Analysis of Tuberculous Meningitis in Albacete (Spain)

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Abstract

Introduction: TBM is the most severe manifestation of extrapulmonary TB with a high mortality rate and high rate of secondary results among survivors. Cerebrovascular complications of TBM are common, and this may represent its most serious legacy.

Objectives: The aim our study is to analyze the epidemiologic, clinic and laboratory features of patients with TBM in a regional hospital in Albacete (Spain). It is a retrospective study of TBM cases which were admitted to the General University Hospital Albacete, from 1991 to 2010.

Results: 29 patients were diagnosed with TBM. The average age of the patients was 36.2 years of which 18 (62.1%) were males, 22 (75.9%) were adults, and 2 (6.9%) were non-nationals. Among the total patients, 4 patients were HIV-infected (13.8%). The most common clinical presentations were fever (79.3%) and headache (48.3%). CSF examinations showed increased protein and ADA levels, low glucose levels and lymphocytic pleocytosis in most cases. Corticosteroids were administrated to 75.9% of the patients. There were cases of brain stroke in 10 patients (34.5%). Other complications encountered were syndrome of inappropriate ADH secretion (SIADH) (41.4%) and hydrocephalus (13.8). Neurological sequelae were observed in 31% of the patients, and 3 patients (10.3%) died.

Discussion: In our case study, lower mortality rates were observed than in other studies probably due to the adequate use of corticosteroids, early treatment and the lower rate of HIV-patients, whereas the percentage of cases with fever, SIADH, meningeal signs and brain strokes were similar as observed in other case studies.

Conclusions: TBM is still a diagnostic problem. A high index of suspicion is required in order to make an early diagnosis and treatment.

ABBREVIATIONS

CSF: Cerebrospinal Fluid; CT: Computerized Tomography; HIV: Human Immunodeficiency Virus; MRI: Magnetic Resonance Imaging; MRD: Medical Records Department; PCR: Polymerase Chain Reaction; TB: Tuberculosis; TBM: Tuberculous Meningitis

INTRODUCTION

Tuberculous meningitis is the leptomeninges inflammation caused by Mycobacterium tuberculosis, and accounts for approximately 1% of all cases of tuberculosis [1] and approximately 6% of all extrapulmonary tuberculosis forms in immunocompetent patients [2]. Tuberculous meningitis is the most severe manifestation of extra-pulmonary tuberculosis with a high mortality rate and a high rate of sequelae among survivors. Cerebrovascular complications are common, and may represent its most serious legacy [3]. Other possible complications are syndrome of inappropriate ADH secretion, hydrocephalus, neurologic sequelae and death. The clinical spectrum is broad and non-specific and early diagnosis can be difficult.

The aim our study is to analyze the epidemiologic, clinical and laboratory features of patients with TBM in a regional hospital in Albacete (Spain).

MATERIALS AND METHODS

This study consisted of a retrospective analysis of all TBM cases which were admitted to the General University Hospital of Albacete, from 1991 to 2010. Albacete is a province of 400,000 inhabitants situated in the south-east of Castilla-La Mancha, Spain. The ethnic background of almost all the population in Albacete is Caucasian.

Cases of TBM were recovered with the help of the electronic databases of the Medical Records Department (MRD). The databases include all admissions, classified in accordance with the Spanish version of The International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM).

The following groups of variables were assessed: sociodemographic data, medical histories, clinical presentations, imaging study results, analyses, cerebrospinal fluid (CSF) microbiology, treatment, and the outcome of these cases. A case was considered confirmed if Mycobacterium tuberculosis was isolated in the CSF or if nucleic acid of M. tuberculosis was detected in the CSF. A case was considered as probable if the clinical profile of TBM, with CSF laboratory compatible with TBM, and a clinical response to anti-tuberculous treatment. Statistical analysis was performed with the SPSS® software package version 15. A descriptive study was performed of the results obtained for the different variables. For the univariate analyses the chi-square test or Fisher’s exact test for discrete variables were performed, and the Mann-Whitney U for continuous variables. The statistical significance was determined using an alpha level of 0.05. We compared our results with other series [2,4-6].

RESULTS

29 patients were diagnosed to TBM. They were in the hospital an average of 49.3 days (range 4-330). The average duration of symptoms prior to admission was 14.85 days (SD ± 19.9) (range 0-90).

Sociodemographic data

The average age of patients was 36.2 years (SD ± 23.3; range 1-76), 18 cases (62.1%) were males, 22 (75.9%) were adults. 27 patients were from Spain and 2 (6.9%) were foreign born.

Patients’ medical antecedents

Among the total 4 patients were HIV-infected (13.8%), the CD4 average was 254 (range 103-542). Other relevant pathologies were hepatitis C virus (HCV) 3 patients (10.3%), hepatitis B virus (HBV) 1 patient (3.4%), diabetes mellitus 2 patients (6.9%), chronic obstructive pulmonary disease (COPD) 1 patient (3.4%) and Crohn’s disease 1 patient (3.4%). The Principal risk factors for TBM were TB contact in 3 cases (10.3%), previous TB in 3 patients (10.3%), hematologic diseases 1 patient (3.4%) and pharmacological immunosuppression in 2 cases (6.8%).

Clinical presentation of TBM

Most common clinical symptoms were fever in 23 patients (79.3%), headaches in 14 (48.3%), vomiting in 6 (20.7%) and constitutional syndrome in 3 patients (10.3%). Meningeal signs were present in 18 cases (62.1%), and focal neurological symptoms in 16 cases (55.2%).

Other TB forms observed were, pulmonary in 9 patients (31%), renal in 2 (6.8%), lymph node in 2 (6.8%), miliary in 1 (3.4%), and osteoarticular as vertebral osteomyelitis in 1 patient (3.4%).

Neurological signs upon admission was observed in 16 patients (55.2%): right hemiparesis in 4 cases (13.6%), cranial nerve palsies (III, VI and VII) in 5 (17%), seizures in 1 (3.4%), myelitis in 1 (3.4%), cerebellar syndrome in 1 (3.4%), dysarthria in 1 (3%), right hemiparesis in 4 (13.6%), behavioral changes in 3 (10.2%), and alterations in consciousness in 5 cases (17%).

Diagnostic

CSF results: A lumbar puncture was performed and the CSF was examined microscopically for total and differential leukocyte counts, chemically for glucose and protein content, and bacteriologically by Ziehl-Neelsen acid fast staining and culturing on Lowenstein Jensen average. CSF examinations showed increased protein and ADA levels, low glucose level and lymphocyte pleocytosis in most cases. Proteins: average 2 g/L (range 0.1-5.3); mononuclear: average 80.3% (range 5-98); glucose: average 32.1 mg/dL (range 3-96); ADA: average 11.2 U/L (range 1-34); Ziehl-Neelsen acid fast stain was positive in only 3 patients (10.3%), culture grew M. tuberculosis in 6 cases (20.7%) and nucleic acid test using polymerase chain reaction (PCR) was performed in 6 patients, and was positive in 1 (16.7%) of them (Table 1).

Imaging studies: Chest radiographs was performed on all patients. The study results were normal in 17 patients (58.6%), pulmonary TB in 9 cases (31%) and residual pulmonary TB in 1 (3.4%). Computerized tomography (CT) scans of the head were normal in 12 patients (41.4%). Brain ischaemic lesions were observed in 10 patients (34.5%), in 8 (80%) of them in basal ganglia area, in brainstem in 3 (33.3%), and cortical in 2 patients (20%). Obstructive hydrocephalus was observed in 9 patients (31.3%), tuberculomas in 2 patients (6.8%), localized in cerebellum, cortical area and basal ganglia area, and meningeal uptake in 1 (3.4%). Magnetic resonance imaging (MRI) of the head was performed on 17 patients. The results were normal in 3 cases (10.3%), showed brain strokes in 5 (13.8%), tuberculomas in 2 (6.8%), and meningeal uptake in 7 (24.1%).

Purified protein derivative (5 units) was applied to all patients, and was positive in 6 cases (20.7%) Other explorations that were altered were eye fundus in 6 patients (20.7%) and electroencephalogram in 8 cases (27.5%).

Treatment and outcome: The most common treatment was isoniazid (H), rifampin (R), pyrazinamide (Z) and ethambutol (E) that were administrated to 21 patients (72.4%), the average treatment duration was 11 months (range 6-15). Corticosteroids (dexamethasone 12 to 16 mg/day for adults) were administrated to 22 patients (75.9%) over an average period of 4.6 weeks (1-9). The average period between admission and initiating treatment in days was 7.4 (range 0-96).The treatment consisted of HRZE in 21 cases (72.4%), HRZ in 5 cases (17.2%), HRE in 1 case (3.4%), HRZ and streptomycin in 2 cases (6.9%). The average duration of the treatment was 11 months (6-15).

Complications

15 patients (51.7%) had complications: syndrome of inappropriate ADH secretion (SIADH) in 12 patients (41.4%), hydrocephalus in 9 (31.3%), hepatotoxicity in 4 cases (13.8%), immune reconstitution syndrome in 3 (10.3%), brain stroke in 10 (34.5%), epileptic seizure in 1 case (3.4%), and admission to intensive care unit was necessary in 6 of them (20.7%). No relevant differences were found between patients with...
complications and patients without complications in regards to the starting of anti-biotic treatment (19.3 vs 13.7 days; p = 0.77) or corticoids (12.5 vs 10.3 days; p = 0.36), and symptoms duration (13.7 vs 13.2 days, p = 0.88)

Neurologic sequelae were observed in 9 patients (31%): hemiparesia in 2 cases (6.8%), cranial nerve palsies in 4 (13.8%) and others in 3 cases (10.1%). No relevant differences were found between patients with neurologic sequelae and patients without sequelae in regards to the administrating of corticosteroids (47.4 vs 52.6 Fisher p >0.05)

3 patients died (10.3%) as a result of increased intracranial pressure, 1 of them an HIV-infected patient. The average admission period was 6 days. The average of days before starting treatment was 2.7 days (range 0-5). All of them were treated with corticoids. There were no differences in these patients regarding starting antibiotic treatments (14.7 vs 13.4 days; p = 0.78) or corticoids (8.5 vs 10.2 days; p = 0.69).

No relevant differences were found between HIV-infected and non HIV-infected patients regarding clinical presentation, CSF results, treatment or complications (Table 2).

### DISCUSSION

The average age in our study is similar to other studies. The percentage of HIV patients is similar to some studies (Table 1), although lower than most consulted [2,5,6]. Moreover our work shows a lower rate of altered mental status, vomiting and headache, it shows similar presence of fever, SIADH, meningeal signs and brain strokes than others [7] (Table 1). Most of the strokes were in ganglia basal especially the “tubercular zone” which compromises of the caudate anterior thalamus, anterior limb and genu of de internal capsule [8] (Table 3). Our patients have similar CSF leukocyte count, percentage mononuclear, glucose, ADA and protein to published series. There are a low percentage of positive cultures Lowenstein similar to the work of Hooker et al., [9]. As well as other series, a low rate of PCR positive for M. tuberculosis and Ziehl-Neelsen acid fast staining CSF has been observed in our study. On the other hand, our study shows a similar duration of symptoms, use of corticosteroids and antibiotic treatment regime. Lower mortality rates were observed in our study which are probably due to lower rates of HIV and the early initiation of antibiotic treatment and adequate use of corticosteroids (Table 4).

### Table 1: Clinical characteristics of TBM patients compared with other studies.

<table>
<thead>
<tr>
<th>Country</th>
<th>Girgis et al</th>
<th>Enberg et al</th>
<th>Roca et al</th>
<th>Christensen et al</th>
<th>Our study</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-infected (%)</td>
<td>Egypt</td>
<td>Chile</td>
<td>Spain</td>
<td>Holland</td>
<td>Spain</td>
</tr>
<tr>
<td>Altered mental status (%)</td>
<td>55</td>
<td>66</td>
<td>69</td>
<td>34</td>
<td>36</td>
</tr>
<tr>
<td>Fever (%)</td>
<td>96</td>
<td>76</td>
<td>93</td>
<td>82</td>
<td>79</td>
</tr>
<tr>
<td>Headache (%)</td>
<td>63</td>
<td>68</td>
<td>69</td>
<td>72</td>
<td>48</td>
</tr>
<tr>
<td>Meningeal signs (%)</td>
<td>68</td>
<td>80</td>
<td>69</td>
<td>72</td>
<td>48</td>
</tr>
<tr>
<td>Cranial nerve palsies (%)</td>
<td>80</td>
<td>8</td>
<td>17</td>
<td>36</td>
<td>10</td>
</tr>
<tr>
<td>SIADH (%)</td>
<td>NC</td>
<td>NC</td>
<td>45</td>
<td>NC</td>
<td>41</td>
</tr>
<tr>
<td>Vomiting (%)</td>
<td>49</td>
<td>53</td>
<td>38</td>
<td>NC</td>
<td>21</td>
</tr>
</tbody>
</table>

**Abbreviations**: No.: number. NC: not collected.

### Table 2: Differences between HIV and Non-HIV patients.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>HIV</th>
<th>Non-HIV</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF leukocytes/mm³ (median)</td>
<td>103.5</td>
<td>173.3</td>
<td>0.31</td>
</tr>
<tr>
<td>MN (%)</td>
<td>73.3</td>
<td>81.3</td>
<td>0.13</td>
</tr>
<tr>
<td>Proteins (g/L)</td>
<td>2.55</td>
<td>1.32</td>
<td>0.13</td>
</tr>
<tr>
<td>Glucose mg/dl. (Median)</td>
<td>27.7</td>
<td>32.7</td>
<td>0.75</td>
</tr>
<tr>
<td>ADA</td>
<td>9.9</td>
<td>16.1</td>
<td>0.79</td>
</tr>
<tr>
<td>Lowenstein Jensen culture</td>
<td>1</td>
<td>5</td>
<td>0.81</td>
</tr>
<tr>
<td>Age (years)</td>
<td>38.7</td>
<td>35.9</td>
<td>0.83</td>
</tr>
<tr>
<td>Symptoms duration (days)</td>
<td>16</td>
<td>13</td>
<td>0.47</td>
</tr>
</tbody>
</table>

**Abbreviations**: MN: mononuclear. NC: not collected.

Clinic data and symptoms, such as headache, fever and meningeal signs are useful signs for suspected TBM. The high ADA [10,11], high protein, low prevalence of glucose and CSF MN is useful in our environment for suspected TBM. A CT scan is a useful tool for the detection of hydrocephalus and stroke and should be performed on all patients with TBM to detect complications and prognostic assessment. Nucleic acid test in CSF, although it has a high specificity in the diagnosis of TBM, low sensitivity makes it a test with a limited usefulness in diagnosing this disease [12].

For the treatment four drugs were administered to 21 patients (72.4%), and the average treatment duration was 11 months (range 6-15). A systematic review and meta-analysis concluded that six months of treatment were probably sufficient for TBM [13]. However, most authorities recommend 12 months treatment, prompted by the uncertain influences of disease severity, CNS penetration, undetected drug resistance and patient compliance on response therapy [14,15]. Initially four drugs should be administered to TBM treatment during the first two months and then it should be continued for 12 months with two drugs (HR) [16].

Corticosteroids were administered to 22 patients (75.9%) patients in our study. Several TB guidelines recommend the use of corticosteroids as an adjunct to treatment of TB meningitis internationally (CDC 2003 [17]; BSI 2009 [16]; SNHS 2010 [18]; NICE 2011 [19]. There are high quality evidence of the benefit of corticosteroids in preventing death in people with TBM and then
corticosteroids should be routinely used in HIV-negative people with TBM to reduce death [20,21]. However, there is not enough evidence to support or refute a similar conclusion for those who are HIV positive [17,18]. The drug and dose as used in most trials may be dexamethasone (for adults 12 to 16 mg/day for three weeks, tapered over the next three weeks; for children 0.3 to 0.4 mg/kg/day for one to two weeks and tapered over the next two weeks) or prednisolona (for adults 60 mg/day for three weeks and tapered over the next three weeks; for children 2 mg/kg/day for three weeks and tapered over the next three weeks. In our study no relevant differences were found between patients with neurologic sequelae and patients without sequelae in regards to the administrating of corticosteroids. Corticosteroids may have no effect or rates of disabling neurological deficit in people who survive TBM [21].

**CONCLUSION**

TBM is presently still a diagnostic problem because clinical and analytical presentation of the TBM is not always typical, so we should maintain a high level of suspicion even when the characteristics of CSF are unusual. Moreover TBM is a serious disease in our environment because it can cause important sequelae. In spite of new diagnostic methods a high suspicion index is required in order to make an early diagnosis. Early treatment is necessary in suspected MTB cases to prevent complications and improve the prognosis. Corticosteroids should be administrated to all patients to reduce complications and improve the prognosis. Corticosteroids should be routinely used in HIV-negative people with TBM to reduce death [20,21]. However, there is not enough evidence to support or refute a similar conclusion for those who are HIV positive [17,18]. The drug and dose as used in most trials may be dexamethasone (for adults 12 to 16 mg/day for three weeks, tapered over the next three weeks; for children 0.3 to 0.4 mg/kg/day for one to two weeks and tapered over the next two weeks) or prednisolona (for adults 60 mg/day for three weeks and tapered over the next three weeks; for children 2 mg/kg/day for three weeks and tapered over the next three weeks. In our study no relevant differences were found between patients with neurologic sequelae and patients without sequelae in regards to the administrating of corticosteroids. Corticosteroids may have no effect or rates of disabling neurological deficit in people who survive TBM [21].

**REFERENCES**


