

# Pearls & Oysters: CSF analysis and the therapeutic paradox in tuberculous meningitis

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aramesh@montefiore.org**PEARLS**

1. The diagnosis of tuberculous meningitis (TM) is often based on clinical findings due to the difficulty of isolating acid-fast bacilli (AFB) in the CSF.
2. After initiation of treatment for TM, the CSF profile may switch from a lymphocytic to a neutrophilic predominance, known as the therapeutic paradox.

**OY-STERS**

1. The shift in cellular predominance in the CSF may be used in conjunction with other diagnostic information to aid in the diagnosis of TM.
2. Further studies of TM with microbiologic confirmation of AFB in CSF will help determine the specificity of this finding.

**CASE REPORT** An 18-year-old woman presented with a 10-day history of persistent headache and subjective fever. She had been evaluated previously at 2 nearby hospitals and was treated with metoclopramide and diphenhydramine. She had been treated in the past for latent tuberculosis (TB) with a 9-month course of isoniazid; however, the degree of compliance was unknown. On admission, she was afebrile with normal results on general and neurologic examination. Chest x-ray and head CT scan had normal results. Lumbar puncture showed 164 cells/mm<sup>3</sup> with a lymphocytic predominance (98%), protein 231 mg/dL, glucose 23 mg/dL, and xanthochromia; the opening pressure was not documented. Acyclovir, vancomycin, and ceftriaxone were initiated on admission. On the second hospital day, the patient had intermittent events of staring, confusion, and unresponsiveness. The next day, she was drowsy and had left-sided ptosis, impaired left eye adduction, limited right eye abduction, and asymmetric right-sided forehead wrinkling and facial grimace. There was no evidence of papilledema. During the examination, she experienced 2 brief episodes of left gaze deviation and bilateral upper extremity tonic posturing. A loading dose of fosphenytoin was administered. The initial EEG

showed 2 left temporal electrographic seizures; subsequent continuous EEG monitoring showed background slowing, disorganization, and left frontal sharp waves.

Over the next 24 hours, the patient deteriorated into a coma with intact brainstem reflexes, but with a flaccid paraparesis. Rifampin, isoniazid, pyrazinamide, ethambutol, and corticosteroids were started for possible TM. Repeat head CT showed cerebral edema. HIV testing was negative on hospital day 4. Brain MRI obtained after 1 week of treatment for TM showed marked sulcal CSF abnormalities and multiple bilateral small infarcts due to meningeal exudate. Despite the initiation of anti-TB medications, the patient remained comatose, responding only to painful stimuli since her initial neurologic decline. Repeat lumbar puncture on day 14 showed 250 cells/mm<sup>3</sup> with a neutrophilic predominance (83%), protein 221 mg/dL, and glucose 41 mg/dL. On the 20th hospital day, the diagnosis of TM was confirmed when AFB were isolated from the CSF culture. Sixty-three days after treatment, repeat brain MRI showed enhancing nodular lesions consistent with tuberculomas on T1 postgadolinium images in the left frontal lobe, anterior interhemispheric fissure, and along the margin of the left cerebral peduncle.

**DISCUSSION** The therapeutic paradox refers to a shift in cellular predominance in the CSF after starting empiric treatment for TM.<sup>1</sup> The prevalence of this phenomenon is difficult to interpret as many cases of TM are based on clinical suspicion and only a minority have microbiologic confirmation. One author reviewed 61 cases of TM; 23 patients had a confirmed diagnosis, and 20 patients had repeat lumbar punctures that demonstrated a shift from a lymphocytic predominant pleocytosis to a neutrophilic predominance.<sup>2</sup> The authors did not specify which of those confirmed cases demonstrated this shift. One patient described by another author in addition to our case demonstrated the shift in cellular predominance in the CSF in a confirmed case of TM.<sup>1</sup>

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The exact mechanism for the therapeutic paradox is unknown but thought to be a hypersensitivity reaction to tuberculoproteins in the subarachnoid space.<sup>3</sup> In a recent study, CSF samples along with peripheral venous blood samples on day 0, 14, and 28 were obtained and there was an increased TB-specific  $\gamma$ -interferon-producing T-cell response after therapy for TM was started. The switch in cellular predominance in the CSF preceded the changes observed in peripheral blood.<sup>3</sup>

Prior authors have proposed that the therapeutic paradox may be pathognomonic of TM<sup>2</sup>; however, better data are needed. Documentation of the CSF findings on all successive lumbar punctures to quantify the prevalence of the switch in cellular predominance may determine the specificity of this phenomenon in the diagnosis of TM. The timing of repeat lumbar puncture during the clinical course of TM should be clarified. Finally, a paradoxical TB immune reconstitution inflammatory syndrome exists in patients with TB who are taking anti-TB medications with new symptoms developing after initiation of antiretroviral therapy for HIV.<sup>4,5</sup>

#### AUTHOR CONTRIBUTIONS

Dr. Ramesh: study concept, analysis, literature review, and initial draft of paper. Dr. Hagler: acquisition of data for literature search, critical revision

of manuscript for intellectual content. Dr. Beal: critical revision of manuscript for intellectual content. Dr. Moshé: critical revision of manuscript for intellectual content and clarity.

#### STUDY FUNDING

No targeted funding reported.

#### DISCLOSURE

A. Ramesh, S. Hagler, and J. Beal report no disclosures relevant to the manuscript. S. Moshé received grants from NINDS (NS-20253, NS-43209, NS-45911, NS-78333), Department of Defense, CURE, the Heffer Family and Segal Family Foundations, and consultancy honorarium from Lundbeck and UCB Pharma. Go to [Neurology.org](http://Neurology.org) for full disclosures.

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*Neurology* 2014;83:e145-e146

DOI 10.1212/WNL.0000000000000859

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