www.jmscr.igmpublication.org
Impact Factor (SJIF): 6.379
Index Copernicus Value: 71.58
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v6i6.161

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Original Research Article

Pediatric Tuberculous Meningitis-Clinicoepidemiological, Mortality and Morbidity profile in tertiary care institute in northern India

Authors
Dr Ashish Sharma[1], Dr Ashok Garg[2], Dr Sandhya Kumari[3], Dr Ambuj Shandil[4]
[1,2] Pediatrician, [3]Dermatologist, Indira Gandhi Medical College Shimla; [4]Pediatrician, Civil Hospital Theog
Corresponding Author
Dr Ashok Garg
Address: House no. 35, Ward no. 2, Village Anu kalan, PO/Teh/ Distt. Hamirpur (HP)-177001, India
Email: *ashokgarg44@gmail.com*, 9459930003, 8894903002

Abstract
Introduction: *Tuberculous meningitis (TBM) is a serious public health problem in developing countries and is associated with high mortality and morbidity. A delay in diagnosis and treatment can lead to fatal complications.*
Aim: *To study the incidence, clinicoepidemiological profile and complications of tuberculous meningitis amongst all hospitalized patients of age group of one month to five years of age.*
Settings and Design: *Prospective, observational study including children one month to five years of age with TBM admitted in a tertiary care hospital from northern India.*
Material and Methods: *A prospective observational study was conducted in the Department of Pediatrics Indira Gandhi Medical College Shimla over a period of one year (November 2012 to October 2013) amongst children of age group one month to five years with suspected TBM. The diagnosis of TBM was based on predefined criteria.*
Results: *Out of 160 children suspected of meningitis, 11 were diagnosed TBM. Most (72%) cases were in the age group 13 months to 60 months followed by 27% cases in the age group of 3 months to 12 months while below 2 months no case was seen. 54.5% were females and 45.5% were males with female to male ratio of 1:0.83. Death occurred in 27.5% cases.*
Conclusion: *Newer investigations, early diagnosis and treatment are need of hour to prevent mortality and morbidity related to TBM.*
Keywords: *Meningitis, Tuberculous, Seizures, Hemiparesis.*

Introduction

Tuberculous meningitis (TBM) was first described by Edinburgh physician Sir Robert Whytt in a posthumous report that appeared in 1768. [1] However, the link of Tubercle bacilli with tuberculosis took another 100 years to discover. World Health Organization (WHO) estimates that one third of the world's population is infected with Mycobacterium tuberculosis, with the highest prevalence of tuberculosis in Asia.[2] The risk of progression of the primary tuberculosis (TB) to TBM is higher in children than adults.[1] Tuberculous meningitis (TBM) is one of the most common clinical and morphological manifestations of extra-pulmonary tuberculosis (EPTB) and remains a serious health threat in developing countries.[3] TBM accounts for 20-45% of all types of tuberculosis among children, when compared

with only 2.9-5.9% of adult tuberculosis. [4] With the use of anti-tuberculous drugs the mortality rate has reduced but survivors are left with serious disabling neurological sequelae. It may occur at any age, but the highest incidence is in the first 5 years of the life.[4] TBM is typically a sub acute disease. A prodromal phase of low-grade fever, malaise, headache, dizziness, vomiting, and/or personality changes may persist for a few weeks. After initial symptoms, patients can develop more severe headache, altered mental status, stroke, hydrocephalus and cranial neuropathies. Seizures which are uncommon manifestations of TBM in adults are commonly (50% cases) seen in children with TB.[5] Diagnosis is confirmed in suspected cases by demonstrating *M.* tuberculosis on microscopy or culture of the CSF or demonstrating M. tuberculosis DNA by PCR testing.[5] TBM may be accompanied by tuberculoma, which is detected on CT brain either at diagnosis or develop later during treatment. TBM has a high morbidity and mortality when compared to nearly all other forms tuberculosis. Disability and death can still occur despite early diagnosis and appropriate treatment. [5]

The prognosis of TBM largely depends on time of treatment initiation and neurologic status at the time of presentation. The course of TBM is generally not as rapid or fulminant as meningitis due to pyogenic bacteria. Empirical treatment should be initiated as soon as TBM is suspected since delay in treatment can worsen the outcome. Various case series indicate a mortality rate of 7-65% in developed countries and up to 69`% in underdeveloped countries. [5] Neurologic sequelae occur in up to 50 % of survivors in the form of sensorineural hearing loss, hydrocephalus, cranial nerve palsies, stroke-associated lateralizing neurological deficits, seizures and coma. [6] Prompt and accurate diagnosis with adequate treatment of TBM in children remains a major challenge worldwide as reflected by continued high morbidity and mortalities. There have been a few studies addressing clinicoepidemiological spectrum and outcome of disease in children from India[5]. This study intends to strengthen our existing knowledge about the incidence, clinicoepidemiological, mortality and morbidity profile of TBM among hospitalized patients.

Aims and Objectives

To study the incidence, clinicoepidemiological, mortality and morbidity profile of tuberculous meningitis amongst all hospitalized patients of age group of one month to five years of age.

Materials and Methods

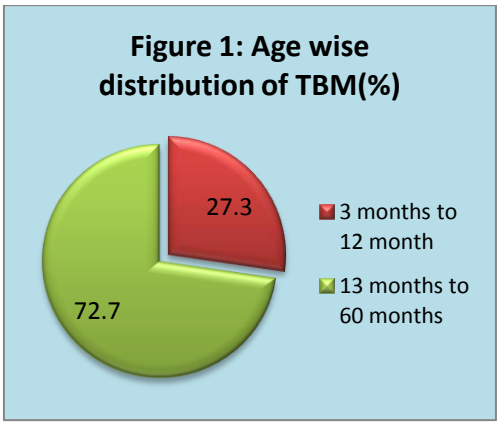
This prospective observational study was conducted in the department of Pediatrics Indira Gandhi Medical College Shimla over a period of one year (November 2012 to October 2013). Children of age group one month to five years with suspected TBM admitted at IGMC Shimla were included in study. Well informed consent was taken from the parent/guardian prior to taking samples. A detailed history was taken and meticulous physical examination was carried out in patients. TBM was suspected based on following features: Fever and/or a cough for ≥2 weeks, neurological symptoms (irritability, refusal to feed, headache, vomiting, altered sensorium, abnormal movements or seizure). Further investigations were done to confirm the diagnosis. Diagnosis of TBM was based on criteria given by—(Table-1)

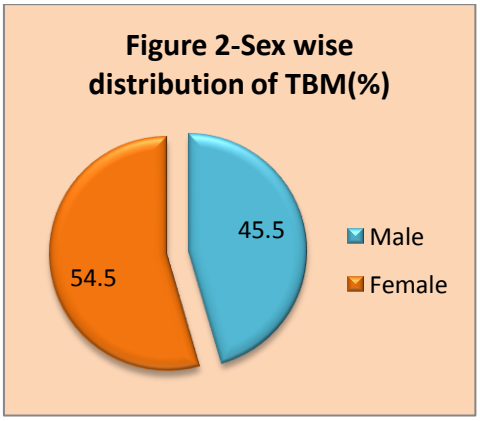
Table 1- Criteria for diagnosis of TBM [8]

Case definition of TBM	The presence of two or more than two clinical symptoms and either Microbiologic or Biochemical or Radiological features suggestive of TBM were taken as diagnostic criteria.
Clinical criteria	Two or more of the following parameters with or without fever were taken as a suspect of TBM- Altered sensorium (drowsiness to coma), irritability, headache, vomiting, convulsions (focal or generalized), meningeal signs, bulging fontanel, papilloedema, cranial nerve palsy and motor weakness of the limbs.
Microbiological criteria	Isolation of *M tuberculosis* from CSF by a. Mycobacterial culture/AFB staining or b. CSF positive for Mycobacterial PCR
Biochemical criteria	Further, CSF samples were obtained in sterile test tubes/ screw capped bottles and sent for biochemistry, cytology, latex agglutination test, gram staining, AFB staining, culture sensitivity and PCR for tuberculosis.
Radiological criteria	Basal enhancement, hydrocephalus, infarcts or tuberculoma on CT scan or MRI brain were included.

Results

A total of 1560 children (1-60 months) were admitted in children ward. Out of them 160 (10.25%) were suspected to be suffering from meningitis. Among these, 11 (0.7%) cases were diagnosed as TBM. Amongst TBM patients, most [8/11 (72.7%)] cases were in the age group 13 months to 60 months followed by 27.3% cases in the age group of 3 months to 12 months while below 2 months no case was there.





Females [6/11(54.5%)] outnumbered the males [5/11(45.5%)] by a ratio of 1:0.83. As per outcome, 8 (72.5%) cases were discharged and 3 (27.5%) cases died thus revealing a fatality of 27.5%.

Table 2: Cases showing positive results on various diagnostic tests in TB

Test	Number	Percentage
CSF Biochemistry and cytology	8	72
AFB Staining	3	27
CSF C/S	0	0
TB PCR	2	18
Basal enhancement	9	81
Tuberculoma	1	9

On subjecting these patients to various investigations it was found that CSF biochemistry was suggestive of TBM in 8 (72%) cases, AFB staining was positive in 3 (27%) cases while CSF culture remained sterile in all cases. PCR on CSF was positive in 2 (18%) cases of TBM. On radiology, basal enhancement on CT scan/ MRI was found in 9 (81%) of cases and tuberculoma was detected in only 1 (9%) case.

Various complications occurred during admission period and also later on follow up. Seizures and hydrocephalus were most commonly [7(63%) for each] noticed complications during hospitalization period. Others were raised ICP [6(54.5%)], decerebration [5(45%)], drowsiness [4(36%)] and subdural effusion [2(18%)] in their descending order. (Figure-3),

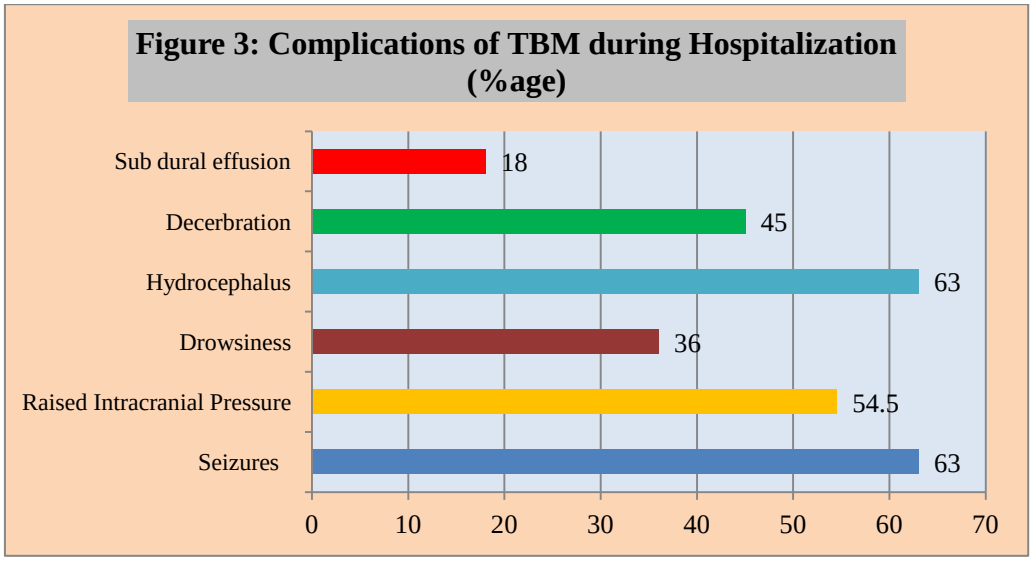


Table 3: Complications of TBM on follow up

Complication	Number(8)	Percentage
Hemiparesis	5	62
Monoparesis	0	0
Quadriparesis	0	0
Seizures on follow up	5	62
Extrapyramidal features	0	0
Infarct	2	25
Hearing deficit	1	12.5
Vision impairment	3	27
Cranial nerve palsy	4	50
Developmental delay	5	62

After discharge, only eight cases could be followed up for complications. Hemiparesis, seizures and developmental delay were most commonly observed sequel with 5 (62%) cases for each. Other complications were cranial nerve palsies in 4 (50%) cases, vision impairment in 3(27%), and brain infarcts in 2 (25%) cases. Monoparesis, quadriparesis and extrapyramidal movements were not found in any case.

Discussion

Tuberculous meningitis occurs when there is hematogenous spread of the TB bacteria to the brain. In the era when treatment was not available, this usually occurred within 12 months of the primary infection. It is sometimes part of a more widespread hematogenous dissemination, with chest X-ray patterns typical of miliary tuberculosis. It can present with systemic features if due to miliary disease, or more local central nervous system signs if limited to the brain. Unlike acute bacterial meningitis, the onset of TB meningitis is insidious over a few weeks.

The incidence of TBM was found 0.7% in our study while Kumar et al reported it between 1-4%. [7] In our study, majority (72%) of cases were between 24 months to 59 months of age with slight predominance of females. Similar distribution of age and gender has been quoted by Gijs *et al* [8]

CSF biochemistry was suggestive of TBM in nine (81%) out of eleven patients. AFB staining was positive in three (27%) of these patients while PCR was positive in two (18%) patients. CT scan was suggestive of TBM in 91%. The CSF biochemical finding suggestive of TBM in terms of lymphocytic pleocytosis, increased proteins and decreased sugar were found in 9 (81%) cases in our study. This finding was in accordance with study done by Thilothammal *et al* [23][5]. In our study basal enhancement and tuberculoma on CT scan were seen in 81% in collaboration with study by Kumar *et al*. [7] Death rate of our study (22%) is comparable to study conducted by Ahmadinejad *et al* [3] and Thilothammal *et al*. [5]

Various complications were seen in admitted cases and rate of such observation was also reported by Singh *et al* in the year 1997. 47 [10] They found seizures in 62% of cases, increased ICP in 54% of cases and decerebration in 38% cases. In another study done by Quamar *et al* [9] in Pakistan, drowsiness was seen in 32% while in our study it was found in 36% of cases. Hydrocephalus developed in 63% cases of TBM in our study, while a great range of 23% to 80% in various studies by Marx *et al* [4] ,Farah *et al* [9] ,Singh *et al* [10] Lamprecht *et al* [11] Davis *et al* [12] and Paganini *et al* [13]. Hemiplegic complications rate was 45% in our study and Singh *et al* [10] reported it as 38%. The percentage of cranial nerve palsies was slightly on higher side in our study which can be explained by early follow up. Finally the percentage of developmental delay in our study was 45% which can be supported by the study done by Thilothammal *et al* [5]

In a study published on TBM in the year 1992 by N. Thilothammal et al on clinical profile mortality and morbidity of bacteriologically confirmed cases, one hundred and seven cases of tuberculous meningitis were registered as a part of a case control study during the period 1990-1992. A study done by S Haldar et al in 2009 on efficient diagnosis of tuberculous meningitis by detection of Mycobacterium tuberculosis DNA in cerebrospinal fluid filtrates using PCR. The study was designed to evaluate the utility of CSF 'filtrates' for the diagnosis of TBM using PCR. One hundred and sixty-seven CSF samples were analyzed from patients with 'suspected' TBM and a control group including other cases of meningitis or neurological disorders. From this

study, they concluded that CSF 'filtrates' contain a substantial amount of M. tuberculosis DNA and 'filtrates' and not 'sediments' are likely to reliably provide a PCR-based diagnosis in 'suspected' TBM patients. [14]

Currently, most experts conclude that commercial NAA tests can confirm TBM but cannot rule it out. Thus, it bears emphasizing that a negative CSF examination for acid-fast bacilli or M. tuberculosis DNA neither excludes the diagnosis of TBM nor obviates the need for empirical therapy if the clinical suspicion is high. After starting treatment, the sensitivity of CSF smear and culture decreases rapidly, while mycobacterial DNA may be detectable in the CSF for up to a month after treatment initiation. Diagnosis of TBM can be helped by neuroimaging. Classic neuroradiological features of TBM are basal meningeal enhancement and hydrocephalus, hypodensities due to cerebral infarcts, cerebral edema and nodular enhancing lesions may also be seen. Magnetic resonance imaging (MRI) is the imaging test of choice for visualizing abnormalities associated with TBM, as it is superior to computed tomography (CT) for evaluating the brainstem and spine. However, CT is adequate for urgent evaluation of TBM-associated hydrocephalus for possible surgical intervention. [4]

Conclusion

India is a high burden TB country and TBM is an important cause of mortality and morbidity in pediatric population. TBM in childhood is difficult to suspect due to similar presentation of many other diseases. A detailed history and meticulous clinical examination is necessary to make diagnosis of TBM. Newer investigations, early diagnosis and treatment are need of hour to prevent mortality and morbidity related to TBM.

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