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Clinical Study

Neurological and systemic complications of tuberculous meningitis and its treatment at Auckland City Hospital, New Zealand

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ABSTRACT

Mortality and serious long-term sequelae still occur in about 50% of patients with tuberculous meningitis. The frequency and the clinical features of neurological and systemic complications were determined in a retrospective review of 104 patients with tuberculous meningitis. Complications occurred in 81 patients (78%). The most common complications were: hyponatraemia 49%, hydrocephalus 42%, stroke 33%, cranial nerve palsies 29%, epileptic seizures 28%, diabetes insipidus 6%, tuberculoma 3%, myeloradiculopathy 3% and hypothalamic syndrome 3%. The most common iatrogenic complication was hepatotoxicity related to anti-tuberculosis treatment in seven patients. Twenty-three patients (22%) died. At last follow-up one patient (1%) remained in a persistent vegetative state, 14 patients (13%) had severe disability and 12 patients (12%) were moderately disabled. The most common complications in the 81 long-term survivors were cognitive impairment (12%) and epilepsy (11%). Neurological and systemic complications of tuberculous meningitis were common and were important causes of mortality and long-term morbidity.

1. Introduction

Neurological and systemic complications are important causes of morbidity and mortality in tuberculous meningitis. Mortality and serious long-term sequelae still occur in about 50% of patients with tuberculous meningitis despite anti-tuberculosis treatment.[1] We have retrospectively reviewed 104 patients who presented to the Auckland City Hospital with tuberculous meningitis over a 40-year period. The clinical features, results of investigations and outcome at the time of discharge from hospital have been reported in the *Journal of Clinical Neuroscience*.[2] In this paper we describe the neurological and systemic complications observed in these patients.

2. Methods

Patients who presented to Auckland Hospital from 1965 to 2004 with tuberculous meningitis were identified from several sources: a retrospective review of chronic meningitis which included patients from 1965 to 1983,[3] hospital discharge diagnoses and the results of culture for *Mycobacterium tuberculosis* (*M. tuberculosis*) and of a polymerase chain reaction (PCR) assay for *M. tuberculosis* deoxyribonucleic acid (DNA) in cerebrospinal fluid (CSF), which has been available in the Auckland City Hospital Microbiology Laboratory since 1994. Patients were considered to have definite tuberculous meningitis if all of the following criteria were met: (i) the patient had one or more of the following clinical features – headache, neck stiffness, altered mental state or fever; (ii) the CSF leukocyte count was greater than 5×10^6/L; and (iii) either *M. tuberculosis* was cultured from the CSF or another site, or the PCR assay for *M. tuberculosis* 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 the diagnosis was confirmed 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 treatment with anti-tuberculosis treatment.

Each patient's hospital records were reviewed and the clinical features, results of investigations, treatment and outcome were recorded. The data were entered on to a Microsoft Excel spreadsheet. The severity at presentation was assigned according to Medical Research Council (MRC) criteria following review of the medical records: stage 1, fully conscious and rational without focal signs; stage 2, lethargy, altered behaviour, meningism or minor focal signs; and stage 3, stupor, coma, or a severe focal neurological deficit.[4]

Long-term outcome was determined by review of the patients' notes. The median duration of follow-up among survivors was 18 months (range: 1–197 months). The Glasgow Outcome Scale (GOS) score was used to grade the outcome at last follow-up: 1,

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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 even though there may be minor neurological and psychological deficits).[5]

A stroke was defined as rapidly developing symptoms and/or signs of a focal or, at times, global loss of cerebral function lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin.[6] In patients who presented before CT scanning became available in Auckland Hospital in 1977, the diagnosis of stroke was based on a history of abrupt onset of symptoms and signs of a focal brain lesion. The clinical features, CSF findings and the outcome of patients with and without stroke were compared by the chi-squared (χ^2) test.

3. Results

A total of 104 patients, 61 males and 43 females, presented with tuberculous meningitis during the 40 years of the study. Seventy-one patients (68%) had definite tuberculous meningitis and 33 patients (32%) had probable tuberculous meningitis. Complications occurred in 81 of the 104 patients (78%) (Table 1). Most patients had multiple complications.

3.1. Hydrocephalus

Hydrocephalus was the most common neurological complication. Forty-four patients (42%) developed hydrocephalus and of these, 23 (22%) were treated with a ventricular drain or a shunt.

3.2. Stroke

In 34 patients (33%), 18 males and 16 females, tuberculous meningitis was complicated by a stroke: in 26 of the 71 patients (37%) with definite tuberculous meningitis and eight of the 33 patients (24%) with probable tuberculous meningitis. The median age of the patients with stroke was 27.5 years (range: 1–80 years). The stroke group had a significantly higher frequency of focal neurological signs, hydrocephalus and Stage 3 disease at presentation than patients without stroke (Table 2). There were no significant differences in the other presenting symptoms or signs, although there was a trend towards a greater frequency of altered mental state in the stroke group. The CSF protein concentration, glucose concentration, leukocyte count and the proportion of neutrophils were not significantly different between the two groups. There was a greater frequency of a poor outcome (GOS score 1–3) at last follow-up in the stroke group (67%) than in the non-stroke group (21%) ($p < 0.001$).

Table 1
Frequency of complications in 104 patients with tuberculous meningitis

	n	(%)
Hyponatraemia[1]	51	(49)
Hydrocephalus	44	(42)
Stroke	34	(33)
Cranial nerve palsies	30	(29)
Epileptic seizures	29	(28)
Diabetes insipidus	6	(6)
Tuberculoma	3	(3)
Myeloradiculopathy	3	(3)
Hypothalamic syndrome	3	(3)
Addison's disease	1	(1)
Cortical blindness	1	(1)
Syringomyelia	1	(1)
Cavernous sinus syndrome	1	(1)
Acute tubular necrosis	1	(1)
Severe metabolic acidosis	1	(1)

[1] Serum sodium ion ($[Na^+] \leqslant 130$ mmol/L).

Table 2
Patient characteristics, presenting symptoms and signs, cerebrospinal fluid analysis and outcome in patients with and without stroke

	Stroke ($n = 34$)	No stroke ($n = 70$)	*p* value
Definite TB meningitis	26 (76)	45 (64)	ns
Males	18 (53)	43 (61)	ns
Age range (yrs)	1–80	1–81	
Median age (yrs)	27.5	28.5	ns
Presenting symptoms and signs			
Headache	21 (62)	51 (73)	ns
Fever	31 (91)	55 (79)	ns
Neck stiffness	24 (71)	48 (69)	ns
Seizures	9 (26)	11 (16)	ns
Cranial nerve palsies	11 (32)	22 (31)	ns
Altered mental state	28 (82)	44 (63)	ns
Focal signs	14 (41)	10 (14)	<0.01
Stage of disease at presentation			
Stage 1	3 (9)	21 (30)	
Stage 2	16 (47)	43 (61)	
Stage 3	15 (44)	6 (9)	<0.001
CSF			
Median leukocyte count ($\times 10^6$/L)	140	215	
Median protein (g/L)	1.78	1.80	
Median glucose (mmol/L)	1.8	1.8	
Hydrocephalus	21 (62)	23 (33)	<0.01
Outcome (GOS score)			
Grade 1	13 (38)	10 (14)	
Grade 2	1 (3)	0 (0)	
Grade 3	9 (26)	5 (7)	
Grade 4	6 (18)	6 (9)	
Grade 5	5 (15)	49 (70)	

CSF = cerebrospinal fluid, ns = not significant, GOS = Glasgow Outcome Scale score, TB = tuberculosis, yrs = years.

Twenty-nine patients (85%) in the stroke group had a severe encephalopathy with superimposed focal neurological signs, two patients (6%) had focal signs with normal mental status and in three patients (9%) the stroke was associated with a severe encephalopathy without focal neurological symptoms or signs. In one patient, a 21-year-old woman, stroke was the main presenting manifestation of tuberculous meningitis. The patient was afebrile, but mild neck stiffness was noted on admission.

The type of stroke could be determined by imaging or autopsy in 23 of the 34 patients. Twenty-two patients had cerebral infarcts, which were multiple in 12 and single in 10 patients. The infarcts were located in the basal ganglia in seven patients, the thalamus in five patients and the internal capsule in three patients. Three patients had brain stem infarcts; one a cerebellar infarct and six patients had a cortical hemispheric infarct (middle cerebral artery territory in three patients, anterior cerebral artery in one patient and posterior cerebral artery in two patients). In one patient the infarct was associated with an intracerebral haemorrhage in another part of the brain. Another patient, a 32-year-old man, had been gradually improving after starting anti-tuberculosis treatment. After 7 weeks of treatment, he abruptly lost consciousness. A CT scan showed haemorrhage in the midbrain and ventricles. He died 24 hours later and post-mortem examination showed gelatinous exudates and granulomata around the base of the brain. An aneurysm adjacent to the midbrain had ruptured into the brain stem, ventricles and subarachnoid space. Histological examination of the aneurysm showed granulomatous inflammation in its wall.

3.3. Cranial nerve palsies

Thirty patients (29%) developed one or more cranial nerve palsies affecting the abducens nerve in 13 patients, oculomotor nerve in 12 patients, optic nerve in five patients, vestibulocochlear nerve in four patients, trigeminal nerve in three patients, facial nerve in

three patients and trochlear nerve in one patient. Another patient had an oculomotor palsy that was not described in greater detail in the hospital notes.

3.4. Epilepsy

Epileptic seizures occurred in 29 patients (28%) during the hospital admission. Partial and secondary generalised seizures were the most common seizure types, but detailed information on the seizures was not available for many patients.

3.5. Tuberculoma

A tuberculoma was identified in only three patients, but other patients were probably missed.

3.6. Spinal complications

A myeloradiculopathy causing sphincter dysfunction, and lower limb weakness and sensory loss, occurred in three patients. The CSF protein concentration was greater than 5 g/L in two of these patients. In two of these patients, the myeloradiculopathy was a late complication, but in the other patient, paraplegia and urinary retention developed 10 days after admission to hospital.

One patient presented 3 years after he was treated for tuberculous meningitis with a progressive neurological deficit caused by syringomyelia. There was no improvement after insertion of a syringoperitoneal shunt.

3.7. Hyponatraemia

Hyponatraemia was the most common systemic complication of tuberculous meningitis. The serum sodium ion (Na^+) concentration at presentation ranged from 115 mmol/L to 147 mmol/L (mean: 131.9 mmol/L) and was less than 135 mmol/L in 67 (64%) patients. Almost one-half of the patients developed significant hyponatraemia (serum $Na^+ \leqslant 130$ mmol/L) during hospitalisation. One patient developed Addison's disease.

In another patient bilateral adrenal infarction was found at post-mortem examination, but adrenal function had not been assessed during life.

3.8. Hypothalamic dysfunction

Diabetes insipidus developed in six patients during the acute phase of their illness. Hypothalamic dysfunction was a late complication in three patients. A 15-year-old boy with moderate cognitive impairment following an episode of tuberculous meningitis developed hyperphagia, personality change and aggressive behaviour 5 months after starting treatment for tuberculosis. His weight increased from 84 kg to 120 kg over the next 4 months. A 3-year-old girl recovered after treatment for tuberculous meningitis, but 4 years later she developed precocious puberty. A third patient had growth hormone deficiency, global developmental delay and severe epilepsy after an episode of tuberculous meningitis when she was 2 years old.

3.9. Complications of treatment

Treatment-related complications occurred in 15 patients (14%) (Table 3). Hepatotoxicity was the most common of these complications. In one patient hepatotoxicity was related to phenytoin, but in another seven patients it was caused by anti-tuberculosis medications.

3.10. Complications in survivors

Twenty-three patients (22%) died in hospital. At last follow-up 54 patients (52%) had made a good recovery (GOS score 5), 12 patients (12%) had moderate disability (GOS score 4), 14 patients (13%) were severely disabled (GOS score 3) and one patient (1%) remained in a persistent vegetative state (GOS score 2). The long-term complications in the survivors are listed in Table 4.

4. Discussion

The frequency of neurological complications was probably underestimated in this study. The data were collected retrospectively and many patients did not have neuroimaging, because they presented before CT scanning and MRI were available. Without brain imaging, many tuberculomas and some cerebral infarcts were probably missed.

Stroke occurred in one-third of our patients. In most clinical and imaging studies, the frequency of stroke has varied from 20% to 66%,[7–18] but lower frequencies have been reported.[19] Variations in the frequency of stroke are probably related to differences in patient selection, different methods of diagnosis of stroke and the use of different definitions for tuberculous meningitis. Diffusion-weighted imaging may detect infarcts that are not visible on T2-weighted MRI.[16]

Necrotising granulomatous exudates in the basal leptomeninges can affect the arteries in the circle of Willis and their deep penetrating branches as they traverse the subarachnoid space.[8,20] Vasculitic abnormalities first appear in the adventitia and spread through the arterial wall to cause a necrotising panarteritis and thrombosis. Vasospasm and ventricular dilatation may contribute to constriction of arteries already compromised by vasculitis.[9,13,21] After recovery from the acute illness, fibrosis around blood vessels

Table 3
Frequency of iatrogenic complications

Complication	Cause	*n*
Hepatotoxicity	Anti-tuberculous drugs	7
	Phenytoin	1
Peripheral neuropathy	Isoniazid	1
Rash	Rifampicin	1
Polyarticular gout	Pyrazinamide	1
Retinopathy	Ethambutol	1
Neutropenic sepsis	Para-aminosalicylic acid	1
Haemothorax	Central line insertion	1
Pyogenic meningitis	Lumbar puncture	1

Table 4
Frequency of long-term complications among 81 surviving patients following treatment for tuberculous meningitis

Complication	*n*	(%)
Cognitive impairment	10	(12)
Epilepsy	9	(11)
Oculomotor palsy	5	(6)
Hemiparesis	4	(5)
Severe hearing loss	4	(5)
Hemi-ataxia	3	(4)
Homonymous hemianopia/cortical blindness	3	(4)
Hypothalamic dysfunction	3	(4)
Dysphasia	2	(2)
Myeloradiculopathy	2	(2)
Other complications[1]	10	(12)

[1] Other complications occurred in one patient each: peripheral neuropathy secondary to isoniazid, syringomyelia, quadriplegia, personality disorder, hemineglect, gait ataxia, trigeminal neuropathy, nystagmus, and bilateral optic neuropathy.

in the subarachnoid space can cause late-onset infarcts.[8,10] Angiography typically shows focal narrowing of the arteries at the base of the brain, most commonly in the terminal portions of the internal carotid arteries and the proximal segments of the middle and anterior cerebral arteries.[8,11] Angiography may be normal if the stroke has been caused by occlusion of a small penetrating artery.

The strokes associated with tuberculous meningitis are usually ischaemic.[17] The infarcts are often multifocal and haemorrhagic conversion is common.[16] The infarcts are often in areas supplied by the deep penetrating arteries: the basal ganglia, internal capsules and thalamus, but cortical and subcortical infarcts are not uncommon.[9–11,13–17]

In one patient, stroke was the first manifestation of tuberculous meningitis, but most infarcts occurred after starting treatment. Our patients with tuberculous meningitis and stroke typically presented with a severe encephalopathy (stupor or coma) and focal neurological signs, but in some patients focal signs were not present. Uncommonly, patients had an abrupt onset of focal neurological symptoms without a severe encephalopathy. In one study movement disorders occurred in one-sixth of patients with tuberculous meningitis and were often related to infarcts in the internal capsules, basal ganglia, diencephalon and mesencephalon.[22] The most common movement disorder was a postural and kinetic tremor, but chorea, dystonia, ballismus and myoclonus also occurred.

In other studies, cerebral infarction has been associated with hydrocephalus, cranial nerve palsies, seizures, a greater proportion of neutrophils in the CSF and meningeal enhancement on CT scans or MRI.[10,15] In our patients, hydrocephalus was significantly more common in the stroke group, but stroke was not associated with other abnormalities. In our patients and in other series, the development of a stroke was associated with a worse prognosis.[9,13,15,16] Cerebral infarcts occur in a smaller proportion of patients treated with dexamethasone than in those receiving placebo.[14] It is not known if anti-thrombotic treatment is beneficial and there is no consistent evidence that early ventricular shunting prevents cerebral infarction.

Intracerebral and subarachnoid haemorrhage caused by bacterial invasion of the arterial wall and rupture of a mycotic aneurysm is a rare complication of tuberculous meningitis.[23–25] Rupture of a mycotic aneurysm may be a late complication. Intracerebral haemorrhage occurred in two of our patients.

Leptomeningeal exudates can cause hydrocephalus by obstructing the flow of CSF from the fourth ventricle, or impairing absorption of CSF by the arachnoid villi. Obstruction of the cerebral aqueduct by a tuberculoma is a less common cause. Hydrocephalus occurred in 42% of our patients. The true frequency was probably higher, because not all patients had neuroimaging. Hydrocephalus is usually present on admission with tuberculous meningitis[27] and when all patients with tuberculous meningitis have been investigated with imaging, hydrocephalus was present in 45% or more.[8,14,26,27] Ventriculo-peritoneal shunting is advocated in patients with obstructive hydrocephalus, or persistent coma,[14] but the timing of shunt surgery, the need for external ventricular drainage or intraventricular pressure monitoring to predict the response to shunting, and the role of corticosteroids are controversial. In some series hydrocephalus has predicted a poor outcome,[12] but surgical drainage does not consistently improve the long-term outcome.[21] Corticosteroids may reduce the number of patients with tuberculous meningitis who develop hydrocephalus.[14]

Cranial neuropathies occurred in 29% of our patients and in 20% to 52% of patients with tuberculous meningitis in other series.[1,18,28,29] The sixth and third cranial nerves were most frequently affected. Cranial nerve lesions usually result from ischaemia or entrapment of the nerve in the subarachnoid space, but tuberculomas in the cerebellopontine angle or the brain stem can compress cranial nerves.[8]

Tuberculomas were uncommon among our patients with tuberculous meningitis, but this was probably due to the low frequency of MRI. When all patients with tuberculous meningitis have been studied with MRI, tuberculomas have been found in up to three-quarters of patients.[14,30] Tuberculous brain abscess is a rare complication, most commonly seen in patients with tuberculous meningitis and concurrent human immunodeficiency virus (HIV) infection.[31] We did not encounter this complication among our patients, but only one patient had an HIV infection.

Three of our patients developed a myeloradiculopathy. The clinical manifestations were radicular pain, sensory loss, mixed upper and lower motor neuron signs in the legs, and sphincter dysfunction. Myeloradiculopathy is caused by leptomeningeal exudates encasing the spinal cord, nerve roots and blood vessels.[32–35] Impairment of venous drainage may result in spinal cord oedema, while infarction of the spinal cord may be secondary to vasculitic occlusion of a spinal artery.[33] The CSF protein concentration is often very high. Myeloradiculopathy can be the primary manifestation of neurological tuberculous infection, or as in our patients, it may appear days, weeks or months after the onset of intracranial manifestations of tuberculous meningitis. Corticosteroids are usually recommended, but convincing evidence of benefit is lacking. Other causes of myelopathy in patients with tuberculosis include intramedullary tuberculoma and spinal cord compression by an intradural or extradural granuloma, or tuberculosis in the vertebral body.[36] Syringomyelia is a rare, delayed complication of arachnoiditis following tuberculous meningitis, which was seen in one of our patients. There is usually a delay of years before the onset of syringomyelia, but occasionally it develops in the first few weeks.[37,38] Surgical drainage of the syrinx may produce a short-term improvement, but the longer term results of surgery are often unsatisfactory.

In children tuberculosis can cause a border-zone encephalitis with oedema, gliosis and perivascular inflammation in the cerebral cortex, but no overt infarction.[39] Typical clinical manifestations include a severe encephalopathy with coma, seizures, involuntary movements and bilateral upper motor neuron signs. Border-zone encephalitis is hard to recognise on MRI, because the increased signal on T2-weighted MRI merges with the signal associated with the leptomeningeal exudates.[40]

In our patients hyponatraemia was the most common metabolic complication. Hyponatraemia occurs in up to 85% of patients with tuberculous meningitis.[18,28,29] Formerly, it was believed that hyponatraemia was secondary to inappropriate antidiuretic hormone secretion, which is managed with fluid restriction.[28] In most patients with tuberculous meningitis, however, hyponatraemia is caused by a cerebral salt wasting syndrome characterised by increased urinary sodium excretion and depletion of extracellular fluid volume.[41] Excessive secretion of atrial natriuretic peptide and brain natriuretic peptide, and a direct neural influence on renal function are involved in the pathogenesis.[42] The cerebral salt wasting syndrome should be treated with volume and salt replacement. Fludrocortisone may be beneficial.[42] Hyponatraemia also can be caused by adrenal failure, which occurred in one of our patients. Other metabolic and endocrine complications of tuberculous meningitis are rare, but hypothalamic complications including precocious puberty and hyperphagia may occur.[43]

Complications of anti-tuberculosis medications occurred in 14% of our patients, but the true frequency of iatrogenic complications probably was greater. Drug-induced hepatitis is the most serious adverse effect of anti-tuberculosis treatment.[44] It can lead to interruption of treatment and in some patients hepatitis is fatal. Isoniazid, rifampin and pyrazinamide are all potential causes of liver disease. Dexamethasone decreases the occurrence of severe hepatitis caused by anti-tuberculosis medication.[45]

Cognitive impairment and epilepsy were common sequelae among our long-term survivors. Permanent visual loss due to

bilateral optic neuropathies or occipital lobe infarction, epilepsy, cranial nerve palsies, hydrocephalus, sexual precocity, obesity and diabetes insipidus also can occur in survivors of tuberculous meningitis.[43,46]

Neurological and systemic complications are common and significant factors contributing to the high rate of mortality and long-term sequelae of tuberculous meningitis. Corticosteroids reduce the frequency of death and disabling neurological deficits amongst survivors,[47] but the best chance of reducing the risk of severe complications is by early diagnosis and treatment of tuberculous meningitis.

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