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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.

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

of other origin, toxoplasmic encephalitis, subarachnoid hemorrhage, epilepsy) in 51 (53.1%) patients. HIV infection was present in 22 (38%) of the patients in the TBM group and 33 (34%) of the patients in the non-TBM group.

Figure 1 shows the distribution of the three investigated diagnostic parameters, which were continuous variables: ADA, protein level, and glucose level in TBM (probable and definite) and non-TBM patients. All of them differed significantly between the TBM and non-TBM groups at a level of $p < 0.001$. Although a comparison between definite and probable TBM was not an objective of the study (and power was limited for a comparison between the subgroups), there were no significant differences between the two groups except in the glucose level (median of 32.5 mg/dl in the definite TBM group vs. 44 mg/dl in the probable TBM group).

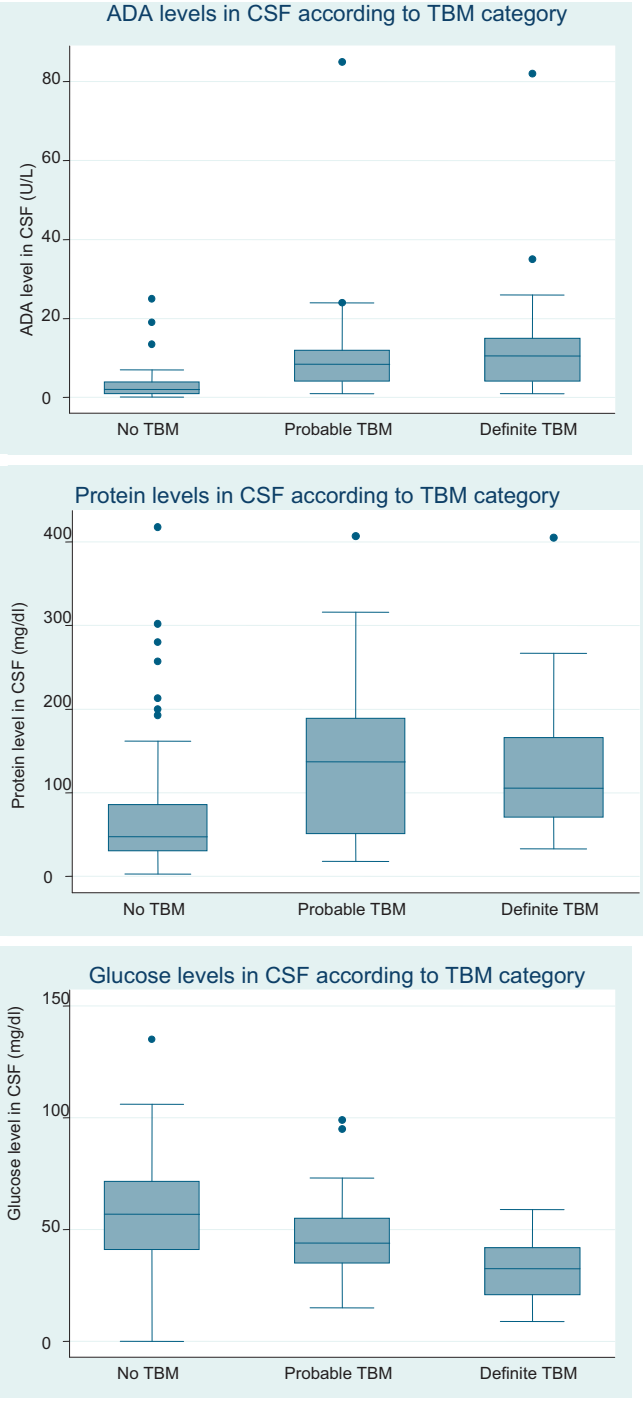

Figure 1. Distribution of diagnostic parameters among TBM (confirmed and probable) and non-TBM patients.

The diagnostic performance of the evaluated parameters for the diagnosis of TBM is shown in Table 1. ADA was the parameter that in isolation performed the best, followed by protein level (area under the ROC curve 82.1% and 75.5%, respectively). Protein level was the most sensitive test, while ADA was the most specific one. The latter attained a positive likelihood ratio of 10.7. Noteworthy, four out of the 34 (12%) patients who did not fulfill any of the four criteria had a final diagnosis of TBM.

When the 41 probable TBM cases were excluded from analysis, this did not affect the diagnostic accuracy estimates for ADA: it had a sensitivity of 55.6%, a specificity of 94.9%, a positive likelihood ratio of 10.9, and a negative likelihood ratio of 0.5.

Although the study was underpowered for comparisons between subgroups, we analyzed the performance of the four parameters according to the HIV status of the patients. Glucose levels and lymphocytic pleocytosis performed less well in HIV patients, with a significantly decreased area under the ROC curve. However, ADA and protein levels did not have a significantly decreased area under the ROC curve (85% vs. 76% for ADA in HIV-negative and HIV-positive patients, respectively).

We evaluated the performance of all possible combinations of the CSF parameters. We considered as patients fulfilling a combination, those who tested positive for at least one of the parameters included in it, and as patients not fulfilling it, those testing negative for all the parameters included in the combination. Table 2 shows the results of the best performing combinations in terms of positive and negative likelihood ratios. None of the combinations attained our definition of fair evidence of the presence or absence of TBM. We also assessed the performance of combinations defined as having at least three positive parameters (any of them) and of having all four parameters positive. The sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio were 64%, 82%, 7.66, and 0.4, respectively, for having at least three positive parameters, and 32%, 100%, 61, and 0.7, respectively, for having all four parameters positive. Nineteen patients (32.2% of TBM patients) belonged to this last category.

4. Discussion

Our most relevant finding was that out of the four evaluated CSF parameters, the best performing one for 'ruling in' TBM was ADA, with a specificity of 95% at a cut-off point of >6 U/l. However, its sensitivity was low (55%). No combinations of the parameters reached the accepted standard for 'ruling out' TBM (a negative likelihood ratio of ≤0.10).

A limitation of our study is that only 30% of our TBM cases were bacteriologically confirmed. However, this proportion lies in the expected range according to the literature.[17] Our definition of 'probable' TBM discarded patients with other likely diagnoses, but the response to anti-tuberculous therapy (and expert consensus for patients under therapy dying before 1 month of follow-up), could be judged as suboptimal evidence for TBM diagnosis. This is mainly because conditions such as viral meningitis could mimic a good response to TB therapy. However, this would not change our main conclusion concerning the high specificity of ADA: viral meningitis does not usually elevate ADA levels,[18,19] and if we had classified patients with viral meningitis as TBM, we would have underestimated its specificity for TBM. Furthermore, it is worth highlighting that, despite our study being underpowered for a subgroup analysis, we found no differences between the 'confirmed' and the 'probable' TBM subgroups except in the glucose level. Finally, the study was performed in Peru, a country with a low HIV prevalence, a high tuberculosis incidence, and decreasing

Table 1
Diagnostic accuracy of the cerebrospinal fluid parameters for the diagnosis of tuberculous meningitis

CSF parameter	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	Area under the ROC curve (95% CI)
ADA >6 U/l	55.9% (43.3–67.9%)	94.8% (88.4–97.8%)	10.7 (4.4–26.0)	0.5 (0.4–0.6)	82.1% (75.0–87.6%)
Lymphocytic pleocytosis[a]	62.7% (50.0–73.9%)	77.1% (67.7–84.4%)	2.74 (1.8–4.2)	0.5 (0.3–0.7)	54.6% (42.8–65.7%)
Protein level >45 mg/dl	81.4% (70.0–89.3%)	53.1% (43.2–62.8%)	1.74 (1.4–2.2)	0.4 (0.2–0.6)	75.5% (67.9–82.0%)
Glucose level ≤50 mg/dl	69.5% (56.9–79.8%)	63.5% (53.6–72.5%)	1.91 (1.4–2.6)	0.5 (0.3–0.7)	70.5% (62.5–77.4%)

CSF, cerebrospinal fluid; CI, confidence interval; ROC, receiver operating characteristics; ADA, adenosine deaminase activity.
[a] Defined as >10 cells/mm^3 and ≥50% lymphocytes.

Table 2
Diagnostic accuracy of the combinations of cerebrospinal fluid parameters for the diagnosis of tuberculous meningitis

Combination of CSF laboratory parameters (tests)	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	Area under the ROC curve (95% CI)
Combination of two parameters					
ADA >6 U/l or lymphocytic pleocytosis	81.4% (69.6–89.3%)	71.9% (62.2–79.9%)	2.9 (2.1–4.1)	0.3 (0.2–0.5)	75.1% (67.2–81.5%)
Lymphocytic pleocytosis or protein >45 mg/dl	89.8% (80.0–95.3%)	45.8% 36.2–55.8%)	1.7 (1.4–2.0)	0.2 (0.1–0.5)	69.2% (61.1–76.2%)
Combinations of three parameters					
ADA >6 U/l or lymphocytic pleocytosis or glucose 50 mg/dl	89.8% (79.5–95.3%)	50.0% 40.2–59.8%)	1.8 (1.4–2.2)	0.2 (0.1–0.5)	70.1% (63.1–78.0%)
Combination of four parameters					
ADA >6 U/l or lymphocytic pleocytosis or protein >45 mg/dl or glucose 50 mg/dl	93.2% (83.8–97.3%)	31.3% 22.9–41.1%)	1.4 (1.2–1.6)	0.2 (0.1–0.6)	66.8% (59.1–74.4%)

CSF, cerebrospinal fluid; CI, confidence interval; ROC, receiver operating characteristics; ADA, adenosine deaminase activity.

morbidity due to bacterial and fungal meningitides. Our results may not be generalizable beyond settings with comparable characteristics.

The study has an important strength: the wider clinical spectrum of patients included in comparison to previously published works. Other studies have focused on distinguishing TBM from specific meningitides, generally acute bacterial meningitis,[11,12] excluding patients with uncertain diagnoses. The latter are precisely the ones that could benefit from the use of clinical tools.[20] Our study makes an attempt to capture the real diagnostic challenge in clinical practice, where TBM is suspected in a wide array of clinical presentations and clinicians have to make quick decisions concerning treatment. Additionally, although TBM is a condition with decreasing prevalence, we managed to include a fair number of patients, which gave us power for statistical comparisons.

Our main finding, the utility of ADA for the diagnosis of TBM, has been the subject of debate for many years, and there are two meta-analyses published on the subject. Tuon et al.[21] found results similar to ours: a specificity of 96% and a sensitivity of 59% for ADA values higher than 8U/l. Xu et al.[22] reported a sensitivity of 79% and a specificity of 91% by pooling studies with various ADA cut-off points. Studies published after these meta-analyses have also found that the use of ADA for the diagnosis of TBM has significant clinical utility.[23,24] However, accuracy estimates vary according to the setting, the patient mix, cut-off point, and laboratory specifications.[6] In settings with a high prevalence of acute bacterial meningitis, ADA can give false-positive results, and most studies assessing clinical predictors for TBM have been conducted in such populations.[10,11] This is possibly the reason why a group of experts who have developed a definition for TBM have refrained from the use of this test.[7] Actually, Peruvian guidelines are amongst the few existing ones that explicitly advocate the determination of ADA in CSF to diagnose TBM.[8] We feel, in the light of new evidence[18] and our present findings, that the use of this test should be further evaluated. Compared to other tools such as CT scans[25] and MRI, which have a specificity up to 90%,[26] and appraisal of macroscopic CSF appearance, which as part of a score achieves a specificity of 77%,[12] ADA can make a more important contribution to the diagnosis of TBM. With a positive likelihood ratio of 10.7 and a pretest probability of 38% as in our setting, the post-test probability of having TBM becomes 87%, and thus treatment initiation should be offered. In our series, 56% of the TBM cases would have benefited from a decision made on this basis. However, the low sensitivity (55%) precludes decision-making in patients with a negative ADA test, and the addition of the other parameters evaluated only marginally increased the number of TBM patients correctly diagnosed.

In recent years, new diagnostic assays, in particular molecular techniques like GeneXpert MTB/RIF, have been developed, and these could contribute to the diagnosis of extrapulmonary forms of tuberculosis;[27–30] however their clinical utility needs further assessment. Furthermore, rolling out these tests will take time and consume considerable resources. Therefore, the use of diagnostic tools that are already implemented, cheap, and easy to perform should be optimized. Our study shows that ADA in CSF above 6 U/l in patients with a meningeal syndrome has a high positive likelihood ratio for TBM. Taking into account the specific clinical context, this should permit the decision to initiate treatment, particularly in settings like ours, with a high prevalence of TBM and low prevalence of acute bacterial meningitis. On the other hand, none of the evaluated combinations of CSF parameters allows the condition to be 'ruled out'. More research should be done on the clinical utility of including ADA alongside other simple diagnostic tests in diagnostic algorithms for TBM.

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