Original Article

A Clinical Study of Miliary Brain Tuberculomas in China

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SUMMARY: Brain tuberculomas can exhibit many different clinical and radiological patterns. However, disseminated or miliary brain tuberculomas are very rare. Miliary brain tuberculomas have specific clinical prognostic implications. Seven patients diagnosed with miliary brain tuberculomas between December 2004 and August 2012 were evaluated retrospectively. Their clinical features, cranial magnetic resonance imaging (MRI) characteristics, treatments, and outcomes were reviewed. The median patient age was 42 years (range, 22–66 years). Six patients presented with fever, 5 with headache, 4 with papilledema, and 3 with diplopia. MRI studies revealed multiple brain lesions. MRI showed 20–50 lesions at the same level. These lesions measured approximately 2–4 mm in diameter and exhibited ring or nodular enhancement after gadolinium injection. All patients began to recover within 2 weeks of initiating antitubercular therapy (ATT). The number of lesions visible on MRI scans was halved within a month, and all lesions had healed without sequelae after 18 months of regular ATT. Miliary brain tuberculoma is a rare form of central nervous system tuberculosis. Some special characteristics of miliary brain tuberculomas are as follows: First, the presence of mild atypical clinical manifestations and almost normal laboratory findings; second, severe radiological features and 20–50 lesions at the same level on MRI scans; and third, a good response to standard ATT. Finally, they are benign; for instance, no patients died in our study. Early diagnosis and treatment can result in full recovery.

INTRODUCTION

A tuberculoma is defined as a space-occupying lesion caused by the tubercle bacillus. It is a parenchymal reaction to hematogenous seeding of the brain surface. Tuberculomas may present with or without meningitis and may lead to meningitis in a later stage (1,2). They are among the most common intracranial mass lesions and the most common manifestations of parenchymal tuberculosis (TB). Tuberculomas develop in 16–40% of patients with central nervous system (CNS) TB (3–5). However, miliary brain tuberculomas are rarely seen in patients with CNS TB, especially in adults. Several isolated case reports and short case series have described this rare disease, which is easily misdiagnosed as neurocysticercosis, metastases, or fungal granulomas (6,7). Because of the insidious onset of nonspecific symptoms and laboratory manifestations, early diagnosis of miliary brain tuberculomas remains challenging, and it is extremely important to achieve an early and accurate imaging diagnosis. The aim of the present study was to analyze detailed clinical manifestations and cranial magnetic resonance imaging (MRI) characteristics of 7 patients with miliary brain tuberculomas. We also discuss the medical treatments and clinical outcomes of these patients.

MATERIALS AND METHODS

We reviewed the medical records of patients diagnosed with miliary brain tuberculomas in the Department of Neurology between December 2004 and August 2012. The diagnostic criteria of CNS TB are shown in Table 1 (8).

Seven patients were diagnosed with miliary brain tuberculomas (3 confirmed, 4 probable), and their clinical manifestations, laboratory findings, radiological features, treatments, and outcomes were reviewed. MRI was performed using a 1.5 T scanner in all patients according to the standard protocol (9). Cranial MRI reports of all patients were reviewed by 3 independent neuroradiologists.

RESULTS

Clinical data: Three male and 4 female patients (age range, 22–66 years; median, 42 years) were included in the study. Five patients had a history of pulmonary TB, and 6 patients had normal laboratory tests. All patients presented with fever, headache, papilledema, and/or diplopia. MRI scans revealed multiple brain lesions, with approximately 20–50 lesions at the same level. These lesions measured approximately 2–4 mm in diameter and exhibited ring or nodular enhancement after gadolinium injection. All patients began to recover within 2 weeks of initiating antitubercular therapy (ATT). The number of lesions visible on MRI scans was halved within a month, and all lesions had healed without sequelae after 18 months of regular ATT. Miliary brain tuberculoma is a rare form of central nervous system tuberculosis. Some special characteristics of miliary brain tuberculomas are as follows: First, the presence of mild atypical clinical manifestations and almost normal laboratory findings; second, severe radiological features and 20–50 lesions at the same level on MRI scans; and third, a good response to standard ATT. Finally, they are benign; for instance, no patients died in our study. Early diagnosis and treatment can result in full recovery.

<table>
<thead>
<tr>
<th>Diagnosis related grading</th>
<th>Confirmed</th>
<th>Probable</th>
<th>Possible</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO.1 Culture positive CSF, stain positive CSF</td>
<td>Biopsy or culture proven pulmonary or nodal TB or miliary TB (on chest X-ray) with abnormal CSF and/or enhancing lesions on brain CT/MRI</td>
<td>Abnormal CSF and/or abnormal MRI and response to treatment with ATT</td>
<td></td>
</tr>
<tr>
<td>NO.2 Culture positive CSF, stain positive CSF</td>
<td>—</td>
<td>—</td>
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</table>
one of whom had concurrent intramedullary spinal cord TB. The clinical characteristics of the patients are summarized in Table 2. Six patients presented with fever, 5 with headache, 4 with papilledema, and 3 with diplopia. Only one patient had body weakness on the right side and disturbed consciousness.

**Laboratory examination:** All patients underwent a blood examination; all results were within normal limits except for the erythrocyte sedimentation rate, which was high (range, 42–89 mm/h). The results of serum cysticercus Immunoglobulin G antibody detection tests and enzyme immunoassays for the human immunodeficiency virus were negative. All the patients were immunocompetent. Two patients had hypoproteinemia due to inappetence for 2 months. Three patients tested positive for acid-fast bacilli staining using a modified Ziehl-Neelsen stain (10). In addition, 3 patients underwent the T-SPOT.TB test (Oxford Immunotec Ltd., Oxford, UK), but only 1 tested positive. Results of cerebrospinal fluid (CSF) analysis are shown in Table 3.

**Radiological features:** MRI studies revealed multiple small lesions in the brain. The lesions were distributed diffusely in the brain parenchyma in both the supratentorial and infratentorial compartments. Most patients had more than 20 lesions at the same level, but some patients had more than 50 lesions. Most of these lesions were at the corticomedullary junction. The lesions measured approximately 2–4 mm in diameter and exhibited ring or nodular enhancement after gadolinium injection. Most were surrounded by edema within the white matter. A representative MRI scan is shown in Fig. 1.

**Treatment:** All patients received antitubercular therapy (ATT) comprising 4 drugs: isoniazid (10–15 mg/kg), rifampicin (10 mg/kg), ethambutol (15–25 mg/kg), and pyrazinamide (20–35 mg/kg). Additionally, methylprednisolone (1.0–1.5 mg/kg for 3–4 weeks, then gradual tapering for 2–3 weeks) was administered for patients with perilesional edema and subsequent mass effects associated with the tuberculomas. After 6 months of ATT, the therapy was limited to rifampicin and isoniazid administration for another 12 months.

**Outcome and follow-up:** All patients began to experience symptom relief within 2 weeks of starting ATT. The number of lesions visible on MRI scans was halved within a month. All patients achieved full recovery in 6 months; all clinical manifestations disappeared and laboratory examination results were normal. The changes in one patient’s MRI scans after 2 months of treatment are shown in Fig. 2.

**DISCUSSION**

The diagnosis of miliary brain tuberculomas in our patients was based on MRI findings. Clinical evaluation of our patients resulted in a strong suspicion of CNS TB. Detection of *Mycobacterium tuberculosis* in the CSF and exclusion of neurocysticercosis, fungal granulomas, and metastases were required for the diagnosis of miliary brain tuberculomas. This was difficult because of poor *M. tuberculosis* yield from the CSF in acid-fast bacillus smears and CSF cultures. Definitive diagnosis of miliary brain tuberculomas requires histopathological confirmation, but a brain biopsy is not practical in most cases. A positive response to ATT further supports the diagnosis.

Previous studies have shown that most patients with miliary brain tuberculomas have a primary pulmonary focus of infection (11–13). During the initial pulmonary infection, tuberculous bacteria may enter the systemic circulation and reach the oxygen-rich CNS, thus establishing foci (14). Stimulation of an immune response limits the development of these lesions to miliary tuberculomas. This was difficult because of poor *M. tuberculosis* yield from the CSF in acid-fast bacillus smears and CSF cultures. Definitive diagnosis of miliary brain tuberculomas requires histopathological confirmation, but a brain biopsy is not practical in most cases. A positive response to ATT further supports the diagnosis.

![Table 2. Summary of clinical features of patients with miliary brain tuberculomas](image)

<table>
<thead>
<tr>
<th>S. no.</th>
<th>Age (yr) /sex</th>
<th>Fever</th>
<th>Headache</th>
<th>Papilledema</th>
<th>Diplopia</th>
<th>Weakness</th>
<th>Consciousness change</th>
<th>Meningeal irritation sign</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>22/F</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>66/M</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>52/M</td>
<td>Present</td>
<td>Present</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>50/F</td>
<td>—</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>—</td>
<td>—</td>
<td>Present</td>
</tr>
<tr>
<td>5</td>
<td>42/F</td>
<td>Present</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Present</td>
</tr>
<tr>
<td>6</td>
<td>35/F</td>
<td>Present</td>
<td>Present</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>27/M</td>
<td>Present</td>
<td>—</td>
<td>—</td>
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<td>—</td>
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![Table 3. Summary of laboratory findings and outcome of patients with miliary brain tuberculomas](image)

<table>
<thead>
<tr>
<th>S. no</th>
<th>CSF pressure (mmH₂O)</th>
<th>Glucose (mmol/L)</th>
<th>Chloride (mmol/L)</th>
<th>Protein (mg/L)</th>
<th>WBC (10⁶/L)</th>
<th>Acid-fast bacilli staining</th>
<th>CSF culture</th>
<th>Outcomes</th>
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<tr>
<td>1</td>
<td>270</td>
<td>3.2</td>
<td>121</td>
<td>390</td>
<td>6</td>
<td>+</td>
<td>–</td>
<td>Recovered</td>
</tr>
<tr>
<td>2</td>
<td>150</td>
<td>2.6</td>
<td>129</td>
<td>517.2</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>Recovered</td>
</tr>
<tr>
<td>3</td>
<td>180</td>
<td>0.9</td>
<td>128</td>
<td>1362.2</td>
<td>115</td>
<td>+</td>
<td>–</td>
<td>Recovered</td>
</tr>
<tr>
<td>4</td>
<td>220</td>
<td>3.08</td>
<td>121</td>
<td>782</td>
<td>4</td>
<td>–</td>
<td>–</td>
<td>Recovered</td>
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<tr>
<td>5</td>
<td>140</td>
<td>3.3</td>
<td>129.3</td>
<td>319.6</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>Recovered</td>
</tr>
<tr>
<td>6</td>
<td>170</td>
<td>3.5</td>
<td>129.5</td>
<td>505.6</td>
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<td>–</td>
<td>–</td>
<td>Recovered</td>
</tr>
<tr>
<td>7</td>
<td>185</td>
<td>2.9</td>
<td>125.7</td>
<td>511.8</td>
<td>3</td>
<td>+</td>
<td>–</td>
<td>Recovered</td>
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</tbody>
</table>
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Fig. 1. (A) Axial T2 MRI illustrating multiple small lesions with hyperintense capsule and isointense core and surrounded by edema. (B) Coronal T1 Flair showing multiple lesions in both the supratentorial and infratentorial compartments. (C) DWI with no obvious restricted diffusion. (D) Axial T1 MRI after gadolinium injection. (E) Coronal T1 MRI after gadolinium injection.

festations without typical systemic signs of TB infection. Only one of our 7 patients showed a disturbance of consciousness. This may have been due to the distribution of the lesions. The lesions were small and focal, and most had no effect on brain function. Small lesions may occasionally develop within regions important for brain
function, or very close to the ventricular ependymal wall or surface of the brain, and subsequently rupture, causing severe clinical manifestations or TB meningitis (15–17).

Second, unlike TB meningitis, miliary brain tuberculomas usually do not result in obvious changes in the
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CSF. Most of our patients had normal glucose levels, white blood cell counts, and chloride levels. These results may have been due to the absence of meningeal involvement. Five patients showed elevated protein levels, suggesting an activated immune response to M. tuberculosis (18). The presence of M. tuberculosis may have stimulated a T-cell-mediated delayed allergic response accompanied by antibody release, resulting in elevated protein levels and the development of focal lesions.

Third, miliary brain tuberculosis has relatively characteristic radiological features and MRI is considered to be the most effective method to diagnose them. The lesions in the present study measured approximately 2–4 mm in diameter. MRI scans showed more than 20 lesions at the same level and more than 50 lesions in some patients. These multiple small lesions displayed a hyperintense core with a hypointense rim on T2-weighted images and without obvious diffusion restriction on diffusion-weighted images. The lesions exhibited ring or nodular enhancement on T1-weighted images after gadolinium injection. Most were located at the corticomedullary junction, suggesting a hematogenous spread of infection because of the narrowing of the arterioles at the gray/white matter junction (11,19,20). Most of the lesions shrank quickly after regular ATT treatment.

Finally, miliary brain tuberculosis are benign lesions with a good prognosis and effective therapeutic options. This is mainly because tuberculosis are focal hyperplastic lesions that do not cause vasculitis, cerebral infarction, or hydrocephalus, all of which can be associated with a poor prognosis (18,21). The main treatment is ATT, and in the present study, all patients recovered after 18 months of regular ATT. Glucocorticoids were required during the early period of intensive treatment. Once ATT was initiated, a heightened inflammatory response was evident, presumably from the release of intracellular antigens. Lesions that had been silent became symptomatic. Steroids helped to diminish the inflammatory immune response.

To conclude, miliary brain tuberculosis are a rare form of CNS TB. They are easily overlooked because of mild atypical manifestations and near-normal laboratory findings. However, characteristic MRI findings are observed. Typical imaging findings are multiple small lesions with a hyperintense core and hypointense rim on T2-weighted images and without obvious diffusion restriction on diffusion-weighted images. Ring or nodular enhancement is present on T1-weighted images after gadolinium injection. Miliary brain tuberculosis are benign conditions, and early diagnosis and treatment can result in a full recovery.

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Conflict of interest None to declare.

REFERENCES