Neuroimaging findings are sensitive and specific in diagnosis of tuberculous meningitis

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Abstract

Objective: The primary objective of this study was to describe the neuroimaging changes of tuberculous meningitis (TBM), and to determine the role of neuroimaging in the diagnosis of TBM.

Methods: Between January 2009 and July 2015, we prospectively recruited TBM patients in two hospitals in Malaysia. Neuroimaging was performed and findings were recorded. The control consists of other types of meningo-encephalitis seen over the same period.

Results: Fifty four TBM patients were recruited. Leptomeningeal enhancement was seen in 39 (72.2%) patients, commonly at prepontine cistern and interpeduncular fossa. Hydrocephalus was observed in 38 (70.4%) patients, 25 (46.3%) patients had moderate and severe hydrocephalus. Thirty four patients (63.0%) had cerebral infarction. Tuberculoma were seen in 29 (53.7%) patients; 27 (50.0%) patients had classical tuberculoma, 2 (3.7%) patients had "other" type of tuberculoma, 18 (33.3%) patients had ≥5 tuberculoma, and 11 (20.4%) patients had < 5 tuberculoma. Fifteen (37.2%) patients had vasculitis, 6 (11.1%) patients had vasospasm. Close to nine tenth (88.9%) of the patients had ≥1 classical neuroimaging features, 77.8% had ≥2 classical imaging features of TBM (basal enhancement, hydrocephalus, basal ganglia/thalamic infarct, classical tuberculoma, and vasculitis/vasospasm). Only 4% with other types of meningitis/encephalitis had ≥1 feature, and 1% had two or more classical TBM neuroimaging features. The sensitivity of the imaging features of the imaging features for diagnosis of TBM was 88.9% and the specificity was 95.6%.

Conclusion: The classic imaging features of basal enhancement, hydrocephalus, basal ganglia/thalamic infarct, classical tuberculoma, and vasculitis are sensitive and specific to diagnosis of TBM.

Key words: tuberculous meningitis, stroke, hydrocephalus, tuberculoma, leptomeningeal enhancement.

INTRODUCTION

Tuberculosis (TB) is the second most common cause of infectious disease resulting in mortality worldwide, after HIV/AIDS. Over 95% of TB mortality occurs in low- and middle-income countries. Tuberculous meningitis (TBM) is a subtype of extra-pulmonary TB which occurs in 4% of patients with tuberculosis.

We have previously reported that infarct is common in TBM, seen in close to two third of patients. The infarcts involved mainly perforators and cortical branches. Infarcts involving multiple vascular territories and bilateral infarcts also represented the imaging features characteristics of TBM. The primary objective of this study was to describe neuroimaging changes of TBM patients, and to determine the role of neuroimaging in the diagnosis of TBM. The secondary objective was to assess the association between radiological changes and clinical outcome.

METHODS

Patient selection

This was a prospective cohort study on patients with TBM. Between January 2009 and July 2015, we prospectively recruited all patients with TBM seen in University Malaya Medical Centre (UMMC) and Kuala Lumpur General Hospital, two large referral hospitals in Kuala Lumpur, Malaysia.

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TBM was classified as “definite” if cerebrospinal fluid (CSF) acid-fast bacilli (AFB) direct smear/mycobacterial culture/polymerase chain reaction (PCR) for mycobacteria tuberculosis or histopathological examination were positive. TBM was defined as “probable” in patients with one or more of the following: suspected active pulmonary tuberculosis (PTB) on chest radiography, acid-fast bacilli in any specimen other than the CSF, and clinical evidence of other extrapulmonary tuberculosis.4 TBM was termed as “possible” in patients with at least four of the following: a history of tuberculosis, CSF pleocytosis, lymphocyte predominance in the CSF, duration of illness of more than five days, a ratio of CSF glucose to plasma glucose of less than 0.5, absence of cryptococcus in CSF; altered consciousness, turbid/yellow CSF, focal neurological signs or response to antituberculous therapy.5,6 The diagnosis was based on modification of Thwaites criteria.4

The study was approved by the Institutional Ethics Committee of UMMC and Ministry of Health. All patients or their legally acceptable representatives provided informed consent for the study. We collected the data on demographic characteristics such as age, gender, ethnic group, period of evolution of the disease, symptoms and signs at the time of admission. CSF opening pressure, glucose, protein, white cell count (differential lymphocyte and neutrophil), TB PCR, acid-fast bacilli (AFB) smear, AFB culture with sensitivity and Mantoux test was recorded; together with information on sputum AFB culture with sensitivity and Mantoux test was recorded; together with information on sputum AFB direct smear/culture/mycobacterial smear/mycobacterial culture/polymerase chain reaction (PCR) for mycobacteria tuberculosis or histopathological examination were positive. TBM was defined as “probable” in patients with one or more of the following: suspected active pulmonary tuberculosis (PTB) on chest radiography, acid-fast bacilli in any specimen other than the CSF, and clinical evidence of other extrapulmonary tuberculosis.4 TBM was termed as “possible” in patients with at least four of the following: a history of tuberculosis, CSF pleocytosis, lymphocyte predominance in the CSF, duration of illness of more than five days, a ratio of CSF glucose to plasma glucose of less than 0.5, absence of cryptococcus in CSF; altered consciousness, turbid/yellow CSF, focal neurological signs or response to antituberculous therapy.5,6 The diagnosis was based on modification of Thwaites criteria.4

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An evaluation of clinical outcome was made using the Modified Rankin scale (mRS). The scale ranged from 0-6.4,5 It consisted of, 0: No symptoms; 1: No significant disability. Able to carry out all usual activities, despite some symptoms; 2: Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities; 3: Moderate disability. Requires some help, but able to walk unassisted; 4: Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted; 5: Severe disability. Requires constant nursing care and attention, bedridden, incontinent; 6: Death. mRS scores of 0-2 were defined as good outcome. Scores of 3-6 were classified as poor outcome.

We graded the severity of meningitis at the time of admission according to British Medical Research Council criteria: stage 1 for GCS 15 with meningeal signs only, stage 2 for GCS 11-14 or 15 with focal neurological signs, and stage 3 for GCS ≤ 10.4 The advanced stages were defined as stages 2 and 3. Clinical conditions were assessed serially.

Methods

Computed tomography (CT) of the brain was performed on admission. Magnetic resonance imaging (MRI) of the brain was performed using 3.0-Tesla Sigma HDx MR system (GE healthcare). T1 weighted image (T1W), T2 weighted image (T2W), T2 fluid-attenuated inversion recovery (T2 FLAIR), and diffusion weighted image (DWI), apparent diffusion (ADC), MRI T1 with gadolinium contrast and Magnetic resonance angiography (MRA) sequences were obtained. CT and MRI of the brain scans were repeated at 1-2 months after admission and when the patients had clinical deterioration.

The findings of leptomeningeal enhancement, hydrocephalus, cerebral infarction, tuberculoma, vasculitis and vasospasm were recorded. The locations of leptomeningeal enhancement, which included preponitine cistern, interpeduncular fossa, ambient cistern, quadrigeminal cistern and Sylvian fissure were documented.4,5 Preponitine cistern surrounds the anterior part of the pons and contains the basilar artery, the origin of the anteroinferior cerebellar artery (AICA) and the origin of the superior cerebellar arteries. Interpeduncular fossa is a wide cavity between the two temporal lobes anteriorly and encloses the cerebral peduncles. It is continuous with the preponitine cistern.4 The ambient cistern is a thin, sheet-like extension of the quadrigeminal cistern that extends laterally around the midbrain. It acts as the connection between the quadrigeminal cistern and interpeduncular fossa. Quadrigeminal cistern is situated dorsal to the midbrain. It contains perforating branches of the posterior cerebral arteries, the third portion of the posterior cerebral arteries and superior cerebellar arteries.7

Hydrocephalus was defined as dilatation of the ventricles, and was classified as mild and moderate/severe. The site and number of tuberculoma (single or multiple) were recorded. The tuberculoma were categorised as “classical” tuberculoma and “others” type of tuberculoma. Classical tuberculoma were defined as small enhancing lesions at the cortical surfaces or grey-white matter junction. The characteristics
of tuberculoma, including single solitary lesion or multiple, disseminated lesions were documented. The number of multiple lesions was divided into <5 and ≥5. Single, large enhancing lesion with oedema and/or mass effect was termed as “others” type of tuberculoma. Cerebral abscess was defined as enhancing lesions on CT or MRI brain, with evidence of pus which was drained or removed surgically.

Vasculitis was defined as short segment narrowing on CTA or MRA. Long segment reversible narrowing was termed as vasospasm.

The non-TBM patients comprising of patients with other types of meningitis and encephalitis were recruited at the same period of time. These patients consisted of bacterial meningoencephalitis, viral meningoencephalitis, anti-NMDA receptor antibody encephalitis (anti-NMDAR), carcinomatous meningitis and cryptococcal meningitis. The neuroimaging findings of the TBM and non-TBM patients were compared. The classical neuroimaging features of TBM were leptomeningeal enhancement, cerebral infarction, hydrocephalus, tuberculoma and vasculitis/vasospasm. The numbers of TBM and non-TBM patients who had these neuroimaging features were recorded.

Statistical analysis
All descriptive statistics were done using Statistical Package for Social Sciences, SPSS (Version 18.0, SPSS Inc., Chicago, USA). Chi square test (or Fisher’s exact test) was used to analyse categorical data. The association between clinical outcome with various radiological features (including basal ganglia infarct) and stage of illness, was analysed with Chi square test (or Fisher’s exact test). A p value of < 0.05 (two-tailed p value) was taken as statistical significance. Sensitivity, specificity, positive predictive value and negative predictive values were also calculated.

RESULTS
Demography characteristics of TBM patients
Fifty four patients with TBM admitted to UMMC and Hospital Kuala Lumpur from January 2009 to July 2015 were recruited. The mean age was 35.0±12.7. The patients with TBM consisted of 31 male (57.4%) and 23 female (42.6%) patients. The ethnic groups of the patients were: 19 Malays (35.2%), 13 Indians (24.1%), 10 Chinese (18.5%) and 12 non-Malaysians (22.2%).

The most common clinical features were: fever (42 patients, 77.8%), headache (37 patients, 68.5%), altered sensorium (35 patients, 64.8%), vomiting (29 patients, 53.7%) and loss of appetite (25 patients, 49.0%). A total of 40 (74.1%) patients presented at advanced stages of illness (stage 2 and 3). The mean Glasgow Coma Scale (GCS) on admission was 12.8±2.4 (range 8-15). Evidence of pulmonary tuberculosis (PTB) on chest radiography was noted in 20 (37.0%) patients. Sputum AFB culture was positive in 14 (25.9%) patients.

The mean CSF opening pressure was 26.3±15.9 cm H2O (range 1.5-75). CSF analysis revealed white blood cell counts ranging from 0 to 1,152 cells/ml with mean of 160.5±235.9 (predominantly lymphocytes, 56.4%). The mean CSF protein level was 3.1±4.7 mg/dl (range 0.19-21.96 mg/dl) and CSF mean glucose level was 1.9±1.3 mmol/L (range 0.3-7.2).

CSF AFB culture was positive in 28 (53.8%) patients, and two patients had multi-resistance to antituberculous therapy. Thirty seven patients had CSF TB PCR examination, of whom 10 (27.0%) were positive. Thirty five (64.8%) patients had definite TB, 8 (14.8%) patients had probable TBM, 11 (20.4%) patients had possible TBM.

Seven (13.0%) patients were HIV positive, 4 (7.4%) patients had hepatitis B, 2 (3.7%) patients had hepatitis C, 5 (9.3%) patients had diabetes mellitus, and 4 (7.4%) patients had hypertension.

Neuroimaging findings of TBM
Leptomeningeal enhancement was seen in 39 (72.2%) patients (Figure 1A). The most common locations were prepontine cistern in 31 (57.4%) patients, interpeduncular fossa in 31 (57.4%) patients, Sylvian fissure in 24 (44.4%) patients, quadrigeminal cistern in 16 (29.6%) patients and ambient cistern in 15 (27.8%) patients. Leptomeningeal enhancement was found in the Sylvian fissure bilaterally in 17 (31.5%) patients.

Hydrocephalus was observed in 38 (70.4%) patients (Figure 1B). 25 (46.3%) of total TBM patients had moderate and severe hydrocephalus. Majority (32 out of 38 patients, 84.2%) of the hydrocephalus were generalized and symmetrical. Only 3 patients (5.6%) had focal or asymmetrical ventricular dilatation which was indicative of focal ventriculitis.

Thirty four TBM patients (63.0%) had cerebral infarction (Figure 1C). The most common locations for cerebral infarction (out of the total number of TBM patients) were globus pallidus in 14 patients (25.9%), thalamus in 13 patients (24.1%), caudate in 13 patients (25.5%) and putamen in 12 (22.2%) patients.
Tuberculoma were seen in 29 (53.7%) patients (Figure 1D). Twenty seven (50.0%) patients had classical tuberculoma, 2 (3.7%) patients had “other” type of tuberculoma, 18 (33.3%) patients had ≥5 tuberculoma and 11 (20.4%) patients had <5 tuberculoma. One (1.9%) patient had cerebral abscess.

Forty three patients had either CTA or MRA or both. Fifteen (37.2%) patients had vasculitis (Figure 1E). Vasospasm was present in 6 (11.1%) patients.
Sensitivity and specificity of the neuroimaging findings of TBM

Regarding the number of patients with one or more of the 5 classic neuroimaging feature which were basal leptomeningeal enhancement (prepontine, interpeduncular or Sylvian fissure), hydrocephalus, infarct in basal ganglia or thalamus, tuberculoma, and vasculitis/vasospasm, 48 (88.9%) patients had at least one neuroimaging feature, 42 (77.8%) patients had at least two neuroimaging features, 36 (66.7%) patients had at least three features, 22 (40.7%) patients had at least four features and 5 (9.3%) patients presented with all five features.

A comparison was made with 198 patients with other types of meningitis/encephalitis seen over the same period, which included 173 patients with bacterial meningitis/viral meningitis and encephalitis, 19 anti-NMDA receptor antibody encephalitis (anti-NMDAR), 4 carcinomatous meningitis and 2 cryptococcal meningitis. Out of the 198 patients, 8 (4%) patients had at least one classical imaging feature of TBM, 2 (1%) patients had two classical imaging features of TBM, and none had three or more classical imaging features of TBM. The sensitivity of the imaging features for diagnosis of TBM was 88.9% and the specificity was 95.6%. The positive predictive value (PPV) was 85.7% and the negative predictive value (NPV) was 96.6%.

Association between clinical outcome of TBM patients with various radiological features and stage of illness (Table 1)

Thirty three (61.1%) patients had poor outcome at 6 months, 18 patients died (mRS 6), whereas
Table 1: Association of clinical outcome at 6 months with clinical and radiological features

<table>
<thead>
<tr>
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<th>Poor outcome (mRS 3-6)</th>
<th>Good outcome (mRS 0-2)</th>
<th>p value</th>
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<td>13 (33.3%)</td>
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<td>6 (37.5%)</td>
<td>10 (62.5%)</td>
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<td>16 (53.3%)</td>
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<td>16 (61.5%)</td>
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<tr>
<td><strong>Thalamic infarct (n, %)</strong></td>
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<td>18 (43.9%)</td>
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<td><strong>Tuberculoma (n, %)</strong></td>
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<td>8 (32.0%)</td>
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<td>No</td>
<td>17 (63.3%)</td>
<td>10 (36.7%)</td>
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<tr>
<td><strong>Vasospasm (n, %)</strong></td>
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<td>2 (33.3%)</td>
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<td>24 (64.9%)</td>
<td>13 (35.1%)</td>
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<tr>
<td><strong>Stage of illness (n, %)</strong></td>
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<td>Stage 3</td>
<td>11 (84.6%)</td>
<td>12 (15.4%)</td>
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21 (38.9%) patients had good outcome. Poor clinical outcome was more frequently associated with stages on presentation to hospital (p=0.007), hydrocephalus (p=0.032), basal ganglia infarct (p=0.024), and in particular bilateral basal ganglia infarct (p=0.002). All the 6 patients with bilateral basal ganglia infarcts had poor outcome (p=0.022).

**DISCUSSION**

Our study showed that neuroimaging changes are common in TBM. The most common neuroradiological features in our patients were leptomeningeal enhancement, hydrocephalus, cerebral infarction, tuberculoma and vasculitis/vasospasm.

The most common neuroimaging finding in this study was leptomeningeal enhancement, affecting 72.2% of the patients. This was in the range of 38-80% reported in the literature. Leptomeningeal enhancement was most common at the basal areas, such as, preponitone cistern, interpeduncular fossa, quadrigeminal cistern and ambient cistern as well as at the Sylvian fissures (mainly bilateral). The leptomeningeal enhancement at the basal area has been said to be likely due to inflammatory exudates settling by gravity at the base of the brain. The leptomeningeal exudate then progresses laterally into the Sylvian fissures.

The next most common neuroimaging finding in our patients was hydrocephalus. More than two thirds (70.4%) had hydrocephalus, of whom 84.2% of these patients had generalised and symmetrical hydrocephalus. The proportion with hydrocephalus was within the range reported by other authors (58-71%). On the other hand, in one study, only 13.1% of the TBM patients aged 50-80 years old had hydrocephalus.

Cerebral infarction was the third most common imaging changes seen in 63.0% of our TBM patients. Cerebral infarction has been reported in 13–35% of the patients on CT scan of the brain, 57% on MRI of the brain and 22–56% in autopsy. In the literature, cerebral infarction was observed in about 20% of TBM patients at initial presentation to the hospital, and can occur in later stages of anti-tuberculous treatment.

Tuberculoma was seen in 53.7% of the patients in this study, similar to that reported in the literature (46-70%). Half of the patients had classical tuberculoma, majority (18/29, 62.1%) being multiple of more than 5.

Vasculitis was seen in 37.2% of our TBM patients. The exact frequencies of the arteries involved differ according to the different studies, probably partly related to the imaging techniques used; MRA/CTA or digital subtraction angiography. Vasospasm was seen in 11.1% of our TBM patients. Vasospasm has not been reported in the imaging of other central nervous system (CNS) infection or malignancy. It may be another specific imaging feature to support the diagnosis of TBM.

Poor outcome was seen in 61.1% of our patients, this included 33.3% mortality. Of the risk factors of poor outcome, hydrocephalus and advanced stage on admission were significant. This is similar to other previous studies. This indicates the importance of early diagnosis of TBM. Our study also showed that patients with basal ganglia infarct had worse outcome, where close to four- fifth of our patients with basal ganglia; and all 6 patients with bilateral basal ganglia infarct had poor outcome. This is consistent with the report by Andronikou et al. on paediatric TBM patients, where the odds ratio for poor outcome with basal ganglia infarct was 5.73 and bilateral basal ganglia infarct was even higher at 12. In another study by Schoeman et al. on 198 children with stage 2 and 3 TBM, the main cause of permanent neurologic disability was also basal ganglia infarct. The authors also commented that the basal ganglia infarct may develop during antituberculous therapy.

We have found brain imaging to be a sensitive marker in the diagnosis of TBM. The presence of at least one classical neuroimaging changes (basal leptomeningeal enhancement, hydrocephalus, basal ganglia/ thalamic stroke, hydrocephalus, tuberculoma and vasculitis) was seen in 88.9%; and two or more classical features in 77.8% of the study patients.

By comparison, only 27.0% of the patients in this study had positive CSF TB PCR. Thus, neuroimaging changes were approximately three times more sensitive as marker to diagnose TBM in comparison to CSF TB PCR. However, the sensitivity of CSF for TB PCR is reported to be higher at >50% in the literature. The sensitivity of CSF mycobacterium tuberculosis culture by Löwenstein Jensen medium is 53.8% in our study, and the figure was higher at 72.7% by Erdem et al. However, as CSF culture takes up to 8 weeks, it is thus more useful in confirming the TBM diagnosis.

When comparing neuroimaging of brain between TBM patients and other causes of meningitis and encephalitis, including bacterial, viral, cryptococcal, carcinomatous meningitis and immune encephalitis (anti-NMDAR encephalitis),
imaging features were also found to be highly specific. Only 4% of non-TB meningitis patients had one or more classic imaging features of TBM versus 88.9% for TB meningitis patients, and 1% of non-TBM patients had two or more classic imaging features, versus 77.8% of TBM patients. This is similar to the studies by Thwaites et al., who found that basal meningeal enhancement, tuberculoma, or both, were 89% sensitive and 100% specific for the diagnosis of TBM.  

In conclusion, this imaging study on TBM in Malaysia showed that TBM had poor prognosis and high mortality. Advanced stage of presentation probably largely reflects late presentation and diagnosis was associated with poor prognosis. The classic imaging features of TBM; basal meningitis, hydrocephalus, basal ganglia/thalamic infarct, classic tuberculoma, and vasculitis were sensitive and specific features of TBM. Its awareness may be helpful in early diagnosis of TBM.

DISCLOSURE

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