Original Article

Print ISSN: 2321-6379
Online ISSN: 2321-595X
DOI: 10.17354/ijss/2018/121

Profile of Cerebrospinal Fluid Analysis in Acute Central Nervous System Infections

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Abstract

Background: Confirmatory diagnosis of acute central nervous system (CNS) infection is a concern. Most often, it is presumed and empirical antimicrobials given. CSF findings may overlap in various infections and partially treated meningitis further complicates the CSF analysis.

Materials and Methods: This study included 90 patients with acute CNS infection admitted between July 2009 and August 2011. Ninety cases of community-acquired CNS infection were included in the study. The diagnosis of CNS infection was made based on the clinical features. Laboratory investigations such as complete blood count, random blood sugar, urine analysis, renal and liver function tests, and serum electrolytes were done in all cases. Cerebrospinal fluid (CSF) samples were collected and sent for cell count, glucose, protein, chloride, Gram stain, bacterial culture, AFB smear, culture of AFB, and viral markers like herpes simplex virus (HSV).

Results: 15 patients (16.7%) had bacterial meningitis, 32 (35.5%) had tuberculous (TB) meningitis, 9 (10%) had aseptic meningitis, 30 (33.3%) had encephalitis, and 4 (4.5%) had cryptococcal meningitis. The CSF sugar-to-blood sugar ratio was found to be <0.5 in 71.1% of all CNS infections. 93.3% of bacterial meningitis, 100% of TB meningitis, and 100% of cryptococcal meningitis had a CSF-to-blood sugar ratio <0.5 while only 33.3% of aseptic meningitis and 40% of encephalitis had such a value. TB meningitis had the maximum mean CSF protein of 275 followed by cryptococcal meningitis - 169. The mean CSF total count was found to be 257 for all CNS infections together. It was found to be maximum 559 for bacterial meningitis. Gram-positive cocci were reported in five patients and Gram-negative coccobacilli were reported in one patient. Polymerase chain reaction (PCR) for TB was positive in 10 (31.2%) patients with TB meningitis. PCR for HSV was positive in 8 (20.5%) patients with aseptic meningitis or encephalitis. IgM HSV was positive in 16 (41%) patients with aseptic meningitis or encephalitis.

Conclusion: Routine CSF cell count and biochemical analysis are of prime importance in differentiating between CNS infections and identifying individual CNS infections. PCR was not found to be useful in the diagnosis.

Key words: Central nervous system infection, Cerebrospinal fluid protein, Cerebrospinal fluid sugar, Cerebrospinal fluid total count, Tuberculous meningitis

INTRODUCTION

Central nervous system (CNS) infections are an important cause of mortality and morbidity. Clinical diagnosis of CNS infections (meningitis and encephalitis) always present with difficulties due to overlapping clinical features such as fever, irritability, altered sensorium, and associated chronic history of fever further compounds the diagnosis, i.e., tuberculous (TB) meningitis and autoimmune diseases. Hence, diagnosing CNS infections is an area of concern. Acute CNS infections can be mistaken for a wide range of conditions including drug intoxications, metabolic derangements, various tropical infections, and sepsis related encephalopathy.[1] The present study focuses on the accurate laboratory diagnosis of CNS infections which predominantly include cerebrospinal fluid (CSF) analysis and help in identifying the CNS infection and aid in the early treatment of these infections. Other investigations like CNS imaging were done in most of the patients to improve diagnostic accuracy.

Access this article online

www.ijss-sn.com

Month of Submission : 02-2018
Month of Peer Review : 03-2018
Month of Acceptance : 04-2018
Month of Publishing : 04-2018

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MATERIALS AND METHODS

The present study is a longitudinal study done between July 2009 and July 2011 at Sri Ramachandra Medical College and Hospital. All adult patients admitted with CNS infection are included in the study. Patients with age <18 years, recent neurosurgical procedure in <1 week, history of head trauma with CSF leak preceding the onset of symptoms, and patients with localized infection of CNS such as brain abscess/space occupying lesion were excluded from the study. Ninety cases of community-acquired CNS infection were included in the study based on the criteria mentioned above. The diagnosis of CNS infection was made by the admitting physician or team based on the clinical features. Laboratory investigations such as complete blood count, random blood sugar, urine analysis, renal and liver function tests, and serum electrolytes were done in all cases. CSF samples were collected through lumbar puncture in all cases, after informed consent. Samples were examined for cell count, glucose, protein, chloride, Gram stain, bacterial culture, AFB smear, culture of AFB, and viral markers like herpes simplex virus (HSV). CSF for polymerase chain reaction (PCR) TB and HSV was done in suspected case of TB and viral etiology, respectively. Neuro imaging computerized tomography (CT) or magnetic resonance imaging (MRI) brain was done in selected patients based on the clinical features such as fundus changes. CNS infections were further divided into bacterial meningitis, tubercular meningitis, aseptic meningitis, encephalitis, and cryptococcal meningitis based on CSF findings. Each group was analyzed in detail. Patients were again reexamined at the time of discharge to look for any neurological sequelae. Results were expressed as mean for continuous variables. For categorical data, univariate analysis was performed using Pearson Chi-square test. A P value < 0.05 is considered to be statistically significant. Statistical analysis was done using SPSS windows version 17.0 Software.

RESULTS

The study included 90 patients, 73 males and 17 females. 15 patients (16.7%) had bacterial meningitis, 32 (35.5%) had TB meningitis, 9 (10%) had aseptic meningitis, 30 (33.3%) had encephalitis, and 4 (4.5%) had cryptococcal meningitis [Table 1].

The mean ESR value was found to the maximum for cryptococcal meningitis (66) followed by TB meningitis (64). Bacterial and aseptic meningitis had a mean ESR value of 24, while encephalitis had a mean ESR of 38.

The CSF sugar-to-blood sugar ratio was found to be <0.5 in 71.1% of all CNS infections. 93.3% of bacterial meningitis, 100% of TB meningitis, and 100% of cryptococcal meningitis had a CSF-to-blood sugar ratio <0.5 while only 33.3% of aseptic meningitis and 40% of encephalitis had such a value. More profound decrease in CSF-to-blood sugar ratio of <0.03 was seen in 75% of patients with TB meningitis and 60% of patients with bacterial meningitis [Table 2].

The mean CSF protein concentration was found to be 154 for all CNS infections together. Individually among CNS infections, TB meningitis had the maximum mean CSF protein of 275, followed by cryptococcal meningitis - 169, aseptic meningitis - 94, bacterial meningitis - 80, and encephalitis - 76 [Table 3].

The mean CSF total count was found to be 257 for all CNS infections together.

It was found to be maximum 559 for bacterial meningitis, followed by 325 for cryptococcal meningitis, 291 for TB meningitis, 188 for aseptic meningitis, and 80 for encephalitis [Table 4].

Table 5 analyzes the CSF differential count.

CSF Gram stain was done in 15 patients. Gram-positive cocci were reported in five patients and Gram-negative coccobacilli were reported in one patient. Out of

Table 1: The etiology of meningitis

Diagnosis	Male (%)	Female (%)	Total
Bacterial meningitis	10 (66.6)	5 (33.7)	15
TB meningitis	11 (34.3)	21 (65.7)	32
Aseptic meningitis	6 (66.7)	3 (33.3)	9
Encephalitis	25 (83.3)	5 (16.7)	30
Cryptococcal meningitis	3 (75)	1 (25)	4
Total	55 (60.3)	35 (39.7)	90

TB: Tuberculous

Table 2: The CSF sugar-to-blood sugar ratio

Diagnosis	<0.3 (%)	0.3–0.5 (%)	>0.5 (%)
All CNS infections (*n*-90)	35 (38.9)	29 (32.2)	26 (28.9)
Bacterial meningitis (*n*-15)	9 (60)	5 (33.3)	1 (6.7)
TB meningitis (*n*-32)	24 (75)	8 (25)	0 (0)
Aseptic meningitis (*n*-9)	0 (0)	3 (33.3)	6 (66.7)
Encephalitis (*n*-30)	1 (3.3)	11 (36.7)	18 (60)
Cryptococcal meningitis (*n*-4)	1 (25)	3 (75)	0 (0)

CSF: Cerebrospinal fluid, CNS: Central nervous system, TB: Tuberculous

Table 3: CSF protein analysis

Diagnosis	Mean CSF protein (mg/dL)
All CNS infection	154
Bacterial meningitis	80
TB meningitis	275
Aseptic meningitis	94
Encephalitis	76
Cryptococcal meningitis	169

CSF: Cerebrospinal fluid, TB: Tuberculous

15 patients for which CSF culture was done, 3 patients' culture grew *Streptococcus pneumoniae* and 1 patient grew *Staphylococcus aureus*.

PCR for TB was positive in 10 (31.2%) patients with TB meningitis.

PCR for HSV was positive in 8 (20.5%) patients with aseptic meningitis or encephalitis. IgM HSV was positive in 16 (41%) patients with aseptic meningitis or encephalitis. Neuroimaging in the form of CT or MRI brain was done in 78 patients (87%). Imaging was found to be normal in 51 patients (56.7%). No patient had a neuroimaging finding suggestive of a mass effect or midline shift. Findings suggestive of viral encephalitis were found in 6 (6.7%) patients. Findings suggestive of TB meningitis were found in 6 (6.7%) patients. 15 (16.6%) of patients had other findings such as chronic infarcts, lacunar infarcts, and age-related atrophy.

DISCUSSION

In our study, of 90 patients with CNS infection, 15 (17%) had bacterial meningitis, 32 (36%) had TB meningitis, 9 (10%) had aseptic meningitis, 30 (33%) had encephalitis, and 4 (4.5%) had cryptococcal meningitis Michael *et al*.[2] have reported the relative incidence of CNS infection as 13 patients (30%) purulent meningitis, 18 patients (40%) aseptic meningitis, and 13 patients (30%) encephalitis.

Table 4: CSF total count

Diagnosis	Mean CSF total count (mg/ml)
All CNS infection	257
Bacterial meningitis	559
TB meningitis	291
Aseptic meningitis	188
Encephalitis	80
Cryptococcal meningitis	325

CSF: Cerebrospinal fluid, TB: Tuberculous, CSF: Cerebrospinal fluid, CNS: Central nervous system

Table 5: CSF differential count

Diagnosis	Polymorphic (%)	Lymphocytic (%)	None (%)
All CNS infection (*n*-90)	18 (20)	63 (70)	9 (10)
Bacterial meningitis (*n*-15)	15 (100)	0 (0)	0 (0)
TB meningitis (*n*-32)	3 (9.4)	29 (90.6)	0 (0)
Aseptic meningitis (*n*-9)	0 (0)	9 (100)	0 (0)
Encephalitis (*n*-30)	0 (0)	21 (70)	9 (30)
Cryptococcal meningitis (*n*-4)	0 (0)	4 (100)	0 (0)

CSF: Cerebrospinal fluid, CNS: Central nervous system, TB: Tuberculous

In our study, of 15 patients with bacterial meningitis, 10 (66.6%) were male and 5 (33.3%) were female. The sex distribution in bacterial meningitis reported by other studies is as follows: Mani *et al*.[3] 76.1% of males and 23.9% of females; Van de Beek *et al*.[4] 49.6% of males and 51.4% of females; Thwaites *et al*.[5] 78% of males and 22% of females; and Moghtaderi *et al*.[6] 71.5% of males and 28.5% of females. Studies done in the Indian subcontinent by Wani *et al*.[7] show TB meningitis to be more prevalent among females as observed in our study in contrast to studies done in the west. Sex distribution in TB meningitis by other studies is as follows: Thwaites *et al*.[5] found 64% of males and 36% of females and Moghtaderi *et al*.[6] found 56.9% of males and 43.1% of females. In our study, of 30 patients diagnosed to have encephalitis, 25 (83.3%) were male and 5 (16.7%) were female. The sex distribution in encephalitis reported by other studies is as follows: Glaser *et al*[8] 53% of males and 47% of females and Mailles and Stahl[9] 61% of males and 39% of females. In our study, of 4 patients diagnosed to have cryptococcal meningitis, 3 (75%) were males and 1 (25%) were females. The sex distribution in cryptococcal meningitis reported by other studies is as follows: Baradkar *et al*[10] found 52.6% of males and 47.4% of female, and in a study by Prasad *et al*.[11] 73.3% were males and 26.7% females.

Among CNS infections, the mean ESR value was found to the maximum for cryptococcal meningitis (66 mm/h) followed by TB meningitis (64 mm/h). Bacterial and aseptic meningitis had a mean ESR value of 24 mm/h, while encephalitis had a mean ESR of 38 mm/h. Wani *et al*.[7] reported elevated ESR in 81% of patients with TB meningitis. Van de Beek *et al*.[4] reported a mean ESR of 46 in patients with bacterial meningitis. The higher ESR value observed for cryptococcal meningitis in our study was probably due to low hemoglobin percentage as all four patients of cryptococcal meningitis were severely anemic. Among CNS infections, hyponatremia was present in 46.7% of cases of bacterial meningitis, 75% of cases of TB meningitis, 33.3% of cases of aseptic meningitis, 36.7% of cases of encephalitis, and 75% of cases of cryptococcal meningitis.

The CSF sugar-to-blood sugar ratio was found to be <0.5 in 71.1% of all CNS infections. 93.3% of bacterial meningitis, 100% of TB meningitis, and 100% of cryptococcal meningitis had a CSF-to-blood sugar ratio <0.5 while only 33.3% of aseptic meningitis and 40% of encephalitis had such a value. More profound decrease in CSF-to-blood sugar ratio of <0.03 was seen on 75% of patients with TB meningitis and 60% of patients with bacterial meningitis. Thwaites *et al*.[5] reported a median CSF/blood glucose ratio of 0.28 for TB and 0.20 for bacterial meningitis. Wani *et al*.[7] reported a CSF/blood glucose ratio of <0.6 for 80%

and <0.4 for 28.6% of TB meningitis. Van de Beek *et al.*[4] reported a mean ratio of 0.2 for bacterial meningitis. Glaser *et al.*[8] reported a ratio <0.4 for only 4% of encephalitis. Both bacterial and TB meningitis had a low CSF/blood sugar ratio in our study as found in other studies. Our study showed a lower ratio for TB meningitis compared to bacterial.

In our study, TB meningitis had the maximum mean CSF protein of 275, followed by cryptococcal meningitis −169 mg/dL, aseptic meningitis −94 mg/dL, bacterial meningitis −80 mg/dL, and encephalitis −76 mg/dL. Thwaites *et al.*[5] reported a median CSF protein level of 191 for TB and 270 for bacterial meningitis. Moghtaderi *et al.*[6] reported a median CSF protein level of 113 for TB and 120 for bacterial meningitis. Van de Beek *et al.*[4] reported a mean CSF protein of 490 mg for bacterial meningitis. Wani *et al.*[7] reported an elevated CSF protein levels of more than 50 mg/dL for 73.7% and more than 150 mg/dL for 14.3% of TB meningitis. Mailles and Stahl[9] reported elevated CSF protein levels of 110 for patients who survived and 290 for patients who expired among cases of encephalitis. Nowak *et al.*[12] reported an elevated protein levels of 138 mg/ dL for patients with aseptic meningitis due to HSV. The mean CSF protein was found to be elevated in all forms of CNS infections in our study with maximum being TB meningitis. Other studies show a more elevated CSF protein for bacterial meningitis compared to TB meningitis.

In our study, the mean CSF total count was found to be 257 for all CNS infections together. It was found to be maximum 559 for bacterial meningitis, followed by 325 for cryptococcal meningitis, 291 for TB meningitis, 188 for aseptic meningitis, and 80 for encephalitis. Thwaites *et al.*[5] reported a median CSF total count of 300 for TB and 2583 for bacterial meningitis.

Moghtaderi *et al.*[6] reported a median CSF total count of 158 for TB and 1000 for bacterial meningitis. Wani *et al.*[7] reported a mean CSF total count of 175 for TB meningitis. Van de Beek *et al.*[4] reported a mean CSF total count of 7753 for bacterial meningitis. Nowak *et al.*[13] reported a mean CSF total count of 285 for aseptic meningitis caused by HSV.

For cryptococcal meningitis, Baradkar *et al.*[10] reported the CSF total counts as non-specific. All studies including ours report the maximum elevation of CSF total count for bacterial meningitis; however, the mean CSF total count found in our study for bacterial meningitis was lower compared to other studies.

In our study, 100% of bacterial meningitis showed a polymorphic predominance. Lymphocytic predominance was showed by 90.6% of TB meningitis, 70% of encephalitis, and all cases of aseptic and cryptococcal meningitis. Thwaites *et al.*[5] reported a polymorphic predominance of 90% for bacterial meningitis and lymphocytic predominance of 64% for TB meningitis.

Moghtaderi *et al.*[6] reported polymorphic predominance of 84% for bacterial meningitis and lymphocytic predominance of 71% for TB meningitis. Wani *et al.*[7] reported lymphocytic predominance of 83% in TB meningitis. Baradkar *et al.*[10] reported the CSF differential count as non-specific for cryptococcal meningitis.

Of 15 patients diagnosed as bacterial meningitis, 5 (33.3%) had a positive Gram stain. 4 showed Gram-positive cocci and 1 showed Gram-negative coccobacilli. Van de Beek *et al.*[4] reported a positive Gram stain in 80% of cases with bacterial meningitis. Mani *et al.*[3] reported positive Gram stain in 65.7% of bacterial meningitis.

Of 15 patients diagnosed as bacterial meningitis, 4 (20%) had a growth of *S. pneumonia* and 1 (6.7%) had a growth of *S. aureus* in CSF culture. Mani *et al.*[3] reported a positive CSF culture in 40.8% of cases of bacterial meningitis. The most common organism isolated was *S. pneumoniae,* followed by *Haemophilus influenza* and *S. aureus*. Van de Beek *et al.*[4] reported the most common organism isolated as *S. pneumoniae,* followed by *Neisseria meningitidis, Listeria Monocytogenes,* and *S. aureus*. The percentage of positive Gram stain and CSF culture in our study was lower compared to others probably due to early treatment with antibiotics before CSF analysis or delay in processing the CSF sample.

In our study, PCR was positive for 10 (31.2%) of 32 cases of TB meningitis and 8 (20.5%) of encephalitis and aseptic meningitis.

The sensitivity of PCR in detecting CNS infection was found to be low in this study.

CONCLUSION

The laboratory diagnosis of CNS infections still remains as a dilemma due to considerable overlap in findings. CSF findings of moderate lymphocytic predominant leukocytosis with low CSF-to-plasma glucose ratio and an increased protein concentration in a patient with longer duration of symptoms are suggestive of TB meningitis. The yield of CSF AFB stain was found to be poor. None of our patients had a positive AFB stain. The yield of Gram staining and culture of CSF was found be less probably due to early treatment with antibiotics. *S. pneumoniae* is found to be the most common etiological agent associated with bacterial meningitis. PCR was found to be not of much use in the diagnosis since it was found to be positive only in less than one-third of the patients. Neuroimaging is not mandatory before LP unless there is a definite indication, since in most of our patients, imaging was found to be normal. Routine CSF cell count and biochemical analysis are of prime importance in differentiating between CNS infections and identifying individual CNS infections.

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How to cite this article: Vasanthan K, Verghese Y, Singh RBS, Damodharan J, Vengadakrishnan K. Profile of Cerebrospinal Fluid Analysis in Acute Central Nervous System Infections. Int J Sci Stud 2018;6(1):99-103.

Source of Support: Nil, **Conflict of Interest:** None declared.