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Original Research Article

Spectrum of cerebrospinal fluid analysis and nervous system diseases in hospitalised patients: a hospital based prospective study from a hilly state of Himachal Pradesh in North India

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ABSTRACT

Background: The cerebrospinal fluid (CSF) analysis is an invaluable diagnostic aid in various nervous system diseases. Many times, alterations in normal CSF parameters with variable and overlapping results are challenging in differential diagnosis and treatment of the diseases. The aim of the study is to know the spectrum of CSF analysis and nervous system diseases with different prevalence in our setup.
Methods: Total 150 hospitalised patients with various nervous system diseases and indications were subjected to lumbar puncture and the CSF analysis was done, in a period of one year study.
Results: A total of 150 patients with mean age of 50.41±19.54 years had male to female ratio of 1.63:1. CSF analysis revealed most of tuberculous meningitis (TBM) in 30(20%) patients with higher adenosine deaminase (ADA) levels of 10.7±20.24 IU/L and lymphocytic leukocytosis (81.93%). Bacterial meningitis in 8(5.3%) patients revealed highest increase in CSF mean protein levels of 349.63±226.39 mg/dL and in mean cell count of 1039.50±930.23 cells/mm^3. There was significant increase in protein levels and decrease in glucose levels of CSF, both in TBM and bacterial meningitis compared to viral, fungal meningitis and other central nervous system (CNS) diseases($p<0.001$).
Conclusions: Spectrum of CSF analysis and CNS diseases revealed consistent findings of alteration of normal CSF variables and therefore, was found as an invaluable, rapid and cost-effective differentiating diagnostic tool.

Keywords: Adenosine deaminase, Cerebrospinal fluid, Meningitis, Sensitivity and specificity

INTRODUCTION

Cerebrospinal fluid (CSF) is a dynamic, metabolically active substance, a clear biological fluid that occupies the space between arachnoid mater and pia mater. CSF protects the brain and spinal cord, maintains stable chemical environment and removes waste products of cerebral metabolism.[1] The first full account of CSF was given by Domenico Contugno in 1764 and Heinrich Quincke performed the first diagnostic lumbar puncture in 1891.[2] Alteration in normal CSF variables occurs in infectious and non- infectious CNS diseases which may be similar or overlapping in different pathological processes and imposes difficulties in interpretation, diagnosis and treatment. CSF is obtained by lumbar puncture and analyzed within 24 hours preferably within 30 minutes.[3] Routine CSF evaluation includes, opening pressure, colour changes, biochemical, microscopy for cytological and microbiological examination and specific immunological assays.[3,4] Increased CSF pressure >250mm of H_2O is diagnostic of elevated intracranial pressure in various CNS diseases. CSF is crystal clear but due to >200 WBCs /mm^3 and 400 RBCs/mm^3 will cause it to appear turbid.[4] Normal CSF contains TLC up to 5

cells /mm^3 in adults and 20 cells /mm^3 in children. TLC >500 cells/ mm^3 with neutrophilic predominance and >100 cells /mm^3 with lymphocytic predominance is characteristic of bacterial and viral meningitis respectively.[5] CSF glucose is about 2/3 of serum glucose and hypoglycorrhachia (low CSF glucose) occurs in chemical meningitis, inflammatory conditions, subarachnoid hemorrhage and hypoglycemia, and there is no pathological process that causes CSF glucose to be elevated.[4,5] Elevated CSF protein concentration (>45mg /dL) is one of the most sensitive indicators of pathology within CNS. The levels of CSF proteins may be falsely elevated but do not decrease in hypoproteinaemia.[5] Characteristic CSF findings for bacterial meningitis consist of polymorphonuclear pleocytosis, hypoglycorrhachia and raised protein levels.[6] Gram stain of CSF is cheap and rapid method of identification of organisms but culture remains the gold standard for diagnosis of bacterial meningitis.[6,7] Majority of TBM patients have raised CSF protein, low glucose in 50% of cases and lymphocytic pleocytosis. Hypoglycorrhachia is characteristic and hydrocephalous the most common complication of TBM.[8] In TBM, factors predicting fatal outcome are very low glucose, low CSF/blood glucose ratio and significantly high CSF protein levels.[9,10] ADA >6.5 IU/L in CSF may differentiate tuberculous from non-tuberculous meningitis.[11] ADA in CSF attains a specificity of 95% and low sensitivity of 55% showing a fair performance for 'ruling out' TBM.[12] ADA is specific and accurate method of differentiating the tuberculous aetiology with very low evidence of presence of mycobacterium.[13] Marked leukocytosis differentiates bacterial from non-bacterial meningitis.[14,15] Fungal meningitis displays decreased predominance of lymphocytes, normal or reduced glucose and slightly increased protein levels in CSF.[16] CSF analysis with C-reactive protein and enzymatic profile differentiates viral meningitis from others types of meningitis.[17] Herpes simplex viruses (HSV) I and II in CSF are detected by PCR assays.[18] Catridge Based Nucleic acid amplification test (CBNAAT) or Gene Xpert, PCR based assays are emerging as novel technology in the diagnosis of resistant tuberculosis. Radioimaging by CT Scan and MRI are also valuable aids to CSF in diagnosis of CNS diseases. The routine CSF analysis remains a valuable, rapid and cost effective tool in differential diagnosis of CNS diseases.

METHODS

The study was conducted from July 2018 to June 2019 over a period of one year in Indira Gandhi Medical College and Hospital Shimla, a tertiary care centre in a hilly state of Himachal Pradesh in north India. A total of 150 hospitalised patients were studied.

Inclusion criteria

- Patients aged 18 years and above of both sexes.
- Patients hospitalised to medicine ward with suspected meningitis and other CNS diseases presenting as altered sensorium, headache, fever, vomiting, seizures, coma, neck stiffness, Kernig's sign, Brudzinski's sign, focal neurological deficit and suggestive radiological findings on computed tomography (CT) scan and magnetic resonance imaging (MRI) were included in the study.

Exclusion criteria

- Patients aged <18 years,
- Patients not consenting,
- Patients with contraindications to perform lumbar puncture such as local infections, subarachnoid hemorrhages and raised intracranial pressure with "coning" and
- Patients already receiving diseases specific treatment were excluded from the study.

Approval from Institutional Ethical Committee was obtained. All the eligible patients were subjected to lumbar punctures observing all standard procedures. CSF samples were sent to the laboratory within 1 hour and analyzed chemically, microscopically, microbiologically, immunologically and also by novel technology using CBNAAT or Gene Xpert based polymerase chain reaction (PCR) assays. CSF variables comprising protein levels of >45 mg/dL, glucose <45mg% (2/3 of blood glucose), total leukocyte count (TLC) >5 cells/mm^3 and ADA>6 IU/L in combination were interpreted for differential diagnosis of infectious and non-infectious CNS diseases.

Statistical analysis

All the data were entered in Excel Sheet and analyzed statistically using EPI info version 7. Chi Square ($\chi 2$) test for comparison of categorical variables and ANOVA for comparison of means were used. For all comparisons p value <0.05 was considered statistically significant.

RESULTS

A total of 150 patients, 93 (62%) male and 57 (38%) female patients (ratio of 1.63:1) revealed mean age of 50.41±19.54, 49.97±19.37 and 51.14±19.97 years respectively (Table 1).

Table 1: Age and sex distribution of study patients.

Sex	Number	Age (range) (years)	Mean age (years)
Male	93 (62%)	18-89	49.97±19.37
Female	57 (38%)	18-85	51.14±19.97
Total	150(100%)	18-89	50.41±19.54

The patients admitted with suspected meningitis and other CNS diseases were maximally elderly, 54(36%) patients in age group of >60years followed by 51(34%) in 18 to 40 years and 45(30%) patients in 41 to 60 years of

age groups with overall prevalence of male patients (Figure 1).

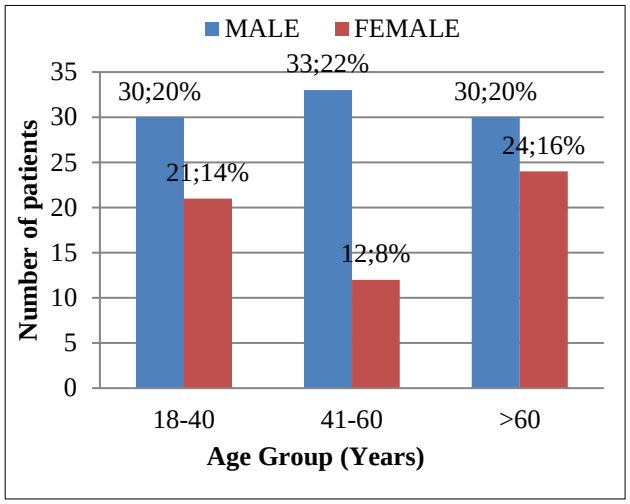

Figure 1: Age distribution of patients.

In all the 150 patients, CSF variables were analysed and interpreted in constellation to make differential diagnosis of various meningitis and other CNS diseases. Accordingly maximum 30(20%) patients were found to have tuberculous meningitis followed by 8(5.3%) patients of bacterial meningitis and 7(4.7%) patients of viral meningitis. 98(65.3%) patients were found to have CSF analysis following no consistent pattern of any disease (Table 2).

Table 2: Distribution of patients according to etiology of diseases.

Diagnosis	Male	Female	Total
Tuberculous Meningitis	18(12%)	12 (8%)	30 (20%)
Bacterial Meningitis	5(3.3%)	3(2%)	8(5.3%)
Viral Meningitis	5 (3.3%)	2 (1.3%)	7 (4.7%)
Fungal Meningitis	0	1(0.66%)	1(0.7%)
GBS	1(0.66%)	3(2%)	4(2.7%)
MS/NMO*	*1(0.66%)	1(0.66%)	2(1.3%)
Others	63(42%)	35(23.3%)	98(65.3%)
Total	93(62%)	57(38%)	150(100%)
p value	0.595		

GBS, Guillain-Barre syndrome ; MS, multiple sclerosis ; NMO, neuromyelitis optica.

The mean TLC was found 126.67±170.98 cells /mm^3 with lymphocytic predominance (81.93%) in 30 patients of TBM and significantly increased mean TLC of 1039.50±930.23 cells /mm^3 in bacterial meningitis (p<0.001). Increased TLC was found lymphocytic predominance in viral and fungal meningitis and normal in Guillain-Barre syndrome (GBS), multiple sclerosis (MS) and neuromyelitis optica (NMO) patients (Table 3). Gram stain, culture and marked pleocytosis were found to have confirmed the cases of bacterial meningitis.

Table 3: TLC and differential cell count (DLC) in CSF in different types of meningitis / diseases.

Diagnosis (No.)	TLC (cells/mm^3)		DLC (N%)		DLC (L%)	
	Range	Mean	Range	Mean	Range	Mean
Tuberculous meningitis (30)	10-850	126.67±170.98	1-90	18.07±24.59	10-99	81.93±24.59
Bacterial meningitis (8)	66-2600	1039.50±930.23	1-89	45.38±34.98	11-99	54.63±34.98
Viral meningitis (7)	0-480	116.00±175.27	0-60	16.43±21.94	0-100	67.86±36.93
Fungal meningitis (1)	88-88	88.00±0.0	25-25	25.0±0.0	75-75	75.0±0.0
GBS (4)	0-5	1.25±2.5	0-9	2.25±4.5	0-91	22.75±45.5
MS/NMO (2)	0-4	2.00±2.82	0-10	5±7.07	0-90	45±63.64
Others (98)	0-200	8.92±24.75	0-96	12.37±21.74	0-100	31.41±39.89
Total (150)	0-2600	92.66±318.30	0-96	15.17±23.78	0-100	44.69±41.88
p value	<0.001 *		0.009 *		<0.001 *	

* Significant; GBS, Guillain-Barre syndrome; MS, multiple sclerosis; NMO, neuromyelitis optica; N%, neutrophil%; L%, lymphocyte%

Mean CSF glucose of 41.13±25.4 mg% in TBM and 43.25±20.48 mg% in bacterial meningitis was significantly reduced compared to 72.71±53.53 mg % in viral meningitis (p <0.001). CSF mean protein levels of 247.5±163.52 mg/dL in TBM and 349.63±226.38 mg/dL in bacterial meningitis were significantly increased compared to viral and fungal meningitis (p<0.001). CSF glucose was also found significantly reduced in 1(0.66%) patient of fungal meningitis (Table 4).

ADA in CSF with mean level of 10.7±20.24 IU/L was increased in TBM as compared to mean levels of 5.84±3.22 and 4.68±1.01 IU/L in bacterial and viral meningitis respectively (Table 5).

Table 4: Biochemical parameters of CSF in different types of meningitis.

Diagnosis (No.)	Glucose (mg%)		Protein (IU/L)	
	Range	Mean	Range	Mean
Tuberculous Meningitis (30)	10-132	41.13±25.4	29-638	247.5±163.52
Bacterial meningitis (8)	8-66	43.25±20.48	145-705	349.63±226.38
Viral meningitis (7)	26-188	72.71±53.53	46-278	121±82.81
Fungal meningitis (1)	12-12	12±0.0	69-69	69±0.0
p Value	<0.001*		<0.001*	

Table 5: CSF ADA levels in different types of meningitis.

Diagnosis	CSF ADA (IU/L)	
	Range	Mean
Tuberculous meningitis (30)	4-115	10.7±20.24
Bacterial meningitis (8)	4-13.6	5.84±3.22
Viral meningitis (7)	4-6.7	4.68±1.01
Fungal meningitis (1)	5-5	5±0
GBS (4)	4-5	4.25±0.5
MS/NMO (2)	4-4	4±0
Others (98)	4-10.58	4.22±0.74
Total (150)	4-115	5.63±9.34
p value	0.076	

GBS, Guillain-Barre syndrome; MS, multiple sclerosis; NMO, neuromyelitis optica.

Out of all 30 TBM patients CSF for CBNAAT was positive in 4(13.3%) and negative in 26(86.7%) patients.

Diagnostic accuracy of CSF parameters was evaluated for the diagnosis of TBM (Table 6). CSF ADA > 6 IU/L with sensitivity of 56.6% and specificity of 97.5% was found most specific showing best performance as an isolated performed test in TBM patients. Protein level >45 mg/dL with sensitivity of 96.6% and specificity of 32.5% was found highly sensitive but less specific in predicting the diagnosis of TBM. Lymphocytic predominance defined as TLC >5 cells /mm^3 and ≥50% lymphocytes in CSF of TBM patients had sensitivity of 86.6% and specificity of 64.1%.

Table 6: Diagnostic accuracy of CSF variables in TBM.

CSF Variables	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
ADA >6 IU/L	56.6	97.5	85	90
Lymphocytic predominance *	86.6	64.1	37.6	95
Protein >45 mg/dL	96.6	32.5	26.3	97.5
Sugar <45 mg %	60	87.5	54.5	89.7

* Defined as >5 cells /mm^3 and ≥50% lymphocytes; PPV, positive predictive value; NPV, negative predictive value.

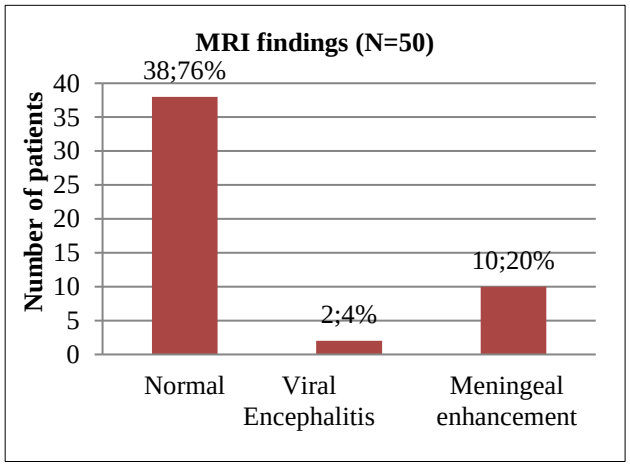

Figure 2: MRI findings of patients.

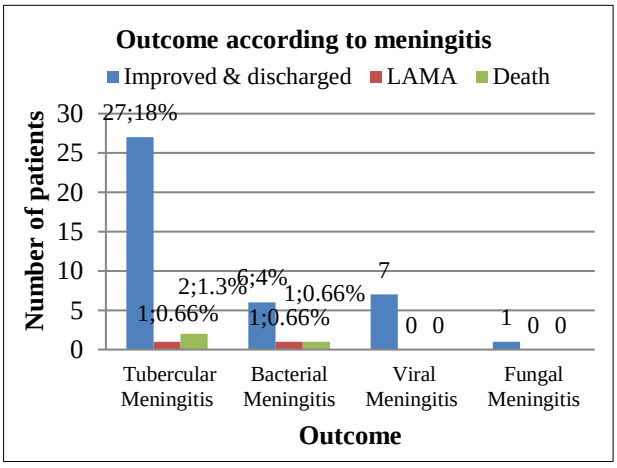

Figure 3: Final outcome of all study patients.

Out of 150 patients only 9(6%) patients were found to have shown the findings suggestive of meningitis on CT scan of head. MRI brain and spine done in a total of 50 patients, 2(4%) patients revealed findings suggestive of viral encephalitis and 10(20%) patients, of meningeal enhancement (Figure 2).

Out of all 150 patients 3(2%) patients died during hospital stay and 142(94.7%) including 98(65.3%) patients without CSF findings suggestive of meningitis were improved with disease specific treatment and discharged. The total mortality was maximum 2(1.3 %) in TBM patients and only 1 (0.66 %) in bacterial meningitis and none in other patients (Figure 3).

DISCUSSION

Amongst 150 patients studied, TBM was found the most common diagnosis in 30 (20%) patients followed by 8 (5.3%) patients of bacterial meningitis, 7 (4.7%) patients of viral meningitis and 1 (0.66%) patients of fungal meningitis. India is highest TB burden in the world, accounts for one fourth of the global TB burden cases, where in 2015, an estimated 28 lakh cases occurred and 4.8 lakh people died due to TB.[19] A study from India by Vasanthan K, et al reported 32 (35.5%) patients of TBM, 15(16.7%) patients of bacterial meningitis and 9 (10%) patients of aseptic meningitis.[20] Higher prevalence of TBM of 57.14% was reported in a study by Aggarwal, et al, and 63.3% by Jain S, et al.[21,22] These results are in accordance with other studies in various parts of India where the prevalence of the TBM was highest. We observed maximum TLC increase in CSF of 1039.50±930.23 cells/mm^3 in bacterial meningitis followed by 126.67±170.98 cells/mm^3 in TBM ($p<0.001$). Moghtaderi et al, in a study reported TLC of 158 cells/mm^3 for TBM and 1000 cells/mm^3 for bacterial meningitis and Wani, et al, reported TLC of 175 cells/mm^3 for TBM.[23,24] Lymphocytic predominance was 81.93% in TBM. However, neutrophilic predominance was 45.38% and lymphocytes were 54.63% in bacterial meningitis, though the TLC was in highest range of 2600 cells/mm^3, explainable by early rise of lymphocytes reported in 10% of cases. Thwaites et al, reported polymorphic predominance of 90% for bacterial meningitis and lymphocytic predominance of 64% for TBM.[25] Increased CSF protein levels and decreased glucose levels were observed in both, TBM and bacterial meningitis compared to other meningitis ($p<0.001$). These results were similar to other studies from India.[22-24] The patients of TBM, in CSF revealed highest ADA levels of 10.7±20.24 IU/L followed by 5.84±3.22 IU/L in bacterial meningitis. ADA >6 IU/L in CSF with specificity of 97.5% was found most specific and protein level >45mg/dL with sensitivity of 96.6% was found highly sensitive in predicting the diagnosis of TBM in our study. ADA was the parameter that in isolation performed the best followed by protein as reported in a similar study.[12] ADA activity was reported, 12.28±2.03 IU/L in TBM and 2.65±0.34 in bacterial meningitis by Jain S, et al.[22] Chotmongkol V, et al indentified ADA levels in CSF of 15.5 IU/L, as the best cut- off value to differentiate TBM from Non TBM.[26] The positivity of CBNAAT, in our study was 13.3% in 30 patients of TBM. Singh A, et al detected 22 patients out of 57 patients of TBM, (38.6%) in their CSF on CBNAAT.[27] Pooled sensitivity of CBNAAT in CSF, in a meta-analysis was reported 80.9%.[28] The viral meningitis found in 7 (4.7%) patients were detected for HSV-I by PCR in CSF. 17.6% samples of CSF were found positive for HSV-I by PCR in a study.[29] PCR assays for HSV in CSF differentiate viral from bacterial meningitis. Only 1(0.66%) case of cryptoccocal meningitis was found which was confirmed by Indian ink preparation in CSF. Cryptoccocal meningitis cases were confirmed by detection of antigen by Latex agglutination test (LAT) and PCR assays in CSF for early diagnosis and treatment.[30] The mortality was found only in 2 (1.3%) patients of TBM and only in 1(0.66%) patient of bacterial meningitis in our study. Better outcome in our study revealed the effectiveness of CSF analysis and early treatment. However higher mortality was reported in other studies.[9,31] The spectrum of CSF analysis and CNS diseases was found consistent with alteration in CSF variables and diseases prevalence.

CONCLUSION

Diagnosis of meningitis is primarily confirmed by CSF analysis. CSF analysis and CNS diseases evaluated in constellation with sensitivity and specificity of different variables and specific tests is valuable and cost effective in early diagnosis and management to prevent complications and fatal outcome. However, studies with larger number of cases need to be conducted for more accurate and precise spectrum of CSF analysis.

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