The Spectrum of Presentation, Diagnosis, and Clinical Outcome of Central Nervous System Tuberculosis: A Case Series in Bangabandhu Sheikh Mujib Medical University

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Introduction
Bangladesh has the highest prevalence of tuberculosis (TB). Of these, tubercular meningitis is the most common and most devastating. The usual course is that of insidious onset and subacute progression. Adults with TBM often present with the classic meningitis symptoms of fever, headache, and meningismus (stiff neck) along with focal neurological deficits, behavioral changes, and alterations in consciousness. TBM is prone to rapid deterioration once meningeal symptoms and focal neurological signs supervene, leading to stupor, coma, and death within 5 to 8 weeks [1,2].

Intracerebral tuberculosis is characterized by tuberculoma or tuberculous brain abscess. Clinical manifestations of tuberculoma or tuberculous brain abscess depend largely on their location, and patients often present with headaches, seizures, papilledema, or other signs of increased intracranial pressure [1,3].

Early diagnosis is difficult due to the wide spectrum of symptoms that are mostly nonspecific at the onset and throughout the course of the illness. Conventional CSF analysis shows mild lymphocytic pleocytosis, slightly elevated protein levels, and hypoglycemia (low glucose), but it is less sensitive and thus less useful in making diagnoses. The detection of AFB in the CSF using both smear and culture techniques is the most important and accessible method for diagnosing CNS tuberculosis. Despite their importance as CNS tuberculosis diagnostic tools, traditional staining, and culture remain largely insensitive. This is most likely due to the scarcity of AFB in a clinical diagnosis of CNS tuberculosis. Although its low sensitivity precludes it from excluding TBM, molecular and biochemical studies may be useful in confirming central nervous system tuberculosis [2-4].

Although NAA and other PCR assays are not the ideal screening method for TBM, they do appear to be a valuable addition to current methods. They may be especially useful once antituberculous therapy has begun or as a means of monitoring treatment response. However, as with any tuberculosis diagnostic test, a negative result does not rule out the possibility of tuberculosis, and clinical judgment is essential [2,5].

While the use of neuroradiographic techniques such as computer tomography (CT) and magnetic resonance imaging (MRI) have vastly improved the diagnostic accuracy of TBM and tuberculomas, no series of radiographic findings are pathognomonic for CNS TB. Commonly identified neuroradiological features of TBM include basal meningeal enhancement, hydrocephalus, and infarctions in the supratentorial brain parenchyma and brain stem [2-4].

The radiographic presentation of tuberculomas depends largely on whether the lesion is noncaseating, caseating with a solid center, or caseating with a liquid center; the degree of edema surrounding the tuberculoma is thought to be inversely proportional to the age of the lesion [2].

Tuberculosis of the central nervous system (CNS) is a particularly lethal form of tuberculosis that, even in the presence of appropriate antituberculous therapy, results in unacceptable morbidity and mortality. Despite the development of promising molecular diagnostic techniques, CNS tuberculosis diagnosis is still largely based on insensitive microbiological methods, making CNS tuberculosis a formidable diagnostic challenge [1,2]. The diagnosis is difficult and often delayed due to the varied and non-specific presentation [1,3]. Aside from clinical indicators, diagnostic indicators in cere-
brospinal fluid (CSF) include mononuclear pleocytosis, low sugar levels, and high protein concentrations. Identifying Mycobacterium tuberculosis in CSF using staining, culture methods, and molecular analysis is confirmatory but may be challenging [3-4].

Here, we present a case series of CNS TB. Our goal is to demonstrate the spectrum of TB’s initial presentation, CSF parameters, imaging pattern, and response to anti-tubercular drug treatment.

Case 1:
A 27-year-old male presented with low-grade fever, anorexia, and significant weight loss for 1 month. For the last 2 weeks prior to admission, he developed insidious onset blurring of vision. He had also a cough, chest pain, and shortness of breath for 2 months. On examination, we found papilloedema otherwise normal neurological examination and no sign of meningeal irritation. Chest findings consistent with left pleural effusion. Routine test along with CSF study and brain imaging was done. Imaging showed multiple contrast-enhancing lesions in different parts of the brain (Figure 1). He was diagnosed with disseminated tuberculosis involving meninges and brain parenchyma and pleura. Then anti-tubercular drug therapy was started. He responded very well to drugs.

Figure 1: Coronal, sagittal and axial pc T'W' image in tuberculous meningitis. Note contrast enhance lesion and hydrocephalus.

Case 2:
A 38-year-old man with a previous history of ischaemic stroke presented with fever for 3 months and headache for 2 months along with an altered level of consciousness for 15 days. He had several episodes of convulsion. After a neurosurgical review, he was found communicating hydrocephalus, and a ventriculoperitoneal shunt was inserted. After admission routine investigations along with CSF study and brain imaging were done. Afterward, he was diag-
nosed with tubercular meningitis, and anti-tubercular drugs were started with a significant response.

**Case 3:**
A 49-year-old man presented with 6 month’s history of undocumented fever, 5-month history of headache and blurring of vision, and diplopia for the last couple of weeks. After admission, we found bilateral papilledema, right 6th nerve palsy otherwise normal neurological examination. Ultimately, he was diagnosed with tubercular meningitis on basis of routine tests, CSF findings, and brain imaging (Figure 2). Then, anti-tubercular drug was started and he got significant improvement.

![Figure 2: Coronal and sagittal post concious T1W1 image in a patient with tuberculous meningitis. Note pachymeningeal enhancement and hydrocephalus.](image)

**Case 4:**
A 59-year-old male presented with 2 weeks history of fever, cough, disorientation, and constitutional symptoms. He was toxic at the time of admission. On examination, we found signs of meningeal irritation and bilateral upgoing plantar response, otherwise unremarkable neurological findings. Routine blood tests were done and found a significantly high rise in ESR, CSF study revealed lymphocytic pleocytosis with raised protein and low blood sugar. MTB was detected in the polymerase chain reaction. MRI of the brain showed multiple infarcts in the right paraventricular, both capsuloganglionic and temporal regions (Figure 3). Finally diagnosed with tubercular meningoencephalitis with tubercular vasculopathy. He was started anti-tubercular therapy and showed a good response.
Figure 3: DWI and ADC map imaging of a case with tuberculous meningitis. Note multiple areas of diffusion restriction and corresponding hypointensity in the ADC map.

**Case 5:**
A 42-year-old man presented with fever, cough, and headache for one month, disorientation for the previous two weeks, and blurred vision for ten days. We discovered bilateral papilloedema and signs of meningeal irritation during the examination. The results of the other systemic examinations were unremarkable. Baseline investigations, CSF studies, and brain imaging were performed. CSF analysis revealed significantly high protein levels (>2500mg/dl), and imaging revealed meningeal enhancement. He was diagnosed with tubercular meningitis and began anti-tubercular therapy which resulted in a good response.

**Case 6:**
A 35-year-old male was admitted with complaints of one-month history of headache and one-week history of disorientation. He denied any seizure, focal neurological, or any constitutional symptoms. CSF study and brain imaging were done along with baseline tests. Imaging revealed multiple contrast-enhancing lesions in both supra and infratentorial regions. All those features were suggestive of tubercular meningitis and CNS tuberculoma (Figure 4). He was started on anti-tubercular drugs with a good response after 3 weeks.
Discussion

CNS tuberculosis is diagnosed on the basis of clinical features and characteristic laboratory, imaging, and histopathological or cytological findings [1]. Most commonly it presents with prolonged fever, chronic headache, blurring vision, focal neurological signs, cranial nerve palsy, and the sign of meningism [1,5]. Typically opening pressure is elevated in lumber puncture and the CSF formula shows a mononuclear pleocytosis (10-1000 cells/ml) with high protein (50-300 mg/dl) and low glucose (less than 45 mg/dl or less than 60% of corresponding blood sugar) concentration. Radiographically, the presence of basal meningeal enhancement, hydrocephalus, and infarction is the diagnostic triad of TBM. Frequently it is associated with tuberculoma [5].

Due to extreme non-specificity, clinical suspiciousness in high prevalence areas and starting anti-tubercular therapy is paramount in the management of CNS TB [1]. We report a case series of six patients of CNS TB from 2022 to 2023 in Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. All patients were diagnosed with high clinical suspicion, based on CSF parameters, imaging, and molecular techniques.

The age of six patients with CNS tuberculosis ranged between 27 and 58 years (median: 40 years). All six of them are male. Co-existing intracranial tuberculoma was present in two patients with tubercular meningitis (TBM) and the rest four patients presented with only TBM. (Table 1)

The most common symptoms or signs were fever (83.3%), headache (66.7%), altered consciousness status (66.67%), and constitutional symptoms (66.67%). (Figure 5)
Patient-reported altered consciousness status or fever more often than any other symptom or sign. Almost all patients reported neurological symptoms or signs including altered mental status (66.67%), headache (66.7%), blurring vision (50%), neck stiffness (33.33%), seizure (16.67%), and double vision (16.7%). (Figure 5) Two of the six patients had concomitant pulmonary TB and had significant chest x-ray and CT chest findings.

Table 1: Clinical, Radiological Characteristics with Anti-Tuberculosis Therapy and Early Clinical Outcome for Six Adult Cases of Central Nervous System Tuberculosis

<table>
<thead>
<tr>
<th>No</th>
<th>Age</th>
<th>Sex</th>
<th>Prior TB</th>
<th>Lesion on MRI brain imaging</th>
<th>Concomitant extracranial tuberculosis</th>
<th>Method of diagnosis</th>
<th>Antitubercular therapy</th>
<th>Clinical outcome at 21 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27</td>
<td>M</td>
<td>No</td>
<td>Meningeal enhancement Multiple contrast-enhancing lesions (supra and infra regions) Hydrocephalus</td>
<td>Pleural</td>
<td>Clinical , lab support and clinician decision</td>
<td>RIF, INH, PZA, ETH</td>
<td>Good response</td>
</tr>
<tr>
<td>2</td>
<td>38</td>
<td>M</td>
<td>No</td>
<td>Meningeal enhancement Hydrocephalus</td>
<td>None</td>
<td>Clinical , lab support and clinician decision</td>
<td>RIF, INH, PZA, ETH</td>
<td>Good response</td>
</tr>
<tr>
<td>3</td>
<td>49</td>
<td>M</td>
<td>No</td>
<td>Meningeal enhancement Hydrocephalus</td>
<td>None</td>
<td>Clinical , lab support and clinician decision</td>
<td>RIF, INH, PZA, ETH</td>
<td>Good response</td>
</tr>
<tr>
<td>4</td>
<td>58</td>
<td>M</td>
<td>No</td>
<td>Meningeal enhancement</td>
<td>Pulmonary</td>
<td>Clinical , lab support and detection of MTB on PCR</td>
<td>RIF, INH, PZA, ETH</td>
<td>Good response</td>
</tr>
</tbody>
</table>
Lumbar punctures were performed on all six patients and Cerebrospinal fluid studies revealed a raised ADA level in 66.67% of cases, along with elevated protein in all cases, low glucose in 50% of cases, lymphocytic pleocytosis in 66.67% of cases (Table 2). Two of six cases CSF fluid color were hazy. No patient had MTB detected in the CSF by smear and culture of acid-fast bacilli (AFB). Only one patient had MTB detected in the CSF by polymerase chain reaction. (Table 2)

Two patients had radiological evidence of at least one intracranial tuberculoma based on MRI with intravenous contrast. All patients had meningeal contrast enhancement in MRI and four of six cases had radiological evidence of a different degree of hydrocephalus. Extracranial ventricular drainage for relieving hydrocephalus was used in one patient. Two patients had small infarcts attributed to obstruction of a perforating branch of the middle cerebral artery, where one was pre-existing evidenced by prior imaging, and another related to MTB infection.

Based on clinical suspicion all patients were initiated on 4-drug anti-tuberculosis therapy during the hospital course. No patients were undergone brain biopsy. Clinical outcomes at 21 days during the hospital admission showed a significant response.

This case series revealed most of the CNS TB patients presented with prolonged fever, altered consciousness level, and constitutional symptoms. CSF study showed raised total protein, lymphocytic pleocytosis, and increased ADA. Imaging mostly found meningeal enhancement with infrequent tuberculoma. MTB was hardly detected in CSF AFB stain, culture, and PCR for MTB. Early and effective treatment leads to rapid response and results in a good outcome [6].

**Conclusion**

Finally, we note that this study highlighted the relative frequency of various types of brain TB lesions, as well as symptoms, signs, laboratory, and imaging findings in six Bangladeshi adult patients. Because brain biopsy and histopathology are not available in many tertiary-level hospitals in Bangladesh, CNS TB was diagnosed primarily based on compatible clinical features, morphological features on MRI of the brain, and CSF findings. Tuberculosis should always be considered as a differential diagnosis in patients with prolonged fever, headache, and altered consciousness level for any duration and in any sex group in Bangladesh.

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**Table 2: Cerebrospinal Fluid Results of 6 Patients with CNS TB on Clinical Presentation**

<table>
<thead>
<tr>
<th>No</th>
<th>WBC</th>
<th>N%</th>
<th>L%</th>
<th>Colour</th>
<th>Apperance</th>
<th>T Protein (mg/dl)</th>
<th>Glucose (mmol/L)</th>
<th>ADA (U/L)</th>
<th>AFB Stain</th>
<th>MTB PCR</th>
<th>MTB culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>0</td>
<td>100</td>
<td>Watery</td>
<td>Clear</td>
<td>114</td>
<td>4.0</td>
<td>09</td>
<td>Not found</td>
<td>Not detected</td>
<td>No growth</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>55</td>
<td>45</td>
<td>Watery</td>
<td>Clear</td>
<td>100</td>
<td>1.9</td>
<td>23.40</td>
<td>Not found</td>
<td>Not detected</td>
<td>NP</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>05</td>
<td>95</td>
<td>Watery</td>
<td>Clear</td>
<td>180</td>
<td>4.3</td>
<td>12</td>
<td>Not found</td>
<td>Not detected</td>
<td>NP</td>
</tr>
<tr>
<td>4</td>
<td>120</td>
<td>10</td>
<td>90</td>
<td>Watery</td>
<td>Clear</td>
<td>158</td>
<td>1.0</td>
<td>10.70</td>
<td>Detected</td>
<td>No growth</td>
<td>No growth</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>15</td>
<td>85</td>
<td>Hazy</td>
<td>Yellow</td>
<td>&gt;2500</td>
<td>2.5</td>
<td>93</td>
<td>Not detected</td>
<td>No growth</td>
<td>No growth</td>
</tr>
<tr>
<td>6</td>
<td>20</td>
<td>96</td>
<td>04</td>
<td>Milky</td>
<td>Clear</td>
<td>58</td>
<td>5.0</td>
<td>1.6</td>
<td>Not found</td>
<td>Not detected</td>
<td>No growth</td>
</tr>
</tbody>
</table>

ADA, adenosine deaminase; AFB, acid-fast bacilli; CSF, cerebrospinal fluid; L%, lymphocyte percentage; MTB, Mycobacterial tuberculosis polymerase chain reaction; N%, neutrophil percentage; NP, not performed; T protein, total protein; WBC, white blood cells.
Conflict of interest:
We declare that we have no conflict of interest.

Funding:
The present study received no specific funding.

Consent for publication:
Written informed consent was obtained from the patients and the patient’s next of kin for the publication of this case series and any accompanying images.

Ethical approval:
Ethical approval has been taken from the appropriate authority.

References