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CLINICAL CHARACTERISTIC, NEUROIMAGING AND NEUROLOGICAL OUTCOME OF TUBERCULOUS MENINGITIS IN PEDIATRIC AGE GROUP AT TERTIARY CARE CENTER OF HAPUR ; "A PROSPECTIVE OBSERVATIONAL STUDY"

Paediatrics

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ABSTRACT

Background: Early diagnosis and treatment is important in reducing mortality and morbidity. The aim of the study was to describe clinical characteristic, neuroimaging and neurological outcome of TBM in pediatric age group.

Methods: A total of 72 patients were included in the study based on inclusion and exclusion criteria. Detailed history and neurological examination, CSF analysis, EEG and CT scan studies done in all patients. Mean age of patient was 59 months (range 6month- 18 year). The majority of these patients were in stage II and III.

Results: Among 72 patients included in the study tuberculous meningitis was common in children under 5 years of age (70%). Out of 72 patients 50 patients (70%) were in advanced stage of disease. Most common symptom were fever (90%), altered sensorium (83%), convulsion (80%), vomiting (75%).7thnerve palsy was most commonly involved (25%), hemiplegia in 15 patients (21%) and papilledema in (14%). CSF culture was positive in 61 patients (85%) with Pleocytosis, lymphocytosis and elevated CSF protein as dominant findings. Abnormal chest X ray present in 11 patients (50%) in stage I, 9 patients (38) in stage II, and 6 patients (23%) in stage III of disease.: In our study Leptomeningeal enhancement was present in 17 patients (77.27%) in stage I, 16 patients (66.6%) in stage II, 18 patients (69.2%) in stage III of disease. Hydrocephalus was presents in 14 patients (63.63%) in stage I, 15 patients (62.5%) in stage II, 17 patients (65.38%) in stage III of disease. Survival with neurological deficit is more in younger age and advanced stage of disease.

Conclusion: TBM is an important cause of mortality and morbidity in pediatric patients especially under 5 years of age in countries where tuberculosis is an endemic disease. In our study we found younger the child and more advanced the stage of disease, higher CSF protein value, the greater was mortality and morbidity.

KEYWORDS

Seizure, TBM, CSF Protein, X-Ray, CT scan, Outcome, Stage

INTRODUCTION

Tuberculous meningitis (TBM) is the severe form of extrapulmonary TB, carrying significantly higher mortality and neurological disability among infected individuals, especially in developing countries endemic to tuberculosis.[1,2] Even though TBM constitutes a small proportion of the total reported TB cases (around 1%), it causes a disproportionate amount of suffering with higher rates of mortality and morbidity, especially in young children. [3] TBM has a poor prognosis, and survivors often have severe disabilities.[4]

TBM frequently presents with non-specific symptoms in the early stages and is diagnosed in the later stages of the illness when brain damage has already occurred. The clinical characteristics of TBM include fever, headache, vomiting, impaired consciousness, focal neurological signs, and seizures. [5]

Seizure is a common feature of TBM that may develop at any time point throughout the disease course, with an estimated incidence of 17 to 93%. Seizures in TBM are more common in children than adults; this may be attributed to the immaturity of the brain.[6,7]

The underlying etiology of seizures in TBM is multifactorial, therefore the type and duration of treatment may vary between individual cases depending on the possible underlying cause of convulsion. Seizures associated with TBM infection can be either acute symptomatic or unprovoked seizures. Acute symptomatic seizures usually occur within the first 2 weeks, and sometimes even later. Although they subside once the acute infection is over and may not recur; there is often an increased risk of developing subsequent epilepsy. Whereas unprovoked seizures occur later after the acute phase of TBM and have a propensity to recur. Status epileptics (SE) is also not uncommon finding in patients with TBM.[8]

Early diagnosis and management of TBM is important, as delay in diagnosis leads to poor outcomes such as death, neurological sequelae and neurocognitive disorders. The success of treatment will depend on how quickly to diagnose the disease.

Hydrocephalus associated with tuberculous meningitis is present in 80% of cases of tuberculous meningitis and may be or not of communicating origin.[9]

The definitive diagnosis of TBM is established by the detection and/or the culture of Mycobacterium tuberculosis in the cerebrospinal fluid (CSF). The necessity of long time for Mycobacterium growth on specific culture medium and the low possibility of direct Mycobacterium identification with CSF smear staining may lead to the delay in diagnosis. In order to prevent the delays in identification, the utilization of auxiliary identification techniques such as nucleic acid amplification (NAA), Polymerase Chain Reaction (PCR), antibody detection, and antigen detection have been used.[10,11]

Electroencephalography (EEG) has been reported to be better in assessing the gravity of lesions and was recently reported to help in prediction of outcomes. The relation of clinical findings and EEG pattern may produce better understanding of TBM management and valuable prognostic clues.[12]

MATERIALS AND METHODS

Research design

An observational study was conducted at Saraswati Medical College, Hapur , Uttar Pradesh, May 2019 to May 2021.

Research subjects

A total of 72 children with TBM were investigated. The age of the subjects ranged between 5 months to 18 year and 40 of them were males and 32 females.

Inclusion Criteria

Two or more of the following features, with or without fever, should be present to suggest a clinical diagnosis of TBM—altered sensorium varying from drowsiness to coma, headache, vomiting, history of convulsions (focal or generalized), meningeal signs, bulging fontanel, papilledema, cranial nerve palsy and motor weakness of the limbs.

Exclusion Criteria

Children suffering from malignancy and children on immuno suppressive drugs were not included in the study.

After registration, detailed history was elicited. Vaccination history and history of contact with a known patient suffering from pulmonary tuberculosis in the house or in the neighborhood was elicited.

Measurements
Clinical manifestations such as seizures, altered consciousness, headache or fever were recorded. The Glasgow coma scale (GCS) was applied to classify consciousness. The TBM diagnosis was based on history, clinical symptoms, and cerebrospinal fluid analysis. The evidence of tuberculosis outside the CNS and response to anti tubercular medication were also observed. The presence of a positive CSF Mycobacterium tuberculosis culture was considered to indicate a case of definite TBM. Growing Mtb in culture provides opportunity for drug sensitivity testing, which may influence the selection of treatment regimen.

EEG recordings had been made on hospitalized children with TBM. The EEG descriptions were classified as abnormal EEG I, II or III. The level of EEG abnormalities depends on the clinical manifestations and correlates with the severity and specificity of cortical dysfunction of the EEG abnormality. Patient with mild slowing of the background activity associated with a mild diffuse functional cerebral disturbance is classified as abnormal I. If there is intermittent slow activity that is obviously localized or lateralized, then it should be classified as abnormal II. An EEG that shows spikes but is otherwise unremarkable is classified as abnormal III.[13]

Mantoux skin test was considered positive in patients with endurance diameter > 15 mm in BCG scar positive patients and > 10 mm in BCG scar negative patients.[14]

Chest radiograph and Mantoux skin test were carried out for all patients. The parents of the children were also screened for pulmonary tuberculosis by examination of sputum and chest radiograph. Almost half of the children may have an abnormal chest X-ray.[15]

Neuroimaging done by computed tomography and in some cases, MRI was also done. Sensitivity of magnetic resonance imaging (MRI) is more than CT in detecting basal meningeal enhancement, granulomas and infarcts in pediatric TBM.

The triad of radiological findings in TBM includes hydrocephalus, infarctions and basal meningeal enhancement. The five major computed tomography (CT) features which support the TBM diagnosis include infarcts, hydrocephalus, tuberculomas, basal meningeal enhancement and pre-contrast basal hyperdensities.[16]

The determination of the clinic stages of TBM was done according to the criteria of Medical Research Council as follows: Stage I, patients with no focal neurological findings and Glasgow Coma Scale (GCS) score 15; Stage II, patients with GCS 15 that presenting with focal neurological deficit or all the patients with GCS between 10 and 14, regardless of the presence of focal neurological deficit; Stage III, all the patients with GCS < 10.

STATISTICAL ANALYSIS
Data was presented as mean, number and percentages.

Ethical clearance
The ethical clearance certificate had been issued by the Ethics Committee of SIMS, Hapur, U.P.

RESULTS
Among the 72 patients enrolled to the study, 40(55.56%) were boys and 32 (44.44 %) were girls. The mean age of the patients was 59 months (range: 6 months – 18 years).

Among 72 cases of TBM, 17 (24%) were less than 2 years of age and 33 (46%) were between 2 and 5 years of age. The rest, 22 (30%) were above 5 years of age.

History of contact with a family member suffering from pulmonary tuberculosis was present in 32 (45%) cases while 14 (20%) gave history of contact with a neighbor suffering from pulmonary tuberculosis. Out of 72 patients 50 patients (70%) presented in advanced stage of disease. 50 were patients (70%) were on antibiotic therapy. 15 patients (20%) were on Anti TB treatment at time of admission. The hospital stays for these patients ranged from 4-40 days. The most common symptoms were: fever (68 patients, 90%), altered sensorium (59 patients, 83%), convulsion (57patients,80 %), vomiting (54patients, 75%), Meningeal irritation (45 patients, 63%), Headache (25 patients ,35%), Cough (14 patients, 20%).

Common signs observed were 7th Nerve palsy (18 patients ,25%), 6th Nerve palsy (5 patients, 7%), 3rd Nerve palsy (2 patients 3%), Papilledema (10 patients 14%), Hemiplegia (15 patients, 21%), Quadriplegia (11 patients, 15%).

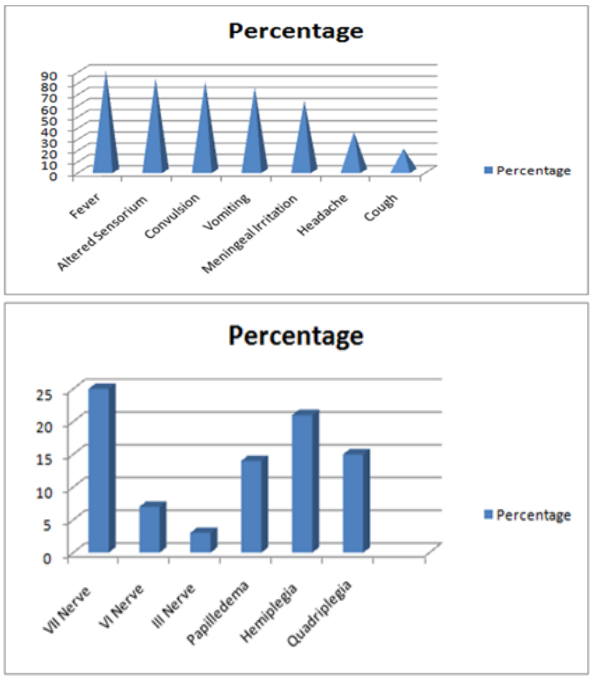

Fig. Presenting signs and symptom

Mantoux skin reaction was positive (>10 mm) in only 10 (14%) patients. BCG scar was present in 24(33%) cases.

CSF Finding:
In 61(85%) cases CSF culture alone was positive for AFB. In 7 cases, smear alone was positive for AFB. In 4 cases both culture and smear were positive.

Pleocytosis (more than 5 cell/Cumm) was seen in 59 (82%). It was lymphocytosis in 42 (58%)

Elevated CSF protein (> 40 mg /dl) were present in 66 (92%).

Chest X ray: In our study Abnormal chest x ray was present in 11 patients (50%) in stage I, 9 patients (38%) in stage II, and 6 patients (23%) in stage III of disease. In other x ray finding Parenchymal involvement was present in 4 patients (18%) in stage I, 10 patients (41.66%) in stage II, 7 patients (26.9%) in stage III of disease. Miliary opacity was present in 3 patients (13.63%) in stage I, 6 patients (25%) in stage II, 4 patients (15.38) in stage III. Mediastinal lymphadenopathy in 3 patients (13.63%) in stage I, 8 patients (33.33%) in stage II, 8 patients (30.76%) in stage III.

Neuroimaging: In our study Leptomeningeal enhancement was present in 17 patients (77.27%) in stage I, 16 patients (66.6%) in stage II, 18 patients (69.2%) in stage III of disease. Hydrocephalus was presents in 14 patients (63.63%) in stage I, 15 patients (62.5%) in stage II, 17 patients (65.38%) in stage III of disease. Cerebral infarction was present in 12 patients (54.54%) in stage I, 13 patients (54.16%) in stage II, 15 patients (57.69%) in stage III of disease. Tuberculoma was present in 8 patients (36.36%) in stage I, 9 patients (37.5%) in stage II, 10 patients (38.46%) in stage III of disease. Vasculitis was present 5 patients (22.72%) in stage I, 5 patients (20.83%) in stage II, 6 patients (23.07%) in stage III of disease.

Table.1 Association between age and outcome of disease

OUTCOME	< 2 Year (n=17)		2-5 year (n =33)		>5 year (n=22)	
	No.	%	No.	%	No.	%
Survive without deficit	8	47	13	39.4	11	50
Survive without deficit	5	29.41	15	45.5	8	36.36
Dead	4	23.52	5	15.1	3	13.64

In our study mortality was greater in younger age group as compared to older age groups. Mortality was more in children under 5 years of age.

Table.2 Association between clinical stage and outcome of disease

OUTCOME	Stage I TBM (n=22)		Stage II TBM(n=24)		Stage III TBM(n=26)	
	No.	%	No.	%	No.	%
Survive without deficit	11	50	12	50	8	30.76
Survive with deficit	9	40.9	9	37.5	11	42.30
Dead	2	9.09	3	12.5	7	26.9

With advancement of stage of disease survival with neurological deficit increases. Early diagnosis is important in preventing development of neurological deficit.

Table.3 Association between CSF Protein level and outcome of disease

Clinical Stage	CSF Protein <100mg/dl (n=31)				CSF Protein >100mg/dl (n=41)			
	Survivors		Death		Survivors		Death	
	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage
I (n=22)	12	38.70	1	3.22	8	19.51	1	2.43
II (n=24)	11	35.48	1	3.22	10	24.39	2	4.87
III (n=26)	6	19.35	0	0	13	31.70	7	17.07

Out of 26 patients in stage III, 20 (76.9%) had CSF Protein level greater than 100mg /dl whereas in stage I, out of 22 children only 9 (40.9%) had such high value. Mortality was higher in children with higher CSF Protein level.

DISCUSSION

Tuberculous Meningitis (TBM) is a severe manifestation of tuberculosis that represents 1% of the cases of infection by Mycobacterium tuberculosis. Children are among the other age groups the most affected- Early diagnosis and treatment of TBM play an important role in decreasing mortality and morbidity.

Out of 72 patients included in our study TBM is more prevalent in children under 5 years (70%). Dodd PJ et al in their study found more than 58 % cases of pediatric TB occur in children less than 5 years.[17]

Most common symptoms in our study were: fever (68 patients, 90%), altered sensorium (59 patients, 83%), convulsion (57patients,80 %), vomiting (54patients, 75%), Meningeal irritation (45 patients, 63%), Headache (25 patients ,35%), Cough (14 patients, 20%).

In our study cranial nerve involvement was 7th Nerve palsy (18 patients ,25%), 6th Nerve palsy (5 patients, 7%), 3rd Nerve palsy (2 patients 3%), Similar finding found in study conducted by Sharma p et al in which cranial nerve palsy observed in 33% of patients. TBM has a high rate of neurological complication and long- term sequelae.[18]

In most studies, three quarters of the patients were at stage II or III and those results have supported delaying in diagnosis.[19]

In our study there were 22 patients (31%) in Stage I ,24 patients (33%) in Stage II and 26 patients (36%) in Stage III.

In our study CSF findings found are Pleocytosis, leukocytosis and elevated protein. Similar finding seen in study conducted by Daniel B.D et al.[20]

Initial cases will have neutrophil predominance versus chronic etiologies will show lymphocytosis.

Diagnosis of TBM is supported by Chest X ray and neuroimaging. Chest radiography findings (especially miliary tuberculosis) are among the diagnostic criteria used for diagnosis of TBM in clinical studies. In our study abnormal chest x ray was present in up to 50% of cases. While the chest X-ray findings favoring pulmonary TB were found in 66 % and 60 % of TBM patients in different studies.[21]

Approximately half of our patients did not have chest X-ray abnormality. Chest X-ray alone is insufficient in diagnosing early TBM.

CT scan is important in diagnosis of TBM. In our study Leptomeningeal enhancement was present in 17 patients (77.27%) in stage I, 16 patients (66.6%) in stage II, 18 patients (69.2%) in stage III of disease. Hydrocephalus was presents in 14 patients (63.63%) in stage I, 15 patients (62.5%) in stage II, 17 patients (65.38%) in stage III of disease. Cerebral infarction, Tuberculoma and vasculitis are other important finding in our study. Similar finding found in study carried out by Marais S et al in which Hydrocephalus and meningeal enhancement are important signs of TBM in CT scan, observed in 80 and 75 per cent of children with TBM, respectively.[22]

CONCLUSION

Tuberculous meningitis is more common in children under 5 years of age and mortality is also more in younger group. Most of patients diagnosed at stage II and stage III. Diagnosis of patients with TBM at earlier stage is crucially important to decrease mortality rates besides appropriate diagnostic and treatment strategies. Chest x-ray alone is not sufficient in diagnosing tuberculosis. Computed tomography helps in early diagnosing TBM in early stages. Hydrocephalus and leptomeningeal enhancement are common CT findings in TBM. Neurological deficit is more in advanced stage. TBM had poor prognosis and high mortality. Advanced stage of presentation probably reflects late presentation and diagnosis was associated with poor prognosis and high mortality.

Abbreviations:

CSF- Cerebrospinal fluid
TBM- Tuberculous meningitis
Mtb - Mycobacterium Tuberculosis
AFB- Acid fast bacilli

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