



NEUROLOGICAL COMPLICATIONS AND BACILLE CALMETTE-GUERIN VACCINATION STATUS OF CHILDREN WITH TUBERCULOUS MENINGITIS: A TERTIARY CARE HOSPITAL EXPERIENCE

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ABSTRACT

OBJECTIVE: To assess for the neurological complications and Bacille Calmette-Guerin (BCG) vaccination status of children with tuberculous meningitis (TBM).

METHODS: This retrospective study was conducted in Ayub Teaching Hospital, Abbottabad, Pakistan. Data of diagnosed case of TBM who received anti-tuberculous therapy from 2017 to 2020 was retrieved from records. Records of children, aged 6 months to 10 years of either gender were included and vaccination status was documented along with CT scan findings. Neurological complications in hospital and outcome were recorded as discharge, expiry and transfer to other hospital.

RESULTS: Out of 40 patients, 17 (42.5%) were males and 23 (57.5%) females. Age ranged from 6 months to 8 years with mean age of 2.81 ± 2.29 years. Weight ranged from 5 to 24 kg and mean weight was 10.36 ± 4.96 kg. About 72.5% patients were <5 years of age. About 47.5% (n=19/40) patients were not vaccinated for BCG. Primary source of tuberculosis in close contacts was identified in 35% (n=14/40) patients. Common findings on CT scan were hydrocephalus (35.0%; n=14/40) & cerebral infarct (15.0%; n=6/40). The common complication observed were hydrocephalus (35%; n=14/40), acute stroke (20%; n=8/40), cranial nerve palsies (12.5%; n=5/40), seizure disorder (12.5%; n=5/40). Mortality rate was 2.5% (n=1/40). Only 35.7% (5/14) of patients with hydrocephalus and no patient with stroke or seizures were fully vaccinated.

CONCLUSION: Hydrocephalus & stroke are the most common complication in children with TBM. Neurological complications were observed more commonly in children who were either not vaccinated or partially vaccinated for BCG.

KEY WORDS: Tuberculosis (MeSH); Meningitis (MeSH); Immunization (MeSH); Hydrocephalus (MeSH); Stroke (MeSH).

THIS ARTICLE MAY BE CITED AS: Aalia B, Shah SSH. Neurological complications and Bacille Calmette-Guerin vaccination status of children with tuberculous meningitis: a tertiary care hospital experience. *Khyber Med Univ J* 2020;12(4): 305-9. DOI: 10.35845/kmu.2020.20431.

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Date Submitted: June 06, 2020
Date Revised: October 24, 2020
Date Accepted: November 09, 2020

is poor if timely diagnosis and treatment is not taken appropriately.⁷ Diagnosis of TBM in children requires high index of suspicion as CSF findings are within normal limits in 30% of patients.⁸ In developing countries due to lack of advance investigations even in tertiary care hospitals diagnosis of TBM can be delayed which may adversely affect the outcome.⁹ Neurological disabled children are not only difficult to manage in hospital but also need continuous care by parents. In Pakistan, local literature is available regarding TBM but has not correlated TBM severity with the Bacille Calmette-Guerin (BCG) vaccination. This study results will emphasize for more rationale coverage of BCG vaccination in children of developing countries to prevent complications of TBM. This study was done to describe the neurological complications and vaccination status of children with TBM

INTRODUCTION

Tuberculosis (TB) in this era is still widespread especially in third world countries like Pakistan. According to World Health Organization (WHO) Global tuberculosis report 2019, in 2018 about 10 million new cases of TB were reported worldwide and out of these 1.1 million were children.¹ Tuberculous meningitis (TBM) accounts for 1-2% of active tuberculosis but even with appropriate treatment, it is

associated with neurologic sequelae and death.^{2,3} In children, studies have shown that TB has different clinical manifestations and history as compared to adults. As children tend to have high risk of progressive disease and present with disseminated TB including TBM.⁴

Though TB in children is reported about 10-20% and may rise to 40% in TB endemic area yet it may be underestimated.⁵ TBM in children has high morbidity and mortality.⁶ Outcome

METHODS

This retrospective study has been done in Paediatric B ward of Ayub Teaching Hospital, Abbottabad, Pakistan. Data of children with TBM has been retrieved from the patient records from April, 2017 till March, 2020 over 3 years after approval from institutional review board. Records of patients who presented and got admitted in Paediatric B ward with diagnosis of TBM and started on Anti-tuberculous

TABLE I: FINDING ON CEREBRO-SPINAL FLUID (CSF) EXAMINATIONS

	CSF sugar (mg/dl)	Lymphocytes (percentage)	CSF Protein (mg/dl)	Polymorphs (percentage)	CSF (cells/cmm)	
Median	42.94	72.50	170.84	27.50	110.00	
Minimum	4	4	24	0	2	
Maximum	117	100	678	96	4000	
Percentiles	25	24.25	69.63	74.00	10.00	34.00
	50	42.94	72.50	170.84	27.50	110.00
	75	60.75	90.00	181.75	30.38	533.06

TABLE II: PRIMARY SOURCE OF TUBERCULOSIS IN CLOSE CONTACTS

Primary case	Frequency	Percent
Parents	6	15.0
Grandparents	5	12.5
Uncle/ aunt	2	5.0
Siblings	1	2.5
Not known	26	65.0
Total	40	100.0

TABLE III: FINDINGS ON COMPUTED TOMOGRAPHIC (CT) SCAN

CT scan finding	Frequency	Percent
Hydrocephalus	14	35.0
Infarct	6	15.0
Tuberculoma	2	5.0
Meningeal enhancement	2	5.0
Normal study	4	10.0
Not done	12	30.0
Total	40	100.0

TABLE IV: COMPLICATIONS OBSERVED AT THE TIME OF DISCHARGING THE PATIENT

Complications	Frequency	Percent
Hydrocephalus	14	35.0
Hemiplegia/	8	20.0
Seizures	5	12.5
Cranial nerve palsies	5	12.5
Hearing loss	2	5.0
Aspiration pneumonia	1	2.5
Nil	11	27.5

Treatment (ATT) were included in study. Patients, who were known case of TBM taking ATT or completed the treatment before April, 2017 were not included. Patients known case of developmental delay due to any etiology, syndromic children, seizure disorders were also not included in the study. Children aged from 6 month to 10 years of either sex were included. Vaccination status was documented as up to date vaccinated if vaccine schedule was complete according to Expanded

Programme on Immunization (EPI) vaccine card. If missed any dose according to age then taken as partially vaccinated and if none of vaccine given apart from polio drop then taken as not vaccinated. BCG scar of BCG vaccine given as birth also documented. History of contact was documented if known otherwise unknown was assigned for primary case. Patient age, weight, sex, vaccination status, BCG scar, cerebrospinal fluid (CSF) cell count, percentage of polymorph count and

lymphocyte count, CSF sugar and protein documented on specific proforma. Findings of computed tomography (CT) scan brain were also documented. Patient's outcome was assessed in hospital. Discharge, expiry and transfer to other hospital were taken as outcome. Complications at time of discharge from hospital were documented. Data was analyzed using SPSS 20.

RESULTS

During the study period, forty patients were diagnoses as case with TBM. Out of 40 patients, 17 (42.5%) were male and 23 (57.5%) were females. Age ranged from 6 months to 8 years with mean age of 2.81 ± 2.29 years. Weight ranged from 5 to 24 kg with mean weight of 10.36 ± 4.96 kg. Majority of patients (n=18/40; 45%) were less than 2 years, 11 (27.5%) patients were from 2 to 5 years and 11 (27.5%) patients were more than 5 years of age.

Vaccination status showed that 11 (27.5%) were fully vaccinated (up to date), 10 (25%) were partially vaccinated and 19 (47.5%) patients were not vaccinated. BCG scar was present in only 10 (25%) patients. Cerebrospinal fluid findings are shown in Table I. History of TB was present in family of 35% (n=14/40) patients (Table II).

Outcome as "discharge from hospital" was documented in 38 (95%) patients. Only one (2.5%) patient expired and one patient (2.5%) transferred to another hospital. CT scan brain was not done in 12 (30%) patients. The most common finding on the CT scan done was hydrocephalus (n=14) [Table III].

The common complication observed were hydrocephalus (35%; n=14/40), acute stroke (20%; n=8/40), cranial nerve palsies (12.5%; n=5/40) [Table VI]. There was no complication in 11 (27.5%) patients at time of discharge from hospital. One patient with coma/decerebrate posture had aspiration pneumonia and expired. Mortality rate was 2.5% (n=1/40). Three patients with hydrocephalus required ventriculoperitoneal shunt.

The children who were not vaccinated had more complications. All three patients who required VP shunt were not vaccinated. Only 35.7% (n=5/14) of patients with hydrocephalus and no patient with stroke or seizures were fully vaccinated. (Table V)

DISCUSSION

In our study, almost half (47.5%) of TBM patients were not vaccinated for BCG. The common complication observed were hydrocephalus (35%), acute stroke (20%), cranial nerve palsies (12.5%) and seizure disorder (12.5%). Mortality rate was 2.5% (n=1/40). Common findings on CT scan were hydrocephalus (35.0%) & cerebral infarct (15.0%). Majority of patients with hydrocephalus, stroke and seizures were either not vaccinated or partially vaccinated.

Pakistan is one of the endemic countries with TB and included in list of top 8 countries having TB, according to WHO report 2019. Among the eight countries which account for 66% of new cases of TB, Pakistan accounts for 6% of new TB cases.¹ The presentation of TB in children with central nervous system involvement is in form of TBM, post TBM hydrocephalus. Also the tuberculoma can present as space occupying lesion.¹⁰

Nataprawira HM et al¹¹ did one retrospective/prospective study and included 29 children with TBM and follow them. In their 16 were male and 13 were female. About ¾ of patients had delayed mental and neurological development. While in our study majority were females and 60% patient had neurological complications which is near to their study. Hearing loss was also one of major complication in

Nataprawira HM, et al. study; while in our study we only observed it in two (5%) patients. Faried A, et al.¹² in one of case series done in Indonesia reported 7 children with TBM and the most common complication was hydrocephalus with and without tuberculoma. In our study the most frequent complication was hydrocephalus in 35% of patients. The CT finding showing tuberculoma was in 5% patients.

BCG vaccine protection against TB varies and it has been reported between 0 to 80% as shown by different studies.¹³ In our study only 27.5% patients were fully vaccinated and 25% patients were partially vaccinated. Out of 11 patients who were vaccinated up to date, 4 patients did not have BCG scar. In partially vaccinated children 7 patients out of 10 were not having BCG scar.

Afridi JK, et al.¹⁴ studied the clinical features for diagnosis of TBM in children in one of teaching hospital of KP, Pakistan. The majority of patient having TBM was less than five years of age and accounted for 82% of total patients. In our study 72.5% patients were under five years of age which affirms the findings of Afridi JK, et al. study findings.¹⁴ The literature also documented that children with younger age are more associated with TBM.¹⁵ Rashid A, et al.¹⁶ in one of the tertiary care hospitals of Pakistan studied Tuberculosis among admitted children. In their study majority of females (60.57%) were having TB. In comparison in our study 57.5% with TBM were females. In their study TBM was present in 13.14% patients. Their study recommended that the index case should be traced. In our study in 65% of patients family history of TB was not

known and only was traced in 35% of patients.

Qureshi S, et al.¹⁷ studied the diagnostic modalities in children with TB. In their study the majority of patients (54.9%) were also female; this is as compare to our study having 57.5% females with TBM. Khan IM, et al.¹⁸ in their research letter included 34 children from northern Pakistan. Out of 34 patient, 26 patients had TBM. Females were 58.8% as like in our study where females were 57.5%. In literature we could not find the exact reason for increased incidence in females but may be due to social reason that female are more malnourished and prone for disease. In their study 52.9% cases were having known TB index case, while in our only 35% patients had family history of TB. Majority (57.5%) of patients were not vaccinated with no BCG scar while in our study 72.5% were either not vaccinated or partially vaccinated with BCG scar only present in 3 out of 10 patients who were partially vaccinated.

Anjum N, et al.¹⁹ in their study included 40 patients with TBM. In contrast to our study, their study included males (62.5%) in majority. Like our study (72.5%), in Anjum N, et al. study majority (65%) of patient were less than 5 years of age. Morality in our study was 2.5% while in their study the mortality was 5%. All the survivors in their study were having neurological issues while in our study only 40% patients were having neurological issues. Miftode EG, et al.²⁰ retrospective analysis of Paediatric and adult patients who were diagnoses with TBM. In their analysis 77 children were included. Index case was identified in 30% of patients while in our study 35% patients had a family history of TB in close contacts. Cranial nerve palsies were observed in 10% patients

TABLE V: VACCINATION STATUS VS COMPLICATIONS OBSERVED

Vaccination status (n=40)	Nil (n=11)	Hydrocephalus (n=14)	Hemiplegia (n=8)	Seizures (n=5)	Nerve palsies (n=5)	Hearing loss (n=2)	Aspiration pneumonia (n=1)
Up to date (n=11)	4 (36.4%)	5 (35.7%)	0	0	2 (40%)	0	0
Partial vaccinated (n=10)	1 (9.1%)	5 (35.7%)	2 (25%)	2 (40%)	1 (20%)	0	1 (100%)
Not vaccinated (n=19)	6 (54.5%)	4 (28.6%)	6 (75%)	3 (60%)	2 (40%)	2 (100%)	0

while in our study 12.5% patients were having cranial nerve palsies. Permanent neurological deficits were observed in 23% children while in our study patients it was 20%.

Mihailidou E, et al.²¹ done study in Greece. Their retrospective study included 43 children with TBM but 63% of their patients were not vaccinated at all. In comparison, 47.5% of our patients were not vaccinated at all. Index case was identified in 42% of cases while in our study 35% of patient's primary source was identified. Their expiry was 5% in comparison to our study expiry rate of 2.5%. Permanent neurological deficit was observed in 14% cases, as it was 20% in our patients.

There are limitations in our study. The study was retrospective. Other limitation was that the outcome was only assessed in hospital. For better understanding of impact of TBM on central nervous system, long term follow-up is required. There was family history of TB in 35% of cases. If some child is diagnosed with TB involving any system, whole of the family should be screened for the contact, if index case is not known. No family screening was possible for this study.

CONCLUSION

Hydrocephalus, stroke, seizures & cranial nerve palsies are the most common complication in children with TBM. Majority of children were either not vaccinated or partially vaccinated. Neurological complications were more commonly observed in children having no or partial vaccination for BCG.

RECOMMENDATIONS

TBM in children is very serious condition in children with lifelong impact on the development and neurological outcome. Multicenter studies with long term follow up should be done for better understanding of TBM impact in our population. Community and parents should be encouraged for the vaccination of children starting with BCG vaccination at birth.

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AUTHORS' CONTRIBUTIONS

Following authors have made substantial contributions to the manuscript as under:

BA: Analysis and interpretation of data, drafting the manuscript, critical review, approval of the final version to be published

SSHS: Conception & study design, acquisition, analysis and interpretation of data, drafting the manuscript, approval of the final version to be published

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST

Authors declared no conflict of interest

GRANT SUPPORT AND FINANCIAL DISCLOSURE

NIL

DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.



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