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Original Research Article

A study on differentiation of tubercular meningitis from acute bacterial meningitis using simple clinical and laboratory parameters along with CBNAAT

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Abstract

Introduction: Meningitis is a serious infection of the meninges, the membranes covering the brain and spinal cord. It is a devastating disease and remains a major public health challenge. Acute bacterial meningitis (ABM) remains a serious global health threat with high mortality and morbidity, despite advances in antibiotic therapy and modern vaccination strategies. Tuberculosis (TB) remains the major cause of ill health, one of the top 10 causes of death worldwide and the leading cause of death from a single infectious agent.
Methods and Methodology: A hospital-based simple prospective observational study was carried out among 56 cases, between the age groups 2 months to 14 years, who fit into clinical diagnosis of bacterial meningitis.
Results: A total of 56 cases of meningitis were included &analyzed for the study. Mean CSF cell count was significantly higher in ABM group as compared to TBM (374.67±252.55 vs 175±78.64). Lymphocyte predominance is seen in all the TBM cases and Neutrophils predominance is seen in majority of ABM cases (p<0.05). CSF ADA >8 is seen significantly in all the TBM cases compared to ABM cases (p<0.05). CSF CBNAAT was positive significantly in TBM cases compared to ABM (p<0.05). Mean CSF protein count was significantly higher in TBM group as compared to ABM (219.4±55.64 vs 108.44±33.04).
Conclusion: CBNAAT should be used in preference to conventional methods as the initial diagnostic test for patients suspected of having TB. CBNAAT positivity shows significant association with positive Mantoux test and CSF analysis suggestive of TBM.

Keywords: Tubercular meningitis, bacterial meningitis, CBNAAT

Introduction

Meningitis is a serious infection of the meninges, the membranes covering the brain and spinal cord. It is a devastating disease and remains a major public health challenge. The disease can be caused by many different pathogens including bacteria, fungi, or viruses, but the highest global burden is seen with bacterial meningitis [1].
Several different bacteria can cause meningitis. Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis are the most frequent ones. N. meningitidis, causing meningococcal meningitis, is the one with the potential to produce large epidemics. There are 12 serogroups of N. meningitidis that have been identified, 6 of which (A, B, C, W, X and Y)

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can cause epidemics [1].

Meningococcal meningitis can affect anyone of any age, but mainly affects babies, preschool children, and young people. The disease can occur in a range of situations from sporadic cases, small clusters to large epidemics throughout the world, with seasonal variations. Geographic distribution and epidemic potential differ according to serogroup. The largest burden of meningococcal meningitis occurs in the meningitis belt, an area of sub-Saharan Africa, which stretches from Senegal in the west to Ethiopia in the east [1].

N. meningitidis can cause a variety of diseases. Invasive meningococcal disease (IMD) refers to the range of invasive diseases caused by N. meningitidis, including septicemia, arthritis, and meningitis. Similarly, S. pneumoniae causes other invasive diseases including otitis and pneumonia [1].

Acute bacterial meningitis (ABM) remains a serious global health threat with high mortality and morbidity, despite advances in antibiotic therapy and modern

vaccination strategies. Children are particularly vulnerable to ABM because of their relatively immature immune systems, particularly their impaired immunity to the polysaccharide capsule of bacteria commonly associated with ABM. It has been estimated that over 75% of all cases of ABM occur in children under 5 years of age, and it is one of the most common life-threatening infections in children worldwide [2].

Tuberculosis (TB) remains the major cause of ill health, one of the top 10 causes of death worldwide and the leading cause of death from a single infectious agent. According to the Global TB Report released by WHO in October 2020, there were an estimated 10 million new TB cases worldwide, children accounted for 12% and India accounts for one-fourth (26%) of the global TB burden. Extra-pulmonary TB represented 16% of the cases that were notified in 2019 [3]. According to the India TB report released by MHFW, GOI in March 2020, 24 lakh cases of TB were notified in year 2019, an increase of over 12% compared to previous year [4]. Clinicians face substantial challenges in the diagnosis and management of tubercular meningitis. Prevention of neurological disability and Good prognosis of tubercular meningitis (TBM) depends on early detection and treatment [5, 6].

Prompt and accurate diagnosis of TBM is a daunting challenge especially in pediatrics because of difficulty in obtaining a precise history, collecting an adequate volume of CSF for laboratory investigations, and the paucibacillary nature of tubercular bacilli.**7** CSF smear microscopy is inexpensive and rapid but insensitive (10%-20%). Culture on Lowenstein-Jensen (L-J) medium takes a long time for the result and Bactec MGIT 960 are not suitable for routine use due to high cost. Although diagnosis based on culture is the reference standard, results are obtained after 2-8 wk which is too slow to aid in clinical decision making. Nucleic acid-based amplification (NAA) tests have emerged as potentially important tools for diagnosing TBM. The Xpert MTB/RIF is a closed cartridge-based system that is easy to operate and gives results in approximately 2 h. Xpert MTB/RIF test was approved by WHO in 2010, for diagnosis of pulmonary TB. In 2013 WHO has recommended the use of Xpert MTB/RIF for the use in children and extra-pulmonary form. In 2015 WHO strongly recommended the use of Xpert MTB/RIF in preference to conventional microscopy and culture as the initial diagnostic test [8].

Studies to identify useful biomarkers for TBM in CSF and blood are ongoing. Tests such as the adenosine deaminase assay (ADA) have been evaluated and may be used as an aid in diagnosis; however, they are not specific enough to differentiate TB meningitis from other forms of bacterial meningitis.

Several studies have reported successful use of the Xpert MTB/RIF test on extra pulmonary samples, with overall sensitivities of over 80% and specificity reaching 100%.

Hence the present study was undertaken to differentiate of tubercular meningitis from acute bacterial meningitis using simple clinical and laboratory parameters along with CBNAAT.

ISSN 2515-8260 Volume 09, Issue 06, 2022

Methodology

Study population: All patients who were suspected clinically and supported by laboratory investigations of bacterial meningitis in PICU.
Study period: One year.
Study design: Descriptive observational study.

Inclusion criteria

- The patients of both sexes aged 1 month to 14 years with the clinical diagnosis of Meningitis admitted in PICU.

Exclusion criteria

- Subjects who do not consent to the study.
- Subjects more than 14 years of age and less than 1 month of age.
- Cases not satisfying the diagnostic criteria of tubercular and acute bacterial meningitis are excluded from the study.

Methods of data collection

Pre-test counselling will be given to parents/guardians. After taking written informed consent from parents, the case will be enrolled, data will be collected in a predesigned semi-structured questionnaire.
A complete physical examination was carried out at admission and each patient underwent lumbar puncture Cerebrospinal fluid (CSF) was tested for glucose and total protein concentration, as well as total and differential leukocyte counts. Microbiologic tests included Gram stain, Ziehl-Neelsen stain, bacterial cultures (blood and chocolate agar and Lowenstein-Jensen media), and CBNAAT.

Diagnostic criteria for tubercular meningitis clinical signs and symptoms

- Fever lasting more than 14 days.
- **Optional:** Headache, vomiting, altered sensorium, seizures, and focal deficits.

Results

Table 1: Distribution according to age group

		ABM (n-36)		TBM (n-20)	
		Frequency	**Percent**	**Frequency**	**Percent**
Age group in years	< 5	17	47.2	14	70.0
	6 to 10	16	44.4	4	20.0
	11 to 15	3	8.3	2	10.0
	Total	36	100.0	20	100.0

We included total 56 patients of meningitis in our study. Out of that, 36 patients were diagnosed of having acute bacterial meningitis i.e. ABM and 20 were diagnosed of having tubercular meningitis i.e. TBM. Out of 36 cases of ABM, majority were from under-five age i.e. 17(47.2%), from 6-10 years age group i.e. 16(44.4%) and >10 years age group i.e. 3(8.3%). Out of 20 cases of TBM, majority were from under five age i.e. 14(70%), from 6-10 years age group i.e. 4(20%) and >10 years age group i.e. 2(10%).

ISSN 2515-8260 Volume 09, Issue 06, 2022

Table 2: Distribution according to CSF CBNAAT reports

		ABM (n-36)		TBM (n-20)		P
		Frequency	Percent	Frequency	Percent	
CSF CBNAAT	Negative	36	100.0	18	90.0	0.0001 Highly Significant
	Positive	0	0.0	2	10.0	
	Total	36	100.0	20	100.0	

CSF CBNAAT was positive in 2 TBM cases i.e., 10% (p<0.05).

Table 3: Comparison of blood parameters between ABM and TBM

Diagnosis		N	Mean	Std. Deviation	t	p	Inference
GRBS	ABM	36	123.67	33.70	2.096	0.041 (<0.05)	Significant
	TBM	20	106.60	18.16			
HB	ABM	36	9.74	1.90	1.721	0.091 (>0.05)	Not significant
	TBM	20	8.94	1.17			
TLC	ABM	36	19028.61	8811.42	2.024	0.048 (<0.05)	Significant
	TBM	20	14715.00	4795.86			
Platelet	ABM	36	1.07	0.98	-5.489	0.00001 (<0.01)	Highly significant
	TBM	20	2.71	1.22			
DLC-N	ABM	36	76.00	8.23	18.115	0.00001 (<0.01)	Highly significant
	TBM	20	31.60	9.74			
DLC-L	ABM	36	19.86	8.25	-18.793	0.000 (<0.01)	Highly significant
	TBM	20	63.00	8.19			

Mean GRBS was significantly higher in ABM group as compared to TBM (123.67±33.7 vs 106.6±18.16). Mean TLC was significantly higher in ABM group as compared to TBM (19028.61±8811.42 vs 14715±4795.86). Mean platelet was significantly less in ABM group as compared to TBM (1.07±0.98 vs 2.71±1.22). Mean neutrophil count was significantly higher in ABM group as compared to TBM (76±8.23 vs 31.6±9.74). Mean lymphocyte count was significantly higher in TBM group as compared to ABM (19.86±8.25 vs 63±8.19).

Table 4: Comparison of ESR and CRP between ABM and TBM

Diagnosis		N	Mean	Std. Deviation	t	p	Inference
ESR	ABM	36	24.61	5.87	-8.026	0.001 (<0.01)	Highly significant
	TBM	20	39.50	7.89			
CRP	ABM	26	128.38	46.40	5.202	0.001 (<0.01)	Highly significant
	TBM	20	62.51	36.94			

Mean ESR count was significantly higher in TBM group as compared to ABM (39.5±7.89 vs 24.61±5.87).
Mean CRP was significantly higher in ABM group as compared to TBM (128.38±46.4 vs 62.51±36.94).

Table 5: Comparison of CSF parameters between ABM and TBM

Diagnosis		N	Mean	Std. Deviation	t	p	Inference
CSF Protein	ABM	36	108.44	33.04	-9.385	0.001 (<0.01)	Highly significant
	TBM	20	219.40	55.64			
CSF Sugar	ABM	36	43.16	11.01	-2.937	0.005	Highly significant

ISSN 2515-8260 Volume 09, Issue 06, 2022

	TBM	20	52.00	10.41		(<0.01)	

PRE LP RBS	ABM	36	111.97	21.74	0.563	0.575	Not significant
	TBM	20	109.00	12.09		(<0.05)	
CSF Cell	ABM	36	374.67	252.55	3.432	0.001	Highly significant
	TBM	20	175.00	78.64		(<0.01)	
CSF LDH	ABM	36	71.31	16.94	3.687	0.001	Highly significant
	TBM	20	52.55	20.45		(<0.01)	
CSF ADA	ABM	36	2.57	1.32	-3.632	0.001	Highly significant
	TBM	20	13.48	18.06		(<0.01)	

Mean CSF protein count was significantly higher in TBM group as compared to ABM (219.4±55.64 vs 108.44±33.04). Mean CSF sugar level was significantly higher in TBM group as compared to ABM (52±10.41 vs 43.16±11.01). Mean CSF cell count was significantly higher in ABM group as compared to TBM (374.67±252.55 vs 175±78.64). Mean CSF LDH was significantly higher in ABM group as compared to TBM (71.31±16.94 vs 52.55±20.45). Mean CSF ADA level was significantly higher in TBM group as compared to ABM (13.48±18.06 vs 2.57±1.32).

Discussion

In our study, CSF CBNAAT was positive in 2 TBM cases i.e. 10%.
YADAV RK *et al*. [9] reported that CBNAAT was positive in 17.8% cases which is higher as compared with our findings.
Das PK *et al*. [10] reported, 3% to 5% quarter-to-quarter period CBNAAT positivity in the paediatric age group and prevalence of MTB detection was reported to be 3.88% which is less as compared with our findings.
Das PK *et al*. [11] reported 11.1% CBNAAT positivity in children which is comparable to our findings.
Kasat S. *et al*. [12] found 15% positivity of CBNAAT in adult extra pulmonary TB cases, which is higher as compared with our findings.
In our study, blood culture found significantly positive in ABM as compared to TBM i.e. 33.3%.
In our study, CSF cells > 500 were seen in 0% of TBM cases as compared to 25% of ABM (p<0.05). Plasma RBS-CSF RBS> 40% were seen in 95% of TBM cases as compared to 41.7% of ABM (p<0.05). Neutrophil predominance is seen in 97.2% cases of ABM i.e., 35 cases and Lymphocyte predominance is seen in all cases of TBM i.e., 20 cases (100%) (p<0.05).
In the study conducted by Modi M. *et al*. [13] out of 203 patients 179 (88%) patients had lymphocytic predominant (>90%) pleocytosis,101 (44%) patients had glucose <30mg/dl.
In a study by Moghtaderi *et al*. [14] mean CSF protein was 80 mg/dl, mean CSF glucose was 34 mg/dl and lymphocyte predominance (80%) mean value being 18 cells/microliter.
In our study, CSF ADA>8 was seen in all the TBM cases i.e., 20(100%) and 1(2.8%) of ABM cases (p<0.05).
Lavanya SR *et al*. [15] reported that majority of the patients had CSF ADA level in range of 11-15U/Litre. Mean ADA level in this study was 11.22 U/Litre and S.D. was 4.8.
In our study, mean CSF protein count was significantly higher in TBM group as compared to ABM (219.4±55.64 vs 108.44±33.04). Mean CSF sugar level was significantly higher in TBM group as compared to ABM (52±10.41 vs 43.16±11.01). Mean CSF cell count was significantly higher in ABM group as compared to TBM (374.67±252.55 vs 175±78.64). Mean CSF LDH was significantly higher in ABM group as compared to TBM (71.31±16.94 vs 52.55±20.45). Mean CSF ADA level was significantly higher in TBM group as compared

to ABM (13.48±18.06 vs 2.57±1.32).

Lavanya SR *et al*. [15] reported that in Cerebrospinal Fluid (CSF) analysis mean CSF protein was 136.5 mg/dl, mean CSF glucose was 56.4 mg/dl and CSF cell count was 66.7 cells/microliter. Mean Adenosine Deaminase (ADA) was 11.22 U/L.CSF CBNAAT was positive in 9 patients out of which 8 were sensitive to rifampicin and one resistant to it.

Conclusion

In order to reach a quick diagnosis using CSF specimens, CBNAAT should be preferentially used as rapid diagnosis and treatment is a strong prognostic indicator for reduced death and neurologic deficit. Even though CSF cytology gives good estimate of suspected TBM patient the test is not confirmative for bacilli demonstration. Hence CBNAAT has to be endorsed in every centre as the test gives rapid result and also detects rifampicin resistance which is the major concern for every clinician.

CBNAAT testing of CSF samples should be done in all suspected TBM patients so that this rapid test would play a major role in diagnosis and treatment of one of the most common medical emergencies in India.

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ISSN 2515-8260 Volume 09, Issue 06, 2022

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