TUBERCULOUS MENINGITIS, ABBASSIA FEVER HOSPITAL - NAVAL MEDICAL RESEARCH UNIT NO. 3 - CAIRO, EGYPT, FROM 1976 TO 1996

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Abstract. A total of 1,430 patients with the presumptive diagnosis of tuberculous meningitis were admitted to the U.S. Naval Medical Research Unit No. 3/Abbassia Fever Hospital in Cairo, Egypt from January 1976 to January 1996. Diagnosis was confirmed by culture of the mycobacteria from the cerebrospinal fluid CSF of 857 patients and these patients are included in the final analysis. There were 497 males and 360 females. The patients ranged in age from five months to 55 years. The number of patients admitted during the months of March, April, and May were more than double those admitted during October, November, and December. The duration of symptoms prior to admission ranged from seven to 90 days (mean = 29.5 days). Upon admission, 4% of the patients were alert, 34% were drowsy, and 62% were in a coma. Of the 857 patients studied, 490 (57%) died, 256 (30%) recovered completely, and 11 (13%) recovered with sequelae. The mortality and neurologic sequelae were directly related to the stage of disease and duration of symptoms prior to admission. Mortality was significantly lower in patients admitted in stage II and or with short duration of disease compared with those in stage III and or with prolonged duration of symptoms prior to admission. The use of dexamethasone in patients with tuberculous meningitis significantly reduced the ocular complications that occur in these patients and also significantly reduced the fatality rate.

Tuberculosis continues to be a major health problem all over the world. In 1982, the World Health Organization (WHO) estimated that 8–10 million new cases of tuberculosis occur each year, and of these approximately three million die.

Tuberculous meningitis (TBM) is a life-threatening form of tuberculosis and is the most common form of central nervous system (CNS) tuberculosis. The disease is less common in technically advanced countries but is a serious cause of mortality and morbidity in developing nations.

The incidence of TBM in a given community is directly proportional to the prevalence of tuberculous infection in the general population, which in turn is dependent on the socioeconomic and hygienic conditions of the community. Tuberculous meningitis occurs in approximately 7–12% of patients with tuberculosis disease.

Despite the advent of new neuroimaging techniques and rapid diagnostic tests, the diagnosis of TBM can be difficult and or delayed, thus increasing the morbidity and mortality.

The mortality rate in different studies varied from 20% to 50% and of the survivors, 20–30% were left with permanent neurologic sequelae. The high mortality rate is due to the fact that the clinical presentation of TBM is notoriously variable, making the clinical diagnosis of the disease a problem. Evidence indicates that institution of treatment during the early phase of infection can significantly improve the outcome, and thus any patient suspected of having TBM based on the symptoms (prolonged fever, night sweats, cachexia) and/or signs of increased intracranial pressure (headache, vomiting, confusion, cranial nerve affections) and cerebrospinal fluid (CSF) findings compatible with the disease (moderate pleocytosis predominantly lymphocytic, decrease in glucose and increase in protein content) should be started on anti-tuberculous chemotherapy without awaiting for the CSF laboratory results.

PATIENTS AND METHODS

Data from records of patients with TBM admitted to the Abbassia Fever Hospital, Cairo, Egypt during the period from January 1976 to January 1996 were entered into a computer database program at the Naval Medical Research Unit No. 3, thus facilitating analysis of information. The Abbassia Fever Hospital is the largest fever hospital in Egypt and to which all febrile patients from the greater Cairo area are referred. The U.S. Naval Medical Research Unit No. 3 is adjacent to the fever hospital, thus facilitating collaborative studies in the field of infectious disease.

One of these projects was initiated during the early part of 1970 to study the prevalence and clinical presentation of TBM and to evaluate the efficacy and safety of new potent therapeutic regimens that could be used in the treatment of the infection. The data on the prevalence, etiology, age, sex, clinical presentation, laboratory results, therapy, and outcome included in this report are only from the patients in whom Mycobacteria tuberculosis was isolated from the CSF. Non-tuberculous mycobacteria were not isolated from any of the patients in this study.

All patients suspected of having TBM from their medical history and or physical findings were admitted to the meningitis ward where self-histories were obtained and complete physical examinations were conducted. Informed consent was obtained from all subjects and the guidelines of the U.S. Department of Health and Human Services and Naval Medical Research Unit No.3 Committee for the Protection of Human Subjects were followed in conducting this research.

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 media. Blood was drawn for a complete blood analysis, glucose, blood urea nitrogen (BUN), creatinine, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and total bilirubin. Follow-up examination of the CSF and blood to monitor the progress of the disease and efficacy and side reactions of treatment was carried out once a month for six months, every two months for one year, and then every four months.
for an additional two years. Chest radiographs and a tuberculin (purified protein derivative) (5 units) skin test were performed on admission on the patients whenever feasible. Ophthalmologic examination was carried out on all patients upon admission. The examination included, pupillary reactions, cranial nerve affections, and fundus examination to detect any abnormalities. Tests for color vision and field of vision were not carried out on admission because most of the patients were unable to cooperate or irritable, but were carried out once patients were alert. Follow-up ophthalmologic examination was carried out twice a week for six months then monthly thereafter.

The severity of the disease was classified into three stages according to the method of Gordon and Parson.14 Stage I: patients were fully alert, Stage II: patients were drowsy or had focal neurologic signs, Stage III: patients were in a coma and responded only to deep stimuli.

During the 20-year period of the study, the efficacy, safety, and tolerability of different combinations of anti-tuberculous drugs used to treat these patients were evaluated.

RESULTS

During the 20-year period from January 1976 to January 1996, 1,430 patients were admitted to the Naval Medical Research Unit No. 3/Abbasia Fever Hospital meningitis ward with the presumptive diagnosis of TBM. Diagnosis was confirmed by culture of the M. tuberculosis from the CSF in 857 (60%) patients and these are the patients included in the final analysis. There was no significant difference between patients with positive or negative CSF cultures with regard to age, sex, duration, severity, and outcome of the disease. In 97% of these patients the clinical course was consistent with TBM, and the remaining 3% were diagnosed as having fungal meningitis. A smear of the CSF for acid-fast bacilli using Ziehl-Neelsen stain was positive in only 5% of the patients suspected of having TBM. There was no correlation between a positive smear and clinical stage or outcome.

The yearly incidence of TBM is shown in Figure 1. There was no apparent difference in the yearly number of patients admitted during the study period. However, the number of patients admitted during the months of March, April, and May were more than double those admitted during October, November, and December (Figure 2). The increase in TBM admissions during the months of March to May may be due to the fact that viral infections such as influenza, measles, and mumps are very common during the months of February and March, causing a decrease in immunity; thus, the chance for dissemination of mycobacteria is greater. The rapid expansion of the Cairo metropolitan area and the vast increase in the population from approximately 11 million during the early phase of the study to 16 million at present accounted for the increase in the total number of admissions to the hospital and in the number with tuberculosis. None of the patients received bacille Calmette-Guerin vaccine because it is not compulsory in Egypt.

Clinical data. There were 497 males and 360 females in the study. The patients ranged in age from five months to 55 years (mean ± SD = 16.8 ± 13.2 years) (Figure 3). The prevalence of the disease was much higher in patients less than five years of age compared with other age groups. Twenty-six percent of the patients were less than five years of age. The major presenting symptoms and signs in these patients are shown in Table 1. At the time of the first examination, only 4% of the patients were alert, 34% were drowsy, and 62% were in a coma. Cranial nerve palsy was seen in 50% of the patients, affection of the sixth nerve was
the most common and occurred in 35% followed by the third and seventh cranial nerves. Fundus changes were present in 17% of the patients, papilloedema in 7%, temporal pallor of optic discs in 6%, and optic atrophy in 4%. Pupillary reflex to light was abnormal in 82% of the patients, 44% had a sluggish reaction, 28% were dilated nonreactive, and 10% were constricted nonreactive.

Duration of symptoms prior to admission ranged from seven to 90 days (mean = 29.5 days) (Table 2). Only 29% of the patients were sick for less than 14 days, 45% were sick for less than 28 days, and 26% were sick for more than 28 days. Forty-five percent of the patients with symptoms of less than 14 days were in Stage III compared with 74% of the patients with symptoms of more than 28 days (Table 2).

All patients tested were negative for human immunodeficiency virus with no other underlying disease.

**Findings on chest radiography.** Due to the lack of bedside radiograph facilities, chest radiographs could not be done on all patients on admission. Chest radiographs were performed on 423 patients, and of these 169 (40%) had normal radiographs. In 254 (60%) patients, radiographic findings were consistent with pulmonary tuberculosis. The abnormalities detected were nodular perihilar infiltrates in 125 patients, upper lobe infiltrates in 40 patients, lower lobe infiltrates in 50, diffuse infiltrates in 30, and a miliary pattern in nine.

**TABLE 1**

Presenting signs and symptoms in patients with tuberculous meningitis

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Percent</th>
<th>Signs</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever &gt;38°C</td>
<td>90</td>
<td>Stiff neck</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kerning sign positive</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Brudzinski sign positive</td>
<td>65</td>
</tr>
<tr>
<td>Headache</td>
<td>63</td>
<td>Abnormal mental state</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drowsy</td>
<td>34%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comatose</td>
<td>62%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alert</td>
<td>4%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>49</td>
<td>Cranial nerve palsy</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sixth</td>
<td>35%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Third</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Seventh</td>
<td>5%</td>
</tr>
<tr>
<td>Lethargy</td>
<td>32</td>
<td>Fundus changes</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Papilloedema</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Optic atrophy</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Temporal pallor</td>
<td>6%</td>
</tr>
<tr>
<td>Cough</td>
<td>32</td>
<td>Weight loss</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Night sweats</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sluggish</td>
<td>44%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dilated</td>
<td>28%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Constricted</td>
<td>10%</td>
</tr>
</tbody>
</table>
Duration of symptoms and stage of disease in patients with tuberculous meningitis*

<table>
<thead>
<tr>
<th>Duration (days)</th>
<th>Total</th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
</tr>
</thead>
<tbody>
<tr>
<td>7–14</td>
<td>29</td>
<td>3</td>
<td>52</td>
<td>45</td>
</tr>
<tr>
<td>15–28</td>
<td>45</td>
<td>5</td>
<td>30</td>
<td>65</td>
</tr>
<tr>
<td>&gt;28</td>
<td>26</td>
<td>4</td>
<td>21</td>
<td>74</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>4</td>
<td>34</td>
<td>62</td>
</tr>
</tbody>
</table>

*Range = 7–90; Mean ± SD = 29.5 ± 13.2.

Skin test. Purified protein derivative (5 units) was applied to 360 patients. The test result was considered positive if the induration was ≥ 10 mm in diameter 48 hr after the application. Of the 360 patients tested, the reaction was positive in 62 (17%) and negative in 298 (83%). The number of patients with a positive skin reaction was significantly higher in patients admitted in stage I (alert) (P < 0.03), in patients with symptoms of less than 14 days duration (P < 0.003), and in patients more than five years of age (P < 0.02).

Laboratory findings. The mean peripheral white blood count was 11,600/mm³ (range = 4,800–18,700/mm³). Mild to moderate elevations in the serum transaminases, BUN, and creatinine were observed in approximately 20% of the patients.

The CSF findings on admission are shown in Table 3. The total leukocyte count was moderately elevated (mean = 437 cells/mm³; range = 30–900 cells/mm³), the glucose level was markedly decreased (mean = 22.5 mg/dL, range = 5–55 mg/dL), and the protein level was markedly elevated (mean = 220 mg/dL, range = 214–780 mg/dL). Return of the CSF changes to normal levels from the time of initiation of therapy was gradual and it took six months for all parameters to return to normal levels. Three months after the initiation of therapy the CSF cultures were negative in all the patients, the glucose content was within normal levels in 85% of the patients, the protein content was within normal levels in 50% of the patients, and leukocyte count was within normal levels in 70% of the patients. Six months after the initiation of therapy, the CSF findings were normal in all patients (Table 3).

Drug sensitivity testing was carried out on 150 of the isolates. Resistance to rifampin was observed in 3%, to ethambutol in 7%, and to isonicotinic acid hydrazide (INH) in 10% of the isolates tested. Multidrug resistance or resistance to pyrazinamide was not observed in any of the isolates. There was no correlation between resistance and outcome.

Treatment. In all instances anti-tuberculous therapy was instituted within 72 hr of admission without waiting for the culture results. Therapy was given based on history of the disease (subacute-prolonged fever, malaise, night sweats, cachexia, mental disorientation), CSF findings compatible with TBM (moderate pleocytosis, decreased glucose levels, and elevated protein content), and failure to respond to a trial of broad spectrum antibacterial agents in 72 hr.

During the different phases of the study two therapeutic regimens containing three drugs each were compared and evaluated for their efficacy and safety. Upon admission to the ward, selection of the patients into one of two regimens used was done according to a computer-generated randomization number chart and the institution of empiric therapy was initiated prior to the confirmation of disease by culture.

Anti-tuberculous chemotherapy was given to all patients for a period of two years. Patients remained in hospital for six months and were then followed-up monthly on an outpatient basis for the remaining two years.

During the early phase of the study, two regimens were evaluated and consisted of 1) p-aminosalicylic acid plus INH and streptomycin and 2) ethambutol plus INH and streptomycin. In the second phase the drugs used were 1) ethambutol plus INH and streptomycin compared with 2) rifampin plus INH and streptomycin. Selection of the patients into one of the regimens used was according to a computer-generated randomization number chart. At a later stage the use of dexamethasone as an adjunctive to anti-tuberculous therapy was evaluated. In this trial all patients received ethambutol plus INH and streptomycin. The first group of patients received dexamethasone at a dose of 12 mg/day in adults more than 12 years old and 8 mg/day in children for three weeks, then tapered off over a three-week period, together with three anti-tuberculous drugs. The second group received anti-tuberculous drugs alone. In all the trials, streptomycin was discontinued after six weeks and the other two drugs were continued for two years.

There was no significant difference in the mortality or sequelae between the various regimens used except for the significant decrease in mortality and morbidity observed in the group of patients receiving dexamethasone compared with those not receiving this drug. Ocular complications developed in four (9%) patients and permanent neurologic sequelae developed in six (14%) patients receiving dexamethasone compared with 10 (28%) and 13 (38%), respectively, in those not receiving dexamethasone (Table 4). Similarly, the mortality rate, particularly in patients admitted in Stage II, was significantly lower (43%) in patients receiving...
The mortality and neurologic sequelae were directly related to the stage of disease on admission (Table 5). The mortality was significantly higher \((P < 0.001)\) in patients admitted in stage III compared with those in stage II or I. Of the 528 patients in stage III, 383 (72%) died compared with 100 (34%) of 292 in stage II and only seven (18%) in stage I. Similarly, the number of patients who recovered completely without any sequelae was significantly higher \((P < 0.05)\) in patients admitted in stage I compared with those in stages II or III (Table 5). Of 145 survivors in stage III, only 50 (10%) after 28 days of the initiation of anti-tuberculous chemotherapy, which was administered within 72 hr of admission (Table 6).

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**DISCUSSION**

Tuberculous meningitis usually arises as a complication immediate or remote of the primary infection and reaches the CNS by way of the blood stream. In the majority of children, TBM is usually slowly progressive and occurs as a result of hematogenous spread following a primary focus. In adults, however, the infection may occur in association with clinically apparent progressive disease, but a significant percent of cases of TBM occur in the absence of clinically evident extracranial infection. Evidence of extracranial involvement cervical and abdominal lymph nodes tuberculosis peritonitis, and renal tuberculosis were diagnosed in 3% of our patients. Brain autopsies were carried out on approximately 10% of the patients with tuberculous meningitis to confirm the diagnosis.

Reactivation of latent tuberculosis as a result of local conditions or general depression of host immunity leads to generalized tuberculous infection and involvement of the CNS occurs in 54% of these patients.

Tuberculous meningitis is characterized by diffuse or circumscribed granulomatous involvement of the meninges, particularly around the base of the brain, and this is the main pathology responsible for the majority of sequelae that develop with the disease. While the major impact involves the basal meninges, parenchymatous lesions of the brain itself due to direct extension of the inflammatory process or secondary to the vascular changes are always encountered. Dastur in 1970 emphasized the high incidence of frank infarction of the brain consequent to compression and inflammation of the large basal arteries by adhesive proliferative meningitis. The majority of the infarcts are seen around the area of the middle cerebral arteries and may involve the basal ganglia and hypothalamus because of the involvement of the perforating vessels, which are the main blood supply to these areas. The most constant finding in the affected arteries is gross swelling of the adventitial coat and subsequent adventitial fibrosis. The ultimate decrease in blood flow re-
Permanent neurologic sequelae in patients with tuberculous meningitis two years after initiation of therapy

<table>
<thead>
<tr>
<th>Nature of sequelae</th>
<th>No. of patients</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovery with sequelae</td>
<td>111</td>
<td>13</td>
</tr>
<tr>
<td>Nature of sequelae</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cranial nerve palsy</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>Fundus changes</td>
<td>30</td>
<td>27</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>30</td>
<td>27</td>
</tr>
<tr>
<td>Hemiparesis-paraplegia</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>Cerebral atrophy</td>
<td>11</td>
<td>10</td>
</tr>
</tbody>
</table>

Results in areas of ischemia in the cerebral cortex, pons, and cerebellum leading to the development of the permanent sequelae of which the most drastic are hydrocephalus and optic atrophy.21

Typically, the admission CSF findings in the majority of patients with TBM are that of a subacute lymphocytic meningitis with a decrease in glucose and an increase in protein content. However, in a number of patients the CSF findings are not consistent with that of subacute lymphocytic meningitis due to a predominance of polymorphonuclear cells and a mild decrease in glucose content.22-24 Polymorphonuclear predominance was seen in 15±20% of our patients on admission.

The tuberculin skin test should not be relied upon in the diagnosis of patients with TBM because the rate of positive skin reactions is usually low and depends to a great extent on the age of the patients and duration and severity of the disease.25,26

Despite the introduction of new and potent anti-tuberculous drugs, the mortality and morbidity in patients with TBM remains exceptionally high. The mortality and sequelae are directly related to the stage of the disease at the time of initiation of appropriate therapy. Jacobs and others27 and Kent and others13 found that the mortality in patients admitted in stage III was approximately 50% while for those in stages II and I it was 30% and 15%, respectively. Although the mortality in our series was higher, it was dependent on the stage of disease, being 75% for patients in stage III, 34% for patients in stage II, and 19% for those in stage I. In the patients who survived, 13% were left with permanent sequelae. This is much lower than the 53% observed by Idriss and others.8 However, their mortality rate was much lower and thus most of the survivors developed sequelae.

Clinical trials to evaluate the efficacy of adjuvant compounds given in conjunction with anti-tuberculous chemotherapy in reducing the mortality and morbidity rates have been carried out.15 The most promising of these agents were the corticosteroids. However, the use of corticosteroids has been controversial, with some investigators advocating their routine use only in patients in the advanced stage of the disease at presentation and some recommending that they be used only rarely.4,9,28

The criticisms put forward regarding the use of corticosteroids in TBM were that they may have an effect on the immune response and interfere with the interpretation of CSF results, or they may reduce the penetration of anti-tuberculous drugs into the CSF.28 However, in recent studies, it was shown that the use of corticosteroids did not alter significantly the CSF findings and that there was no difference in the CSF concentration of the commonly used anti-tuberculous drugs in patients receiving corticosteroids compared with those not receiving them.13,29

In the studies carried out by O’Toole and others30 and Fishman,31 they concluded that favorable outcome in patients with TBM treated with corticosteroids was demonstrated. However, both these studies were not blinded, the number of patients was small, and there was no mention regarding the time at which the corticosteroids were administered. They stated that the beneficial effect of the corticosteroids was due to the decrease in cerebral edema that is associated with TBM and that the decrease in edema markedly improves mental status.

Recent controlled trials from Abbassia Fever Hospital10,17 demonstrated that dexamethasone reduced the ocular complications in patients with tuberculous meningitis but did not reverse damage to optic nerves. Also, a significant reduction in the fatality rate was achieved by adding steroids to anti-tuberculous therapy (43% compared with 59%; P < 0.05) and was even greater in patients who were alert or drowsy when admitted than in those already in a coma (13% compared with 64%; P < 0.01).

Similarly, the dramatic response we observed in the return to normal levels of CSF leukocytes, glucose, and protein denotes that dexamethasone as a potent anti-inflammatory agent was useful in decreasing the inflammatory response and preventing the complications that occur in patients with TBM. No serious adverse reactions attributable to dexamethasone were observed in any patient. For this reason, we believe that dexamethasone should be included in anti-tuberculous therapy for the treatment of patients with TBM.

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