Case 41

The patient was a 13-month-old child who, on the day of admission, seemed fine according to his mother except for a runny nose and a low-grade fever which she treated with Tylenol. Later in the day, while riding in the car with his mother, he suddenly had a grand mal seizure with shaking of the arm and legs. The seizure lasted 2 min. She called an ambulance. The emergency medical technicians found him limp, unresponsive, and apparently post ictal. In the emergency room he had a second seizure. On physical examination he had a temperature of 39.5°C, pulse of 160/min, and respiratory rate of 35/min. He was noted to be lethargic, but his neck was supple. Except for a runny nose, the rest of his physical examination was normal. Blood and urine cultures were obtained to rule out sepsis, and the child was begun on intravenous ceftriaxone. His past medical history was significant for his having received all appropriate immunizations for his age.

The patient's mental status did not improve overnight, and a lumbar puncture was performed which showed a cerebrospinal fluid (CSF) white blood cell (WBC) count of 4,650/μl with 95% neutrophils, glucose of 48 mg/dl (normal, 50 to 75 mg/dl), and protein of 107 mg/dl (normal, 15 to 45 mg/dl). Overnight his peripheral WBC count had increased from 6,600 to 14,600 cells per μl. He was transferred to a university hospital, where he was found to be irritable and to have a stiff neck. His admission blood culture was positive. CSF culture was negative, but a bacterial antigen test on his CSF was consistent with the admission blood culture results. Because of concern of immunodeficiency, antibody levels for pneumococci and *Haemophilus influenzae* type b were determined. Both were within normal limits, as were complement, immunoglobulin class and subclass levels, and lymphocyte function. HIV serology was negative. Gram stain of the organism grown from the blood culture is shown in Fig. 1. Growth of the organism on blood and chocolate agar plates is shown in Fig. 2.

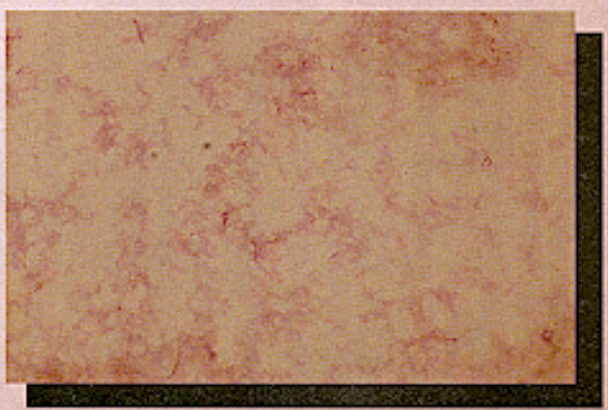

Figure 1

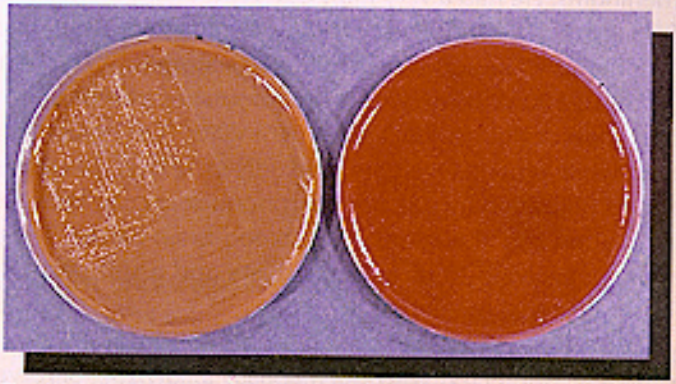

Figure 2

1. What was wrong with this child when he was transferred to the university hospital?

2. Based on your interpretation of Fig. 1 and 2, what organism do you think is most likely causing his illness? How has the epidemiology of disease caused by this organism changed in the last 5 years? Why has it changed?

3. Briefly describe the pathogenesis of this infection.

4. What is detected by a bacterial antigen test? Explain why it was positive in this patient's CSF when the culture was negative. When is the use of this test indicated?

5. What bacterial vaccines should this child have received by this time, including the numbers of doses? Based on the information in this case, do you think this child had received these vaccines? Why was HIV serology done on this patient?

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Case Discussion

1. The lumbar puncture and other clinical findings indicate that this child had bacterial meningitis. He had a very high CSF WBC count of 4,650/μl (normal, 0 to 3/μl), with 95% neutrophils. Both findings are consistent with bacterial meningitis. In cases of fungal, viral, and mycobacterial meningitis, cell counts usually are in the range of 50 to 500 WBC/μl, with a predominance of mononuclear rather than polymorphonuclear cells. In bacterial meningitis, CSF glucose levels are generally decreased while protein levels are markedly increased. Decreased CSF glucose is due in part to its utilization by CSF polymorphonuclear cells. Increased CSF protein is due to inflammation and alterations in the blood-brain barrier. The occurrence of seizure and lethargy, evolving to include irritability and a stiff neck, is also a clinical manifestation of bacterial meningitis.

2. The patient is infected with *Haemophilus influenzae*. Serotyping of the organism revealed that the patient was infected with serotype b. Prior to 1990, *H. influenzae* type b was the most common cause of bacterial meningitis in children from 6 months to 5 years of age. With the development and widespread use of a conjugated vaccine against serotype b *H. influenzae*, the number of cases of meningitis and other invasive infections due to this organism (bacteremia, septic arthritis, buccal cellulitis, epiglottitis) has declined dramatically. This patient represents the only case of *H. influenzae* type b meningitis seen in a 650-bed university hospital in a 4-year period (January 1993 to December 1996). In the era before *H. influenzae* type b vaccine, 6 to 12 cases were seen annually at that institution.

3. The initial stage in the development of bacterial meningitis in infants and young children is frequently an upper respiratory tract illness, characterized by a "runny nose" or otitis media with a low-grade fever, due to an encapsulated organism, in this particular case *H. influenzae* type b. From the upper respiratory tract, *H. influenzae* type b invades the bloodstream. In the absence of opsonic antibodies, the capsule surrounding this bacterium allows it to evade phagocytosis. By a process that is not clearly understood, the organism is able to cross the blood-brain barrier and infect the meninges. Many of the pathologic events that follow, including inflammation and edema, are due to the host's release of cytokines (tumor necrosis factor, interleukins) in response to the presence of the lipooligosaccharide found in the outer membrane of these gram-negative bacteria.

4. Bacterial antigen tests detect the presence of bacterial antigens, typically capsular polysaccharides, in body fluids, most commonly CSF, but also urine, serum, and joint and pleural fluids. These antigens are detected by mixing fluids suspected of containing them with latex particles coated with an antibody which is specific for a particular antigen. The latex particle-body fluid mixture is examined for agglutination (a particular type of clumping). Latex particles which are not coated with specific antibodies are used as a negative control.

If the control latex gives a positive agglutination test, the test results are uninterpretable. The results of the bacterial antigen test for this patient are shown in the following table.

Antibody coating latex	Agglutination reaction
H. influenzae type b	Positive
Streptococcus pneumoniae	Negative
Group B streptococci	Negative
Neisseria meningitidis A, B, C, W135, Y	Negative
None (control reagent)	Negative

Bacterial antigen tests are of very limited value. First, they should only be used in patients who have good evidence of bacterial meningitis, including a CSF cell count of 50 WBC/μl, decreased CSF glucose, and increased CSF protein. Second, the test is most valuable in patients who have received antimicrobial agents before the abnormal CSF specimen was obtained for culture and bacterial antigen detection. In those patients, bacterial cultures may be negative but the antigen, which can remain in CSF for as long as 2 to 3 weeks after initiation of therapy, will often be detectable. This is one of the two situations in which this testing is useful. The other is in distinguishing group B streptococci from *S. pneumoniae* in children in the 1- to 3-month age range who have a CSF Gram stain showing gram-positive diplococci. Bacterial antigen testing has little diagnostic value in all other patients who have positive CSF Gram stains because the identity of the organism can usually be determined by the organism's morphology and Gram reaction. With the decline in the incidence of *H. influenzae* type b meningitis, many hospital laboratories either no longer offer this test or strictly limit its use.

5. According to the recommendations of the American Academy of Pediatrics, this child should have received vaccines against diphtheria, tetanus, pertussis, and *H. influenzae* type b at 2, 4, and 6 months of age. He was due for a booster for each of those vaccines at 12 to 15 months of age.

Since vaccine failures are rare with *H. influenzae* type b vaccine, the assumption was that this child was not vaccinated. However, his medical records revealed that he had in fact received the three doses of this vaccine appropriate for his age. This indicates that this child was a vaccine failure. Since vaccine failures are uncommon, a variety of tests were done to determine if the child was immunodeficient. All were negative, indicating that the child was immunologically normal, at least by standard testing methods. HIV serology was done because infection with this virus is one of the leading causes of immunodeficiency in young children. HIV-infected children have a much higher rate of infection with encapsulated bacteria than immunocompetent children of the same age.

The reasons for this patient's vaccine failure were never determined. He survived his infection.

References

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2. **Shinefield, H. R., and S. Black.** 1995. Post licensure surveillance for *Haemophilus influenzae* type b invasive disease after use of *Haemophilus influenzae* type b oligosaccharide CRM_{197} conjugate vaccine in a large defined United States population: a four-year eight-month follow-up. *Pediatr. Infect. Dis. J.* **14:**978–981.