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Fever and Seizure Activity in a 10-Month-Old Boy

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CASE PRESENTATION

Initial Presentation and History

A previously healthy 10-month-old boy presented to the emergency department (ED) with his mother following a generalized tonic-clonic seizure. Two days prior to presentation, the patient had a fever to 103°F, was acting more fussy than usual, and developed a decreased appetite. He later had 2 episodes of non-bloody, nonbilious emesis and was taken to his pediatrician, who diagnosed him with acute otitis media and prescribed azithromycin. Symptoms persisted, and on the night of presentation to the ED, the patient was febrile and had an episode where he screamed, grabbed his head, and went limp for a brief time. This was followed by a generalized tonic-clonic seizure. He continued to seize while en route to the ED.

In the ED, the patient received diazepam, lorazepam, and a loading dose of phenytoin before the seizure activity abated after almost 2 hours. Shortly thereafter, he developed respiratory failure requiring intubation (caused by the antiepileptic medications). Once the patient's airway was secured, initial blood work and cultures were obtained, and he was given an initial dose of ceftriaxone. He was transferred to the pediatric intensive care unit (PICU) of a tertiary care center for further care.

The patient's past medical history included a prior hospitalization at age 2 months for pneumonia. The prenatal course was uncomplicated, and he was born at term. Developmental milestones were met with no delays noted by his pediatrician. He took no medications regularly and had no known drug allergies. His immunizations were current except for the pneumococcal conjugate 7-valent vaccine (PCV7), which was not routinely administered at his pediatrician's office.

Evaluation and Initial Management

On examination in the PICU, the patient was febrile

and did not appear to be in acute distress. The anterior fontanel was open, flat, and soft. Pupils were equal, round, and reactive to light. There were no cranial nerve deficits. Heart, lung, abdominal, and dermatologic examinations were unremarkable. The patient had appropriate tone throughout all 4 extremities, 2+ deep tendon reflexes, and no further evidence of seizure activity. The complete blood count (CBC) was unremarkable. An initial metabolic panel performed in the ED prior to administering fluid therapy was significant for a serum sodium level of 126 mEq/L (normal, 136–145 mEq/L); the patient's sodium level was 144 mEq/L upon arrival to the PICU. A lumbar puncture (LP) was performed, and he was subsequently continued empirically on ceftriaxone and vancomycin for suspected meningitis as well as acyclovir for possible herpes simplex virus (HSV) encephalitis. Cerebrospinal fluid (CSF) testing revealed an elevated protein level of 214 mg/dL (normal, 15–45 mg/dL), a glucose level of less than 20 mg/dL (normal, 50–75 mg/dL), and a white blood cell count of 94 cells/ μ L (normal, < 6 cells/ μ L). The differential was remarkable for 78% neutrophils. Taken together, these indices were suggestive of bacterial infection. CSF Gram stain revealed no organisms. CSF culture and HSV polymerase chain reaction (HSV PCR) assay were obtained. A latex agglutination test was negative for *Neisseria meningitidis*, *Haemophilus influenzae*, and *Streptococcus pneumoniae*. The patient was extubated on hospital day 1 with no complications.

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Hospital Course

The patient's blood culture from the ED was positive for *S. pneumoniae*. The same organism was isolated from the CSF, and he was continued on ceftriaxone and vancomycin empirically. Acyclovir was discontinued after the HSV PCR assay returned negative. Vancomycin was discontinued when antibiotic sensitivities demonstrated a pan-sensitive organism. However, the patient remained febrile for the next 3 days, and a second LP on hospital day 4 showed gram-positive cocci on the Gram stain, with a negative culture. The white blood cell count had increased to 258 cells/ μ L. Rifampin was added to the regimen, and the fever resolved on hospital day 8. A third LP performed on hospital day 8 showed improved parameters, including a white blood cell count of 39 cells/ μ L, protein level of 138 mg/dL, glucose level of 45 mg/dL, no organisms on the Gram stain, and no growth on culture. Rifampin was discontinued after 7 days, and he ultimately completed a 14-day course of high-dose ampicillin.

An initial computed tomography (CT) scan of the head revealed benign external hydrocephalus, and an electroencephalogram was unremarkable. The patient's seizure activity on presentation (noted to be status epilepticus) was attributed to the meningitis. Phenobarbital was continued for baseline control until the meningeal inflammation resolved. The patient experienced 1 additional simple partial seizure, and the phenobarbital level was found to be subtherapeutic; he had no additional episodes once appropriate anticonvulsant levels were achieved. In addition, the patient had Todd's paralysis post-ictally from his second seizure, which resolved within 1 day. Magnetic resonance imaging of the head revealed no findings suggestive of acute hemorrhage or infarction but did show abnormal enhancement of the leptomeninges consistent with meningitis (Figure). The patient's parents were concerned about his hearing, and a brainstem auditory evoked response test was performed, which revealed mild low-frequency hearing loss and mild to moderate loss in the 3 to 4 Hz range.

- How do children with meningitis differ from adults in regard to epidemiology and clinical presentation?

EPIDEMIOLOGY OF PNEUMOCOCCAL MENINGITIS

Bacterial meningitis remains a common cause of morbidity and mortality across all age-groups. Historically, *H. influenzae* type B (Hib) was the primary cause of bacterial meningitis prior to the widespread use of the Hib vaccine in the early 1990s. With vaccination, bacterial meningitis has shifted from being a disease

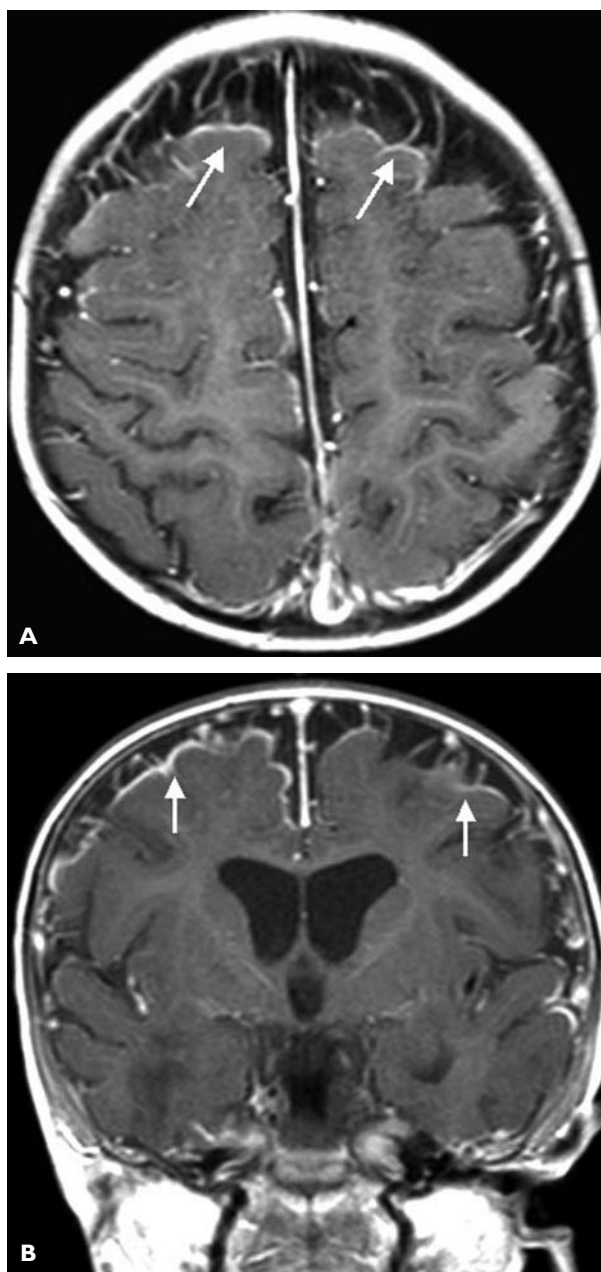


Figure. Magnetic resonance imaging of the case patient's head, with (A) axial and (B) coronal postcontrast T1-weighted images showing enhancement of the leptomeninges over the bilateral frontal convexities (arrows) consistent with meningitis.

primarily of infants and young children to being a disease that most commonly affects adults. Surveillance has shown that the median age of those with bacterial meningitis increased from 15 months to 25 years between 1986 and 1995, largely due to the Hib vaccine.¹ The causative pathogens have variable

frequencies depending on age. In neonates, group B streptococcus accounts for approximately 70% of cases, followed by *Listeria monocytogenes* (20%) and *S. pneumoniae* (10%). Between age 1 month and 2 years, the most frequently seen pathogens are *S. pneumoniae* (47%), *N. meningitidis* (30%), and group B streptococcus (18%). From age 2 to 18 years, *N. meningitidis* is most common (60%), followed by *S. pneumoniae* (25%) and Hib (8%). Among the agents that commonly affect otherwise healthy people, pneumococcal meningitis is associated with the highest mortality, with rates approaching 21%.¹ Although persons older than 65 years are at highest risk of death from pneumococcal meningitis, the majority of pneumococcal meningitis cases are seen in children younger than 2 years of age.²

CLINICAL PRESENTATION AND WORK-UP

Children with meningitis often present with nonspecific symptoms and no clear focus of infection. Furthermore, the presentation is often subacute and progresses over several days. Physical findings of meningitis commonly seen in adults may be difficult to detect or absent in infants and children. Specifically, children may not always present with Kernig's or Brudzinski's signs, may have nonspecific signs such as fever or hypothermia, and may or may not complain of headaches, neck/back pain, photophobia, or vomiting. Recognizing meningitis in infants is particularly challenging because they may only be irritable or fussy and have nonspecific findings similar to those seen in viral illnesses (eg, gastrointestinal and upper respiratory tract). An estimated 20% to 30% of children with bacterial meningitis will present with seizures.³

Key Point

The younger the patient, the more nonspecific and ambiguous the clinical presentation of bacterial meningitis.

There is no single history or physical examination finding that is diagnostic for bacterial meningitis. Not all cases of meningitis are bacterial in origin, with 1 study reporting an incidence rate of 8.6 cases of bacterial meningitis per 100,000 person-years compared with 10.9 cases of aseptic meningitis per 100,000 person-years.⁴ Nevertheless, one must maintain a high index of suspicion, and if bacterial meningitis is suspected based on the history and presentation, an LP should be obtained and appropriate antibiotics should be started immediately. Additional laboratory studies include a CBC, blood culture, and metabolic panel. A urinalysis and urine culture also may be obtained as appropriate. CT of the head should be considered

prior to the LP if there are concerns for increased intracranial pressure; this is particularly important if the patient has focal neurologic findings, papilledema, or mental status changes. If a head CT is required or if the LP is difficult to obtain, antibiotics should be started empirically without delay.

Key Point

Antibiotics should be initiated upon suspicion of meningitis and should not be delayed if a head CT is necessary or if the LP is difficult to obtain.

CSF findings suggestive of bacterial meningitis include an elevated white blood cell count, decreased glucose level, and elevated protein level. CSF Gram stains may be up to 90% sensitive and can help guide treatment while cultures are pending,⁵ as was the case when gram-positive diplococci were detected on the case patient's CSF Gram stain. Latex agglutination can be used to detect bacterial antigens, and this test often is used if the Gram stain and culture are negative but bacterial infection is still suspected, or if antibiotics are started before obtaining the LP. However, latex agglutination can yield false-negative results, as in this patient's case. One study reported only 49 positive latex agglutination tests out of 74 CSF culture-positive samples (66%).⁵ Normal CSF findings do not entirely rule out meningitis, especially if the LP is obtained early in the course of the infection.

- What are the current antibiotic recommendations in light of growing resistance?

ANTIBIOTIC THERAPY

It is imperative that antibiotic treatment be started quickly employing bactericidal agents that effectively cross the blood-brain barrier. Penicillin was the antibiotic of choice for the treatment of pneumococcal meningitis before the emergence of resistant strains.⁶ The current recommendations for empiric treatment of presumed bacterial meningitis in children older than 1 month include cefotaxime 225 to 300 mg/kg daily in divided doses every 6 to 8 hours (maximum, 12 g daily) or ceftriaxone 100 mg/kg daily in divided doses every 12 to 24 hours (maximum, 4 g daily) plus vancomycin 60 mg/kg daily in divided doses every 6 hours (maximum, 2 g daily).⁷ Cefotaxime and ceftriaxone are effective against most of the major pathogens in bacterial meningitis with the exception of *Listeria* species. Vancomycin is included empirically because of the increasing numbers of pneumococcal strains now resistant to penicillin and cephalosporins.⁸

Key Point

Empiric coverage for bacterial meningitis is based on the most common etiologic agents, including *S. pneumoniae*. Current recommendations for initial treatment include vancomycin in combination with either cefotaxime or ceftriaxone.

Antimicrobial therapy is adjusted once pathogens are identified and sensitivities are determined. Vancomycin should be continued until pneumococcus is ruled out or CSF cultures indicate that it is not necessary. If the organism is resistant to penicillin and cephalosporins but not to vancomycin, then vancomycin should be continued in conjunction with the chosen cephalosporin. Vancomycin should not be used as monotherapy to treat meningitis because of the difficulty in maintaining bactericidal levels of this drug in the CSF; however, vancomycin acts synergistically with cephalosporins in these situations.⁹ Rifampin may be added in certain cases, such as in children who are hypersensitive to β -lactams or if the expected clinical or bacteriologic response to the initial treatment regimen is delayed. Rifampin can pass into the CSF unaffected by steroids and therefore may be added if corticosteroids have been administered (*see Steroid Therapy*). Alternative agents such as meropenem¹⁰ or fluoroquinolones¹¹ may be effective against resistant strains, but there are insufficient data to recommend routine use of these agents at this time. The optimal duration of therapy for pneumococcal meningitis is undetermined; however, the typical treatment duration is 10 to 14 days.

The case patient was started on empiric coverage according to these guidelines. The CSF culture isolated pan-sensitive pneumococcus; however, the patient remained febrile despite appropriate therapy, and rifampin was added to his regimen until the CSF culture returned negative. He ultimately finished a 14-day course on high-dose ampicillin without further event.

- **Are steroids indicated for pneumococcal meningitis in children? If so, when should they be given?**

STEROID THERAPY

Steroid administration for bacterial meningitis in children aged 1 month and older remains controversial.⁵ Bacterial meningitis is associated with neurologic sequelae, including seizures, deafness, and mental retardation. Although mental status changes and seizures may precede the diagnosis, other effects may not be detected until after recovery from the acute infection. In 1 meta-analysis, 16% of children in developed countries and 26% in developing countries had

long-term neurologic complications. Hearing deficits were found in 10.5% of these children, followed by mental retardation (4.2%), seizures (4.2%), and spasticity and/or paresis (3.5%).¹² *S. pneumoniae* infection in particular has a higher rate of complications when compared with other common pathogens in bacterial meningitis.¹³ The acute release of bacterial debris into the subarachnoid space after the initiation of antibiotics can lead to greater host inflammatory response, further exacerbating tissue damage. Therefore, steroid therapy, especially given prior to or during administration of antibiotics, should be helpful in reducing some of these complications.⁹

Sensorineural hearing loss is one of the common morbidities associated with meningitis for which early steroid administration may be beneficial. Hearing loss is more likely to be caused by *S. pneumoniae* than other pathogens and occurs as a result of bacterial labyrinthitis, inflammation of the hair cells, damage to the auditory nerve, and/or later calcification of the perilymphatic channels.¹³ Although hearing loss generally might not be detected until later follow-up, it may occur at any stage of the illness. The case patient suffered hearing loss and did not receive steroids during his treatment course. The patient was also treated with vancomycin, which may have ototoxic effects. Whether steroids would have minimized this patient's hearing loss remains uncertain.

There is evidence that administration of dexamethasone shortly before or with the initiation of antibiotics for pneumococcal meningitis can decrease the incidence of neurologic sequelae, such as hearing loss, with overall mortality rates unaffected.^{14,15} A Cochrane review found that adjuvant corticosteroids are beneficial in the treatment of children with acute bacterial meningitis.¹⁶ Dexamethasone has been shown to have concrete benefits when the etiologic agent is Hib. However, data for other pathogens (eg, *S. pneumoniae*) are not as conclusive. Thus, the American Academy of Pediatrics currently recommends that dexamethasone be considered for infants and children beyond the neonatal period with pneumococcal meningitis but note that the data are not sufficient to demonstrate a clear benefit in this age-group.⁹ One reason steroids are not recommended universally at this time is the concern that dexamethasone may impair the penetration of certain bactericidal agents into the CSF. Vancomycin is one such agent that may have decreased efficacy passing through the blood-brain barrier with steroid administration; inflammation caused by meningitis actually improves its access into the CSF. Nevertheless, some evidence suggests that vancomycin may penetrate

adequately when steroids are used.⁸ Rifampin is able to pass into the CSF unaffected by concomitant steroid administration.¹⁷ Therefore, while steroid use in adults is more straightforward, the benefit remains uncertain in children and there are no definitive recommendations to date. Dexamethasone, if used, must be administered either prior to or with the initiation of antibiotics to be most effective. Treatment duration is up to 4 days, although 2 days appears to be sufficient.¹⁸

Key Point

Steroids are beneficial in adults and in children with meningitis caused by Hib. However, data are more limited for other pathogens (eg, *S. pneumoniae*) in children. Consequently, steroid use in children older than 1 month remains controversial and is not routinely recommended; if undertaken, steroids should be given before or with the initiation of antibiotics.

- **What are the current recommendations for fluid management?**

FLUID MANAGEMENT

Children with bacterial meningitis initially may be hyponatremic due to the syndrome of inappropriate antidiuretic hormone (SIADH), which traditionally has been addressed with fluid restriction. However, there is evidence that fluid restriction does not improve outcomes in children with bacterial meningitis.¹⁹ It is now recognized that autoregulatory mechanisms of cerebral perfusion pressure are lost in meningitis and perfusion becomes dependent on mean systemic arterial pressure.²⁰ Fluid management is now undertaken more cautiously, as suboptimal systemic pressures lead to inadequate cerebral perfusion. In addition, cerebral edema can increase intracranial pressure, decreasing cerebral blood flow. Cerebral edema can arise from various factors, including inflammation of the subarachnoid space that interferes with CSF resorption, cytokine-induced increased vascular permeability, and cell death.

Given these findings, it is now recommended that fluids be given initially at a rate of 50% to 75% of normal maintenance volume, using quarter-normal to half-normal saline with 5% dextrose as well as 20 to 40 mEq/L of potassium if the patient is euolemic (with fluid choices influenced by initial serum sodium values and calculated via standard methods, such as the Holliday-Segar method). Serum sodium must be followed closely regardless of fluid choice, and once found to be greater than 135 mEq/L, the fluid rate can be increased toward 100% of the maintenance volume with continued close observation. Fluids should

not be restricted if the patient is hypotensive, as this could lead to inadequate cerebral perfusion. Patients in shock should receive appropriate fluid resuscitation with close monitoring in an intensive care unit setting to ensure adequate perfusion while avoiding harmful increases in intracranial pressure.

This patient was initially hyponatremic and dehydrated upon presentation, and he received fluid resuscitation in the ED. The patient's hydration status and serum sodium level had improved by the time he was transferred to the PICU. Maintenance intravenous hydration was continued under close monitoring, but this was quickly weaned as his oral intake improved and he was able to maintain appropriate hydration on his own. He showed no further evidence of SIADH.

Key Point

In the past, fluid restriction was a common practice in patients with bacterial meningitis. However, fluid resuscitation is currently recommended based on the patient's clinical condition and must be undertaken carefully to maintain the correct balance between adequate systemic and cerebral perfusion and to avoid harmful increases in intracranial pressure.

- **How effective is the pneumococcal conjugate vaccine?**

PREVENTION

Vaccinations against the most common agents responsible for meningitis are now available, including *H. influenzae*, *N. meningitidis*, and *S. pneumoniae*. Hib has been the most common cause of meningitis but is now rarely seen in meningitis due to the widespread success of the Hib vaccine. Meanwhile, *S. pneumoniae* remains one of the most common pathogens responsible for hospitalization in all age-groups. Ninety pneumococcal serotypes have been identified based on surface capsular polysaccharide compositions; however, a minority of these account for the majority of infections. Vaccines have subsequently been developed to target the most common pathologic serotypes.

A 23-valent polysaccharide vaccine against *S. pneumoniae* has been available since the 1980s. However, it is not immunogenic in children aged younger than 2 years due to their decreased immunologic response to T-cell-independent antigens, such as these pure polysaccharides. This age-group is at highest risk for invasive pneumococcal disease (defined as isolation of *S. pneumoniae* from a usually sterile source, such as CSF or blood). The PCV7 vaccine targeted against *S. pneumoniae*, introduced in 2000, conjugates selected polysaccharides to a nonpneumococcal protein, which

allows infants and children to mount a better immune response due to the presence of T-cell–dependent antigens. PCV7 is now recommended as part of the routine immunization schedule for all children aged younger than 2 years as well as for older at-risk individuals. The PCV7 series (given at ages 2, 4, and 6 mo plus a booster usually given at age 12–15 mo) was estimated to prevent up to 83% of invasive pneumococcal infections in a prelicensure study,²¹ while other studies estimated even greater efficacy.

Key Point

Children aged younger than 2 years are at highest risk for invasive pneumococcal disease. The PCV7 vaccine effectively targets the 7 most common serotypes responsible for invasive pneumococcal disease in this age-group.

Several surveillance reports have shown a decreased incidence of invasive *S. pneumoniae* since the introduction of PCV7 in 2000, particularly of targeted and cross-reactive serotypes.²² Evidence suggests an associated decrease in resistant strains; this may be due in part to a decrease in the overall acquisition of resistant strains and to less antibiotic use in those who are vaccinated.²³ However, surveillance data also indicate that nonvaccine serotypes are now causing a higher proportion of invasive disease than in previous years. Therefore, while vaccination remains effective, it is important to monitor for the rise of nonvaccine serotypes. This patient was not immunized with PCV7, which left him at risk for invasive pneumococcal disease. It is likely that vaccination would have prevented this patient's illness.

CONCLUSION

Despite advances in prevention, diagnosis, and management, pneumococcal meningitis remains a severe and life-threatening illness. When treating the pediatric population, it is important to remember that the younger the patient, the more nonspecific and ambiguous the clinical presentation of bacterial meningitis. Empiric treatment should include vancomycin in combination with either cefotaxime or ceftriaxone in order to cover for resistant *S. pneumoniae* as well as other common pathogens. The use of steroids to prevent neurologic sequelae in suspected cases of pneumococcal meningitis remains controversial, but if undertaken, steroids must be given before or with the initiation of antibiotics. Close neurologic follow-up is indicated. SIADH remains a risk in bacterial meningitis, and fluid management should be undertaken carefully. Ultimately, considering the clinical challenges presented by bacterial meningitis and the observed

benefits of vaccination, the best treatment for most causes of meningitis is prevention. **HP**

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