Title
Fever and Headache in a 10-year-old Boy

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Title: Fever and Headache in a 10-year-old Boy

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A previously healthy 10-year-old boy presents with twelve days of headache, eight days of fever, and three days of generalized weakness. His headaches are associated with photophobia and localize to the right retro-orbital region. The headaches and daily fevers of 102-104^{o}F are unresponsive to medications. On the day of admission, he has developed worsening fatigue, weakness, intermittent pain in his posterior thighs and calves, a limp favoring his left side, and has started dropping objects. His eyes also appeared red one day prior to admission. His mother has noted a two-pound weight loss over the last week. There is no congestion, rhinorrhea, sore throat, chest pain, abdominal pain, emesis, hematuria, dysuria, diarrhea, rash, easy bruising, or easy bleeding. He lives in a suburban home with four dogs and one cat. Other animal exposures include multiple rats in the backyard but no known direct contact with the patient. He has not traveled recently and denies new food exposures or sick contacts. He is fully immunized.

His temperature is 103.1^{o}F (39.5^{o}C), heart rate is 146 beats/min, blood pressure is 115/64 mmHg, respirations are 22 breaths/min, and oxygen saturation is 100% on room air. On physical exam, he is tired but well-appearing with no pallor or jaundice. No conjunctivitis is noted. There is pain on passive neck flexion. A 1 cm left anterior cervical lymph node is palpated. Mucous membranes are dry, lips are cracked, and he is tachycardic with a 2/6 systolic murmur at the left sternal border. Neurologic and musculoskeletal exams are normal except for an antalgic gait favoring the left side. Laboratory evaluation is significant for a white blood cell count of 3.2×10^{3}/mcL (3.2×10^{9}/L) with 49% neutrophils and 5% bands, hemoglobin of 9.8 g/dL, and platelets of 160 $\times10^{3}$/mcL (160×10^{9}/L); an erythrocyte sedimentation rate of 63 mm/hr and C-reactive protein of 3.49 mg/dL; a sodium of 130 mmol/L, albumin of 3.3 mg/dL, AST of 83 units/L, ALT of 120 units/L, and lactate dehydrogenase of 359 g/dL. The remainder of the electrolyte and liver panel, creatine kinase, and uric acid are within normal limits. Chest radiography shows no consolidation. Non-contrast CT of the brain is unremarkable. Further blood and CSF studies ultimately reveal the diagnosis.

Differential Diagnosis

The differential diagnosis for prolonged fever is broad and includes infectious, malignant, and rheumatologic etiologies. The localized headache, pain with neck flexion, and persistent fever were concerning for viral or bacterial meningitis. The prominence of his musculoskeletal complaints raised concern for osteomyelitis, but the absence of localizing symptoms made this less likely. The patient's fatigue and myalgias hinted at a more generalized infection, for which we considered CMV, EBV, HIV, influenza, or endemic mycosis (coccidioidomycosis). Animal exposures raised the possibility of various zoonoses such as Rickettsial disease (primarily *R. typhi*), Bartonella infection, brucellosis, lymphocytic choriomeningitis, and leptospirosis. Rat-bite fever (*Streptobacillus moniliformis*) was less likely given no direct rat contact but occasionally is transmitted by contaminated food or water. Q Fever (*Coxiella burnetii*) was also a possibility. Rheumatologic conditions, such as systemic juvenile idiopathic arthritis, were considered. The patient's prolonged fevers, cracked lips, and elevated ESR could have been explained by a diagnosis of incomplete Kawasaki disease. Finally, the leukopenia, anemia, and borderline-low platelet count was suspicious for malignancy.

Clinical Course and Management

Antibiotics were not started on admission because the patient was well-appearing. His fever and tachycardia resolved with acetaminophen. However, four hours after admission, he became febrile, hypotensive, and tachycardic. Ceftriaxone and vancomycin were initiated. The hypotension was unresponsive to 60mL/kg of normal saline, and he was transferred to the intensive care unit. Doxycycline was also started due to concern for potential Rickettsia-like infection. His blood pressure and other vital signs normalized after these interventions. CSF studies, including a PCR panel for bacterial, viral, and fungal causes of meningoencephalitis, were negative. A urine culture, rickettsia antibody panel, and respiratory viral panel were negative. At 70 hours, the blood culture grew Gram-negative coccobacilli. Given the clinical picture, the laboratory was warned about the suspected pathogen, which later was identified as *Brucella melitensis*.

The Condition

Brucellosis is a zoonotic infection that is endemic in the developing world, where it is underdiagnosed, and lack of access to treatment is an important barrier to eradication. Brucella is most commonly transmitted to humans through ingestion of contaminated raw dairy products.[1]Outbreaks can be associated with strains both from imported or domestic sources. In the United States, 115 cases were reported in 2010, with the highest concentration in California.[2] In 2018, a case of brucellosis caused by a drug-resistant strain of Brucella was linked to unpasteurized milk consumption from a dairy farm in Pennsylvania; exposures have been suspected in 19 other states.[3] From 2007-2012, an increasing number of illness outbreaks were associated with the legalization and consumption of unpasteurized milk.[4] This recent trend may have the potential to cause further resistant strains of Brucella. Efforts to prevent and control brucellosis include vaccination of livestock and pasteurization of dairy products. Because brucellosis can also be transmitted through the air, it is a potential bioterror agent. The greatest threat it poses is to laboratory workers who handle the specimens. If Brucella infection is suspected, the laboratory should be notified so that they may take biosafety level two precautions, especially if gram-negative coccobacilli are seen.[5] Brucellosis is a reportable disease.

The clinical presentation includes fever in 90%, arthritis or arthralgias in 70%, and weakness in 30% of children. Leukopenia, thrombocytopenia, and elevated liver enzymes are found in a minority of patients. Hepatomegaly and splenomegaly are common physical exam findings, and abdominal pain may be associated.[6] Rarely, bacteremia can lead to osteomyelitis, meningitis, and endocarditis.

Culture remains the gold standard, with blood cultures most commonly yielding the diagnosis, followed by bone marrow or tissue cultures. Brucella is slow-growing and can require prolonged incubation periods of up to 28 days. With newer culture techniques, often cultures are positive within seven days.[7] In cases where suspicion is high, having the laboratory hold cultures longer can be considered. Serology can be used as an adjunct, but this requires samples drawn two weeks apart. Patients with active infections will have titers of 1:160 or higher; however, there is potential for cross-reactivity with other antibodies against Gram-negative organisms.

Treatment

As a facultative intracellular pathogen, Brucella requires treatment with combination therapy for extended courses to avoid relapses. First-line treatment for children over the age of eight is doxycycline and rifampin for a minimum of six weeks. For children under the age of eight, combination therapy with trimethoprim-sulfamethoxazole and rifampin is the treatment of choice. Monotherapy or premature cessation of antibiotics are both associated with relapse. There is some evidence from adult studies that an intramuscular or parenteral aminoglycoside for the first two to three weeks can also reduce the risk of recurrent disease, which may apply to older children.[6,8] If there is bacteremia, meningitis, or endocarditis, an aminoglycoside should be considered for the first one to two weeks.[7] When a patient is diagnosed, the entire family should be screened for symptoms, since it is common that they were exposed to the same contaminated foods.

Patient Course

On further questioning, the patient's mother remembered that she had received cotija unpasteurized soft cheese from Mexico. She did not immediately recall giving it to the patient, but later the patient stated that he had eaten some. The unpasteurized cheese was presumed to be the source of the patient's Brucella infection. The patient continued treatment with doxycycline and rifampin for eight weeks and his headaches, malaise, and myalgias improved. Since he had already dramatically improved by the time the diagnosis was made, an aminoglycoside was not added. The possibility of relapse and the need for continued follow-up were reviewed with the family.

Lessons for the Clinicians:

- Consider brucellosis in evaluation of a patient with prolonged fever.
- Often, repeated history-taking is needed to obtain the clues to make the diagnosis of brucellosis.
- Notify the microbiology laboratory as soon as brucellosis is suspected.
- Notify the public health department when there is a positive result for Brucella.
- The most common cause of Brucella transmission to humans is ingestion of unpasteurized dairy products.

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