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Original Research Article

Prior treatment with non anti-TB antibiotics, and the duration of symptoms have no effect on diagnostics of tuberculous meningitis



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ABSTRACT

Purpose: Our objective was to investigate whether diagnosis of tuberculous meningitis (TBM) with microbiological and molecular analysis was affected by prior empirical non anti tuberculosis antibiotics or by duration of symptoms before lumbar puncture.

Materials and methods: We retrospectively evaluated medical records of patients with TBM confirmed by positive culture, nucleic acid amplification techniques (NAATs) or Ehrlich–Ziehl–Neelsen staining (EZNs) from the cerebrospinal fluid (CSF) or by characteristic results of biochemical analysis of CSF combined with a typical clinical manifestation.

Results: 68 adult patients were analyzed. The isolation rates for NAATs, Lowenstein–Jensen (LJ) culture, BACTEC and EZNs were 70.6%, 69.1%, 67.6% and 26.5%, respectively. Biochemical analysis of CSF samples revealed: pleocytosis (median 224 [range 78–380] cells/mm³) with lymphocyte predominance (76 [45–90]%), elevated levels of protein (2.43 [1.50–3.84] g/l) and lactic acid (5.0 [3.9–7.2] mmol/l). Forty (65%) patients received no anti-tuberculosis antibiotic treatment before the diagnostic lumbar puncture. There were no significant differences in the microbiological and biochemical CSF analyses, between the patients who received and those who did not receive non anti-TB empirical antibiotic treatment. The median duration of symptoms before the diagnostic lumbar puncture was 24 (range 11–61) days. No significant differences in microbiological and biochemical analysis of CSF were found when comparing patients with duration of symptoms lasting above and less than the median time.

Conclusions: Neither prior non anti-TB antibiotic therapy, nor the duration of symptoms before diagnostic lumbar puncture have any effect on confirmation of TBM by microbiological and biochemical CSF analysis.

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1. Introduction

Tuberculous meningitis is a rare manifestation of tuberculosis, but the involvement of the central nervous system is associated with a high mortality rate and severe permanent neurological sequelae [1]. Tuberculous meningitis develops as a complication of a primary infection and the initial signs and symptoms, such as loss of weight, fever, vomiting, malaise and cough are non-specific. Due

to the non-specific clinical presentation, TBM might be confused with other central nervous system infections, especially bacterial meningitis, therefore empirical antibiotic therapy other than for tuberculosis is often initially administered. The progression of the disease results in the presentation of more specific neurological features, such as confusion, cranial nerve paralysis, and convulsions [2]. In this phase of the disease a lumbar puncture is performed. Examination of cerebrospinal fluid (CSF) is crucial for the diagnosis. Simple biochemical analyses of CSF, such as glucose and protein level, number and formula of leukocytes are helpful in the initial diagnosis but non-specific [3]. Microbiological confirmation of TBM is made by smear examination, culture or nucleic acid examination techniques (NAATs), but these tests have

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limitations in sensitivity, are time-consuming, or not widely affordable. Establishing a diagnosis of TBM is especially difficult in HIV-positive patients, due to a wide spectrum of potential opportunistic co-infection and interfering symptoms connected with HIV infection [4–6]. Difficulties in clinical diagnosis might result in a substantial delay in the initiation of treatment, which may have a detrimental effect on the outcome [1,7]. *Mycobacterium tuberculosis* complex bacilli might be partially sensitive to empirical antibiotics used when bacterial meningitis is suspected and the influence of such therapy on diagnostic effectiveness has not been studied. The aim of this study was therefore to investigate whether the biochemical and microbiological analysis of CSF in patients with confirmed TBM was affected by prior non anti-TB empirical therapy or by the duration of symptoms before the diagnostic lumbar puncture was performed.

2. Materials and methods

We retrospectively analyzed the medical records of adult patients admitted to the Hospital for Infectious Diseases in Warsaw between 01.01.2003 and 31.12. 2014. The initial diagnosis of TBM was based on the clinical manifestation, biochemical analysis of CSF, cerebral imaging, and evidence of tuberculosis elsewhere. All of the patients conform to the consensus case definition for TBM of Marais [8] and according to these standardized criteria were grouped as definitive, probable and possible cases. The suspicion of TBM was confirmed microbiologically by Ehrlich–Ziehl–Neelsen staining (EZNs), culture or NAATs. Each CSF sample was examined by microscopy with EZNs, cultured on conventional Lowenstein Jensen medium and in liquid mycobacterial growth indicator tubes for automated culture systems (BACTEC). CSF polymerase chain reaction was performed in every case, using MTD (*Mycobacterium tuberculosis* Direct Test, Gen-probe INC) or GeneXpert MTB/RIF assay. Cases with microbiological identification made from CSF were classified as definitive. Cases without microbiological confirmation were classified as probable and possible according to the criteria of Marais. The microbiological and biochemical CSF analysis results of patients with definitive TBM who received non anti-TB empirical antibiotic treatment were compared to the results of those patients with definitive TBM who had not received any empirical treatment. The non anti-TB empirical therapy was defined as the administration of at least one dose of antibiotic used in the empirical treatment of patients with suspected bacterial infection. We also divided the patients with definitive TBM into two groups according to the duration of symptoms before the lumbar puncture: one group with symptoms lasting more than the median time (24 days) and one group with symptoms lasting less than the median time. The CSF analysis results of these two groups were then compared. The patients who were treated for tuberculosis (empirically or for pulmonary tuberculosis) prior to the lumbar puncture were excluded from both of these comparisons. In statistical analyses the *U* Mann Whitney test was used to compare continuous variables and the chi-square test was used to evaluate nominal variables. A *p* value of <0.05 was considered significant. All statistical analyses were performed using Stat Soft STATISTICA.

3. Results

Sixty eight patients with a mean age of 52.2 ± 16.4 years met the TBM diagnostic criteria of Marais. In 55 (80.9%) cases definitive diagnosis of TBM was confirmed microbiologically. The remaining 13 patients were defined as possible (6 cases) and probable (7 cases). Ten patients (14.7%) treated for tuberculosis prior to the lumbar puncture were excluded from the analysis of the effects of prior non anti-TB empirical antibiotic therapy and duration of

symptoms on microbiological and biochemical CSF examination. Sixty two patients (91.3%) were Polish; the remaining 6 patients (8.7%) were immigrants: three from Vietnam, one from Sri Lanka, Ukraine and Georgia. Forty seven (69.1%) patients had pre-existing diseases and conditions including: HIV infection (7), immunosuppressive therapy (7), alcoholism (17), malignancy (4), diabetes mellitus (9), cirrhosis (1). The median values of all the CSF analyses were as follows: median leukocyte count was 224 (78–380) cells/mm³, median lymphocyte percentage was 76% (45–90), median glucose level 1.66 (0.98–2.66) mmol/l, median protein content 2.43 (1.50–3.84) g/l, median lactic acid level 5.0 (3.9–7.2) mmol/l, median chloride 113 (105–117) mmol/l. The effect of prior non anti-TB empirical antibiotic therapy and the duration of TBM symptoms before the lumbar puncture on the microbiological and biochemical CSF analysis results was analyzed in the group of patients (50 cases, 73.5%) with definitive TBM who had not received anti-TB treatment. Thirty five (70%) of these patients received prior non anti-TB empirical antibiotic therapy with a median duration of 2.50 (range 0.5–11.5) days. The non anti-TB antibiotics which were administered included: ceftriaxone (23 cases), penicillin (13 cases), metronidazole (11 cases), ampicillin (10 cases), amikacin (8 cases), amoxicillin clavulanate (8 cases), vancomycin (5 cases), cefotaxime (5 cases), ciprofloxacin (4 cases), cefuroxime (2 cases), cefepime (2 cases), meropenem (2 cases), cloxacillin (2 cases), gentamicin (2 cases), imipenem (1 case), doxycycline (1 case). The median time between the onset of clinical symptoms and the diagnostic lumbar puncture was 24 (range 11–61) days. There were no significant differences in the statistical analysis of the CSF biochemical markers, pleocytosis and lymphocyte percentage, when comparing the patients with definitive TBM who had received prior non anti-TB empirical antibiotic therapy to those who had not received any such treatment (Table 1). The CSF microbiological results did not differ significantly between these two groups of patients either (Table 2). We also compared the patients with definitive TBM who had symptoms before their lumbar puncture lasting longer than the median time to those who had symptoms lasting less than the median time. CSF pleocytosis, lymphocyte percentage and biochemical results did not differ significantly between these two groups (Table 1), nor did the CSF microbiological results (Table 2).

Table 1

Comparison of biochemical and cytological CSF analysis in patients with definitive TBM.

CSF	Antibiotics +	Antibiotics –	<i>p</i> value
Leukocyte cells (mm ³)	264 (101–380)	279 (88–573)	0.74
Lymphocytes (%)	69.5 (38.5–91)	80 (55–91)	0.76
Glucose (mmol/l)	1.66 (0.98–2.70)	1.87 (0.65–3.23)	0.97
Protein (g/l)	2.4 (1.5–4.0)	1.8 (0.9–3.0)	0.28
Lactic acid (mmol/l)	6.1 (4.4–7.2)	5.1 (4.4–10.5)	0.97
Chloride (mmol/l)	114.5 (105–120)	110.5 (107–116.0)	0.48

CSF	Duration <24 days	Duration ≥24 days	<i>p</i> value
Leukocyte cells (mm ³)	260 (101–478)	313 (101–380)	0.92
Lymphocytes (%)	72.0 (32–92)	73.5 (48–90)	0.65
Glucose (mmol/l)	1.43 (0.66–2.69)	1.80 (0.98–3.28)	0.32
Protein (g/l)	2.50 (1.60–3.85)	1.68 (1.37–3.10)	0.35
Lactic acid (mmol/l)	6.2 (4.4–7.7)	5.7 (4.2–8.7)	0.81
Chloride (mmol/l)	112.5 (103–116.5)	115 (105–120)	0.29

Median values and the interquartile range are presented. Antibiotics: patients who received (+) or did not receive (–) antibiotic therapy other than for tuberculosis before lumbar puncture. Duration <24: duration of symptoms shorter than 24 days. Duration ≥24: duration of symptoms no shorter than 24 days.

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