The experience of a tertiary care hospital in Colombia in the diagnosis of meningeal tuberculosis

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Abstract

Introduction: tuberculosis is one of the most widely disseminated infectious diseases worldwide, and meningeal tuberculosis is one of its most devastating manifestations. Its diagnosis and microbiological confirmation is not always easy.

Objective: to describe the experience in diagnosing meningeal tuberculosis through molecular tests compared to a culture, characterize the main clinical manifestations, and determine factors associated with mortality.

Methods: we retrospectively identified adult patients diagnosed with meningeal tuberculosis through molecular and/or culture tests for *M. tuberculosis* who were admitted to our institution between January 2018 and March 2020. A descriptive analysis was performed. Pregnant women and patients who did not have a molecular test for *M. tuberculosis* were excluded.

Results: a sample of 33 patients was obtained. The most relevant cerebrospinal fluid (CSF) cytochemical analysis findings were low glucose, with a median of 34.2 mg/dL (IQR 2.0-95.0 mg/dL) and high protein, with a median of 265 mg/dL (IQR 24.0-600 mg/dL). The most significant result was elevated serum C-reactive protein in all cases, with a median of 53.3 mg/L (IQR 22.9 – 89.6 mg/L) and neutrophilia in 75.8% (25). Mortality was 54.5% (18), the sensitivity of the CSF molecular test was 38.46% and the positive predictive value was 58.82%.

Conclusions: the diagnosis of meningeal TB continues to be a challenge. While molecular tests can help provide an early diagnosis, their sensitivity is low in extrapulmonary forms. **(Acta Med Colomb 2022; 47. DOI: https://doi.org/10.36104/amc.2022.2115).**

Key words: *Abbott RealTime MTB, real-time polymerase chain reaction, tuberculosis, mycobacterium tuberculosis, extrapulmonary tuberculosis, meningeal tuberculosis, HIV.*

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Introduction

Tuberculosis (TB) is one of the most widely distributed infectious diseases in the world and constitutes one of the main causes of death in patients with AIDS, especially in developing countries like ours. Worldwide, 7.1 million new cases of TB infection were reported in 2019, a progressive increase over the last few years (1). By 2018, the incidence of all types of tuberculosis in Valle del Cauca, excluding Buenaventura, was 44 cases per 100,000 inhabitants, with Cali having the third highest incidence at 51 cases per 100,000 inhabitants (44 for pulmonary TB, seven for extrapulmonary TB) (2). Regarding mortality, in Cali from 2005-2018, TB was the third cause of death in men and the fourth cause in women, with rates of 4.5 and 1.3 cases per 100,000 inhabitants (3).

The dissemination of human immunodeficiency virus (HIV) infection has contributed to exacerbating the impact of TB (4), increasing the risk of nonpulmonary forms of the disease. Extrapulmonary TB occurs as a consequence of *Mycobacterium tuberculosis* dissemination to other organs through the lymph vessels or the bloodstream. The most commonly affected areas include the meninges, pleura, skin, lymph nodes, abdomen and genitourinary tract (5). Meningeal tuberculosis (MTB) is one of the most devastating of the various extrapulmonary locations due to its high mortality and severe neurological sequelae in those who survive (5). The diagnosis of MTB continues to be a medical challenge, since none of the currently used methods meet the ideal criteria for a suitable diagnostic test, they have low sensitivity or specificity, and the results are usually delayed or hard to access (6).

Methods

This retrospective study was carried out in the Department of Internal Medicine at Universidad del Valle, at Hospital Universitario del Valle in Cali, Colombia. This hospital is a tertiary care referral center for a large part of the department's and southwestern Colombia's vulnerable population. The data were collected from the medical charts of patients diagnosed with MTB who were admitted from January 1, 2018, through March 1, 2020. Patients under the age of 18, as well as pregnant women and those who did not have a molecular cerebrospinal fluid (CSF) test were excluded. Of 39 patients with confirmed MTB, six were excluded due to incomplete data. A manual and digital data collection sheet was used which included demographic variables; the patients' past medical history, including a history of pulmonary or extrapulmonary tuberculosis, coinfection with human immunodeficiency virus or chronic noncommunicable diseases; the main signs and symptoms on admission according to the medical chart, as well as their time of onset; and laboratory data (both blood and CSF), including molecular studies and bacterial, mycobacterial and fungal cultures. An accessory sheet was established for the characteristics of the population with HIV coinfection. Finally, data on inpatient mortality were collected. A descriptive statistical analysis was carried out; continuous variables are expressed as medians and interquartile range (IQR). Categorical variables are presented as absolute and relative frequencies for each category. The diagnosis was confirmed and was based on a CSF culture or an *M. tuberculosis-positive* polymerase chain reaction *(MTB PCR)*. The cultures used in our institution are grown on Ogawa Kudoh solid media; the molecular test was performed using an *Abbott RealTime MTB RIF/INH Resistance m2000®* assay. The *Abbott RealTime MTB RIF/INH Resistance m2000® assay identifies M. tuberculosis* from insertion sequence 6110 (IS6110) and protein antigen b (Pab) in sputum or bronchoalveolar lavage samples, with a detection limit of 60 CFU/ml. It also qualitatively detects rifampicin and isoniazide resistance (7).

A history or the presence of TB required a current culture or prior notification of a culture through epidemiological reporting. The time of onset of symptoms was considered from the patient's first "complaint " up until the initial consult. The neurological status on admission was estimated using the Glasgow scale. Those with a score of 13 and 14 out of 15 possible points were considered to be mildly affected, those with 9-12 points moderately affected, and those with a Glasgow score on admission of eight or fewer points were considered to have severe impairment. The CSF findings on

Table 1. *General characteristics.*

	Women	Men	Total	P Value
Sex	7 (21.2%)	26 (78.8%)	33	-
Age	30.0 (27.5 – 49.0)	34.5 (28.3 – 39.75)	34.0 (28.0 – 42.0)	0.86
History of TB	2 (28.6%)	4 (15.45)	6 (18.2%)	0.46
Headache	3 (42.9)	17 (65.4)	20 (60.6)	0.65
Seizure	0	2 (7.06%)	2 (6.06%)	-
Drowsiness	6 (85.7%)	12 (46.1%)	18 (54.5%)	0.09
Disorientation	2 (28.5%)	13 (50%)	15 (45.5%)	0.41
Fever	3 (9.0%)	20 (60.6%)	23 (69.6%)	
Suggestive findings on brain CAT/NMR	6 (85.7%)	15 (57.6%)	21 (63.6%)	0.97
Glasgow on admission				0.64
15	4 (57.1%)	11 (42.3)	15 (45.5%)	-
13 - 14	3 (42.8%)	8 (30.7%)	11 (33.3%)	-
9 - 12	0	6 (23.0%)	6 (18.1%)	-
≤ 8	0	1 (3.84%)	1 (3.03%)	-
Time elapsed since onset of symptoms				1.0
1 - 7 days	3 (42.8%)	11 (42.3%)	14 (42.4%)	-
8 - 14 days	1 (14.2%)	3 (11.5%)	4 (12.1%)	-
15 - 30 days	2 (28.5%)	7 (26.9%)	9 (27.2%)	-
> 30 days	1 (14.2%)	5 (19.2%)	6 (18.1%)	-

admission were reviewed; elevated opening pressure was defined as >20 cm H_2O, pleocytosis >10/mm^3, elevated protein >45 mg/dL and low CSF glucose levels <40 mg/dL. The CSF ADA test was not recorded, as it is not available in the institution. Tomography and cerebral magnetic resonance brain imaging data showing findings suggestive of meningeal tuberculosis (tuberculomas, vasculitis, infarcts, meningeal enhancement, ventriculitis, ventriculomegaly or hydrocephaly) were gathered. Finally, a univariate logit model was run to detect risk factors associated with patient mortality, and a multivariate logit model was run with the variables the investigators considered to be risk factors.

Results

Thirty-three patients with meningeal tuberculosis were included, of whom 79% were men and 21% were women, with a mean age of 34 years (34.5 years in men, 30 years in women). A total of 18.2% of the cases (6) had a current or prior diagnosis of pulmonary tuberculosis. The median duration of neurological symptoms prior to admission was eight days (3-15 days); 69.6% reported a fever, 60.6% reported a headache, and only 45.5% of the cases (15) had a normal Glasgow on admission (Table 1). The CSF findings on admission were as follows: 84.8% had pleocytosis; of these, 53.5% had lymphocyte predominance on the initial lumbar puncture and 42% had a polymorphonuclear (PMN) predominance, 70% had low CSF glucose levels and 91% of the cases had high CSF protein levels, with a mean glucose level of 34.2 mg/dL (IQR 2.0-95.0 mg/dL) and mean proteins at 265 mg/dL (IQR 24.0-600 mg/dL) (Table 2). The opening pressure was elevated in 48% of the study group (16). Overall, an average of 3-4 (3.3) lumbar punctures were performed, with more performed on those with an initially elevated opening pressure. The most significant laboratory result was elevated serum C-reactive protein in almost all cases, with a median of 53.3 mg/L (IQR 22.9-89.6 mg/L)

Table 2. *General characteristics, comparison between HIV (+) and HIV (-) patients.*

	HIV + (n=20)	HIV - (n=13)	Total (n=33)	P Value
Age	35.5 (29.7-40.5)	33.0 (25.0-53.0)	35.5 (29.7-40.5)	0.65
Sex				0.39
Female	3 (15.0%)	4 (30.8%)	7 (21.2 %))	-
Male	17 (85.0%)	9 (69.2%)	26 (78.8%)	-
History of tuberculosis				0.99
Yes	4 (20%)	2 (15.3%)	6 (18.2%)	-
No	16 (80%)	11 (84.6%)	27 (81.8%)	-
Headache				1.0
Yes	12 (60%)	8 (61.5%)	20 (60.6%)	-
No	8 (40%)	5 (38.4%)	13 (39.3%)	-
Glasgow on admission				0.69
15	10 (50%)	5 (38.4%)	15 (45.5%)	-
14 to 13	6 (30%)	5 (38.4%)	11 (33.3%)	-
9 to 12	4 (20%)	2 (15.3%)	6 (18.1%)	-
≤ 8	0	1 (7.6%)	1 (3.0%)	
Suggestive lesions on CAT or NMR				0.015
Yes	13 (65%)	8 (61.5%)	21 (63.6%)	-
CSF characteristics				
Glucose (mg/dL)	35.4 (2.0-95.0)	32.3 (17.0-78.0)	34.2 (2.0-95.0)	0.36
Protein (mg/dL)	272 (24.0-600)	296 (70.0-600)	265 (24.0-600)	0.77
Lymphocytes (cells/mm^3)	78.5 (0-415)	166 (0-698)	113 (0.0-698)	0.14
PMNs (cells/mm^3)	108 (0-621)	172 (1.0-1034)	136 (0.0-1034)	0.54
Anti-TB treatment prior to LP				
Yes	0	0	0	-
No	20 (100%)	13 (100%)	33 (100%)	-
Death				1.0
Yes	11 (55%)	7 (53.8%)	18 (54.5%)	-

Table 3. *Characteristics of patients with HIV infection/AIDS.*

Time of diagnosis	
Novo	13 (65.0%)
3 months - 1 year	3 (15.0%)
1 to 5 years	2 (10.0%)
More than 5 years	2 (10.0%)
Antiretroviral treatment prior to admission	
Yes	12 (60.0%)
No	8 (40.0%)
Adherence to ART	
Yes	4 (33.3%)
No	8 (66.6%)
HIV viral load (copies/ml)	
Global (IQR)	208,500 (3,516 – 1,221,184)
Less than 50	3 (15.0%)
50 and 10,000	5 (25.0%)
10,000 – 100,000	2 (10.0%)
100,000 - 500,000	3 (15.0%)
Greater than 500,000	7 (35.0%)
CD4+ T-lymphocyte count (cells/mm^3)	
Global (IQR)	54.0 (37.0 – 119.0)
Less than 50	8 (40.0%)
50 - 100	6 (30.0%)
100 - 200	3 (15.0%)
200 - 500	3 (15.0%)

and neutrophilia in 75.7% of the cases (25). Altogether, 63.6% had findings suggestive of *M. tuberculosis infection on cerebral tomography or magnetic nuclear resonance imaging (Table 1)*.

Regarding the main association, 60.6% (20) of the patients had HIV infection. Of these, 65% had a new onset diagnosis (less than three months); 15% (3) had been diagnosed for three months to one year; 85% had a detectable viral load, with a median for the whole group of 208,500 copies/ml (IQR 3,516-1,221,184 copies/ml); 50% had more than 100,000 copies/ml, and the CD4+ T-lymphocyte count showed a median of 54.0 cells/mm^3 (IQR 37.0-119.0 cells/mm^3), with a count under 200 cells/mm^3 in 85% of the cases (n=17), with 70 and 40% having counts under 100 and 50 cells/mm^3, respectively. Only 33% of the patients for whom antiretroviral therapy (ART) was ordered adhered to treatment (Table 3). Microscopy had a sensitivity of 15.3% in serial CSF samples; in seven (21.2%) of the cases, MTB PCR was the only positive diagnostic test. A sensitivity of 38.46% was found for CSF MTB PCR, with a positive predictive value of 58.82%. The total mortality was 54.5% (18): 53.8% (7 of 13) for the group of patients without HIV infection and 55% (11 of 20) for the HIV group. (Tables 4 and 5).

A univariate logit model was run to detect risk factors

Table 4. *Culture/N-33 molecular test correlation.*

	CSF-TB-Culture		
CSF PCR-MTB	Positive	Negative	
Positive	10	7	
Negative	16	0	
Total	**26**	**7**	**33**

associated with mortality. The only significant marker found was increased ultrasensitive serum CRP. Subsequently, a multivariate logit model was run with the variables the investigators considered to be risk factors, with no statistical significance contributed for the associated variables (Table 6).

Discussion

Meningeal tuberculosis poses a diagnostic and therapeutic challenge in our daily clinical practice. The diagnostic section of the World Health Organization's (WHO) latest guidelines on tuberculosis includes the CSF Xpert MTB/RIF Ultra (*Cepheid, Sunnyvale, USA*) test as the initial test for adults with suspected tuberculous meningitis, with no other recommendations regarding other nucleic acid amplification assays, such as the *Abbott RealTime MTB RIF/INH Resistance m2000®* assay, which we used in our study as it was available in our institution and is considered to be an initial option for diagnosing pulmonary tuberculosis in respiratory samples (8). This study documented that 18.2% of the cases had a history of concomitant or prior TB when the meningeal involvement was diagnosed. It is not unusual for central nervous system (CNS) TB to occur in people treated for pulmonary TB years or even decades earlier (9). In large trials, young adults 15-30 years old have been reported as the group with the highest incidence rate (10). The mean age in our study was 34 years. In most cases, CNS infection shows nonspecific symptoms such as fever, headache, vomiting and focal neurologic signs; the persistence of these symptoms helps distinguish MTB from other diseases (11). In our study, the most common clinical manifestations were fever (69.7%), headache (60.6%) and drowsiness (54.5%). On hospital admission, 54.5% of the patients had a Glasgow <15 and 21.2% of our cases had moderate to severe neurological impairment, similar to what was reported in Sütlas et al.›s study (12). As far as the duration of the symptoms, the presentation is generally subacute; the study population described a mean of eight days (3.0-15 days) of neurological symptoms prior to admission. In a similar article in Istanbul, Andréjak C. et al. described the time between symptom onset and clinical presentation as less than one week in 7% of cases, one to three weeks in 57%, and more than three weeks in 36% (13). Lesions suggestive of MTB on imaging were identified in 63.6% of the patients, 85.7% of whom had a

Tabla 5. *Discordancia cultivo/PCR* **Table 5.** *Culture/PCR discordance for MTB.*

	Culture + / PCR MTB +	Culture + / PCR MTB -	Culture - / PCR MTB +	P Value
Number of patients	10	16	7	
History of HIV				0.65
Yes	5	11	4	-
No	5	5	3	-
History of TB				0.42
Yes	2 (20%)	4 (25%)	0	-
No	8 (80%)	12 (75%)	7 (100%)	-
Headache				0.65
Yes	5 (50%)	11(68.7%)	4 (57.1%)	-
No	5 (50%)	5 (31.2%)	3 (42.8%)	-
Glasgow on admissioin				0.26
15	4 (40%)	10 (62.5%)	1 (14.2%)	-
13 - 14	4 (40%)	3 (18.7%)	4 (57.1%)	-
9 - 12	2 (20%)	2 (12.5%)	2 (28.5%)	-
Less than/equal to 8	0	1 (6.25%)	0	-
Suggestive lesions on CAT/MR				0.40
Yes	7 (70%)	11 (68,7%)	3 (42.8%)	-
No	3 (30%)	4 (25%)	4 (57.1%)	-
CSF characteristics				
Glucose (mg/dL)	32 (17.0-59.0)	33.75 (18.0-95.0)	38.4 (2.0-78.0)	-
Lymphocytes (mm^3)	99 (0-415.0)	114 (0-698)	129 (1.0-594)	-
Protein (mg/dL)	248 (70.0-600)	307 (43-600)	167 (24.0-357)	-
PMNs (mm^3)	188.1 (4.0-621)	74 (0-360)	192 (0-1,034)	-
Anti-TB treatment prior to the LP				
Yes	0	0	0	-
No	10 (100%)	16 (100%)	7 (100%)	-

positive MTB culture. This result could be related to the greater host immune response to tuberculosis bacilli in the subarachnoid space and the basal meninges (14). The main findings were meningeal enhancement, vasculitis and hydrocephaly.

In the presented results, 60.6% of the patients had HIV coinfection, this being the main associated risk factor for developing meningeal TB. Although HIV-infected TB patients have a greater risk of meningeal involvement, HIV infection does not appear to change the manifestations, but does seem to increase mortality (15, 16).

In addition, in patients with HIV infection, unmasking immune reconstitution inflammatory syndrome (IRIS) must be considered, which may lead to the manifestation of MTB. In our population, 60% of the cases were on ART, only 33% of whom reported medication adherence.

Regarding diagnostic tests, MTB was diagnosed by culture in 78.7% of the cases, 61.5% of whom were HIV coinfected patients. This despite the low sensitivity of the Ogawa Kudoh method which could be related to the high rate of late HIV diagnosis, in an advanced stage. In an analysis of four studies of MTB in Vietnam from 2004 to 2016, which included 1,048 patients, microbiological confirmation was achieved in 70% of the cases in which there was HIV coinfection vs. 50% of the cases without coinfection (17-18). This result could be related to the fact that the cerebrospinal bacillary load in patients with tuberculous meningitis rarely exceeds 100-1,000 colonies

Table 6. *Multivariate Logit model.*

Variables	Adjusted OR (95% CI)	P Value
Age	0.99 (0.83 -1.20)	0.92
Serum CRP	1.02 (0.99 – 1.06)	0.2
Neutrophilia	0.06 (0.0 -4.54)	0.33
Fever	0.43 (0.002 – 18.5)	0.65
Glasgow on admission	5.16 (0.06 – 168.1)	0.5
Lesions on brain CAT or NMR	0.29 (0.003 – 46.5)	0.57
Glucose in CSF	0.89 (0.708 – 0.97)	0.1
HIV (+/-)	0.17 (0.00 -17.2)	0.43
Protein in CSF	1 (0.99 – 1.02)	0.41
Time elapsed since the onset of symptoms	0.99 (0.00 – 1.05)	0.99
TB culture (+/-)	2.84 (0.13 – 693.8)	0.65
PCR MTB (+/-)	0.47 (0.008 – 19.9)	0.67

per ml. Therefore, the results of diagnostic tests based on *M. tuberculosis* detection are influenced by the volume and preparation of the CSF drawn (19). In HIV coinfection, the mycobacterial count in the CSF tends to be greater than that of patients without HIV infection; this could account for the differences in diagnostic yield (19).

Simultaneously, we found a 38.46% sensitivity for CSF PCR MTB, with a positive predictive value of 58.82%, and in 21.2% of the cases it was our only confirmation method. The microscopy sensitivity was 15.3% in the serial samples. Polymerase chain reaction studies have previously reported very different sensitivities and specificities (4, 20–23, 14). Most of the studies found a low sensitivity for this test; approximately 50%, however, exceed the sensitivity of Ziehl-Neelsen staining, which has a CSF sensitivity as low as 30% (24). While there have been diagnostic advances, a single test cannot be used to rule out the disease (14).

Tuberculous meningitis mortality is as high as 55-75%, especially in those with advanced disease at the time of consult (25, 26). We documented a total mortality of 54.5% (18), as the articles generally show. Mortality was 53.8% (7 of 13) for the group of patients without HIV infection and 55% for the HIV group (11 of 20). We did not analyze the treatment strategies and start time of four-drug treatment, and therefore do not offer an analysis of the possible factors contributing to these mortality figures. Our univariate analysis to detect factors associated with mortality suggests ultrasensitive serum CRP (OR 1.02 1.01-1.04 95% CI) as a statistically significant risk factor, a result which other articles have suggested (27). The multivariate analysis did not show any statistically significant data.

Consequently, as with all forms of TB, MTB continues to be a significant health problem in our country. The diversity of clinical findings and lack of practical, fast and reliable methods for early diagnosis are the main difficulties in the initial approach. Due to their sensitivity and rapidity, molecular tests, coupled with clinical findings, other laboratory results and imaging, increase the possibility of an earlier diagnosis, compared with the gold standard which continues to be liquid medium culture. This approach favors an early start to specific treatment and decreased complications, including death.

This study's limitations include the fact that the negative culture results may be due to low test sensitivity, given the method employed. The negative results of the molecular test may be associated with the type of test performed and its low sensitivity in CSF.

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