Neuroradiology (2003) 45: 277–282
DOI 10.1007/s00234-003-0958-4

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Serial study of clinical and CT changes in tuberculous meningitis

Received: 15 September 2002
Accepted: 21 January 2003
Published online: 10 April 2003

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Abstract Clinical and radiological changes in tuberculous meningitis (TBM) have been reported but there is paucity of comprehensive serial clinicoradiological follow-up. In this prospective hospital based study, we investigated serial changes in the clinical and radiological findings and their relationships over 6 months in 31 consecutive patients with TBM, diagnosed on the basis of clinical, radiological and spinal fluid criteria. We graded the severity of the TBM as I–III. Detailed clinical examination, contrast-enhanced CT and activities of daily living (ADL) assessments were made on admission, and 3 and 6 months after therapy. Further CT was carried out as required. Patients received four-drug antituberculous therapy (RHZE) and underwent a ventriculoperitoneal shunt if necessary. Outcome was defined as poor, partial or complete recovery using the Barthel index score at 6 months. The age of the patients was 6–80 years, mean 35.2 years; four were children and 13 female. Meningitis was stage I in 5, stage II in six and stage III in 20 patients. Focal weakness was present in nine, papilloedema in six and ophthalmoplegia in ten. There were ten patients who deteriorated within first 6 weeks of therapy. Mean Glasgow coma score (GCS) deteriorated from 12.5 to 11.4; the grade of meningitis increased by two stages in one patient, one stage in another, and motor deficits appeared in four and optic atrophy in four; four patients required shunt surgery. By 3 months most patients were stable. At 6 months 17 patients had complete, four partial and nine poor recovery. Initial CT was abnormal in 28 patients, revealing hydrocephalus and exudates in 15 each, infarcts in ten and tuberculomas in 13. It was repeated in ten patients who deteriorated, showing new abnormalities such as hydrocephalus in two, infarcts in four, exudates in four and granulomas in two, with worsening of the previous findings. CT at 3 and 6 months was still abnormal in most patients. At 6 months hydrocephalus had disappeared in four, as had tuberculomas in seven and exudates in six, but infarcts did not change. Initial deterioration was related to weakness on admission and the GCS. Cognitive impairment significantly correlated with exudates and tuberculomas and motor deficits with infarcts. Thus, a third of patients with TBM may deteriorate within 6 weeks of starting treatment and CT can be helpful in managing them. Worsening on treatment was related to weakness and GCS on admission. In most patients CT remained abnormal at 6 months despite clinical recovery.

Keywords Meningitis · Tuberculosis · Computed tomography

Introduction

Tuberculous meningitis (TBM) is the commonest subacute meningitis in developing countries. Even in the developed countries its incidence has been rising because of AIDS, organ transplantation and the use of immunosuppressive drugs. With antituberculous therapy, improvement may begin after weeks to months; the patients may worsen, and subsequently recover [1, 2]. It is therefore of interest to monitor the clinical findings closely and to repeat CT studies if appropriate. The literature contained only two studies in which serial changes have been reported. In one, the importance of basal exudates resulting in infarcts and hydrocephalus was highlighted. Development of radiological abnormalities during treatment and their persistence even after a year have been reported [3]. In other study enhancing exudates were associated with poorer outcome than nonenhancing exudates [4]. These studies, however, were retrospective, follow-up was not uniform and did not address clinicoradiological correlations, especially changes during the treatment and the factors responsible for worsening of the clinical picture. We report serial clinical and radiological changes in TBM and analyse the clinical and radiological findings which may be associated with worsening during treatment.

Materials and methods

We studied 31 consecutive patients with TBM seen during 1999–2001. The diagnosis was based on clinical, radiological and spinal fluid (CSF) criteria. Essential criteria included fever, headache and neck stiffness for more than 2 weeks in patients in whom malaria, septic and fungal meningitis were excluded. Supportive criteria included predominant lymphocytic pleocytosis and raised protein in the CSF; CT findings such as exudates, hydrocephalus, tuberculomas or infarcts singly or in combination; evidence of tuberculosis outside the central nervous system (CNS); and a response to antituberculous therapy. The essential criteria plus three of the four supportive criteria were considered suggestive [5]. The presence of acid-fast bacilli (AFB) in the CSF, and a positive polymerase chain reaction, IgM ELISA or culture for AFB were considered as definite evidence of TBM.

The patients underwent detailed clinical examination. Consciousness was assessed using the Glasgow coma scale (GCS), and cognitive function by the mini mental state examination (MMSE) in the patients who could cooperate. Cognitive impairment was diagnosed when the score was below 22 in patients with 0–4 years of schooling, 26 in those with 5–8 years and below 29 for those with 9 years or more [6]. Cranial nerve palsies, focal weakness, muscle tone, reflexes and sensation were noted. The CSF was examined for cells, protein, sugar, AFB, fungi and bacteria. CT before and after contrast medium was carried out in all patients and the presence of hydrocephalus, infarcts, exudates and tuberculomas was noted. We graded the severity of meningitis as: stage I: meningitis only; stage II: meningitis with neurological signs; and stage III: meningitis with altered sensorium [7].

All patients received four-drug antituberculous therapy (RHZE); in children we prescribed streptomycin instead of ethambutol. A ventriculoperitoneal (VP) shunt was carried out as and when indicated. Anticonvulsants were prescribed for seizures.

Most patients were admitted for 4–10 weeks and during their hospital stay CT was repeated if they deteriorated clinically. They were followed up clinically and radiologically at 3 and 6 months. Cognitive impairment, visual loss, optic atrophy, motor deficits, recurrence of seizures and other neurological deficits were noted. CT studies were compared with the previous examinations and we noted new lesions, plus persistence or disappearance of previous abnormalities. Functional outcome at 3 and 6 months was assessed using the Barthel index (BI) score as poor (<12), partial (12–19) and complete (20) recovery [5].

We correlated various clinical and radiological parameters with neurological sequelae using the chi-square test. To assess factors associated with initial deterioration on treatment, we looked at clinical (age, sex, duration of illness, weakness, seizures, GCS, BCG vaccination, cranial nerve palsies, stage of meningitis, BI score, drug-induced hepatitis, use of corticosteroids), laboratory (sedimentation rate, CSF cells and protein) and CT (exudates, hydrocephalus, infarcts and tuberculomas) findings employing univariate logistic regression analysis.

Results

The patients' age ranged between 6 and 80 years, mean 35.2 years; 13 were female and four children. The duration of illness was 0.5–12 months, mean 2.8 months. On admission, most patients had severe meningitis: 20 were in stage III and six in stage II. Two patients were deeply comatose ($GCS<6$) and 11 had moderately impaired consciousness (GCS 6–12). There were 13 who had seizures, partial in three and generalised tonic/clonic in ten. Cranial nerve palsies were present in 15 patients, six had papilloedema and nine focal motor deficits (Table 1). Cranial CT was abnormal on admission in 28 patients, including hydrocephalus in 15 (communicating in 12), exudates in 15 (mild in ten, moderate in five), infarcts in ten (cortical in three, subcortical in five and in the brain stem in two) and tuberculomas in 13 (supratentorial in eight, infratentorial in four and both in one).

On antituberculous treatment, ten patients deteriorated during first 6 weeks of their admission, the mean GCS score falling to11.4 from 12.5. There was two-stage deterioration in severity of meningitis in one patient, a one-stage deterioration in another, new motor deficits appeared in four patients and four more developed optic atrophy. CT in these patients revealed either new hydrocephalus, infarcts, exudates or tuberculomas, or progression of existing abnormalities (Table 2). We inserted a VP shunt in four patients, following which hydrocephalus became less marked in three; in one patient the shunt had to be revised.

At 3-month follow-up all but four patients were conscious; 17 had improved from stage III to stage II and one from stage III to stage I. A patient with paraparesis improved but one more patient developed a quadriparesis; three more patients developed optic atrophy. The MMSE could be performed in 22 patients (mean score 23) and 11 had cognitive impairment. There

Table 1 Serial clinical findings. *MMSE* Mini mental state examination

	Initial (31 patients)	Admission–6 weeks (31 patients, 10 worsened)	3 months (31 patients)	6 months (30 patients)
Mean Glasgow coma score	12.5	11.4	14.7	15
Stage I	5	4	5	5
Stage II	6	5	22	25
Stage III	20	22	4	0
Focal deficit	9	13	13	11
Hemiparesis	6	9	9	7
Paraparesis	1	1	0	0
Quadriparesis	2	3	4	4
Optic atrophy	2	6	9	9
Ophthalmoplegia	10	11	11	7
Cognitive impairment			11/22 (mean MMSE score −23)	13/24 (mean MMSE score –24)
Ataxia	2	2	3	2
Deafness	2	2	2	2
Activities of daily living score				
Poor recovery			12	
Partial recovery			4	9
Complete recovery			14	4
Dead			1	17

Table 2 Serial CT findings

	Initial (31)	Admission–6 weeks (10)		3 months (31)	6 months (30)
		Increased	New		
Hydrocephalus	15	6	2	20	16
Exudates	15	3	4	14	8
Infarction	10	2	4	16	16
Tuberculoma	13	1	2	15	9
Calcification					1
Ventriculoperitoneal shunt			4	2	

were 12 patients who had a poor, four partial and 14 complete recovery; one patient had died. CT was abnormal in 29 patients: three had developed hydrocephalus, four patients had developed infarcts, exudates had resolved in five patients and tuberculomas were unchanged. One patient each had diffuse cortical atrophy and a subdural hygroma. One patient underwent a VP shunt and another a revision of a shunt.

At 6 months 17 patients had complete, four partial and nine poor recovery .These last nine patients did not show any improvement from their 3month status. Neurological sequelae were present in all but five patients (Table 1). CT became normal in four patients but remained abnormal in 26. Hydrocephalus had resolved in four patients, who had all undergone VP shunting, exudates and tuberculomas had disappeared in six patients each but infarcts remained the same. In one patient a tuberculoma resolved by calcification (Table 2; Figs. 1, 2, 3).

Correlating the worst CT appearances with 6-month clinical sequelae, a motor deficit correlated with exudates ($X^2 = 3.96$, $df = 1$, $P < 0.05$) and infarcts ($X^2 = 12.38$ $df = 1$, $P < 0.05$). Hydrocephalous and tuberculoma did not correlate with sequelae. Correlating the 6-month CT findings with neurological sequelae at 6 months, motor deficit correlated with infarcts ($X^2 = 12.381$, $df = 1$, $P < 0.05$), cognitive impairment with exudates {$X^2 = 4.531$, $df = 1$, $P < 0.05$) and tuberculomas {$X^2 = 3.545$, $df = 1$, $P < 0.05$) (Table 3). Functional outcome at 6 months was related to the presence of exudates at 6 months ($X^2 = 6.86$, $df = 2$, $P < 0.05$) and infarcts ($X^2 = 8.06$, $df = 2$, $P < 0.05$).

As regards factors responsible for worsening during initial treatment, logistic regression analysis indicated that the presence of motor deficits on admission ($Z = 2.10$) and the GCS ($Z = 1.97$) were significantly related to deterioration. Male sex ($Z = 1.15$), stage of TBM ($Z = 1.49$), CSF protein level ($Z = 1.62$) and initial ADL score ($Z = 1.62$) had borderline significance.

Discussion

In our study one-third patients with TBM deteriorated in the first 6 weeks of treatment. A number of clinical and radiological phenomena in TBM may be due to ongoing infection or inflammation which could result in continued deterioration. This may be attributed to reduced drug concentrations due to the blood-brain barrier, the use of corticosteroids and altered immunity. None of our patients was on corticosteroids and there was no apparent immunosuppression or compromise. The initial deteriorations on treatment were significantly related to weakness and the GCS. Weakness in TBM may suggest underlying infarcts due to ongoing tuber-

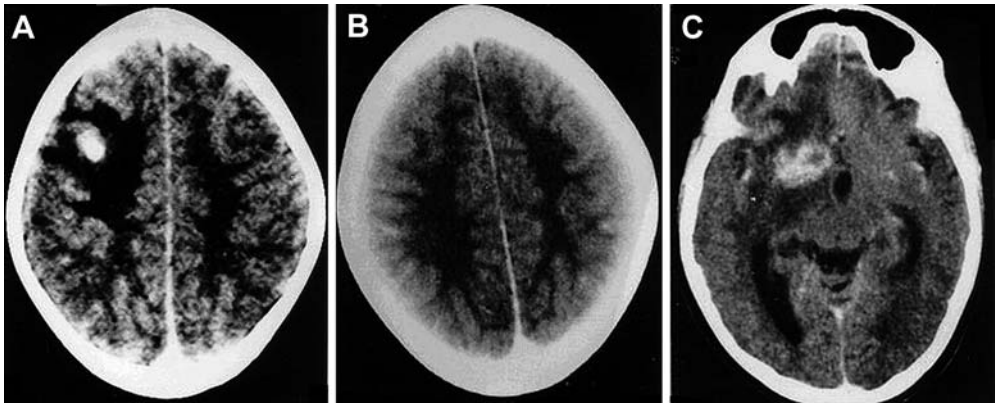

Fig. 1A–C Contrast-enhanced CT of a patient with stage II tuberculous meningitis (TBM). **A** There is a right enhancing disc lesion with perifocal oedema which disappeared after 3 months of antituberculous therapy **B**. **C** At 6 months the patient developed another disc lesion with perifocal oedema in the inferior frontal region. CT also showed dilatation of the posterior horn of the lateral ventricle and the 3rd ventricle. There were mild exudates in the sylvian fissure, but the patient was improving clinically

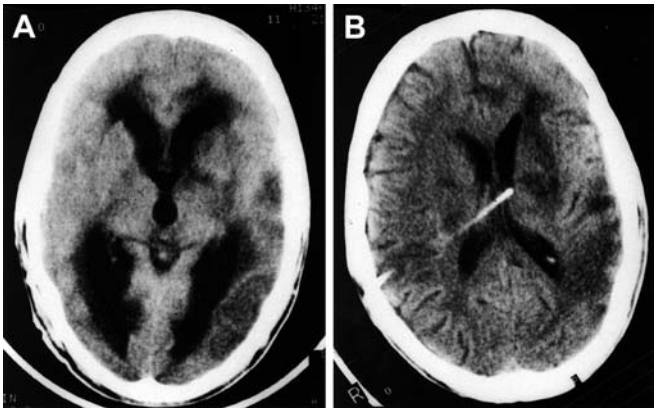

Fig. 2A, B A patient with stage I TBM had a normal CT at presentation. **A** After 1 week of antituberculous therapy he deteriorated to stage III and CT showed hydrocephalous, periventricular capping and infarcts in the basal ganglia. **B** At 6 months, following a ventriculoperitoneal shunt, CT revealed regression of hydrocephalus and persist basal ganglia infarcts

culous vasculopathy [8]. The latter may progress and result in new infarcts, producing both clinical and radiological deterioration, including an altered sensorium. Low GCS score and borderline significance of stage of TBM and low ADL score also suggest that more severe forms of meningitis are more likely to show deterioration.

BCG vaccination, therapy-induced hepatitis and corticosteroids, however, were not significantly related to deterioration. BCG vaccination has been reported to be effective in limiting the severity of tuberculosis and CNS invasion, especially in children [9]. In another study, however, BCG vaccine had little effect on the clinical findings or subsequent CNS tuberculosis [10]. Hepatitis induced by therapy, resulting in withdrawal of rifampacin and isoniazid for 2–3 weeks has been associated with poor outcome [11]. Lack of correlation with drug-induced hepatitis in our patients may be due to poor CSF penetration of rifampacin. Outcome has not changed in miliary tuberculosis before and after the introduction of rifampacin [12, 13]. Corticosteroids have been reported to reduce the sequelae of TBM [14] but in our earlier study, corticosteroid therapy was not related to 6-month outcome [5]; similar observations have been reported from Thailand [15].

The initial deterioration in TBM could be due to an immunoallergic reaction resulting in liberation of cytokines and lymphokines and subsequent appearance or organisation of basal exudates, termed a ''paradoxical response''. This is an uncommon hypersensitivity reaction to massive release of tuberculoprotein into the subarachnoid space, manifest clinically within days of commencement of treatment; the patient may rapidly deteriorate to coma or even death [16]. This therapeutic paradox has been regarded as pathognomonic of TBM [17]. The initial deterioration in at least two of our patients could be due to a paradoxical response. One, in stage I on admission, deteriorated to stage III and also developed a hemiplegia after a few days of treatment. CT, normal on admission, revealed hydrocephalus with enhancing exudates and corona radiata infarction. He underwent a VP shunt and started improving after 1 month . Another patient, in stage II with mild right-sided weakness on admission, had increased headache and vomiting after initiation of therapy and deteriorated to stage III with increased weakness. Repeat CT showed an increase in hydrocephalus with enhancing exudates and a fresh basal ganglia infarct. He also improved 4–6 weeks after a VP shunt.

By 3 months, however, most of our patients, including those who deteriorated initially either became stable or started improving. Radiological follow up revealed new hydrocephalus and infarcts, both of which could be due to organisation of basal exudates, in three patients each.

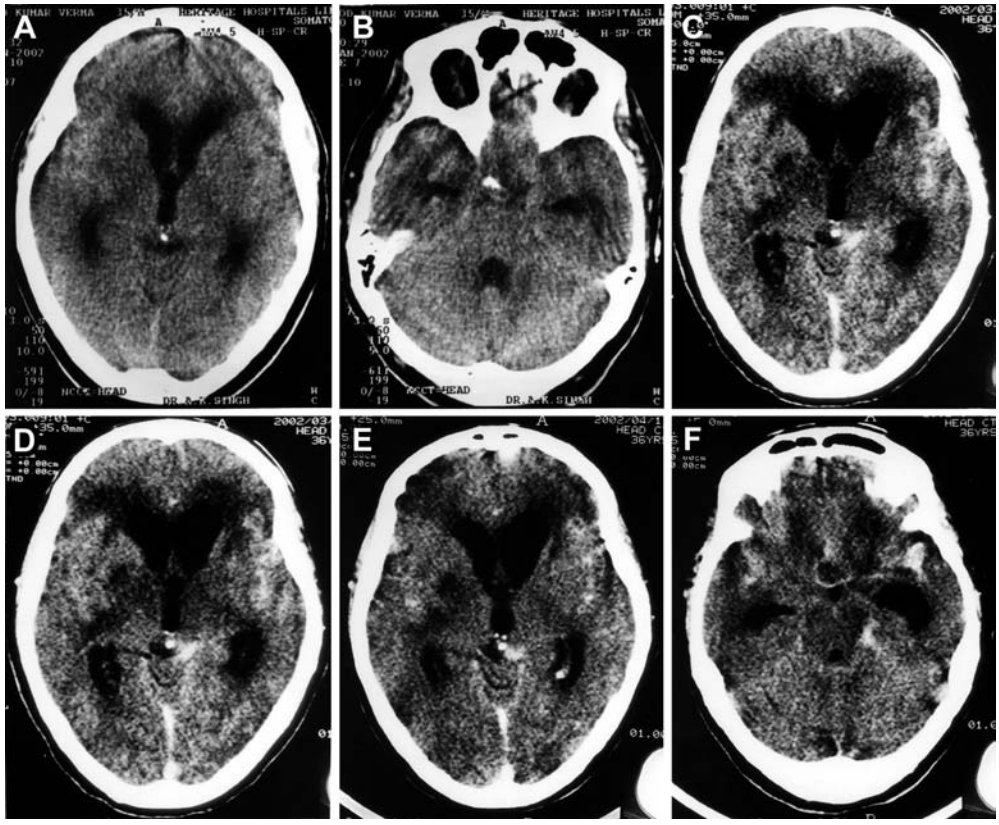

Fig. 3A–F A patient with stage III TBM. **A, B** CT reveals communicating hydrocephalus. **C, D** After about 6 weeks' hospital stay the patient deteriorated, with decreased visual acuity and quadriparesis. CT showed increased hydrocephalus, enhancing exudates and multiple infarcts. **E, F** CT at 3 months showed only minimal improvement in hydrocephalus and exudates although the patient had improved clinically

Table 3 Clinical sequelae and CT correlations

	Cognitive impairment		Weakness		Optic atrophy	
	Yes	No	Yes	No	Yes	No
Worst CT (within 3 months)						
Hydrocephalus						
Yes	6	6	8	12	5	15
No	7	5	3	7	4	6
Exudate						
Yes	10	6	10	9	7	12
No	3	5	1	10	2	9
Infarct						
Yes	8	4	11	5	5	11
No	5	7	0	14	4	10
Tuberculoma						
Yes	9	4	8	7	5	10
No	4	7	3	12	4	11
6 months						
Hydrocephalus						
Yes	7	4	7	9	3	13
No	6	7	4	10	6	8
Exudate						
Yes	6	0	6	2	4	4
No	7	11	5	17	5	17
Infarct						
Yes	7	4	11	5	5	11
No	6	7	0	14	4	10
Tuberculoma						
Yes	7	1	4	5	4	5
No	6	10	7	14	5	16

At 6 months no patient worsened clinically or radiologically but 26 of 30 CT studies remained abnormal. In one serial study of CT and MRI in TBM all abnormal CT findings except infarcts disappeared [18]. This difference from our study could be attributed to milder illness and use of MRI in the previous study. More severe illness in our patients is evidenced by stage III meningitis in 65% and hydrocephalus in 50%.

In a clinical and CT follow-up of 25 patients with TBM, 18 had hydrocephalus on admission and hydrocephalus developed in three during follow-up. In seven patients exudates persisted for 11–96 months. New tuberculomas appeared even after 7 months of treatment [3]. This study, however, did not have a uniform follow-up protocol and nor did it systematically address initial clinicoradiological deterioration and factors associated with it. In another study [19], there was initial deterioration in a subgroup of patients during treatment but the factors associated with this were not examined.

It can be concluded that close monitoring of patients with TBM during the first 6 weeks of treatment is essential as one third may deteriorate, especially those with low GCS and weakness. Repeating CT can be valuable in their management. Most CT abnormalities persist even after 6 months despite clinical improvement.

Acknowledgements We are thankful to Mr. Rakesh Kumar Nigam for secretarial help.

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