ORIGINAL ARTICLE

Clinical presentations and outcomes of the children with tuberculous meningitis: An experience at a tertiary care hospital

Naveed Anjum, Nuzhat Noureen, Imran Iqbal

Abstract

Objective: To determine the clinical presentations and outcomes of the children suffering from tuberculous meningitis.

Methods: This prospective, descriptive study was conducted at the Children's Hospital and the Institute of Child Health, Multan, Pakistan, from February to December 2015.

The Pakistan Paediatric Association scoring chart for tuberculosis was used as a tool for the probable diagnosis. The clinical symptoms with their durations were noted. Clinical stages of tuberculous meningitis, cerebrospinal fluid analysis and computerised tomography brain findings were noted for each patient. The outcomes in the form of death or neurological disabilities at the time of hospital discharge were noted. SPSS 19 was used for data analysis.

Results: Of the 40 participants, 25(62.5%) were males and 15(37.5%) were females. The mean age of the patients was 4.24±3.32 years. Besides, 26(65%) patients were less than 5 years of age. All the patients (100%) were categorised as stage 3 tuberculous meningitis. The history of prolonged duration of fever 39(97.55%) and altered level of sensorium 40(100%) were the most common clinical presentations. Moreover, 2(5%) patients died during this study. All the 38(95%) survivors had neurological disabilities. There were motor deficits in 37(97.4%) patients, altered level of sensorium in 35(92%), cranial nerve palsies in 9(23.5%), epilepsy in 29(76.3%) and hydrocephalus in 32(84%) patients.

Conclusion: The children were the most vulnerable group for the worst form of tuberculous meningitis and had a grave outcome.

Keywords: Tuberculous meningitis, Children, Clinical presentations, Outcomes. (JPMA 68: 10; 2018)

Introduction

Tuberculosis (TB) is a chronic infectious disease caused by Mycobacterium (M.) tuberculosis. It is a gram-positive, aerobic, rod-shaped organism that was discovered by Dr. Robert Koch in 1882. It can infect any part of the body and is a major public-health problem. It is estimated that one-third population on this planet is infected with M. Tuberculosis, but only about 5-10% of these infected persons develop active TB in their lifetime.[1]

Tuberculosis is one of the common and serious diseases of children. Globally in 2014, one million children were infected with TB and 0.14 million children died because of TB.[2]

It is reported that up to 25% of cases occur in the child age group. Pakistan is one of the high-risk countries for tuberculosis. The exact number of children with TB in Pakistan is not known.[3]

Tuberculosis is a preventable disease. Bacillus Calmette-Guérin (BCG) vaccine, a live attenuated vaccine is used for the prevention of tuberculosis. In Pakistan it is a part of the Extended Programme of Immunisation (EPI) and is administered at birth. It reduces the risk of all forms of TB by 50%. It also reduces severe, non-pulmonary forms such as childhood meningitis by 70%. Immunity induced by it lasts from 3-12 years and 5-8 years on an average.[4]

Tuberculous meningitis (TBM) is the most common manifestation of central nervous system (CNS) tuberculosis in the child age group. It is 100% fatal if left untreated and delays in treatment lead to permanent brain damage.[5]

Tuberculous meningitis is difficult to diagnose because of early non-specific clinical features and lack of readily available sensitive test.

The definitive diagnosis of Tubercolous meningitis depends on the recovery of Mycobacterium tuberculosis organism from the cerebrospinal fluid (CSF) sample but that needs a large CSF sample almost of 10-20 ml, takes long time of 6-8 weeks for results but the sensitivity of CSF culture is very low (12.5%).[6]

The Children's Hospital & The Institute of Child Health, Multan.
Correspondence: Naveed Anjum. Email: drnaveedanjum284@gmail.com

The Pakistan Paediatric Association's (PPA) scoring chart for tuberculosis contains all the characteristics findings required for the probable diagnosis and is a very helpful tool, especially in the resource-restricted countries like ours. The sensitivity of PPA scoring chart for TBM is 91%.[7,8]

According to the medical research council guidelines, the clinical severity of TBM is characterised into three stages. Stage 1is characterised by the non-specific symptoms such as fever, headache, irritability, drowsiness and malaise. Stage 2 is characterised by the low Glasgow Coma Scale (GCS) of 11-14, with or without focal neurological deficit or GCS 15 with neurological deficit. Stage 3 is characterised by GCS of 10 or less than10, with or without a focal neurological deficit.[9]

There is no clear-cut time period in which one stage of TBM shifts to the next stage. The prognosis very much correlates with the clinical stages of tuberculous meningitis. TBM stage 3 has the worst prognosis. Its mortality is 55% and morbidity is 75%. The patients who survived suffer severe neurological disability, including motor deficits, cognition decline, seizures, hydrocephalus and cranial nerve palsies.[10,11]

The current study was planned to identify the clinical presentations and outcomes of TBM.

Patients and Methods

This prospective, descriptive study was conducted from February to December 2015 at the paediatric neurology department of the Children's Hospital and the Institute of Child Health, Multan, Pakistan

The Children's Hospital and the Institute of Child Health is a 150-bed tertiary care hospital that receives complicated and referral patients not only from the whole of the southern Punjab but also from other provinces as well. An average of 43,000 patients are admitted to the hospital and 340,000 patients visit its outpatient department (OPD) each year. We see a large number of TBM patients on a regular basis in our paediatric neurology department. The study protocol was approved by the research institutional ethics committee. Written informed consent was obtained from the patients' parents. Children aged 1 month to 12 years were enrolled by using the purposive consecutive sampling technique.

The sample size was calculated according to the study type.[12]

All the demographic information was noted in a pre-designed proforma, including age, gender, history of tuberculosis infection in the immediate family members, vaccination against tuberculosis and the presenting complaints with the durations. All the children underwent comprehensive physical and neurological examination at the time of admission especially the weight, presence of BCG scars, GCS level, motor system examination, cranial nerves and fundoscopic examination. CSF analysis and computerised tomography (CT) scan of brain (plain and intravenous (IV)contrast)were performed on each patient.

As the sensitivity of CSF culture is very low and the process is cumbersome, the CSF culture for Mycobacterium tuberculosis was not included in our study. We focused more on the probable diagnosis based on pertinent clinical grounds and readily available investigations like CSF result and neuroimaging that are in accordance with the other international studies.[13]

The PPA scoring chart for the tuberculosis was used for the probable diagnosis of TBM. The patients who had a score of $\geq$7 were enrolled in the study.

Nutritional status of participants was assessed by using the Gomez classification. The severity of TBM was clinically categorised as per the British Medical Research Council guidelines.[14]

CSF analysis included cytology and biochemistry was done. The radiological findings typical of TBM, such as basilar meningeal enhancement, hydrocephalus, infarction and tuberculoma, were recorded. The patient's outcome at the time of hospital discharge were noted that were in the form of neurological disabilities, such as motor deficits, altered GCS, feeding problems, cranial nerve palsies, epilepsy or hydrocephalus.

All children were given the same anti-tuberculosis drugs regimen. The intensive phase included treatment with four anti-tuberculosis drugs, i.e. isoniazid, rifampicin, pyrazinamide and streptomycin, for 2 months. The continuation phase included treatment with 2 drugs, i.e. isoniazid and rifampicin, for 10 months. Streptomycin is a first-line anti-tubercolous drug which has bactericidal properties and high CSF penetration. As we were dealing with severe form of TBM and our patients belonged to the child age group, we used parenteral therapy of streptomycin instead of oral ethambutol which has the side effect of optic neuritis that leads to blindness. All drugs were given as a single dose before breakfast. Adjunctive treatment in the form of

dexamethasone was given to the patients for 6 weeks.

The patients were also provided the appropriate symptomatic treatment, including the management of raised intracranial pressure, antiepileptic drugs for seizures, physiotherapy and nutritional care. Patients with gross hydrocephalus received ventriculoperitoneal shunts, while mild to moderate hydrocephalus were treated with oral acetazolamide.[15]

All the data was analysed using SPSS 19. Clinical characteristics were summarised in terms of the frequencies and percentages for the categorical variables and the mean and standard deviation were calculated for the continuous variables.

Results

Of the 40 participants, 25(62.5%) were males and 15(37.5%) were females. The mean age of the patients was 4.24±3.32 years. Moreover, 26(65%) participants were less than 5 years of age. The mean duration of admission to the beginning of anti-tuberculosis treatment was 2.76±2.57 days (range: 1-12 days). The mean duration of hospital stay was 12.95±7.11 days (Table-1).

History of prolonged fever and altered level of consciousness were the most common clinical presentations, occurring in 39(97.55%) and 40(100%) patients, respectively (Table-2).

Fundoscopy examination revealed optic disc atrophy in 19(47.5%) patients. The mean CSF white blood cell count was 98.03±160.16 per cm, mean protein level was 131.5±104.04 mg/dl and mean sugar level was 42.53±30.17 mg/dl (Table-3).

Regarding the outcome, 2(5%) patients died during the hospital stay and the severe neurological disabilities

Table-2: Frequencies and percentages of clinical presentations with their mean duration.

Clinical presentations	Number (%)	Duration of symptoms (days) Mean ± SD
Fever	39 (97.55)	71.93 days ± 74. 98
Headache	12 (30)	22.13 ± 44.56
Vomiting	19 (47.5)	19.45 ± 33.49
Seizures	29 (72.5)	12.25 days ± 17. 51
Altered conscious level	40 (100)	15.08 days ± 23. 70

SD: Standard deviation.

Table-3: Cerebrospinal fluid and CT brain findings in TBM patients.

CSF		Mean ± SD	
CSF WBC (/cm)		98.03 ± 160.16	
Neutrophils (%)		18.52 ± 31.71	
Lymphocytes (%)		78.97 ± 34.07	
Protein (mg/dl)		131.50 ± 104.04	
Sugar (mg/dl)		42.53 ± 30.17	
CT Brain (plain and IV Contrast)	Findings	No.	Percentage
	Hydrocephalus	32	80 %
	Basilar cistern enhancement	6	15 %
	Tuberculomas	8	2 0%

CT: Computerised tomography
TBM: Tuberculous meningitis
CSF: Cerebrospinal fluid
WBC: White blood cells
IV: Intravenous.

Table-1: Demographic data of TBM patients.

Age (years)			
Mean:	4.24 ± 3.32.		
Range:	8 month to 12 years.		
Age groups:	· < 5 years. ---------26 (65%)		
	· 6-10 years. -------- 11(27.5%)		
	· 11-15 years. -------0 3 (7.5%)		
Gender	Male: No. (%)	Female: No. (%)	Male: Female ratio
	25 (62.5%)	15 (37.5%)	1.6:1
H/O TB contact:	Positive: No (%)	Negative: No (%)	
	19 (47.5%)	21 (52.5%)	
BCG scar	Present	Absent	
	23 (57.5%)	17 (42.5%)	
3rd degree Malnutrition	Present	Absent	
	13 (32.5%)	27 (67.5%)	
Stages of TBM	Stage 3 in 40 (100%) patients		
Duration of stay (days)	Mean: 12.95 ± 7.11 days	Range: 1 -33 days	

TBM: Tuberculous meningitis.
TB: Tuberculosis. H/O: History of.
BCG: Bacillus Calmette-Guérin.

were observed in 38(95%) patients at the time of discharge. All of the survivors had more than one disability at the time of hospital discharge. The numbers and percentages of the neurological disabilities among the survivors were as follows: motor disability in 37(97.4%), low GCS in 35(92 %), epilepsy in 29(76.3%), hydrocephalus in 32(84.2%), cranial nerve palsies in 9(23.5%) and 32(84.2%) patients were discharged on the nasogastric (NG) feed. Because of the severe hydrocephalus, the neurosurgical procedure of ventriculo-peritoneal shunts were done in 11(28.9%) patients.

Discussion

Tuberculosis meningitis is one of the serious manifestations of CNS tuberculosis. It is a major cause of neurological disabilities and death in developing countries like Pakistan. Unfortunately, it mostly occurs in the child age group.

The gold standard in diagnosing TBM is positive culture of Mycobacterium tuberculosis from CSF. A new test known as GeneXpert test for the diagnosis of TB was endorsed by the World Health Organisation (WHO) in December 2010. However, studies show a decreased sensitivity of GeneXpert in CSF compared to sputum. The facility of GeneXpert test is not available in our institution and our patients could not afford this test from the private laboratory. We believe that tuberculosis is common in our area and our patient's profile in which clinical features, CSF and radiological findings were very much consistent with the diagnosis of tuberculosis meningitis. We used PPA scoring chart for the probable diagnosis of tuberculosis.

The diagnosis of definite TBM was based on acid-fast bacilli (AFB) staining or mycobacterial culture, but that needs a long time to wait for the results. These tests are not widely available everywhere and the sensitivity of these tests are low. A scoring system was adopted internationally as well as by the WHO to diagnose tuberculosis in childhood. This scoring system is based on the following characteristics: (1) clinical history and examination (2) CSF results and (3) neuroimaging findings that are in favour of TBM. In our study, the focus was on the probable diagnosis that was based on the PPA scoring chart for the diagnosis of TBM.[16,17]

In this study, we found that the majority of the enrolled patients were males (62.5%) most participants were less than 5 years of age (65%). This shows that this age group is more susceptible to this deadly infectious disease. BCG scar was present in 23(57.5%) patients. The preponderance of children less than 5 years of age with severe form of TBM in our study is consistent with other international studies.[18-20]

All of our patients fell into the category of stage 3 TBM, which means that our children suffered with very severe form of TBM. In a study conducted by Günes et al., 32.4% patients had TBM stage 3, but in a study by Van Well GT et al., 97% patients had stage 3 TBM.[21,22]

The common presentations in the TBM stage 3 patients were: fever of prolonged duration, headache, vomiting, seizures and altered conscious level. A study conducted by Shrestha S. et al. had similar results regarding clinical presentations.[23]

The mean time interval from the onset of symptoms to the hospital admission was 28.17±38.85 days. In contrast to a study by Shaikh MA, in which the mean time interval from onset of illness to admission in the hospital was 21.75±9.75 days.[24] The duration of symptoms in our patients was much longer. This may be one reason that our patients had very severe form of tuberculous meningitis. It is documented in the literature that the duration of symptoms before presentation ranges from several days to several months.[25,26]

The late admission may be one reason that our children had severe neurological sequelae of TBM.

In our patients, the funduscopy examination findings were of optic disc atrophy in 47.5% patients and papilledema in 20% patients, but in a study conducted by Sher K. et al., papilledema was the most common (46.4%) fundoscopy findings in TBM stage 3 patients. Again, the findings of optic atrophy in the patients, support our observation that the patients presented late to our department.[27]

CSF analysis results were similar to the Van Toorn R and Solomons R study.[28]

CT brain imaging was abnormal in all of our patients. The most common finding was hydrocephalus (80%), which was similar to the results mentioned in the Tinsa et al. study.[29]

In our study, mortality was 5%, and 95% patients survived with severe neurological disabilities. This number is very much higher than documented in the international studies. It means that we are at the worse end of tuberculous meningitis. In the Nicolette NB et al. study, the outcome at discharge was: 8%

patients died, 43% improved without neurological disability and 49% improved with neurological disability.[30]

The neurological sequelae were in the form of low GCS, motor handicapped, speech and vision problems, epilepsy and hydrocephalus. These outcomes regarding neurological sequalae are in accordance with the Saitoh A. et al. study.[31]

Our patients had more than one disability at the time of discharge. This result also favours our point that our department received patients with the severe form of infection and the disease was so advanced that the brain damage had already occurred.

The current study had its limitations as well. For instance, we studied only acute outcome of probable TBM stage 3 patients at the time of hospital discharge and the sample size was small. Moreover, CSF culture, staining or GeneXpert test was not done .We recommend a larger prospective study to further understand the outcome of children with TBM.

Conclusion

The children were the most vulnerable group for the worst form of tuberculous meningitis and had a grave outcome. There was 100% morbidity with multiple and severe neurological sequelae. Tuberculous meningitis is disastrous for patients as well as their families, and puts much burden on the health care system which is already under stress. There should be high index of clinical suspicion for this grave diseases and early treatment is utmost important.

Disclaimer: None.

Conflict of Interest: None.

Source of Funding: None.

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