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Clinical Reasoning: A 44-year-old woman with headache followed by sudden neurologic decline

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SECTION 1

A 44-year-old woman with a history of migraines and idiopathic intracranial hypertension presented to the emergency room with 1 day of headache and nausea. She had been otherwise healthy with no sick contacts. She was afebrile without nuchal rigidity, rash, or cardiac murmur, and her neurologic examination was normal. Migraine therapy was initiated with IV prochlorperazine, ketorolac, and magnesium. Two hours later, she developed fever (101.4°F) and confusion, continually stating, "It hurts," but unable to answer questions or follow commands despite an otherwise unremarkable examination. Noncontrast head CT demonstrated mastoid sinus opacification, but no abnormalities of her brain parenchyma or ventricular system.

Question for consideration:

1. How should one evaluate and manage the patient?

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SECTION 2

The patient's headache, fever, and confusion raise concern for meningitis or encephalitis, and likely sinusitis on CT implicates a potential source for infection. Antibiotics should be initiated immediately when meningitis is considered likely. Until culture results are obtained, therapy should target the most likely pathogens in a given patient population. Vancomycin and a third-generation cephalosporin (e.g., ceftriaxone) are recommended to treat *Streptococcus pneumoniae* and *Neisseria meningiditis*, the 2 most common pathogens in immunocompetent children (older than 1 month) and adults up to age 50. Immunocompromise, infancy, or advanced age warrant ampicillin therapy against *Listeria monocytogenes*. A third-generation cephalosporin effective against *Pseudomonas* (i.e., cefepime, ceftazidime) should be considered in patients with penetrating trauma, ventriculoperitoneal shunt, or following neurosurgery. If there is concern for encephalitis, acyclovir should be empirically initiated while awaiting herpes simplex virus PCR. Antibiotics should be administered prior to lumbar puncture (LP), since CSF cultures do not become sterile until 2 hours from antibiotic administration for meningococcus and 6 hours for pneumococcus, and cellular/biochemical changes last 48–68 hours.[1]

Dexamethasone is recommended in the treatment of adults with meningitis, based on the results of a randomized trial studying 301 patients.[2] Patients who received dexamethasone (10 mg every 6 hours for 4 days) beginning 15–20 minutes prior to or with the first dose of antibiotics had a significant decrease in unfavorable outcomes and death. This result was driven by patients with pneumococcal meningitis, with no significant benefit to dexamethasone therapy for other organisms, and greatest benefit seen in moderate to severe cases of meningitis.

In our patient, ceftriaxone, vancomycin, and dexamethasone were initiated. LP revealed opening pressure of 49 cm CSF, protein of 286 mg/dL, glucose less than assay, 117,200 white blood cells (100% polymorphonuclear cells), 30 red blood cells, and moderate Gram-positive cocci in pairs (cultures grew penicillin-sensitive *Streptococcus pneumoniae*). The patient was admitted to the medical intensive care unit (ICU) where she opened her eyes to voice, tracked, had bilaterally reactive pupils, and moved all 4 extremities equally, but was not following commands. Due to persistent complaints of pain, she received several doses of IV opiates over the 8 succeeding hours. Approximately 12 hours after her initial presentation (6 hours after her LP), her oxygen saturation suddenly fell to 80% and she was found to be apneic.

Question for consideration:

1. What is the differential diagnosis for her sudden respiratory arrest?

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Complications of meningitis that can cause acute deterioration include cerebral edema, hydrocephalus, cerebral infarction, cerebral venous sinus thrombosis, and seizure.[3] The patient received naloxone in the event that recent opiate administration had caused her decline, but she did not improve and was intubated. On examination off sedation, she opened her eyes to voice, tracked, had equal and reactive pupils, full extraocular movements to command with prominent gaze-evoked nystagmus in all directions, corneal reflexes bilaterally, and spontaneous, symmetrical mouth movements. She was unable to protrude her tongue, had no gag reflex, and could not move any extremity spontaneously or to noxious stimuli. She had no spontaneous respirations.

Question for consideration:

1. What is the localization of her examination findings?

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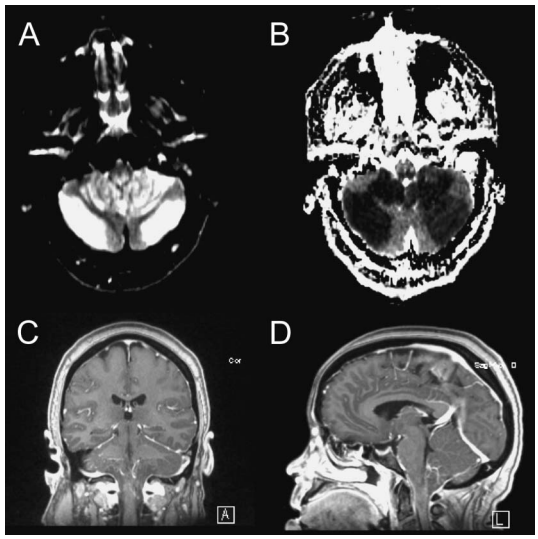
SECTION 4

The patient's ability to follow commands demonstrates preserved function of the cerebral cortex and its projections from the reticular activating system in the midbrain and thalami. Her preserved eye and mouth movements indicate intact brainstem function above the caudal pons. Prominent nystagmus in all directions of gaze indicates vestibulocerebellar dysfunction. Lack of gag, inability to move the tongue, apnea, and flaccid paralysis also suggest dysfunction at the level of the medulla. Head CT revealed no abnormalities. Brain MRI (obtained 12 hours after her acute decline) demonstrated diffusion restriction consistent with acute infarction in the bilateral cerebellar hemispheres as well as the medulla extending into the cervicomedullary junction (figure). CT angiogram obtained after her MRI did not reveal arterial occlusion, dissection, or venous sinus thrombosis. Echocardiogram was normal, with no valvular abnormalities or vegetations.

Question for consideration:

1. What is the cause and management of her condition?

Figure MRI



(A) Axial diffusion-weighted imaging (DWI) and (B) apparent diffusion coefficient (ADC) sequences show infarction of the bilateral cerebellar hemispheres as well as portions of the medulla. (C) Coronal and (D) sagittal postcontrast T1 magnetization-prepared rapid gradient echo (MPRAGE) sequence images show descent of the cerebellar tonsils into the foramen magnum, compressing the brainstem.

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The patient likely developed increased intracranial pressure (ICP) causing transforaminal herniation of the cerebellar tonsils. This led to compression of the arterial supply to structures near the foramen magnum, resulting in infarction of her cerebellum and medulla. To relieve her increased ICP and prevent complications from further cerebral edema, she was treated with hyperosmolar agents (hypertonic saline and mannitol), placement of an external ventricular drain (EVD) for CSF diversion, and decompressive suboccipital craniectomy. Despite these measures and the eradication of her infection, there was no improvement in her quadriplegia, anarthria, or ventilator dependence.

DISCUSSION Brain herniation in acute bacterial meningitis has been described in a number of case reports and series, and has been estimated to occur in 5% of cases.[1] Severe inflammation can cause cerebral edema and impairment of CSF flow. The resultant elevated ICP may create a pressure gradient between the skull contents and spinal column. LP may precipitate herniation due to exacerbation of this pressure gradient, though a cause-effect relationship is debated.[1,4] In a review of 98 reported cases of herniation in acute bacterial meningitis, 11% of herniation events occurred prior to LP, 38% occurred within 3 hours of LP, and 41% occurred between 4 and 12 hours following LP.[1] While imaging findings of midline shift and effacement of the fourth ventricle or cisterns are obvious contraindications to LP, CT is insensitive for predicting elevated ICP in the setting of meningitis, since decreased compliance of inflamed meninges and ventricular walls may counteract the forces of cerebral edema, yielding a falsely reassuring ventricular appearance.[1,5]

Seizures, focal neurologic deficits, papilledema, and altered consciousness may predict increased ICP in the setting of normal-appearing radiologic images in acute meningitis.[1,6] While some experts propose that these clinical signs warrant performance of CT prior to LP,[7] others suggest that their presence should lead to deferment of LP.[1] The potential diagnostic uncertainty if LP is deferred may be mitigated by laboratory testing such as blood cultures (positive in 40%–50% of patients with meningococcal meningitis and 80%–90% with pneumococcal or *Hemophilus* meningitis).[1] The theoretical risk of inadequately treating an undetermined bacterial pathogen insensitive to typical coverage may be minimal (0.3%) compared to the overall incidence of herniation in meningitis (5%), and the risk of missing alternative diagnoses without LP data could potentially be compensated for by alternative means of data collection (e.g., signs of tuberculosis on imaging, malaria on blood smear, or CSF cultures obtained via EVD, if one is placed for management of elevated ICP).[1]

Our patient had an initial Glasgow Coma Scale score (GCS) of 13 without focal neurologic deficits or seizures and had a normal head CT, yielding no clear contraindication to LP. Although her fundi were not visualized on presentation, papilledema had been noted during prior evaluation for idiopathic intracranial hypertension, complicating the interpretation of funduscopy in her case. Her opening pressure, however, was 49 cm CSF. In patients with clinical signs concerning for impending herniation (e.g., declining GCS, pupillary dilatation, focal examination findings), the need for urgent management of ICP is evident. How should one proceed in a patient such as ours with no clinical or radiographic signs of impending herniation? Her acute change in mental status may have been a clue to intracranial hypertension, though LP is routinely performed in the diagnostic evaluation of altered consciousness. Elevated ICP in acute bacterial meningitis is associated with decreased survival.[8] An elevated opening pressure on LP in this setting reflects an acute process, and requires urgent intervention to reduce the risk of brain herniation. In presumed acute bacterial meningitis, if LP reveals an elevated opening pressure, we recommend immediate cessation of CSF removal, treatment with hyperosmolar therapy, consideration of placement of an ICP monitor and CSF diversion, and close monitoring in an ICU. A randomized controlled trial examining use of an osmotic agent (glycerol) in children with meningitis demonstrated a significant decrease in death and severe neurologic sequelae with hyperosmolar therapy.[9] Hyperosmolar therapy is considered safe and effective,[10] and the risk of complications (e.g., renal failure and volume overload or depletion) is balanced by the potential for prevention or reversal of brain herniation. ICP monitoring allows for tailored hyperosmolar therapy and CSF diversion (if an EVD is used), benefits that may outweigh the risks of the procedure (e.g., intracerebral hemorrhage and insertion of a foreign body during active infection) in acute bacterial meningitis with elevated ICP.

AUTHOR CONTRIBUTIONS

Dr. Berkowitz drafted the initial manuscript, revised the manuscript, and was involved in the clinical care of the patient. Dr. Kimchi drafted the initial manuscript, revised the manuscript, and was involved in the clinical care of the patient. Dr. Hwang revised the manuscript and was involved in the clinical care of the patient. Dr. Vaitkevicius was involved in the clinical care of the patient. He reports no disclosures. Dr. Henderson revised the manuscript and was involved in the clinical care of the patient. Dr. Feske revised the manuscript and was involved in the clinical care of the patient. Dr. Chou drafted the initial manuscript, revised the manuscript, and was involved in the clinical care of the patient.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

A. Berkowitz reports no disclosures relevant to the manuscript. E. Kimchi, D. Hwang, H. Vaitkevicius, and G. Henderson report no disclosures.

S. Feske receives funding from the National Institute of Neurological Disorders and Stroke–sponsored NeuSTART trial. He is a member of the endpoint adjudication committee for the NHLBI-sponsored FREEDOM trial. S.H.-Y. Chou is funded by the National Institute of Health and the American Heart Association, and receives consultation fees as a member of the endpoint adjudication committee for CANTOS clinical trial funded by Novartis. Go to Neurology.org for full disclosures.

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Neurology 2013;80;e136-e141
DOI 10.1212/WNL.0b013e318289704c