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Cerebral infarction in chronic meningitis: a comparison of tuberculous meningitis and cryptococcal meningitis

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Summary

Twenty-eight patients with cerebral infarction secondary to chronic meningitis were retrospectively identified at our institution over a period of 5 years. They accounted for 47% (17/36) of tuberculous meningitis (TBM) and 32% (11/34) of cryptococcal meningitis cases. Single infarctions were found in 15 patients and multiple infarctions in 13. The distribution of single infarctions was: basal ganglia 7; internal capsule 3; thalamus 1; cerebellum 1; and cortical infarct 3. Therapeutic outcomes at 3 months were determined using a modified Barthel Index. At follow-up of 3 months or more, 10 had good outcomes while the other 18 had poor outcomes. The 18 with poor outcomes included six who died, and 12 who had severe neurological sequelae. TBM and cryptococcal meningitis shared similar clinical features, both being frequently associated with other neurological complications, including hydrocephalus, cranial nerve palsy, and seizures in our patients. However, extracranial involvement, such as spinal and pulmonary involvement, was more commonly found in TBM patients. Cerebral infarction can occur in both the acute stage and later stages of treatment. Mortality and morbidity are high, and early diagnosis and appropriate antimicrobial treatment are essential. If hydrocephalus is demonstrated, early ventricular decompression is needed to prevent further cerebral ischaemia.

Introduction

Tuberculous meningitis (TBM) and cryptococcal meningitis are the two most common types of chronic meningitis, and they share similar clinical features and cerebrospinal fluid (CSF) findings.[1,2] In Western countries, both are common opportunistic types of life-threatening meningitis, and important causes of morbidity and mortality among immunocompromised patients.[3–5] Despite the advent of new antimicrobial drugs and modern imaging techniques, mortality and morbidity remain high.[1,2,6–8] Delay in diagnosis and treatment is directly related to a poor outcome, including various degrees of residual neurological sequelae.[1,2,6–8] Cerebral infarction secondary to infection is a common complication of chronic meningitis, but little information about its epidemiology and therapeutic outcome has been collected. Over 5 years, we identified 28 adult

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patients with cerebral infarction secondary to chronic meningitis. We aimed to study and compare: (i) the localization of the cerebral infarctions; (ii) the clinical features relevant to the associated ischaemic lesions; (iii) the association between cerebral infarctions and other neurological complications such as hydrocephalus and basal exudates; and (iv) the therapeutic outcome of TBM and cryptococcal meningitis. We hoped to improve our therapeutic strategies for this group of patients.

Methods

Over a period of 5 years (1995–99), 70 patients at Kaohsiung Chang Gung Memorial Hospital, aged 16 years or older, were retrospectively identified as having chronic meningitis, including 36 with tuberculous meningitis (TBM) and 34 with cryptococcal meningitis. This facility is a 2482-bed acute-care teaching hospital, the largest medical centre in southern Taiwan, which provides both primary and tertiary referral care of patients. Of these 70 patients, 28 suffering from cerebral infarction secondary to meningitis were enrolled in this study.

Cerebral infarction was defined according to WHO criteria,[9] and cerebral infarction secondary to chronic meningitis was defined as new-onset cerebral infarction demonstrated by brain computed tomographic (CT) scan or magnetic resonance imaging (MRI) during hospitalization. The pathogenesis of ischaemic stroke was defined as: (i) large-vessel infarction if the ischaemic event was due to atherosclerosis of large vessels or cardioembolism; or (ii) lacunae if the ischaemic event was due to the occlusion of perforating arteries. Patients were considered to have multiple infarctions if at least two locations with infarctions were found. A multiple infarction at more than one location which included a large-vessel infarction, was classified as a large-vessel infarction.

TBM was defined as either: (i) isolation of *Mycobacterium tuberculosis* in one or more CSF cultures and/or positive polymerase chain reaction (PCR) with clinical features of chronic meningitis; or (ii) isolation of M. *tuberculosis* from outside the CNS, with clinical presentations of chronic meningitis, and typical CSF features.[10,11] Cryptococcal meningitis was defined as either: (i) isolation of *Cryptococcus neoformans* in one or more CSF cultures, positive CSF cryptococcal antigen titre, or positive CSF India ink and clinical features of meningitis, or (ii) isolation of *C. neoformans* in blood culture with clinical presentations of meningitis and typical CSF features.[2] Patients were excluded from the study (i) if they had evidence of concomitant acute meningitis not due to *M. tuberculosis* or *C. neoformans*, (ii) if they lacked follow-up for anti-tuberculosis or anti-fungal treatment or (iii) if they had nosocomial or recurrent chronic meningitis.

Cranial CT scans and/or MRI studies were done in all patients at the time of admission, as well as a follow-up CT and/or MRI if clinical deterioration was found. In our institution, PCR for the detection of *M. tuberculosis* was done in accordance with previous descriptions and has been evaluated for its clinical applicability of aiding the diagnosis of TBM.[11]

The therapeutic regimens of TBM consisted of isoniazid (INH) 300 mg/day, rifampicin 450 mg/day, pyrazinamide 1500 mg/day, and ethambutol 800 mg/day.[1,6,7] Patients with cryptococcal meningitis were given antifungal drugs, which included amphotericin B or fluconazole, or both.[2] Patients with increased intracranial pressure (IICP) were given intravenous mannitol. Patients who suffered clinical deterioration during hospitalization were given corticosteroids. Patients with hydrocephalus who also had evidence of IICP or clinical deterioration underwent a ventriculo-peritoneal shunt.

Therapeutic outcomes at 3 months were determined using a modified Barthel Index (BI). For the purposes of analysis, a score <12 was defined as a poor outcome, and $\geqslant 12$ as good. Death was included in the poor outcome group.

Results

The 28 patients included 17 males (aged 16–83 years; mean 55 years) and 11 females (20–83 years; mean 42 years). Of these 28 patients with chronic meningitis, 17 had TBM and 11 had cryptococcal meningitis. The interval between onset of cerebral infarction and hospitalization was 3–30 days (mean 12 days). At follow-up of 3 months or more, 10 had good outcomes and 18 poor outcomes (Table 1). Mean age at onset was 30 years for those patients with a good outcome and 61 years for those with a poor outcome. Of the 28, six had one or more underlying diseases; the underlying diseases were iatrogenic Cushing's syndrome (2), diabetes mellitus (2), systemic lupus erythematosus (1), and acquired immune deficiency syndrome (1).

Clinical manifestations are shown in Table 2. Hydrocephalus (71%), fever (64%), headache (57%), and disturbed consciousness (57%) were the four major manifestations. The others included difficult micturition, seizures, cranial nerve involvement, spinal involvement and syndrome of inappropriate antidiuretic hormone (SIADH). In this study, the abducen nerve was the most commonly involved cranial nerve. Extracranial tuberculosis,

Table 1 Relation between therapeutic outcomes and stroke subtypes

Outcomes	Tuberculous meningitis ($n = 17$)		Cryptococcal meningitis ($n = 11$)		Total (%) ($n = 28$)
	Non-lacunar stroke	Lacunae	Non-lacunar stroke	Lacunae	
Good	2	4	0	4	10 (35.7)
Poor					18 (64.3)
Poor: BI < 12	3	6	2	1	
Poor: death	2	0	4	0	

BI, modified Barthel Index.

Table 2 Relation between therapeutic outcome and clinical features

Clinical features	Tuberculous meningitis ($n = 17$)		Cryptococcal meningitis ($n = 11$)	
	Good outcome	Poor outcome	Good outcome	Poor outcome
Hydrocephalus ($n = 20$)	3	11	1	5
Fever ($n = 18$)	6	7	4	1
Headache ($n = 16$)	6	3	2	5
Disturbed consciousness ($n = 16$)	3	7	1	5
Pulmonary infection ($n = 8$)	2	6	0	0
Micturition disorder ($n = 7$)	0	6	0	1
Cranial nerve involvement ($n = 7$)				
Abducen nerve palsy	2	0	3	1
Optic neuritis	0	1	0	0
Spinal involvement ($n = 4$)				
Infectious spondylitis*	0	2	0	0
Transverse myelitis	0	2	0	0
Seizure ($n = 5$)	0	3	0	2
Peritonitis ($n = 1$)	0	1	0	0
SIADH ($n = 1$)	0	1	0	0

SIADH, syndrome of inappropriate antidiuretic hormone. *One had infectious spondylitis with cervical intramedullary tuberculoma.

diagnosed either before or during hospitalization, was found in 11 patients: pulmonary tuberculosis in six, pulmonary tuberculosis with transverse myelitis in two, spinal involvement in two (infectious spondylitis in one and infectious spondylitis with cervical intramedullary tuberculoma in the other), and peritonitis in one. Various degrees of paraparesis were most often found when the spine was involved, with one in a vegetative state and three in paraparesis. None of our patients with cryptococcal meningitis had extracranial involvement.

The neuroimaging findings of these 28 patients are listed in Table 3. Single infarctions were found in 15 patients and multiple infarctions in 13 (Figures 1, 2a and 2b). The single infarctions were: in basal ganglia 7, internal capsule 3, thalamus 1, cerebellum 1, and cortical infarct 3. Hydrocephalus was found in 20 patients, 17 with communicating hydrocephalus and three with obstructive hydrocephalus. Other neuroimaging findings included gyral enhancement, exudates in basal cistern or sylvian fissures, and space-occupying lesions. Chest radiography was abnormal in eight patients (29%), all of whom had TBM. Of these eight, a miliary pattern was found in three, parenchymal infiltration and/or effusion in two, lobar consolidation in one, and fibroproductive lesion in two.

Treatment produced a good outcome in 35% (6/17) of the TBM group and 36% (4/11) of the cryptococcal meningitis group (Table 1). Severe neurological deficits (Barthel Index < 12) occurred in 53% (9/17) of the TBM group and 27% (3/11) of the cryptococcal meningitis group. Death occurred in 12% (2/17) of the TBM group and 36% (4/11) of the cryptococcal meningitis group. Corticosteroids were given to 19 patients who suffered clinical deterioration during hospitalization: 14 with poor outcomes and five with good outcomes. Ten patients had hydrocephalus and underwent neurosurgical procedures: five with TBM and five with cryptococcal meningitis. Of these 10 patients, the reasons for ventricular relief included deterioration of consciousness in three, persistence of IICP in three, and persistently disturbed consciousness in

four. Of the 10 patients who underwent a surgical procedure during anti-microbial treatment, seven showed improvement despite active CNS infection, while three showed no improvement. In these 10, no micro-organisms were found in either the peritoneum or bloodstream after the neurosurgical procedures. Of the 28 total patients, 22 patients survived and six died: an overall mortality of 21%. Of the 22 survivors, 10 resumed normal life, and 12 were left with various neurological sequelae. The neurological sequelae in the latter 12 cases included vegetative state in five, hemiparesis or paraparesis in six, and poor visual acuity due to ischaemic optic neuritis in one.

Table 3 Neuroimaging findings and proportion of stroke subtypes of patients

Finding	Tuberculous meningitis ($n = 17$)*	Cryptococcal meningitis ($n = 11$)**
1. Cerebral infarction		
a. Non-lacunar stroke	*7 (41%)*	*6 (54%)*
MCA infarct	3	0
Cerebellar infarct	1	0
Multiple	3	6
b. Lacunae	*10 (5%)*	*5 (46%)*
Basal ganglia	4	3
Internal capsule	2	1
Thalamus	1	0
Multiple	3	1
2. Gyral enhancement	6 (35%)	3 (27%)
3. Exudates in basal cistern or in sylvian fissures	7 (41%)	1 (9%)
4. Hydrocephalus	14 (82%)	6 (54%)
5. Cerebral tuberculoma or cryptococcoma	2	1

*Six of these patients had multiple infarctions during hospitalization. **Seven of these patients had multiple infarctions during hospitalization.

Discussion

Differences in the relative prevalence in underlying patient status associated with chronic meningitis vary with geographic and climatic factors, time period, and socioeconomic status.[3–5,12–14] In Western countries, while both cryptococcal meningitis and TBM types of chronic meningitis are common among patients with an immunocompromised state or low socioeconomic status,[3–5] most of our patients did not have severe illnesses before they developed meningitis. Although studies from the tropical and subtropical areas indicated that few patients with cryptococcal meningitis reported had identifiable underlying diseases,[2,12–15] the association with increasing numbers of AIDS patients after 1995 was noted in one study from Northern Taiwan.[15] In Taiwan, tuberculosis is an endemic problem,[16,17] which has recently again become an important public health issue, because of increased incidence in immunocompromised patients,[18] and increasing initial resistance of *M. tuberculosis* to traditional anti-tuberculosis agents. Coccidioidal meningitis, a fungal CNS infection endemic to the southwestern US and Northern Mexico,[19,20] is uncommon in Taiwan.

Cerebral infarction is a common complication found in both TBM and fungal meningitis, and its frequency varies in different study series. Cerebral infarction secondary to TBM can be found in

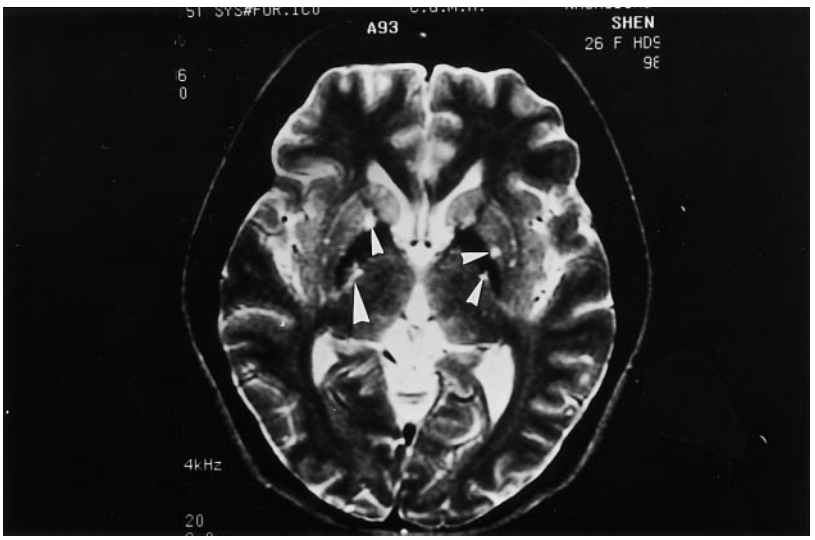

Figure 1. A case of cryptococcal meningitis. MRI axial view TIWI shows hyperintense lesions in bilateral basal ganglia (arrow heads) consistent with infarction.

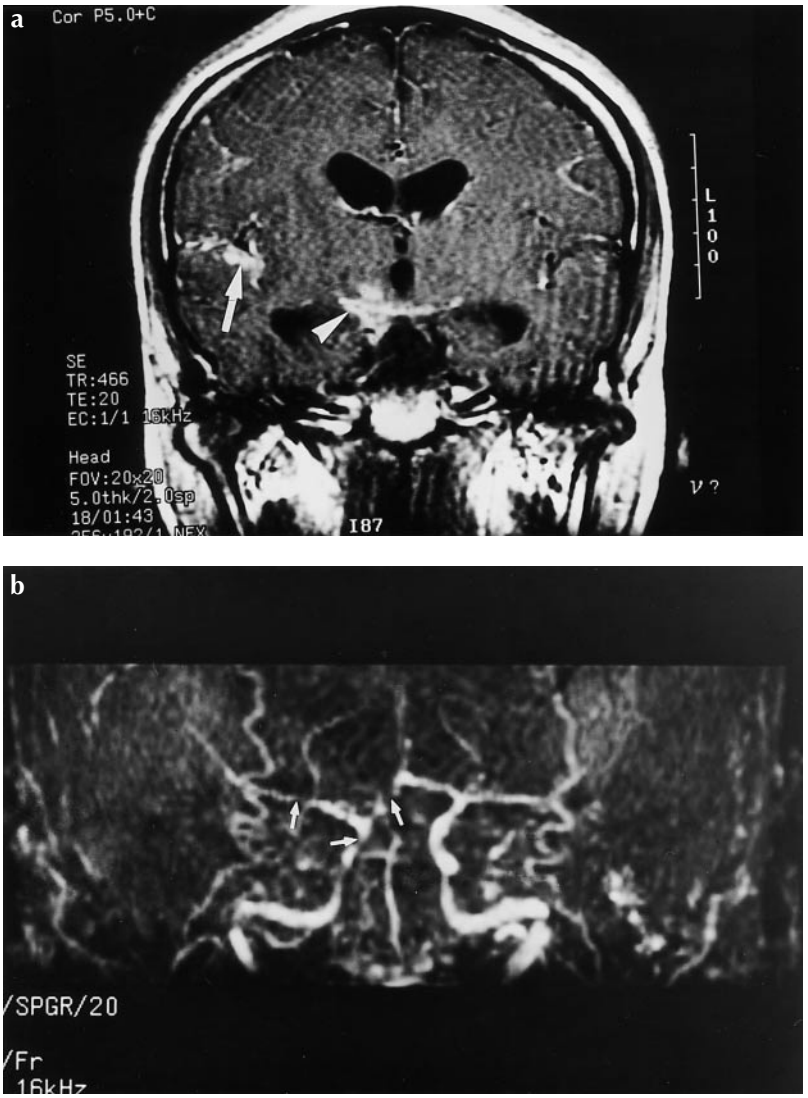

Figure 2. A case of tuberculous meningitis. **a** MRI coronal view TIWI after intravenous administration of gadolinium-DTPA contrast shows abnormal enhancement in right sylvian fissure (arrow), and basal cistern (arrow head); **b** Three-dimensional time-of-flight MRI angiogram of the same case shows multiple narrowings of the vessels (arrows) consistent with arteritis.

6–41% of TBM patients,[21,22] 4% of cryptococcal meningitis patients,[14] and 9–40% of coccidioidal meningitis patients.[19,20] In this study, cerebral infarction accounted for 47% (17/36) and 32% (11/34), respectively, of the complications of TBM and cryptococcal meningitis. Moreover, cerebral infarction can occur both in the acute stage and in the later stages of treatment. Several mechanisms are implicated in the development of cerebral infarctions in chronic meningitis, including: (i) vessels that transverse the exudates at the base of the brain, resulting in strangulation of the vessels and development of vasculitis with inflammation, spasms, constriction, and eventually thrombosis;[6,10] (ii) meningeal inflammatory exudate involving the adventitia and which progressively spreads, affecting the entire vessel wall, leading to necrotizing panarteritis with secondary thrombosis and occlusion;[23] and (iii) dilated ventricles stretching the already-compromised vessel and possibly developing an infarction.[24]

The majority of infarctions in chronic meningitis are located in the basal ganglia, internal capsule, and thalamus, and are rare in the major vascular territory and brain stem.[25–27] The basal exudates of chronic meningitis are usually most severe at the circle of Willis, which might explain why cerebral infarctions are frequently located in these areas.[28,29] The stem and/or cortical branches of the middle cerebral artery in the sylvian fissure, the supraclinoid portion of the internal carotid artery, and the vertebrobasilar system may also be damaged, though this is uncommon.[25–27] In our study, major vascular territory involvement was not unusual.

The clinical features of chronic meningitis relevant to associated ischaemic lesions deserve consideration here. Although both TBM and cryptococcal meningitis share similar clinical features,

according to this and other studies,[14,30] extracranial involvement, such as spinal and pulmonary involvement, is a common finding in TBM, while it is uncommon in cryptococcal meningitis. In this study, cranial nerves involvement was commonly found, and the possible mechanisms included consequences of IICP and basal arachnoiditis, which was more obvious in this specific group of patients. Difficulty in micturition, an uncommon presentation of cryptococcal meningitis, was common in our TBM patients. Several possible mechanisms are implicated in the development of micturition difficulty, including hydrocephalus and spinal involvement.

In this study, 71% of our patients had associated hydrocephalus, a common complication of chronic meningitis.[6,30] Usually a diagnosis of chronic meningitis precedes hydrocephalus by a matter of weeks or months, and the clinical course may be indolent. Hydrocephalus may be the result of several factors in combination or isolation, including blockage of CSF egress, absorption by exudates, and the impairment of absorption by high protein levels. Hydrocephalus can stretch already-compromised vessels and lead to further ischaemia; satisfactory circulation can be restored on relief of hydrocephalus, with resultant improvement in neurological status and prevention of cerebral ischaemiai.[6,24,28,30–32] Nevertheless, in patients with chronic meningitis, cerebral infarction and the severity on admission may play a much more significant role in altering the level of consciousness than does hydrocephalus,[6,24,28,30–32] and in such patients, surgical intervention to relieve hydrocephalus may not change the outcome. In this study, shunting procedures were effective treatment for chronic meningitis with hydrocephalus during active CNS infection, and these procedures did not disseminate micro-organisms into the peritoneum or bloodstream. Although most patients with hydrocephalus undergoing shunting procedures show clinical improvement, 80% (16/20) of our hydrocephalus patients, with or without shunt procedures, had poor outcomes, which may be attributed to additional cerebral lesions contributing to neurological deterioration and to the severity of meningitis on admission.

Although the routine use of steroids for treatment of chronic meningitis is still debated, some investigators suggest that patients presenting with severe disease may benefit from steroid therapy.[30,33] Its value in reducing cerebral oedema and inflammatory exudates and preventing spinal block, particularly in infants, appears to be generally accepted, whereas its role in preventing cerebral infarcts secondary to vasculitis is questioned.[33,34] It is not at all clear that steroid intervention, when, used, was associated with any prolonged benefit in any of our cases. However, intravenous dexamethasone therapy was most often begun hours to days after the onset of stroke-like symptoms. Because this is a retrospective study, it was not possible to assess the effect of steroid treatment or draw any conclusions.

In summary, cerebral infarctions secondary to infection, a common complication of chronic meningitis, with high mortality and morbidity rates, were found in this group of 28 patients. Although TBM and cryptococcal meningitis shared similar clinical features, extracranial involvement was more commonly found in TBM. In this study, cerebral infarctions were frequently associated with other neurological complications, such as hydrocephalus and seizures, which produced therapeutic challenges. Although cerebral infarctions can occur in both the acute stage and later stages of treatment, early diagnosis and appropriate antimicrobial treatment, as well as early ventricular decompression to prevent further cerebral ischaemia if hydrocephalus is demonstrated, are essential to maximize the potential for survival.

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