J Forensic Sci, May 2008, Vol. 53, No. 3
doi: 10.1111/j.1556-4029.2008.00696.x
Available online at: www.blackwell-synergy.com

Dennis J. Chute,[1] *M.D. and Kari Reiber,*[1] *M.D.*

Three Unusual Neuropathologic-Related Causes of Sudden Death*

ABSTRACT: We discuss the autopsy findings of three medico-legal cases of sudden death associated with uncommon neuropathologic findings of which the general forensic pathologist may not be familiar. Case 1 was a 43-year-old man who died of a seizure due to malignant melanoma of the temporal lobe associated with neurocutaneous melanosis (NCM). Case 2 was a 57-year-old woman with a history of mental retardation and incoordination because of chronic lead poisoning, who died of a pulmonary thromboembolism due to deep venous thrombosis status post left leg fracture after a fall down a staircase. Autopsy revealed atrophy and gliosis of her cerebellum as a result of childhood lead poisoning. The third patient was a 75-year-old woman who died as a result of acute bacterial leptomeningitis at the cervico-medullary junction with acute inflammation of the connective tissue of her upper cervical spinal column associated with subluxation of her atlantoaxial (AA) joint, also known as Grisel's syndrome.

KEYWORDS: forensic science, neuropathology, sudden death, neurocutaneous melanosis, lead encephalopathy, Grisel's syndrome

Forensic pathologists routinely certify death certificates in cases of sudden, unexpected deaths. Because of the broad scope of this casework, medical examiners and coroners inevitably investigate rare diseases that culminate in death. Three such neurologic-related cases recently fell under the jurisdiction of the Dutchess County Medical Examiner's Office and are presented below. Neurocutaneous melanosis (NCM) is an entity that typically presents in early childhood, but may also be found in adults. This rare neuroectodermal dysplasia consists of one or more large congenital nevi associated with infiltration of the leptomeninges by benign or, less commonly, malignant melanocytes (1). Lead encephalopathy is the clinical manifestation of the adverse effects of lead on the central nervous system (CNS). In the United States, this usually follows exposure to lead-based paints or absorption of environmental deposits of lead (2). Grisel's syndrome is an inflammatory weakening of the ligaments that support the upper cervical spinal column (3). This may rarely follow some otolaryngologic procedures and it occurs more often in children than in adults. We present these cases as examples of unfamiliar entities and because they emphasize the value of a neuropathologic consultation in the forensic setting.

Materials and Methods

Case files were reviewed over a 2-year period (2005–2006) from the Dutchess County Medical Examiner's Office. This office investigates all cases of sudden, unexpected, violent, and unattended deaths in this county of southeastern New York State. During that time period, 1264 cases were reported and 392 underwent complete postmortem examination. Clinical history, medical records, relevant radiologic films, and autopsy findings with toxicologic testing from three case files were reviewed by two board-certified forensic pathologists (D.J.C. and K.R.), one of whom is also a board-certified neuropathologist (D.J.C.). Histologic sections were stained with H & E. In addition, for case 1, immunohistochemistry was performed for S100 (Dako-rabbit polyclonal), and in case 3 a Gram stain was performed.

[1]Dutchess County Medical Examiner's Office, 387 Main Street, Poughkeepsie, NY 12601.

*Presented in poster format at the 59th Annual Meeting of the American Academy of Forensic Sciences, San Antonio, TX, February 19–24, 2007.

Received 6 Jan. 2007; and in revised form 9 Sept. 2007; accepted 15 Sept. 2007.

Results

Case 1

A 43-year-old African-American man with a history of congenital nevi of his head, torso, and extremities (Fig. 1*a*) was brought into an Emergency Department of a community hospital in cardiac arrest. His past medical history was hypertension, chronic alcoholism, and a poorly controlled grand mal seizure disorder that began 5 years earlier. His girlfriend discovered him unresponsive at home in a bathroom. An axial T1-weighted magnetic resonance imaging (MRI) study of his head performed approximately 3 months prior to his death demonstrated a hyperintense lesion located within the cortex of the left temporal pole (Fig. 1*b*). This was interpreted as possibly because of subarachnoid hemorrhage, a pigmented melanocytic lesion or, less likely, fat. No premortem biopsy of this brain abnormality was taken. At autopsy, the external examination revealed multiple, large pigmented melanocytic skin lesions (>40 cm) covering parts of the head, trunk, and extremities, including one about the lower torso and thighs consistent with what has been described as a "bathing trunk/garment/torso nevus." Internal examination of the head demonstrated a dark brown/black pigmented area covering part of the left temporal lobe's superior and middle gyri with extension medially along the Sylvian fissure (Fig. 2*a*). Coronal sections of the brain demonstrated that it appeared to be confined to the leptomeninges and cerebral cortex with relative sparing of the underlying temporal white matter. Away from the left temporal lobe, the brain appeared normal without evidence of hydrocephalus. Microscopic sections of the temporal lobe showed infiltration of the leptomeninges and Virchow-Robin spaces by a malignant melanocytic tumor (Fig 2*b*). In many areas, there was also single cell infiltration into the neuropil of the left temporal cortex. These tumor cells were S100 immunoreactive. Away from this area, microscopic examination of the brain was unremarkable. Further investigation into the circumstances surrounding the patient's cardiac arrest was

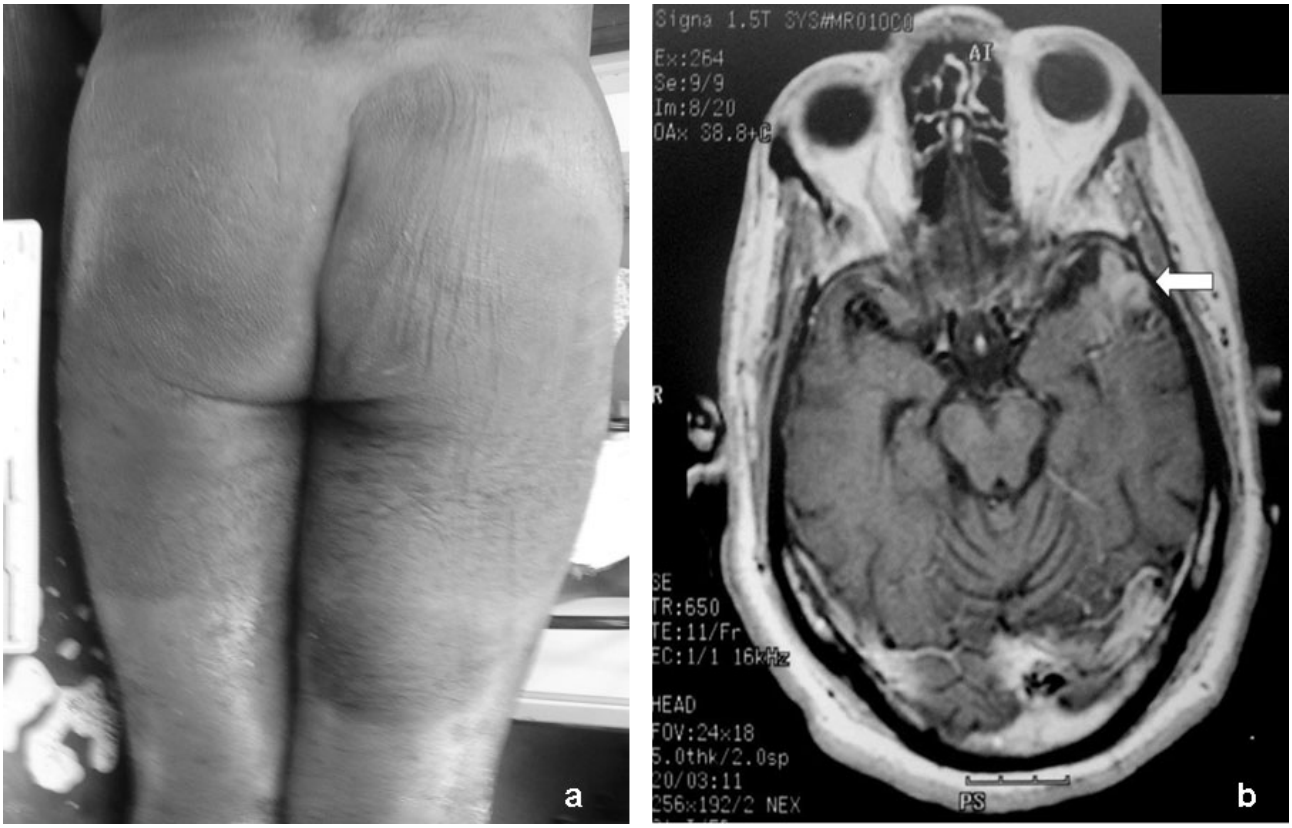

FIG. 1—*(a) "Garment/bathing trunk" nevi; (b) axial T1-weighted magnetic resonance imaging (MRI) study of head demonstrates a hyperintense lesion located within the cortex of the left temporal pole.*

noncontributory. The cause of death was attributed to a seizure due to a malignant melanoma of the temporal lobe arising in the context of NCM.

Case 2

A 57-year-old morbidly obese white female with a history of mental retardation, clumsiness, incoordination, and a childhood seizure disorder all of which were attributed to the sequel of chronic infantile lead poisoning was discovered unresponsive and asystolic on her bedroom floor. Twelve days prior to her death, she had a witnessed fall down a set of stairs, and sustained a fracture of her left tibia bone which was treated with a cast, pain relievers, and rest. Per history as related by the mother, who also served as the long-time caretaker, her daughter had ingested lead-based paint early in childhood by "teething" on a windowsill and crib. This history was confirmed by the patient's pediatrician; however, record of the childhood blood lead level was no longer available. The patient reportedly had a mental capacity of a 5-year-old with little verbalization.

Although the patient was chronically prescribed an anticonvulsant (primidone), the mother admitted that the patient's seizure disorder had occurred only during childhood and that there had been no recent seizure activity. At autopsy, the deceased appeared extremely obese with a BMI >40; she wore an orthopedic cast on her left lower extremity and there was moderate swelling with resolving contusion of the left leg, ankle, and heel. Internally, a thromboembolism was found to occlude the proximal branches of the right and left pulmonary arteries. Examination of the brain showed gross atrophy of the inferior half of the cerebellum including vermis and both hemispheres (Fig. 3*a*); total weight of the brain was 1070 g. The cerebral hemispheres, white matter and deep central nuclei, and brainstem were grossly normal. Microscopic examination confirmed marked loss of Purkinje cells and also a moderate loss of internal granule neurons within the inferior half of the cerebellar hemispheres and vermis; there was also Bergmann gliosis noted (Fig. 3*b*). The superior aspect of the cerebellum showed preservation of usual architecture with normal compliment of Purkinje and internal granule neurons. Hippocampi showed pyramidal neuron loss within sectors CA-1, -3, -4, and the prosubiculum with reactive astrogliosis. The cause of death was a pulmonary thromboembolism due to deep venous thrombosis status post left leg fracture as a result of blunt trauma as a long-term complication of chronic lead poisoning.

Case 3

This 75-year-old woman was found by her husband dead in bed. When queried by police, the husband appeared confused and proved to be a poor historian, unable to provide details of the patient's care, or of the circumstances that led up to and surrounded her death. The police found his behavior suspicious enough to request that a postmortem examination be performed to rule out foul play. The patient's personal physician later provided her past medical history of chronic osteoarthritis, hypertensive atherosclerotic cardiovascular disease, depression, and sharp pains in her neck and head of several months' duration. She had visited the Emergency Department at a local hospital once prior to her death and received referrals for a computerized axial tomography of her head and neck and a referral to a spine surgeon but she did not follow up on this. She was given a diagnosis of degenerative changes of the spine and prescribed pain relievers that included narcotics, a

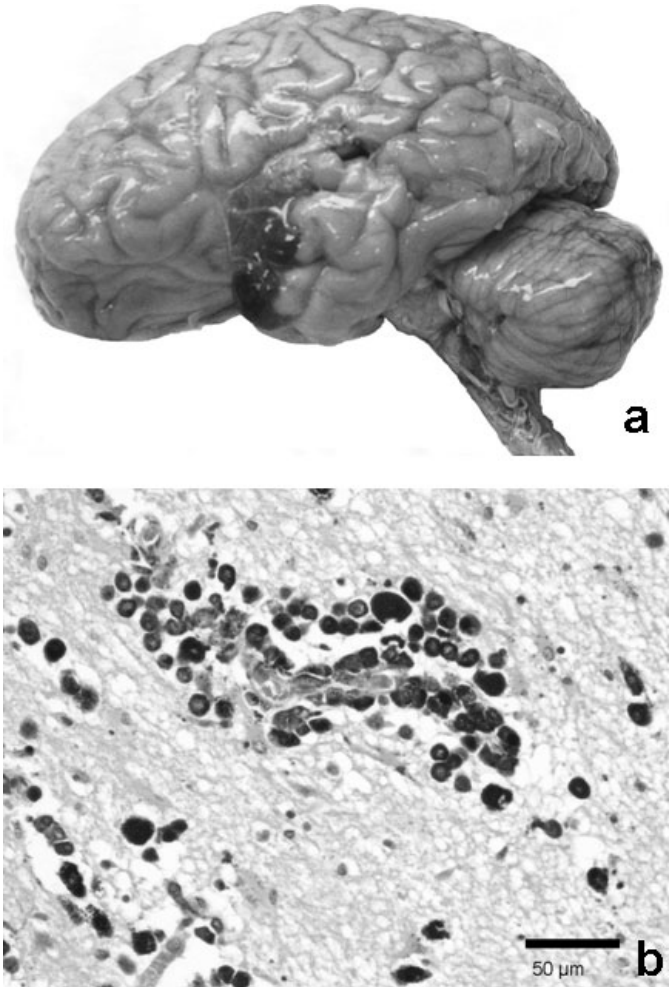

FIG. 2—*(a) Pigmented lesion on surface of superior and middle gyri of left temporal lobe; (b) infiltration of Virchow-Robin spaces by malignant melanocytic tumor. H & E ×200; bar = 50 microns.*

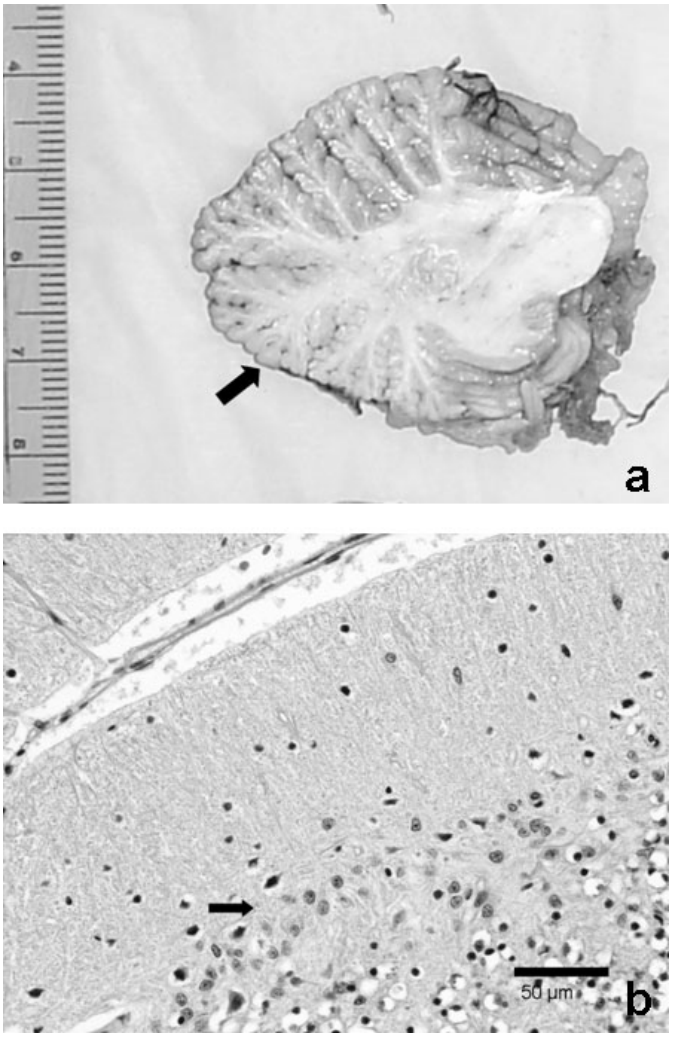

FIG. 3—*(a) Cross section of left cerebellar hemisphere with atrophy (arrow); (b) cerebellar cortex with loss of Purkinje neurons. H & E ×200; bar = 50 microns.*

muscle relaxant, and benzodiazepines. At autopsy, she appeared thin but not malnourished and without obvious deformities or external trauma. Internal examination demonstrated moderate degree of coronary atherosclerosis and osteoarthritic changes of her spinal column in the cervical and thoraco-lumbar regions. Of note, upon removal of the brain, an area of hemorrhage was noted on the inferior aspect of the brainstem and upper cervical cord region. Closer examination of the foramen magnum and upper spinal canal demonstrated compromise of the lumen due to posterior displacement of the odontoid process by subluxation of the atlantoaxial (AA) joint due to abnormal laxity within the cruciate and alar ligaments (Fig. 4*a*). The corresponding lower medulla and upper cervical cord region appeared compressed in an anterior–posterior plane. Anterior and posterior separate neck dissections did not reveal evidence of hemorrhage or trauma. Microscopic examination of the brainstem and spinal cord, as well as the dural and ligamentous connective tissue from the area involved by the subluxation, grossly revealed a hemorrhagic, acute and, to a lesser degree, chronic inflammatory cell infiltration of the leptomeninges and dense dural and ligamentous connective tissue (Fig. 4*b*). This inflammation was associated with numerous clusters of Gram positive cocci.

No microbiologic culture was taken at the time of autopsy because an infectious etiology was not considered. No source of bacterial infection was found elsewhere in the oral cavity or throat. The deceased was edentulous except for an upper denture plate. After further consideration of the pathologic findings and review of the literature, we concluded that this case compares to what has been called Grisel's syndrome. The cause of death was certified as acute leptomeningitis and hemorrhage of the cervicomedullary junction and subluxation of the AA joint.

Discussion

These unusual forensic cases, although unrelated neurologic processes, have one thing in common, namely, all contributed to sudden deaths investigated by our medical examiner system. NCM is a rare disease involving skin and CNS. It includes large (>20 cm) congenital melanocytic nevi (LCMN) or three or more smaller congenital pigmented nevi plus leptomeningeal melanosis or malignant melanoma in the CNS (1,4,5). Symptomatology for this phacomatosis typically starts early in life and may include seizures, psychomotor delay, and/or intracranial hypertension (6). Obstructive hydrocephalus may complicate the infiltration of leptomeninges by melanocytes causing blockage of cisternal pathways and arachnoid villi (5). Clinical criteria for NCM according to Fox are as follows: (1) large or unusually numerous pigmented nevi in association with leptomeningeal melanosis or melanoma, (2) no evidence of

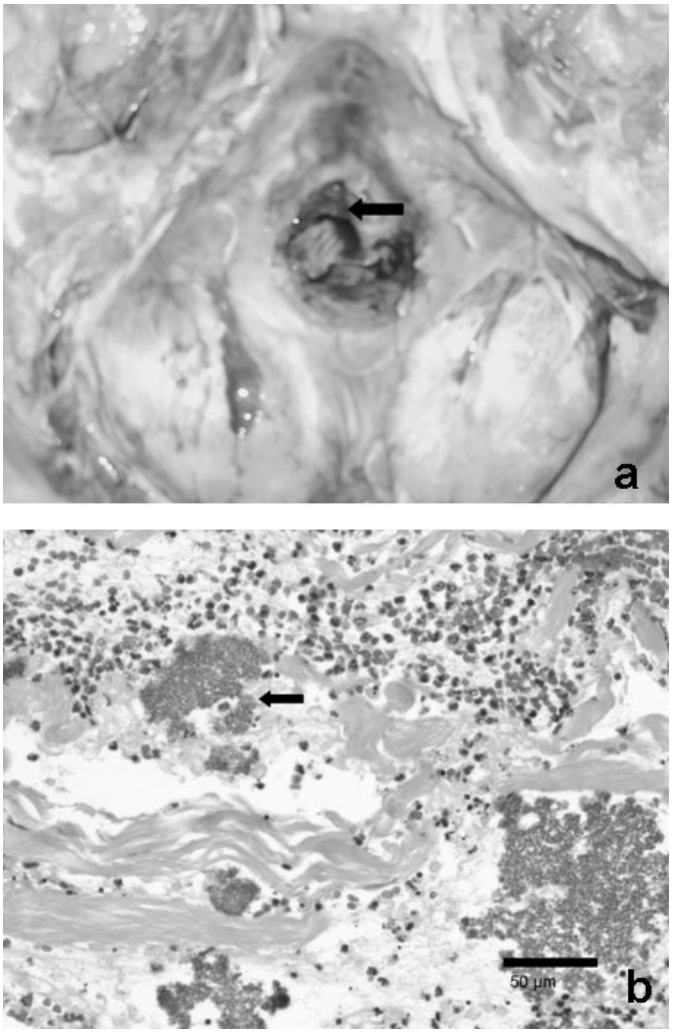

FIG. 4—*(a) Subluxation of atlantoaxial joint; (b) dense connective tissue infiltrated by coccal bacteria (arrow). H & E ×200; bar = 50 microns.*

malignant change in any cutaneous lesions, and (3) no evidence of malignant melanoma in any organ apart from the meninges (7). Our case consisted of an adult with numerous and LCMN on his body as well as a focal, infiltrating malignant melanoma concentrated within the leptomeninges and cortex of his left temporal lobe. A few months prior to his death, an axial T1-weighted MRI of the head demonstrated a hyperintense lesion in this area of his brain. Leptomeningeal melanoma can be visualized on MRI due to the characteristic paramagnetic properties of melanin (bright on T1-similar to fat and subacute hemorrhage, dark on T2-weighted images) as was noted in our case (8). It is unclear if resection of this lesion would have prolonged his life or relieved his seizure disorder. A recent review on treatment options for metastatic melanoma to the brain suggests that surgery for single lesions may, in some cases, give local control of disease and ameliorate symptoms (9). It should be noted that leptomeningeal lesions associated with NCM usually undergo malignant transformation and have very poor prognosis (1). In a study (n = 160) of patients with LCMN who were followed prospectively for an average of 5.5 years in the New York University (NYU)-LCMN Registry, Bittencort et al. found that the 5-year cumulative life-table risk for developing melanoma was 2.3% with a standardized morbidity ratio (observed/expected) of 101% (4). Similar to our patient, those patients in the NYU-LCMN Registry who had LCMN in paravertebral, posterior cervical, and/or cephalic locations were found to be at increased risk of developing NCM. The authors concluded that all patients with LCMN should undergo MRI screening of the CNS to rule out NCM. In a review of 14 series of patients with congenital melanocytic nevi of all sizes, Krengel et al. found that the overall risk of developing malignant melanoma is 0.7% (n = 6571 followed for 3.4–23.7 years) with the highest risk in those patients with nevi traditionally designated "garment nevi" (10). A large database (n = 1008) composed of information submitted by patients to The Nevus Network support group, unconfirmed by the patient's physician, was recently reported (11). This group found that of the cases with truncal LCMN, 4.8% developed symptomatic NCM and 2.3% died from benign or malignant NCM or cutaneous melanoma.

Our second case demonstrates the CNS injury following remote exposure to lead ingestion during early childhood, i.e., "teething" upon a windowsill presumably covered by a lead-based paint. Currently the major source of lead absorption is by oral ingestion (lead-based paint) (2), but it should be mentioned that at the time of our patient's poisoning three-quarters of a century earlier, combustion of lead-based gasoline also contributed to environmental lead exposure. Lead can produce effects on the central (encephalopathy) and peripheral (motor neuropathy with axonal degeneration) nervous system (12). Lead toxicity in childhood can produce the following: (1) lower IQ, (2) behavioral abnormalities, and (3) visual, hearing, and balance deficiencies (2). Within the cerebellum, lead can acutely produce edema and petechiae, rarely herniation; chronically it can produce Purkinje and internal granule layer neuron loss associated with astrogliosis, affecting vermis and lateral hemispheres. In our case, there was marked loss of Purkinje cells in the inferior half of the cerebellum with relative sparing of the superior half suggestive of a vascular distribution or ischemic contribution to the final pathology. Lead substitutes for polyvalent cations in the human body, viz., calcium, zinc, and magnesium. Proposed mechanisms of lead injury are many and some are speculative: (1) modifying signaling cascades, (2) mitochondrial damage/apoptosis, (3) inhibition DNA repair/transcription, (4) lipid membrane peroxidation (13,14).

Grisel's syndrome is nontraumatic AA joint subluxation due to inflammatory laxity or distension of the ligaments usually caused by an infectious process of the head or neck (3,15). Patients may complain of throat or neck pain, have symptoms of torticollis, radiculopathy, myelopathy, or rarely death (3). The pathogenesis of Grisel's syndrome is not completely understood. Some have implicated an anatomic connection between periodontal vascular plexuses that drain into the posterior superior pharynx that permit septic exudates to pass to the C1-C2 joint (16–18). For some patients, otolaryngologic procedures (tonsillectomy, adenoidectomy, mastoidectomy) appear to predispose to these sequelae (18,19). Based upon the case of a 6-year-old boy who was followed by serial CT scans for two months, Welinder et al. concluded that the AA subluxation is due to distension of the ligaments between C1-2 rather than loosening due to spreading inflammatory edema from the neck (15). Recently, Tang et al. proposed that the larger synovial folds present in children, compared to adults, contribute to an increased incidence of Grisel's syndrome in childhood (20). Pathogenesis does not appear to be restricted to the AA joint for similar cases referred to as variants of Grisel's syndrome have also been reported for subluxations of C2-3 and C3-4 (21,22). In our case, there was no known predisposing condition (no oro-pharyngeal abscess or preceding otolaryngologic surgery). The duration of her symptoms together with the mixed acute and chronic inflammation suggests that her condition may have been smoldering for some time. Given the marked laxity of her cruciate and alar ligaments,

we favor this area of the AA joint to be the initial focus of her pathology.

In summary, we described three forensic cases of sudden death with rare neuropathologic findings. Such findings would have been missed had a partial or limited autopsy been requested and granted, such as, "chest only," "abdomen only," or "excluding the brain." As shown in these cases, such limitations can result in the pathologist missing significant findings and, even, the cause of death.

Disclaimers

None.

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Additional information and reprint requests:
Dennis J. Chute, M.D.
Dutchess County Medical Examiner's Office
387 Main Street
Poughkeepsie, NY 12601
E-mail: dchute@co.dutchess.ny.us