA, and PACNS. Interestingly, imaging studies obtained in healthy volunteers also showed that asymptomatic hemorrhages occur in roughly 3%–5% of the population.[38,107] While initially considered to be incidental in nature, evidence now suggests that lobar microhemorrhages are predictive of the future lobar hemorrhages.[104] As discussed below, the presence of asymptomatic microhemorrhages also has significant implications for elderly patients requiring antiplatelet or anticoagulant therapies.

The number of microhemorrhages present at baseline is correlated with an increased risk for recurrent ICH, as well as a decline in cognitive function.[27] Figure 4 shows an example of the appearance of these microhemorrhages on MRI. This study also fortified the use of gradient echo imaging as a surrogate marker for disease severity in CAA. Nakata-Kudo and colleagues[71] demonstrated that microhemorrhages were more common in patients with Alzheimer disease and more likely to be due to CAA rather than cerebrovascular risk factors such as hypertension. The Prospective Study of Pravastatin in the Elderly at Risk (or PROSPER) study recently investigated the presence and location of microhemorrhages and their correlation with declining cognitive function. Although

the results were not statistically significant, the study did demonstrate a trend toward worsening cognitive function in patients with infratentorial microhemorrhages.[109]

Illustrative Case

This 69-year-old man presented to the hospital with acute onset of right-sided visual field deficit. At the time of presentation, his blood pressure was 160/100 mm Hg; other vital signs were within normal limits. Neurological examination revealed the presence of a right homonymous hemianopia with no associated long tract signs. Funduscopic examination was unremarkable. The patient's medical history was significant for hypertension, dyslipidemia, and coronary artery disease. He was taking a daily aspirin but was not compliant with his antihypertensive regimen. A CT scan of the head revealed the presence of an acute left occipital ICH measuring 13.4 cm^3 in volume without any evidence of midline shift (see Fig. 5A). Magnetic resonance imaging and MR angiography of the brain were performed to further elucidate the cause of hemorrhage. Gradient echo and T2 sequences demonstrated the presence of microhemorrhages in the right occipital, left occipital, and left frontal lobes, suggestive of a CAA (Fig. 4). The images additionally showed diffuse hypointensities within the left occipital convexity cistern, suggestive of subarachnoid hemorrhage. The patient was started on antihypertensive medication, and his aspirin was withheld due to concern for CAA-associated ICH. Additional cranial CT scanning performed 6 months later demonstrated interval resolution of the occipital hemorrhage (Fig. 5B). The patient was readmitted to the hospital 11 months later with rehemorrhage into the region of the previous left occipital lobar ICH. He was not hypertensive at the time of his second admission. The patient was treated conservatively and discharged home. He returned again after 6 months with a third ICH, again in the right occipital lobe (Fig. 5C).

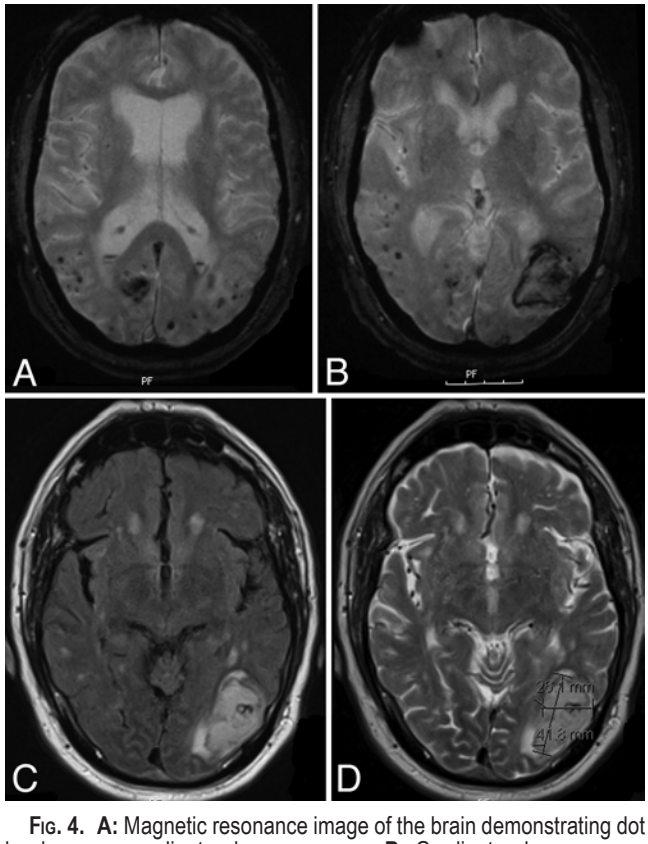

Fig. 4. A: Magnetic resonance image of the brain demonstrating dot burden on a gradient echo sequence. **B:** Gradient echo sequence demonstrating acute CAA-associated ICH in the left parietooccipital region. **C:** A FLAIR sequence showing acute CAA-associated ICH. **D:** Axial T2-weighted image showing the extent of acute CAA-associated ICH in the left parietooccipital region.

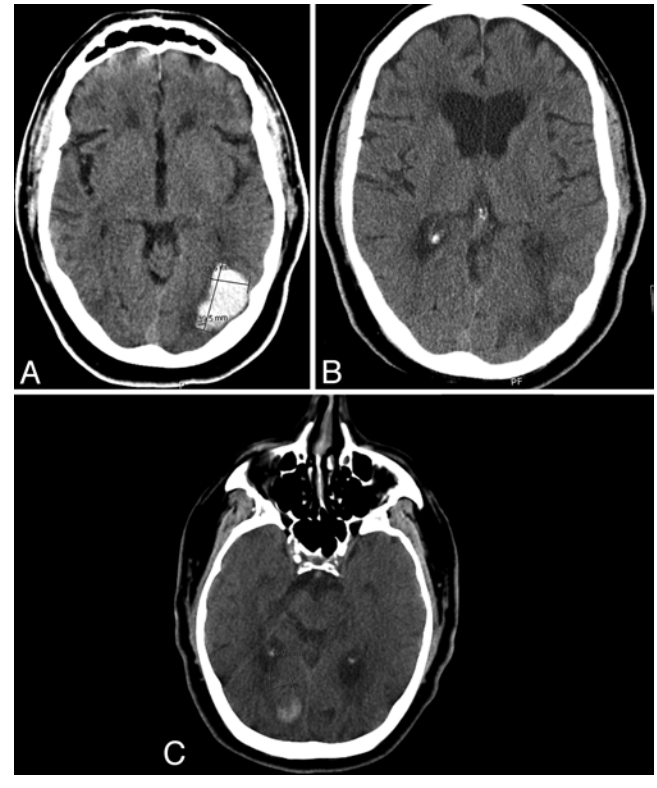

Fig. 5. A: Non–contrast administered CT scan of the head showing the patient's first diagnosed CAA-associated ICH in the left parietooccipital lobe. **B:** Interval CT of the head without contrast demonstrating resolution of the previous CAA-associated ICH at a 6-month follow-up visit. **C:** Non–contrast administered CT scan of the head in the same patient several months later, demonstrating a new ICH in the right occipital lobe. This occurred in the region of previous gradient echo changes seen in Fig. 4A.

The recurrence of lobar hemorrhages in a patient with controlled hypertension along with imaging evidence of multiple microhemorrhages are indicative of CAA-associated ICH. As seen in this case, the presence of multiple microhemorrhages is a significant risk factor for the development of recurrent hemorrhages. It should be noted that, in our illustrative case, the microhemorrhages visualized on gradient echo MRI sequences were not appreciated on the initial cranial CT (Fig. 5A).

Medical Management of CAA-Associated ICH

The most recent update to the guidelines by the American Heart Association/American Stroke Association did not embrace amyloid-associated ICH as a separate

entity from all other causes of ICH.[70] Therefore, medical management of CAA-associated ICH does not differ from other causes of ICH. Hematoma enlargement in all-cause ICH occurs to a great extent within 3 hours of symptom onset, although it has been seen to continue up to 12 hours after onset.[13] Recent studies have focused on control of early hematoma growth by intensive antihypertensive therapy, as well as the use of procoagulants.[3,13] Similar to any ICH, emergency radiological examination with MRI or CT scanning should be pursued to differentiate it from ischemic stroke (Class IA). After diagnosis, patients with severe coagulopathy or thrombocytopenia should receive appropriate reversal (Class IC). Similarly, anticoagulant and antiplatelet therapies should be held with reversal of any iatrogenic coagulopathy (Class IC). Prevention of venous thromboembolism should be undertaken with use of elastic stockings and intermittent pneumatic compression devices (Class IB). Initial monitoring of these patients should occur in the ICU and, if available, under the guidance of staff familiar with neurological intensive care (Class IB). Blood glucose should be routinely monitored, and maintenance of normoglycemia is recommended (Class IC). Patients with clinical seizures should be started on appropriate antiepileptic drugs (Class IA). Antiepileptic therapy should also be started if a patient has a change in mental status with electroencephalographic evidence of electrographic seizures (Class IC).

The safe use of antiplatelet therapy in patients with CAA is considered controversial. Gorelick[25] demonstrated that cerebral microhemorrhages were more prevalent among patients taking antiplatelet medications (adjusted OR 1.71 [95% CI 1.21–2.41]), and these microhemorrhages were more likely to be in lobar locations among aspirin users than in nonusers (adjusted OR compared with nonusers 2.70 [95% CI 1.45–5.04]). In a similar study by Ge and colleagues,[22] patients using aspirin for longer than 5 years had a higher frequency of microhemorrhage than those taking aspirin for less than 5 years ($p < 0.0001$). Biffi and colleagues[10] showed that, after CAA-associated ICH, antiplatelet therapy significantly increased the risk of recurrent hemorrhage only if patients had MRI evidence of microhemorrhage at follow-up. In contrast to these retrospective analyses, studies by Viswanathan and colleagues[111] and Taylor and colleagues[102] demonstrated that the risk of antiplatelet agents on ICH recurrence and severity was substantially smaller than that for anticoagulation, suggesting that antiplatelet treatment may be a safer alternative to anticoagulation after ICH.

Recently, the ACTIVE A (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events–Aspirin) study[1] reported the impact of dual antiplatelet therapy versus warfarin on vascular events in patients at high risk for anticoagulation. Although previous ICH was listed as an inclusion criterion, the authors did not report the proportion of patients with previous ICH. Even though dual antiplatelet therapy reduced vascular events by 0.8% at the expense of a 0.7% increase in bleeding events, the results of this study cannot be extrapolated to those with previous ICH or microhemorrhages. The American Heart Association guidelines on management of spontaneous ICH recommend consideration of anticoagulation and antiplatelet therapy after all ICH, particularly when there are definite indications for these agents (Class IIB; Level of Evidence: B).

McCarron and colleagues[61] described 36 patients with CAA-associated hemorrhage, of whom 44% had one or more dysfunctional *APOE-ε* alleles. Those with an *ε2* allele were younger at the age of onset of their first documented hemorrhage than those without the *ε2* allele, although the difference was not statistically significant ($p = 0.088$). This study underscored the importance of using anticoagulant and antiplatelet therapy with caution as these therapies appear to further increase the risk of ICH in patients with CAA associated with the *APOE-ε2* allele.

Surgical Management of Amyloid-Associated ICH

The commonly superficial location of CAA-associated ICH makes it an attractive surgical target for hematoma evacuation. The primary goals of hematoma evacuation are prevention of hematoma expansion, reduction of mass effect and edema, and decompression to improve local perfusion. Ultimately, halting the progression of these pathological processes is hoped to salvage the perilesional penumbra. The following discussion outlines the historical results of surgical management in CAA-associated ICH and provides prognostic data to guide operative management of CAA-associated ICH.

Concern for an increased risk of postoperative ICH after surgery in patients with amyloid angiopathy arose after Torack's description[106] of a cerebral biopsy and ventriculoperitoneal shunt placement in a patient with CAA, which resulted in a fatal postoperative ICH. Initially, 4 other authors reported difficulty with intraoperative hemostasis.[14,35,41,78] However, since those early reports, there have been numerous surgical series reporting safe performance of hematoma evacuation and cortical biopsy (Table 4).[16,19,24,29,33,49,56,97] Many of these case series specifically state that the authors experienced no problems with intraoperative hemostasis.[29,49,56,68] The establishment of surgical safety in CAA is extremely important when discussing minimally invasive techniques where hemostasis can be more cumbersome to attain.

Literature Review of Surgical Case Series

We performed a MEDLINE search to locate all of the case series discussing surgical management of CAA-associated ICH. Seventeen relevant studies are summarized in Table 4. There is a paucity of literature regarding prospective randomized control trials that investigate surgical clot evacuation in patients with CAA-associated ICH. As summarized in Table 4, there are a number of small, retrospective studies reporting surgical outcomes. The comparison of results in medically treated patients with CAA-associated ICH is difficult, as accurate diagnosis of CAA requires a tissue diagnosis. One study demonstrated that biopsy at the time of surgical evacuation of a lobar hematoma had a 67% sensitivity (4 of 6 patients) for diagnosing CAA-associated hemorrhage.[61] This study also emphasized that, in addition to leptomeningeal vessel biopsy, cortical vessels should be biopsied whenever possible to provide the most accurate diagnosis of CAA.

TABLE 4: Case series describing a total of 304 patients that underwent surgical intervention for CAA-associated ICH*

Authors & Year	No. of Patients	Age (yrs)	% w/ Dementia	% on Anti-PLT Therapy	HTN	Hemorrhage Vol (ml)	% w/ IVH	% w/ POH	Mortality Rate (%)	% w/ Good Outcome†
Gilles et al., 1984	6	69.5	27	—	18	—	18	0	67	—
Kalyan-Raman & Kalyan-Raman, 1984	10	70.6	10	10	30	—	10	0	70	20
Cosgrove et al., 1985‡	4	75.2	46	—	59	—	24	—	75	6
Roosen et al., 1985	1	59.0	0	—	0	—	—	0	0	—
Filloux & Townsend, 1985	1	64.0	100	—	0	—	—	0	0	100
Greene et al., 1990	9	72.9	22	—	33	—	—	0	33	44
Leblanc et al., 1991	12	75.6	17	—	—	—	25	17	42	—
Lange & Feiden, 1991	5	78.2	0	—	—	—	—	20	40	40
Matkovic et al., 1991	8	73.0	25	—	63	—	—	13	67	25
Wakai et al., 1992	6	70.0	—	—	33	—	—	0	—	50
Mehdorn et al., 1992	15	65.2	—	—	—	—	—	20	40	27
Minakawa et al., 1995	10	70.0	—	—	—	59	60	0	17	33
McCarron & Nicoll, 1999	12	69.7	—	—	—	—	—	0	66	75
Izumihara et al., 1999	37	75.6	19	0	41	60§	14	5	11	54
Chen et al., 2004	5	76.2	0	0	20	28.5	80	0	0	40¶
Petridis et al., 2008	99	75.0	—	—	72.7	—	24	22	16	11
Hirohata et al., 2010	41	73.2	14.6	7	0**	—	16	2.9	19.5	—
Zhang et al., 2012	23	73.2	17	39	57	51§	43	17	13	44
mean		72.2	16.4	10.3	46.0	55.0	24.9	11.8	24.4	33.8

* HTN = reported history of hypertension; POH = postoperative hemorrhage within the first 48 hours of surgery; — = not reported.
† Good outcome defined as a GOS score greater than 3.
‡ Only 4 patients underwent surgery, but demographics were available for all 17 patients with CAA-associated ICH in this series.
§ These authors provided hematoma volume by groups. The mean listed here is extrapolated from that data by assuming a uniform distribution.
¶ The GOS score was unavailable. Good outcomes here are based on a modified Rankin Scale score less than 3.
** Patients with a history of hypertension were excluded. These patients were not included when computing the mean prevalence of hypertension.

In the reviewed studies, we found that 42% of patients with CAA-associated ICH had a history of hypertension.[14,19,24,29,36,56,113,119] The prevalence of hypertension in those patients is significantly lower than that found in the general population 65–74 years old.[52] In studies reporting estimated hematoma volume, the average volume was 57 cm^3.[15,36,68] In more familiar terms, this result equates to a spherical hematoma that measures 4.8 cm in diameter.

In surgical case series reported in the neurosurgical literature, the indicators of poor prognosis are low preoperative functional status,[49] poor preoperative neurological examination,[60,63,88,119] age older than 75 years,[36,88] presence of IVH,[15,36,49,88] preoperative diagnosis of dementia,[24,36,119] and postoperative hemorrhage.[48,56] Additionally, there is a report of a trend toward poor outcome in CAA-associated ICH with hematoma volume greater than 60 ml,[36] which has been demonstrated as a statistically significant predictor of poor outcome in all-cause ICH.[12]

Izumihara and colleagues[36] demonstrated that the strongest predictor of poor outcome following surgery for CAA-associated ICH is the presence of IVH, with an OR of 50.5. Age older than 75 years was the second strongest predictor of poor outcome (OR 35). Patients with pathologically confirmed CAA-associated ICH have a significantly higher rate of Alzheimer disease.[110] In a study comparing CAA-associated ICH with other causes of ICH, patients with CAA-associated ICH were 9.7 years older but had a disproportionately higher rate of Alzheimer disease (68% vs 9%).[7]

The most recent case series of CAA-associated ICH was published by Zhang and colleagues[119] and demonstrated that a preoperative diagnosis of dementia is a strong predictor of poor outcome. As discussed previously, a preoperative diagnosis of dementia is a relatively common occurrence in older patients with CAA-associated ICH. However, this study showed that it is an independent predictor of poor outcome and should be considered separately from the patient's age. In their case series of 23 patients who were treated for CAA-associated ICH,[119] they reported a 13% mortality. Favorable outcome (GOS score > 3) at discharge was found in 22% of patients and at 6- to 12-month follow-up in 47% of patients. The authors noted that a history of hypertension and degree of preoperative midline shift on imaging were associated with a prolonged length of stay. Intraventricular hemorrhage was also associated with poor outcome at discharge.

Historical concerns over difficult intraoperative hemostasis have been addressed; however, postoperative hemorrhage is still a source of significant morbidity and mortality. Notably, 1 of the 4 deaths that occurred in the series by Zhang and colleagues[119] was due to a postoperative hemorrhage. Postoperative hemorrhage is not unique to CAA-associated ICH; however, it occurs much more frequently in CAA-associated ICH. As seen

in Table 1, clinically relevant postoperative hemorrhage is a relatively frequent occurrence after evacuation of CAA-associated ICH. Palmer and colleagues[84] reported only a 3.1% incidence of postoperative hemorrhage following evacuation of all-cause ICH.[86] This rate was one-fourth the historical rate we found in our meta-analysis of surgical series of CAA-associated ICH (12%) (Table 4). Palmer and colleagues[84] identified antiplatelet therapy as the most common risk factor for postoperative hemorrhage following craniotomy. Similarly, the case series of patients with CAA-associated ICH by Zhang and colleagues[119] reported that all 4 of their patients with postoperative hemorrhage were on antiplatelet therapy prior to hospitalization. We were unable to find data to support or refute any benefit of antiplatelet agent reversal in CAA-associated ICH. However, data from previous case reports suggest that these patients should therefore be monitored closely for rebleeding in the immediate postoperative setting.

When postoperative hemorrhage occurs, age appears to be the primary determinant of mortality. In a series of CAA-associated ICH surgically treated by Petridis and colleagues,[88] patients with postoperative hemorrhage who were older than 75 years had a 55% mortality rate, compared with a 30% mortality rate in patients younger than 75 years. Notably, survivors of postoperative hemorrhage all had a GOS score of 3. Repeat hematoma evacuation decreases mortality but still results in poor functional outcomes, especially in elderly patients.

As illustrated in Table 4, the two primary patient-centered outcomes of this meta-analysis are mortality and functional status. These outcomes can be compared with results from management of all-cause ICH in the STICH trial.[65] Our meta-analysis revealed that, after surgical management of CAA-associated ICH, the average mortality was 24% at 1 year, comparing favorably with the surgically treated group in STICH, which reported a 6-month mortality rate of 36%. In the reviewed studies of patients with CAA-associated ICH that was treated surgically, 33.8% attained a good outcome (GOS score > 3) at 1 year. This finding is better than the 26% of surgically treated patients in the STICH trial that had a good outcome at 6 months.

In comparison with the STICH trial, these case series are most notably limited by their retrospective nature and small patient populations.[90] Given the advanced age and increased rate of Alzheimer disease of patients with CAA-associated ICH, a concern about surgical treatment would be the reduction of mortality with worsened functional outcomes. Our findings suggest the possibility that surgical management of CAA-associated ICH may actually improve both morbidity and mortality. The results of this comparison are encouraging, especially after considering that the average age of patients in our meta-analysis was 72 years, compared with 62 years in the STICH trial. However, without prospective randomized trials of surgical management in CAA-associated ICH, it is not possible at this time to confidently state that there is a benefit from surgical intervention.

Subgroup analysis of the STICH trial suggested better functional outcomes after surgery in patients with superficial as well as lobar ICH in the absence of IVH. These outcome measures formed the basis of STICH II, aimed at randomized early evacuation of lobar ICH.[66] The results of this trial will have large implications on both the surgical management of all-cause ICH as well as the subset of these patients who have CAA-associated ICH.

Minimally Invasive Surgical Techniques for the Treatment of CAA-Associated ICH

The use of minimally invasive surgical techniques in the treatment of hypertensive hemorrhage has produced interest in applying those techniques to CAA-associated lobar ICH. Stereotactic aspiration of ICH was originally described by Backlund and von Holst[8] in 1978, using an instrument based off of Archimedes' screw. Improvements in instrumentation and technique have expanded stereotactic aspiration to include the use of endoscopy, chemothrombolysis, and sonothrombolysis. Minakawa and colleagues[68] used stereotactic aspiration with CT guidance for aspiration of lobar ICH in 6 patients, 2 of whom had confirmed CAA-associated ICH. There were no problems with intraoperative or postoperative hemorrhage; however, no long-term functional outcomes were available for these patients.

The Minimally Invasive Surgery Plus tPA for ICH Evacuation (MISTIE) trial is currently underway, comparing the best medical management against stereotactic aspiration of all-cause ICH along with periodic injection of tPA. Preliminary results showed that this technique is safe and effective at decreasing the volume of the hematoma.[69] There is also a clinical trial currently underway for endoscopic hematoma evacuation in all-cause ICH (MISTIE-ICES). Most recently, Newell and colleagues[73] used adjuvant sonothrombolysis to attain an average of 59% hematoma reduction at 24 hours following evacuation. Results from these trials will further characterize the possible role of minimally invasive techniques in the surgical treatment of CAA-associated ICH.

Conclusions

The increasing longevity of our patient population, advances in the medical management of cerebrovascular risk factors, and increased use of thrombolytic therapy are likely to make CAA-associated ICH a more prominent clinical problem in years to come. The Boston criteria can be used for the clinical diagnosis of CAA-associated ICH. After putative diagnosis, the clinician is faced with the difficult decision of choosing which treatment modality will provide the best outcome. From the available retrospective data, traditional open craniotomy is safe in the setting of CAA. Surgical clot evacuation in CAA-associated ICH often results in a poor outcome when the following are present: dementia, age older than 75 years, hematoma volume and location, preoperative Glasgow Coma Scale Score 8 or lower, and intraventricular extension. With the occurrence of postoperative hemorrhage after hematoma evacuation, reoperation has been

shown to be safe, with a significant decrease in mortality. However, elderly patients who undergo evacuation of postoperative hemorrhage rarely have a good functional outcome. Future prospective, randomized clinical trials of hematoma evacuation in CAA-associated ICH will be able to further characterize the role of surgery in the rather morbid natural history of CAA-associated ICH.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Selman, Mehndiratta, Manjila, Cohen, Sila. Acquisition of data: all authors. Analysis and interpretation of data: Mehndiratta, Manjila, Ostergard, Eisele. Drafting the article: Mehndiratta, Manjila, Ostergard, Eisele. Critically revising the article: all authors. Reviewed submitted version of manuscript: Selman, Mehndiratta, Manjila, Ostergard, Eisele, Cohen. Approved the final version of the manuscript on behalf of all authors: Selman. Administrative/technical/material support: Selman, Mehndiratta, Manjila, Cohen, Sila. Study supervision: Selman, Manjila, Cohen, Sila.

References

1. ACTIVE Investigators, Connolly SJ, Pogue J, Hart RG, Hohnloser SH, Pfeffer M, Chrolavicius S, et al: Effect of clopidogrel added to aspirin in patients with atrial fibrillation. **N Engl J Med 360:**2066–2078, 2009
2. Alemany Ripoll M, Stenborg A, Sonninen P, Terent A, Raininko R: Detection and appearance of intraparenchymal haematomas of the brain at 1.5 T with spin-echo, FLAIR and GE sequences: poor relationship to the age of the haematoma. **Neuroradiology 46:**435–443, 2004
3. Anderson CS, Huang Y, Arima H, Heeley E, Skulina C, Parsons MW, et al: Effects of early intensive blood pressure-lowering treatment on the growth of hematoma and perihematomal edema in acute intracerebral hemorrhage: the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT). **Stroke 41:**307–312, 2010
4. Atlas SW, Mark AS, Grossman RI, Gomori JM: Intracranial hemorrhage: gradient-echo MR imaging at 1.5 T. Comparison with spin-echo imaging and clinical applications. **Radiology 168:**803–807, 1988
5. Attems J: Sporadic cerebral amyloid angiopathy: pathology, clinical implications, and possible pathomechanisms. **Acta Neuropathol 110:**345–359, 2005
6. Attems J, Jellinger KA, Lintner F: Alzheimer's disease pathology influences severity and topographical distribution of cerebral amyloid angiopathy. **Acta Neuropathol 110:**222–231, 2005
7. Attems J, Lauda F, Jellinger KA: Unexpectedly low prevalence of intracerebral hemorrhages in sporadic cerebral amyloid angiopathy: an autopsy study. **J Neurol 255:**70–76, 2008
8. Backlund EO, von Holst H: Controlled subtotal evacuation of intracerebral haematomas by stereotactic technique. **Surg Neurol 9:**99–101, 1978
9. Bahmanyar S, Higgins GA, Goldgaber D, Lewis DA, Morrison JH, Wilson MC, et al: Localization of amyloid beta protein messenger RNA in brains from patients with Alzheimer's disease. **Science 237:**77–80, 1987
10. Biffi A, Halpin A, Towfighi A, Gilson A, Busl K, Rost N, et al: Aspirin and recurrent intracerebral hemorrhage in cerebral amyloid angiopathy. **Neurology 75:**693–698, 2010
11. Briceno CE, Resch L, Bernstein M: Cerebral amyloid angiopathy presenting as a mass lesion. **Stroke 18:**234–239, 1987
12. Broderick JP, Brott TG, Duldner JE, Tomsick T, Huster G: Volume of intracerebral hemorrhage. A powerful and easy-to-use predictor of 30-day mortality. **Stroke 24:**987–993, 1993
13. Brott T, Broderick J, Kothari R, Barsan W, Tomsick T, Sauerbeck L, et al: Early hemorrhage growth in patients with intracerebral hemorrhage. **Stroke 28:**1–5, 1997
14. Case records of the Massachusetts General Hospital: Weekly clinicopathological exercises. Case 49-1982. A 63-year-old man with recurrent intracerebral hemorrhage. **N Engl J Med 307:**1507–1514, 1982
15. Chen CS, Lo YK, Yan SH, Lin YT, Lai PH, Lo YS: Lobar cerebral hemorrhage from amyloid angiopathy: clinical, neuroimaging, pathologic and outcome correlations. **Acta Neurol Taiwan 13:**14–19, 2004
16. Cosgrove GR, Leblanc R, Meagher-Villemure K, Ethier R: Cerebral amyloid angiopathy. **Neurology 35:**625–631, 1985
17. Eng JA, Frosch MP, Choi K, Rebeck GW, Greenberg SM: Clinical manifestations of cerebral amyloid angiopathy-related inflammation. **Ann Neurol 55:**250–256, 2004
18. Fazekas F, Kleinert R, Roob G, Kleinert G, Kapeller P, Schmidt R, et al: Histopathologic analysis of foci of signal loss on gradient-echo T2*-weighted MR images in patients with spontaneous intracerebral hemorrhage: evidence of microangiopathy-related microbleeds. **AJNR Am J Neuroradiol 20:**637–642, 1999
19. Filloux FM, Townsend JJ: Congophilic angiopathy with intracerebral hemorrhage. **West J Med 143:**498–502, 1985
20. Fountain NB, Eberhard DA: Primary angiitis of the central nervous system associated with cerebral amyloid angiopathy: report of two cases and review of the literature. **Neurology 46:**190–197, 1996
21. Frackowiak J, Zoltowska A, Wisniewski HM: Non-fibrillar beta-amyloid protein is associated with smooth muscle cells of vessel walls in Alzheimer disease. **J Neuropathol Exp Neurol 53:**637–645, 1994
22. Ge L, Niu G, Han X, Gao Y, Wu Q, Wu H, et al: Aspirin treatment increases the risk of cerebral microbleeds. **Can J Neurol Sci 38:**863–868, 2011
23. Gebel JM, Sila CA, Sloan MA, Granger CB, Mahaffey KW, Weisenberger J, et al: Thrombolysis-related intracranial hemorrhage: a radiographic analysis of 244 cases from the GUSTO-1 trial with clinical correlation. Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries. **Stroke 29:**563–569, 1998
24. Gilles C, Brucher JM, Khoubesserian P, Vanderhaeghen JJ: Cerebral amyloid angiopathy as a cause of multiple intracerebral hemorrhages. **Neurology 34:**730–735, 1984
25. Gorelick PB: Cerebral microbleeds: evidence of heightened risk associated with aspirin use. **Arch Neurol 66:**691–693, 2009
26. Greenberg SM, Briggs ME, Hyman BT, Kokoris GJ, Takis C, Kanter DS, et al: Apolipoprotein E epsilon 4 is associated with the presence and earlier onset of hemorrhage in cerebral amyloid angiopathy. **Stroke 27:**1333–1337, 1996
27. Greenberg SM, Eng JA, Ning M, Smith EE, Rosand J: Hemorrhage burden predicts recurrent intracerebral hemorrhage after lobar hemorrhage. **Stroke 35:**1415–1420, 2004
28. Greenberg SM, Vonsattel JP, Stakes JW, Gruber M, Finklestein SP: The clinical spectrum of cerebral amyloid angiopathy: presentations without lobar hemorrhage. **Neurology 43:**2073–2079, 1993
29. Greene GM, Godersky JC, Biller J, Hart MN, Adams HP Jr: Surgical experience with cerebral amyloid angiopathy. **Stroke 21:**1545–1549, 1990
30. Hemphill JC III, Bonovich DC, Besmertis L, Manley GT, Johnston SC: The ICH score: a simple, reliable grading scale for intracerebral hemorrhage. **Stroke 32:**891–897, 2001
31. Hendricks HT, Franke CL, Theunissen PH: Cerebral amyloid angiopathy: diagnosis by MRI and brain biopsy. **Neurology 40:**1308–1310, 1990
32. Hendriks L, van Duijn CM, Cras P, Cruts M, Van Hul W, van

Harskamp F, et al: Presenile dementia and cerebral haemorrhage linked to a mutation at codon 692 of the beta-amyloid precursor protein gene. **Nat Genet 1:**218–221, 1992
33. Hirohata M, Yoshita M, Ishida C, Ikeda SI, Tamaoka A, Kuzuhara S, et al: Clinical features of non-hypertensive lobar intracerebral hemorrhage related to cerebral amyloid angiopathy. **Eur J Neurol 17:**823–829, 2010
34. Inaji M, Tomita H, Tone O, Tamaki M, Suzuki R, Ohno K: Chronological changes of perihematomal edema of human intracerebral hematoma. **Acta Neurochir Suppl 86:**445–448, 2003
35. Ishii N, Nishihara Y, Horie A: Amyloid angiopathy and lobar cerebral haemorrhage. **J Neurol Neurosurg Psychiatry 47:**1203–1210, 1984
36. Izumihara A, Ishihara T, Iwamoto N, Yamashita K, Ito H: Postoperative outcome of 37 patients with lobar intracerebral hemorrhage related to cerebral amyloid angiopathy. **Stroke 30:**29–33, 1999
37. Jarvik LF: Treatments for Alzheimer patients—above all do no harm. **Alzheimer Dis Assoc Disord 1:**123–127, 1987
38. Jeerakathil T, Wolf PA, Beiser A, Hald JK, Au R, Kase CS, et al: Cerebral microbleeds: prevalence and associations with cardiovascular risk factors in the Framingham Study. **Stroke 35:**1831–1835, 2004
39. Jellinger KA: Alzheimer disease and cerebrovascular pathology: an update. **J Neural Transm 109:**813–836, 2002
40. Jung SS, Zhang W, Van Nostrand WE: Pathogenic A beta induces the expression and activation of matrix metalloproteinase-2 in human cerebrovascular smooth muscle cells. **J Neurochem 85:**1208–1215, 2003
41. Kalyan-Raman UP, Kalyan-Raman K: Cerebral amyloid angiopathy causing intracranial hemorrhage. **Ann Neurol 16:**321–329, 1984
42. Kandzari DE, Granger CB, Simoons ML, White HD, Simes J, Mahaffey KW, et al: Risk factors for intracranial hemorrhage and nonhemorrhagic stroke after fibrinolytic therapy (from the GUSTO-i trial). **Am J Cardiol 93:**458–461, 2004
43. Kang J, Lemaire HG, Unterbeck A, Salbaum JM, Masters CL, Grzeschik KH, et al: The precursor of Alzheimer's disease amyloid A4 protein resembles a cell-surface receptor. **Nature 325:**733–736, 1987
44. Kase CS: Cerebellar infarction. **Heart Dis Stroke 3:**38–45, 1994
45. Kennedy DN, Lange N, Makris N, Bates J, Meyer J, Caviness VS Jr: Gyri of the human neocortex: an MRI-based analysis of volume and variance. **Cereb Cortex 8:**372–384, 1998
46. Knudsen KA, Rosand J, Karluk D, Greenberg SM: Clinical diagnosis of cerebral amyloid angiopathy: validation of the Boston criteria. **Neurology 56:**537–539, 2001
47. Labovitz DL, Halim A, Boden-Albala B, Hauser WA, Sacco RL: The incidence of deep and lobar intracerebral hemorrhage in whites, blacks, and Hispanics. **Neurology 65:**518–522, 2005
48. Lange M, Feiden W: Amyloid angiopathy—a rare cause of intracerebral hemorrhage. **Neurosurg Rev 14:**297–301, 1991
49. Leblanc R, Preul M, Robitaille Y, Villemure JG, Pokrupa R: Surgical considerations in cerebral amyloid angiopathy. **Neurosurgery 29:**712–718, 1991
50. Lee JM, Yin KJ, Hsin I, Chen S, Fryer JD, Holtzman DM, et al: Matrix metalloproteinase-9 and spontaneous hemorrhage in an animal model of cerebral amyloid angiopathy. **Ann Neurol 54:**379–382, 2003
51. Lee SS, Stemmermann GN: Congophilic angiopathy and cerebral hemorrhage. **Arch Pathol Lab Med 102:**317–321, 1978
52. Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K, et al: Heart disease and stroke statistics—2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. **Circulation 119:**480–486, 2009
53. Mandybur TI: Cerebral amyloid angiopathy: the vascular pathology and complications. **J Neuropathol Exp Neurol 45:**79–90, 1986
54. Mandybur TI, Balko G: Cerebral amyloid angiopathy with granulomatous angiitis ameliorated by steroid-cytoxan treatment. **Clin Neuropharmacol 15:**241–247, 1992
55. Masuda J, Tanaka K, Ueda K, Omae T: Autopsy study of incidence and distribution of cerebral amyloid angiopathy in Hisayama, Japan. **Stroke 19:**205–210, 1988
56. Matkovic Z, Davis S, Gonzales M, Kalnins R, Masters CL: Surgical risk of hemorrhage in cerebral amyloid angiopathy. **Stroke 22:**456–461, 1991
57. McCarron MO, Delong D, Alberts MJ: APOE genotype as a risk factor for ischemic cerebrovascular disease: a meta-analysis. **Neurology 53:**1308–1311, 1999
58. McCarron MO, Nicoll JA: Cerebral amyloid angiopathy and thrombolysis-related intracerebral haemorrhage. **Lancet Neurol 3:**484–492, 2004
59. McCarron MO, Nicoll JA: Surgery for cerebral amyloid angiopathy-related hemorrhage. **Stroke 30:**1291–1292, 1999
60. McCarron MO, Nicoll JA, Ironside JW, Love S, Alberts MJ, Bone I: Cerebral amyloid angiopathy-related hemorrhage. Interaction of APOE epsilon2 with putative clinical risk factors. **Stroke 30:**1643–1646, 1999
61. McCarron MO, Nicoll JA, Love S, Ironside JW: Surgical intervention, biopsy and APOE genotype in cerebral amyloid angiopathy-related haemorrhage. **Br J Neurosurg 13:**462–467, 1999
62. McCarron MO, Nicoll JA, Stewart J, Ironside JW, Mann DM, Love S, et al: The apolipoprotein E epsilon2 allele and the pathological features in cerebral amyloid angiopathy-related hemorrhage. **J Neuropathol Exp Neurol 58:**711–718, 1999
63. Mehdorn HM, Gerhard L, Müller SP, Olbrich HM: Clinical and cerebral blood flow studies in patients with intracranial hemorrhage and amyloid angiopathy typical of Alzheimer's disease. **Neurosurg Rev 15:**111–116, 1992
64. Melo TP, Bogousslavsky J, Regli F, Janzer R: Fatal hemorrhage during anticoagulation of cardioembolic infarction: role of cerebral amyloid angiopathy. **Eur Neurol 33:**9–12, 1993
65. Mendelow AD, Gregson BA, Fernandes HM, Murray GD, Teasdale GM, Hope DT, et al: Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomised trial. **Lancet 365:**387–397, 2005
66. Mendelow AD, Gregson BA, Mitchell PM, Murray GD, Rowan EN, Gholkar AR, et al: Surgical trial in lobar intracerebral haemorrhage (STICH II) protocol. **Trials 12:**124, 2011
67. Miller JH, Wardlaw JM, Lammie GA: Intracerebral haemorrhage and cerebral amyloid angiopathy: CT features with pathological correlation. **Clin Radiol 54:**422–429, 1999
68. Minakawa T, Takeuchi S, Sasaki O, Koizumi T, Honad Y, Fujii Y, et al: Surgical experience with massive lobar haemorrhage caused by cerebral amyloid angiopathy. **Acta Neurochir 132:**48–52, 1995
69. Morgan T, Zuccarello M, Narayan R, Keyl P, Lane K, Hanley D: Preliminary findings of the minimally-invasive surgery plus rtPA for intracerebral hemorrhage evacuation (MISTIE) clinical trial. **Acta Neurochir Suppl 105:**147–151, 2008
70. Morgenstern LB, Hemphill JC III, Anderson C, Becker K, Broderick JP, Connolly ES Jr, et al: Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. **Stroke 41:**2108–2129, 2010
71. Nakata-Kudo Y, Mizuno T, Yamada K, Shiga K, Yoshikawa K, Mori S, et al: Microbleeds in Alzheimer disease are more related to cerebral amyloid angiopathy than cerebrovascular disease. **Dement Geriatr Cogn Disord 22:**8–14, 2006
72. Neumann MA: Combined amyloid vascular changes and argyr-

ophilic plaques in the central nervous system. **J Neuropathol Exp Neurol 19:**370–382, 1960
73. Newell DW, Shah MM, Wilcox R, Hansmann DR, Melnychuk E, Muschelli J, et al: Minimally invasive evacuation of spontaneous intracerebral hemorrhage using sonothrombolysis. Clinical article. **J Neurosurg 115:**592–601, 2011
74. Nicoll JA, Burnett C, Love S, Graham DI, Dewar D, Ironside JW, et al: High frequency of apolipoprotein E epsilon 2 allele in hemorrhage due to cerebral amyloid angiopathy. **Ann Neurol 41:**716–721, 1997
75. NINDS t-PA Stroke Study Group: Intracerebral hemorrhage after intravenous t-PA therapy for ischemic stroke. **Stroke 28:** 2109–2118, 1997
76. O'Donnell HC, Rosand J, Knudsen KA, Furie KL, Segal AZ, Chiu RI, et al: Apolipoprotein E genotype and the risk of recurrent lobar intracerebral hemorrhage. **N Engl J Med 342:**240–245, 2000
77. Oh U, Gupta R, Krakauer JW, Khandji AG, Chin SS, Elkind MS: Reversible leukoencephalopathy associated with cerebral amyloid angiopathy. **Neurology 62:**494–497, 2004
78. Ojemann RG, Heros RC: Spontaneous brain hemorrhage. **Stroke 14:**468–475, 1983
79. Okazaki H, Reagan TJ, Campbell RJ: Clinicopathologic studies of primary cerebral amyloid angiopathy. **Mayo Clin Proc 54:**22–31, 1979
80. Olichney JM, Hansen LA, Galasko D, Saitoh T, Hofstetter CR, Katzman R, et al: The apolipoprotein E epsilon 4 allele is associated with increased neuritic plaques and cerebral amyloid angiopathy in Alzheimer's disease and Lewy body variant. **Neurology 47:**190–196, 1996
81. Olichney JM, Hansen LA, Hofstetter CR, Grundman M, Katzman R, Thal LJ: Cerebral infarction in Alzheimer's disease is associated with severe amyloid angiopathy and hypertension. **Arch Neurol 52:**702–708, 1995
82. Opeskin K: Cerebral amyloid angiopathy. A review. **Am J Forensic Med Pathol 17:**248–254, 1996
83. Oppenheim G: Über "drusige nekrosen" in der grosshirnrinde. **Neurol Centrabl 28:**410–413, 1909
84. Palmer JD, Sparrow OC, Iannotti F: Postoperative hematoma: a 5-year survey and identification of avoidable risk factors. **Neurosurgery 35:**1061–1065, 1994
85. Pantelakis S: [A particular type of senile angiopathy of the central nervous system: congophilic angiopathy, topography and frequency.] **Monatsschr Psychiatr Neurol 128:**219–256, 1954 (Fr)
86. Pardoe HR, Pell GS, Abbott DF, Jackson GD: Hippocampal volume assessment in temporal lobe epilepsy: How good is automated segmentation? **Epilepsia 50:**2586–2592, 2009
87. Pendlebury WW, Iole ED, Tracy RP, Dill BA: Intracerebral hemorrhage related to cerebral amyloid angiopathy and t-PA treatment. **Ann Neurol 29:**210–213, 1991
88. Petridis AK, Barth H, Buhl R, Hugo HH, Mehdorn HM: Outcome of cerebral amyloid angiopathic brain haemorrhage. **Acta Neurochir (Wien) 150:**889–895, 2008
89. Pezzini A, Del Zotto E, Volonghi I, Giossi A, Costa P, Padovani A: Cerebral amyloid angiopathy: a common cause of cerebral hemorrhage. **Curr Med Chem 16:**2498–2513, 2009
90. Prasad K, Mendelow AD, Gregson B: Surgery for primary supratentorial intracerebral haemorrhage. **Cochrane Database Syst Rev (4):**CD000200, 2008
91. Premkumar DR, Cohen DL, Hedera P, Friedland RP, Kalaria RN: Apolipoprotein E-epsilon4 alleles in cerebral amyloid angiopathy and cerebrovascular pathology associated with Alzheimer's disease. **Am J Pathol 148:**2083–2095, 1996
92. Qureshi AI, Tuhrim S, Broderick JP, Batjer HH, Hondo H, Hanley DF: Spontaneous intracerebral hemorrhage. **N Engl J Med 344:**1450–1460, 2001
93. Revesz T, Ghiso J, Lashley T, Plant G, Rostagno A, Frangione B, et al: Cerebral amyloid angiopathies: a pathologic, biochemical, and genetic view. **J Neuropathol Exp Neurol 62:**885–898, 2003
94. Revesz T, Holton JL, Lashley T, Plant G, Rostagno A, Ghiso J, et al: Sporadic and familial cerebral amyloid angiopathies. **Brain Pathol 12:**343–357, 2002
95. Riemer G, Lamszus K, Zschaber R, Freitag HJ, Eggers C, Pfeiffer G: Isolated angiitis of the central nervous system: lack of inflammation after long-term treatment. **Neurology 52:**196–199, 1999
96. Roob G, Fazekas F: Magnetic resonance imaging of cerebral microbleeds. **Curr Opin Neurol 13:**69–73, 2000
97. Roosen N, Martin JJ, de la Porte C, Van Vyve M: Intracerebral hemorrhage due to cerebral amyloid angiopathy. Case report. **J Neurosurg 63:**965–969, 1985
98. Rosand J, Muzikansky A, Kumar A, Wisco JJ, Smith EE, Betensky RA, et al: Spatial clustering of hemorrhages in probable cerebral amyloid angiopathy. **Ann Neurol 58:**459–462, 2005
99. Schwab P, Lidov HGW, Schwartz RB, Anderson RJ: Cerebral amyloid angiopathy associated with primary angiitis of the central nervous system: report of 2 cases and review of the literature. **Arthritis Rheum 49:**421–427, 2003
100. Scolding NJ, Joseph F, Kirby PA, Mazanti I, Gray F, Mikol J, et al: Abeta-related angiitis: primary angiitis of the central nervous system associated with cerebral amyloid angiopathy. **Brain 128:**500–515, 2005
101. Sloan MA, Price TR, Petito CK, Randall AM, Solomon RE, Terrin ML, et al: Clinical features and pathogenesis of intracerebral hemorrhage after rt-PA and heparin therapy for acute myocardial infarction: the Thrombolysis in Myocardial Infarction (TIMI) II Pilot and Randomized Clinical Trial combined experience. **Neurology 45:**649–658, 1995
102. Taylor FC, Cohen H, Ebrahim S: Systematic review of long term anticoagulation or antiplatelet treatment in patients with non-rheumatic atrial fibrillation. **BMJ 322:**321–326, 2001
103. Tamargo RJ, Connolly ES Jr, McKhann GM, Khandji A, Chang Y, Libien J, et al: Clinicopathological review: primary angiitis of the central nervous system in association with cerebral amyloid angiopathy. **Neurosurgery 53:**136–143, 2003
104. Thijs V, Lemmens R, Schoofs C, Görner A, Van Damme P, Schrooten M, et al: Microbleeds and the risk of recurrent stroke. **Stroke 41:**2005–2009, 2010
105. Tomonaga M: Cerebral amyloid angiopathy in the elderly. **J Am Geriatr Soc 29:**151–157, 1981
106. Torack RM: Congophilic angiopathy complicated by surgery and massive hemorrhage. A light and electron microscopic study. **Am J Pathol 81:**349–366, 1975
107. Tsushima Y, Tanizaki Y, Aoki J, Endo K: MR detection of microhemorrhages in neurologically healthy adults. **Neuroradiology 44:**31–36, 2002
108. Van Broeckhoven C, Haan J, Bakker E, Hardy JA, Van Hul W, Wehnert A, et al: Amyloid beta protein precursor gene and hereditary cerebral hemorrhage with amyloidosis (Dutch). **Science 248:**1120–1122, 1990
109. van Es AC, van der Grond J, de Craen AJ, Westendorp RG, Bollen EL, Blauw GJ, et al: Cerebral microbleeds and cognitive functioning in the PROSPER study. **Neurology 77:** 1446–1452, 2011
110. Vinters HV: Cerebral amyloid angiopathy. A critical review. **Stroke 18:**311–324, 1987
111. Viswanathan A, Rakich SM, Engel C, Snider R, Rosand J, Greenberg SM, et al: Antiplatelet use after intracerebral hemorrhage. **Neurology 66:**206–209, 2006
112. Vonsattel JP, Myers RH, Hedley-Whyte ET, Ropper AH, Bird ED, Richardson EPJ Jr: Cerebral amyloid angiopathy without and with cerebral hemorrhages: a comparative histological study. **Ann Neurol 30:**637–649, 1991
113. Wakai S, Kumakura N, Nagai M: Lobar intracerebral hemorrhage. A clinical, radiographic, and pathological study of

29 consecutive operated cases with negative angiography. **J Neurosurg 76:**231–238, 1992
114. Weller RO, Massey A, Newman TA, Hutchings M, Kuo YM, Roher AE: Cerebral amyloid angiopathy: amyloid beta accumulates in putative interstitial fluid drainage pathways in Alzheimer's disease. **Am J Pathol 153:**725–733, 1998
115. Wijdicks EF, Jack CRJ Jr: Intracerebral hemorrhage after fibrinolytic therapy for acute myocardial infarction. **Stroke 24:**554–557, 1993
116. Wisniewski HM, Wegiel J: Beta-amyloid formation by myocytes of leptomeningeal vessels. **Acta Neuropathol 87:**233–241, 1994
117. Woo D, Sauerbeck LR, Kissela BM, Khoury JC, Szaflarski JP, Gebel J, et al: Genetic and environmental risk factors for intracerebral hemorrhage: preliminary results of a population-based study. **Stroke 33:**1190–1195, 2002
118. Yamaguchi H, Yamazaki T, Lemere CA, Frosch MP, Selkoe DJ: Beta amyloid is focally deposited within the outer basement membrane in the amyloid angiopathy of Alzheimer's disease. An immunoelectron microscopic study. **Am J Pathol 141:**249–259, 1992
119. Zhang Y, Wang X, Schultz C, Lanzino G, Rabinstein AA: Postoperative outcome of cerebral amyloid angiopathy-related lobar intracerebral hemorrhage: case series and systematic review. **Neurosurgery 70:**125–130, 2012

Manuscript submitted December 16, 2011.
Accepted January 20, 2012.
Please include this information when citing this paper: DOI: 10.3171/2012.1.FOCUS11370.

Address correspondence to: Warren R. Selman, M.D., Department of Neurological Surgery, University Hospitals Case Medical Center, 11100 Euclid Avenue, HAN 5042, Cleveland, Ohio 44106. email: Warren.Selman@UHHospitals.org.

Neurosurg Focus 32 (4):E8, 2012

Thrombin and hemin as central factors in the mechanisms of intracerebral hemorrhage–induced secondary brain injury and as potential targets for intervention

Ranjith Babu, M.S.,[1] Jacob H. Bagley, B.S.,[1] Chunhui Di, M.S.,[1] Allan H. Friedman, M.D.,[1] and Cory Adamson, M.D., Ph.D., M.P.H., M.H.Sc.[1–3]

[1]Division of Neurosurgery, Department of Surgery, and [2]Department of Neurobiology, Duke University Medical Center; and [3]Durham Veterans Affairs Medical Center, Durham, North Carolina

Intracerebral hemorrhage (ICH) is a subtype of stoke that may cause significant morbidity and mortality. Brain injury due to ICH initially occurs within the first few hours as a result of mass effect due to hematoma formation. However, there is increasing interest in the mechanisms of secondary brain injury as many patients continue to deteriorate clinically despite no signs of rehemorrhage or hematoma expansion. This continued insult after primary hemorrhage is believed to be mediated by the cytotoxic, excitotoxic, oxidative, and inflammatory effects of intraparenchymal blood. The main factors responsible for this injury are thrombin and erythrocyte contents such as hemoglobin. Therapies including thrombin inhibitors, *N*-methyl-D-aspartate antagonists, chelators to bind free iron, and antiinflammatory drugs are currently under investigation for reducing this secondary brain injury. This review will discuss the molecular mechanisms of brain injury as a result of intraparenchymal blood, potential targets for therapeutic intervention, and treatment strategies currently in development.
(http://thejns.org/doi/abs/10.3171/2012.1.FOCUS11366)

Key Words • intracerebral hemorrhage • thrombin • hemin • brain injury • neuroprotective drug • protease-activated receptor

Stroke affects 15 million people worldwide and accounts for approximately 10% of all deaths.[40] Strokes are classified as either ischemic or hemorrhagic, and occur due to blood vessel occlusion or blood vessel rupture, respectively. Approximately 13% of strokes are of the hemorrhagic subtype and include ICH and SAH.[107] Intracerebral hemorrhage is the most common cause of hemorrhagic stroke and causes extravasation of blood into the parenchyma and subsequent hematoma formation, resulting in brain damage.[40] Intracerebral hemorrhage frequently causes significant morbidity and death, with as many as 50% of patients dying within 1 month of presentation, and only 20% of survivors able to function independently at 6 months.[33] Also, with a worldwide incidence of 10–20 cases per 100,000 people, ICH is a global public health problem.[99,118]

Abbreviations used in this paper: ATP = adenosine triphosphate; BBB = blood-brain barrier; ICH = intracerebral hemorrhage; IL = interleukin; MMP = matrix metalloproteinase; NF = nuclear factor; NMDA = *N*-methyl-D-aspartate; PAR = protease-activated receptor; RBC = red blood cell; rCBF = regional cerebral blood flow; SAH = subarachnoid hemorrhage; TNF = tumor necrosis factor.

Spontaneous ICH is mainly caused by hypertension, which causes microaneurysms at the bifurcation of intracerebral arterioles that can immediately rupture.[29,123] These microaneurysms may be different from the berry aneurysms at the Circle of Willis branch points that cause SAHs. Intracerebral hemorrhage may also be due to cerebral amyloid angiopathy, anticoagulant use, hematological disorders, arteriovenous malformations, arteriovenous fistulas, cavernous angiomas, and brain tumors. Intracerebral hemorrhage can be further distinguished from SAH as it is more commonly found near gray-white junctions in cerebral lobes, subcortical structures such as the basal ganglia, the brainstem, and deep cerebellar nuclei.[99,101] Current management for ICH immediately after onset involves airway management, monitoring of hemodynamic parameters, control of intracranial pressure, and hematoma evacuation.

Brain injury from ICH can be described by primary and secondary mechanisms (Fig. 1). The majority of the brain injury due to ICH typically occurs within the first few hours as a result of mass effect due to hematoma formation.[98] This primary injury results in increased pressure and disruption of the surrounding neural structures,

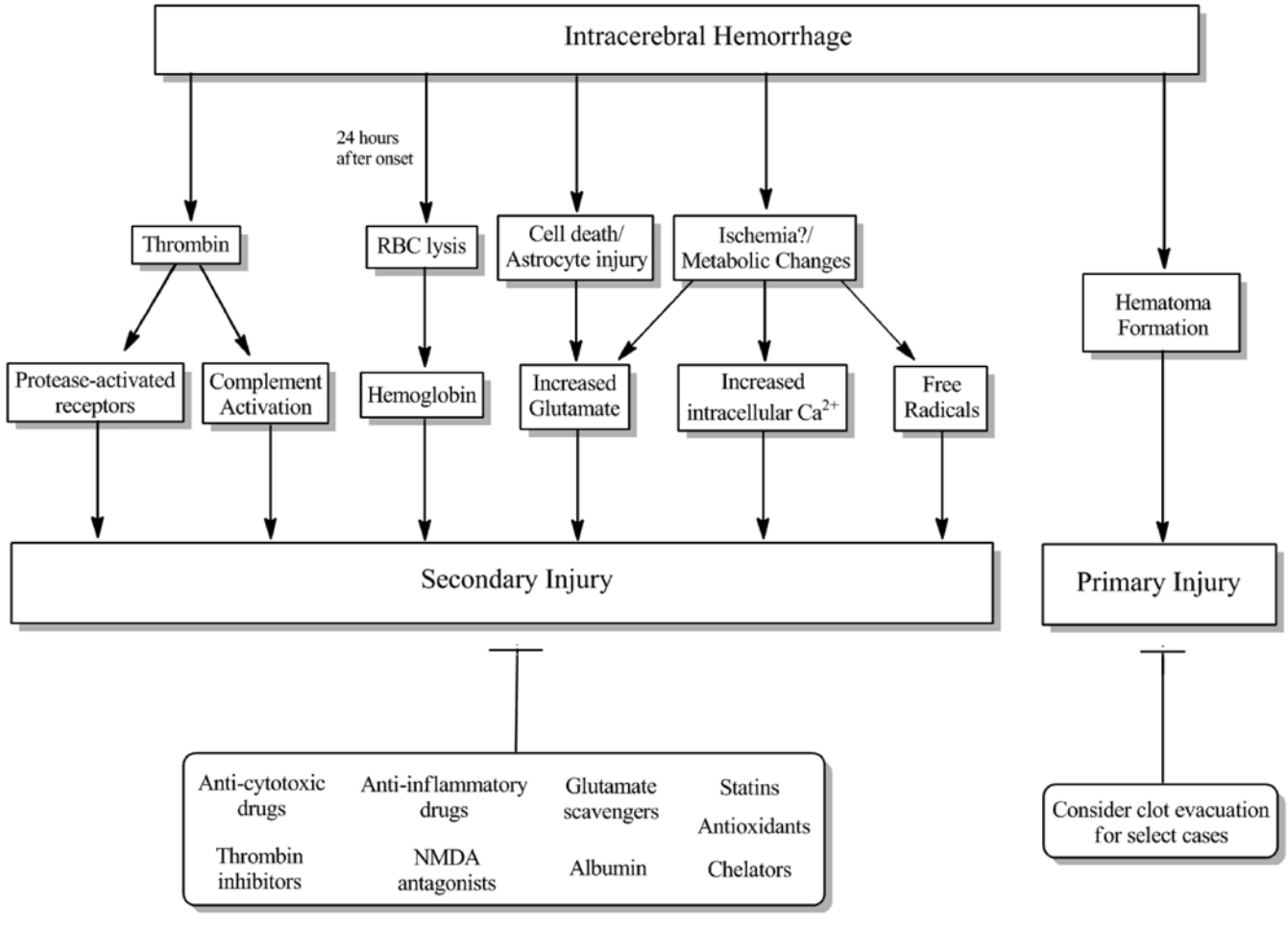

Fig. 1. Mechanisms and potential treatments for primary and secondary brain injury following ICH.

resulting in early neurological deterioration. Although randomized trials have not consistently shown a clear benefit of surgical management compared with medical therapy, there may be a role for ICH evacuation in an attempt to reduce intracranial pressure and reduce mass effect to try and improve outcomes in select cases. Lack of Class I data supporting evacuation may be due to the added morbidity of the surgical procedure in eloquent areas (such as the basal ganglia), inappropriate timing of clot evacuation, variability of ICH and techniques used, and insufficient sample sizes in clinical trials.

Because the optimal therapy for treating the primary injury associated with ICH has not yet been identified, prevention and treatment of secondary injury is imperative. As many patients continue to deteriorate clinically despite no signs of rehemorrhage or hematoma expansion, there is increasing interest in the mechanisms of secondary brain injury following ICH.[30] Vasogenic and cytotoxic edema due to the breakdown of the BBB and cellular injury have been implicated in this process.[146] Additional mechanisms for this secondary injury are believed to be due to the intraparenchymal accumulation of various blood components following ICH, activating cytotoxic, excitotoxic, oxidative, and inflammatory pathways.[61] As a result of increased awareness of this secondary injury, specific therapeutic targets have been identified in hopes of preventing further brain damage following ICH. In this review, we will discuss the various molecular mechanisms of secondary brain injury as a result of intraparenchymal blood, potential therapeutic targets, and the various treatment strategies currently under investigation.

Mechanisms of Secondary Brain Injury

Thrombin-Induced Injury

Thrombin, a serine protease found in the brain after ICH, has been shown to induce brain injury (Fig. 2). This enzyme is produced on the plasma membranes of platelets, neutrophils, monocytes, and lymphocytes as a result of cleavage of prothrombin following activation of the intrinsic and/or extrinsic coagulation cascades.[137,148] Entry of blood into the brain parenchyma activates this process, releasing large amounts of thrombin that is known to cause perihematomal edema formation after ICH due to endothelial cell damage.[75,146,148] Studies have also shown continuous release of thrombin from intracerebral hematomas for 2 weeks after clot formation due to fibrinolysis.[121]

Thrombin-induced injury may be a central mechanism for secondary injury in ICH, as many pathways are

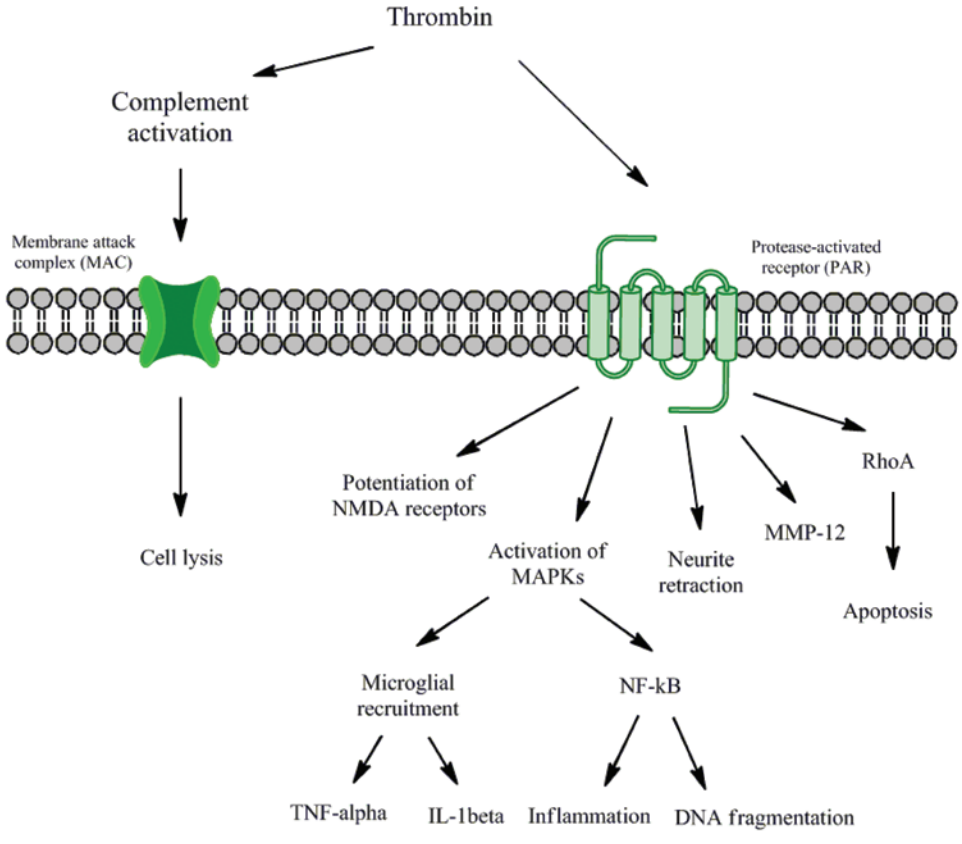

Fig. 2. Once released after ICH, thrombin is able to activate the complement pathway and PARs. This leads to a variety of cytotoxic, excitotoxic, and inflammatory effects that all lead to secondary brain injury. MAPKs = mitogen-activated protein kinases.

implicated. Secondary injury due to thrombin primarily occurs through PARs, a family of G protein–coupled proteins found on the surface of various cells including platelets, neurons, and endothelial cells.[24] Of these receptors, PAR-1, PAR-3, and PAR-4 have been shown to be activated by thrombin.[24–26] This activation occurs by cleavage of the exodomains of PARs, forming a new amino terminus that acts as a tethered ligand for receptor activation, resulting in the activation of various signaling pathways.[49,78,132] Protease-activated receptor-1 has been shown to be upregulated in ischemia models and is implicated in potentiation of NMDA receptors, neurite retraction, and cell death.[37,119,128,129] It has been shown that mice lacking PAR-1 have a reduction in infarct volume following focal ischemia, indicating its importance in brain injury.[64,149] Additionally, studies have shown continued PAR-1 activation following ICH, with PAR-1 levels peaking at 3 days after onset.[162] This effect may last for up to 14 days, implicating this process in cerebral edema initiation as it often peaks approximately 3 days after ICH.[162] Protease-activated receptors also activate various intracellular enzymes such as mitogen-activated protein kinases, which play a role in the recruitment of microglia and neuronal injury.[91]

Red Blood Cell Lysis

The presence of extravasated RBCs in the brain following ICH also stimulates a variety of cytotoxic, oxidative, and inflammatory processes (Fig. 3). Red blood cell lysis begins to occur approximately 24 hours following ICH and occurs for several days after onset.[87,133,139] This primarily occurs due to intracellular energy depletion, loss of structural integrity, and the formation of the membrane attack complex due to activation of the complement system.[55] The release of the intracellular contents of these cells induces brain edema, as studies have shown increases in edema volume following reductions in hematoma size due to clot lysis.[138] Studies in animals have shown delayed brain injury with intracerebral infusion of packed RBCs and dramatic edema formation within 24 hours following infusion of lysed RBCs.[53,133,140,145] Infusion of lysed RBCs also causes disruption of the BBB, DNA injury, and expression of heat shock proteins, indicating cell stress.[80,140,143,145] Once released from RBCs, hemoglobin is degraded into heme and iron, causing injury to surrounding cells.[95,133,139,157]

Cytotoxicity

Thrombin has been shown to induce various components of the complement system, an enzymatic cascade of blood and cell surface proteins. Thrombin primarily activates complement C3d and C9.[38,50,55] The presence of C3d following ICH indicates activation of the complement cascade, while deposition of C9 on the neuronal cell membranes indicates membrane attack complex formation.[13,55] This activity leads to the formation of a trans-

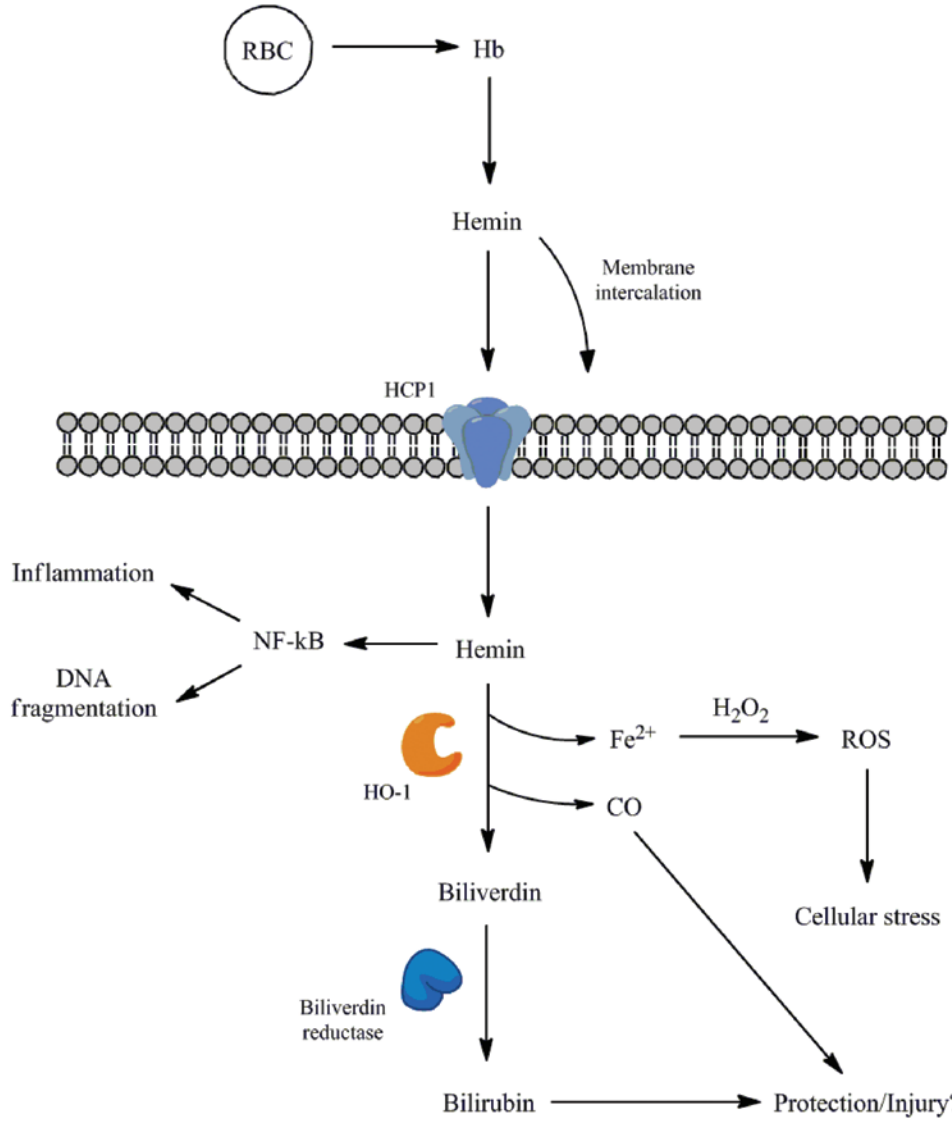

Fig. 3. Hemolysis leads to the release of hemin into the extracellular space. Hemin may then intercalate into cell membranes or enter cells via the heme carrier protein 1 (HCP1). Intracellularly hemin may activate cytotoxic and inflammatory pathways. It is then degraded by heme oxygenases, producing prooxidative iron, carbon monoxide (CO), and bilirubin. Thus far, the role of CO and bilirubin in ICH-mediated injury is unclear. Hb = hemoglobin; HO-1 = heme oxygenase-1; ROS = reactive oxygen species.

membrane pore and subsequent cell lysis, which may be one of the mechanisms of neuronal death and disruption of the BBB as a result of endothelial cell damage following ICH.[55] Additionally, lysis of erythrocytes may result in further damage through hemoglobin-mediated edema formation.[145]

Thrombin is also able to induce apoptosis in neurons and astrocytes by activation of various intracellular pathways.[27,90] This occurs via RhoA, a small guanosine triphosphate-binding protein part of the Ras superfamily.[27] RhoA inhibitors have been noted to attenuate thrombin-mediated cell death, implicating this mechanism as a major cause of neuronal loss following ICH. However, the exact mechanism by which RhoA induces apoptosis is currently unknown. This process may involve caspase activation, as inhibitors to these enzymes have been shown to prevent thrombin-induced cell death.[128]

Excitotoxicity

Potentiation of NMDA receptors by PAR-1 may cause neuronal death following ICH due to glutamate-induced excitotoxicity.[37,43] This notion is supported by studies showing that PAR-1 knockout mice had reduced thrombin-mediated NMDA receptor potentiation.[37,43] Also, removal of PAR-1 and the addition of NMDA receptor antagonists reduce neuronal injury associated with the addition of NMDA and transient middle cerebral artery occlusion.[43] The potentiation of NMDA by PAR-1 occurs through the activation of Src, a proto-oncogene tyrosine-kinase, which is known to augment NMDA activity by phosphorylation of these receptors.[113] This activity is confirmed by increased expression of Src kinases following ICH.[113]

Levels of extracellular amino acids such as glutamate have been shown to increase following ICH, resulting in

glutamate-mediated excitotoxicity.[97] This increase in levels of extracellular amino acids may be due to the release of these molecules as a result of active ischemia, as in vivo models have shown 80-fold increases in glutamate levels after middle cerebral artery occlusion.[47] Because neurons have high intracellular concentrations of glutamate, ICH-induced cell death may result in the release of these stores into the extracellular space.[97] Additionally, injury of astrocytes may impair glutamate removal, resulting in extracellular accumulation.

Oxidative Injury

Hemin, the oxidative form of heme, is a potent oxidant that injures cells and is well known to cause brain injury.[103] Its mechanism of action occurs through oxidative stress and the activation of caspases, resulting in the injury of astrocytes, neurons, and microglia.[102,135] However, microglia that clear hemin have protective mechanisms that prevent cell death.[17] Following ICH, hematogenous phagocytes, microglia, and surrounding astrocytes and neurons attempt to sequester hemin.[103,156] This primarily occurs via the heme carrier protein 1.[103] Once within the cell, hemin is degraded by heme oxygenases, producing biliverdin, carbon monoxide, and iron.[70,103] Iron released due to hemin degradation can reach high levels within the brain following ICH, resulting in the formation of hydroxyl radicals and subsequent cellular stress and DNA damage via interaction with hydrogen peroxide.[3,86,133,139] Iron levels after ICH may increase up to 3-fold and remain elevated for 1 month, causing continued brain injury following the initial insult.[139] However, hemin itself can also participate in redox reactions, producing free radicals that can damage intracellular structures and cause oxidative stress.[57] Additionally, because hemin is lipophilic, it may intercalate into lipid membranes, altering function and fluidity.[4] The roles of biliverdin, which is converted to bilirubin by biliverdin reductase, and carbon monoxide are unclear.[70] Small concentrations of bilirubin have been demonstrated to inhibit glutamate uptake and induce inflammation, oxidative stress, and apoptosis.[16,34,115] However, bilirubin and carbon monoxide have also been shown to have antioxidant and antiinflammatory effects.[103] Also unclear is the amount of bilirubin accumulation due to hemin degradation following ICH.

Inflammation

Thrombin has also been observed to increase proinflammatory cytokines such as TNF-α and IL-1β.[54,142] This increase may occur through the activation of microglia via PARs, resulting in recruitment and proliferation of these cells at the site of injury.[108,120] Tumor necrosis factor-α has been shown to increase in ICH models and is implicated in edema formation because TNF-α knockout mice have less brain edema and neurological deficits compared with wild-type mice.[54] Plasma TNF-α has been shown to correlate with the amount of brain edema in patients.[19] Other studies have also raised other mechanisms of TNF-α mediated injury such as enhancement of leukocyte infiltration, resulting in BBB disruption and cellular apoptosis.[6] Thrombin also stimulates microglia to secrete IL-1β, resulting in similar damaging effects as TNF-α, such as neurotoxicity, opening of the BBB, and induction of apoptosis.[142] The role of this mechanism in ICH-mediated injury is supported by studies showing attenuation of brain edema by the overexpression of IL-1β receptor antagonists.[142]

Matrix metalloproteinases are zinc-containing proteases that are involved in extracellular matrix remodeling, chemotaxis, and proteolytic cleavage of various molecules.[35] These proteins are produced by microglia, pericytes, and astrocytes, and when found in high levels in the brain, result in extracellular matrix degradation, BBB disruption, and neuronal death.[149] The mechanism for MMP-mediated brain injury is due to activation of microglia and subsequent release of inflammatory cytokines, release of neutrophil-derived toxins from infiltrated leukocytes, and generation of toxic molecules from interaction with nitric oxide. Several MMPs including MMP-2, -3, -9, and -12 have been observed to increase following ICH and can affect clinical outcome.[2,96] Additionally, studies have shown that MMP-3, -9, and -12 null mice have less brain injury as a result of ICH.[136,149,150] As thrombin is able to increase expression of various MMPs, the effects of thrombin on microglial activation and neuronal apoptosis may be due to these mediators.[67,150]

Nuclear factor-κB, a transcription factor involved in inflammatory processes, also contributes to brain injury following ICH.[5] In response to various cytokines and free radicals, NF-κB translocates to the nucleus, inducing the transcription of inflammatory enzymes, chemokines, and cytokines. Activation of NF-κB occurs within minutes of ICH and can remain active for 7 days following onset.[161] This activity results in DNA fragmentation, causing cell death.[46] Elucidation of the mechanisms of DNA fragmentation following NF-κB may allow for the development of therapeutic interventions to inhibit this process.

Nonhematogenous Perihematomal Mechanisms of Secondary Injury

Ischemia has been believed to play a role in secondary brain injury following ICH. Several animal studies have shown reductions in rCBF and the presence of tissue ischemia around hematomas, even though blood flow is reestablished quickly.[81,88,89,100,106,151] This return to normal perfusion is observed as early as 10 minutes following hemorrhage but is likely variable, depending on factors such as size of the hematoma and the presence of increased intracranial pressure. Although there may be quick recovery, ischemic damage to the cortex overlying the hematoma has been noted, consistent with histological findings of ischemia following 5 minutes of CBF cessation.[89,122] In ICH, ischemia of the surrounding tissue may be due to mechanical compression of the surrounding microvasculature by the hematoma, resulting in a hypoxic environment.[82,89] Hypoxia causes brain injury by a multitude of mechanisms. The inability to synthesize ATP results in Na^+/K^+ ATPase dysfunction, leading to neuronal membrane depolarization and ionic imbalance.[28] This may impair the function of many enzymes such as sodium-dependent glutamate transporters, resulting in increased extracellular glutamate levels and

excitotoxicity.[28] Low concentrations of ATP also prevent the maintenance of low calcium concentrations within cells by disrupting the Ca^{2+} ATPase, leading to high intracellular calcium levels that activate many DNAses and calcium-dependent proteases.[28] Additionally, energy depletion results in the production of reactive oxygen species and the release of cytochrome c from the outer mitochondrial membrane, both of which result in apoptosis and further brain injury.[28,126] Many of these mechanisms of injury overlap with the excitotoxic and oxidative pathways induced by thrombin and hemin, demonstrating the complexity of these damaging pathways and challenge of designing drugs to prevent this injury.

However, some animal and human studies have shown evidence against a significant ischemic penumbra following ICH.[18,32,36,44,45,48,100,109,134,153] These studies did not show any ischemic tissue surrounding the clot, although there was evidence of hypoperfusion. Positron emission tomography has shown reductions in the oxygen extraction fraction in tissue surrounding hematomas, contrasting with what occurs during acute ischemia.[153] Magnetic resonance imaging in patients has not shown significant changes in the apparent diffusion coefficient or mean transit time, both of which are markers of irreversible ischemia and hypoperfusion.[109] The lack of prolonged reductions in rCBF after ICH may be due to incomplete vascular compression by the hematoma.[100] This idea is supported by studies demonstrating rCBF within hematomas in regions of intact neural tissue.[100] Complete compression of intracerebral vessels by the expanding hematoma may result in the disruption of the pia-microvasculature interface, potentially causing alterations in BBB integrity.[100] Because this has not been noted to occur immediately following ICH, complete vessel compression is unlikely. In addition, white matter fibers are dense structures that provide mechanical resistance against the expanding hematoma.[84] Finally, robust collateral circulation from penetrating cortical arterioles and pial vessels from other cerebral arteries may prevent significant changes in rCBF and tissue ischemia.[84,100] However, due to the relatively small sample sizes in many studies, larger human studies are needed to provide more conclusive data.

Therefore, it is unclear whether perihematomal ischemia is a significant factor in secondary brain injury following ICH. Recently there has been a paradigm shift in thinking toward a metabolic instead of an ischemic penumbra. Increases in perihematomal glucose uptake and use (hyperglycolysis) have been observed in patients following ICH, consistent with what is noted following traumatic brain injury.[14,154] The mechanism of focally increased glucose uptake may be due to nonconvulsive seizure activity, which is found in many patients with acute ICH.[131] These repetitive depolarizations may lead to secondary injury by increasing extracellular glutamate, resulting in intracellular calcium accumulation and excitotoxicity.[130] The role of seizures as a cause of increased glucose utilization is supported by the suppression of hyperglycolysis by anticonvulsant glutamate receptor antagonists.[20] Further studies are needed to elucidate additional metabolic changes in this perihematomal tissue and investigate potential interventions to this ongoing injury.

Potential Therapeutic Targets and Current Treatments Under Investigation

Understanding the mechanisms of secondary injury following ICH has allowed for the development of treatments aimed at preventing this damage. Some agents have been validated in in vivo studies but have not yet been evaluated in clinical trials. However, several clinical trials have already been conducted to evaluate various neuroprotective drugs for the treatment of secondary injury from ICH.

Prevention of Cytotoxicity

One promising therapy for the prevention of secondary brain injury following ICH is the use of direct thrombin inhibitors. As thrombin plays a major role in cellular injury via a variety of pathways, inhibiting its activity would be beneficial. Inhibitors such as hirudin (a thrombin inhibitor found in leeches) and argatroban (a synthetic, direct thrombin inhibitor) have been shown to reduce brain edema following ICH in in vivo models, possibly by inhibiting PAR-1 expression.[68,69,74,163] Although there is concern of prolonged bleeding with the use of these anticoagulants, the use of direct thrombin inhibitors has been shown to not cause enlargement of hematoma volume, unlike with other anticoagulants such as warfarin.[72] Clinical trials are needed to evaluate the efficacy of these drugs for the prevention of brain injury following ICH.

However, complete inhibition of thrombin may actually be deleterious as low concentrations have been shown to be neuroprotective.[148] This protective effect has been observed in neurons and astrocytes in in vitro models. Pretreatment with thrombin has been shown to prevent brain edema and damage induced by large doses of thrombin, ICH, and cerebral ischemia,[79,144,147] but these protective effects are eliminated by thrombin inhibitors.[147] Although the exact mechanism by which thrombin exerts its neuroprotective effects is unknown, it is believed to be due to the activation of PARs, production of heat shock proteins, and upregulation of endogenous thrombin inhibitors.[56,62,144,147] Additionally, thrombin preconditioning has been shown to increase levels of hypoxia inducible factor-1α, transferrin, and transferrin receptor, increasing brain tolerance to erythrocyte- and iron-mediated injury.[52] Further research elucidating the mechanisms of this protective effect are needed for the development of therapeutic strategies aimed to enhance this effect. The doses of thrombin inhibitors that simply reduce thrombin concentration without complete inhibition need to be clarified to augment neuroprotection. Alternatively, specific thrombin inhibitors that do not affect neuroprotective pathways should be investigated.

Due to the activation of numerous apoptotic pathways following ICH, molecules that inhibit this process have been investigated for use in ICH. One such drug is tauroursodeoxycholic acid, the taurine conjugate of the endogenous bile acid ursodeoxycholic acid.[105] Tauroursodeoxycholic acid is able to inhibit production of reactive oxygen species, stabilize the mitochondrial membrane, activate antiapoptotic proteins such as Bcl-2, and inhibit the activity of proapoptotic proteins such as Bad.[104,105] A

Phase I trial investigating the safety of this drug has been designed.

Albumin has also been investigated as a neuroprotective agent. Studies have demonstrated numerous mechanisms of this neuroprotection including reduction of brain edema, inhibition of oxidative damage, and maintenance of normal endothelial and astrocytic function.[7,8,10,12] In vivo studies have demonstrated improved functional outcome and BBB integrity following administration of albumin after ICH.[9,11] The Albumin for Intracerebral Hemorrhage Intervention (ACHIEVE) trial is currently evaluating the effects of albumin in 40 patients with ICH.

Inhibition of Excitotoxicity

Gavestinel, a drug that functions as an antagonist by binding to the glycine site on the NMDA receptor, has been investigated in the Glycine Antagonist in Neuroprotection (GAIN) International and Americas trials.[83] In these trials, patients were randomized to receive the drug or placebo within 6 hours of symptom onset. This time point is considered to be crucial as the majority of hematoma enlargement occurs within this period due to continuous bleeding or rebleeding.[65] Outcomes of the trial were death or functional ability as determined by the Barthel Index.[42] Of the 3450 patients randomized in these trials, 571 had ICH. Analysis of these patients revealed no significant differences in mortality rates between the 2 groups ($p = 0.38$). There was also no difference in the distribution of Barthel Index scores at 3 months between the 2 groups, although there was a trend favoring gavestinel ($p = 0.091$). It may be beneficial to test this agent later during the peak of secondary brain injury from ICH.

As glutamate levels have been shown to increase following ischemic injury and ICH, glutamate scavenging may provide neuroprotection. Oxaloacetate has been shown to be neuroprotective in traumatic brain injury models by reducing glutamate levels.[164] The mechanism for this effect is due to the transformation of glutamate to 2-ketoglutarate by glutamate-oxaloacetate transaminase, an enzyme found in the blood.[39] Human studies are needed to evaluate the efficacy of this mechanism in ICH.

Protection From Oxidative Injury

Three clinical trials have been conducted to evaluate citicoline (cytidine-5-diphosphocholine), an intermediate in the phospholipid synthetic pathway.[1] Studies have shown its neuroprotective effects occur by maintaining the integrity of various cellular membranes, attenuating lipid peroxidation, restoring Na^+/K^+-ATPase activity, and enhancing the glutathione system.[1] Additionally, citicoline may decrease glutamate release from neurons and improve astrocyte uptake, decreasing extracellular glutamate levels.[58] In a randomized study of 32 patients, those receiving citicoline experienced improved muscle strength following ICH.[60] Another study involving treatment of 19 patients with citicoline found that treated patients were 5-fold more likely to be functionally independent following ICH compared with those who received a placebo.[110] Finally, a trial of 182 patients revealed that treatment with citicoline resulted in improvement in the Barthel Index, although no effect on the modified Rankin Scale or NIH Stroke Scale was noted.[66]

Due to the neurotoxic effects of iron, there is interest in the use of iron chelators for prevention of this iron-mediated injury. In vivo studies have demonstrated that deferoxamine rapidly accumulates within brain parenchyma and reduces iron concentration, brain edema, neuronal death, and neurological deficits following ICH.[41,51] A multicenter Phase I trial showed that infusions of deferoxamine are tolerable and safe up to a daily dose of 6000 mg.[112] Preliminary data in 4 patients with hemorrhagic stroke and 3 with ischemic stroke showed decreases in serum markers of oxidative stress.[111] Currently, a Phase II trial is underway to evaluate the efficacy of deferoxamine in ICH.

Peroxisome proliferator-activated receptor γ is a transcription factor that plays a role in cellular defense mechanisms and hematoma clearance.[159] This activity occurs through the upregulation of *CD36*, the phagocytosis-facilitating gene, resulting in faster hematoma clearance.[159] In addition, it enhances expression of antioxidant molecules such as catalase and superoxide dismutase, preventing the oxidative damage of neurons and microglia.[114,160] In vivo studies have demonstrated improvements in hematoma resolution and functional outcome following treatment with peroxisome proliferator-activated receptor γ agonists in ICH models.[159] Currently the Safety of Pioglitazone for Hematoma Resolution in Intracerebral Hemorrhage (SHRINC) trial is evaluating the use of such agonists in 80 patients with ICH.

Haptoglobin is a protein found in blood plasma that has the ability to bind hemoglobin. It functions to bind extracellular hemoglobin, preventing hemoglobin-mediated oxidative damage.[157] In the brain, haptoglobin is synthesized by oligodendrocytes, thereby protecting against extravascular hemoglobin toxicity. Animal models of ICH have demonstrated increased haptoglobin production following injury. Animals that are hypohaptoglobinemic are more susceptible to injury and have more brain damage following ICH, whereas those that overexpress haptoglobin are more protected. Haptoglobin is therefore a potential therapeutic target for the prevention of brain injury following ICH. Thus far, sulforaphane, a NF-E2–related factor–2 activator, has been shown to increase haptoglobin in the brain and reduce injury following ICH.[158] Additional in vivo and human studies are needed to identify other agents that increase haptoglobin levels and establish their efficacy in preventing ICH-induced brain injury.

Another agent known to bind heme is hemopexin, a glycoprotein found in plasma.[125] However, hemopexin is also expressed by neurons and is present throughout the brain.[76] Mice that do not express hemopexin have greater infarct volumes and neurological deficits following middle cerebral artery occlusion.[76] Hemopexin knockout mice also had increased protein oxidation and tissue heme, and decreased cell viability and locomotor activity.[22] This protein may also be another modifiable target to decrease brain injury following ICH.

Reduction of Inflammation

Rosuvastatin, a competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase, has been inves-

tigated for its neuroprotective effects. Statins may exhibit their neuroprotective effects via a variety of mechanisms such as reduction of inflammation through inhibition of NF-κB, TNF-α, and chemokine expression,[63,92] upregulation of nitric oxide synthase,[31,63,73] and protection from glutamate-induced excitotoxicity.[15] A prospective/retrospective nonrandomized study treated 18 patients with rosuvastatin and found improved outcomes compared with control subjects (mortality rate 5.6% vs 15.8%, respectively; NIH Stroke Scale score ≥ 15, OR 0.04).[124] Larger studies are needed to provide more conclusive evidence on the efficacy of statins for the prevention of secondary brain injury following ICH. Due to the neuroprotective effects of statins, there has also been considerable interest in using these drugs following aneurysmal SAH. A meta-analysis of double-blind randomized controlled trials showed significant reductions in delayed ischemic deficits (OR 0.41, 95% CI 0.20–0.82; $p < 0.001$) and mortality (OR 0.29, 95% CI 0.09–0.93; $p = 0.04$) following statin therapy for SAH.[127]

Celecoxib is a nonsteroidal antiinflammatory drug that has been shown to reduce perihematomal inflammation and cell death in ICH.[23,116] Because celecoxib selectively inhibits cyclooxygenase-2, it is a potential treatment for ICH because cyclooxygenase-2 is activated in ICH models, resulting in increased levels of prostaglandin E2.[23] As prostaglandin E2 can induce free radical formation and glutamate-mediated excitotoxicity due to glutamate release from astrocytes, the neuroprotective effects of celecoxib are believed to occur through the reduction of prostaglandin E2 synthesis via cyclooxygenase-2 inhibition.[23,59] One retrospective study analyzed the volumes of hematoma and edema in 17 patients treated with celecoxib.[93] Treatment significantly reduced the volume of brain edema and the ratio of initial hematoma and edema volumes to follow-up volumes compared with the control group. The results of a Phase II trial investigating the efficacy of celecoxib are currently pending. Although trials have shown increased risk of serious cardiovascular events with use of celecoxib, short-term use in ICH may not increase these risks significantly.[117]

Minocycline, a broad-spectrum tetracycline antibiotic, has also been investigated as a neuroprotective agent due to its antiinflammatory properties. In vivo studies have shown reduced perihematomal brain edema, neuronal loss, BBB disruption, and improved functional outcome following ICH with minocycline treatment.[141,155] Minocycline also reduces brain iron accumulation and resulting toxicity by chelating iron.[21] In an open-label, blinded study, 74 patients were treated with minocycline 6–24 hours after acute ischemic stroke.[71] Those treated had significantly lower NIH Stroke Scale and modified Rankin Scale scores, with higher Barthel Index scores, indicating significantly better outcome. Currently, 3 trials are in progress for evaluation of the neuroprotective effects of minocycline in stroke.

Other Investigated Agents

Other studies have evaluated the use of mannitol, glycerol, and NXY-059 (disufenton sodium) for neuroprotection in patients with ICH but did not observe any improvement in mortality or functional outcome.[77,83,152] Mannitol exerts its neuroprotective effects by functioning as an osmotic diuretic, thus reducing brain edema.[85] It also functions as an antioxidant, protecting against free radical–mediated damage. Neuroprotection due to glycerol occurs by hemodilution, which results in increased cerebral perfusion and reduction of cerebral edema, thereby reducing intracranial pressure.[152] The free radical trapping agent NXY-059 prevents brain injury by quenching free radicals formed by hemoglobin degradation and ischemic tissue.[94]

Conclusions

The mechanisms of secondary brain injury following intracerebral hemorrhage are numerous and involve the initiation of cytotoxic, excitotoxic, oxidative, and inflammatory pathways. Optimal management of patients with ICH remains undefined. Surgical therapies have shown disappointing results in primary brain injury treatment. Medical therapies aimed at prevention of continued insult may improve mortality rates and functional outcomes. Although there is not yet an effective medical treatment, advances have been made in elucidating the mechanisms of brain injury following ICH. These advances have led to the development of neuroprotective therapies, many of which show promise in early clinical testing. However, further research is required to illuminate and better define the multitude of mechanisms involved in ICH pathogenesis in the hope of revealing targets for novel therapeutics. Additionally, large randomized trials are needed to establish the efficacy and safety of currently identified neuroprotective agents. Nonetheless, our focus must also be on finding efficient interventions to prevent ICH, decreasing the severe morbidity and mortality associated with this disease.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Adamson, Babu. Acquisition of data: Babu, Bagley, Di. Analysis and interpretation of data: Adamson, Babu. Drafting the article: Babu. Critically revising the article: Adamson, Friedman.

References

1. Adibhatla RM, Hatcher JF, Dempsey RJ: Citicoline: neuroprotective mechanisms in cerebral ischemia. **J Neurochem 80:** 12–23, 2002
2. Alvarez-Sabín J, Delgado P, Abilleira S, Molina CA, Arenillas J, Ribó M, et al: Temporal profile of matrix metalloproteinases and their inhibitors after spontaneous intracerebral hemorrhage: relationship to clinical and radiological outcome. **Stroke 35:**1316–1322, 2004
3. Aronowski J, Zhao X: Molecular pathophysiology of cerebral hemorrhage: secondary brain injury. **Stroke 42:**1781–1786, 2011
4. Balla G, Jacob HS, Eaton JW, Belcher JD, Vercellotti GM: Hemin: a possible physiological mediator of low density lipoprotein oxidation and endothelial injury. **Arterioscler Thromb 11:**1700–1711, 1991
5. Barnes PJ, Karin M: Nuclear factor-kappaB: a pivotal transcription factor in chronic inflammatory diseases. **N Engl J Med 336:**1066–1071, 1997

6. Barone FC, Feuerstein GZ: Inflammatory mediators and stroke: new opportunities for novel therapeutics. **J Cereb Blood Flow Metab 19:**819–834, 1999
7. Belayev L, Busto R, Zhao W, Clemens JA, Ginsberg MD: Effect of delayed albumin hemodilution on infarction volume and brain edema after transient middle cerebral artery occlusion in rats. **J Neurosurg 87:**595–601, 1997
8. Belayev L, Liu Y, Zhao W, Busto R, Ginsberg MD: Human albumin therapy of acute ischemic stroke: marked neuroprotective efficacy at moderate doses and with a broad therapeutic window. **Stroke 32:**553–560, 2001
9. Belayev L, Obenaus A, Zhao W, Saul I, Busto R, Wu C, et al: Experimental intracerebral hematoma in the rat: characterization by sequential magnetic resonance imaging, behavior, and histopathology. Effect of albumin therapy. **Brain Res 1157:**146–155, 2007
10. Belayev L, Pinard E, Nallet H, Seylaz J, Liu Y, Riyamongkol P, et al: Albumin therapy of transient focal cerebral ischemia: in vivo analysis of dynamic microvascular responses. **Stroke 33:**1077–1084, 2002
11. Belayev L, Saul I, Busto R, Danielyan K, Vigdorchik A, Khoutorova L, et al: Albumin treatment reduces neurological deficit and protects blood-brain barrier integrity after acute intracortical hematoma in the rat. **Stroke 36:**326–331, 2005
12. Belayev L, Zhao W, Pattany PM, Weaver RG, Huh PW, Lin B, et al: Diffusion-weighted magnetic resonance imaging confirms marked neuroprotective efficacy of albumin therapy in focal cerebral ischemia. **Stroke 29:**2587–2599, 1998
13. Bellander BM, von Holst H, Fredman P, Svensson M: Activation of the complement cascade and increase of clusterin in the brain following a cortical contusion in the adult rat. **J Neurosurg 85:**468–475, 1996
14. Bergsneider M, Hovda DA, Shalmon E, Kelly DF, Vespa PM, Martin NA, et al: Cerebral hyperglycolysis following severe traumatic brain injury in humans: a positron emission tomography study. **J Neurosurg 86:**241–251, 1997
15. Bösel J, Gandor F, Harms C, Synowitz M, Harms U, Djoufack PC, et al: Neuroprotective effects of atorvastatin against glutamate-induced excitotoxicity in primary cortical neurones. **J Neurochem 92:**1386–1398, 2005
16. Brito MA, Rosa AI, Falcão AS, Fernandes A, Silva RF, Butterfield DA, et al: Unconjugated bilirubin differentially affects the redox status of neuronal and astroglial cells. **Neurobiol Dis 29:**30–40, 2008
17. Cai Y, Cho GS, Ju C, Wang SL, Ryu JH, Shin CY, et al: Activated microglia are less vulnerable to hemin toxicity due to nitric oxide-dependent inhibition of JNK and p38 MAPK activation. **J Immunol 187:**1314–1321, 2011
18. Carhuapoma JR, Wang PY, Beauchamp NJ, Keyl PM, Hanley DF, Barker PB: Diffusion-weighted MRI and proton MR spectroscopic imaging in the study of secondary neuronal injury after intracerebral hemorrhage. **Stroke 31:**726–732, 2000
19. Castillo J, Dávalos A, Alvarez-Sabín J, Pumar JM, Leira R, Silva Y, et al: Molecular signatures of brain injury after intracerebral hemorrhage. **Neurology 58:**624–629, 2002
20. Chapman AG: Glutamate receptors in epilepsy. **Prog Brain Res 116:**371–383, 1998
21. Chen L, Zhang X, Chen-Roetling J, Regan RF: Increased striatal injury and behavioral deficits after intracerebral hemorrhage in hemopexin knockout mice. Laboratory investigation. **J Neurosurg 114:**1159–1167, 2011
22. Chen-Roetling J, Chen L, Regan RF: Minocycline attenuates iron neurotoxicity in cortical cell cultures. **Biochem Biophys Res Commun 386:**322–326, 2009
23. Chu K, Jeong SW, Jung KH, Han SY, Lee ST, Kim M, et al: Celecoxib induces functional recovery after intracerebral hemorrhage with reduction of brain edema and perihematomal cell death. **J Cereb Blood Flow Metab 24:**926–933, 2004
24. Coughlin SR: How the protease thrombin talks to cells. **Proc Natl Acad Sci U S A 96:**11023–11027, 1999
25. Coughlin SR: Thrombin signalling and protease-activated receptors. **Nature 407:**258–264, 2000
26. Déry O, Corvera CU, Steinhoff M, Bunnett NW: Proteinase-activated receptors: novel mechanisms of signaling by serine proteases. **Am J Physiol 274:**C1429–C1452, 1998
27. Donovan FM, Pike CJ, Cotman CW, Cunningham DD: Thrombin induces apoptosis in cultured neurons and astrocytes via a pathway requiring tyrosine kinase and RhoA activities. **J Neurosci 17:**5316–5326, 1997
28. Doyle KP, Simon RP, Stenzel-Poore MP: Mechanisms of ischemic brain damage. **Neuropharmacology 55:**310–318, 2008
29. Eastern Stroke and Coronary Heart Disease Collaborative Research Group: Blood pressure, cholesterol, and stroke in eastern Asia. **Lancet 352:**1801–1807, 1998
30. Elijovich L, Patel PV, Hemphill JC III: Intracerebral hemorrhage. **Semin Neurol 28:**657–667, 2008
31. Endres M, Laufs U, Huang Z, Nakamura T, Huang P, Moskowitz MA, et al: Stroke protection by 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase inhibitors mediated by endothelial nitric oxide synthase. **Proc Natl Acad Sci U S A 95:** 8880–8885, 1998
32. Fainardi E, Borrelli M, Saletti A, Schivalocchi R, Azzini C, Cavallo M, et al: CT perfusion mapping of hemodynamic disturbances associated to acute spontaneous intracerebral hemorrhage. **Neuroradiology 50:**729–740, 2008
33. Fayad PB, Awad IA: Surgery for intracerebral hemorrhage. **Neurology 51 (3 Suppl 3):**S69–S73, 1998
34. Fernandes A, Falcão AS, Silva RF, Brito MA, Brites D: MAPKs are key players in mediating cytokine release and cell death induced by unconjugated bilirubin in cultured rat cortical astrocytes. **Eur J Neurosci 25:**1058–1068, 2007
35. Galis ZS, Khatri JJ: Matrix metalloproteinases in vascular remodeling and atherogenesis: the good, the bad, and the ugly. **Circ Res 90:**251–262, 2002
36. Gass A: Is there a penumbra surrounding intracerebral hemorrhage? **Cerebrovasc Dis 23:**4–5, 2007
37. Gingrich MB, Junge CE, Lyuboslavsky P, Traynelis SF: Potentiation of NMDA receptor function by the serine protease thrombin. **J Neurosci 20:**4582–4595, 2000
38. Gong Y, Xi GH, Keep RF, Hoff JT, Hua Y: Complement inhibition attenuates brain edema and neurological deficits induced by thrombin. **Acta Neurochir Suppl 95:**389–392, 2005
39. Gottlieb M, Wang Y, Teichberg VI: Blood-mediated scavenging of cerebrospinal fluid glutamate. **J Neurochem 87:**119–126, 2003
40. Grysiewicz RA, Thomas K, Pandey DK: Epidemiology of ischemic and hemorrhagic stroke: incidence, prevalence, mortality, and risk factors. **Neurol Clin 26:**871–895, vii, 2008
41. Gu Y, Hua Y, Keep RF, Morgenstern LB, Xi G: Deferoxamine reduces intracerebral hematoma-induced iron accumulation and neuronal death in piglets. **Stroke 40:**2241–2243, 2009
42. Haley EC Jr, Thompson JL, Levin B, Davis S, Lees KR, Pittman JG, et al: Gavestinel does not improve outcome after acute intracerebral hemorrhage: an analysis from the GAIN International and GAIN Americas studies. **Stroke 36:**1006–1010, 2005
43. Hamill CE, Mannaioni G, Lyuboslavsky P, Sastre AA, Traynelis SF: Protease-activated receptor 1-dependent neuronal damage involves NMDA receptor function. **Exp Neurol 217:** 136–146, 2009
44. Herweh C, Jüttler E, Schellinger PD, Klotz E, Jenetzky E, Orakcioglu B, et al: Evidence against a perihemorrhagic penumbra provided by perfusion computed tomography. **Stroke 38:**2941–2947, 2007
45. Herweh C, Jüttler E, Schellinger PD, Klotz E, Schramm P: Perfusion CT in hyperacute cerebral hemorrhage within 3 hours after symptom onset: is there an early perihemorrhagic penumbra? **J Neuroimaging 20:**350–353, 2010
46. Hickenbottom SL, Grotta JC, Strong R, Denner LA, Aronowski J: Nuclear factor-kappaB and cell death after experimental intracerebral hemorrhage in rats. **Stroke 30:**2472–2478, 1999

47. Hillered L, Hallström A, Segersvärd S, Persson L, Ungerstedt U: Dynamics of extracellular metabolites in the striatum after middle cerebral artery occlusion in the rat monitored by intracerebral microdialysis. **J Cereb Blood Flow Metab 9:** 607–616, 1989
48. Hirano T, Read SJ, Abbott DF, Sachinidis JI, Tochon-Danguy HJ, Egan GF, et al: No evidence of hypoxic tissue on 18F-fluoromisonidazole PET after intracerebral hemorrhage. **Neurology 53:**2179–2182, 1999
49. Hollenberg MD, Compton SJ: International Union of Pharmacology. XXVIII. Proteinase-activated receptors. **Pharmacol Rev 54:**203–217, 2002
50. Hua Y, Keep RF, Hoff JT, Xi G: Brain injury after intracerebral hemorrhage: the role of thrombin and iron. **Stroke 38 (2 Suppl):**759–762, 2007
51. Hua Y, Keep RF, Hoff JT, Xi G: Deferoxamine therapy for intracerebral hemorrhage. **Acta Neurochir Suppl 105:**3–6, 2008
52. Hua Y, Keep RF, Hoff JT, Xi G: Thrombin preconditioning attenuates brain edema induced by erythrocytes and iron. **J Cereb Blood Flow Metab 23:**1448–1454, 2003
53. Hua Y, Schallert T, Keep RF, Wu J, Hoff JT, Xi G: Behavioral tests after intracerebral hemorrhage in the rat. **Stroke 33:**2478–2484, 2002
54. Hua Y, Wu J, Keep RF, Nakamura T, Hoff JT, Xi G: Tumor necrosis factor-alpha increases in the brain after intracerebral hemorrhage and thrombin stimulation. **Neurosurgery 58:** 542–550, 2006
55. Hua Y, Xi G, Keep RF, Hoff JT: Complement activation in the brain after experimental intracerebral hemorrhage. **J Neurosurg 92:**1016–1022, 2000
56. Hua Y, Xi G, Keep RF, Wu J, Jiang Y, Hoff JT: Plasminogen activator inhibitor-1 induction after experimental intracerebral hemorrhage. **J Cereb Blood Flow Metab 22:**55–61, 2002
57. Huffman LJ, Miles PR, Shi X, Bowman L: Hemoglobin potentiates the production of reactive oxygen species by alveolar macrophages. **Exp Lung Res 26:**203–217, 2000
58. Hurtado O, Moro MA, Cárdenas A, Sánchez V, Fernández-Tomé P, Leza JC, et al: Neuroprotection afforded by prior citicoline administration in experimental brain ischemia: effects on glutamate transport. **Neurobiol Dis 18:**336–345, 2005
59. Iłzecka J: Prostaglandin E2 is increased in amyotrophic lateral sclerosis patients. **Acta Neurol Scand 108:**125–129, 2003
60. Iranmanesh F, Vakilian A: Efficiency of citicoline in increasing muscular strength of patients with nontraumatic cerebral hemorrhage: a double-blind randomized clinical trial. **J Stroke Cerebrovasc Dis 17:**153–155, 2008
61. James ML, Warner DS, Laskowitz DT: Preclinical models of intracerebral hemorrhage: a translational perspective. **Neurocrit Care 9:**139–152, 2008
62. Jiang Y, Wu J, Hua Y, Keep RF, Xiang J, Hoff JT, et al: Thrombin-receptor activation and thrombin-induced brain tolerance. **J Cereb Blood Flow Metab 22:**404–410, 2002
63. Jung KH, Chu K, Jeong SW, Han SY, Lee ST, Kim JY, et al: HMG-CoA reductase inhibitor, atorvastatin, promotes sensorimotor recovery, suppressing acute inflammatory reaction after experimental intracerebral hemorrhage. **Stroke 35:**1744–1749, 2004
64. Junge CE, Sugawara T, Mannaioni G, Alagarsamy S, Conn PJ, Brat DJ, et al: The contribution of protease-activated receptor 1 to neuronal damage caused by transient focal cerebral ischemia. **Proc Natl Acad Sci U S A 100:**13019–13024, 2003
65. Kazui S, Naritomi H, Yamamoto H, Sawada T, Yamaguchi T: Enlargement of spontaneous intracerebral hemorrhage. Incidence and time course. **Stroke 27:**1783–1787, 1996
66. Kellner CP, Connolly ES Jr: Neuroprotective strategies for intracerebral hemorrhage: trials and translation. **Stroke 41 (10 Suppl):**S99–S102, 2010
67. Kim YS, Kim SS, Cho JJ, Choi DH, Hwang O, Shin DH, et al: Matrix metalloproteinase-3: a novel signaling proteinase from apoptotic neuronal cells that activates microglia. **J Neurosci 25:**3701–3711, 2005
68. Kitaoka T, Hua Y, Xi G, Hoff JT, Keep RF: Delayed argatroban treatment reduces edema in a rat model of intracerebral hemorrhage. **Stroke 33:**3012–3018, 2002
69. Kitaoka T, Hua Y, Xi G, Nagao S, Hoff JT, Keep RF: Effect of delayed argatroban treatment on intracerebral hemorrhage-induced edema in the rat. **Acta Neurochir Suppl 86:**457–461, 2003
70. Kutty RK, Maines MD: Purification and characterization of biliverdin reductase from rat liver. **J Biol Chem 256:**3956–3962, 1981
71. Lampl Y, Boaz M, Gilad R, Lorberboym M, Dabby R, Rapoport A, et al: Minocycline treatment in acute stroke: an open-label, evaluator-blinded study. **Neurology 69:**1404–1410, 2007
72. Lauer A, Cianchetti FA, Van Cott EM, Schlunk F, Schulz E, Pfeilschifter W, et al: Anticoagulation with the oral direct thrombin inhibitor dabigatran does not enlarge hematoma volume in experimental intracerebral hemorrhage. **Circulation 124:**1654–1662, 2011
73. Laufs U, Gertz K, Huang P, Nickenig G, Böhm M, Dirnagl U, et al: Atorvastatin upregulates type III nitric oxide synthase in thrombocytes, decreases platelet activation, and protects from cerebral ischemia in normocholesterolemic mice. **Stroke 31:** 2442–2449, 2000
74. Lee KR, Colon GP, Betz AL, Keep RF, Kim S, Hoff JT: Edema from intracerebral hemorrhage: the role of thrombin. **J Neurosurg 84:**91–96, 1996
75. Lee KR, Kawai N, Kim S, Sagher O, Hoff JT: Mechanisms of edema formation after intracerebral hemorrhage: effects of thrombin on cerebral blood flow, blood-brain barrier permeability, and cell survival in a rat model. **J Neurosurg 86:**272–278, 1997
76. Li RC, Saleem S, Zhen G, Cao W, Zhuang H, Lee J, et al: Heme-hemopexin complex attenuates neuronal cell death and stroke damage. **J Cereb Blood Flow Metab 29:**953–964, 2009
77. Lyden PD, Shuaib A, Lees KR, Davalos A, Davis SM, Diener HC, et al: Safety and tolerability of NXY-059 for acute intracerebral hemorrhage: the CHANT Trial. **Stroke 38:**2262–2269, 2007
78. Macfarlane SR, Seatter MJ, Kanke T, Hunter GD, Plevin R: Proteinase-activated receptors. **Pharmacol Rev 53:**245–282, 2001
79. Masada T, Xi G, Hua Y, Keep RF: The effects of thrombin preconditioning on focal cerebral ischemia in rats. **Brain Res 867:**173–179, 2000
80. Matz PG, Weinstein PR, Sharp FR: Heme oxygenase-1 and heat shock protein 70 induction in glia and neurons throughout rat brain after experimental intracerebral hemorrhage. **Neurosurgery 40:**152–162, 1997
81. Mendelow AD: Mechanisms of ischemic brain damage with intracerebral hemorrhage. **Stroke 24 (12 Suppl):**I115–I119, 1993
82. Mendelow AD, Bullock R, Teasdale GM, Graham DI, McCulloch J: Intracranial haemorrhage induced at arterial pressure in the rat. Part 2: Short term changes in local cerebral blood flow measured by autoradiography. **Neurol Res 6:**189–193, 1984
83. Misra UK, Kalita J, Ranjan P, Mandal SK: Mannitol in intracerebral hemorrhage: a randomized controlled study. **J Neurol Sci 234:**41–45, 2005
84. Mutlu N, Berry RG, Alpers BJ: Massive cerebral hemorrhage. Clinical and pathological correlations. **Arch Neurol 8:**644–661, 1963
85. Nakajima R, Nakamura T, Miyakawa H, Kudo Y: Effects of mannitol on ischemia-induced degeneration in rat hippocampus. **J Pharmacol Sci 95:**341–348, 2004
86. Nakamura T, Keep RF, Hua Y, Hoff JT, Xi G: Oxidative DNA injury after experimental intracerebral hemorrhage. **Brain Res 1039:**30–36, 2005

87. Nakamura T, Keep RF, Hua Y, Schallert T, Hoff JT, Xi G: Deferoxamine-induced attenuation of brain edema and neurological deficits in a rat model of intracerebral hemorrhage. **J Neurosurg 100:**672–678, 2004
88. Nath FP, Jenkins A, Mendelow AD, Graham DI, Teasdale GM: Early hemodynamic changes in experimental intracerebral hemorrhage. **J Neurosurg 65:**697–703, 1986
89. Nath FP, Kelly PT, Jenkins A, Mendelow AD, Graham DI, Teasdale GM: Effects of experimental intracerebral hemorrhage on blood flow, capillary permeability, and histochemistry. **J Neurosurg 66:**555–562, 1987
90. Noorbakhsh F, Vergnolle N, Hollenberg MD, Power C: Proteinase-activated receptors in the nervous system. **Nat Rev Neurosci 4:**981–990, 2003
91. Ohnishi M, Katsuki H, Fujimoto S, Takagi M, Kume T, Akaike A: Involvement of thrombin and mitogen-activated protein kinase pathways in hemorrhagic brain injury. **Exp Neurol 206:** 43–52, 2007
92. Ortego M, Bustos C, Hernández-Presa MA, Tuñón J, Díaz C, Hernández G, et al: Atorvastatin reduces NF-kappaB activation and chemokine expression in vascular smooth muscle cells and mononuclear cells. **Atherosclerosis 147:**253–261, 1999
93. Park HK, Lee SH, Chu K, Roh JK: Effects of celecoxib on volumes of hematoma and edema in patients with primary intracerebral hemorrhage. **J Neurol Sci 279:**43–46, 2009
94. Peeling J, Del Bigio MR, Corbett D, Green AR, Jackson DM: Efficacy of disodium 4-[(tert-butylimino)methyl]benzene-1,3-disulfonate N-oxide (NXY-059), a free radical trapping agent, in a rat model of hemorrhagic stroke. **Neuropharmacology 40:** 433–439, 2001
95. Peeling J, Yan HJ, Chen SG, Campbell M, Del Bigio MR: Protective effects of free radical inhibitors in intracerebral hemorrhage in rat. **Brain Res 795:**63–70, 1998
96. Power C, Henry S, Del Bigio MR, Larsen PH, Corbett D, Imai Y, et al: Intracerebral hemorrhage induces macrophage activation and matrix metalloproteinases. **Ann Neurol 53:**731–742, 2003
97. Qureshi AI, Ali Z, Suri MF, Shuaib A, Baker G, Todd K, et al: Extracellular glutamate and other amino acids in experimental intracerebral hemorrhage: an in vivo microdialysis study. **Crit Care Med 31:**1482–1489, 2003
98. Qureshi AI, Mendelow AD, Hanley DF: Intracerebral haemorrhage. **Lancet 373:**1632–1644, 2009
99. Qureshi AI, Tuhrim S, Broderick JP, Batjer HH, Hondo H, Hanley DF: Spontaneous intracerebral hemorrhage. **N Engl J Med 344:**1450–1460, 2001
100. Qureshi AI, Wilson DA, Hanley DF, Traystman RJ: No evidence for an ischemic penumbra in massive experimental intracerebral hemorrhage. **Neurology 52:**266–272, 1999
101. Rasool AH, Rahman AR, Choudhury SR, Singh RB: Blood pressure in acute intracerebral haemorrhage. **J Hum Hypertens 18:**187–192, 2004
102. Regan RF, Wang Y, Ma X, Chong A, Guo Y: Activation of extracellular signal-regulated kinases potentiates hemin toxicity in astrocyte cultures. **J Neurochem 79:**545–555, 2001
103. Robinson SR, Dang TN, Dringen R, Bishop GM: Hemin toxicity: a preventable source of brain damage following hemorrhagic stroke. **Redox Rep 14:**228–235, 2009
104. Rodrigues CM, Solá S, Brito MA, Brondino CD, Brites D, Moura JJ: Amyloid beta-peptide disrupts mitochondrial membrane lipid and protein structure: protective role of tauroursodeoxycholate. **Biochem Biophys Res Commun 281:**468–474, 2001
105. Rodrigues CM, Sola S, Nan Z, Castro RE, Ribeiro PS, Low WC, et al: Tauroursodeoxycholic acid reduces apoptosis and protects against neurological injury after acute hemorrhagic stroke in rats. **Proc Natl Acad Sci U S A 100:**6087–6092, 2003
106. Ropper AH, Zervas NT: Cerebral blood flow after experimental basal ganglia hemorrhage. **Ann Neurol 11:**266–271, 1982
107. Rosamond W, Flegal K, Furie K, Go A, Greenlund K, Haase N, et al: Heart disease and stroke statistics—2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. **Circulation 117:**e25–e146, 2008 (Erratum in **Circulation 122:**e10, 2010)
108. Ryu J, Min KJ, Rhim TY, Kim TH, Pyo H, Jin B, et al: Prothrombin kringle-2 activates cultured rat brain microglia. **J Immunol 168:**5805–5810, 2002
109. Schellinger PD, Fiebach JB, Hoffmann K, Becker K, Orakcioglu B, Kollmar R, et al: Stroke MRI in intracerebral hemorrhage: is there a perihemorrhagic penumbra? **Stroke 34:**1674–1679, 2003
110. Secades JJ, Alvarez-Sabín J, Rubio F, Lozano R, Dávalos A, Castillo J: Citicoline in intracerebral haemorrhage: a double-blind, randomized, placebo-controlled, multi-centre pilot study. **Cerebrovasc Dis 21:**380–385, 2006
111. Selim M: Deferoxamine mesylate: a new hope for intracerebral hemorrhage: from bench to clinical trials. **Stroke 40 (3 Suppl):**S90–S91, 2009
112. Selim M, Yeatts S, Goldstein JN, Gomes J, Greenberg S, Morgenstern LB, et al: Safety and tolerability of deferoxamine mesylate in patients with acute intracerebral hemorrhage. **Stroke 42:**3067–3074, 2011
113. Sharp F, Liu DZ, Zhan X, Ander BP: Intracerebral hemorrhage injury mechanisms: glutamate neurotoxicity, thrombin, and Src. **Acta Neurochir Suppl 105:**43–46, 2008
114. Shimazu T, Inoue I, Araki N, Asano Y, Sawada M, Furuya D, et al: A peroxisome proliferator-activated receptor-gamma agonist reduces infarct size in transient but not in permanent ischemia. **Stroke 36:**353–359, 2005
115. Silva RF, Rodrigues CM, Brites D: Rat cultured neuronal and glial cells respond differently to toxicity of unconjugated bilirubin. **Pediatr Res 51:**535–541, 2002
116. Sinn DI, Lee ST, Chu K, Jung KH, Song EC, Kim JM, et al: Combined neuroprotective effects of celecoxib and memantine in experimental intracerebral hemorrhage. **Neurosci Lett 411:**238–242, 2007
117. Solomon SD, McMurray JJ, Pfeffer MA, Wittes J, Fowler R, Finn P, et al: Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. **N Engl J Med 352:**1071–1080, 2005
118. Steiner T, Rosand J, Diringer M: Intracerebral hemorrhage associated with oral anticoagulant therapy: current practices and unresolved questions. **Stroke 37:**256–262, 2006
119. Suidan HS, Stone SR, Hemmings BA, Monard D: Thrombin causes neurite retraction in neuronal cells through activation of cell surface receptors. **Neuron 8:**363–375, 1992
120. Suo Z, Wu M, Ameenuddin S, Anderson HE, Zoloty JE, Citron BA, et al: Participation of protease-activated receptor-1 in thrombin-induced microglial activation. **J Neurochem 80:**655–666, 2002
121. Suzuki M, Ogawa A, Sakurai Y, Nishino A, Venohara K, Mizoi K, et al: Thrombin activity in cerebrospinal fluid after subarachnoid hemorrhage. **Stroke 23:**1181–1182, 1992
122. Suzuki R, Yamaguchi T, Kirino T, Orzi F, Klatzo I: The effects of 5-minute ischemia in Mongolian gerbils: I. Blood-brain barrier, cerebral blood flow, and local cerebral glucose utilization changes. **Acta Neuropathol 60:**207–216, 1983
123. Tanaka H, Ueda Y, Hayashi M, Date C, Baba T, Yamashita H, et al: Risk factors for cerebral hemorrhage and cerebral infarction in a Japanese rural community. **Stroke 13:**62–73, 1982
124. Tapia-Perez H, Sanchez-Aguilar M, Torres-Corzo JG, Rodriguez-Leyva I, Gonzalez-Aguirre D, Gordillo-Moscoso A, et al: Use of statins for the treatment of spontaneous intracerebral hemorrhage: results of a pilot study. **Cen Eur Neurosurg 70:** 15–20, 2009
125. Tolosano E, Altruda F: Hemopexin: structure, function, and regulation. **DNA Cell Biol 21:**297–306, 2002
126. Traystman RJ, Kirsch JR, Koehler RC: Oxygen radical mechanisms of brain injury following ischemia and reperfusion. **J Appl Physiol 71:**1185–1195, 1991
127. Tseng MY: Summary of evidence on immediate statins therapy

following aneurysmal subarachnoid hemorrhage. **Neurocrit Care 15:**298–301, 2011
128. Turgeon VL, Lloyd ED, Wang S, Festoff BW, Houenou LJ: Thrombin perturbs neurite outgrowth and induces apoptotic cell death in enriched chick spinal motoneuron cultures through caspase activation. **J Neurosci 18:**6882–6891, 1998
129. Turgeon VL, Milligan CE, Houenou LJ: Activation of the protease-activated thrombin receptor (PAR)-1 induces motoneuron degeneration in the developing avian embryo. **J Neuropathol Exp Neurol 58:**499–504, 1999
130. Vespa P, Prins M, Ronne-Engstrom E, Caron M, Shalmon E, Hovda DA, et al: Increase in extracellular glutamate caused by reduced cerebral perfusion pressure and seizures after human traumatic brain injury: a microdialysis study. **J Neurosurg 89:** 971–982, 1998
131. Vespa PM, O'Phelan K, Shah M, Mirabelli J, Starkman S, Kidwell C, et al: Acute seizures after intracerebral hemorrhage: a factor in progressive midline shift and outcome. **Neurology 60:**1441–1446, 2003
132. Vu TK, Hung DT, Wheaton VI, Coughlin SR: Molecular cloning of a functional thrombin receptor reveals a novel proteolytic mechanism of receptor activation. **Cell 64:**1057–1068, 1991
133. Wagner KR, Sharp FR, Ardizzone TD, Lu A, Clark JF: Heme and iron metabolism: role in cerebral hemorrhage. **J Cereb Blood Flow Metab 23:**629–652, 2003
134. Wagner KR, Xi G, Hua Y, Kleinholz M, de Courten-Myers GM, Myers RE, et al: Lobar intracerebral hemorrhage model in pigs: rapid edema development in perihematomal white matter. **Stroke 27:**490–497, 1996
135. Wang X, Mori T, Sumii T, Lo EH: Hemoglobin-induced cytotoxicity in rat cerebral cortical neurons: caspase activation and oxidative stress. **Stroke 33:**1882–1888, 2002
136. Wells JE, Biernaskie J, Szymanska A, Larsen PH, Yong VW, Corbett D: Matrix metalloproteinase (MMP)-12 expression has a negative impact on sensorimotor function following intracerebral haemorrhage in mice. **Eur J Neurosci 21:**187–196, 2005
137. West KL, Adamson C, Hoffman M: Prophylactic correction of the international normalized ratio in neurosurgery: a brief review of a brief literature. A review. **J Neurosurg 114:**9–18, 2011
138. Wu G, Xi G, Huang F: Spontaneous intracerebral hemorrhage in humans: hematoma enlargement, clot lysis, and brain edema. **Acta Neurochir Suppl 96:**78–80, 2006
139. Wu J, Hua Y, Keep RF, Nakamura T, Hoff JT, Xi G: Iron and iron-handling proteins in the brain after intracerebral hemorrhage. **Stroke 34:**2964–2969, 2003
140. Wu J, Hua Y, Keep RF, Schallert T, Hoff JT, Xi G: Oxidative brain injury from extravasated erythrocytes after intracerebral hemorrhage. **Brain Res 953:**45–52, 2002
141. Wu J, Yang S, Xi G, Fu G, Keep RF, Hua Y: Minocycline reduces intracerebral hemorrhage-induced brain injury. **Neurol Res 31:**183–188, 2009
142. Wu J, Yang S, Xi G, Song S, Fu G, Keep RF, et al: Microglial activation and brain injury after intracerebral hemorrhage. **Acta Neurochir Suppl 105:**59–65, 2008
143. Xi G, Hua Y, Bhasin RR, Ennis SR, Keep RF, Hoff JT: Mechanisms of edema formation after intracerebral hemorrhage: effects of extravasated red blood cells on blood flow and blood-brain barrier integrity. **Stroke 32:**2932–2938, 2001
144. Xi G, Hua Y, Keep RF, Hoff JT: Induction of colligin may attenuate brain edema following intracerebral hemorrhage. **Acta Neurochir Suppl 76:**501–505, 2000
145. Xi G, Keep RF, Hoff JT: Erythrocytes and delayed brain edema formation following intracerebral hemorrhage in rats. **J Neurosurg 89:**991–996, 1998
146. Xi G, Keep RF, Hoff JT: Mechanisms of brain injury after intracerebral haemorrhage. **Lancet Neurol 5:**53–63, 2006
147. Xi G, Keep RF, Hua Y, Xiang J, Hoff JT: Attenuation of thrombin-induced brain edema by cerebral thrombin preconditioning. **Stroke 30:**1247–1255, 1999
148. Xi G, Reiser G, Keep RF: The role of thrombin and thrombin receptors in ischemic, hemorrhagic and traumatic brain injury: deleterious or protective? **J Neurochem 84:**3–9, 2003
149. Xue M, Hollenberg MD, Demchuk A, Yong VW: Relative importance of proteinase-activated receptor-1 versus matrix metalloproteinases in intracerebral hemorrhage-mediated neurotoxicity in mice. **Stroke 40:**2199–2204, 2009
150. Xue M, Hollenberg MD, Yong VW: Combination of thrombin and matrix metalloproteinase-9 exacerbates neurotoxicity in cell culture and intracerebral hemorrhage in mice. **J Neurosci 26:** 10281–10291, 2006
151. Yang GY, Betz AL, Chenevert TL, Brunberg JA, Hoff JT: Experimental intracerebral hemorrhage: relationship between brain edema, blood flow, and blood-brain barrier permeability in rats. **J Neurosurg 81:**93–102, 1994
152. Yu YL, Kumana CR, Lauder IJ, Cheung YK, Chan FL, Kou M, et al: Treatment of acute cerebral hemorrhage with intravenous glycerol. A double-blind, placebo-controlled, randomized trial. **Stroke 23:**967–971, 1992
153. Zazulia AR, Diringer MN, Videen TO, Adams RE, Yundt K, Aiyagari V, et al: Hypoperfusion without ischemia surrounding acute intracerebral hemorrhage. **J Cereb Blood Flow Metab 21:**804–810, 2001
154. Zazulia AR, Videen TO, Powers WJ: Transient focal increase in perihematomal glucose metabolism after acute human intracerebral hemorrhage. **Stroke 40:**1638–1643, 2009
155. Zhao F, Hua Y, He Y, Keep RF, Xi G: Minocycline-induced attenuation of iron overload and brain injury after experimental intracerebral hemorrhage. **Stroke 42:**3587–3593, 2011
156. Zhao X, Grotta J, Gonzales N, Aronowski J: Hematoma resolution as a therapeutic target: the role of microglia/macrophages. **Stroke 40 (3 Suppl):**S92–S94, 2009
157. Zhao X, Song S, Sun G, Strong R, Zhang J, Grotta JC, et al: Neuroprotective role of haptoglobin after intracerebral hemorrhage. **J Neurosci 29:**15819–15827, 2009
158. Zhao X, Sun G, Zhang J, Strong R, Dash PK, Kan YW, et al: Transcription factor Nrf2 protects the brain from damage produced by intracerebral hemorrhage. **Stroke 38:**3280–3286, 2007
159. Zhao X, Sun G, Zhang J, Strong R, Song W, Gonzales N, et al: Hematoma resolution as a target for intracerebral hemorrhage treatment: role for peroxisome proliferator-activated receptor gamma in microglia/macrophages. **Ann Neurol 61:**352–362, 2007
160. Zhao X, Zhang Y, Strong R, Grotta JC, Aronowski J: 15d-Prostaglandin J2 activates peroxisome proliferator-activated receptor-gamma, promotes expression of catalase, and reduces inflammation, behavioral dysfunction, and neuronal loss after intracerebral hemorrhage in rats. **J Cereb Blood Flow Metab 26:**811–820, 2006
161. Zhao X, Zhang Y, Strong R, Zhang J, Grotta JC, Aronowski J: Distinct patterns of intracerebral hemorrhage-induced alterations in NF-kappaB subunit, iNOS, and COX-2 expression. **J Neurochem 101:**652–663, 2007
162. Zheng GQ, Wang XT, Wang XM, Gao RR, Zeng XL, Fu XL, et al: Long-time course of protease-activated receptor-1 expression after intracerebral hemorrhage in rats. **Neurosci Lett 459:**62–65, 2009
163. Zhou ZH, Qu F, Zhang CD: Systemic administration of argatroban inhibits protease-activated receptor-1 expression in perihematomal tissue in rats with intracerebral hemorrhage. **Brain Res Bull 86:**235–238, 2011
164. Zlotnik A, Gurevich B, Tkachov S, Maoz I, Shapira Y, Teichberg VI: Brain neuroprotection by scavenging blood glutamate. **Exp Neurol 203:**213–220, 2007

Manuscript submitted December 15, 2011.
Accepted January 27, 2012.
Please include this information when citing this paper: DOI: 10.3171/2012.1.FOCUS11366.

Address correspondence to: Cory Adamson, M.D., Ph.D., M.P.H., M.H.Sc., DUMC Box 2624, Durham, North Carolina 27710. email: cory.adamson@duke.edu.

Tarlov cysts

To The Editor: The recent review on the surgical treatment of sacral Tarlov cysts (TCs) by Lucantoni et al.[5] is useful (Lucantoni C, Than KD, Wang AC, et al: Tarlov cysts: a controversial lesion of the sacral spine. *Neurosurgical Focus 31 (6):*E14, December 2011). Few physicians know that TCs can cause radicular and regional pain syndromes, and the disorder remains undiagnosed and untreated in many symptomatic patients.[3] The perpetuation of incorrect information about TCs also hinders medical care. Neurosurgeons particularly need accurate data because definitive treatment is procedural.

The Lucantoni et al.[5] review restates some opinions about TCs that lack evidentiary support and thus merit further discussion. For instance, although outcomes of the reviewed surgical series were favorable in about three-fourths of the patients, with no deaths or neurological injuries, the authors summarize these as "conflicting results . . . and not without significant complications." In actuality, the data they review show surgical outcomes comparable to or better than those for many other common neurosurgical procedures.

Additionally, some of their epidemiological conclusions diverge from the evidence. Although Lucantoni and colleagues[5] stated that "the incidence does not significantly differ between sexes," the study they cited, which found 59% female prevalence among 27 patients with TCs,[7] was too small to be conclusive. They did not mention the largest survey of lumbosacral imaging, which found 70% female prevalence among 54 patients with MRI-visualized TCs.[4] Together, these studies reveal a strong female predominance among patients with visualized TCs (χ^2 = 8.35; 2-tail p = 0.0039, assuming 51% population female sex prevalence).

The sex imbalance is even greater among patients with symptomatic TCs. Case series reveal an 86% female predominance (for example, 8 of 10 patients,[10] 5 of 9 patients,[1] 5 of 6 patients,[4] 5 of 5 patients,[8] 4 of 5 patients,[2] and 2 of 2 patients[11]). Plus 84% of 122 patients with TCs treated with percutaneous cyst sealing were women.[6] The striking sex differences between patients with TCs and their surgeons probably contributed to the mistaken impression that TCs are clinically insignificant. Female patients often report "don't ask, don't tell" discussions with male surgeons concerning their sacral radicular symptoms. This is evident in the literature as well, as some studies on TC function did not inquire about bladder, bowel, or sexual function.[4]

The most important correction, however, concerns the proportion of radiologically visualized TCs that are symptomatic. The majority are indeed asymptomatic, although extrapolations from radiological surveys are methodologically compromised by the fact that symptoms are prerequisite for imaging. Additionally, nothing is known about the lifetime risk of symptoms. Regardless, Lucantoni and colleagues[5] err in reporting the proportion of TCs that are symptomatic as approximately 1%. Perhaps they used the number of patients undergoing lumbosacral MRI as the comparator rather than the total number of patients with TCs? Reading their source papers analyzed in Table 3 shows that Paulsen et al.[8] actually reported 22% (5 of 23 cases) of visualized TCs as symptomatic, and Langdown et al.[4] actually reported 30% (16 of 54 cases) symptomatic cysts among 54 visualized TCs. Seventeen percent were thought to be partially causal because of additional at-level pathology, and 13% were judged to be totally causal.[4] The Park et al.[7] study, which cited a 0% prevalence of symptomatic TCs, was a radiological survey that did not actually measure patient symptoms, so it should not have been included in Lucantoni and coworker's analysis. Conversely, a key surgical series was omitted. Van de Kelft and Van Vyve found TCs to be responsible for symptoms in 75% of patients (15 of 20) with otherwise unexplained chronic perineal pain, with 10 of 12 (83%) surgically treated patients achieving symptom remission.[9]

To summarize, the published data suggest that roughly one-fourth of TCs are symptomatic at the time of discovery and that TCs disproportionately affect women, often causing intimate symptoms that may be under-reported to male physicians. Surgical treatment of symptomatic cysts has reasonable outcomes and few serious adverse events. Perhaps more accurate information will encourage neurosurgeons to better serve these neglected patients.

(http://thejns.org/doi/abs/10.3171/2012.1.FOCUS11374)

Anne Louise Oaklander, M.D., Ph.D.
Massachusetts General Hospital
Boston, Massachusetts

Disclosure

Dr. Oaklander receives research support from the National Institutes of Health, the Department of Defense, and several nonprofit private foundations. She serves on the editorial boards of *PAIN, Neurology Today,* and *Pain Research Forum*. She is a member of the Scientific Advisory Committee of the RSD Syndrome Association Foundation and the Guideline Development Subcommittee of the American Academy of Neurology.

References

1. Abbott KH, Leimbach WH, Retter RH: The role of perineurial sacral cysts in the sciatic and sacrococcygeal syndromes: a review of the literature and report of 9 cases. **J Neurosurg 14:**5–21, 1957
2. Davis SW, Levy LM, LeBihan DJ, Rajan S, Schellinger D: Sacral meningeal cysts: evaluation with MR imaging. **Radiology 187:**445–448, 1993
3. Hiers RH, Long D, North RB, Oaklander AL: Hiding in plain

sight: a case of Tarlov perineural cysts. **J Pain 11:**833–837, 2010
4. Langdown AJ, Grundy JR, Birch NC: The clinical relevance of Tarlov cysts. **J Spinal Disord Tech 18:**29–33, 2005
5. Lucantoni C, Than KD, Wang AC, Valdivia-Valdivia JM, Maher CO, La Marca F, et al: Tarlov cysts: a controversial lesion of the sacral spine. **Neurosurgical Focus 31(6):**E14, 2011
6. Murphy KJ, Nussbaum DA, Schnupp S, Long D: Tarlov cysts: an overlooked clinical problem. **Semin Musculoskelet Radiol 15:**163–167, 2011
7. Park HJ, Jeon YH, Rho MH, Lee EJ, Park NH, Park SI, et al: Incidental findings of the lumbar spine at MRI during herniated intervertebral disk disease evaluation. **AJR Am J Roentgenol 196:**1151–1155, 2011
8. Paulsen RD, Call GA, Murtagh FR: Prevalence and percutaneous drainage of cysts of the sacral nerve root sheath (Tarlov cysts). **AJNR Am J Neuroradiol 15:**293–297, 1994
9. Van de Kelft E, Van Vyve M: Sacral meningeal cysts and perineal pain. **Lancet 341:**500–501, 1993
10. Voyadzis JM, Bhargava P, Henderson FC: Tarlov cysts: a study of 10 cases with review of the literature. **J Neurosurg 95 (1 Suppl):**25–32, 2001
11. Younes M, Korbaa W, Zrour S, Bejia I, Touzi M, Bergaoui N: [Sciatica due to unusual causes: Tarlov cysts and nerve root anomalies.] **Rev Neurol (Paris) 165:**282–287, 2009 (Fr)

Response: We thank Dr. Oaklander for her thoughtful and careful assessment of our literature review on TCs published in *Neurosurgical Focus*. Her criticisms of our review are three-fold and concern 1) the epidemiology of TCs, 2) the incidence of symptomatic TCs, and 3) the benefit of surgery.

In her letter, Dr. Oaklander presents a strong case that "studies reveal a strong female predominance among patients with visualized TCs," which is contrary to our statement that "the incidence does not significantly differ between sexes." After re-reviewing the studies, we find that Dr. Oaklander is correct. In the studies identified in Table 1 of our paper, 72% were women. In fact, in only 2 of the smaller studies (11 and 12 patients) did the number of male patients exceed the number of females.[1,4] This was an error that occurred during our data analysis, and we appreciate the opportunity to correct this mistake.

Dr. Oaklander also asserts that we "err in reporting the proportion of TCs that are symptomatic as approximately 1%," perhaps because we "used the number of patients undergoing lumbosacral MRI as the comparator rather than the total number of patients with TCs." This was not an error. It is clear from Table 3 how the value was obtained. In our paper we state that "the reported incidence of symptomatic TCs is approximately 1% or less." We intended this to refer to the likely incidence of symptomatic TC in the general population (Column 4 in Table 3 of our paper), and we apologize for any confusion our wording may have caused. We agree that the percentage of TCs that are symptomatic is > 1%, which can be determined in Table 3. Based on the studies that mentioned the number of symptomatic versus asymptomatic TCs, out of 77 patients with TCs, 12 (15.6%) were symptomatic.[2,3]

Lastly, Dr. Oaklander poses the question of whether the available surgical series in the literature can meaningfully inform treatment. Symptomatic improvement in the reviewed studies ranged between 38% and 100% of patients, and the duration of improvement was variable. In addition, the majority of the studies had small numbers of patients, the surgical procedure often differed between studies, and the methodology by which symptoms were assessed was inconsistent. In fact, the only surgical study that had a conservatively treated comparison group revealed no difference in outcomes. Therefore, these largely retrospective studies offer poor-quality evidence for surgery.

In summary, our paper does include the aforementioned epidemiological error: TCs appear to exist more commonly in women than in men. Operative intervention for symptomatic patients can be considered, as a number of patients who undergo surgery for symptomatic TC may experience improvement postoperatively. However, the evidence for this remains far from conclusive.

Khoi D. Than, M.D.
Paul Park, M.D.
University of Michigan
Ann Arbor, Michigan

References

1. Guo D, Shu K, Chen R, Ke C, Zhu Y, Lei T: Microsurgical treatment of symptomatic sacral perineurial cysts. **Neurosurgery 60:**1059–1066, 2007
2. Langdown AJ, Grundy JR, Birch NC: The clinical relevance of Tarlov cysts. **J Spinal Disord Tech 18:**29–33, 2005
3. Paulsen RD, Call GA, Murtagh FR: Prevalence and percutaneous drainage of cysts of the sacral nerve root sheath (Tarlov cysts). **AJNR Am J Neuroradiol 15:**293–297, 1994
4. Tanaka M, Nakahara S, Ito Y, Nakanishi K, Sugimoto Y, Ikuma H: Surgical results of sacral perineural (Tarlov) cysts. **Acta Med Okayama 60:**65–70, 2006

Please include this information when citing this paper: DOI: 10.3171/2012.1.FOCUS11374.