

## Tuberculous meningitis: a retrospective review of 21 cases

Chai Beng TAN MBBS MMed, Bee Wah LEE MMed MD, \*Helen TL TJIA MBBS MMed

*The Brain and Spine Centre, Tan Tock Seng Hospital, Singapore, \*Department of Paediatric, National University Hospital, Singapore*

### Abstract

We present a retrospective review of 21 cases of tuberculous meningitis seen in a single institution over a 4-year period. All the patients were adults. The majority of the patients presented as a subacute meningitis. Diagnosis was confirmed by positive cerebrospinal fluid culture in 24% and by the polymerase chain reaction for *Mycobacterium tuberculosis* DNA in the cerebrospinal fluid in another 14%. The mortality rate was 10% and 48% of survivors were left with significant neurological deficits. Severe cognitive dysfunction was seen in 24%. Predictive factors for poor outcome were severity of disease on admission and the presence of hydrocephalus.

**Key words:** Tuberculous meningitis, Singapore.

### INTRODUCTION

Tuberculosis (TB) remains an important public health problem in South East Asia, despite improvement in living standards brought about by rapid economic growth over the past decade. In Singapore, the incidence rate among residents had fallen from 100 cases per 100,000 population in 1980 to 49 cases per 100,000 population in 1994 (Epidemiology Unit report, 1994). TB continues to be a disease of adults. The incidence rate for children was less than 5 per 100,000 population in 1994. Extrapulmonary TB accounted for 8% of all cases. Despite a decline in pulmonary TB brought about by an efficient national immunisation programme and stringent tracing of contacts by the Tuberculous Control Unit, the incidence of extrapulmonary TB, including neurotuberculosis in Singapore has remained fairly constant over the past 5 years. We present a retrospective review of all patients with tuberculous meningitis (TBM) seen over a 4-year period at Tan Tock Seng Hospital, a major tertiary urban general hospital in Singapore. The aims of the study were to determine factors that may affect the outcome, the influence of newer diagnostic techniques like the polymerase chain reaction (PCR) to detect *M. tuberculosis* DNA in the cerebrospinal fluid (CSF) and the impact of combination chemotherapy.

### MATERIALS & METHODS

All patients admitted to Tan Tock Seng Hospital between 1992 and 1995 and diagnosed to have TBM were reviewed retrospectively. The

diagnosis of definite TBM was based on either positive culture of *M. tuberculosis* from the CSF, positive smear for acid-fast bacilli with standard Ziehl-Neelsen stain to centrifuged CSF or positive PCR for *M. tuberculosis* DNA in the CSF. Cases were classified as probable TBM based on the initial presentation of subacute meningitis with CSF pleocytosis, CSF protein exceeding 40 mg/dl, negative bacterial and fungal culture and response to treatment with anti-tuberculous drugs. Evidence of tuberculous infection outside the central nervous system was considered strongly supportive of the diagnosis of TBM.

The patients were classified on admission into 3 stages using criteria established by the Medical Research Council (MRC)<sup>1</sup>. In Stage 1, patients were fully conscious and rational with meningeal irritation but no focal neurological signs. Patients in Stage 2 were confused and/or had focal neurological signs or hemiparesis. In Stage 3, patients were stuporous or comatose and/or had complete hemiplegia or paraplegia.

### RESULTS

#### *Clinical Features*

A total of 21 patients were treated for TBM over the 4-year study period. There were 10 female and 11 male patients. Their age range from 19-70 with a mean of 42 years. There were 15 Chinese, 4 Indians and 2 Malay patients. Three patients had diabetes, 1 had carcinoma of the colon and another rheumatoid arthritis prior to admission. Patients were symptomatic for periods ranging from 1 to 16 weeks. The most common

presenting symptoms were changes in mental status (15 patients), fever (14 patients) and headache (9 patients). Six patients were on diagnosis, in Stage 1, 12 were in Stage 2 and 3 were in Stage 3. Neurological signs detected on hospitalisation include neck stiffness (9), papilloedema (3 patients), cranial nerve deficits (7 patients), brainstem signs (1 patient), unilateral (3 patients) or bilateral corticospinal tract dysfunction (2 patients) and paraparesis (2 patients). Cranial nerve deficits were confined to the III, IV and VI nerves. Bilateral or unilateral sixth nerve palsy, which might have resulted from raised intracranial pressure, was seen in 4 patients. The remaining 3 patients had unilateral 3rd nerve, unilateral 3rd and 6th and bilateral 3rd and 4th nerve palsies. Seizures developed during the course of treatment in 1 patient.

#### Laboratory findings

*M. tuberculosis* was detected either through positive smear or culture in the CSF in 5 patients and from a lymph node biopsy in another. Three additional patients had *M. tuberculosis* DNA detected in the CSF through the PCR test. The other 11 patients were diagnosed to have probable tuberculous meningitis.

The peripheral white blood count ranged from 5,400 to 23,600/mm<sup>3</sup>. Eleven patients had counts of less than 10,000/mm<sup>3</sup> whereas only 1 had count exceeding 20,000/mm<sup>3</sup>. The hemoglobin was less than 12 gm/dl in 6 patients. Ten patients had serum sodium level of less than 135 meq/liter. The CSF white cell count ranged from 1-650/mm<sup>3</sup>. Three patients had normal CSF white cell counts, 9 had counts of less than 100/mm<sup>3</sup> and the remaining 9 had counts above 100/mm<sup>3</sup>. The CSF glucose level was below 40 mg/dl in 13 patients and above 40 mg/dl in 8 patients. Two patients had normal CSF protein levels while 15 had levels ranging from 40-200 mg/dl whereas only 4 had levels exceeding 200mg/dl.

#### Radiology

Eight patients had abnormal findings on chest X-ray, 4 of whom had miliary pulmonary tuberculosis. One patient who had a miliary pattern on his chest X-ray also had tuberculosis of the spine and lymphadenitis. All patients had at least one computed tomographic (CT) scans of the head. Ten patients had normal CT scans. Hydrocephalus (7 patients) and infarcts (7 patients) were the most common abnormalities. All patients except one who had cortico-spinal dysfunction had infarcts demonstrated on neuroimaging. Six patients had meningeal

enhancement. Magnetic resonance imaging of the head in 3 patients showed tuberculomas in 2 patients and basal enhancement in another. Another patient who developed paraparesis had multiple tuberculomas demonstrated on MRI scan of the thoracic spine.

#### Treatment

Fourteen patients were treated with 3 drugs while 7 were treated with 4 drugs. All patients received isoniazid (INH); 20 received rifampicin, 15 received pyrazinamide, 10 received ethambutol and 3 received streptomycin. Most patients were treated for 12-18 months. Of those who were treated with 3 drugs, 8 recovered without deficit, 4 had neurological sequelae and 2 died. In the group who were treated with 4 drugs, 1 recovered without complication while 6 others had neurological deficits. Adverse reactions to anti-tuberculous drugs were seen in 5 patients. Three patients had pyrazinamide substituted because of liver dysfunction. One patient developed hemolytic anemia to rifampicin and another ethambutol induced optic neuritis. Two patients had ventriculo-peritoneal shunt inserted for hydrocephalus. Intravenous dexamethasone was used in 1 patient.

#### Outcome (table 1)

There were 2 deaths. Both were in Stage 2 by MRC criteria on admission. Nine patients in the whole series recovered completely without neurological deficit. Five were in Stage 1 and 4 in Stage 2. Neurological sequelae in the remaining 10 patients include hemiparesis (4 patients), cognitive impairment (5 patients), paraparesis (2 patients), radiculitis and tetraparesis (1 patient each). Among the patients who had moderate to severe cognitive dysfunction, 4 of 5 had hydrocephalus. Two were in Stage 3 and 3 in Stage 2 on admission. Conversely only 2 of 14 patients who recovered without cognitive dysfunction had hydrocephalus. The mean age of the group of patients with cognitive deficit was 30.6 years while the group without cognitive deficit was 43 years. The duration of illness before diagnosis did not adversely affect the outcome.

#### DISCUSSION

In Singapore, a comprehensive system of notification for tuberculosis has been maintained for many years. Medical practitioners and clinical laboratories are required to notify all cases of tuberculosis to the Epidemiology Unit of the Ministry of Health.



**TABLE 1: Neurological outcome in relation to age, duration of illness, MRC grade and CT scan findings.**

Patients	Neurological sequelae	Age	MRC Stage	Duration of illness (weeks)	CT scan findings
1	No deficit	26	2	2	Meningeal enhancement
2	No deficit	58	1	3	Normal
3	No deficit	49	1	6	Normal
4	No deficit	38	2	<1	Normal
5	No deficit	66	1	8	Normal
6	No deficit	70	1	8	Normal
7	No deficit	21	2	14	Normal
8	No deficit	35	1	16	Hydrocephalus
9	No deficit	29	2	2	Normal
10	Died	66	2	<1	Hydrocephalus, cerebral infarct
11	Died	65	2	4	Normal
12	Radiculitis	64	2	<1	Normal
13	Hemiparesis	50	1	<1	Hydrocephalus
14	Hemiparesis	19	2	<1	Hydrocephalus, cerebral infarct, meningeal enhancement
15	Paraparesis	36	3	2	Cerebral infarct, meningeal
16	Paraparesis	44	2	3	Normal
17	Cognitive impairment	23	2	<1	Hydrocephalus, meningeal enhancement
18	Cognitive impairment hemiparesis	36	2	<1	Hydrocephalus, cerebral infarct
19	Cognitive impairment hemiparesis	23	3	4	Cerebral infarct, meningeal enhancement
20	Cognitive impairment tetraparesis	34	3	3	Hydrocephalus, cerebral infarct
21	Cognitive impairment paraparesis	37	2	8	Hydrocephalus, cerebral infarct, meningeal enhancement

The TB Control Unit traces contacts of notified cases and ensures that patients do not default on treatment. The treatment of tuberculosis is free. The efficient case finding with high rate of completion of treatment are probably the main reasons for the low prevalence of tuberculosis in Singapore when compared with many countries in South East Asia. Mass BCG vaccination was started in Singapore in the mid-1950s. Over the past 8 years the BCG vaccination coverage has exceeded 95%. There is controversy regarding the effectiveness of BCG. A recent meta analysis of published BCG vaccination trials suggested that BCG is 50% effective in preventing pulmonary tuberculosis. The protective effect for meningitis is higher at 64%.<sup>2</sup> A recent epidemiological studies have revealed a greater than 80% efficacy of BCG for

the prevention of TBM in children.<sup>3</sup> This is another factor why all the patients in this series were adults. Indeed, there has been no TB meningitis reported in children in Singapore for the past 8 years. It is widely accepted that tuberculous meningitis can develop from the breakdown of old cortical tubercles or meningeal plaques after primary infection rather than by direct, hematogenous extension during primary infection.

The diagnosis of TBM can be difficult and treatment is often started empirically. The clinical presentation and CSF profile are varied and non-specific for TBM. Disturbance in mental status, fever and headache were the most frequent presenting symptoms in accordance with other reported series.<sup>4-10</sup> Underlying diseases that may predispose to TBM were seen only in 24%. The

laboratory parameters were similar to those reported in other series.<sup>4-10</sup> Leucocytosis and hyponatremia were seen in about 50% of the patients. All patients except one had abnormal CSF findings of pleocytosis, hypoglycorrhachia or elevated protein levels. None of the subjects had CSF cell count exceeding 650/mm.<sup>4</sup> The CSF protein was elevated in the majority of the patients while the CSF blood sugar was less helpful with 62% showing hypoglycorrhachia. Pulmonary infection, mainly miliary TB was detected in 38%. The most common CT abnormalities were hydrocephalus and cerebral infarcts, seen in 52%. Positive CSF culture for *M. tuberculosis* was seen in 24%. This is lower than the 45-90% positive rate reported in other series.<sup>9</sup> Owing to the difficulty in diagnosis attempts have been made to improve the accuracy of diagnosis. These include the radiometric BACTEC system (Johnson Laboratories Inc., Towson, MD)<sup>11-12</sup> and immunological methods to detect *M. tuberculosis* antigens and antibodies.<sup>13</sup> Recently, selective DNA sequence amplification by the PCR method has been used for the detection of *M. tuberculosis* DNA in CSF.<sup>14-15</sup> We have shown the MPB 64 protein encoding gene to be specific for the diagnosis of TBM in a recent study.<sup>15</sup> In this series, *M. tuberculosis* DNA was detected in the CSF of 3 patients in whom the test was performed. All 3 were culture negative for *M. tuberculosis*. Although PCR protocols permit early diagnosis of TBM, the major disadvantage is their extreme sensitivity. Proper selection of *M. tuberculosis* specific DNA sequence and extreme care to avoid cross contamination are prerequisites to avoid false positive results.<sup>15</sup>

The treatment of TBM remains controversial as there is no consensus on the ideal combination of drugs or the duration of treatment.<sup>16-17</sup> INH and rifampicin are both potent bactericidal drugs<sup>18-19</sup> and pyrazinamide with its excellent penetration in the meninges is considered an efficient anti-tuberculostatic drug.<sup>20-22</sup> The majority of our patients were treated with the combination of INH, rifampicin and pyrazinamide for 2 months followed by INH and rifampicin for 10-16 months. There was no difference in the cure rate between those on quadruple or triple drugs therapy. Those on quadruple therapy appeared to have a higher incidence of neurological deficits. The reason may be because patients who were on quadruple therapy had more advanced disease at the onset of treatment. Elevated transaminases to pyrazinamide were the most common adverse

effects noted in this series. The role of steroid till to-day is still controversial.<sup>23</sup> Only one patient received steroid among our patients.

The mortality in this series was 10% and in recent series has ranged from 15-36%.<sup>6</sup> Forty eight per cent were left with neurological deficits. Adverse prognostic factors identified in previous studies include severity of the disease as reflected by the MRC rating scale, delay in diagnosis, duration of disease, extreme of ages and the presence of underlying disease.<sup>4-10</sup> Poor outcome, particularly cognitive impairment, was related to the severity of disease as measured by the MRC scale and the presence of hydrocephalus in this small series.

In conclusion, early diagnosis of TBM remains elusive although the detection of *M. tuberculosis* DNA by PCR may permit a definitive diagnosis within 3 days. While the results are encouraging, further experience with larger number of patients are needed before the test can be recommended for routine use. Drug resistance or toxicity from INH and rifampicin, employed in most combination therapy, have not been a significant problem with modern combination chemotherapy. Serious neurological sequelae from the disease are common and poor prognostic factors identified in this study include advanced stage of disease on presentation and the presence of hydrocephalus.

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