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CLINICAL PROFILE, BIOCHEMISTRY AND NEUROIMAGING IN CHILDREN WITH NEUROTUBERCULOSIS

Neurology

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ABSTRACT

CNS TB is usually paucibacillary in nature, rarely smear positive and also lack specific sign and symptoms. Diagnosis is based on clinical evaluation, Cerebral spinal fluid (CSF) finding ,CBNAAT and neuroimaging

Objective: The study was conducted to assess the clinical presentation of neurotuberculosis and its association with neuroimaging and CSF analysis.

Material And Method: This was a prospective descriptive study conducted from July 2019 to June 2020 in the department of paediatrics, JLN Medical College , Ajmer (Rajasthan). The age group of 6 months to 15 years were screened out of which 65 cases of CNS TB were enrolled in this study according to clinical features, CSF study and neuroimaging.

Results: Thirty seven children (56.9%) admitted with neurotuberculosis were below five years of age group while 13 patients (20%) were in the age group of 5- 10 years and 15 patients (23.10%) in the age group of 10-15 years. Fever was present in the majority of patients (92%). All patients had clear and cellular CSF. In the majority of patients (80%) cell counts were in the range of 50-200 cells/µl (>50% lymphocytic pleocytosis presented in all cases). TB meningitis was the most common MRI based diagnosis in the majority of patients (87.68 %). TB meningitis had frequently cerebral infarction (38.5% of total TB meningitis patients) and basal exudates (33.8%) while hydrocephalus was less frequently observed (15.4%). Mycobacterial culture was present in 63.08% of patients and CBNAAT was positive in 53.84% patients.

Conclusion: CNS TB is a paucibacillary state so mycobacterial culture and CBNAAT are helpful in half of the cases only. Early diagnosis of TB vasculitis , meningitis , hydrocephalus with help of neuroimaging can be lifesaving and prevents severe physical and mental sequelae.

KEYWORDS

INTRODUCTION-

Tuberculosis (TB) is one of the widespread infectious diseases with a high prevalence, particularly in India. The pediatric population has 10-20% of the total burden.[1] The burden of central nervous system (CNS) TB is directly proportional to the prevalence of TB infection. CNS TB is classified into three clinicopathological categories: tubercular meningitis, tuberculoma and tubercular arachnoiditis.[2] CNS TB is usually paucibacillary in nature, rarely smear positive and also lack specific sign and symptoms.[3] Diagnosis is based on clinical evaluation, Cerebral spinal fluid (CSF) finding (increased protein, low glucose and mononuclear pleocytosis, the result of cartridge based nucleic acid amplification test-CBNAAT) and neuroimaging.[4] Children who demonstrate a subacute clinical feature: headache, vomiting, pyrexia and anorexia should be suspected of having neurotuberculosis. The Gene Xpert (CBNAAT) is an automated real time polymerase chain reaction (PCR) assay designed for the rapid and simultaneous detection of mycobacterium tuberculosis .[5,6,7] Neuroimaging is essential as it helps in demonstrating the complications of TBM besides playing an important role in its diagnosis. Common findings on imaging are abnormal meningeal enhancement in the basal cisterns, hydrocephalus and vascular complications. Early diagnosis of CNS TB is necessary for appropriate treatment to reduce this morbidity and mortality. This study was conducted to assess the clinical presentation of neurotuberculosis and its association with neuroimaging and CSF analysis.

MATERIAL AND METHODS-

This was a prospective descriptive study conducted from July 2019 to June 2020 in the department of paediatrics, JLN Medical College and associated group of hospitals, Ajmer (Rajasthan).

A total of 198 cases presenting to the pediatric department with a history of fever and neurological involvement (encephalopathy and altered behaviour) in the age group of 6 months to 15 years were screened out of which 65 cases of CNS TB were enrolled in this study based on pathognomonic CSF analysis and radiological (CT scan or MRI brain) features confirming CNS TB. Study cases were enrolled after diagnosis of CNS tuberculosis based on clinical evaluation (fever, nausea, vomiting, headache, stiff neck, seizures, behaviour changes and altered consciousness) with or without signs of meningeal irritation, peculiar CSF finding (moderate lymphocytic pleocytosis, moderately elevated protein levels, low glucose) and favourable finding on brain imaging (hydrocephalus, basal meningeal enhancement, tuberculoma, vasculitis leading to infarcts). We excluded patients with CNS abnormalities such as anatomical malformations, epilepsy, and other infections (bacterial and viral meningitis).

Procedure-

This was a prospective descriptive single centre study. Detailed clinical history, demographic profile, history of contact with pulmonary tuberculosis (within 2 years), and vaccination history was recorded. General physical examination and systemic examination was performed including the level of consciousness, signs of meningeal irritation (neck stiffness, kernig's sign, brudzinski's sign), cranial nerve involvement, etc. Complete blood count, erythrocyte sedimentation rate, chest x-ray, tuberculin skin test, CBNAAT of CSF and gastric aspirate sample, CSF biochemistry analysis and computed tomography (CT)/ Magnetic resonance imaging (MRI) were done for all patients. All samples were taken with informed consent and under all aseptic precautions sent in sterile containers with no time delay. About 3 ml CSF fluid was drawn by lumbar puncture using standard procedure protocol and 2 ml for biochemistry analysis and 1 ml was sent for CBNAAT test. CBNAAT was done by using geneXpert machine available in the TB clinic of the institute. All the information was recorded in predesigned proforma. Bacterial, viral and fungal meningitis were ruled out by clinico-radiological, and biochemical examinations.

OBSERVATION AND RESULT-

Sixty-five children between 6 months to 15years of age with the diagnosis of CNS tuberculosis based on clinical evaluation, CSF examination and neuroimaging were included in this study during the study period of one year (July 2019 to June 2020).

Thirty seven children (56.9%) admitted with neurotuberculosis were below five years of age group while 13 patients (20%) were in the age group of 5- 10 years and 15 patients (23.10%) in the age group of 10-15 years.

Fever was present in the majority of patients (92%). Three fourth of patients had a typical neurological presentation with a complaint of altered sensorium (76.9%) and positive meningeal irritation signs (70.6%). Seizure was seen in around two third patients (69.2%). Weight loss, decreased appetite and headache were present in around half of the patients. (Table- 1)

History of contact with TB patient was present in more than half of the patients (60%). Only 55.4% of cases had reactive mantoux test (induration >10 mm).

As patients were enrolled on basis of clinical plus CSF analysis, all patients had typical biochemistry pattern (low glucose, high protein). All patients had clear and cellular CSF. In the majority of patients (80%) cell counts were in the range of 50-200 cells/µl (>50% lymphocytic pleocytosis presented in all cases). (Table 1)

Patients with only MRI findings suggestive of CNS TB were enrolled, so all patients had abnormal MRI study. TB meningitis was the most common MRI based diagnosis in the majority of patients (87.68 %). TB meningitis had frequently cerebral infarction (38.5% of total TB meningitis patients) and basal exudates (33.8%) while hydrocephalus was less frequently observed (15.4%). CNS tuberculoma and tuberculous cerebritis were rarely seen (6.15% each).

Mycobacterial culture was present in 63.08% of patients and CBNAAT was positive in 53.84% patients. Overall CBNAAT's diagnostic yield was nearby to culture.

Table: 1 Symptomatology Of Study Population

Characteristic	Number of patients (%)
Clinical presentation	
Fever >2 weeks	60 (92)
Meningeal irritation	46 (70.7)
Altered sensorium	50 (76.9)
Headache	29 (44.6)
Seizures	45 (69.2)
Decreased appetite	31 (47.6)
Weight loss / failed to gain weight	32 (49.2)
Nausea/Vomiting	45 (69.2)
CSF Examination	
Appearance	
Clear	65 (100)
Turbid	0 (0.0)
Protein level(mg/dl)	
51-100	0 (0)
101-200	10 (15.9)
201-400	55 (84.6)
Sugar level(mg/dl)	
Normal	0 (0)
Decreased	65 (100)
Cell Count mm^3	
05-50	0
50-200	52 (80)
>200	13 (20)
Microbiological test of CSF	
Positive CBNAAT	35 (53.8%)
Positive Mycobacterial culture	41 (63.1%)

Table No 2: Distribution Of Cases According To Brain MRI

Type of CNS TB	MRI Finding	N (%)
TBM with cerebral Infarction	Axial T2W FLAIR: Diffuse hyperintensity in the right parasagittal region with restriction on DWI.	25 (38.5)
TBM with basal exudate	Axial T1W post-contrast image: Meningeal enhancement in and around the basal cisterns and subarachnoid spaces.	22 (33.8)
TBM with Hydrocephalus	Ventriculomegaly, Periventricular Hyperintensity signal on T2W FLAIR Evan's ratio >30 %	10 (15.4)
CNS Tuberculoma	Axial T2W and post-contrast T1W: Round Hypointense lesion (tuberculous granuloma with caseation), lobulated ring like enhancement surrounded by edema.	4 (6.15)
Tuberculous cerebritis	Axial T2W FLAIR: Well- defined round hypo-intense tuberculous nodule with caseation Post-contrast T1W: Patchy enhancement.	4 (6.15)

TBM – TB Meningitis, T1W - T1 weighted, T2W- T2 weighted, FLAIR - Fluid-attenuated

DISCUSSION-

Central nervous system TB in the pediatric age group has a high risk of death (~20%) and neurologic sequelae in more than half of survivors.**8** Out of 65 studied patients, the mean age of the admitted patient was 4.1 years, and the majority of patients were in the age group of 1–5 years (56.9%). In most of the continental and worldwide studies, it's been reported that **8,9** that early pediatric age and infancy were the high risk group of CNS tuberculosis same as this study.

Goyal G et al, reported that fever was present in 100% of patients followed by altered sensorium (54.5%), vomiting (50%), headache (45.4%) and seizure (40.9%).[10] Similarly in our study 92% of children presented with complaint of fever >2 weeks, 76.9% with altered sensorium, 70.6% with meningeal irritation, 69.2% cases with seizure and 44.6% with a headache. As meningitis was observed in most of the cases, so meningeal sign and symptoms were frequently observed. **Jain et al** also observed that the majority of presenting patients were with meningeal irritation and altered sensorium.[11]

History of contact with TB patient was present in more than half of the patients (60%). These phenomenal results can be well explained on basis of large prevalence of TB in India. Only 55.4% of cases had reactive mantoux test (induration >10 mm). Compared to pulmonary tuberculosis CNS TB cases were less likely to have a positive tuberculin skin test (TST), so one cannot rule out CNS TB on basis of negative TST test.

CSF Examination:

CSF Proteins and sugar levels were rightly observed according to their cut off limits to label a tubercular CSF (protein>100mg/dl and sugar <40 mg/dl). CSF was always clear, lymphocytic with near 85% cases had >200 mg/dl protein level.[12]

Neurotuberculosis is a paucibacillary disease; numbers of bacteria are scanty and difficult to demonstrate. That's why mycobacterial detection in CSF fluid is always not that high as in the bronchial samples in pulmonary tuberculosis. According to the latest literature 13,14 the sensitivity of CBNAAT in the diagnosis of tubercular meningitis was less than 50 %. In our study, CBNAAT was positive in around half of the cases (53.8%). Most clinical and neurological manifestation or complications in neurotuberculosis are because of inflammatory immune response rather than direct damage because of mycobacterium tuberculosis.[15]

MRI brain was used as a screening tool in our study, so all patient had peculiar MRI features suggestive of CNS TB. TB meningitis was seen in the majority of patients (87.68 %) as previously reported.[8] Some studies have reported less number of TB meningitis among all CNS TB cases.[10]

In our study in MRI brain finding of various type of CNS tuberculosis cerebral infarction was most common (38.46%) followed by leptomeningeal enhancement (33.8%), TBM with hydrocephalus (15.38%), CNS tuberculoma (6.15%) and TB vasculitis (6.15%). Saigal et al also observed the same results during MRI imaging of CNS TB patients and reported leptomeningeal tuberculosis in 41%, tubercular brain abscess in 10% cases, CNS tuberculoma in 12% of cases.[16]

Hydrocephalus was less frequently observed compared to other studies.17 Low incidence in newer studied could be because of the better implication of tuberculosis program and health awareness, so patients are diagnosed in earlier stages. High TB meningitis (87.68 %)

along with a high number of positive meningeal irritation sign and/or symptoms favoured role of detailed clinical examination in early screening and diagnosis.

In our study, 72% improved with treatment. 18.6% had complications. 9.23% of cases died out of 65 cases.

CONCLUSIONS-

Neurotuberculosis occurs with increased frequency in early pediatric age group (1-5 years). CNS TB can be precisely diagnosed on basis of clinical evaluation, CSF biochemistry plus microbiology and MRI brain. Clinically presentation and CSF analysis are well correlated with brain imaging. One can't solely rely on the same diagnosis protocol as used in pulmonary TB because CNS TB is a paucibacillary state so mycobacterial culture and CBNAAT are helpful in half of the cases only. **E**arly diagnosis of TB vasculitis TB meningitis TB hydrocephalus with help of neuroimaging can be lifesaving and prevents severe physical and mental sequelae.

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