ORIGINAL ARTICLE

CLINICAL PROFILE OF CHILDREN TREATED FOR TUBERCULOUS MENINGITIS AT ST. PAUL'S AND YEKATIT 12 MEMORIAL HOSPITALS IN ADDIS ABABA: A THREE YEAR RETROSPECTIVE CROSS-SECTIONAL ANALYSIS

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ABSTRACT

Background: *Tuberculous Meningitis (TBM) is the most severe form of tuberculosis in children and incurs high mortality and morbidity. Globally the incidence of tuberculous meningitis is not exactly known especially in developing countries [2]. Roughly about 1% of all TB diseases develop tuberculous meningitis [6].*

Methodology: *This study employed a retrospective cross-sectional analysis of the archives of pediatrics patients admitted to St. Paul Hospital Mellinium Medical College (SPHMMC) and Yekatit 12 Hospital Medical College with the assessment of TBM during the time from July 1, 2014-June 30, 2017GC.*

Results: *In this study 70 patients files with the assessment of TBM was collected from the record room and 63 of these fulfilled the diagnostic criteria to be included in the final analysis. According to consensus case definition 1 (1.6%) case was definite, 22(34.9%) cases were probable and 40(63.5%) cases were possible. Nine of them (14.3%) died within the hospital, 29(46%) survived with sequel and 19(30.2%) survived with no apparent recorded sequel. Forty eight (76.2%) of patients had brain imaging, of which (93.8%) of them had recorded abnormalities. The commonest abnormality was hydrocephalus 24(50%) and basal meningeal enhancement 22(45.8%). Gene Xpert MTB detection rate was about 33.3%.*

Conclusion*: Tuberculous meningitis continued to be a cause of significant sequel and mortality in children. Stage of TBM at presentation, increased intracranial pressure (ICP) and altered mentation on presentation has statically significant association with sequel on discharge while altered mentation on presentation has statically significant association with mortality.*

INTRODUCTION

Globally about one-third of the world's population is infected with mycobacterium tuberculosis (MTB). These individuals carry a lifetime risk of 10% for the development of active TB disease [1]. The risk of TB disease development is very high, especially in young children. The risk of progression to TB disease is about 50% in infants, 20-30% in Children 1-2years, 5% in those 3-5years, 2% in those 5-10years and about 5% in older children in their life time [2]. In children with HIV the risk is even higher (about 10% annually) [2]. Young children are also more likely to develop the most severe forms of TB such as TB meningitis and Miliary TB

[3].

In 2015, there were an estimated 10.4 million new TB cases worldwide, of which 1.0 million (10%) were among children. People living with HIV accounted for 1.2 million (11%) of all new TB cases [3]. There are currently no estimates of the number of children that develop TB meningitis worldwide or that die from the disease, largely due to difficulties with diagnosis [20]. Roughly about 1% of all TB diseases develop tuberculous meningitis [6].

Methodology

The objective of this study is to assess the clinical outcome and presenting characteristics in children admitted with TBM to SPHMMC and Yekatit 12 Memorial Hospital Medical College from July 1, 2014 – June 30, 2017GC. A retrospective cross-sectional study was designed and analyzed the charts of pediatric patients admitted during the above period. Tuberculous meningitis case definition is classified as Definite TBM if AFB seen on cerebrospinal fluid (CSF) microscopy or MTB detected by Gene Xpert or culture from CSF; Probable TBM if total score of ≥ 12 when neuroimaging available or total score of ≥ 10 when neuroimaging unavailable; and Possible TBM if total score of 6-11 when neuroimaging available and total score of 6–9 when neuroimaging unavailable (Table 1). Data entry was done using epi-info-7 and it was exported to SSPS version 20 for analysis.

Criteria	Diagnostic score
Clinical criteria(maximum category score = 6)	
Symptoms duration > 5days	4
Systemic symptoms suggestive of tuberculosis > 2weeks	2
History of recent close contact with confirmed pulmonary TB case	2
Focal neurologic deficit excluding cranial nerve palsy	1
Cranial nerve palsy	1
CSF criteria(maximum category score = 4)	
Clear appearance	1
Cells: 5 - 500/µl	1
Lymphocyte predominance (>50%)	1
Protein concentration(1gm/dl)	1
CSF glucose 40mg/dl(2.2mmol/l)	1
Cerebral imaging criteria(maximum category score = 6)	
Basal meningeal enhancement	2
Hydrocephalus	1
Tuberculoma	2
Infarct	1
Precontrast basal hyperdensity	2
Evidence of tuberculosis elsewhere(maximum category score = 4)	
Chest x-ray suggestive of active tuberculosis(excludes miliary tuberculosis)	2
Chest x-ray suggestive of miliary tuberculosis	4
CT/MRI/Ultrasound evidence for tuberculosis outside the CNS	2
AFB identified or MTB detected/cultured from another source, ie.sputum, blood, lymph node, gastric washing, urine	4

Results

Demographic characteristics

In this study seventy (70) children's charts was collected from record room. All of them were admitted and treated for TBM in SPHMMC and Yekatit 12 Hospital Medical College with the diagnosis of TBM from July 1, 2014 to June 30, 2017GC. Sixty three (63) of them fulfilled the diagnostic criteria used in this study and were included for analysis (Table 2). The median age of the children was 6 years, ranging from 3 months to 14 years. The male: female ratio was 0.85: 1. All patients were from three Regions of the country; majority (57.1%) was from Oromia region 31.8% and 11.1% from Addis Ababa and South Nations Nationality Peoples Region (SNNPR) respectively. Twenty seven (42.9%) of children were severely malnourished. Based on case definition used in this study (40) 63.5% were possible cases, (22) 34.9% were probable cases and only (1) 1.6% was definitive case.

Table 3: Common presenting signs and symptoms of patients admitted with tuberculous meningitis to SPHMMC and Yekatit 12 Hospitals, from July 1, 2014 to June 30, 2017GC, (n = 63)

	Frequency	**Percentage**
Fever	56	88.9
Vomiting	41	65.1
Altered mental Status	37	58.7
Weight loss	34	54
Headache	31	49.2
Cough	29	46
Seizures	27	42.9
Neck stiffness	25	39.7
Cranial nerve palsy	5	7.9

The median length of time from the time symptoms started (according to patients recall) to the time treatment initiated was 21days (ranging from 5days to 331days).

Tuberculous meningitis was staged using the modified criteria of the British Medical Research Council for all cases from documentation about Glasgow coma scale and neurologic deficit on patients file to determine the severity of TBM. Twelve (19%) were stage I; twenty one (33.3%) were stage II and thirty (47.7%) were stage III (Figure 3). Thirty six (57.1%) of children had motor examination abnormality on presentation. The commonest motor abnormalities were quadriparesis 27(42.9%) and hemiparesis 8(12.6%). Thirty one (49.2%) had evidence of elevated ICP. Twenty nine (46%) had cranial nerve palsy.

Clinical documentations

Fifty three (84.1%) of patients file had documentation about their HIV status, of these 8 (12.7%) were HIV positive. Forty one (65.1%) had documentation in there chart that they are fully vaccinated according to Expanded Program on Immunization (EPI). There was no any documentation on the presence or absence of BCG scars. Nineteen (30.2%) of patients had recent close contact with confirmed pulmonary TB case. (Table 4)

Nineteen (30.2%) patients admitted with tuberculous meningitis had documentation in their charts about ophthalmologic evaluation. Fifteen (78.9%) patients had ophthalmologic evaluation abnormalities documented in their charts (exotropia, optic atrophy, papilledema, esotropia and retinal detachment) (Table 5). Five (7.9%) patients had hearing evaluation documentation in their charts and three (60%) of them had sensory neural hearing loss (SNHL)

Recorded Investigations for TBM

Brain imaging

Forty eight (76.2%) of patients had brain imaging, forty five (93.8%) of patients having brain imaging had abnormal findings. The findings were hydrocephalus 26(51%), basal meningeal enhancement 24 (47.1%), Tuberculoma 17(33.3%) and infarction 12(23.5%).

Chest radiography

Forty six (73%) of patients had chest X-ray imaging records in their files; for twenty nine (63%) the imaging had abnormal findings. Hilar lymphadenopathy 9(19.6%) was the commonest abnormality, followed by collapse consolidation 8(17.4 %) and miliary pattern 8(17.4%).

Laboratory investigation

CSF analysis

Gene Xpert from CSF was done and documented for only three (4.8%) patients. Only one patient had MTB detected on CSF Gene Xpert test and had no rifampicin resistance detected.

Out of the twenty six patients who had CSF analysis documentation, Acid fast bacilli (AFB) were not seen on CSF AFB stain. In eleven (42.3%) of cases the cells count was abnormal (> 5cells). Ten (91%) of patients

with documented abnormal cells count had lymphocyte predominance (>50%). The cells count ranged between 6 - 750cells/ mm3 (mean of 70cells). CSF protein was reported in only five cases and ranged between 30 -320mg/dl (mean of 179.2mg/dl). CSF glucose was reported in 14 patients and only 4 of them had glucose record less than 40mg/dl.

Gastric aspirate

Thirteen (20.6%) patients had gastric aspirate AFB stain report in their chart and only 2(15.4%) had AFB positive results. Gene Xpert from gastric aspirate was done for 13 (20.6%) patients, three (23.1%) had MTB detected with no rifampicin resistance detected.

Outcome of tuberculous meningitis

The average hospital stay was about 28 days (range 2 to 101days). Nine (14.3%) of patients died; within 4 days of admission; forty eight (76.2%) of patients were discharged, twenty nine (46%) with some form of sequel (Table 6) while 19 (30.2%) of patients discharged improved with no sequel. Five (7.9%) of patients were left the hospital against medical advice and one patient was referred to another Hospital for pediatric intensive care unit care.

Associated factors with outcomes of TBM

Different factors were tested for statistical association with mortality and with sequel on discharge. Altered mentation on presentation has statically significant association with mortality (Table 7), while stage of TBM, altered mentation on presentation and presence of increased ICP had stastically significant association with sequel on discharge (Table 8).

Table 7: Mortality of tuberculous meningitis in patients admitted with tuberculous meningitis to St. Paul and Yekatit Hospital in relation with various factors, from July 1, 2014 to June 30, 2017GC, (n = 63)

		Number Of children		**P-value**
		Surviving	Dying	
Stage of TBM	Stage I and stage II	31	2	0.054
	stage III	23	7	
Mentation	Altered mentation	28	9	0.005*
	Not altered mentation	26	0	
Elevated ICP	Present	24	7	0.067
	Not present	30	2	
Age	< 5years	27	4	0.521
	≥ 5years	27	5	
Duration of symptoms before treatment initiated	< 20days	24	5	0.396
	≥ 20days	30	4	
	> 3days	31	2	

Table 8: Sequel of tuberculous meningitis in patients admitted to St. Paul and Yekatit 12 Hospital in relation with various factors from July 1, 2014 to June 30, 2017GC at the time of discharge

Characteristics		**Number of children**		**P-value**
		surviving with no sequel	Surviving with sequel	
Stage of TBM	Stage I and stage II	18	12	<0.000*
	stage III	1	17	
Mentation	Altered mentation	19	9	<0.000*
	Not altered mentation	3	20	
Elevated ICP	Present	14	13	0.040*
	Not present	5	16	
Age	< 5years	7	16	
	≥ 5years	12	13	0.429
Duration of symptoms before treatment initiated	< 20days	6	14	
	≥ 20days	13	15	0.242

Discussion

Tuberculous meningitis is still the cause of high mortality and morbidity. In this study 9 (14.3%) patients died, 29(46%) patients survived with sequel on discharge and 19 (30.2%) survived with no sequel. This outcome is comparable with study done in Vietnam (mortality of 15%, sequel of 33%) and slightly higher than study done in South Africa (mortality of 8%, sequel 50%). In this study outcome was assessed on discharge which was too short duration to conclude on the outcome of tuberculous meningitis. In the Vietnam study the duration of follow up was from admission to the time of treatment completion. Outcome would also be different at the end of treatment completion compared to the time of hospital discharge when the neurological outcome is still evolving. In the south African study the duration of follow up was similar to this study(from admission to discharge), but only 28.1% patients were stage III TBM on admission and the rest were stage I and stage II TBM. This may explain the apparent low mortality of less than 10%.

The clinical outcome of this study is much lower than a previous study done in Ethiopia which showed mortality of about 46% and neurological sequel of 64%. This difference is probably due to; the mean duration of symptoms before presentation is longer (3.2months) and all cases were in stage II (29%) and stage III (71%) on presentation in previous study. In addition in this study the mean duration of symptoms before presentation was only 38 days, about 19% of patients were also presented in stage I TBM and the use of Cerebral imaging had role in early diagnosis and management of TBM which decreased the mortality and sequel significantly compared to the previous one.

The median age was 58months (range 3months to 14years). This is comparable with other study like South African (mean of 48months), indicate that TBM more affects young children.

On imaging of the brain about 93.8% have abnormalities. The commonest abnormality was hydrocephalus and basal meningeal enhancement. This finding is also comparable with the finding in other study, in Vietnam 86% brain imaging had abnormalities. In which basal enhancement and hydrocephalus were the commonest abnormalities.

On chest radiography about 63% had abnormality, which includes hilar lymphadenopathy, miliary pattern and collapse consolidations. This is higher than the study done in Vietnam in which 42% of chest x-rays had abnormal findings. Hilar lymphadenopathy and consolidation were the commonest abnormalities. The CSF leukocytosis is detected in only 42.3% and of the abnormal CSF cell count about 91% had lymphocyte predominance.

This finding is much lower than the finding in other studies where leukocytosis is present in 99% of CSF analysis (Silvia S Chiang and et al). The reason may be in that most of cases the CSF cells count where not reported. CSF MTB detection rate by Gene Xpert is about 33.3% whereas AFB stain MTB detection rate is null. In Silvia S Chiang and et al. study the CSF AFB positivity 8.9% which is higher than this study and the CSF culture positivity rate is 35.1% which is comparable with the CSF Gene Xpert MTB detection rate in this study.

Gastric aspirate/ sputum AFB detection rate is 2/13(15.4%) which is higher than the study done in South Africa and no AFB seen at all. Gastric aspirate Gene Xpert MTB detection rate is 3/13(23.4%) which is slightly higher than the gastric aspirate culture MTB detection rate in South Africa (14%). Eight (12.7%) patients were HIV positive. This is comparable with study done in South Africa which showed 9.7% of children with TBM were HIV positive. It is significantly lower than the study done in Ethiopia, which shows HIV infection rate of about 28.6% among pulmonary TB cases [21]. This low in HIV prevalence among children with TBM is probably because in TB high burden region children affected regardless of their HIV status.

Like in other studies, stage III TBM was strongly associated with sequel on discharge [2, 10, and 12]. In this study altered mentation on presentation is strongly associated with mortality and altered mentation and elevated ICP was associated with sequel on discharge.

Conclusion

Tuberculous meningitis continued to be a cause of significant sequel and mortality in children in Ethiopia. Stage of TBM, increased ICP and altered mentation on presentation has statically significant association with sequel on discharge while altered mentation on presentation has statically significant association with mortality. In this study the use of Molecular test like Gene Xpert from CSF is Very low. Majority of patients who had ophthalmologic and hearing evaluation had abnormal findings.

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Ethical consideration

Ethical clearance was obtained from the respective IRBs of the two hospitals before starting data collection.

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