

Long Survival Following Bacterial Meningitis-Associated Brain Destruction

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ABSTRACT

This report describes the brain autopsy of a boy who at age 4½ years experienced an episode of fulminant *Haemophilus influenzae* type b bacterial meningitis, resulting in massive brain destruction and the clinical signs of brain death. However, medical intervention maintained him for an additional two decades. Subsequent autopsy revealed a calcified intracranial spherical structure weighing 750 g and consisting of a calcified shell containing grumous material and cystic spaces with no recognizable neural elements grossly or microscopically. This case represents an example of long survival of brain death with a living body. (*J Child Neurol* 2006;21:591–595; DOI 10.2310/7010.2006.00137).

Acute bacterial meningitis is a rapidly progressive and potentially devastating disease that can result in significant morbidity and mortality. According to the Centers for Disease Control and Prevention (CDC), the three leading causes of bacterial meningitis in the United States from 1978 to 1981 were *Haemophilus influenzae* type b (48.3%), *Neisseria meningitidis* (19.6%), and *Streptococcus pneumoniae* (13.3%), whereas a wide variety of less common organisms caused the additional 18.8% of cases.¹ Although the incidence of meningitis caused by *H influenzae* type b was estimated at 60 cases per 100,000 children younger than age 5 years² before a vaccine became commercially available in wide distribution in 1988, now cases are, fortunately, rare.³ Recently, we had the opportunity to examine the brain from a patient who developed *H influenzae* type b meningitis in the era before the wide availability of the vaccine. The intriguing aspect of this case was the survival for two decades after loss of recordable electroencephalographic (EEG) brain activity and clinical brainstem function.

CASE REPORT

Clinical Summary

This male patient was born in 1979 and died at age 24 years of complications of *H influenzae* type b meningitis acquired at age 4½ years. He was an only child and was the product of an unremarkable

pregnancy, labor, and delivery. His early childhood development was normal, and his only problems were frequent ear infections, tonsillitis, and at least one episode of sinus infection. At the age of 22 months, he underwent myringotomy with ear tube insertions.

At the age of 4 years, he complained one evening of a headache, had a fever of 38.9°C, and vomited once. He was treated symptomatically with antipyretics. He initially felt well the next morning, but later that morning, he vomited and did not play or eat lunch. In the early afternoon, he again complained of headache and became febrile. He was taken to his physician's office, where a rectal temperature of 40.7°C was recorded. He was noted to be somnolent but was arousable. Examination revealed no nuchal rigidity or focal neurologic findings, and on ophthalmologic examination, there were normal optic disk margins bilaterally and venous pulsations noted on the right. He was immersed in cool water to lower his body temperature to 38.9°C. He subsequently became even more somnolent and was immediately sent to the hospital, which was approximately 12 miles away from the clinic office.

On arrival in the hospital emergency department, he was comatose and had bilaterally fixed and dilated pupils. After blood cultures, a chest radiograph, and a head computed tomographic (CT) scan were obtained, a lumbar puncture was performed that revealed grossly cloudy fluid that subsequently grew *H influenzae* type b. He was treated with boluses of chloramphenicol and ampicillin. He was intubated and was ventilator dependent. Severely increased intracranial pressure developed and resulted in spreading of the cranial sutures. Despite EEG evidence of electrocerebral inactivity, the family was opposed to his removal from life support.

His early course was complicated by severe temperature and blood pressure fluctuations, and he often required days of dopamine infusion to support his blood pressure. Urine output fluctuated tremendously (consistent with diabetes insipidus), along with dramatic shifts in his serum sodium. Thyroid function tests were normal, but he had evidence of hypocortisolism, necessitating cortisone replacement. After a number of weeks, temperature, blood pressure, urine output, and serum sodium

Received May 4, 2006. Accepted for publication May 5, 2006.

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levels became more stable. Episodes of cyanosis were treated as suspected sepsis, but blood cultures were consistently negative.

During the rest of his life, he was ventilator dependent. Reflex responses of the limbs and trunk to tactile stimuli consisting of nonpurposeful muscular movements were noted, along with occasional apparently spontaneous limb movements. There were no pupillary or corneal reactions and no electrophysiologic evidence of brainstem responses. The initial EEG showed no electrocerebral activity, and subsequent EEG studies showed similar electrocerebral inactivity (despite using recording sensitivities up to 2 μ V/mm).

He received low caloric feedings (750 calories/day) through a gastric tube. Infections and other complications were treated as necessary. Most infections responded to oral medications administered through the gastric tube, and aggressive intravenous antibiotics were only rarely necessary. However, during one episode of intravenous antibiotic therapy for a urinary tract infection, dopamine infusion was also required, and the serum creatinine rose to 2 mg/dL but later normalized to 0.4 mg/dL. After a number of initial urinary tract infections, the bladder catheter was removed, and he voided with the help of Credé massage by caregivers and had no further urinary tract infections.

He was weaned from hydrocortisone treatment at age 6 years (although he continued on treatment with fludrocortisone), but his cushingoid appearance of facial rounding and truncal obesity persisted until his death. He developed minimal pubic and axillary hair but little other evidence of secondary sexual characteristics (such as no penile or scrotal enlargement). At the age of 11 years, he underwent partial tarsorrhaphy, bringing the temporal upper and lower eyelids together to decrease corneal drying and ulceration. At the age of 18 years, he underwent neurodiagnostic testing: brain magnetic resonance imaging (MRI) and evoked potential studies. The MRI revealed marked calvarial thickening, extensive calcification, no identifiable normal brain structures, and trace intracranial blood flow adjacent to the clivus and at the anterior end of the middle cranial fossae. Brainstem auditory evoked potentials were absent following stimulation of either the right or left ear. Median nerve somatosensory evoked potentials were recorded following stimulation of both the right and left sides, with normal values for the median nerve conduction velocity (right 68.3 milliseconds left 66.6 milliseconds, N13 latency (right 11.04 milliseconds; left 10.88 milliseconds), and P14 latency (right 11.68 milliseconds; left 11.60 milliseconds); no N18 or N20 responses could be elicited.⁴

He required chronic care for most of his life. He was initially transferred from a hospital setting to a chronic care facility that specialized in ventilator patients. Eventually, arrangements were made for his care in a small apartment in the basement of his mother's home. However, he later again required placement in a chronic care facility and developed increasingly frequent respiratory infections, necessitating more vigorous antibiotic therapy. In his final 2 months of life, he was hospitalized twice with pneumonia and on the second hospitalization developed transient diabetes insipidus, which had not been evident for many years. On discharge from his last hospitalization, his mother decided that no further resuscitative efforts should be undertaken, and he experienced a cardiac arrest in January 2004. Following his death, a brain-only autopsy was performed.

Pathology

At the time of the autopsy, the body measured approximately 104 cm in length and had an approximate weight of 70 kg. The extremities were symmetric but poorly developed, with atrophic musculature. Cushingoid facies and body habitus was observed, including truncal obesity and a

suprascapular fat pad. The testes were bilaterally descended, and there was only scant pubic hair.

The head was microcephalic. On opening the cranium, prominent calvarial thickening up to 2.5 cm was evident, and the cranial sutures were fused at the inner table of the skull but not the outer table. The inner table of the calvarium was not smooth but was covered with irregular projections nearly 1 cm in height. The dura was difficult to separate from the inner table of the skull, densely adherent to the brain, and mostly calcified. The combined weight of the brain and adherent dura was 750 g. The removed brain was cut at the foramen magnum; thus, the spinal cord was not examined. After formalin fixation, the brain/dura specimen was evaluated. It was a hard, nearly spherical mass of approximately 10.5 cm in diameter with an irregular surface (Figure 1). No definite posterior fossa structures (including the cerebellum, brain stem, vessels comprising the circle of Willis, or cranial nerves) were identifiable.

CT of the formalin-preserved brain and adherent dura (performed in the coronal plane at 3 mm slice thickness) revealed extensive irregular nodular parenchymal densities (consistent with calcification) with similar thick irregular nodular densities covering the brain surface (Figure 2A). Individual anatomic brain structures could not be identified. MRI of the same specimen (using multiple pulse sequences on a 1.5 T unit in the horizontal plane) revealed extensive heterogeneous signal changes that were mainly hypointense on hemoflash and of medium to bright intensity on T₁-weighted and T₂-weighted images throughout the brain, without identifiable specific anatomic brain structures (Figure 2B).

The anterior half of the brain mass with adherent dura was sectioned (using a saw) as close as possible in the coronal plane. On the cut sections, the specimen was seen to consist of a hollow hard-calcified shell containing mostly semisolid and some cystic areas (see Figure 1): (1) semisolid areas consisted of tan (and scattered intermixed orange, red, and brown), grumous, focally mineralized material, with no identifiable cerebral structures, and (2) cystic areas were irregularly shaped and spaced and measured up to several centimeters in diameter. A fibrotic and partially calcified falx cerebri was identifiable posteriorly, but a tentorium cerebelli could not be identified. Although cystic spaces were evident bilaterally adjacent to the falx, a ventricular system was not apparent.

For histologic examination, multiple sections were taken from the areas of grumous material (Figure 3). On hematoxylin-eosin staining, areas of extensive mineralization were identified, with focal ossification and extramedullary hematopoiesis. Samples taken near the calcified shell also showed small foci of highly vascular loose collagenous tissue. Mineralized deposits appeared in several forms, including lamellated spherules, mineralized cell processes, and amorphous deposits. Clumped hemosiderin deposition was also evident. The grumous material examined appeared to be necrotic and mummified, containing no recognizable cellular elements, with the exception of mineralized cell processes. No neural elements were recognizable at the light microscopic level on any of the stains or with the immunohistochemical markers (including antibodies to various neural elements, such as the antibodies directed at glial fibrillary acidic protein [GA5, Cell Marque, Hot Springs, AR], neurofilament [NE14, BioGenex, San Ramon, CA], neuron-specific enolase [E27, Cell Marque], synaptophysin [polyclonal, Cell Marque], and S-100 [polyclonal, Ventana, Tucson, AZ] antigens).

DISCUSSION

This unusual case demonstrates the devastatingly destructive consequences of *H influenzae* type b meningitis. Interestingly, the clinical course was rapid and without one of the classic signs

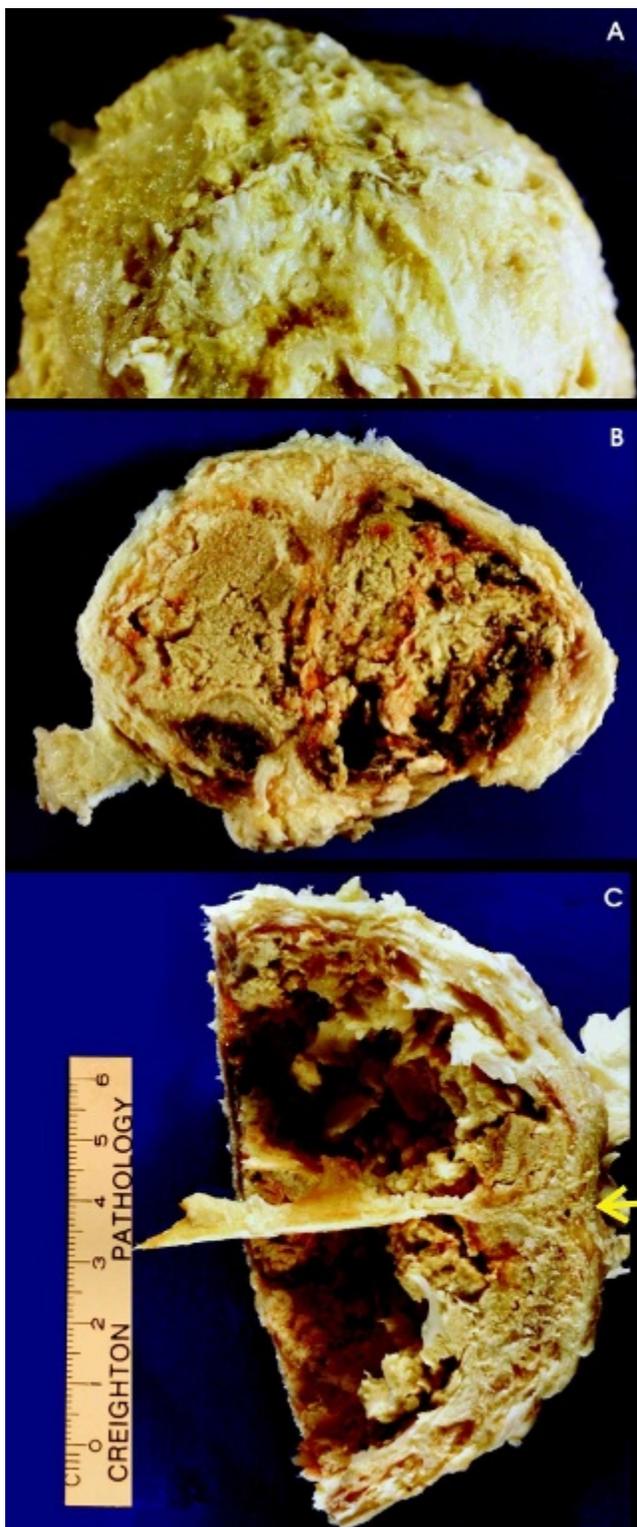


Figure 1. Gross appearance of the autopsy brain specimen with adherent dura. *A*, External surface of the nearly spherical specimen (diameter of approximately 10.5 cm) showing irregularity and hard calcification. *B*, Most anterior (frontal) section in the coronal plane (after saw-cutting the brain specimen) revealing a hard calcified shell containing mostly tan (and intermixed orange, red, and brown) grumous material and cystic spaces, with no identifiable brain structures. *C*, Posterior half of the brain specimen (horizontally cut at the presumed level of the torcular Herophili [yellow arrow]) viewed from below showing the residual posterior portion of the falx cerebri, along with grumous material and cystic spaces.

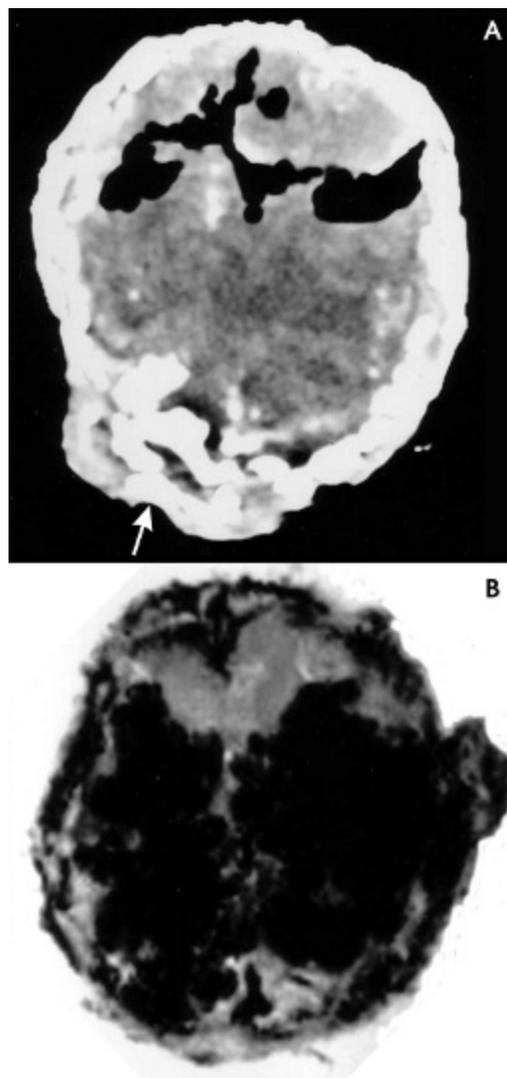


Figure 2. *A*, A computed tomographic scan in the coronal plane through the posterior aspect of the autopsy brain specimen showing extensive calcifications (arrow points to presumed posterior fossa); air lucency superiorly is iatrogenic. *B*, Magnetic resonance imaging hemoflash (repetition time 1050 milliseconds, echo time 22 milliseconds, flip angle 25 degrees) in the horizontal plane through the base of the autopsy brain specimen showing extensive hypointensity consistent with calcifications.

of purulent bacterial meningitis, nuchal rigidity.⁵⁻⁷ It is likely in this case that the episode of meningitis produced the brain destruction (resulting in the clinical signs indicating loss of brain function) by the mechanism of either or both the increase in intracranial pressure producing herniation⁸ or the altered cerebral blood flow from vasculitis.^{9,10} Although the brain had been destroyed during his acute illness, medical intervention over the subsequent nearly two decades allowed the intracranial changes to take place that were revealed at the time of autopsy. Given that there was no brain to grow and enlarge the skull, the head was microcephalic, and the calvarium was thickened. Although, by definition, brain death entails no internal carotid or vertebralbasilar artery blood flow,^{11,12} external carotid artery flow continued and permitted the dense calcification of the dura and replacement of adjacent brain parenchyma by ossification and focal areas of loose collagenous tissue. The finding that the

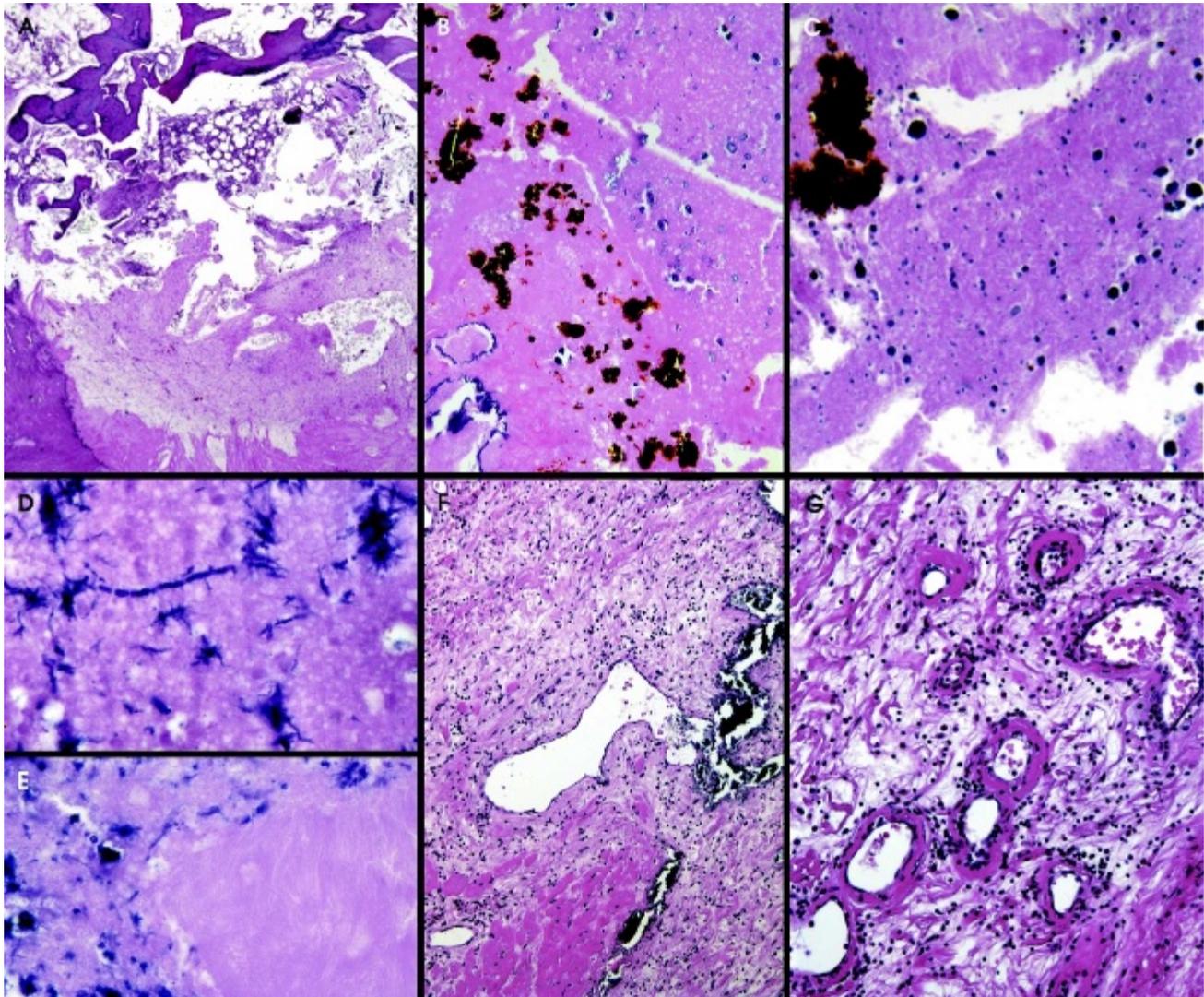


Figure 3. Microscopic sections from various areas of the brain specimen. *A*, Bone spicules and bone marrow in areas of extensive calcification and ossification (sampled near the calcified shell). *B* and *C*, Mummified material with clumps of iron pigment and extensive small focal calcifications. *D* and *E*, Mineralized cell processes and clumped calcium deposits next to mummified material. *F* and *G*, Samples from near the calcified shell showing loose connective tissue with calcification and cystic spaces (*F*) and loose connective tissue containing numerous hyalinized blood vessels and collections of macrophages (*G*). (Hematoxylin-eosin stain; original magnification: *A*, $\times 20$; *B*, $\times 200$; *C*, $\times 100$; *D*, $\times 400$; *E*, $\times 400$; *F*, $\times 100$; *G*, $\times 200$.)

interior of the specimen consisted mainly of mummified grumous material (with intermixed calcium deposits, clumped hemosiderin pigment, and focally mineralized cell processes) and only a few foci of connective tissue indicates that blood flow was insufficient over the two decades for macrophages to arrive and remove most of the debris. This appearance of mummification is very different from the pathologic changes reported following meningitis in which death and autopsy occur a short period after the onset of the bacterial meningitis.^{13,14}

In a 1998 article, Shewmon described a condition he termed chronic "brain death," which is characterized by survival owing to the body remaining alive while the brain is dead, and he provided as an example a one-paragraph clinical summary of the status of our case at that time:

The other ("TK") is now an 18½-year-old boy who contracted *Haemophilus influenzae* meningitis at age 4. Cerebral edema

was so extreme that the cranial sutures split. Multiple EEGs have been isoelectric, and no spontaneous respirations or brainstem reflexes have been observed over the past 14½ years. Multimodality evoked potentials revealed no intracranial peaks, magnetic resonance angiography disclosed no intracranial blood flow, and neuroimaging showed the entire cranial cavity to be filled with disorganized membranes, proteinaceous fluids, and ghost-like outlines of the former brain. He is fed by gastrostomy, and for the last 6 years has been thriving *sui generis* on a ventilator at home.¹⁵

Our pathologic findings at autopsy confirmed that his brain had been destroyed by the events associated with the episode of *H influenzae* type b meningitis, whereas his body remained alive (brain death with living body) for an additional two decades, a duration of survival following brain death that far exceeds that of any other reports.¹⁵

References

- Schlech WF, Ward JI, Band JD, et al: Bacterial meningitis in the United States 1978 through 1981, The National Bacterial Meningitis Surveillance Study. *JAMA* 1985;253:1749-1754.
- Cochi S, Broome CV, Hightower AW, Immunization of U.S. children with *Haemophilus influenzae* type b polysaccharide vaccine: A cost-effectiveness model of strategy assessment. *JAMA* 1985;253:521-529.
- Adams WG, Deaver KA, Cochi SL, et al: Decline of childhood *Haemophilus influenzae* type b (Hib) disease in the Hib vaccine era. *JAMA* 1993;269:221-226.
- Sonoo M, Tsai-Shozawa Y, Aoki M, et al: N18 in median somatosensory evoked potentials: A new indicator of medullary function useful for the diagnosis of brain death. *J Neurol Neurosurg Psychiatry* 1999;67:374-378.
- Valmari P, Pelola H, Ruuskanen O, Korvenranta H: Childhood bacterial meningitis: Initial symptoms and signs related to age, and reasons for consulting a physician. *Eur J Pediatr* 1987;146: 515-518.
- Gururaj VJ, Russo RM, Allen JE, Herszkowicz R: To tap or not to tap: What are the best indicators for performing a lumbar puncture in an outpatient child? *Clin Pediatr* 1973;12:488-493.
- Geiseler PJ, Nelson KE: Bacterial meningitis without clinical signs of meningeal irritation. *South Med J* 1982;75:448-450.
- Dodge PR, Swartz MN: Bacterial meningitis—A review of selected aspects. II. Special neurologic problems, postmeningitis complications and clinicopathologic correlations. *N Engl J Med* 1965;272:954-960.
- Horowitz SJ, Boxerbaum B, O'Bell J: Cerebral herniation in bacterial meningitis in childhood. *Ann Neurol* 1980;7:524-528.
- Raimondi AJ, DiRocco C: The physiopathogenetic basis for the angiographic diagnosis of bacterial infection of the brain and its coverings in children. I. Leptomeningitis. *Childs Brain* 1979;5: 398-413.
- Wijdicks EF: The diagnosis of brain death. *N Engl J Med* 2001; 344:1215-1221.
- Morenski JD, Oro JJ, Tobia JD, Singh A: Determination of death by neurological criteria. *J Intensive Care Med* 2003;18:211-221.
- Rorke LB, Pitts FW: Purulent meningitis: The pathologic basis of clinical manifestations. *Clin Pediatr* 1963;2:64-71.
- Adams RD, Kubik CS, Bonner FJ: The clinical and pathological aspects of B influenza meningitis. *Arch Pediatr* 1948;65:408-441.
- Shewmon DA: Chronic "brain death": Meta-analysis and conceptual consequences. *Neurology* 1998;51:1538-1545.

Special Article

Mobile Medical Computing Driven by the Complexity of Neurologic Diagnosis

Michael M. Segal, MD, PhD

ABSTRACT

Medical computing has been split between palm-sized computers optimized for mobility and desktop computers optimized for capability. This split was due to technology too immature to deliver both mobility and capability in the same computer and the lack of medical software that demanded both mobility and capability. Advances in hardware and software are ushering in an era in which fully capable computers will be available ubiquitously. As a result, medical practice, education and publishing will change. Medical practice will be improved by the use of software that not only assists with diagnosis but can do so at the bedside, where the doctor can act immediately upon suggestions such as useful findings to check. Medical education will shift away from a focus on details of unusual diseases and toward a focus on skills of physical examination and using computerized tools. Medical publishing, in contrast, will shift toward greater detail: it will be increasingly important to quantitate the frequency of findings in diseases and their time course since such information can have a major impact clinically when added to decision support software. (*J Child Neurol* 2006;21:595-599; DOI 10.2310/7010.2006.00155).

Received April 21, 2006. Accepted for publication April 21, 2006.

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Medical computing has been split into two varieties: simple programs that run on palm-sized devices and sophisticated programs that run on desktop computers. The reason for the split is that sophisticated programs (such as electronic health records and Web browsers) require full computers, whereas simple tasks, such as checking laboratory tests or writing

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