Original Article

Tubercular Meningitis: Clinical Profile And Validation Of Thwaites Diagnostic Criteria

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Abstract

Back ground

Tubercular meningitis (TBM) has protean manifestations and there is no gold standard test. Thwaites criteria help in differentiating pyogenic meningitis from tubercular meningitis. The main objective was to study the clinical profile and validate Thwaites diagnostic criteria.

Methods

The case records of all patients admitted for TBM irrespective of all age and gender for the past three years were obtained from the medical record department using International Classification of Diseases code A170 G01. From each medical case file, the patient's demographics, clinical features, medication and medical history, physical findings, radiographs and reports of biochemical laboratory investigations and other investigation were extracted. Thwaite's diagnostic criteria were used to calculate the diagnostic index score. Data were analyzed using SPSS 20.0 version

Results

A total of 95 patients were diagnosed with TBM and 61(64.2%) were males. The mean age was 35.3 ±17.3 years. Thwaite's diagnostic criteria were used to calculate the diagnostic index score for TBM, in which out of 95 patients 91(95.8%) scored <4 indicating TBM and 4 (4.2%) scored >4 indicating bacterial meningitis respectively. Among the study population 63 (66.3%) were diagnosed at earlier stage and in 32 (33.7%) the diagnosis was delayed. Forty (42.1%) patients were in BMRC stage I (early –lasts up to 2 weeks), 27 (28.4%) were in stage II (intermediate –lasts from days to weeks) and 28 (29.5%) were in stage III (advanced**).** Head ache is the most common symptom (68.4%). Characteristic features at presentation include fever 17(17.9%), meningismus

53(55.8%), cranial nerve palsy 7(7.4%) and Monteux positivity in 3 (3.2 %). Neuroimaging showed hydrocephalus in 24(25.3%) patients. In this analysis the true positivity rate for Thwaites is found to be 0.96 and for Ahujas 0.62."KAPPA" measure of agreement showed Kappa statistic =0.07, p=0.298. We observe Poor agreement between Thwaites and Ahuja criteria.

Conclusion: Our results show poor correlation between Ahuja's and Thwaites Criteria in diagnosing Tubercular meningitis and more number of cases could be diagnosed when Thwaites diagnostic criteria are applied. TBM can present with many protean clinical manifestations and a high index of suspicion is warranted to diagnose TBM. Thwaites criteria have high specificity and are useful in Indian setting.

Key words: Tubercular meningitis, clinical profile, Thwaites diagnostic criteria

Introduction

Tubercular meningitis (TBM) is the most dreaded complication of Mycobacterium tuberculosis infection of the central nervous system. Its prevalence in India is documented in very few studies in adults. The mortality rate of TBM in India is 1.5 per 100,000 populations[1] .The data regarding clinical, radiological and laboratory parameters and the final outcome of TBM patients in India is scanty.[2]

TBM has protean clinical manifestations and its onset is very innocuous and more often is diagnosed when the disease has already progressed to an advanced stage. The diagnosis of TBM is based on the isolation of Mycobacterium tuberculosis. The bacilli are isolated by different staining and culture techniques, which require incubation for several weeks. There is no quick diagnostic test for TBM. Clinical presentation, cerebrospinal fluid analysis, microbiological and neuroimaging findings are vital to make diagnosis and to initiate appropriate treatment.[3.]

In order to reduce the mortality and morbidity TBM should be diagnosed and treated early. Ahuja et al criteria categorize TBM into "definite", "highly probable", "probable", and "possible TBM".[4]The validity of the criteria is tested based on the bacterial isolation and polymerase chain reaction (PCR) for tuberculosis. In the highly probable cases PCR was positive in 75%. About 90% of the patients with highly probable and 65% of the patients with probable TBM improved with anti-tuberculosis treatment. There are therapeutic dilemmas regarding duration of anti-tubercular treatment and steroid administration. TBM has high mortality and survivors are often left with chronic deficits if treatment is delayed[5.] TBM in India is often diagnosed using Ahuja criteria and the diagnosis remains empirical until a good clinical response to anti-tubercular therapy is seen.

Thwaite's described a scoring system to improve diagnostic accuracy of TBM using five parameters- Age, the duration of illness, total white blood cell count, the CSF cell count and the percentage of CSF neutrophils [6] and totaling a maximum score of 13. If the total score is 4 or less then it is classified as tubercular meningitis and if the score is more than 4 it is suggestive of bacterial meningitis.[7] Thwaites criteria are useful in making an early diagnosis of TBM. In TBM early diagnosis and appropriate intervention will achieve favorable outcome.[8] Thwaites Criteria have not been validated in Indian subcontinent.

Methodology:

A retrospective observational study was conducted for a period of 6 months at a tertiary care teaching hospital in Udupi District, Karnataka, India from 11 July 2017 to 10 Jan 2018. The study was approved by the institutional ethical committee. The patients admitted with clinical features and laboratory findings suggestive of TBM with positive lumbar puncture were included in the study. Patients with viral meningitis and Brucella meningitis were excluded from the study. Clinical symptoms and signs of fever, headache, duration of illness, meningismus, an altered level of consciousness, and neurological deficits were extracted. Cerebrospinal fluid cell count per millimeter, protein, glucose, and Adenosine deaminase levels were included. Thwaites diagnostic scoring using parameters such as age, history of illness, white blood cell count (WBC), total CSF white cell count and the percent of neutrophils in CSF were applied to all the 95 patients. The diagnostic index for each of the five variables is shown in table 1.

Table 1: Thwaites diagnostic index scores:

Variable	Cutoff	Score
1.Age (years)		
	>36	2
	<36	0
2.Blood WCC (10^3/ml)		
	>15000	4
	<15000	0
3.History of illness (days)		
	>6	-5
	<6	0
4.CSF total WCC (10^3/ml)		
	>900	3
	<900	0
5.CSF % neutrophil		
	>75	4
	<75	0

Thwaites diagnostic scoring system is used to calculate diagnostic index (DI) for each patient according to the formula: DI (age) + DI (blood WBC) + DI (history of illness) + DI (CSF white cell count) + DI (CSF % neutrophils). The data were analyzed using SPSS 20.0 version. The categorical variables were analyzed by means and standard deviations. Contingency table analysis was used to calculate the sensitivity and specificity rates. The agreement between the two criteria was assessed by Kappa statistic.

Results:

A total of 95 patient records of chronic meningitis were analyzed out of which 91 patients were diagnosed as TBM and four as partially treated bacterial meningitis cases. Among TBM cases 61 (64.2%) were males. The mean age of

the study population was 35.3 ±17.3 (Mean ± SD) years. TBM was more frequent in the age group 21-30 years (23.2%). About 71 (74.7%) patients didn't have any prior history of tuberculosis, and 12 (12.6%) patients had evidence of extra-neural (pulmonary) tuberculosis. [Table 2].

Table 2: Demographics profile of 95 patients diagnosed with TBM:

1.	Gender:	
	Male	61(64.2%)
	Female	34(35.8%)
2.	Age (Mean ± SD)	35.3 ±17.3
3.	Age groups:	
	0-10	6(6.3%)
	11-20	13(13.7%)
	21-30	22(23.2%)
	31-40	18(18.9%)
	41-50	16(16.8%)
	51-60	11(11.6%)
	61-70	7(7.4%)
	70-80	2(2.1%)
4.	Prior history of tuberculosis:	
	No history of tuberculosis	71(74.7%)
	Pulmonary tuberculosis	12(12.6%)

	Disseminated tuberculosis	4(4.2%)
	Potts Spine	1(1.1%)
	Tuberculous Cervical Lymphadenitis	2(2.1%)
	Tuerculous Myelitis	1(1.1%)
	Tuberculous Empyema	1(1.1%)
	MillaryTuberculosis	2(2.1%)
	Tuberculous Choroiditis	1(1.1%)
	Types of co morbidities present in the study population:	
5.	No co morbidity	
	Retro Viral Disease	57(60%)
	SLE	14(14.7%)
	Stroke	2(2.1%)
	Type II diabetic mellitus	5(5.3%)
	Hypertension	9(9.5%)
	Pneumonia	3(3.2%)
	Sepsis	4(4.2%)
		1(1.1%)

Thwaite's diagnostic criteria were used to calculate the diagnostic index score for TBM, in which out of 95 patients 91(95.8%) scored <4 indicating TBM and 4 (4.2%) scored >4 indicating bacterial meningitis respectively. Among the study population 63 (66.3%) were diagnosed at earlier stage and in 32 (33.7%) the diagnosis was delayed.

Fifty six cases were diagnosed as TBM by both Thwaites and Ahujha's criteria. In one case Thwaites was negative where as Ahujas criteria were supportive of TBM diagnosis. In three cases both Thwaites and Ahujas criteria supported a negative diagnosis of TBM. In this analysis the true positivity rate for Thwaites is found to be 0.96 and for Ahujas 0.62. Apart from reporting True positive rate, we looked into agreement of the two criteria. For this we used "KAPPA" measure of agreement. Kappa statistic =0.07, p=0.298. We observed Poor agreement between Thwaites and Ahuja criteria. Sample size calculation for comparison of the two true positive rates considering Thwaites as reference is 81.

Staging was done by the British Medical Research Council (BMRC) clinical criterion and 40 (42.1%) patients were in stage I (early –lasts up to 2 weeks), 27 (28.4%) were in stage II (intermediate –lasts from days to weeks) and 28 (29.5%) were in stage III (advanced).

Among the patients with TBM 57(60%) didn't have any co morbidities. Retro viral disease was the most commonly reported co morbidity 14 (14.7%) [Table 2]. Approximately half of the study population had complications and the most common one was hydrocephalus and 11 (11.6%) developed tuberculomas [Table 3].

Table 3: Types of Complication Present in the Study Population:

Types of Complication	(n,%)
No Complication	51(53.7%)
Hyponatraemia	9(9.5%)
Hydrocephalus	11(11.6%)
Stroke	4(4.5%)
Epileptic Seizure	1(1.1%)
Tuberculoma	11(11.6%)
Ethambutol induced optic neurtis	1(1.1%)
Rifampin induced fever	1(1.1%)
ATT induced hepatitis	6(6.3%)

The commonly observed symptoms in tubercular meningitis were headache 65 (68.4%), nausea and vomiting 44(46.3%), apathy and behavioral changes 50 (52.6%), seizures 27(28.4%), and prior history of tuberculosis15 (15.8%).

The signs of tubercular meningitis at presentation were fever 17(17.9%), meningisum 53(55.8%), cranial nerve palsy 7(7.4%) and Monteux positivity in 3 (3.2 %).

Neuroimaging was done in all the patients which showed hydrocephalus 24(25.3%), Basal meningeal enhancement 20(21.1%), tuberculomas 14 (14.7%), infarcts 8(8.4%), pre- contrast basal hyper density 4(4.2%) and normal MRI 25(26.5%) [Table 4].

Table 4: Neuroimaging features

Cerebrallar imaging criteria	n (%)
Hydrocephalus	24(25.3%)
Basal meningeal enhancement	20(21.1%)

Tuberculoma	14(14.7%)
Infarct	8(8.4%)
Pre-contrast basal hyper density	4(4.2%)
Normal MRI	25(26.3%)

Acid – fast bacilli test was positive in 16 (16.8%) subjects. PCR was found to be positive in 19 (20%). Cerebrospinal fluid (CSF) analysis was done in all patients and the average values were: White blood cells 140 ± 270 (cell/mm^3), Glucose 47 ± 30 (mg/dl), Protein133±142 (mg/dl), Adenosine deaminase 7.9±8.9. [Table 5]

Table 5: Analysis of cerebrospinal fluid in patients with tuberculous meningitis

CSF Analysis	Median	IQR
White blood cells (cell/mm^3)	140	270
Glucose (mg/dl)	47	30
Protien (mg/dl)	133	142
Adenosine deaminase (U/L)	7.9	8.9

Discussion:

It was observed that Thwaites diagnostic criteria were found to be robust enough to diagnose TBM in this retrospective study. There was inordinate delay in the diagnosis in approximately 30% patients and they presented in moderate to severe MRC stage. It's a disease of young and affects the economic frame of the entire family. It's extremely difficult to diagnose in the initial two weeks of illness unless one is aware of its prevalence and has knowledge of its protean clinical manifestations. Other causes of chronic meningitis come into differential diagnosis and a reliable diagnostic criterion is a valuable tool. Early treatment with antitubercular therapy and steroids help in cure and prevent complications [9]. Neuroimaging will help in prognosticating the outcome and plan effective interventions.[10]

Effective strategies are to be introduced to address the various complications that arise during the prolonged course of illness. Frequent monitoring is essential to watch out for hydrocephalus and tuberculoma 11 (11.6%), hyponatraemia 9(9.5%), ATT induced hepatitis 6 (6.3%), stroke 4 (4.2%), seizure and optic neuritis 1 (1.1%). Complications of TBM cause mortality and long term morbidity.[11]

Fourteen HIV patient and nine diabetic patients had TBM indicating immunosuppression could be an important predisposing factor. Typical signs of meningeal irritation may be absent in early stages in up to 50% of all cases and a CSF examination will help at times it may have to be repeated[12, 13, 14]

Neuroimaging findings of meningeal enhancement, hydrocephalus, basal exudates, infarcts, and tuberculomas are the most predominantly observed findings that will help in obtaining definitive diagnosis in chronic meningitis.[15]

Using Thwites diagnostic criteria as reference standard for comparison of the two positive rates at 5% alpha and 90% power approximately 81 cases are to be studied prospectively. Well designed and conducted prospective studies should yield reliable and validated diagnostic criteria for use in clinical practice.

Conclusion

In south costal Karnataka region TBM can present with many protean clinical manifestations without meningeal enhancement and a high index of suspicion is warranted in all suspected cases of chronic meningitis. The studies done on TBM are scanty in Indian population. This study should be done in larger population in order to validate the Thwaites diagnostic criteria which will help in the early detection of TBM, and to improve the outcome of the patients with early treatment.

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