

Meningitis in an infant: All that's aseptic is not viral

Meningeal tuberculosis is the most common CNS manifestation of tuberculosis. Children younger than 5 years are among the groups who are most affected.

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CASE

An 11-month-old African-American child was taken to a regional emergency department, where pneumonia, mild dehydration, and mild malnutrition were diagnosed. He was treated and sent home, but he returned that night with worsening symptoms, including new-onset jerking movements of his extremities. He was admitted to the pediatric floor for further evaluation and treatment.

The medical history was noncontributory. The child had not had the third DtaP (diphtheria, tetanus, pertussis) vaccination, but otherwise his immunizations were up to date. His development was within normal limits. His father had recently lost his job and was performing construction day labor. The patient lived with his parents and three siblings. He and his siblings did not attend day care or school. His siblings were ill with a viral syndrome.

Upon admission, the patient had a fever of 101.5°F; vital signs and pulse oximetry results were otherwise normal. The results of the physical examination were unremarkable except for his very lethargic appearance, thin habitus, whimpering during passive neck flexion, muscular hypotonia, and slightly decreased breath sounds in the right lung fields. Analysis of the CSF revealed protein elevated at 158 mg/dL, glucose decreased at 15 mg/dL, WBC count elevated at 386 cells/μL, polymorphoneutrophils (PMNs) of 35 cells/μL, and mononuclear cells of 33/μL. Gram's stain of the CSF showed moderate leukocytes but no organisms. All CSF bacterial antigen tests were negative. Blood, urine, and CSF cultures obtained at admission were negative for growth in 5 days. Two days after admission, follow-up CSF results were as follows: protein still elevated at 157 mg/dL, glucose still decreased at 16 mg/dL, WBC count decreased but still elevated at 57 cells/μL, PMNs at 84 cells/μL, and mononuclear cells at 16/μL. Once again, all CSF bacterial antigen tests were negative. CSF culture and CSF acid-fast bacillus stains were negative.

On the second day after admission, CT of the brain performed without contrast showed edema in the right cerebral peduncle and subcortical white matter, along with

microhemorrhages in the gyri of the posterior left frontal lobe. Follow-up CT done on the twelfth hospital day showed worsening of the edema and microhemorrhages.

The patient remained very lethargic for the first 3 days of hospitalization. On the fourth day, he began having episodes of staring forward to the right, obtundation, and oxygen desaturation that required supplemental oxygen. Antiseizure medications were started. The patient continued to have alterations in consciousness, this time without a need for supplemental oxygen. These alterations increased in frequency and length, and included diaphoresis, tachycardia, and trembling of the head and extremities. At this time, the patient was noted to have a worsening Brudzinski's sign and increased irritability. When new information revealed that his father had had a positive result on a test for pulmonary tuberculosis (TB), the infant was started on the four-antibiotic regimen for meningeal TB. A pediatric infectious disease specialist advised that rifampin should be replaced with ethambutol because of the meningeal involvement. Serial gastric washings were obtained, tested for acid-fast bacilli, and showed the growth of *Mycobacterium tuberculosis*. A chest film demonstrated a developing cavitory lesion within the right upper lung.

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Color-enhanced transmission electron micrograph showing *Mycobacterium tuberculosis*

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DISCUSSION

According to the World Health Organization (WHO), TB kills 2 million people a year worldwide, or 5,000 people a day.¹ Nine million new TB cases occurred in 2004, 80% of those in just 22 countries.¹ Two billion people are infected with *M tuberculosis*, and each person infects 10 to 15 other people per year.¹ The CDC reports that there were 14,097 cases of TB (4.8 cases per 100,000 persons) in the United States in 2005; in 2004, 662 people died from the disease.²

According to the federal TB task force, after more than 3 decades of declining rates of TB, the number of cases in the United States soared 20% between 1985 and 1992.³ The causes included the HIV epidemic, a growing number of TB cases in immigrants, TB outbreaks in communal settings, delays in recognizing the emergence of multidrug-resistant (MDR) TB strains, and decreases in public health funding.^{1,4,7} In 2002, immigrants accounted for 51% of TB cases in the United States.⁵ The remainder occur among the urban poor, the homeless, migrant farm workers, and alcohol and drug abusers.^{1,3,4,6}

Children are disproportionately represented among these groups,^{4,8} and from 1987 to 1991, the number of TB diagnoses in children younger than 5 years increased by 49%.⁸ A child's risk of TB is determined by the risks of the surrounding adults. Typically, TB is diagnosed in a child during the public health investigation of one of these surrounding adults. TB in children is a small percentage of overall TB infections, but children can serve as a reservoir because their immune systems are not fully developed. For instance, children may have TB yet their tuberculin skin test (TST) result may be negative. They are also at increased risk for meningeal TB and miliary TB, which may develop up to 3 months before the skin test result becomes positive.^{5,8}

Types of TB There are two major types of TB: *pulmonary TB* is limited to the lung tissue; *extrapulmonary TB* is TB infection outside the lung tissue and occurs when pulmonary TB spreads via the blood or lymphatic systems. Extrapulmonary TB is most often seen in the lung pleura, lymph nodes, kidneys, GU system, bones, and CNS.^{1,6,9} In the United States before the HIV epidemic, approximately 85% of newly diagnosed TB cases were pulmonary only.⁶ In HIV-infected patients, however, the picture is quite different. One

study of patients with advanced HIV infection and TB showed that 38% had pulmonary infection, 30% had extrapulmonary infection, and 32% had both.⁶ This distribution of TB infection sites is also seen among infants, the elderly, and persons with primary or secondary immunodeficiency.⁹

Pulmonary TB manifests with cough, fever, night sweats, and malaise. The cough is initially dry but eventually becomes productive of yellow sputum and of blood. The

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hemoptysis is due to bronchiectasis, arterial invasion, or cavitory lesions and can lead to shock, asphyxia, and death. Other symptoms of pulmonary TB include pleuritic and radicular chest pain, dyspnea, weight loss or cachexia, emotional lability, and headache.^{6,9}

Auscultation of the lungs reveals dullness to percussion and rales with no consolidation. The classic radiographic signs are upper-lobe infiltrates with nonsymmetrical cavities without air-fluid levels, but these signs are neither specific nor sensitive. Atypical radiographic signs, often seen in immunocompromised patients, include lower-lung infiltrates, mid-lung focal infiltrates, pulmonary nodules, and infiltrates with mediastinal or hilar adenopathy. A normal chest film is not a reason to reject the diagnosis of TB when the patient has a positive epidemiologic history.^{5,6,8,9}

Laboratory diagnosis of pulmonary TB involves culturing sputum, which is quite difficult. Acid-fast staining results depend on the incidence of nontuberculous mycobacterial disease. In developing countries, acid-fast staining is specific, while in industrialized countries it is not. Thus, the incidence of nontuberculous mycobacterial disease is higher in industrialized countries.^{6,9} TST is done by the Mantoux method, which has been standardized and validated statistically.^{6,8,9}

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TEACHING POINTS

- Meningeal TB, or tuberculous meningitis, is the most common CNS manifestation of TB. It is seen most frequently in children younger than 5 years and in the immunocompromised.
- Meningeal TB should always be considered in the differential diagnosis for aseptic meningitis or chronic meningitis.
- When meningeal TB is treated, patients typically have a good prognosis—unless the patient is younger than 2 years, older than 60 years, or has comorbidities or immunodeficiency. When meningeal TB is accompanied by severe neurologic signs and symptoms, the risk of neurologic sequelae and mortality is greater.
- Treatment begins with a 2-month, four-drug regimen. After the first 2 months of treatment, pyrazinamide and ethambutol are discontinued while the two remaining drugs are continued for another 7 to 10 months.

COMPETENCIES

●●●● Medical knowledge

● Interpersonal & communication skills

●● Patient care

● Professionalism

● Practice-based learning and improvement

● Systems-based practice

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Treatment for pulmonary TB is described in Table 1. The treatment principles apply to extrapulmonary TB as well, except for meningeal TB. Radiographic follow-up after treatment is critical; signs and symptoms may take years to resolve, so symptom resolution is not an accurate guide to the efficacy of treatment. Children who are asymptomatic with a positive TST result and an abnormal chest film should be treated with the three-antibiotic regimen. Because isoniazid is a pyridoxine analog, pyridoxine supplementation is recommended for infants, children, adolescents who have nutritional deficiencies, patients with symptomatic HIV infection, and breastfeeding women.^{5,6,8-11}

Drug treatment is very effective, with up to a 95% cure rate when the medications are taken for the specified time period.⁶ But when a patient stops taking the medication early, *M tuberculosis* can mutate into a drug-resistant strain.^{5,6,10,11}

According to the WHO, MDR-TB (multidrug-resistant TB) is present in virtually all 109 countries recently surveyed, and 450,000 new MDR-TB cases are estimated to occur every year.¹ The highest rates of MDR-TB are in countries of the former Soviet Union and China.¹ In the United States, the percentage of MDR-TB cases was 1% in 2005.² However, of the total number of reported primary MDR-TB cases, the proportion occurring in foreign-born

persons increased from 26% in 1993 to 80% in 2005.² The cost of treating a case of MDR-TB in the United States is 100 times that of treating a nondrug-resistant case.²

Directly-observed therapy (DOTS) is a program sponsored by the WHO that aids governments in establishing TB programs with evaluation and monitoring systems to ensure that patients complete their treatment regimen. The principal tenet of DOTS is to have a health official watch as patients swallow their medicine for the entire treatment period, thereby preventing MDR-TB from developing.^{5,6,9} DOTS resulted in a 52% decrease in patients with MDR-TB in New York City between 1991 and 1994.⁶

Meningeal TB, or tuberculous meningitis, is the most common CNS manifestation of TB. It most frequently occurs in children younger than 5 years and in the immunocompromised. The morbidity and mortality rates are high, and meningeal TB is always fatal if untreated. Signs and symptoms result from CNS foci that rupture, causing an inflammatory response.^{5,9,12,13} (see Table 2).

Meningeal TB should always be considered in the differential diagnosis for aseptic meningitis or chronic meningitis. Also consider noninfectious meningitis (including medication-induced meningeal inflammation), meningeal carcinomatosis, CNS vasculitis, and cerebrovascular thrombosis.¹³

The CSF of patients with TB meningitis is characterized by clear fluid, WBC count greater than 1,000 cells/ μ L, cell counts less than 500/ μ L that are mostly lymphocytic (mononuclear), elevated fluid pressure, low glucose levels, and elevated protein levels. Laboratory confirmation of acid-fast bacilli in the CSF is very difficult and usually requires a large volume of fluid. Laboratory cultures for TB take several weeks and may delay definitive diagnosis as well as drug susceptibility results. Detection assays employing polymerase chain reaction technology have recently become available and have the advantages of being rapid, sensitive, and specific. Of patients with meningeal TB, 25% to 50% have pulmonary TB that has been diagnosed by radiographic methods.⁹ Meningeal TB is difficult to diagnose in children as the prodromal symptoms are seen in many viral illnesses.^{5,9,12,13}

TABLE 1: Treatment for pulmonary TB

Drug	Children	Adults
Isoniazid	10-20 mg/kg once daily; maximum, 500 mg/d	5 mg/kg once daily; maximum, 300 mg/d
Rifampin	10-20 mg/kg/d; maximum, 600 mg/d	600 mg/d
Pyrazinamide	15-30 mg/kg once daily; maximum, 2 g/d or 50-70 mg/kg twice weekly based on lean body weight	

Note: Patients should be treated for 6 mo. Data from Gilbert DN et al.¹¹

TABLE 2: Three stages of meningeal TB

Stage	Neurologic symptoms	Other symptoms
Prodromal stage	Fever, malaise, headache	No change in mental status, 1-3 mo in length
Meningeal irritation stage	Single cranial nerve abnormalities (ptosis or facial paralysis), paresis, focal seizures, headache; Kernig's and Brudzinski's signs present; hyperactive deep tendon reflexes may be present	Altered mental status, behavioral changes, fever, lethargy, increasing stupor
Comatose stage	Glasgow coma scale score <8, multifocal seizures, multiple cranial nerve palsies, hemiplegia or paraplegia, hydrocephalus	Coma is the defining symptom of this stage

Data from Chaisson RE and Nachega J.⁹

“The addition of dexamethasone to treatment is recommended, particularly in patients who have meningeal irritation or coma.”

Even with antimicrobial therapy, neurologic sequelae have been reported to occur in patients with meningeal TB. They can be grouped into three categories: hearing impairment; obstructive hydrocephalus; and brain damage. The latter category includes sensory and motor deficits, cerebral palsy, learning disabilities, mental retardation, cortical blindness, and seizures. When meningeal TB is treated, patients typically have a good prognosis. The prognosis is poorer for those younger than 2 years or older than 60 years and for those with comorbidities or immunodeficiency. When meningeal TB is accompanied by severe neurologic signs and symptoms, the risk of neurologic sequelae and mortality is greater than when meningeal TB causes no neurologic manifestations.^{9,12,13}

Treatment begins with a 2-month, four-drug regimen (see Table 3). Isoniazid and pyrazinamide attain efficacious CSF levels. Rifampin penetrates the blood-brain-barrier less efficiently but still achieves sufficient CSF levels. When ethambutol is used in children, monthly visual acuity and color discrimination examinations are required (unless the child is too young for a monthly eye examination). After the first 2 months of treatment, pyrazinamide and ethambutol are discontinued while the two remaining drugs are continued for another 7 to 10 months. Studies regarding the length of treatment are conflicting, but 12 months of treatment is the minimum and some infectious disease experts suggest that treatment continue for as long as 2 years.^{5,9,11-13} Serial lumbar punctures should be performed to monitor treatment efficacy.

The addition of corticosteroids, specifically dexamethasone, to the treatment regimen is recommended, particularly in patients with meningeal irritation or coma. Dexamethasone reduces the inflammation associated with the bacteri-

ocidal effects of the other drugs. The initial corticosteroid dosage should be administered for 3 weeks and then tapered during the next 3 weeks.

Outcome During the hospital stay, the 11-month-old patient's seizure episodes continued to increase in length, which prompted an adjustment in the antiseizure medication. Once the seizures stopped, physical therapy, occupational therapy, and a physiatrist were consulted to develop a rehabilitation plan. The patient was ultimately transferred to a university-affiliated medical center rehabilitation unit upon the physiatrists' recommendation. **JAAPA**

Jason Leaman practices at Knightdale Primary Care in Knightdale, North Carolina. He has indicated no relationships to disclose relating to the content of this article.

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TABLE 3: Treatment for meningeal TB

Drug	Children	Adults
Isoniazid	10-20 mg/kg once daily; maximum, 500 mg/d	5 mg/kg once daily; maximum, 300 mg/d
Rifampin	10-20 mg/kg/d; maximum, 600 mg/d	600 mg/d
Pyrazinamide	15-30 mg/kg once daily; maximum, 2 g/d or 50-70 mg/kg twice weekly based on lean body weight	
Ethambutol	15 mg/kg once daily	
Dexamethasone	8 mg/d for children <25 kg and 12 mg/d for children ≥25 kg	10 mg loading dose; then 4 mg every 4-6 h

Data from Gilbert DN et al.¹¹