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The validity of cerebrospinal fluid parameters for the diagnosis of tuberculous meningitis☆

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SUMMARY

Objectives: To assess the diagnostic validity of laboratory cerebrospinal fluid (CSF) parameters for discriminating between tuberculous meningitis (TBM) and other causes of meningeal syndrome in high tuberculosis incidence settings.
Methods: From November 2009 to November 2011, we included patients with a clinical suspicion of meningitis attending two hospitals in Lima, Peru. Using a composite reference standard, we classified them as definite TBM, probable TBM, and non-TBM cases. We assessed the validity of four CSF parameters, in isolation and in different combinations, for diagnosing TBM: adenosine deaminase activity (ADA), protein level, glucose level, and lymphocytic pleocytosis.
Results: One hundred and fifty-seven patients were included; 59 had a final diagnosis of TBM (18 confirmed and 41 probable). ADA was the best performing parameter. It attained a specificity of 95%, a positive likelihood ratio of 10.7, and an area under the receiver operating characteristics curve of 82.1%, but had a low sensitivity (55%). None of the combinations of CSF parameters achieved a fair performance for 'ruling out' TBM.
Conclusions: Finding CSF ADA greater than 6 U/l in patients with a meningeal syndrome strongly supports a diagnosis of TBM and permits the commencement of anti-tuberculous treatment.
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1. Introduction

The diagnosis of tuberculous meningitis (TBM) continues to be a clinical challenge, even after the introduction of molecular tests.[1] The physiopathology of this condition, in which disproportionate inflammatory phenomena rather than numbers of circulating bacteria play a role, hinders bacteriological diagnosis, and the available microbiological tests fail to attain the accuracy standards required.[2]

As a result, most guidelines for the diagnosis and management of TBM agree on the use of simple cerebrospinal fluid (CSF) analyses, such as determining glucose and protein levels and the number and formula of leukocytes, to guide decision-making.[3,4] Computed tomography (CT) scans and magnetic resonance imaging (MRI)[5] and other biochemical analyses of CSF, in particular adenosine deaminase activity (ADA),[6,7] have also been advocated. Peruvian guidelines recommend the use of changes in protein, glucose, chloride, and ADA levels and the presence of lymphocytic pleocytosis in CSF as key elements for guiding the diagnosis of TBM.[8] However, evidence on the utility of these tests for decision-making in the first hours after admission, when appropriate initiation of anti-tuberculous treatment can prevent disability and mortality, is quite limited.[9] The few studies that have addressed the predictive value of these tests or their combinations have primarily focused on differentiating between TBM and acute bacterial meningitis.[10–12]

The objective of this study was to evaluate the validity of these laboratory tests in CSF, in isolation or in combination, for the diagnosis of TBM in patients with a clinical suspicion of meningitis.

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2. Materials and methods

2.1. Setting

The study was performed in Lima, Peru. Peru is a country with a high incidence of tuberculosis (101/10[5]) and a concentrated HIV epidemic.[13] Adult cases with a clinical suspicion of meningitis are routinely referred to third-level hospitals where they undergo a lumbar puncture. The most frequent causative agents in this context are considered to be *Mycobacterium tuberculosis*, *Cryptococcus neoformans*, common bacteria, and enteroviruses.[14]

2.2. Diagnostic parameters evaluated

The diagnostic parameters in CSF considered in the Peruvian national guidelines were evaluated at their respective cut-off points: elevated proteins (>50 mg/dl), decreased glucose (<50 mg/dl), decreased chloride (<100 mg/dl), lymphocytic pleocytosis (CSF white cell count of >10 cells/mm^3, with lymphocyte predominance >50%), and elevated ADA level (>6 U/l). The chloride level was not included in this study as it is neither routinely performed nor readily available at referral hospitals.

2.3. Patient recruitment and procedures

The sample size needed was 139, considering an overall accuracy of the best combination of predictors of 90% and a precision of 5%. All patients older than 18 years with a clinical suspicion of meningitis, hospitalized in one of two third-level hospitals (Hipolito Unanue and Cayetano Heredia) from November 2009 to November 2011 were invited to participate in the study. A clinical suspicion of meningitis was defined as having any combination of the following symptoms: headache, irritability, vomiting, fever, neck stiffness, convulsions, focal neurologic deficit, and altered consciousness or lethargy, with no other general medical condition explaining them. Patients already receiving specific treatment were excluded (for instance patients with cryptococcal meningitis attending with recurrence of their symptoms, patients already being treated for pulmonary tuberculosis who had developed neurologic symptoms, etc.).

All included patients underwent a lumbar puncture using standard procedures. CSF samples were sent within 1 h to the laboratory to perform microbiological (acid-fast bacillus stain (AFB), culture for mycobacteria in Ogawa medium, Gram stain, culture for common bacteria, cryptococcal antigen agglutination test), molecular (PCR for *Mycobacterium tuberculosis*; IS6110 PCR, Qiagen Multiplex PCR),[15] cytological (total white cell count and determination of the percentage of lymphocytes), and biochemical (glucose, protein, ADA) analyses. According to the clinical findings, the attending physicians requested further tests/procedures (biopsy or culture of other body fluids, lymph node aspiration, etc.).

2.4. Definition of TBM

Our reference standard for the diagnosis of TBM contemplated two categories: 'definite' TBM and 'probable' TBM. All cases were assigned to one of these categories by a data analyst who was blinded to the results of the evaluated CSF parameters. Definite TBM was defined as the presence of AFB in CSF smears, or positive CSF culture for *M. tuberculosis*, or positive CSF PCR test.[7] Probable TBM was defined as a clinical suspicion of meningitis (as described above), with negative Gram stain and cultures for bacteria, negative cryptococcal latex agglutination test and cultures for fungi, and at least one of the following: (1) bacteriological evidence of tuberculosis in other organs (positive culture for *M. tuberculosis* in other body fluids or tissues or biopsies, with histopathological findings of caseous necrosis or granulomas); (2) good response to anti-tuberculous therapy, defined as complete resolution of the constitutional signs at 1 month after treatment initiation. For patients not completing 1 month of follow-up due to death, an expert panel defined whether the case was probable TBM or not.

TBM was defined as definite or probable TBM. All other patients were classified as non-TB, and a diagnosis was reached according to each etiology, for instance: bacterial and fungal meningitis were microbiologically confirmed by cultures or presence of antigen; viral meningitis was defined as a compatible clinical presentation, an abnormal CSF, and complete resolution of symptoms without antibiotic, antifungal, or anti-tuberculous treatment, or a positive PCR for viruses in CSF; metabolic conditions were diagnosed on the basis of laboratory blood tests, etc.

2.5. Analysis

Patients found to have more than one diagnosis (for example tuberculous and bacterial meningitis, or tuberculous and fungal meningitis) were excluded from the analysis. Differences between TBM patients and non-TBM patients with regard to the CSF parameters were compared using their actual values and dichotomized according to the cut-off points suggested in the Peruvian guidelines. To test for significance, we used the Mann–Whitney test and Chi-square test for numerical and categorical variables, respectively. We calculated areas under the receiver operating characteristic (ROC) curve for each parameter, and sensitivity, specificity, and positive and negative likelihood ratios at the suggested cut-off levels. Ninety-five percent confidence intervals (95% CI) were constructed for all estimates. A positive likelihood ratio of ≥10 and a negative likelihood ratio of ≤0.10 were considered to provide convincing evidence in favor or against the diagnosis of TBM, respectively.[16] As a second step, the diagnostic accuracy of all possible combinations of two, three, or four parameters were evaluated, as well as having one, two, three, or four positive parameters present. All statistical analyses were performed with STATA version 11.0 (Stata Corp., College Station, TX, USA).

2.6. Ethical aspects

All included patients, or a direct relative for those with altered consciousness, gave informed consent to participate in the study. The ethics committees of the Universidad Peruana Cayetano Heredia, both participating hospitals, and the Institute of Tropical Medicine, Antwerp, approved the study.

3. Results

One hundred and fifty-seven patients fulfilled the inclusion criteria and agreed to participate in the study. Two patients were excluded from the analysis given co-infection with two pathogens (they had HIV/AIDS, TBM confirmed by a positive PCR in CSF, and meningeal cryptococcosis confirmed by a positive culture). The median age of the 155 patients constituting the study group was 35 years (interquartile range 26–54 years) and 109 (70.3%) were male. Fifty-nine (38.1%) had a diagnosis of TBM. Eighteen (30.5%) were definite TBM and 41 (69.5%) were probable TBM. Of the latter, nine had *M. tuberculosis* isolated in specimens from another body site, 28 had a good response to tuberculosis treatment, and four died before the 1 month of treatment follow-up but were identified as TBM by the expert panel. The most frequent diagnoses in non-TBM cases (n = 96) were viral meningitis in 19 (19.7%), cryptococcal meningitis in 12 (12.5%), liver and other metabolic encephalopathies in eight (8.3%), bacterial meningitis in six (6.3%), and other causes of meningeal syndrome (meningeal carcinomatosis, sepsis

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