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Original Research Article

Comparison of clinical and CSF profiles in 62 Adults with tuberculous and pyogenic meningitis

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ABSTRACT

Background: Many a times differentiating tuberculous meningitis from pyogenic meningitis becomes very difficult. The diagnosis depends upon clinical manifestation and cytochemical analysis of cerebrospinal fluid (CSF). Many researchers found that the CSF glucose: protein ratio less than 0.5 and Adenosine deaminase levels (ADA) in cerebrospinal fluid are useful to differentiate tubercular disease from non-tubercular meningitis.
Methods: Sixty-two patients admitted to our tertiary hospital with symptoms and signs of meningitis were selected and divided into two groups: tubercular (n=39) and pyogenic (n= 23), depending upon the accepted criteria. Clinical features and CSF parameters noted in each patient. Cut off value of ADA kept at or above 10 IU/L for tubercular meningitis.
Results: The mean age of patients with tubercular meningitis was 39.07±16.67 years and that of pyogenic meningitis 34.35±16.73 years. Clinically fever was present in 60 (96.77%), headache in 49 (79.03%), and vomiting in 44 (70.96%) patients. Meningeal signs – neck rigidity in 46 (74.2%), Kernig's sign in 37 (59.68%) and Brudzinski's sign in 18 (29.03%) patients. On CSF cytological and biochemical analysis the mean total white blood cell count was 256.74±184.03 /cmm, mean protein 182.22±113.12 mg/dl and mean sugar 52.85±19.3mg/dl in TBM whereas in pyogenic meningitis 106.17±185.18 / cmm, 88.78±114.35 mg/ dl, and 63.47±19.48 mg/dl respectively. Out of 39 tuberculous patients, 33 patients were found to be having CSF ADA at or above the cutoff value of 10 IU/L while only one among pyogenic meningitis. On comparison between two groups, the CSF ADA level found to be statistically highly significant ($P < 0.001$) with overall accuracy of the test was 85.5 %.
Conclusions: We found that the duration of illness, estimation of cerebrospinal fluid ADA with a cut off value of 10 IU/L and CSF glucose: protein ratio of 0.5 may useful in differentiating tuberculous from pyogenic meningitis. posterior cranial fossa surgeries. This work will also be useful to anthropologists, forensic science experts for determination of sex of the skull along with other parameters.

Keywords: Comparison, CSF profiles, Pyogenic meningitis, Tuberculous Meningitis

INTRODUCTION

Tuberculous meningitis (TBM), characterised by a slowly progressive granulomatous inflammation of the basal meninges, a common cause of morbidity and mortality. Exact prevalence of central nervous system tuberculosis in India is not known, but it accounts for an estimated 1% of all cases of TB, which equates to around 17000 cases in India in 2014.[1] Many a times differentiating tuberculous meningitis from pyogenic meningitis becomes very difficult. The diagnosis depends upon clinical manifestation and cytochemical analysis of cerebrospinal fluid (CSF). Adenosine deaminase (ADA) is now being recognized as a marker of cell mediated

immunity particularly as a marker of T lymphocyte activation. Many researchers uses Adenosine deaminase levels (ADA) in cerebrospinal fluid to differentiate tubercular disease from non-tubercular.[2-5] The aim of the study is to compare the clinical and CSF profiles in patients with tuberculous and pyogenic meningitis, to find out the simple way of differentiation between tuberculous and pyogenic meningitis.[1,2]

METHODS

The study conducted between February 2016 and February 2017 at Sri Krishna Medical College and Hospital, Muzaffarpur, Bihar, a tertiary care centre, in 62 patients with meningitis after prior consent and ethical approval. The diagnosis of meningitis was made on the basis of clinical symptoms and signs like headache, fever, nausea, vomiting, neck rigidity, presence of Kernig's and/or Brudzinski's sign, altered sensorium, any focal neurological deficit with no other general medical condition explaining them. Patients were divided into two groups:

- Group A - Tubercular Meningitis (n=39)
- Group B - Pyogenic Meningitis (n =23)

Presence of above signs and symptoms with one or more of the following criteria was adopted to label a case as tuberculous meningitis:

- Bacteriological proof of presence of Mycobacterium tuberculosis in CSF.
- Biopsy showing caseating granulomas.
- Suspected active pulmonary tuberculosis based on chest X ray.
- Acid fast bacilli found in any sample apart from the CSF,
- Clinico- radiological findings consistent with Tuberculosis.
- Predominance of lymphocytes in the CSF, CSF glucose: protein ratio < 0.5, Raised CSF Protein.
- Definite clinical and radiological improvement in one month after specific anti-tubercular treatment.

For pyogenic meningitis presence of above signs and symptoms for a short period of time and typical CSF findings were elevated pressure, neutrophilic pleocytosis, i.e., cell count >100 WBC/cu. mm consisting of more than 90% polymorphs, elevated protein >40 mg%, sugar ≤50% of the blood sugar, cloudy or turbid appearance, culture and gram staining may be positive for bacteria and full recovery without anti-tuberculosis therapy. Lumbar puncture was done in each case and at least 2ml of CSF was collected in a sterile vial. Hemorrhagic CSF was excluded from the study. This CSF was subjected to biochemical and microscopic examination. ADA activity estimated in all these patients by the method of Guisti 6 and was expressed as IU/L. Cutoff reference range of 10 IU/L CSF ADA was taken as positive.

SPSS 19.0 was used for statistical analyses. Patient's ages were described as mean ± standard deviation. Continuous variables were compared by the t-test and dichotomous variables were compared by Fisher's exact test for two by two comparisons or Pearson $\chi 2$ for greater than two responses.

RESULTS

Out of 62 patients with meningitis admitted to our hospital, 50 were male. (Table 1) Thirty-nine patients (62.9%) with tubercular meningitis and twenty-three (37.1%) pyogenic meningitis. The mean age of patients with tubercular meningitis was 39.07±16.67 years (19-76 years) and that of pyogenic meningitis 34.35±16.73 years (21-45 years).

Table 1. Demography and clinical features of all patients with meningitis.

Characteristic		Tubercular meningitis (Group A), N = 39 (%)	Pyogenic meningitis (Group B), N =23 (%)	All (Group A+B), N= 62 (%)
Sex	Male	36 (92.3 %)	14 (60.9 %)	50 (80.6 %)
	Female	03 (7.7 %)	09 (39.1 %)	12 (19.4 %)
Age (Mean±SD), Years		39.07±16.67	34.35±16.73	37.32±16.67
Fever		37 (94.8 %)	23 (100 %)	60 (96.8 %)
Headache		29 (74.3 %)	20 (86.9 %)	49 (79.0 %)
Vomiting		22 (56.4 %)	22 (95.7 % %)	44 (71.0 %)
Seizure		06 (15.4 %)	00 (0.0 %)	06 (9.7 %)
Neck rigidity		31 (79.5 %)	15 (65.2 %)	46 (74.2 %)
Kernig's sign		17 (43.6 %)	20 (86.9 %)	37 (59.7 %)
Brudzinski's sign		06 (15.4 %)	12 (52.2 %)	18 (29.0 %)
Cranial CT or MRI	Tuberculoma	03 (7.6 %)		
	Hydrocephalous	11 (28.2 %)		
	Arachnnoiditis	02 (5.1 %)		

Table 2: Cerebrospinal fluid results in TBM (n=39) and pyogenic meningitis (n=24) patients.

Variable	TBM (n=39)	Pyogenic meningitis (n=24)
WBC /cmm, Mean±SD	256.74±184.03	106.17±185.18
CSF protein (mg/dl), Mean±SD	182.22±113.12	88.78±114.35
CSF sugar (mg/dl), Mean±SD	52.85±19.3	63.47±19.48
CSF glucose : protein ratio	0.41	0.54

Overall fever was present in 60 (96.77%), headache in 49 (79.03%), and vomiting in 44 (70.96%) patients. The symptom duration range from 7 to 98 days with a median of 28 days and clinically fever was present in 37 (94.8 %), headache in 29 (74.3%), and vomiting in 22 (56.4%) patients with TBM. Four patients (10.25%) with tuberculous meningitis had symptom duration of ≤7 days. Among tubercular meningitis, 6 (15.38%) had seizure. None with pyogenic meningitis had seizure. In pyogenic meningitis group, the symptom duration range from 2 to 21 days with a median of 3 days and clinically fever was present in 23 (100%), headache in 20 (86.9%), and vomiting in 22 (95.7%) patients. Twenty patients (86.9 %) had symptom duration of ≤7 days. Meningeal signs – neck rigidity in 46 (74.2%), Kernig's sign in 37 (59.68 %) and Brudzinski's sign in 18 (29.03%) patients. On CSF cytological and biochemical analysis the mean total white blood cell count was 256.74±184.03 /cmm, mean protein 182.22±113.12 mg/ dl and mean sugar 52.85± 19.3 mg/dl in TBM whereas in pyogenic meningitis 106.17±185.18/cmm, 88.78±114.35 mg/ dl, and 63.47 ±19.48 mg/ dl respectively. (Table 2) The CSF glucose: protein ratio in TBM was 0.41 and 0.54 in pyogenic meningitis. Out of 39 tuberculous patients, 33 patients were found to had CSF ADA at or above the cutoff value of 10IU/L while six had below cutoff value. Of the 23 patients with pyogenic meningitis, one had CSF ADA at or above the cutoff value. In Group A (TBM), the ADA level in CSF ranged between 7 to 112IU/L with mean± SD as 35.72±32.83 IU/L. While in Group B (pyogenic meningitis), the ADA level ranged between 2.4 to 7IU/L with a mean ±SD as 4.21±1.35 IU/L. On comparison between two groups, the CSF ADA level found to be highly significant (P < 0.001) (Table 3).

Table 3. Distribution of the cases according to set criteria and CSF ADA Level.

Group	No. of cases	ADA Level in IU/L	N (%)	Mean ± SD	P- value
Group A (Tubercular meningitis)	39	ADA ≥10	33 (84.6%)	40.67±33.39	<0.001
		ADA <10	6 (15.4%)	8.47±0.81	
Group B (Pyogenic meningitis)	23	ADA ≥10	1 (4.3%)	-	
		ADA <10	22 (95.7%)	4.21±1.35	
Total	62				

Table 4. CSF-ADA level efficacy with a cut off value 10 IU/L.

CSF ADA level	TBM (N =39)	Pyogenic meningitis (N =23)
≥ 10 IU/L	33	01
< 10 IU/L	06	22
Sensitivity	79.48%	
Specificity	95.65%	
Positive predictive value	73.33%	
Negative predictive value	96.87%	
Overall accuracy of test	85.48%	

In our study, the overall accuracy of the CSF ADA test was found to be 85.48% and the sensitivity 79.48%, specificity 95.65%, positive predictive value 73.33% with the negative predictive value of 96.87%. (Table 4).

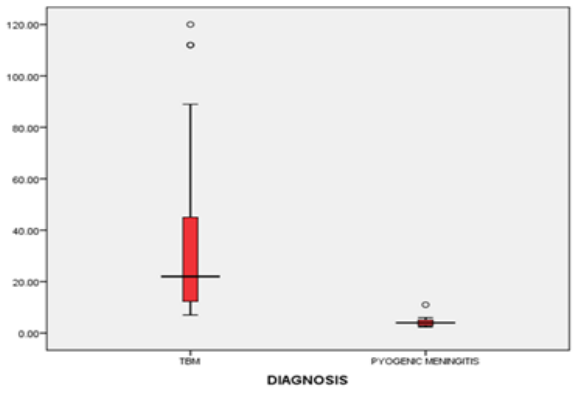

Figure 1: Box plot diagram of CSF - ADA level (IU/L).

DISCUSSION

We analyzed 62 patients with meningitis. On the basis of clinical features and cerebrospinal fluid examination findings patients were divided into two groups: Tubercular meningitis (n=39) and Pyogenic meningitis (n=23). Tuberculous meningitis may have an acute presentation, but generally it is slowly progressive. The length of symptoms before admission was seven days or more with a median of 28 days (7 to 98 days) in TBM. One study found that the length of symptoms before admission, in 21 patients, was five days or more in another study it was 3 to 90 days.[7,8]

In pyogenic meningitis the length of symptoms before admission was two to 21 days with a median of 3 days. Most patients presented acutely. The most common clinical manifestation was fever in 96.8% followed by headache and vomiting in 79 % and 71% respectively. In some studies headache was more common than fever.[8,9] Seizure was found in 15.4% of patients. In one study convulsions occurred in 15.6% where as in another study it was only 1%.[8,9] History of seizures on presentation were common in TBM group but none in other group. This is similar to prior reports.[10] Overall about two-third of the patients had neck rigidity (74.2%), but Kernig's and Brudzinski's signs were present in 59.7% and 29% of patients, respectively. A study by Aminzadeh Z and Mahmoodi T, found that about 50% of the patients had neck stiffness, but Kernig and Brudzinski's signs were found in 45.5% and 23% of patients, respectively.[7] A review by Pehlivanoglu F et al in 160 patients noted that 88% had neck stiffness.[9] On cranial CT or MRI of patients with TBM, 28.2% had hydrocephalous, 7.6% tuberculoma and 5.1% had spinal arachnoiditis presenting as paraparesis. Around 36% patients had tuberculoma, 20% hydrocephalous and 2% arachnoiditis in one study.[9]

Cranial CT or MRI was normal in cases of pyogenic meningitis. On CSF analysis, in TBM, the mean WBC count was 256.74±184.03/ cmm with lymphocyte predominance, mean protein was 182.22±113.12 mg/dl which was more as compared to pyogenic meningitis, 106.17±185.18/cmm and 88.78±114.35 mg/dl respectively. In TBM the CSF glucose: protein ratio was less than 0.5 (0.41). The value of CSF protein and glucose, although well known to be different from bacterial meningitis, has rarely been reported to be significant in cases of TBM.[11,12]

We found that the CSF glucose: protein ratio of <0.5 was found to be significant because of very high protein and moderately low glucose levels found in cases of TBM, in contrast to very low glucose and moderately high protein in cases of bacterial meningitis (ratio>0.5). Adenosine deaminase (ADA) level in CSF estimated in all patients and its level in tubercular meningitis patients were compared with those in pyogenic meningitis patients as control. We found that in TBM group the mean (±SD) CSF ADA was 35.72 (±32.83IU/L), while in pyogenic meningitis it was 4.21 (±1.35IU/L) (Figure 1). A study by Karsen H et al in 24 patients with TBM found a mean ADA values of 28.34 ±14.83IU/L.13 In our study CSF - ADA level 10IU/L as a cutoff value differentiate tuberculous from non-tuberculous meningitis. There was a highly statistically significant difference in the CSF - ADA levels of meningitis due to tuberculosis and pyogenic etiology (P<0.001) (Table 3).

In our study, the overall accuracy of the CSF ADA test was found to be 85.48 % and the sensitivity 79.48%, specificity 95.65%, positive predictive value 73.33% with the negative predictive value of 96.87%. A study by Baheti R et al[14] in 38 patients with meningitis found that CSF ADA (cut off value 6.5IU/L) had a sensitivity of 95.83%, specificity of 92.85%, positive predictive value 95.83%, negative predictive value 92.85% and overall accuracy of test was 94.73%. Rana et al take 10 U/L as cutoff value for diagnosis of TBM and found sensitivity 66.6% and specificity 90% .[15]

In about 84.6% (33/39) of tubercular meningitis patients the CSF- ADA level was more than 10IU/L. Results of our study indicate that ADA levels in CSF are of considerable value in diagnosis of TBM and in differentiating this disease from others because a cut-off value of 10IU/L exhibited fairly high statistical significance and high predictive values. CSF - ADA estimation was reported to be useful in diagnosing TBM and to differentiate TBM from pyogenic and aseptic meningitis.[2, 16]

CONCLUSION

We found that the duration of illness, estimation of cerebrospinal fluid ADA with a cut off value of 10 IU/L and CSF glucose: protein ratio of 0.5 may useful in differentiating tuberculous from pyogenic meningitis. If the clinical and cerebrospinal fluid parametres found significant in this study are further validated on a larger number of patients, they may prove useful in an empiric diagnosis of tubercular meningitis.

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