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NEURO TUBERCULOSIS IN CHILDREN: CLINICOPATHOLOGICAL AND RADIOLOGICAL PROFILE AND FACTORS ASSOCIATED WITH MORTALITY: AN EXPERIENCE FROM TERTIARY CARE TEACHING HOSPITAL

Dr Sanjeevani Satish Masavkar[1], Dr Sadhana Zope[2], Dr Laxmi Kadu[3] & Dr. Sanila Daniel[4]

[1]Associate Professor Department of pediatrics ,Division of pediatric intensive care ,Lokmanya Tilak Municiple Medical College and General Hospital, Sion ,Mumbai-400022(Maharashtra) India

[2]Assistant Professor Department of pediatrics ,Division of pediatric intensive care ,Lokmanya Tilak Municiple Medical College and General Hospital, Sion ,Mumbai-400022(Maharashtra) India

[3]Fellow pediatric critical care Department of pediatrics ,Division of pediatric intensive care ,Lokmanya Tilak Municiple Medical College and General Hospital, Sion ,Mumbai-400022(Maharashtra) India

[4]Fellow pediatric critical care Department of pediatrics ,Division of pediatric intensive care ,Lokmanya Tilak Municiple Medical College and General Hospital, Sion ,Mumbai-400022(Maharashtra) India

Abstract

Background: *Tuberculous Meningitis in children is the most common form of neurotuberculosis contributing to neurological disabilities and death in developing countries like India*

Aims and objectives*: To study clinical and diagnostic profile (patho radiological) and to determine the factors associated with mortality in children with neurotuberculosis.*

Settings: Tertiary care teaching hospital

Design: *Retrospective descriptive analysis .*

Material and methods: *A retrospective analysis of children between age group of 1month to 12 years with neurotuberculosis admitted in a tertiary care teaching hospital from Mumbai over a period of 3 years from Jan 2013 to December 2015. Fourty one children with neurotuberculosis diagnosed based on predefined criteria were included for analysis. The demographic and clinical parameters such as presenting symptoms and signs, Glasgow coma scale (GCS), intracranial pressure, staging of TBM as per British Medical Council staging system were entered from records .Mantoux test ,BCG immunisation, nutritional status, cerebrospinal fluid(CSF) analysis ,neuroimaging and other investigations to confirm tuberculosis were noted along with treatment and outcome as survival or death. Statistical analysis was done using SPSS(version).Various risk factors were determined using Chi square tests.*

Results: Fourty one children were included, of which 12(29.3%) died. Fever and vomiting were the most common symtoms and meningeal irritation was the most common sign.Children presented with stage III disease were15(36.6%).Low scores of GCS was predictor of mortality.

Conclusion : *we conclude that TBM presents with nonspecific clinical features.Stage III TBM ,raised intracranial pressure, hydrocephalus were not predictors of mortality due advances in management but leads to morbidity. Low GCS was the important predictor of mortality.*

key words: *childhood ,neurotuberculosis, predictor ,mortality*

Introduction

India has one of the highest tuberculosis (TB) burdens globally, accounting for 20% of the new 8.6 million TB cases annually. [1,2] Childhood TB accounts for 8-20 % of TB related deaths. [3]

The incidence of tuberculosis is increasing worldwide,Neurotuberculosis mainly tuberculous meningitis is the most devastating manifestation of tuberculosis is often missed or overlooked because of its nonspecific symptoms and difficulties in diagnosis. High index of suspicion is needed to diagnose it at first stage with vital clinical information along with supportive patho radio neurological investigations.[5] It is an important cause of morbidity and mortality in spite of treatment in late stages. Several retrospective and prospective studies have been conducted to predict outcome of TBM in childhood.[6,7,8,9] However most of the studies were in the era where imaging modalities like computerised tomography, spectroscopy and magnetic resonance studies were not available.[11] Treatment protocols were not uniform and incidence of HIV and multidrug resistance tuberculosis was low. There have been few studies done from western India.[10]. In the new era of drug resistance tuberculosis we wanted to study the patient characteristics, clinicopathological and neuroradiological profile, treatment details ,immediate outcome and to determine factors predicting mortality. We considered demographic and clinical variables for study such as age sex, nutrition status, contact with tuberculosis, BCG immunisation at birth, presenting symptoms,stage of the disease, GCS. cerebrospinal fluid picture,and neuroimaging findings hydrocephalus, raised intracranial tension, need for shunt or extraventricular drainage,presence or absense of extracranial tuberculosis, treatment details , complications ,requirement of ventilation ,duration of stay and outcome in the form of survival and death.

Material and methods:

Study design:Retrospective descriptional study

Place of study :Pediatric wards and pediatric intensive care unit,Lokmanya tilak Municiple medical college and General Hospital,Sion, Mumbai-400022.

Inclusion Criteria

All children diagnosed with neurotuberculosis admitted to pediatric ward and intensive care of tertiary care teaching hospital between age group of 2months to 12 years during January 2013 to December 2015 were included in this retrospective study.

Diagnosis of neurotuberculosis and TBM was based on clinical case definition devised by Doerr et al . [12]

Exclusion criteria

TBM cases with underlying chronic illness or malignancy were excluded

Methodology

All pediatric cases of neurotuberculosis who fulfilled the inclusion criteria admitted in the pediatric wards and intensive care in the defined period were included in the study.

Institutional ethics approval for accessing medical records and publishing this data was obtained.

Diagnosis of neurotuberculosis and TBM was based on clinical case definition devised by Doerr et al[12] Table 1

	Clinical definition of tuberculous meningitis devised by Doerr et al
	Abnormal neurological signs and symptoms and two or more of the following
1	Discovery of adult source patient with contagious tuberculosis who had significant contact with child
2	Presence of Mantoux(5 Tuberculin units)skin test reaction . 10 mm of induration,or>-5 mm of induration if child had close contact with infected adult
3	Cerebrospinal fluid abnormalities without evidence of other infectious cause
4	Abnormalities of crenial computed tomography consistent with central nervous system tuberculosis.

We recorded all clinical details with reference to neurotuberculosis and its outcome.This included demographic details,nutritionalstatus,detailed history regarding contact with tuberculosis, tuberculosis in the past, BCG received at birth , clinical symptoms such as fever, vomiting, headach ,seizures ,altered sensorium, weakness ,involuntary movements with duration , detailed physical and neurologic examination at the time of diagnosis, cerebrospinal fluid (CSF) examination and cranial CT scan reports.[10,11]

.Central nervous system examination with special reference to GCS ,stage of TBM,signs of raised intracranial tension,meningeal irritability,dystonia was noted.Staging of TBM was done according to British Medical Counsil staging system[13]

Table 2 British Medical Counsil staging system for TBM

Stage I	No definite neurological symptoms on admission or in the history before admission,with or without meningismus
Stage II	Signs of meningeal irritation withor without slight clouding of consciousness with focal neurological signs such as cranial nerve palsies or hemiparesis.
Stage III	Severe clouding of consciousness or delirium,convulsions, focal neurological deficit and or involuntary movements.

Treatment details like category of antituberculosis therapy, convensional or DOTS were noted. CSF examination with refence to proteins ,total cells and percentage of lymphocytes and sugar was noted and neuroimging details such as meningeal enhancement, infarcts ,hydroceplalus ,tuberculoma, abscess and hemorrhage were noted, The evidence of raised intracerebral pressure and need for ventriculoperitoneal shunt or extraventricular drainage were noted.Duration of stay , complications such as ventilation, sepsis, shunt block,shunt infection, ATT induced hepatitis were noted.Outcome was recorded as survival or death at the time of discharge,

Data analysis

The data was analysed using the statistical softwarePSPP version 0.8.5 .Qualitative data was represented in the form of frequency and percentage.Asoociation between qualitative variables was assessed by Chi -Square test, with continuity correction and by Fischer'sExact test where Chi -Square test was not valid.Quantitative data was represented using Mean +/- SDd and Median and IQR(interquartile range).Comparision of quantitative data between died and survived cases was done using Unpaired t- test and or by using Mann-Whiteny test as per appropriateness.

Results:

Fourty one children were included in the study. The demographic characrteristics of children with neurotuberculosis are presented in Table 3. Majority of children were <5 years 24(70.7%).The mean age was 4.8years+/- SD 3.4years.Boys were 23 (56.1%) and girls were 18(43.9%).

Major types of neuro tuberculosis were TBM(28,58.5%),TBM with infarcts (6,14.6%), followed by TB encephalitis (2),TBM with tuberculoma(1) ,tuberculoma with tuberculous abscess(1),Tuberculoma with infarcts(1)TBM with sudural hemorrhage (1) tuberculous meningoenceplalitis with tuberculoma (1).Almost 2/3 of children(28/41) were malnourished.Twelve children (29.3%) had positive history of contact with adult tuberculosis.

Clinical characteristics are presented in Table 4. Altered sensorium 33(80.5%) was the most common symptom followed by fever in (28, 68.3%) vomiting in (28, 68.3%) seizure in (25,61.1%) , headach in (13, 31.7%) focal deficits in (10,24.4%) and involuntary movements in (2, 4.9%).On central nervous system examintion meningeal irritation(18,43.9%) was most common sign. On assesing GSC 19 children had score of less than 7 and rest had above 7. Intracranial pressure was raised in (27,65.9%) of children and required anti odema measures in the form of 3% sodium chloride, mannitol.At admission ,(7,17.1%) children had Stage I disease,(19,46.3%) children had Stage II disease and (15,36.6%)had Stage III disease .

Mantoux was positive in (6,14.5%)children.Cerebrospinal fluid examination was abnormal in most of the children.Cellular response was mainly lymphocyte predominant.the mean range of CSF cell count ,protein and glucose were 76(1-250) cells/cumm, 139.59(-1000) mg/dl,and 40.32(10-88) mg/dl respectively. cranial CT scan showed Meningeal enhancement in (16,39%),Hydrocephalus in (23,56.1%), Infarcts in (15,36.6%),Tuberculoma in (7,17.1%) and abscess in (1,2.4%) children. Meningeal enhancement was most commonly seen in basal cistern.Hydroceplalous was mild to severe grade with periventricular ooze.Infarctions were most common in basal ganglion followed by cortex,Tuberculoma were mainly observed in parieto temporal region.Twenty one children required ventriculoperitoneal shunt surgery and in two patients external drainage of CSF was done at bedsite in view of poor GCS.

Of 41 children (21,51.2%) had complications like requirement of ventilation, shunt block, shunt revision, sepsis, Anti Tubeculosis Treatment (ATT) induced hepatitis. Children received category I ATT were (36,87.8%) and category II were ATT (6,19.5%).

The mortality rate was 29.3%.(12/41 died). Of the children survived 7 were Stage I,14 were stage II,and 8 were Stage III.70.7% survived with minimal to severe disability according to stage of disease. Patient died were none with Stage I , 5 with stage II, and 7 with stage III disease. The mean length of stay for children who survived to discharge was 16.48(3-51,+/-14.16) days:for those who died was 9.58(1-21+/-6.87) days.Various risk factors associated with increased mortality were analysed.These were age <5 years, gender ,contact with adult tuberculosis., nutritonal state (SAM), BCG immunisatin, MT positivity, stage of TBM, raised intracranial pressure, presence of hydrocephalous, infarction, low GCS and associated complications. Severe acute malnutrition, low GCS score and complications were associated with increased mortality.(Table 6) whereas biochemical and cytological parameters did not affect the outcome. A low GCS score less than 7 was important predictor of mortality.

Discussion:

We highlighted clinic pathological and radiological features of neurotuberculosis in children and analysed risk factors associated with mortality. We also assessed risk of mortality with associated complications and severe acute malnutrition in childen. Children with neurotuberculosis had non specific clinical picture which can be seen in other CNS infections.Boys were commonly affected but there was no significant gender bias. Mantoux positivity was in 29.3%.The major form of neurotuberculosis found was tuberculous meningitis.Hydrocephalous was mainly communicating accounted for most common neuroimaging finding in cranial CT. In nutritional status, severe acute malnutrition(SAM), low GCS less than 7 and associated complications such as ventilation requirement, shunt block, shunt infection, shunt revision, sepsis,ATT induced hepatitis were associated with increased mortality.The male dominance in this study was consistent with studies from India (6,7, pre) and studies outside India (philipines).Most affected age group was less than 5 years which (70.74%) as compared to 12(29.26%).[18,19,20]It shows the vulnerability of this age group to aquire tuberculosis easily.[18,19]Only 29.3 % children gave history of positive contact with tuberculosis from adult.This is reported much higher in other studies.[11,19,20].This point is needed to consider while elicing the detailed history and family screening for tuberculosis of the affected of child.In spite of recommendation and effectiveness of doing family screening and giving preventive therapy to close contact, it is not stringently followed.[21].Though BCG is included in universal immunisation programme and is given at birth , the coverage was 34(84.9%) children in this study.BCG vaccination gives protection agaist severe form of tuberculosis.Studies from India and western countries have documented the effect of BCG vaccine in reducing mortality from TBM.[22-24.]Our study had only 14.6 % Mantoux positivity which was similar in other studies done by Israni ,et.alon tuberculous meningitis in children.This may be because of extrapulmonary disease. The rates

of positivity varies in different studies.[11,15,19].We had majority of children detected as TBM at stage II(46.3%) and III(36.6%).

. This may be because ours being referral centre we received cases in late stages.Though in advanced stage we had (8,53%)children who survived and(7,47%) children died.These survival may be because of intensive antiodema and supportive care. Thus it reduced mortality but these patients had severe disability at discharge. It was found to be important marker of mortality in various studies.[10,21] We did not get any significant association with mortality.Mortality in stage I was nil which showed that picking up patients in early stage and appropriate treatment is associated with good outcome.

Basal exudate entrapping cranial nerves has been recognized as the clinical marker in differentiating TBM from pyogenic meningitis [25].In our study only 4 patient had cranial nerve involvement .About 12/19 patient with poor GCS died and was the only predictor of mortality we got in our study.This has been shown in other Indian studies besides raised ICP and advanced stage of TBM [10,15].We had 27 children with raised ICP, out of which 17 survived and 10 died. This may be because of intensive antiodema measures ,supportive care and ventriculoperitoneal shunt.This has reduced mortality but has led to survival with disability. On correlating CT brain findings we got hydrocephalus as most common finding but it was not statistically significant causing mortality.

Comparing cerebrospinal fluid values in children who survived and died we did not get any significant finding.We got low sugars and predominantly lymphocytes in total CSF cell count. Overall mortality was 12/41(29.3%.) which was high little high than Karande etal and Israni et al studies.On literature review it was found to be 19.3% [26]. In one of the retrospective study it was reported as 85 in children with TBM.

The strength of our study was we also looked up for complications and severe acute malnutrition children and mortality association.We analysed low GCS as predictor of mortality.We checked number of children discharged who were enrolled in DOTS which were 25(61%). But we did not get follow up of these patient. The limitations of the study were being tertiary care hospital reffering bias is difficult to ruled out. The number of patients enrolled were less.TB culture and nucleic acid amplification tests wee not conductd on all CSF specimen.The treatment outcome at the end of therapy and follow up of patient to look for neurological sequally was not done.The incidence of indicates annual risk of infection.Hence through surveillance system to document occurance of TBM in young children can hep in estimating and monitoring TB burden and related mortality in children.[27].A long term follow up of these patient and their treatment outcome either on conventional daily therapy or under DOTS scourse need to be done.The long term neurological sequelae in children in terms of scholastic performace and behavioural abnormalities needs close and regular follow up.

Conclusion:Amongst Neurotuberculosis TBM continues to be associated with high mortality and morbidity in TB endemic areas like India.In spite of advancement in scientific knowledge and technologies in the form of laboratory testing and neuroimaging it is difficult to predict outcome and prognosis.Our study got association of severe acute malnutrition, complications and poor GCS with TBM mortality.GCS is the only predictor of mortality.

Hence there is need for early diagnosis and prompt treatment to reduce mortality and morbidity.

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References

1. World Health Organization (WHO). Global Tuberculosis Report 2013. Geneva: WHO; 2013. Available from: http://www.apps.who.int/iris/bitstream/10665/91355/1/9789241564656_eng.pdf.

2. Marais BJ, Hesseling AC, Gie RP, Schaaf HS, Beyers N. The burden of childhood tuberculosis and the accuracy of community-based surveillance data. Int J Tuberc Lung Dis 2006;10:259-63.

3. Jain SK, Ordonez A, Kinikar A, Gupte N, Thakar M, Mave V, et al. Pediatric tuberculosis in young children in India: A prospective study. Biomed Res Int 2013;2013:783698.

4. Wolzak NK, Cooke ML, Orth H, van Toorn R. The changing profile of pediatric meningitis at a referral centre in Cape Town, South Africa. J Trop Pediatr 2012;58:491-5.

5. van Toorn R, Solomons R. Update on the diagnosis and management of tuberculous meningitis in children. Semin Pediatr Neurol 2014;21:12-8.

6. Delage G, Dusseault M. Tuberculous meningitis in children: a retrospective study of 79 patients, with an analysis of prognostic factors. Can Med Assoc J 1979;120:305-9.

7. Humphries MJ, Teoh R, Lau J, Gabriel M. Factors of prognostic significance in Chinese children with tuberculous meningitis. Tubercle 1990;71:161-8.

8 Paganini H, Gonzalez F, Santander C, Casimir L, Berberian G, Rosanova MT.

Tuberculous meningitis in children: clinical features and outcome in 40 cases. Scand J Infect Dis 2000;32:41-5.

9 Lee LV. Neurotuberculosis among Filipino children: an 11 years experience at the Philippine Children's Medical Center. Brain Dev 2000;22:469-74.

10. Anil V. Israni, Divya A. Dave, 1 Tubercular meningitis in children: Clinical, pathological and radiological profile and factors associated with mortalityJ Neurosci Rural Pract. 2016 Jul-Sep; 7(3): 400–404

11. Thilothammal N, Krishnamurthy PV, Banu K, Ratnam SR. Tuberculous meningitis in children – Clinical profile, mortality and morbidity of bacteriologically confirmed cases. Indian Pediatr 1995;32:641-7.

12. Doerr CA, Starke JR, Ong LT. Clinical and public health aspects of tuberculous meningitis in children. J Pediatr 1995;127:27-33.

13. British Medical Research Council. Streptomycin treatment of tuberculous meningitis. Br Med J 1948;1:582-97.

14. Ramzan A, Nayil K, Asimi R, Wani A, Makhdoomi R, Jain A. Childhood tubercular meningitis: An institutional experience and analysis of predictors of outcome. Pediatr Neurol 2013;48:30-5.

15. Karande S, Gupta V, Kulkarni M, Joshi A. Prognostic clinical variables in childhood tuberculous meningitis: An experience from Mumbai, India. Neurol India 2005;53:191-5.

16. Kumar N, Shekhar C, Kumar P, Kundu AS. Kuppuswamy's socioeconomic status scale-updating for 2007. Indian J Pediatr 2007;74:1131-2.

17. Khadilkar VV, Khadilkar AV, Choudhury P, Agarwal KN, Ugra D, Shah NK. IAP growth monitoring guidelines for children from birth to

18 years. Indian Pediatr 2007;44:187-97.

18. Humphries MJ, Teoh R, Lau J, Gabriel M. Factors of prognostic significance in Chinese children with tuberculous meningitis. Tubercle 1990;71:161-8.

19 . van Well GT, Paes BF, Terwee CB, Springer P, Roord JJ, Donald PR, et al. Twenty years of pediatric tuberculous meningitis: A retrospective cohort study in the western cape of South Africa. Pediatrics 2009;123:e1-8.

20 . Lee LV. Neurotuberculosis among Filipino children: An 11 years experience at the Philippine Children's Medical Center. Brain Dev 2000;22:469-74.

21 . Hill PC, Rutherford ME, Audas R, van Crevel R, Graham SM. Closing the policy-practice gap in the management of child contacts of tuberculosis

cases in developing countries. PLoS Med 2011;8:e1001105.

22. Kelekçi S, Karabel M, Karabel D, Hamidi C, Hosoglu S, Gürkan MF, et al. Bacillus Calmette-Guerin is a preventive factor in mortality of childhood tuberculous meningitis. Int J Infect Dis 2014;21:1-4.

23. Kumar R, Dwivedi A, Kumar P, Kohli N. Tuberculous meningitis in BCG vaccinated and unvaccinated children. J Neurol Neurosurg Psychiatry 2005;76:1550-4.

24. Chiang SS, Khan FA, Milstein MB, Tolman AW, Benedetti A, Starke JR, et al. Treatment outcomes of childhood tuberculous meningitis: A systematic review and meta-analysis. Lancet Infect Dis 2014;14:947-57.

25. Moghtaderi A, Alavi-Naini R, Rashki S. Cranial nerve palsy as a factor to differentiate tuberculous meningitis from acute bacterial meningitis. Acta

Med Iran 2013;51:113-8

26. Graham SM, Donald PR. Death and disability: The outcomes of tuberculous meningitis. Lancet Infect Dis 2014;14:902-4.

27. Styblo K, Sutherland I. The epidemiology of tuberculosis in children. Bull Int Union Tuberc 1982;57:133-9

Table 3 Baseline characteristics of children with Neurotuberculosis

Sr NO	Characteristics	n=41	Percentage
1	Gender		
	Male	23	56.1
	Female	18	43.9
2	Age distribution in months		
	i)<2years	16	39.02
	ii)2yrs to 5yrs	13	31.70
	iii)>5 years	12	29.26
3	Nutritional status		
	Mam	15	36.6
	Sam	6	14.6
	Thin	6	14.6
	Severe thin	1	2.4
4	Positive history of contact with adult Tb	12	29.3
5	BCG Vaccination	34	82.9

Table 4 Clinical characteristics of children with Neurotuberculosis

Sr NO	Characteristics	n=41	Percentage
1. Symptoms			
	i) altered sensorium	33	80.5
	ii) Fever	28	68.3
	iii)vomiting	28	68.3
	iv)seizure	25	61.1
	v)headache	13	31.7
	vi) focal deficits(weakness)	10	24.4
	vii)involuntary movements	2	4.9
2. Signs	meningeal irritation	18	43.9
	hemiparesis	06	14.6
	cranial nerve palsy	04	9.8
	quadriparesis	10	24.4
	abnormal movements	03	7.3
3.ICP	Raised ICP	27	65.9
4. Stage of TBM	I	7	17.1
	II	19	46.3
	III	15	36.6

5. Shunt	Required shunts	21	51.2

Table 5 Laboratory parameters and neuro-radiological features:

Parameters	Variables	n=41	%
1. Mantoux test	Positive	6	14.6
2.CSF protein	<40mg/dl	5	12.20
	40-400mg/dl	34	82.93
	.400mg/dl	2	4.88
3.CSF glucose(mg/dl)	CSF glucose(mg/dl)		
	<20	4	9.76
	20-60	35	85.36
	>60	2	4.88
4. CSF total cells/mm3	CSF total cells/mm3		
	< 20	7	17.08
	20-80	20	48.78
	>80	14	34.15
5.Abnormalities on neuroimaging of CT brain	Meningeal	16	39
	enhancement	23	56.1
	Hydrocephalus	15	36.6
	Infarcts	7	17.1
	Tuberculoma	1	2.4
	Abscess		

Table 6: Factors Associated With Mortality In children with Neurotuberculosis

Risk factors	Categories	Survived	Expired	OR	P
Age	<5 years	22	7	0.445	0.258
gender	males	14	4	1.867.	0.595
TBcontact	present	10	2	0.38	0.45
Nutritional status	SAM	1	5	12.08	0.0053
BCG	unvaccinated	5	2	1.042	1
MT	negative	24	11	0.436	0.651
Stage of TBM	III	8	7	0.272	0.083
Raised ICP	Present	17	10	3.529	0.165
Hydrocephalus	Present	15	8	1.867	0.595
Infarct	Present	10	5	1.357	0.730
GCS	<7	7	12	-	0.018
Complications	Present	10	11	2.65	0.0027