Original Research Article

Microbiological study of cerebrospinal fluid in suspected cases of central nervous system infection

Shivprasad Mundada[1], Pushpa Yadav[2*]

[1]Professor & HOD, [2]Junior Resident, Department of Paediatrics, Vilasrao Deshmukh Government Institute of Medical Sciences, Latur, Maharashtra, INDIA.
Email: dhanmati25@gmail.com

Abstract

Background: Central nervous system (CNS) infections are the infections involving the brain (cerebrum and cerebellum), spinal cord, optic nerves, and their covering membranes and is a life- threatening condition. A detailed examination and an extensive diagnostic workup is needed as many conditions, such as infections are well treatable. The present study is an attempt to diagnose the etiology of the suspected CNS infection in paediatric population so as to contribute in better outcome of the patients. **Material and Methods:** Present study was single-center, descriptive study conducted in children between 1month to 12 years of age admitted in Paediatric ward of tertiary care center with clinical features suggestive of CNS infection. The primary data was collected by interviewing the parents of the children between 1month to 12 years with suspected central nervous system infection admitted in the Paediatric ward of the tertiary care center. The secondary data was collected from the clinical examination and the laboratory investigations of the patients. **Results:** Total 90 cases of suspected central nervous system infection were studied. maximum number of patients (48.9%) belonged to 2-5 years age group and least cases (8.9%) from 11-15 years of age group. Male were 51 (56.7%) and females 39 (43.3%) of all cases with M:F ratio of 1.3:1. The presenting features included fever in all 90 cases (100%), altered sensorium in 70(77.8%), seizures in 87(96.7%), posturing in 23(25.6%) and signs of meningitis like irritability, headache, vomiting, neck rigidity in 64(71.1%) cases. The mean age was 4.8±3.3 years. The mean weight of cases was 15.3±6.3 kgs. The mean hemoglobin Hb was 10.09±1.48 g/dl. The mean blood WBC was 13388.4±6747.9 /cumm. The mean CSF protein and sugar were 47.2±33.7 mg/dl and 44.29±25.3 mg/dl. Diagnosis of viral meningitis/encephalitis was made in 50 cases (55.6%), bacterial in 30 (33.3%), TBM in 8 (8.9%), and Rickettsial and Fungal (Candida albicans) meningitis in 1 (1.1%) case each. Outcome wise, total deaths i.e. case fatality rate (CFR) was 13 (14.4%) and 74 (82.2%) patients were discharged. **Conclusion:** Most common cause of CNS infection in children is viral meningitis/encephalitis, however below 1 year of age the most common cause is bacterial meningitis. The most common age group affected is below 5 years of age. Male children are more commonly affected than females. However, definitive diagnosis could be made in less proportion of cases. Thus, it ascertains the fact that it may not be able to identify the etiology of CNS infection in many cases from CSF study alone and we have to rely on the history, clinical findings and other supportive investigations to come to a probable diagnosis.

Keywords: viral meningitis/encephalitis, CNS infection, CSF study, meningitis

[*]**Address for Correspondence:**
Dr Pushpa Yadav, Junior Resident, Department of Paediatrics, Vilasrao Deshmukh Government Institute of Medical Sciences, Latur, Maharashtra 413512, INDIA.
Email: dhanmati25@gmail.com

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INTRODUCTION

Central nervous system (CNS) infections are the infections involving the brain (cerebrum and cerebellum), spinal cord, optic nerves, and their covering membranes.[1] Infection of the central nervous system (CNS) is a life- threatening condition, especially In paediatric population which needs an immediate attention from the attending physician or surgeon, the clinical pathologist as well as the microbiologist. The incidence of acute encephalitis syndrome (AES) in western countries is 7.4 per 100,000

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population per year. In tropical countries like India, it is 6.4 (3.5 to 7.4) per 100,000 population per year.[2] Around 0.5 to 2.6% of hospital admissions are acute bacterial meningitis (ABM) with mortality of around 16-30% in developing nations.[3] The common causes of ABM are different depending on patient's age and most common ones in first two months of life are Group B streptococci (GBS), gram-negative bacilli and Listeria monocytogenes. Beyond this age the common pathogens are Streptococcus pneumoniae, Neisseria meningitidis and Haemophilus influenzae type b.[4] A detailed examination and an extensive diagnostic workup is needed as many conditions, such as infections are well treatable. The present study is an attempt to diagnose the etiology of the suspected CNS infection in paediatric population so as to contribute in better outcome of the patients.

MATERIAL AND METHODS

Present study was single-center, descriptive study conducted in department of paediatrics with help of department of microbiology at XXX medical college and hospital, XXX, India. Study duration was of 18 months. Approval from the Institutional Ethics Committee was taken before starting the study in the tertiary care center. A prior informed consent was obtained from the parents of all the cases.

INCLUSION CRITERIA:

- All the children between 1month to 12 years of age admitted in Paediatric ward of tertiary care center with clinical features suggestive of CNS infection such as fever or history of fever (>38°C), encephalopathy (altered level of consciousness persisting >24 hours), convulsions, lethargy/ irritability, change in personality and behaviour, neck rigidity, Kernig's sign/ Brudzinski's sign and photophobia

EXCLUSION CRITERIA:

- Patients who are known case of seizure disorder or febrile convulsions
- Patients with non-infectious CNS disorders due to hypoxic, ischaemic, vascular, toxic and metabolic causes.

On admission, details of the patients in terms of age, gender and address were noted. The parents were interviewed about the complaints pertaining to central nervous system like fever, convulsions, altered consciousness or behaviour; past and family history holding importance with respect to central nervous system involvement like immunization, developmental, seizure disorder, history of chronic infections or conditions like tuberculosis, immunocompromised states, diabetes, hypertension, surgery and medications. The patients were then thoroughly examined including anthropometry and signs of meningitis or raised intracranial pressure like neck rigidity, Kernig's and Brudzinski's sign, bulging anterior fontanelle and papilledema and Glasgow coma scale scoring was done for all patients. Basic blood investigations done were complete blood count, liver and kidney function test, serum electrolyte, and blood sugar level. Blood culture and sensitivity by BACTEC method was done in all cases. Other tests done as per indications of the case were Dengue Rapid antigen test, Widal test, Peripheral smear (PS) for malarial parasite, Weil-Felix test, arterial blood gas (ABG), erythrocyte sedimentation rate (ESR), C-Reactive protein (CRP), HIV, HBsAg and CBNAAT of gastric lavage, sputum and Mantoux test. Cerebrospinal fluid (CSF) was collected by lumbar puncture and sent for routine microscopy, biochemistry for protein and sugar levels, staining like Gram and AFB, culture and sensitivity, CSF CBNAAT (Gene-Xpert for MTB) and CSF sample to National Institute of Virology, Pune for virology study with filled form like JE IgM antibody, HSV PCR etc. Imaging studies were also done like Chest Xray, USG(A+P), USG skull, CT brain and MRI brain based on the indications. The primary data was collected by interviewing the parents of the children between 1month to 12 years with suspected central nervous system infection admitted in the Paediatric ward of the tertiary care center. The secondary data was collected from the clinical examination and the laboratory investigations of the patients. Data was collected and compiled using Microsoft Excel, analysed using SPSS 23.0 version. Difference of proportions between qualitative variables were tested using chi- square test or Fisher exact test as applicable. P value less than 0.5 was considered as statistically significant.

RESULTS

Total 90 cases of suspected central nervous system infection admitted in Paediatric ward of the tertiary care center were included in the study based on the inclusion and exclusion criteria. maximum number of patients (48.9%) belonged to 2-5 years age group and least cases (8.9%) from 11-15 years of age group. Male were 51 (56.7%) and females 39 (43.3%) of all cases with M:F ratio of 1.3:1.

Table 1: Age and gender distribution

Age group in years	Frequency	Percent
≤ 1	11	12.2
2 to 5	44	48.9
6 to 10	27	30.0
11 to 15	8	8.9
Gender		
Female	39	43.3
Male	51	56.7

The presenting features included fever in all 90 cases (100%), altered sensorium in 70(77.8%), seizures in 87(96.7%), posturing in 23(25.6%) and signs of meningitis like irritability, headache, vomiting, neck rigidity in 64(71.1%) cases.

Table 2: Clinical features and history

Clinical features and history	Present		Absent	
	Frequency	Percent	Frequency	Percent
Seizures	87	96.7	3	3.3
Altered sensorium	70	77.8	20	22.2
Posturing	23	25.6	67	74.4
Significant past history related to CNS	4	4.4	86	95.6
Significant family history related to CNS	4	4.4	86	95.6
Signs of meningitis	64	71.1	26	28.9

The mean age was 4.8±3.3 years. The mean weight of cases was 15.3±6.3 kgs. The mean hemoglobin Hb was 10.09±1.48 g/dl. The mean blood WBC was 13388.4±6747.9 /cumm. The mean CSF protein and sugar were 47.2±33.7 mg/dl and 44.29±25.3 mg/dl.

Table 3: general characteristics

characteristics	Mean ± Std. Deviation
Age (years)	4.87 ± 3.33
Weight (kg)	15.31 ± 6.37
Head circumference (cm)	50.63 ± 2.91
Hb (g/dL)	10.09 ± 1.48
WBC	13388.44 ± 6747.93
Lymphocytes %	77.56 ± 28.09
CSF protein	47.42 ± 33.70
CSF sugar	44.29 ± 25.39

CSF was yellow in 2.2% cases and overall macroscopic appearance of CSF was turbid in 15(16.7%) cases. CSF Gram staining for Gram negative bacilli was seen in 4 cases (4.4%) and Gram-positive cocci in 4(4.4%) cases. The ZN staining showed acid fast bacilli (AFB) in 2 cases (2.2%). The total blood leukocyte count was >11000 in 54 (60%) cases. CSF cell count in majority patients 69 cases (76.6%) ranged from 10 to 99 cells/cumm. and 100-1000/cumm. in 19(21.1%) cases of which maximum were bacterial meningitis. Polymorphs were more than 50% of all cells in 16(17.8%) cases, all of which were bacterial meningitis. CSF protein was raised i.e. >45mg/dl in 32(35.6%) cases particularly in cases of bacterial meningitis (76.7%) and TBM cases. CSF glucose was low i.e. <40mg/dl in 45(50%) of total cases with 76.7% cases of bacterial meningitis and 87.5% of TBM cases. CSF CBNAAT (Cartridge based nucleic acid amplification test) showed mycobacterium in 1 (1.1%) case. CSF detection of viral agent showed JE IgM positive in 1 case (1.1%). Dengue Rapid test was positive in 7 cases of which NS1 positive was seen in 3 cases (3.3%), IgM positive in 2(2.2%), both IgM and IgG positive in 1(1.1%) and both NS1 and IgM positive in 1case (1.1%). The Widal test was positive in 4 cases (4.4%).

Table 4: Cerebrospinal fluid (CSF) characteristics

Cerebrospinal fluid (CSF) characteristics	Frequency	Percent
Cerebrospinal fluid (CSF) colour - Yellow	2	2.2
Cerebrospinal fluid (CSF) Appearance - Turbid	15	16.7
No Cerebrospinal fluid (CSF) cob web	90	100.0
Cerebrospinal fluid (CSF) Gram Staining		
Gm - Bacilli	4	4.4
Gm + cocci	4	4.4
Not seen	82	91.1

Cerebrospinal fluid (CSF) Ziehl- Nielsen staining - AFB seen	2	2.2
Blood White Blood Cells (WBCs)		
< 4000	5	5.6
4000-11000	31	34.4
> 11000	54	60.0
Cerebrospinal fluid (CSF) Total leukocyte count (TLC)		
6 to 9	2	2.2
10 to 99	69	76.7
100 to 1000	19	21.1
Cerebrospinal fluid (CSF)Polymorphs		
≤ 50	74	82.2
> 51	16	17.8
CSF protein mg/dl		
< 15	1	1.1
15-45	57	63.3
> 45	32	35.6
Cerebrospinal fluid (CSF) sugar		
< 40	45	50.0
40-70	38	42.2
> 70	7	7.8
Cerebrospinal fluid (CSF) CBNAAT Positive	1	1.1
Cerebrospinal fluid (CSF) JE IgM positive	1	1.1
negative	89	98.9
Dengue Rapid test		
Negative	83	92.2
Positive IgM	2	2.2
Positive IgM/IgG	1	1.1
Positive NS1	3	3.3
PositiveNS1/IgM	1	1.1
Widal test Positive	4	4.4
PS for MP - negative	90	100.0

The aetiological diagnosis with evidence of etiology in CSF could be made in 1 case for viral encephalitis with JE IgM positive, CSF culture showed growth in 12 cases of bacterial meningitis, CSF CBNAAT detected Mycobacterium in 1 case, Gastric lavage CBNAAT in 1 case and CSF Gram staining was positive in total 8 cases and ZN staining for AFB in 2 cases. Otherwise, based on history, clinical features, CSF analysis and other diagnostic tests, diagnosis of viral meningitis/encephalitis was made in 50 cases (55.6%), bacterial in 30 (33.3%), TBM in 8 (8.9%), and Rickettsial and Fungal (Candida albicans) meningitis in 1 (1.1%) case each.

Table 5: Aetiology of CNS infection

Aetiology of CNS infection	Frequency	Percent
Bacterial	30	33.3
Fungal	1	1.1
TBM	8	8.9
Rickettsial	1	1.1
Viral	50	55.6
Total	**90**	**100.0**

The blood culture showed growth in 22 cases of which MRSA was seen in 6(6.7%); Salmonella enteritidis and Streptococcus pyogenes in 3 cases each(3.3%); Non-fermenters and Pseudomonas aeruginosa in 2 cases each(2.2%); Streptococcus pneumoniae, Group B Streptococcus, E. coli, Citrobacter, Acinetobacter and Candida albicans in 1 case each(1.1%). CSF culture showed growth in 12 cases of which Salmonella enteritidis, Pseudomonas aeruginosa, MRSA and Non-fermenters were seen in 2(2.2%) cases each while E. coli, CoNS, Citrobacter, Acinetobacter were seen in 1 case each (1.1%).

Table 6: Blood and Cerebrospinal fluid (CSF) culture of organisms.

	Blood culture growth		Cerebrospinal fluid (CSF) culture	
organism	Frequency	Percent	Frequency	Percent
Acinetobacter spp	1	1.1	1	1.1
Citrobacter spp	1	1.1	1	1.1

E.Coli spp	1	1.1	1	1.1
MRSA	6	6.7	2	2.2
Pseudomonas aeruginosa	2	2.2	2	2.2
Salmonella ENTERITIDIS	3	3.3	2	2.2
streptococcus pneumoniae	1	1.1		
Grp B streptococcus	1	1.1		
streptococcus pyogenes	3	3.3		
Candida Albicans	1	1.1		
Cons			1	1.1
Non-fermenters	2	2.2	2	2.2
No growth	68	75.6	78	86.7
Total	**90**	**100.0**	**90**	**100.0**

There is a significant (p=0.001) correlation between age group and etiology with maximum patients (56.7%) of bacterial meningitis in age group 2-5 years while viral meningitis is mainly seen in both 2-5 years and 6-10 years of age group (42% each).

Table 7: Correlation of age group with etiology

Age group in years	Bacterial (n=30)	Fungal (n=1)	Rickettsia l (n=1)	TBM (n=8)	Viral (n=50)	total
≤ 1	9 (30 %)	1 (100 %)	0	1 (12.5%)	0	11
2 to 5	17 (56.7 %)	0	1 (100 %)	5 (62.5%)	21 (42%)	44
6 to 10	4 (13.3 %)	0	0	2 (25%)	21 (42%)	27
11 to 15	0	0	0	0	8 (16%)	8

Chi square-34.72, p-0.001, Significant

Outcome wise, total deaths i.e. case fatality rate (CFR) was 13 (14.4%) and 74 (82.2%) patients were discharged.

Table 8: Outcome

Outcome	Frequency	Percent
DAMA	2	2.2
Death	13	14.4
Discharge	74	82.2
Referred	1	1.1

DISCUSSION

In our study, prevalence of CNS infection was maximum in the age group of 2-5 years (48.9%, 44 cases) which is in accordance with study by S.A Karmarkar *et al.*[5] and C.M. Bokade *et al.*[6] where too the mean age group was 3.2±2.9 years. The male to female ratio M:F in present study is 1.3:1 which is comparable to studies by Garg *et al.*[4], SK Rathore *et al.*[2], SA Karmarkar *et al.*[5] and Debnath *et al.*[7] where the M:F ratio is 2:1, 1.6:1, 1.7:1 and 1.8:1 respectively. The lower prevalence in females can be attributed to production of gamma-globulin regulated by certain factors on X chromosome.[4,8] The higher incidence of CNS infections in males compared to females can also be explained by the time spent outdoor by male children and indulging in unhygienic activities resulting in an increased exposure to certain vectors and agents which might increase the risk of infection.[9] The Case fatality rate (CFR) in present study was 13(14.4%) which is comparable to studies by Garg *et al.* (10.5%)[4,] Debnath *et al.* (13.9%)[7] and C.M. Bokade *et al.*[6] (19.3%). The presenting features included fever in all 90 cases (100%), altered sensorium in 70 (77.8%), seizures in 87 (96.7%), posturing in 23 (25.6%) and signs of meningitis like irritability, headache, vomiting, neck rigidity in 64(71.1%) cases. This is higher when compared to the results of SK Rathore *et al.*[2] where convulsion was seen in 46.7%, and signs of meningitis in 26.2% cases, Adhikary *et al.*[10] study fever in 100% and meningeal signs in 46.9% cases, SA Karmarkar *et al.*[5] study seizures in 75.3% and meningeal signs in 59.64% cases and Garg *et al.*[4] study seizures in 45.6% cases. The diagnosis of viral meningitis/encephalitis was made in 50 cases (55.6%), bacterial in 30(33.3%), TBM in 8(8.9%), and Rickettsial and Fungal (candida albicans) meningitis in 1(1.1%) case each. This is similar to study by CM Bokade *et al.*[6] in which viral (46.59%), bacterial (22.16%), TBM (15.3%) and cerebral malaria in 15.9% of cases. Also, study done by Huttunen *et al.*[11], showed comparable results with aetiological agent identified in 56 cases (85%) of which 38%were bacterial meningitis, 45% viral meningitis/encephalitis, 16% neuroborreliosis, and 1 child with fungal (Candida albicans) infection. The CSF study in this present study supported the evidence of raised CSF leukocytes mostly>100/cumm., predominantly polymorphs, raised protein and low sugar in bacterial

meningitis compared to viral meningitis as is also evident in study conducted by Pandey *et al.*[12] CSF Gram staining showed Gram positive cocci and Gram -negative bacilli in 4 cases each out of which 7 cases also showed growth of organism on CSF culture. CSF ZN staining detected AFB in 2 cases while CBNAAT detected mycobacterium in CSF of 1 case and gastric lavage of 1 case. The viral etiology of CNS infection was considered in 50 cases (55.6%) more prevalent in age group of 2-10 years, of which only one case was JE IgM positive. SA Karmarkar *et al.*[5] noted most common viral cause was Enterovirus followed by JEV and HSV. In 2014, SK Rathore *et al.*[2] did a study which showed HSV I or II as most common cause followed by measles, JEV and DENV. Huttumen *et al.*[11] conducted a study in which enteroviruses were most common accounting for 22% of all viruses and 44% of proven meningitis/encephalitis. Other common viruses were VZV and HHV6. The CSF and blood were sent for culture in institute's microbiology laboratory prior to starting antibiotic. Bacterial meningitis was diagnosed in 30(33.3%) cases, maximum number of cases in age group of 2-5 years followed by less than 1 year of age; of which CSF culture positive were 12(13.3%) cases, blood culture positive 22(24.4%) cases and both CSF and blood culture positive 3 cases (MRSA (2) and Salmonella enteritidis (1)). This lower rate of detection of bacteria in CSF is comparable to study conducted by Garg *et al.*[4] and Debnath *et al.* (13.9%)[7] which can be attributed to prior use of antibiotic, contamination of blood culture sample and poor quality of blood culture medium. The most common organism isolated in blood was MRSA in 6 cases and in CSF were MRSA, Salmonella enteritidis, Non-fermenters and Pseudomonas aeruginosa in 2 cases each. Pyogenic meningitis was most common cause in studies by SA Karmarkar *et al.*[5], Garg *et al.*[4], Adhikary *et al.*[8] and Debnath *et al.*[7] where the common bacterial isolates from both CSF and blood were Klebsiella pneumoniae, followed by Non-fermenters and Streptococcus pyogenes. E. coli and Staphylococcus aureus were the most common cause of pyogenic meningitis in the study by Adhikary *et al.*[8] as seen in our present study. Chinchankar *et al.*[13] did the study on diagnosis of acute bacterial meningitis in early childhood age between 1month to 5 years. CSF was turbid in majority of cases (85%), CSF proteins ranged 40-660 mg/dl, sugar 8-72 mg/dl, and leukocytes 40- 10000/cmm, majority of leukocytes were neutrophils and 10 children (19%) showed 10-30% lymphocytes. CSF culture was positive in 27 (50%) cases and etiology based on culture was S. pneumoniae in 21 (39%) and H. Influenzae type b in 14 (26%), 2 (3.6%) each were positive for Pseudomonas, Staphylococcus and streptococci (beta hemolytic) and 1 each for Streptococcus pyogenes and Citrobacter in 1 (1.3%) each. The results in this present study are consistent with the above results of Chinchankar *et al.*[13] Tubercular meningitis was diagnosed in 8 (8.9%) cases 5 were in age group of 2-5 years. Similar prevalence of TBM was found in study by SA Karmarkar *et al.*[41] where TBM cases accounted for 7.9% of total cases, while it was higher in study conducted by CM Bokade *et al.*(58) where TBM was diagnosed in 15.3% cases. Since CNS infections can be caused by almost any agent like bacteria, viral, tubercular, fungal, rickettsial; a wide panel of agents should be studied wherever feasible. In settings with resources constrains, depending upon the symptoms and examination findings, the most specific viruses can be studied. However, considering that delaying treatment can lead to severe morbidity in form of neurological sequalae and morbidity, it is always beneficial to begin the antibacterial or antiviral treatment empirically even before the results of CSF panel study is received. Treatment with steroids and anticonvulsants should be based on clinical judgement.

CONCLUSION

Most common cause of CNS infection in children is viral meningitis/encephalitis, however below 1 year of age the most common cause is bacterial meningitis. The most common age group affected is below 5 years of age. Male children are more commonly affected than females. However, definitive diagnosis could be made in less proportion of cases. Thus, it ascertains the fact that it may not be able to identify the etiology of CNS infection in many cases from CSF study alone and we have to rely on the history, clinical findings and other supportive investigations to come to a probable diagnosis.

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