Journal of Clinical Neuroscience 17 (2010) 1018–1022

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Clinical Study

A review of tuberculous meningitis at Auckland City Hospital, New Zealand

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ARTICLE INFO

Article history:
Received 16 June 2009
Accepted 1 January 2010

Keywords:
Cerebrospinal fluid
Meningitis
Tuberculosis

ABSTRACT

The clinical features, investigations, treatment and outcome were studied in 104 patients with definite or probable tuberculous meningitis. The diagnosis of definite tuberculous meningitis required the growth of *Mycobacterium tuberculosis* from cultures, or a positive polymerase chain reaction (PCR) assay for *M. tuberculosis*. In probable tuberculous meningitis, cultures and the PCR assay were negative, but other causes of meningitis were excluded and there was a response to anti-tuberculosis treatment. Of the 104 patients, 36% had a poor outcome (severe disability, persistent vegetative state or death), 12% moderate disability and 52% good recovery. A diagnosis of definite tuberculous meningitis, the severity of the symptoms at presentation and the occurrence of a stroke were significant predictors of a poor outcome. The most common reasons for a delayed diagnosis were presentation with mild symptoms wrongly attributed to a systemic infection, incorrectly attributing CSF abnormalities to non-tuberculous bacterial meningitis and failure to diagnose extraneural tuberculosis associated with meningitis. Recognition of the difficulties in making a diagnosis of tuberculous meningitis may facilitate earlier diagnosis in the future.

1. Introduction

After anti-tuberculous drugs were introduced, there was an initial decrease in the mortality of tuberculous meningitis,[1] but since then the mortality and morbidity may not have changed.[2,3] In most recent hospital-based studies about 40% of patients have died or survived with severe disability,[3–11] but lower mortality rates have been recorded.[12] A delay in starting anti-tuberculosis treatment is associated with an increased risk of death or survival with severe neurological sequelae.[13] We have retrospectively reviewed 104 patients with tuberculous meningitis who presented to Auckland Hospital during the last 40 years: attention was focussed on the difficulties in making a diagnosis of tuberculous meningitis in these patients and the neurological and systemic complications will be described in a further article in the *Journal of Clinical Neuroscience*.[14]

2. Methods and patients

Patients were considered to have definite tuberculous meningitis if: (i) the patient had one or more of the following clinical features – headache, neck stiffness, altered mental state or fever; (ii) there was a cerebrospinal fluid (CSF) pleocytosis (leukocytes > 5×10^6/L); and (iii) either *Mycobacterium tuberculosis* (*M. tuberculosis*) was cultured from the CSF or another site, or the polymerase chain reaction (PCR) assay for *M. tuberculosis* deoxyribonucleic acid (DNA) in the CSF was positive. One patient did not have a lumbar puncture but was included in the group with definite tuberculous meningitis after *M. tuberculosis* was identified at autopsy. A diagnosis of probable tuberculous meningitis was accepted if the first two criteria were met, other causes of meningitis were excluded and there was a definite improvement following anti-tuberculosis treatment.

Patients who presented from 1963 to 1983 have been identified in a previous retrospective review of chronic meningitis[15] and those who presented after 1983 were traced from hospital discharge diagnosis records, the results of cultures for *M. tuberculosis* and since 1993, the results of PCR tests for *M. tuberculosis* DNA in CSF.

Each patient's hospital records were reviewed. The clinical features, results of investigations, treatment and outcome were recorded. The interval between presentation to hospital and the time anti-tuberculosis treatment was started was determined from review of the hospital notes. For patients in whom anti-tuberculosis treatment was delayed more than 3 days after arrival in hospital, the reasons for the delay were obtained by review of the clinical notes. The severity of the disease at presentation was retrospectively graded according to the Medical Research Council (MRC) criteria: stage 1, normal level of consciousness and no focal signs; stage 2, lethargy, altered behaviour, meningism or minor fo-

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doi:10.1016/j.jocn.2010.01.007

cal signs (e.g. cranial nerve palsies); stage 3, stupor, coma, or severe focal deficit.[16]

The status of survivors was determined by review of the case notes. The median duration of follow-up among the survivors was 18 months (range: 1–197 months). The Glasgow Outcome Scale (GOS) score was assigned retrospectively to grade the outcome at last follow-up: 1, death; 2, persistent vegetative state; 3, severe disability (dependent for daily support because of mental or physical disability); 4, moderate disability (disabled, but independent); and 5, good recovery (resumption of normal life although there may be minor neurological and psychological deficits).[17] A GOS score of 1–3 was considered to be a poor outcome and a GOS score of 4 or 5, a good outcome.

The data were entered into a Microsoft Excel spreadsheet. Statistical Analysis System software (SAS Institute; Cary, NC, USA) was used for data analysis. To determine which factors predicted a good or poor outcome the following parameters were entered into a logistic regression analysis: diagnosis of definite or probable tuberculous meningitis, age, date of presentation, duration of symptoms before presentation, a history of alcoholism, CSF leukocyte count, CSF glucose, CSF protein, presence or absence of hydrocephalus or stroke, time between presentation and the initiation of anti-tuberculosis treatment, MRC stage on admission to hospital, the use of anti-tuberculosis treatment, treatment with rifampicin and treatment with steroids. The observations for 10 patients were deleted because there were missing values.

3. Results

A total of 104 patients, 61 males and 43 females, presented with tuberculous meningitis (Table 1). Seventy-one patients (68%) had definite tuberculous meningitis and 33 patients (32%), probable tuberculous meningitis. Definite tuberculous meningitis was confirmed by growth of *M. tuberculosis* from CSF cultures in 57 patients (55%), positive *M. tuberculosis* cultures of a specimen obtained from another site in 10 patients (10%), positive PCR assay for *M. tuberculosis* DNA in the CSF in three patients (3%) and post-mortem examination in one patient. The proportion of people from the Pacific, Maori and Asian ethnic groups with tuberculous meningitis was much higher than the proportion of these ethnic groups in the general population.

Table 1
Characteristics of 104 patients with tuberculous meningitis

Characteristic	*n* = 104 (%)
Age (years)	
Range	0.4–81
Mean	28.6
Median	28
No. <5 years	24 (23)
Past history of TB	9 (9)
TB contact	39 (38)
Predisposing illness[1]	22 (21)
Ethnic group	
European	29 (28)
Maori	29 (28)
Pacific	34 (33)
Asian	9 (9)
African	1 (1)
Missing	2
Date of presentation	
1965–74	19 (18)
1975–84	34 (33)
1985–94	25 (24)
1995–2004	26 (25)

TB = tuberculosis.
[1] Predisposing illnesses: alcoholism – 15, diabetes mellitus – three, chronic renal impairment – three, current or recent corticosteroid treatment – three, human immunodeficiency virus infection – one, myelodysplasia – one.

3.1. Presenting symptoms and signs

The median duration of symptoms before presentation was 21 days (range: 1 day–12 months). The most common presenting symptoms were: headache (69%), fever (69%), altered mental state (58%), drowsiness (28%) and non-specific systemic symptoms including nausea/vomiting (61%), anorexia (54%), lethargy (46%), weight loss (37%) and cough (35%). Fewer than 20% of people presented with seizures, limb weakness and diplopia.

The most common signs were fever (83%) and neck stiffness (69%). Mental state was abnormal in 68 (65%) patients: confusion in 45%, stupor in 15% and coma in 5%. Cranial nerve palsies and signs of a focal cerebral hemisphere lesion, including hemiparesis, dysphasia, apraxia or homonymous hemianopia, occurred in fewer than one-third of the patients. The MRC stage on admission to hospital was stage 1 in 24 patients (23%), stage 2 in 59 patients (57%) and stage 3 in 21 patients (20%).

3.2. Cerebrospinal fluid

All but one patient had a pleocytosis in the initial CSF sample (range: 1–3860 $\times$ 10^6/L; median 181 $\times$ 10^6/L). The CSF leukocyte differential count was available for 93 patients. In 73 patients (78%) more than 50% of the cells were lymphocytes, but in 20 patients (22%) the CSF leukocytes were predominantly polymorphs. The CSF protein concentration was elevated in 95% of the patients (range: 0.19–44.0 g/L; median: 1.79 g/L). The CSF glucose was less than 2.5 mmol/L in 66/101 patients (65%) and less than 1.0 mmol/L in 20% (median: 1.8 mmol/L). Acid-fast bacilli were identified in the CSF with the Ziehl–Neelsen (ZN) stain in 16/95 (17%) patients. The PCR assay for *M. tuberculosis* DNA in the CSF was positive in 17/22 (77%) patients who were tested. Of the 17 PCR-positive patients, *M. tuberculosis* grew in CSF cultures of 12 patients and from another site in two patients. In the other three patients, cultures for *M. tuberculosis* were negative. In one of the five PCR-negative patients, *M. tuberculosis* was grown in CSF cultures, but the other PCR-negative patients had negative cultures.

3.3. Other investigations

Hyponatraemia was present at presentation in 64/101 (63%) patients (range: 115–147 mmol/L). In 32% the serum sodium was less than 130 mmol/L. An abnormality on CT scan was noted in 44/59 (75%) patients: ventricular enlargement in 27 patients (46%), meningeal enhancement in 24 (41%) and an infarct in 10 patients (17%). The MRI was abnormal in 10/10 patients. In addition to meningitis, 59 patients (57%) also had tuberculosis outside the central nervous system. The chest X-ray was abnormal in 55 patients (53%).

A meningeal or brain biopsy was obtained in 10 patients, which showed granulomatous inflammation in two patients, non-specific inflammation in five patients and normal findings in two patients. The tissue from one patient was submitted only for ZN stain and culture. Cultures were negative in all 10 patients.

3.4. Treatment

In three patients the diagnosis of tuberculous meningitis was not made until post mortem and they had not been treated with anti-tuberculosis treatment. The other 101 patients received anti-tuberculosis treatment. The combination of antibiotics and the duration of treatment varied because management decisions were made by individual clinicians. Three patients were treated with

two drugs with activity against *M. tuberculosis*, but the other 98 patients received three or four anti-tuberculosis drugs. The median duration of treatment, which was known in 67 of the 85 patients who survived until discharge from hospital, was 12 months (range: 3–36 months). An organism resistant to one or more anti-tuberculosis drugs was identified in four patients. One of these patients had a concurrent infection with the human immunodeficiency virus. Three of the patients with a drug-resistant organism had a poor outcome. Sixty patients (58%) received corticosteroids in addition to anti-tuberculosis treatment.

3.5. Difficulties in the diagnosis and treatment

Tuberculous meningitis was considered in the differential diagnosis by the admitting team in 51 patients (49%). In the 101 patients in whom the diagnosis was made before death, the median delay between admission and the start of anti-tuberculosis treatment was 2 days (range: 0–45 days). The median delay was 2 days for each of the first 3 decades and 1 day from 1995 to 2004.

Several reasons for a delay in the diagnosis of tuberculous meningitis of more than 3 days after hospital admission were identified. Tuberculous meningitis was not initially suspected in 11 patients (11%) with an oligo-symptomatic presentation, who were initially thought to have a systemic infection rather than meningitis. Three of these patients were less than 2 years old and presented with fever, irritability, drowsiness, failure to thrive, cough, nausea and vomiting. The other eight patients with an oligo-symptomatic presentation were older (mean age: 57 years; range: 27–81 years) and presented with only 1 or 2 of the following symptoms: headache, fever, mild confusion and non-specific systemic symptoms. Altered mental state and fever were initially attributed to a systemic illness in another four adults aged 49 years to 75 years, who had unrecognised spinal or articular tuberculosis. In two patients who presented with a posterior fossa mass, a diagnosis of tuberculous meningitis was not considered until biopsy of the lesion showed granulomatous inflammation. One patient presented with unexplained thrombocytopenia and during the admission developed headache, fever and vomiting. An incomplete history contributed to delay in the diagnosis of tuberculous meningitis in a 30-year old street-dweller found lying on the roadside. She was obtunded, severely confused and febrile. She was treated for suspected herpes simplex encephalitis, but died soon after admission. The diagnosis of tuberculous meningitis was made at autopsy.

In another 12 patients (12%) a lumbar puncture was performed promptly, but anti-tuberculosis treatment was delayed for more than 3 days after the lumbar puncture was performed. In six of these patients the CSF abnormalities were initially attributed to non-tuberculous bacterial meningitis and at first they were treated with antibiotics with no activity against *M. tuberculosis*. Three of these six patients died. Another patient had an atypical presentation with headache, unilateral cavernous sinus syndrome and lymphocytic pleocytosis, and treatment was delayed because of initial uncertainty about the diagnosis. In one patient the leukocyte count was normal in the first CSF specimen. In the other four patients the reason for a delay in starting treatment after a lumbar puncture was unclear.

3.6. Outcome

Tuberculous meningitis was complicated by hydrocephalus in 44 patients (42%) and 34 patients (33%) developed a stroke during the course of their illness. The median ages of the patients with (27.5 years) and without a stroke (28.5 years) were similar. At last follow-up, 52% of patients had made a good recovery (GOS score 5), 12% had moderate disability (GOS score 4) and 36% had a poor outcome (GOS score 1–3) (Table 2). The frequency of a poor outcome during each decade was 37% in 1965–74, 41% in 1975–84, 32% in 1985–94 and 35% in 1995–2004. In the logistic regression analysis the only factors that were significant predictors of a poor outcome were the MRC stage at presentation (chi-squared test [χ^2] 0.038; odds ratio [OR] 0.425, 95% confidence limits 0.190, 0.953), the presence of a stroke (χ^2 0.002; OR 0.189, 95% confidence limits 0.067, 0.533) and a diagnosis of definite tuberculous meningitis (χ^2 0.007; OR 0.188, 95% confidence limits 0.056, 0.633). A poor outcome was more common when treatment was delayed more than 3 days (47%) than if there was no delay (31%), but the time from admission to hospital to the initiation of treatment was not a significant predictor of outcome in the logistic regression analysis. There was a poor outcome in 71% of patients with MRC stage 3 on admission to hospital. Two of the three patients who received only two anti-tuberculosis drugs died in hospital.

4. Discussion

As in other developed countries, tuberculosis was an uncommon cause of meningitis at Auckland Hospital. Only two or three patients presented with tuberculous meningitis each year. In countries where there is a low prevalence of tuberculosis, tuberculous meningitis is more common in adults.[7,13,18] In Auckland Hospital the median age was only 28 years and almost one-quarter of the patients were younger than 5 years old. Alcoholism and other chronic debilitating diseases increase the risk of developing tuberculous meningitis.[2–4,19–21] Fifteen patients (14%) had alcoholism, but 79% of patients did not have a predisposing illness. Patients co-infected with HIV and *M. tuberculosis* have a particularly high risk of developing tuberculous meningitis,[22] but only one patient had tuberculous meningitis and concurrent HIV infection.

The gold standard for the diagnosis of tuberculous meningitis is the growth of *M. tuberculosis* from the CSF, but 4 to 8 weeks are required for cultures to become positive and up to 45% of patients with presumed tuberculous meningitis have negative CSF cultures.[23] The ZN stain and assays employing amplification of *M. tuberculosis* DNA are faster methods of diagnosis. The specificity of tests using nucleic acid amplification is 98%, but the sensitivity is only 56%. A negative result can not be used alone to exclude tuberculous meningitis.[24] In our study, the PCR assay was positive in three patients in whom CSF cultures were negative. In five patients the PCR assay was negative, but only one of those patients had positive cultures for *M. tuberculosis*. The ZN stain is helpful if positive, but in most laboratories, including Auckland Hospital, acid-fast bacilli are found in the CSF in less than 20% of patients with tuberculous meningitis.[3,4,10,19–21,25] Extra diagnostic information may come from repeating the lumbar puncture when the initial CSF specimen is not diagnostic of tuberculous meningitis.

Leptomeningeal biopsy usually showed non-specific inflammation and cultures of the leptomeninges were negative. Biopsy of clinically involved extra-neural tissue is more likely to confirm the diagnosis of tuberculosis than a leptomeningeal biopsy.[15,26]

Table 2
Outcome in 104 patients after tuberculous meningitis by Glasgow Outcome Scale score

GOS score	Definition	Total *n* (%)
1	Death	23 (22)
2	Persistent vegetative state	1 (1)
3	Severe disability	14 (13)
4	Moderate disability	12 (12)
5	Good recovery	54 (52)

We have had no experience with other methods for the early diagnosis of tuberculous meningitis.[13]

A delay in starting anti-tuberculosis medications is associated with a higher rate of mortality and serious neurological sequelae among survivors. In the absence of a rapid and highly sensitive test for tuberculous meningitis, decisions about treatment often must be made before the diagnosis has been confirmed. However, the diagnosis of tuberculous meningitis is often challenging in countries where tuberculosis is an uncommon cause of meningitis. The clinical, CSF and imaging findings are non-specific, but can help identify patients with tuberculous meningitis.

Tuberculous meningitis is more common in Maori people and immigrants from countries where tuberculosis has a high incidence.[27,28] In Auckland 70% of the patients with tuberculous meningitis had a Pacific, Maori or Asian ethnic background. Europeans constitute two-thirds of the Auckland population, but only 28% of the patients with tuberculous meningitis were European. A past or family history of tuberculosis and contact with a person affected by tuberculosis should immediately raise concern that meningitis is caused by *M. tuberculosis*.[25]

The duration of symptoms before admission varied from a few days to many months, but tuberculous meningitis typically has a longer history than bacterial or viral meningitis.[29,30] The median duration of symptoms before admission to Auckland Hospital (3 weeks) was similar to the length of history observed in other large series of patients with tuberculous meningitis.[7,25] Most patients presented with headache, fever, meningism, altered mental state and non-specific symptoms. Tuberculous meningitis typically affects the basal meninges, where it may involve cranial nerves and arteries as they traverse the subarachnoid space. Cranial nerve palsies and other focal signs are more common in tuberculous meningitis than in most other types of chronic meningitis.[15]

When present, severe hyponatraemia helps to distinguish tuberculous meningitis from other causes of chronic meningitis, but other blood tests are usually unhelpful.[4,12,15,19,20] The typical CSF profile of tuberculous meningitis is a mild to moderate lymphocytic pleocytosis, increased protein and reduced glucose concentration,[11,18,29] but exceptions were common in our patients. The CSF leukocyte count and protein concentration occasionally were normal, polymorphs outnumbered lymphocytes in 22% of the patients and the CSF glucose was normal in one-third.

The Mantoux test is often negative in patients with tuberculous meningitis.[7,18] A positive Mantoux test occurs after the Bacille Calmette-Guerin (BCG) vaccination, which has been widely used in New Zealand. Fifty-seven percent of our patients had extra-neural tuberculosis and when present, it was a helpful clue to the diagnosis of tuberculous meningitis. In several patients, however, the significance of monoarticular arthritis, haematuria or a cold abscess was overlooked.

Neuroimaging shows basal meningeal enhancement and hydrocephalus in many patients with tuberculous meningitis. However, these abnormalities occur with other causes of chronic meningitis and typical changes may be absent in older patients.[31–33] The presence of a cerebral infarct is a useful clue that *M. tuberculosis* is the cause of the meningitis.

In one-half of our patients tuberculous meningitis was not considered in the admitting differential diagnosis and in three patients the diagnosis was not made until post-mortem. Thirty-six percent of the patients had a poor outcome. Other centres have reported similar delays in the diagnosis and treatment of tuberculous meningitis.[4,9,20,21,34,35] A severe neurological deficit (stupor, coma or hemiparesis) at presentation was a predictor of a poor outcome. A poor outcome was more common when treatment was delayed more than 3 days after presentation, but the time between presentation and treatment was not a significant predictor of outcome in the logistic regression analysis. Any effect of a delay in starting treatment on outcome was overshadowed by the severity of the neurological deficit at presentation. Patients who were obtunded (MRC stage 3) usually had a poor outcome regardless of the time taken to start treatment.

The diagnosis of tuberculous meningitis was most difficult in young children and older patients presenting with relatively mild symptoms, which were incorrectly attributed to a suspected systemic infection. Failure to recognise tuberculosis as the cause of concurrent extra-neural infection also contributed to a delay in diagnosis. Another common problem, especially in patients with an acute presentation with tuberculous meningitis, was attribution of the CSF abnormalities to non-tuberculous bacterial meningitis. Some of these patients had a polymorphonuclear cell-predominant pleocytosis. An atypical clinical presentation led to a delay in diagnosis in only one patient. Tuberculous meningitis can present with a myeloradiculopathy, but we observed this only as a late complication in three patients. Recognition of the difficulties in the diagnosis of tuberculous meningitis should facilitate earlier diagnosis and treatment.

Acknowledgements

The assistance of Ian Wood in the statistical analysis and the financial support of the Julius Brendel Trust are gratefully acknowledged.

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