Original Research Article

Study on biochemical and radiological profile in children clinically diagnosed as tubercular meningoencephalitis: a prospective study from a tertiary care centre in Rajasthan

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ABSTRACT

Background: Objective of the current study was to assess biochemical profile and neuroimaging findings in children diagnosed with neurotuberculosis in a tertiary care centre in Southern Rajasthan, India.

Methods: A prospective randomized controlled trial was conducted in Department of Pediatrics, tertiary care centre in Southern Rajasthan, India from July 2017 to June 2018. Total 110 children of age group of 6 months to 18 years with the diagnosis of tubercular meningoencephalitis (TBME) on the basis of clinical evaluation, cerebrospinal fluid (CSF) examination and neuroimaging were included in the study.

Results: Among 110 children included in the study, CSF lymphocytic pleocytosis was seen in all. Majority of children (56.36%) cell counts were in the range of 101-500 cells/µl and mean CSF cell count was 198.09±177.86 per µl. CSF protein ranges from 100 to 400 mg/dl in 68.2% children and 19 children had CSF protein >400 mg/dl with mean of 230.98±167.73 mg/dl. In majority of patients (40%) CSF glucose level was in range of 20-40 mg/dl and in 31.82% children CSF glucose was <20 mg/dl. Mean CSF sugar level was 33.86±18.22 mg/dl. None of them demonstrated acid fast bacillus (AFB) on Ziehl-Neelsen staining of CSF sample. Chest radiographic abnormality was found in 41.82% cases. Mantoux test was positive in 16.36% (18) children admitted with TBME. Common abnormalities noted on neuroimaging were: Communicating hydrocephalus (77.27%), meningeal enhancement (40%), infarction (27.27%), cerebral oedema (11.82%) and 9.09% has tuberculoma on neuroimaging. CSF and gastric aspirate were examined by cartridge based nuleic acid amplification test (CBNAAT) for Mycobacterium Tuberculosis (MTB), among them 5 (4.55%) children had positive in CSF and 16 (14.55%) had gastric aspirate positive for MTB by CBNAAT.

Conclusions: Clinical, biochemical and radiological parameters is sufficient enough to diagnose TBME in children.

Keywords: Cartridge based nuleic acid amplification test, Cerebrospinal fluid, Neuroimaging, Tubercular meningoencephalitis, X-ray chest

INTRODUCTION

Worldwide, tuberculosis (TB) is one of the top 10 causes of death and the leading cause of disease from a single infectious agent. India has one of the highest burden of tuberculosis globally, accounting for around 20% of all new TB cases annually.1 It is estimated that childhood TB constitutes 10-20% of all TB cases in high burden countries.2 Approximately, 25% of pediatric TB cases are extrapolmonary, with tuberculous meningitis (TBM) being the most severe form.3 Central nervous system (CNS) TB is usually paucibacillary in nature and neurological manifestation in tubercular meningoencephalitis (TBME) are more often because of immune mechanism rather than directly because of mycobacterium. TB affecting other sites known as extra-pulmonary TB is rarely smear-positive. Most patient of TBME diagnosed on the basis of clinical evaluation, cerebrospinal fluid (CSF) findings and
neuroimaging. Approximately a third of patients die soon after presenting to hospital and many of those surviving are left with severe neurological sequelae. Overall mortality associated with TBME is reportedly around 22-39%.

**METHODS**

A prospective randomized controlled trial was conducted in Department of Pediatrics, tertiary care centre in Southern Rajasthan, India from July 2017 to June 2018.

**Study population**

Total 110 children between 6 months to 18 years of age group admitted with a clinical diagnosis of TBME were enrolled in the study.

**Inclusion criteria**

Children between 6 months to 18 years of age admitted in Balchikitsalaya, tertiary care centre in southern Rajasthan, India with diagnosis of TBME on the basis of clinical evaluation (fever, headache, stiff neck, seizures, abnormal sleepiness and irritability) with or without signs of meningeal irritation and CSF finding (moderate lymphocytic pleocytosis, moderately elevated protein levels and low glucose), with or without favourable finding on cranial imaging (hydrocephalus, basalmeningeal enhancement, tuberculoma and vasculitis leading to infarcts) and parents giving written informed consent were enrolled.

**Exclusion criteria**

Age less than 6 months and parents not giving consent for participation in study.

**Procedure**

It was a prospective single centre study. Written informed consent was taken from parents of all children who fulfilled the inclusion criteria.

Detailed clinical history, demographic profile, anthropometric data and socioeconomic status was recorded. Previous history of tuberculosis, history of contact with pulmonary tuberculosis (within 2 years), vaccination history, past history of medical illness and history of co-morbid illnesses were also taken.

General physical examination and complete systemic examination was done including level of consciousness, signs of meningeal irritation (neck stiffness, Kernig's sign, Brudzinski's sign) and cranial nerve involvement. Skigram chest, tuberculin skin test, complete blood count (CBC), erythrocyte sedimentation rate (ESR), CSF analysis, neuroimaging, cartridge based nucleic acid amplification test (CBNAAT) of CSF sample and gastric aspirate sample were done in all the patients. A standard tuberculin skin test was performed, and results read after 48-72 hours (positive: induration of >10 mm). All samples were taken with informed consent and under all aseptic conditions and sent in sterile containers with no time delay for analysis.

The essential criteria for diagnosis of TB meningitis were CSF pleocytosis with >50% lymphocytes and protein >60 mg/dl whereas supportive criteria included fever for more than 2 weeks, history of contact with TB, generalized lymphadenopathy, positive mantoux test >10 mm, positive chest x-ray findings, computed tomography (CT) showing hydrocephalus or basal exudates, gastric juice acid-fast bacilli (AFB) positive or isolation of AFB from other sites and proven tuberculous lymphadenitis.

About 3 ml CSF fluid was drawn by lumbar puncture using standard procedure protocol and 1 ml was sent for CBNAAT test and 2 ml for routine as well as bacteriological examination. CBNAAT was done by using gene Xpert machine available in TB clinic of the institute, with the results in less than 2 hours.

All the information was recorded in tested proforma formed in Microsoft excel for final analysis. Bacterial meningitis, viral meningitis and fungal meningitis were ruled out by clinico-radiological, biochemical and bacteriological examinations. CNS tuberculosis was diagnosed based on history, clinical evaluation, CSF finding and neuroimaging findings. Statistical analysis was done using Statistical Package for the Social Sciences (SPSS) version 20.0 software.

**RESULTS**

Among 110 children included in the study, CSF lymphocytic pleocytosis was seen in all. Majority of children (56.36%) cell counts were in the range of 101-500 cells/µl and mean CSF cell count was 198.09±177.86 per µl (Figure 1). CSF protein ranges from 100 to 400 mg/dl and in 31.82% children CSF glucose was <20 mg/dl and in 50% lymphocytic pleocytosis presented in all cases). Mean CSF cell count was 198.09±177.86 per µl.

CSF was examined in all children included in the study. Majority of children (56.36%) cell counts were in the range of 101-500 cells/µl (>50% lymphocytic pleocytosis presented in all cases). Mean CSF cell count was 198.09±177.86 per µl. In this study of 110 children of TBME, 68.2% children CSF protein level was in range of 100-400 mg/dl. Mean CSF protein level was 230.98±167.73 mg/dl (Table 1).

<table>
<thead>
<tr>
<th>Table 1: CSF Analysis Results</th>
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</thead>
<tbody>
<tr>
<td>Cell Count (cells/µl)</td>
</tr>
<tr>
<td>-------------------------</td>
</tr>
<tr>
<td>Mean: 198.09±177.86</td>
</tr>
<tr>
<td>Range: 101-500</td>
</tr>
</tbody>
</table>

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In this study of 110 children, CSF was analyzed for glucose levels. In majority of patients (40%) CSF glucose level was in range of 20-40 mg/dl and in 31.82% children CSF glucose was <20 mg/dl (Table 2). Mean CSF sugar level was 33.86±18.22 mg/dl (Table 2).

<table>
<thead>
<tr>
<th>CSF glucose level (mg/dl)</th>
<th>No. of patients</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>35</td>
<td>31.82</td>
</tr>
<tr>
<td>20-40</td>
<td>44</td>
<td>40.00</td>
</tr>
<tr>
<td>&gt;40</td>
<td>31</td>
<td>28.18</td>
</tr>
<tr>
<td>Total</td>
<td>110</td>
<td>100</td>
</tr>
</tbody>
</table>

Chest radiographic abnormality were found in 41.82% cases. Maximum patients had hilar lymphadenopathy (20%) followed by patchy parenchymal consolidation (14.55%). Eight children had military pattern opacities (7.27%) on x-ray chest. Rest 58.18% had normal x-ray chest (Table 3).

<table>
<thead>
<tr>
<th>Chest radiographic findings</th>
<th>No. of patients</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>64</td>
<td>58.18</td>
</tr>
<tr>
<td>Patchy parenchymal consolidation</td>
<td>16</td>
<td>14.55</td>
</tr>
<tr>
<td>Hilar lymphadenopathy</td>
<td>22</td>
<td>20.00</td>
</tr>
<tr>
<td>Miliary pattern opacities</td>
<td>8</td>
<td>7.27</td>
</tr>
</tbody>
</table>

Common abnormalities noted on neuroimaging were: communicating hydrocephalus (77.27%), meningeal enhancement (40%), infarction (27.27%), cerebral edema (11.82%) and 9.09% has tuberculoma on neuroimaging. 18 (16.36%) patients had normal neuroimaging (Table 4).

<table>
<thead>
<tr>
<th>Neuro imaging findings</th>
<th>No. of patients</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocephalus</td>
<td>85</td>
<td>77.27</td>
</tr>
<tr>
<td>Meningeal enhancement</td>
<td>44</td>
<td>40.00</td>
</tr>
<tr>
<td>Cerebral edema</td>
<td>13</td>
<td>11.82</td>
</tr>
<tr>
<td>Infarction</td>
<td>30</td>
<td>27.27</td>
</tr>
<tr>
<td>Tuberculoma</td>
<td>10</td>
<td>9.09</td>
</tr>
<tr>
<td>Normal</td>
<td>18</td>
<td>16.36</td>
</tr>
</tbody>
</table>

CSF and gastric aspirate were examined by CBNAAAT for MTB. Only 5 (4.55%) children had CBNAAAT positivity in CSF. Gastric aspirate was positive among 16 (14.55%) children. None of the patient had CBNAAAT positive result both in CSF and gastric aspirate.

**DISCUSSION**

In the current study, majority of children (56.36%) CSF cell counts were in the range of 101-500 cells/µl (>50% lymphocytic pleocytosis presented in all cases). Mean CSF cell count was 198.09±177.86 per µl (Figure 1). Mean CSF protein level was 230.98±167.73 mg/dl (Table 1). Mean CSF sugar level was 33.86±18.22 mg/dl (Table 2). None of the CSF sample among the study group demonstrated AFB on Ziehl-Neelsen staining. In a study conducted by Karande et al on prognostic clinical variables in childhood tuberculous meningitis also shows similar results as present study. Among 123 children, cerebrospinal fluid examination was abnormal in all the children. Cellular response was lymphocytic predominance in 98 (80%) children. The means (range) of CSF cell count, protein and glucose were 254 (8-8200) cells/mm³, 160 (20-840) mg/dl and 43 (10-150) mg/dl, respectively.

In a study by Singh et al on clinical profile of pediatric neurotuberculosis, CSF analysis was done in 37 cases out of 46. CSF protein was elevated in 30 cases (65.22%), CSF glucose was decreased in 19 cases (41.30%), normal in 13 cases (28.26%) while an elevated level was seen in 5 cases (10.87%). Lymphocytic predominance in CSF was seen in 29 cases (65.22%). CSF smear microscopy for acid-fast bacilli were negative in all the cases similar to current study.

Chest radiographic abnormality was found in 41.82% cases. Maximum patients had hilar lymphadenopathy (20%) followed by patchy parenchymal consolidation (14.55%). Eight children had military pattern opacities (7.27%) on x-ray chest (Table 3). In a study by Singh et al on clinical profile of pediatric neurotuberculosis. Chest X-
In the present study, CSF and gastric aspirate were examined by CBNAAT for Mycobacterium tuberculosis (MTB). Only 5 (4.55%) patients had CSF positive for MTB by CBNAAT and 16 (14.55%) had positive for MTB in gastric aspirate. None of the patient had CBNAAT positive result both in CSF and gastric aspirate. Hillemann et al in 2011 compared gene Xpert MTB/RIF (Xpert) assay system with conventional liquid and solid culture methods shows similar results.11 521 specimens (91 urine, 30 gastric aspirate, 245 tissue, 113 pleural fluid, 19 CSF and 23 stool specimens) were submitted. The combined sensitivity and specificity of the Xpert assay were calculated to be 77.3% and 98.2%, respectively. In CSF samples all (19) were negative for gene Xpert and 8/30 (26.67%) were positive for CBNAAT in gastric aspirate samples.12-15

CONCLUSION

Neotuberculosis is a pauci bacillary disease, number of bacteria are scanty and difficult to demonstrate. Most clinical and neurological manifestation or complication in neotuberculosis are because of inflammatory immune response rather than direct damage because of MTB. Approximately a third of patients die soon after presenting to hospital and many of those surviving are left with severe neurological sequelae. Early diagnosis and treatment for TBME have been shown in numerous studies to be the best predictor of survival. However, many patients are diagnosed late because initial signs are non-specific and rapid and sensitive diagnostic tests are lacking as quantum of bacterial load is very low.

A negative tuberculin test is common due to immune suppression in patients with neotuberculosis. CSF findings of elevated proteins, depressed to normal glucose levels, and a lymphocytic predominance is strong grounds in favour of neotuberculosis. Neuroimaging brain is pivotal in establishing the diagnosis of neotuberculosis. Most patient of TBME diagnosed on the basis of clinical evaluation, CSF findings and neuroimaging.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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