TO DETERMINE THE ACCURACY OF HIGHLY SUSPECTED CLINICAL FEATURES FOR THE DIAGNOSIS OF TUBERCULOUS MENINGITIS

Jehanzeb Khan Afridi, Ahmad Saud Dar, Rahida Karim, Muhammad Younas, Muhammad Aqeel Khan

ABSTRACT

Introduction: Annually, 2 million people die as a result of this disease. Tuberculous meningitis (TBM) is the most severe complication of tuberculosis and frequently occurs in childhood. According to WHO an estimated 13.7 million population has active TB with 9.3 million new cases and 1.8 million deaths. Pakistan ranks sixth among the 22 countries and has 44% TB burden in Eastern Mediterranean Region of WHO. There are 4% registered cases of TB in children in Pakistan, 2.5% are at risk of getting infection. Only 5-10% of infected children will progress to primary progressive disease while 80-90% will get latent TB. It accounts for 8-20%of all deaths in children. Meningitis is an important cause of mortality and morbidity in children. It carries a risk of fatal outcome or severe neurological deficit, especially when the diagnosis and treatment are delayed

Objective: To determine the accuracy of highly suspected clinical features for the diagnosis of tuberculous meningitis confirmed by cerebrospinal fluid culture.

Methods: This was a cross sectional descriptive study of one year on 116 patients. All those children presenting with highly suspected clinical features of duration > 4 weeks, Glasgow coma scale < 7, cranial nerve palsy and hemiplegia suspected for having tuberculous meningitis who present through Out-patient department (OPD) or Emergency department were admitted in Pediatric "A" Unit, of Postgraduate Medical Institute, Hayatabad Medical Complex, Peshawar. Patients who fulfill the inclusion criteria were included in the study. Under strict aseptic conditions, lumber puncture were done to collect CSF and were sent to the laboratory for the confirmation of Tuberculous Meningitis to check the accuracy of clinical features.

Results: In this study, 116 patients with average clinical symptoms duration 30 days+ 8.66SD had observed, in which Male to female ratio was 1.9:1. Average age was 37.83 months + 25.58SD. Accuracy of Clinical parameter to detect tuberculosis meningitis in the study was 76(65.52%) while 40(34.48%) were found non-accurate results.

Conclusion: Tuberculous meningitis starts with nonspecific symptoms and is often only diagnosed when brain damage has already occurred. Earlier diagnosis will improve outcome significantly and clinical parameters show a huge role in diagnosis.

Keywords: Tuberculous Meningitis, Glasscoma scale, Cranial Nerve Palsy, Hemiplegia.

INTRODUCTION

Tuberculosis (TB) is no longer the scourge it once was, but it remains an important cause of morbidity and mortality worldwide. Recent estimates are that 8-10 million new tuberculosis (TB) cases occur each year in the world.[1] Although the incidence of tuberculosis is increasing, prevalence and mortality rates are declining. Annually, 2 million people die as a result of this disease. Tuberculous meningitis (TBM) is the most severe complication of tuberculosis and frequently occurs in childhood.[2,3]

Department of Peads, Hayatabad Medical Complex, Peshawar - Pakistan.

Address for correspondence:
Dr. Jehanzeb Khan Afridi
Senior Registrar, Peads B Unit, HMC, Peshawar, Pakistan.
Contact: 03213030107

According to WHO an estimated 13.7 million population has active TB with 9.3 million new cases and 1.8 million deaths. Pakistan ranks sixth among the 22 countries and has 44% TB burden in Eastern Mediterranean Region of WHO. There are 4% registered cases of TB in children in Pakistan, 2.5% are at risk of getting infection. Only 5-10% of infected children will progress to primary progressive disease while 80-90% will get latent TB. It accounts for 8-20% of all deaths in children.[4]

Meningitis is an important cause of mortality and morbidity in children. It carries a risk of fatal outcome or severe neurological deficit, especially when the diagnosis and treatment are delayed.[5] TBM is a chronic serious illness with varied presentation and relatively high mortality and morbidity.[6] Young children, in particular, are most susceptible to tuberculous meningitis (TBM).[7, 8]

One large study examining hospitalized cases for 32 years revealed that 54% of cases were considered confirmed meningitis, and the remainders were consid-

ered probable[9]. Tuberculous (TB) meningitis is difficult to diagnose and has a high mortality rate, particularly when presentation is delayed.

Diagnosis is most accurately achieved by direct Ziehl–Neelsen staining or by culture of cerebrospinal fluid (CSF). The former has a low sensitivity, and the latter is too slow to be useful in making therapeutic decisions. Delays in diagnosis greatly increase mortality[10]. A study in Johannesburg described an increase in mortality rate from 56% to 90.5% when treatment was delayed for longer than 24 h[11].

In a study, the confirm cases of tuberculosis meningitis among patients with pre defined features was 74% and in this study 21% of patients have GCS < 10,[12] while in another study 24% of TBM had hemiplegia and 29% have cranial nerve (CN) palsies.[13]. In another study, 77.7% of patients who were confirmed of having TBM on culture had suspected clinical features on history and examination.[11]

The rationale of the study will be to determine the accuracy of highly suspected clinical features for TBM in our population and to compare it with local and international studies.

OBJECTIVE

To determine the accuracy of highly suspected clinical features for the diagnosis of tuberculous meningitis confirmed by cerebrospinal fluid culture.

OPERATIONAL DEFINITIONS

HIGHLY SUSPECTED CLINICAL FEATURES OF TBM:

It was considered if patient presents with any two of the following features with a minimum duration of 4 weeks.

GCS < 7: it was determined by using Glasgow coma scale (GCS) score.(Annexure 1)

CN Palsy: paralysis of any of the twelve cranial nerves is referred to as cranial nerve palsies and was diagnosed on neurological examination.

Hemiplegia: it was considered as complete weakness affecting one side of the body, and was diagnosed on clinical examination.

TUBERCULOSIS MENINGITIS ON CSF CULTURE:

It was diagnosed on Cerebrospinal fluid culture in the laboratory showing growth of Mycobacterium Tuberculosis on Lowensteen Jensen Media Incubated at 35°-37°C.

Accuracy: was measured in terms of number of patients who come to be positive for TBM on CSF Culture among patients with highly suspected clinical features.

MATERIAL AND METHODS

This was a descriptive cross-sectional study. Conducted in Pediatric "A" Unit, PGMI/HMC Peshawar. The duration of study was one year (From 11th Nov 2012 to10th Nov 2013).

Total 116 patients were selected for the study. Sample size was calculated by using 95% confidence, 74% accuracy of suspected clinical feature for the diagnosis of TBM, 08% margin of error under WHO formula for sample size determination in health studies. The sampling technique was Consécutive (non-probability) Sampling.

All children presenting with highly suspected clinical features of TBM, of age 1-12 years, of Either gender were included in study.

Children already diagnosed cases of tuberculous meningitis, patients having cerebral malaria diagnosed by history and malarial parasite positivity, patients who have received anti tuberculous treatment in the past two months were excluded from study.

The above mentioned conditions in exclusion criteria were act as confounders and introduce bias in the study results.

DATA COLLECTION PROCEDURE

Data were collected of all those children presenting with highly suspected clinical features of duration > 4 weeks, Glasgow coma scale < 7, cranial nerve palsy and hemiplegia suspected for having tuberculous meningitis who present through Out-patient department (OPD) or Emergency department were admitted in Pediatric "A" Unit, of Postgraduate Medical Institute, Hayatabad Medical Complex, Peshawar. Patients who fulfill the inclusion criteria were included in the study.

All patients were subjected to detailed history followed by clinical examination and routine baseline investigations. Under strict aseptic conditions, lumber puncture was done to collect CSF and was sent to the laboratory for the confirmation of Tuberculous Meningitis to accuracy of clinical features.

DATA ANALYSIS PROCEDURE

Data were entered into SPSS version 12 for windows. Frequencies and percentages were calculated for categorical variables like gender and accuracy. Mean ± standard deviation were calculated for continuous variables like age and duration of symptoms. Accuracy was stratified among age, gender, duration of symptoms and baseline suspected clinical features at presentation to see the effect modifications.

RESULTS

In this study, 116 patients with children presenting with highly suspected clinical features of duration > 4

weeks, Glasgow coma scale < 7, cranial nerve palsy and hemiplegia suspected for having tuberculosis meningitis with average clinical symptoms duration 30 days+ 8.66SD had observed, in which 76(65.52%) were male and 40(34.48%) were female patients. Male to female ratio was 1.9:1.

Patients age was divided in four categories, out of which most presented in younger age i.e. less than or equal to 30 months which were 77(66.4%) while 15(12.9%) patients were in the age range of 31-55 months, 10(8.6%) were of age range 56-80 months and 14(12.1%) presented at age more than 81 months. The study included age ranged from 15 up to 103 months. Average age was 37.83 months + 25.58SD. (Table 1).

Accuracy of Clinical parameter to detect tuberculosis meningitis in the study was 76(65.52%) while 40(34.48%) were found non-accurate results.

Age wise distribution of accuracy shows that almost same accuracy was found in all age group. Accuracy was 10(66.7%) in 31-55 months of age while 5(33.3%) was not accurate, 50(64.9%) patients were correctly diagnose as tuberculosis meningitis in age groups of less than 30 months while 27(35.1%) were not accurate, 7(70%) accuracy was observed in the age range of 56-80 months while 3(30%) were not accurate and 9(64.3%) cases have accurate diagnosis in age range of more than 80 months of age while 5(35.7%) were not accurate. (Table 2)

The majority of males i.e. 55(72.4%) presented with clinical features were accurately diagnosed while 21(27.6%) were not accurate and 21(52.5%) accuracy was noted in female patients while 19(47.5%) were not accurate. This shows that gender shows role over the accuracy of clinical parameter in diagnoses of tuberculosis meningitis. (Table 3)

Table 1: Age Wise Distribution of the Patients

	FRE-QUENCY	PERCENT	CUMU-LATIVE PERCENT
<= 30.00	77	66.4	66.4
31.00 - 55.00	15	12.9	79.3
56.00 - 80.00	10	8.6	87.9
81.00+	14	12.1	100.0
TOTAL	116	100.0	

Table 2: Age Wise Distribution of Accuracy

		Accuracy		Total
		Yes	No	
Age (in Years)	<= 30.00	50	27	77
		64.9%	35.1%	100.0%
	31.00 - 55.00	10	5	15
		66.7%	33.3%	100.0%
	56.00 - 80.00	7	3	10
		70.0%	30.0%	100.0%
	80.00+	9	5	14
		64.3%	35.7%	100.0%
		76	40	116
Total		65.5%	34.5%	100.0%

Table 3: Accuracy Wise Distribution of Gender

		Accuracy		Total
		Yes	No	
Sex	Male	55	21	76
		72.4%	27.6%	100.0%
	Female	21	19	40
		52.5%	47.5%	100.0%
		76	40	116
Total		65.5%	34.5%	100%

DISCUSSION

This study confirms that TBM mainly affects young children, because 82% of our patients were under 5 years of age. The mean age of 37 months is comparable to other studies; with mean ages ranging from 23 to 49 months.[14-15] Young ages at presentation and the nonspecific nature of presenting symptoms partly explain the difficulty of early diagnosis. Presentation is often subacute, and the early symptoms of stage I TBM, such as low-grade fever, cough, vomiting, and general apathy, are often wrongly interpreted.

This delay in diagnosis and start of tuberculosis treatment are supported by the finding that 57% of our cohorts were unwell for 7 days before admission. We demonstrated previously that missed opportunities for early diagnosis rather than late presentation or inaccessibility to medical care is the most common cause for delayed diagnosis of childhood TBM.

This study evaluating the prognostic significance of clinical and neurophysiological changes in predicting the outcome of TB meningitis. The best set of predictors outcome of TB meningitis comprised focal weakness, GCS score, and somatosensory evoked potential (SEP). The GCS is one of the most established predictors of outcome of TB meningitis. The importance of altered sensorium in the outcome of TB meningitis has been highlighted in earlier studies.[16] TB meningitis is associated with a variable degree of encephalitis, which is primarily responsible for altered sensorium. The

other factors contributing to altered sensorium in TB meningitis may include hydrocephalus, infarction, or tuberculoma in a strategic location.

In an earlier study, the presence of infarction was found to be an important predictor of TB meningitis.[17] Infarction, however, has not figured as an important predictor in the present study; focal weakness was present in 27 and infarction in 25 patients. In an earlier study, presence of focal weakness was an important predictor of 3 month outcome and infarction was an important predictor of 6 and 12 month outcome of TB meningitis.[17]

The SEPs on the other hand have the advantage of not requiring any patient cooperation. Most of our patients were in stage II or III and in these patients SEPs may be helpful in documenting the sensory deficit. Based on the regression coefficient (0.56) and odds ratio (1.75) SEPs significantly contribute to the prediction of outcome of TB meningitis. In the earlier studies employing multivariable analysis, only clinical and radiological indices have been evaluated.[17] The predictors of outcome in these studies included stage, age, focal weakness, and cranial nerve palsies and stage, age, infarction, and GCS.[17]

Some studies have assessed the clinical and laboratory indices that might predict outcome. The early trials used univariate analysis assessing prognostic variables without adjusting for the effect of covariables.[18] From these studies, some poor prognostic indicators arose extremes of age, advanced stage of disease, concomitant extrameningeal TB, and evidence of raised intracranial pressure. Studies employing multivariate analyses that adjust for the influence of other variables are scarce.

One such study in children found that the age of the patient and stage of disease were two independent variables associated with prognosis. A more recent study looked at clinical, laboratory, and CT features in[19]adults and children with TBM. A multivariate logistic regression model showed that the most significant variables for predicting outcome in TBM were age, stage of disease, focal weakness, cranial nerve palsy, and hydrocephalus.

Serological techniques that detect the intrathecal synthesis of antimycobacterial antibodies have been studied. A good test will require an antigen with high species specificity and good immunogenicity to be sensitive. The use of crude antigens such as PPD results in low sensitivity and specificity.[20] Basic enzyme linked immunosorbent assays (ELISAs) have lacked sensitivity.[20] The adaptation of ELISA techniques and the identification of specific M tuberculosis antigens have improved results. Using a solid phase antibody competition assay with mouse monoclonal antibodies to the 38 kDA antigen (also known as antigen 5, or antigen 78), a large study was performed in pulmonary and extrapulmonary TB. In extrapulmonary TB diagnostic sensitivity was 73%, specificity 98%, regardless of organ site.

Sensitivity improves when ELISA is used to detect anti-BCG secreting cells in the CSF of those with TBM72), but the test is technically demanding. A sensitivity of 96% and specificity of 92% is reported with this method. A cell-ELISA method allowing quantitative detection of CSF anti-PPD IgG produced similar diagnostic sensitivity and specificity.[21]

CONCLUSION

TBM affects mainly children under 5 years of age. Presentation is often subacute, and early symptoms are nonspecific. Recent poor weight gain, low grade fever, vomiting, and recent contact with a tuberculosis patient are important clues for an early diagnosis of TBM. Outcome is directly associated with the stage of TBM. Delayed treatment because of missed diagnosis will result in progression to stage II and III disease with high morbidity and mortality rates. In multivariate analyses, we could identify several presenting variables independently associated with poor clinical outcome of TBM. Tuberculous meningitis starts with nonspecific symptoms and is often only diagnosed when brain damage has already occurred. Earlier diagnosis will improve outcome significantly.

REFERENCES

1. Khurshid R, Shore N, Saleem M, Naz M, Zameer N. Diagnostic significance of adenosine deaminase in pleural tuberculosis. Pak J Physiol. 2007;3:1-3.
2. 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. Pediat. 2009;123:1-8.
3. Van den Bos F, Terken M, Ypma L, Kimpen JLL, Nel ED, Schaaf HS, et al. Tuberculous meningitis and miliary tuberculosis in young children. Trop Med Intern Health. 2004;9:309–13.
4. Masood N, Sharif M, Asghar R. Spectrum of tuberculosis in BCG vaccinated and unvaccinated children. J Rawalpindi Med Coll. 2010;14(2):60-3.
5. Khan DA, Rahman A, Khan FA, Najmal-ul-Hassan. Comparison of serum procalcitonin and c-reactive protein in diagnosis of bacterial meningitis. Pak Armed Forces Med J. 2009;59:159-64.
6. Fazel PA, Makki KU, Haroon H, Soomro IB, Afzal U. Clinical spectrum and outcome of patients with tuberculous meningitis. Med Channel. 2006;12:21-3.
7. Van Rensburg PJ, Savvas Andronikou S, van Toorn R, Pienaar M. Magnetic resonance imaging of miliary tuberculosis of the central nervous system in children with tuberculous meningitis. Pediatr Radiol. 2008;38:1306-13.
8. Yaramış A, Bükte Y, Katar S, Özbek MN. Chest com-

puterized tomography scans findings in 74 children with tuberculous meningitis in southeastern Turkey. Turkish J Pediatr. 2007;49:365-9.

9. Theodoridou MN, Vasilopoulou VA, Atsali EE, Pangalis AM, Mostrou GJ, Syriopoulou VP, et al. Meningitis registry of hospitalized cases in children: epidemiological patterns of acute bacterial meningitis throughout a 32-year period. BMC Infect Dis. 2007;7:1-12.

10. Karstaedt AS, Valtchanova S, Barriere R, Crewe-Brown HH. Tuberculous meningitis in South African urban adults. Quarterly Journal of Medicine 2005;91:743–7.

11. Checkley AM, Njalale Y, Scarborough M, Zjilstra EE. Sensitivity and specificity of an index for the diagnosis of TB meningitis in patients in an urban teaching hospital in Malawi. Tropical Medicine & International Health 2008;13(8):1042–6.

12. Gijs TJ, Berbe F, Caroline B, Priscilla, Roord JJ, Donald PR, et al. Twenty Years of Pediatric Tuberculous Meningitis: A Retrospective Cohort Study in the Western Cape of South Africa. Peds. 2008;1353.

13. Hien, Farrar J, Dung H, Quy HT, Bang ND, Chau TT, et al. Pretreatment Intracerebral and Peripheral Blood Immune Responses in Vietnamese Adults with Tuberculous Meningitis:Diagnostic Value and Relationship to Disease Severity and Outcome. J Immunol. 2006;176;2007-14.

14. Farinha NJ, Razali KA, Holzel H, Morgan G, Novelli VM. Tuberculosis of the central nervous system in children: a 20-year survey. J Infect. 2000;41(1):61–8

15. Doerr CA, Starke JR, Ong LT. Clinical and public health aspects of tuberculous meningitis in children. J Pediatr. 1995;127(1):27–33

16. Freiman I, Geefhuysen J. Evaluation of intrathecal therapy with streptomycin and hydrocortisone in tuberculous meningitis. J Pediatr. 1970;76:895–901.

17. Kalita J, Misra UK. Outcome of tuberculous meningitis at 6 and 12 months: a multivariate regression analysis. Int J Tubercl Int Lung Dis. 1999;3:261–5.

18. PD Gulati, GP Mathur, H Vaishnavah. Prognosis and sequelae of tuberculous meningitis in adults. J Assoc PhysiciansIndia. 1970;18:281–6.

19. Karstaedt AS, Valtchanova S, Barriere R. Tuberculous meningitis in South African urban adults. Q J Med. 1988;91:743–7.

20. Misra UK, Kalita J, Srivastava M. Prognosis of tuberculous meningitis: a multivariate analysis. J Neurol Sci. 1996;137:57–61.

21. Baig SM. Anti-purified protein derivative cell-enzymelinked immunosorbent assay, a sensitive method for the early diagnosis of tuberculous meningitis. J Clin Microbiol. 1995;33:3040–1.