

Tuberculous Meningitis: Successful Use of Delayed Corticosteroids in Treatment and Polymerase Chain Reaction in Diagnosis

Patricia Lopez-Po, MD, and Suresh J. Antony, MD

The diagnosis of tuberculous meningitis remains an enigma despite recent technologic advances, such as computerized tomography (CT), magnetic resonance imaging (MRI), and more recently, polymerase chain reaction of the cerebrospinal fluid. We report a patient with tuberculous meningitis who, when treated with appropriate antitubercular medications, made no progress in her recovery. Approximately 5 weeks into therapy, she began oral corticosteroid therapy and had a successful resolution of her neurologic deficits and intracranial symptoms. Polymerase chain reaction on four samples of cerebrospinal fluid was consistently negative for *Mycobacterium tuberculosis*. We describe the usefulness and problems associated with polymerase chain reaction and discuss the controversy regarding the late or delayed use of corticosteroids in the treatment of tuberculous meningitis.

Case Report

A 48-year-old previously healthy woman was admitted to the hospital in Mexico for evaluation of a 3-week history of fever and headaches that were persistent and increasing in intensity. She underwent a lumbar puncture and was given intravenous ciprofloxacin and ceftriaxone. Results from the lumbar puncture were a leukocyte count of $1/\mu\text{L}$, glucose 34 mg/dL, and protein 300 mg/dL. The opening pressure, Gram stain, and culture results were unavailable. During this course of antibiotics, her condition worsened - she continued to have high fever, developed right-sided hemiparesis, and became somnolent. Consequently, she was transferred to El Paso, Texas.

When examined, she had a temperature of 98.3°F , her blood pressure was 110/70 mm Hg, and

her heart rate was 58 beats per minute. She was awake but somnolent and appeared to be oriented to time, place, and person. She had nuchal rigidity, generalized hyperreflexia, and evidence of right sixth nerve palsy. Kernig and Babinski signs were normal. Findings during the rest of her physical examination were unremarkable.

Laboratory evaluation included a complete blood count, metabolic panel, chest-radiograph, electrocardiogram, and a CT scan of the head, the findings from all of which were normal. A lumbar puncture was performed. The opening pressure was 130 mm H_2O , the leukocyte count was $533/\mu\text{L}$, glucose was 27 mg/dL, and protein was 267 mg/dL. Gram stain and acid-fast stain were negative for bacteria. A polymerase chain reaction for *M tuberculosis* was negative.

Viral and fungal tests of the cerebrospinal fluid were negative. Cultures of sputum, blood, and urine for bacteria were also negative. The patient's clinical diagnosis was partially treated bacterial meningitis, and she was given intravenous ampicillin, vancomycin, and ceftriaxone. Twelve hours after admission she developed bradycardia and agitation and became obtunded. A second lumbar puncture showed an opening pressure of 500 mm H_2O ; the leukocyte count was $174/\mu\text{L}$, glucose 27 mg/dL, and protein 268 mg/dL.

Gram stains, acid-fast stains, and tests for viral and fungal infections, as well as a polymerase chain reaction for *M tuberculosis*, were negative.

Antituberculous therapy was started on day 3 of the hospital course based on her persistently low glucose and high protein levels. The patient was given ethambutol, rifampin, isoniazid, vitamin B_6 , and pyrazinamide. Diflucan was added to the treatment, and vancomycin, ampicillin, and gentamicin were discontinued. The patient continued to have headaches consistent with elevated intracranial pressure. She underwent four additional lumbar punctures, all of which had consistently elevated opening pressures, leukocytosis, elevated protein

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From the Department of Family Medicine, Texas Tech University Health Sciences Center (PLP), and Texas Oncology Physicians Associates (SA), El Paso. Address reprint requests to Suresh J. Antony, MD, Texas Oncology, 7848 Gateway East, El Paso TX 79915.

levels, and decreased glucose levels. Polymerase chain reactions for *M tuberculosis* in all four lumbar punctures were consistently negative. On day 14, an MRI of the head showed mild ventriculomegaly.

On day 18 one of the previous cultures of cerebrospinal fluid grew *M tuberculosis*. Cultures of sputum and urine were negative. On day 22 cultures of sputum and urine were positive for acid-fast bacilli. Findings from fungal and viral serologic tests remained negative.

Despite the medications the patient continued having headaches and subsequently developed right-sided ocular motor palsy. At this point, because of the rapidly progressive neurologic involvement, she was given prednisone, 80 mg/d. Her response to the addition of prednisone was dramatic. She had marked improvement, with resolution of headaches, stabilization of cranial nerve involvement, and an increased general sense of well-being. Her fever dropped rapidly, and her cranial nerve palsy resolved completely. She continued with prednisone therapy for 4 weeks, which was then slowly tapered. Antitubercular treatment continued for 12 months. At her 12-month follow-up visit, she was free of symptoms and doing well.

Discussion

Untreated tuberculous meningitis characterized by progressive stupor often has a fatal outcome within 4 to 8 weeks of symptom onset. Rapid detection of the pathogen and early institution of treatment are therefore vitally important. The diagnosis of tuberculous meningitis is based on neurologic signs and symptoms and cerebrospinal fluid findings.¹ The definitive diagnosis depends on microscopy and culture of the cerebrospinal fluid. Culture is still regarded as the reference standard in the diagnosis of tuberculous meningitis.² Identification of acid-fast bacteria on microscopy occurs in only a few patients, however, because many bacteria (>10/mL) must be present to be detected reliably.³ In addition, cultures of cerebrospinal fluid require several weeks (4 to 8 weeks) to become positive because the organisms grow slowly. Thus rapid bacteriologic diagnosis of tuberculous meningitis with these conventional techniques is extremely difficult.²

With the advent of the polymerase chain reaction for identification of *M tuberculosis*, its useful-

ness in reducing morbidity and mortality in patients infected with this organism has been well documented in the infectious disease literature. The late use of corticosteroids has not been well studied, however. Our patient clearly showed improvement after the institution of corticosteroids, and although we cannot strongly recommend it as adjunctive therapy, it should be considered for extremely ill patients with neurologic deficits.

Imaging studies, such as CT and MRI scans, are of additional use when diagnosing tuberculous meningitis, because meningeal enhancement is seen on the MRI in 80% of the cases with tuberculous meningitis. This meningeal enhancement is thought to represent inflammation, an early sign of arachnoiditis.⁴

Outcomes of tuberculous meningitis treated with corticosteroid therapy vary with design, end points, and regimens.⁵ Investigators from Egypt who undertook the largest randomized (but not blinded) study using corticosteroid therapy for tuberculous meningitis found that patients taking corticosteroids in whom cultures were positive had lower mortality than a control group.⁶ Others⁷ have found that cerebrospinal fluid parameters (white blood cell count, glucose level, and protein level) return to normal faster in the corticosteroid group, and there was a substantial benefit for patients with intermediate disease (single nerve palsy, drowsiness, or hemiparesis). Fewer complications occurred in the corticosteroid group than in the control group. A regimen of dexamethasone at 8 to 12 mg/d,⁶ or a prednisone equivalent,⁸ seems as effective and has fewer side effects than higher doses. Corticosteroids also appear to alleviate elevated intracranial pressure as well.⁹

This case illustrates several important points. First, tuberculous meningitis is a medical emergency that requires urgent empirical treatment based on neurologic signs, symptoms, and cerebrospinal fluid findings. Early diagnostic and medical intervention greatly reduces morbidity and mortality. Second, polymerase chain reaction has been used more recently to confirm the clinical diagnosis of tuberculous meningitis and appears to be rapid, sensitive, and specific for *M tuberculosis*. False-positive and false-negative results do occur, however, as in this case. Third, local signs and symptoms of tuberculous meningitis are caused by the host's inflammatory response; therefore, corticosteroid therapy appears to be useful as adjunctive therapy

in the management of tuberculous meningitis in both early and late stages of the disease.

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