

Original Research Article

Burden of central nervous system infection in cases of fever with seizure and its association with outcome: an experience in a tertiary care center of Uttarakhand, India

Ramesh Chand, Yuvraj Sharma*, Ritu Rakholia

Department of Pediatrics, Government Medical College, Haldwani, Nainital, Uttarakhand, India

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***Correspondence:**

Dr. Yuvraj Sharma,

E-mail: yuvrajsharmamd@gmail.com

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ABSTRACT

Background: CNS infections have been linked to adverse neurological sequelae notably seizures and mortality. Although, various etiologies of AFE have been studied, but the mystery still remains untangled for the substantial risk factors for the diagnosis and outcome.

Methods: This prospective study was carried out on 67 children between 2 months to 15 years, from (May 2016 to April 2017) tertiary care centre of Uttarakhand. Patients were analysed for demographic variables, haematological parameters, CSF analysis, neuroimaging and their outcome was assessed at one month of follow up.

Results: This study showed, 70% (n=47) of the cases presented in acute febrile encephalopathy. Most cases were diagnosed with pyogenic meningitis (40%, n=27) and More commonly occur during rainy season (39%; n=26) radiologically meningeal enhancement (28%; n=18) as the most common finding. Cases of acute febrile encephalopathy with GCS ≤ 5 had significant association with mortality. (Fischer exact value of 0.005; significant at $p < 0.05$).

Conclusions: Clinical signs of meningitis are not always reliable, and a laboratory support is required to reach early diagnosis hence. Pseudomonas and MRCONS were the major pathogens responsible for the bacterial meningitis among the paediatric age groups, hence antibiotic management should be planned intensively while culture reports are awaited. Cluster of cases with meningoencephalitis were found in rainy season hence suggested possible etiologies are JE/ Scrub/ Enterovirus. Mortality as well as morbidity was high in cases with acute encephalitis syndrome cause? JE/unknown etiology in this era for modern medicine hence vector control strategies be encouraged.

Keywords: Acute febrile encephalopathy, Central nervous system infection, Encephalitis, Meningitis, Seizure

INTRODUCTION

Distinct presentations and devastating tolls of the central nervous system (CNS) infections have always drawn an appetite of interest among the clinicians. Whistle-stop progression of the disease often makes it difficult to understand the underlying leading pathology. Neurological tragedies like meningitis and encephalitis

still prevail in this modern era of medicine among the leading illnesses in pediatrics despite current healthcare policies. Encephalitis manifests as a syndrome of altered mental status accompanied with fever and/or seizures, neurologic deficits.¹ It is characterized by CSF pleocytosis, electroencephalographic and radiological abnormalities. CNS infections have had an upper hand for the causation of non-traumatic coma and acute febrile

encephalopathy (AFE) in developing countries.² Due to varying etiologies, characteristic risk factors for susceptibility, geographic and seasonal patterns of CNS infections remain poorly understood.^{3,4}

CNS infections often pose as an immediate life-threatening emergency to the diseased, by issuing an ultimatum of challenging diagnostic and therapeutic demands to a pediatrician. India is in a phase of diagnostic dilemma, where newer etiologies of CNS infections await revisions in diagnostic tests for improved accuracy and antibiotic therapies for the management. Present study is based on such stories which set the path towards a learning culture which would further evolve our practice standards.

METHODS

This study is an observational prospective study and was carried out in Dr. Susheela Tiwari Hospital, GMC Haldwani from May 2016 to April 2017. Patients satisfying the inclusion criteria and exclusion criteria were enrolled into the study, after getting written informed consent from the parents/guardians.

Inclusion criteria

- Children from age group 1 month to 15 years presenting with fever with seizures in the Emergency Department and Pediatrics wards.

Definitions used for the diagnosis and study purpose are defined in Table 1.

Exclusion criteria

- Hypoglycemia <70mg/dl
- Hypoxia with partial pressure of oxygen < 60 mmHg
- Patients with traumatic coma
- Febrile convulsions
- Cerebral palsy
- Epilepsy
- Intracranial space occupying lesion
- Endocrinal encephalopathy.

A detailed history in all cases was taken with emphasis on the onset of first seizure, duration of seizure, number of seizures, type of seizure, antenatal, natal and post-natal risk factors. Thorough clinical examination was done including vitals, general physical examination and systemic examination with special reference to central nervous system. Patients were divided into four age groups: age group (1-month to 12 months), (13 months to 5 years), (6-10 years) and (11-15 years). The following information was obtained from each patient: age, sex, type of seizure, associated symptoms (fever, cough, rhinorrhoea, vomiting, diarrhoea and headache, and family history of seizure or epilepsy, etc). Laboratory tests (haemogram, C-reactive protein, serum electrolytes, blood sugar, microbiological studies etc) were done.

Table 1: Definitions.

Definitions used for the diagnosis	
Acute febrile encephalopathy (AFE)	Acute onset of fever (less than or equal to 14 days) with altered mental status lasting for more than 4 hours ± seizures. ⁵
Pyogenic meningitis (PM)	Fever ± altered sensorium (without focal symptoms/signs) ± neck signs + CSF cytology (predominantly polymorphs) + biochemistry ± abnormal neuroimaging study. ⁶
Tubercular meningoencephalitis (TBM)	Fever ± altered sensorium + typical CSF picture (mainly lymphocytes) with or without abnormal neuroimaging study. ⁶
Cerebral malaria (CM)	Fever + altered sensorium + blood smear positive for malarial parasite. ³
Aseptic meningitis (AM)	Fever ± neck signs + CSF normal or mild pleocytosis + biochemistry + absence of bacteria on direct microscopy or culture ± abnormal neuroimaging study + no other alternative diagnosis. ⁷
Acute encephalitis syndrome cause? JE/unknown agent (AES)	Acute (≤14 days) onset of fever with altered sensorium ± seizures + CSF normal or mild pleocytosis + biochemistry + absence of bacteria on direct microscopy or culture ± abnormal neuroimaging study + no other alternative diagnosis. ⁸

Neuroimaging: computed tomography (CT) scan head or cranial magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) analysis was done wherever indicated and results were recorded. The laboratory tests were performed in the distinct laboratories of clinical analysis of the Dr. Susheela Tiwari Government Medical College, using their habitual methodology and techniques. The decision to perform a lumbar puncture was made by the patient's attending paediatrician and conducted after the obtained permission from the child's parent/guardian. CSF samples were examined for total WBC count, WBC differential, gram staining, acid fast staining, protein concentration, glucose concentration, and bacterial culture. According to the duration of illness, clinical presentation, CSF analysis and brain imaging studies, patients were sub classified according to their aetiology.

Statistical analysis

Statistical analysis descriptive statistics were expressed as number and percentages. Data was analysed using Microsoft excel 2016 and SPSS statistical software 24.0. The values were expressed as mean and percentages.

Fisher's exact test was used as the test of significance. P-value ≤ 0.05 was considered statistically significant.

RESULTS

Out of all the cases presenting with fever with seizures; a total of 67 cases were diagnosed as the cases of neurological illness of infective origin. These cases were further studied as a case of CNS infection (Figure 1).

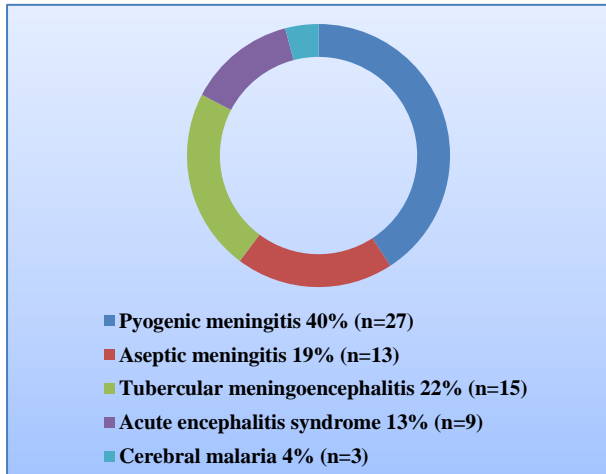


Figure 1: Incidence of CNS infections in cases of fever with seizures (percentage of cases).

Most of these cases had pyogenic meningitis as the diagnosed aetiology, with 40% (n=27) cases belonging to the category. Thirteen percent (n=9) cases presented with acute onset of fever and seizures with altered sensorium and were diagnosed with acute encephalitis syndrome cause? JE/ unknown agent.

Maximum cases of CNS infections lied in the age group of 13 months to 5 years. Majority of the cases of pyogenic meningitis (51%; n=14) were in the age group of 1 months to 12 months; and the cases of AES cause? JE/ unknown agent presented in the children with 6 years to 10 years of age (Table 2).

Most of the cases with CNS infections were found to occur during rainy season (39%; n=26); especially the

cases of acute encephalitis syndrome were found to be clustered in the rainy season (89%; n=8) (Figure 2).

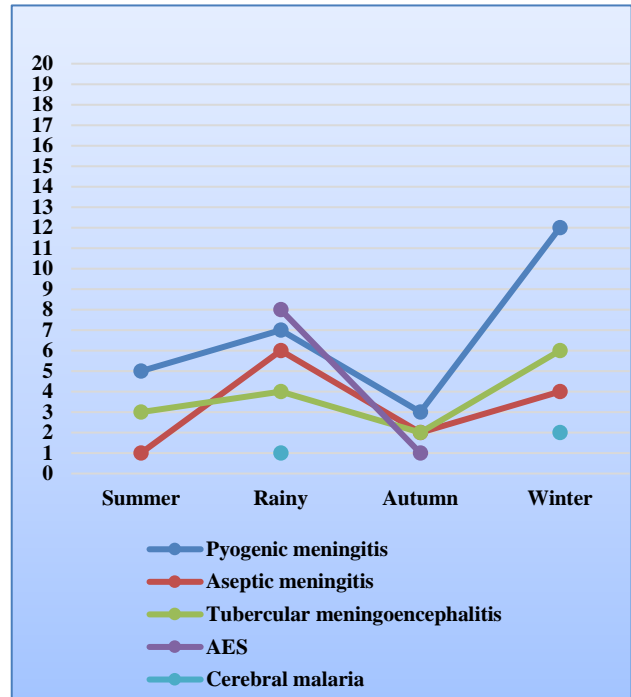


Figure 2: Seasonal distribution of the cases of CNS infections in cases with fever with seizures.

CNS infections were predominant in male population in the current study, with 57% (n=38) cases under the category. Majority of the cases belonged to rural residence (55%; n=37). Most of the cases had of generalized tonic-clonic seizures (97%; n=65) and had moderate grade fever (61%; n=41) at the time of admission. URTI (43%; n=29) was identified as the most common predisposing illness among the cases. Anaemia was very common and was diagnosed in 49% (n=33) cases (Table 3).

The clinical presentation of the cases, fever at the time of admission and vomiting were the major presentation states. All of the cases of AES cause? JE/ unknown agent presented in altered sensorium (100%; n=9); with status epileptics in 67% (n=67) cases. (Table 4).

Table 2: Age distribution of the cases.

Age groups ↓ / diagnosis →	PM (N=27)	TBM (N=15)	AM (N=13)	AES (N=9)	CM (N=3)	Men. total (N=64)	Grand total (N=67)
1 month to 12 months	14 (51%)	3 (20%)	2 (15%)	-	1 (33%)	19 (30%)	20 (30%)
13 months to 5 years	9 (33%)	4 (27%)	5 (38%)	3 (33%)	1 (33%)	21 (33%)	22 (33%)
6 years to 10 years	4 (15%)	7 (47%)	4 (31%)	5 (56%)	1 (33%)	20 (31%)	21 (31%)
11 years to 15 years	-	1 (7%)	2 (15%)	1 (11%)	-	4 (6%)	4 (6%)

Abbreviations: PM- Pyogenic meningitis, TBM- Tubercular meningoencephalitis, AM- Aseptic meningitis, AES- Acute encephalitis syndrome, CM-Cerebral (severe) malaria, Men- total- total cases of meningoencephalitis

Table 3: Clinical history and epidemiological profile in the cases.

Clinical history/ epidemiological profile ↓	Characteristics subtype ↓ /diagnosis →	PM (N=27)	AM (N=13)	AES (N=9)	TBM (N=15)	CM (N=3)	Men. (N=64)	Grand total (N=67)
Sex	Male	15 (55%)	10 (76%)	3 (33%)	7 (47%)	3 (100%)	35 (55%)	38 (57%)
	Female	12 (44%)	3 (23%)	6 (66%)	8 (53%)	-	29 (45%)	29 (43%)
Residence	Urban	10 (37%)	5 (38%)	4 (44%)	9 (60%)	2 (67%)	28 (44%)	30 (45%)
	Rural	17(62%)	8 (62%)	5 (56%)	6 (40%)	1 (33%)	36 (56%)	37 (55%)
Mode of onset of illness	Acute	17 (63%)	13 (100%)	5 (33%)	9 (100%)	3 (100%)	44 (69%)	47 (70%)
	Subacute	10 (37%)	-	6 (40%)	-	-	16 (25%)	16 (24%)
	Chronic	-	-	4 (27%)	-	-	4 (6%)	4 (6%)
Character of seizure	GTCS	27 (100%)	13 (100%)	8 (89%)	15 (100%)	2 (67%)	63 (98%)	65 (97%)
	Focal seizures	-	-	1 (11%)	-	1 (33%)	1 (2%)	2 (3%)
Temperature at the time of admission	Afebrile	7 (26%)	1 (8%)	-	2 (13%)	-	10 (16%)	10 (15%)
	Low grade	2 (33%)	1 (8%)	3 (3%)	7 (46%)	1 (33%)	13 (20%)	14 (21%)
	Moderate grade	17 (63%)	11 (84%)	6 (66%)	5 (33%)	2 (67%)	39 (61%)	41 (61%)
	High grade	1 (4%)	-	-	1 (7%)	-	2 (3%)	2 (3%)
Presentation	Status epilepticus	2 (7%)	1 (8%)	6 (67%)	2 (13%)	-	11 (17%)	11 (16%)
Duration of seizure	Less than 5 minutes	11 (41%)	2 (7%)	3 (33%)	7 (47%)	1 (33%)	23 (36%)	24 (36%)
	5 to 15 minutes	16 (59%)	11 (85%)	6 (67%)	8 (53%)	2 (67%)	41 (64%)	43 (64%)
Birth history	Perinatal asphyxia	5 (19%)	2 (15%)	-	3 (20%)	-	8 (13%)	8 (12%)
Parental history	Consanguinity of parental marriage	15 (56%)	10 (77%)	8 (89%)	5 (33%)	2 (67%)	38 (59%)	40 (60%)
Family history	FHFS	4 (15%)	1 (8%)	-	3 (20%)	-	8 (13%)	8 (12%)
	FHE	6 (22%)	-	-	1 (6%)	-	7 (11%)	7 (10%)
Predisposing illness	URTI	9 (33%)	5 (38%)	4 (44%)	11(73%)	-	29 (45%)	29 (43%)
	GE	6 (22%)	6 (46%)	4 (44%)	2 (13%)	3 (100%)	18 (28%)	21 (31%)
	Pneumonia	3 (11%)	2 (15%)	-	2 (13%)	-	7 (11%)	7 (10%)
	UTI	3 (11%)	-	1(11%)	-	-	4 (6%)	4 (6%)
Haematological parameters	Acuteotitis media	6 (22%)	-	-	-	-	6 (9%)	6 (9%)
	Anaemia	16 (59%)	6 (40%)	3 (33%)	5 (33%)	3 (100%)	30 (47%)	33 (49%)
	Hyponatremia	9 (33%)	2 (13%)	2 (22%)	5 (33%)	2 (67%)	18 (28%)	20 (30%)

Table 4: Clinical Presentation in the cases.

Clinical presentation ↓ / Diagnosis →	PM (N=27)	AM (N=13)	TBM (N=15)	AES (N=9)	CM (N=3)	Men total (N=64)	Grand total (N=67)
Fever	20 (74%)	12 (92%)	13 (87%)	9 (100%)	3 (100%)	54 (84%)	57 (85%)
Status epilepticus	2 (7%)	1 (8%)	2 (13%)	6 (67%)	-	11 (17%)	11 (16%)
Headache	8 (30%)	10 (77%)	11(73%)	6 (67%)	2 (67%)	35 (55%)	37 (55%)
Vomiting	22 (81%)	13 (100%)	15 (100%)	8 (89%)	2 (67%)	58 (91%)	60 (90%)
Pallor	20 (74%)	9 (69%)	6 (40%)	3 (33%)	3 (100%)	38 (59%)	41 (61%)
Jaundice	-	-	-	-	-	-	-
Lymphadenopathy	-	-	12 (80%)	-	-	12 (19%)	-
Hepatomegaly	-	-	4 (27%)	-	1 (33%)	4 (6%)	5 (7%)
Splenomegaly	2 (7%)	-	4 (27%)	1 (11%)	2 (67%)	7 (11%)	9 (13%)
Meningeal signs	10 (37%)	10 (77%)	11 (73%)	7 (78%)	-	38 (59%)	38 (57%)
Papilledema	23 (85%)	5 (38%)	10 (67%)	7 (78%)	-	45 (70%)	45 (67%)
Altered mental status	-	-	14 (93%)	9 (100%)	3 (100%)	23 (36%)	26 (39%)
GCS <5	-	-	2 (13%)	4 (44%)	-	6 (9%)	6 (9%)
AFE	-	-	5 (33%)	9 (100%)	3 (100%)	14 (22%)	17(26%)
Hemiparesis	-	-	1 (7%)	1 (11%)	-	2 (3%)	2 (3%)
Para paresis	-	-	1 (7%)	1 (11%)	-	2 (3%)	2 (3%)
Speech disturbances	-	-	1 (7%)	1 (11%)	-	2 (3%)	2 (3%)
Cranial nerve palsy	-	-	2 (13%)	2 (22%)	-	4 (6%)	4 (6%)

Abbreviations: PM- pyogenic meningitis, TBM- tubercular meningoencephalitis, AM- aseptic meningitis, AES- acute encephalitis syndrome, CM- cerebral (severe) malaria, Men- total- total cases of meningoencephalitis, GCS- Glasgow com score, AFE- acute febrile encephalopathy

Table 5: Radiological profile in the cases.

Radiological findings (NC- CT /MRI) ↓ / Diagnosis	PM (N=27)	TBM (N=15)	AM (N=13)	AES (N=9)	Men. Total (N=64)
Meningeal enhancement	2 (7%)	3 (20%)	8 (62%)	5 (56%)	18 (28%)
Hydrocephalus	-	13 (87%)	-	-	13 (20%)
Vasculitis/ infarcts	-	8 (53%)	-	5 (56%)	13 (20%)
Granuloma	-	2 (13%)	-	-	2 (3%)
VP shunt	2 (7%)	-	-	-	2 (3%)

Abbreviations: PM- pyogenic meningitis, TBM- tubercular meningoencephalitis, AM- aseptic meningitis, AES- acute encephalitis syndrome, Men- total- total cases of meningoencephalitis, NC- CT- non-contrast computed tomography, MRI- magnetic resonance imaging, VP- ventriculo-peritoneal.

Table 6: CSF profile in the cases.

CSF profile parameters ↓	CSF analysis ↓ /Diagnosis →	PM (N=27)	AM (N=13)	TBM (N=15)	AES (N=9)	CM (N=3)	Men. total (N=64)	Grand total (N=67)
CSF appearance	Clear	-	11 (85%)	5 (33%)	5 (56%)	3 (100%)	21 (33%)	24 (36%)
	Turbid	23 (85%)	1 (8%)	5 (33%)	2 (22%)	-	31 (48%)	31 (46%)
	Clear faint xanthochromia	-	1(8%)	-	2 (22%)	-	3 (5%)	3 (4%)
	Turbid faint xanthochromia	4 (15%)	-	-	-	-	4 (6%)	4 (6%)
	Cobweb formation	-	-	5 (33%)	-	-	5 (8%)	5 (7%)
CSF cell count (Leucocytes/ μ L)	0-10	-	-	-	7 (78%)	3 (100%)	7 (11%)	10 (15%)
	10-100	27 (100%)	13 (100%)	12 (80%)	2 (22%)	-	54 (84%)	54 (81%)
	101-1000	-	-	3(20%)	-	-	3 (5%)	3 (4%)
	1001-5000	-	-	-	-	-	-	-
CSF Glucose (mg/dl)	10-45	19 (70%)	-	10 (67%)	1 (11%)	-	30 (47%)	30 (45%)
	46-65	3 (11%)	7 (54%)	2 (13%)	4 (44%)	2 (67%)	16 (25%)	18 (27%)
	65-100	5 (18%)	6 (46%)	3 (20%)	4 (44%)	1 (33%)	18 (28%)	19 (28%)
CSF Micro protein (mg/dl)	<15	-	-	-	-	-	-	-
	16-40	-	-	-	-	3 (100%)	-	3 (4%)
	41-100	22 (81%)	12 (92%)	4 (27%)	7 (78%)	-	45 (70%)	45 (67%)
	101-200	4 (15%)	1 (8%)	7 (47%)	2 (22%)	-	14 (22%)	14 (21%)
	201-500	1(4%)	-	4(27%)	-	-	5 (8%)	5 (7%)
	>500	-	-	-	-	-	-	-

Radiological evaluation of the cases revealed meningeal enhancement (28%; n=18) as the most common finding. Although the cases of the neuro-tuberculosis had broad spectrum of radiological presentations, but majority of the cases had hydrocephalus (87%, n=13) as the most common radiological pattern (Table 5).

CSF analysis was performed in the cases after prior consent from the attending guardians/ parents under strict sterile precautions.

The CSF analysis revealed that the turbidity of the CSF correlated to diagnosis of pyogenic meningitis (85%, n=23), and cobweb formation was seen in 33% (n=5) cases of tubercular meningoencephalitis. CSF glucose was decreased in the majority of the cases of meningoencephalitis (47%, n=30); especially pyogenic meningitis, with 70% (n=19) cases having low CSF glucose values.

Highly raised CSF micro protein was associated with the cases of tubercular meningoencephalitis; as 27% (n=4) cases had micro protein levels of 201-500mg/dl (Table 6).

Conventional methods were tested for the sensitivity and specificity analysis among the cases of meningoencephalitis. Blood culture was the most sensitive (59%) and CSF culture was the most specific (100%) microbiological investigation among the cases of meningoencephalitis. CSF- AFB was more sensitive (53%) and specific (100%) over Montoux test, for the diagnosis of tubercular meningitis (Table 7).

Cases of acute febrile encephalopathy with GCS \leq 5, when analyzed by Fisher exact test which revealed a significant association with mortality. (Fisher exact value of 0.005; significant at p<0.05) (Table 8).

The immediate outcome of the cases of CNS infections was evaluated at the end of one month. The cases of Aseptic meningitis had the best outcome with 92% (n=12) cases making complete recovery. 67% (n=6) cases

of AES cause? JE/ Unknown agent had further developed post encephalitis neurological sequelae that affected their activities of daily life and 16% (n=11) cases of CNS infection succumbed to the illness (Table 9).

Table 7: Microbiological profile in the cases.

Org. name	GS	Type	Body fluid	PM (N=27)	AM (N=13)	TBM (N=15)	AES (N=9)	Men. total (N=64)
MSCONS	GP	Cocci	Urine	-	-	-	-	1
			Blood	1	-	-	-	
			CSF	-	-	-	-	
MRCONS	GP	Cocci	Urine	-	-	-	-	8
			Blood	4	-	1	-	
			CSF	3	-	-	-	
Listeria	GP	Bacilli	Urine	-	-	-	-	1
			Blood	1	-	-	-	
			CSF	-	-	-	-	
<i>E. coli</i>	GN	Bacilli	Urine	1	-	-	-	2
			Blood	-	-	-	-	
			CSF	1	-	-	-	
Pseud.	GN	Bacilli	Urine	-	-	-	-	7
			Blood	4	-	1	-	
			CSF	2	-	-	-	
Proteus	GN	Bacilli	Urine	1	-	-	-	1
			Blood	-	-	-	-	
			CSF	-	-	-	-	
Acineto	GN	Bacilli	Urine	-	-	-	-	1
			Blood	-	-	-	-	
			CSF	1	-	-	-	

Abbreviations: PM- pyogenic meningitis, TBM- tubercular meningitis, AES- acute encephalitis syndrome cause? JE/unknown agent, Men. Total- total cases of meningoencephalitis, %- percentage, org- organism. GS- gram stain, Bo. Flu. Body fluids, MSCONS- methicillin sensitive coagulase negative staphylococcus aureus, MRCONS- methicillin resistant coagulase negative staphylococcus aureus, Pseud- Pseudomonas species. Proteus- proteus species, Acineto- Acinetobacter Baumannii, GP- gram positive, GNB- gram negative, org- organism

Table 8: Fisher exact test of significance.

Diagnosis ↓ / Outcome →	Mortality	Survived	Total	Fischer exact value	Significance
AFE + GCS <5	5	1	6	0.005	At P<0.05
AFE + GCS >5	1	10	11		

Table 9: Outcome analysis in the cases.

Outcome ↓ / Diagnosis →	PM (N=27)	AM (N=13)	TB (N=15)	AES (N=9)	CM (N=3)	Men. total (N=64)	Grand total (N=67)
Survival with complete recovery	24 (89%)	12 (92%)	-	-	2 (67%)	36 (56%)	38 (57%)
Survival with post encephalitis sequelae/ Partial recovery	-	-	12 (80%)	6 (67%)	-	18 (28%)	18 (27%)
Death	3 (11%)	1 (8%)	3 (20%)	3 (33%)	1 (33%)	10 (16%)	11 (16%)

Abbreviations: PM- pyogenic meningitis, TBM- tubercular meningoencephalitis, AM- aseptic meningitis, AES- acute encephalitis syndrome, CM- cerebral (severe) malaria, Men- total- total cases of meningoencephalitis

DISCUSSION

In the present study authors studied 67 children admitted in the tertiary center of Kumaon which caters to hilly areas of Kumaon and adjoining areas of Uttar Pradesh.

These cases formed a bulk of the cases that presented with fever with seizures and were diagnosed with an infective aetiology of the CNS. There were few significant differences between the pattern of aetiologies of CNS infections in Uttarakhand and elsewhere.

Authors found that out of all (158) the children admitted as the cases of fever with seizures, a total of 42% or 67 cases were diagnosed with an infective etiology of CNS. Among the cases of CNS infections, 40% (n=27) cases were of pyogenic meningitis, 19% (n=13) cases were of aseptic meningitis, 22% (n=15) cases were of tubercular meningitis, 4% (n=3) cases were of cerebral malaria with seizures. Similar results with acute bacterial meningitis predominating the cases evaluated for meningoencephalitis were also seen in other studies.^{5,6,8,9}

Ninety % (n=60) cases of meningoencephalitis presented with vomiting. Meningitis is studied to be associated with headache, fever and vomiting due to raised intracranial pressure. The age group of the population studied included pediatric population and headache being a difficult symptom to interpret in children below 5 years, exact prevalence was hence not known. The percentage was much higher for the cases presenting with vomiting when compared to the results of study by Jain B et al.⁶ 13% (n=9) cases presented with fever with seizures and/or altered sensorium with acute onset with meningeal signs, as no firm diagnosis was established in these cases and were kept under diagnosis of acute encephalitis syndrome due to J.E or unknown agent. Laboratory confirmed diagnosis for J.E/ or other agents could not be made due to lack of PCR and ELISA testing for the same in the hospital.

In the present study the peak incidence age of the cases with CNS infections, as well as meningoencephalitis was between 13 months to 5 years. Most of the cases were male with sex ratio (male: female) of 1.3. CNS infections, especially pyogenic meningitis was found to be more common in males in the present study. The predominance for the male sex was also noted in the cases of pyogenic (bacterial) meningitis in Indian studies by Yadav et al, Adhikary et al.^{10,11}

Fifty-five percent (n=37) of all the cases with CNS infections were from rural civilization. 56% (n=36) of the cases of meningoencephalitis were from rural civilization. Predominance of the cases of meningoencephalitis from rural population could be explained as poor vector control in rural setup, poor compliance for immunization, lack of concern for the disease due to poor knowledge and preferring superstitious remedies over medical help for treatment. This study also shows that cases of CNS infections, especially meningoencephalitis were both predominant in the months of rainy season. 39% (n=25) cases of meningoencephalitis occurred in July, August, September when rainy season in Uttarakhand is prevalent. Environmental humidity and pollens may also contribute to this peak and viral prodromal illnesses with respiratory tract infections are very common. The peak for the cases of pyogenic meningitis with 44% (n=12) of the cases was seen in winter season, similar results were also noted by other studies.^{12,13}

Duration of seizures though well associated with the etiology is not diagnostic. Status epilepticus can be the presentation associated with any of the infectious agent. However, authors found out that majority of the cases with meningoencephalitis, especially acute encephalitis syndrome cause? JE/ unknown agent presented with history of seizures lasting 5 to 15 minutes and in status epilepticus (67%; n=6). The data collected was based on the memory of the caregivers and as most of the cases of meningoencephalitis produced from rural background due to the lack of knowledge and concern for the disease, the cases had seizure for longer periods. Superstitious remedies in rural population are a common notion, it further delays medical treatment. A lack of EEG monitoring lead to potential lack of detection of seizure episodes and its characteristics. Twelve percent (n=8) of the children has the history of birth asphyxia and parenteral consanguinity of marriage was present in 60% (n=40) cases, family history of febrile seizures and epilepsy was present in 12% (n=8) and 10% (n=7) cases respectively, which are potential risk factors for epilepsy. Therefore, EEG, genetic analysis, with clinical follow up in the children presenting with fever with seizures with an underlying infectious etiology for the better understanding of the diagnosis and sequelae of post encephalitis epilepsy is advised.

Fever and seizures were the most common presentation and present in all the cases evaluated. Eighty-five percent (n=57) cases were recorded to be febrile at the time of admission, while others had positive history for fever in recent past. As in present study it was not possible to detect the peak temperature before the seizure, the temperature at the time of admission was recorded. Most of the cases with meningoencephalitis were from rural setup, which lacked proper medical care for temperature control hence it is justified to have raised temperature at time of presentation in such cases.

In the present study, 61% (n=41) cases with CNS infection had pallor and anaemia was found in 49% (n=33) cases. Pallor is a subjective sign, thus the increased prevalence of pallor in the cases could be explained due to observer bias. Papilledema followed by meningeal signs were the next most common signs in the cases of fever with seizures in 28% cases (n=45). Papilledema is earliest sign to be found in the cases of raised intracranial tension and thus it could be explained. In the cases of fever with seizures which presented with neurological deficits, cranial nerve paralysis (lateral rectus palsy and facial weakness) was most common and was present in 6% (n=4) of the cases. Abducens nerve is the first nerve compressed due to raised intracranial pressure, various explanations have been made due to its longest intracranial course hence its involvement is justified. Therefore, in the cases of fever with seizures, the presence of papilledema, meningeal signs or neurologic deficit, favors towards the diagnosis of a serious CNS infection.

Iron deficiency is the most common nutritional disorder affecting at least one third of world's especially between 6 and 24 months. It is explainable due to many reasons like, increased nutritional requirements of dietary iron during the growth of the child especially in the preterm infants as they have low total body iron, cow's milk fed infants and iron losses during episodes of diarrhea. Among various biological effects of iron, it is responsible for neurotransmitter metabolism, myelin formation and brain energy metabolism. The more severe stages of iron deficiency are associated with anaemia and anaemia is the most common manifestation of Iron deficiency. In present study, in the cases of meningoencephalitis anaemia was present in 49% (n=33) cases and all of these cases of anaemia were microcytic hypochromic, more likely to be suggestive of Iron deficiency. As most of the cases of meningoencephalitis came from rural population, due to their poor economic conditions, their Iron profile could not be studied in this study and was advised in follow up. As some cases of meningoencephalitis also had history of blood products transfusion in view of bleeding and/or intracranial pressure management the exact prevalence for anaemia was not known. Authors therefore suggest continued surveillance with more detailed studies to know the disease burden.

Hyponatremia was present in 28% (n=18) cases of meningoencephalitis. Electrolyte disturbances have been linked to increased susceptibility of seizures in febrile illness in childhood. Furthermore, SIADH as an underlying cause of euvolemic hyponatremia has been linked to meningoencephalitis in various studies.^{14,15} It is explained as due to deficiency of sodium ions, leads to more influx of calcium ions, further leading to generation of repetitive action potential and hence it leads to repetitive seizure initiation. So more prospective studies in this aspect are needed to be conducted for better understanding of the emerging trends in dyselectrolytemia as a result of CNS infection.

Meningeal enhancement was the most common MRI finding found in 28% (n=18) of the cases of meningoencephalitis. Most common association of meningeal enhancement could be seen with the cases of aseptic meningitis (62% n=8) and acute encephalitis syndrome (56%, n=5). HSV, JE, are well known to be the causative agents for the sporadic and epidemic cases of viral meningoencephalitis respectively in the area under study and meningeal enhancement could be thus explained due to viral pathology leading to pathologic condition due to cerebral ischemia and active inflammation and raised intracranial pressure. In the cases with tuberculosis, hydrocephalus was present in 87% (n=13) cases followed by vasculitis/ infarcts 53% (n=8) cases as the most common MRI finding. In most (77%, n=10) of the cases hydrocephalus was non-obstructive type. In the present study radiological findings of hydrocephalus, and micro-vascular infarcts were associated with tubercular pathology, which is consistent in the lines of other studies.¹⁶

Most of the cases with CNS infections (70%; n=47), especially with meningoencephalitis (69%; n=44) had acute onset of the disease and tubercular meningitis/encephalitis had subacute disease onset in 40% (n=6) cases. Case burden with meningoencephalitis was underestimated due to cases of meningoencephalitis which could not be brought to our center due to remote access of the hospital from the rural areas and fulminant nature of the disease leading to lost lives in the primary and community health centers.

In the current study most of the cases presenting in the state of acute febrile encephalopathy were the cases of acute encephalitis syndrome cause? JE/ unknown agent (n=9). Twenty-six percent cases (n=17) of CNS infections presented in the state of acute febrile encephalopathy in the present study. The cases of fever with seizures with an underlying CNS infection, when presenting in, the state of acute febrile encephalopathy with GCS \leq 5 were found to be significantly associated with mortality. These cases presented in altered sensorium with decerebrate extension, and respiratory failure followed. The accelerate disease progression can be attributed to the viral transmission dynamics. Due to limited role of antibiotics and indeterminate vaccine status of the rural community, a formidable challenge for an effective vaccination strategy for the poor is advocated. Increasing living standards, vaccination strategies implementation for better compliance and delivery can help decline the incidence of the infectious etiologies. Chemical control of the pests and vectors, along with the mechanization of agriculture can help prevent the disease among the population at the risk. On the basis of current study, we predict the viral CNS infections, especially JE will remain a substantial public health issue in the upcoming years; hence, we recommend social economic and health policy changes and increased funding for vaccination programs.

In present study we found that out of all the cases of meningoencephalitis, in cases of pyogenic meningitis, CSF and Blood culture correlated with the gram stain and positive cultures were found in 37% (n=10) and 30% (n=7) cases of pyogenic meningitis respectively. CSF and Blood culture studies were inconclusive for other causes. In the cases of meningoencephalitis, via culture of bodily fluids like urine blood and cerebrospinal (CSF) fluid, bacterial pathogens were isolated in 33% cases (n=21). CSF cultures were positive in 11% (n=7) cases of meningoencephalitis, which on further analysis with gram stain revealed the predominance of gram-negative bacilli (57%; n=4) in CSF cultures which had a CSF growth for strain of organisms. Our result could relate with other studies for the predominance pattern found in gram negative bacilli over gram positive cocci in CSF cultures.¹⁷

The prevalence of hospital acquired infections and nosocomial sepsis, and pseudomonas being a common species associated, further adds to the risk of gram-

negative septicemia in the cases admitted in the wards. Fifty eight percent (n=7) of the cases which tested positive for blood culture had a growth for gram positive organism. In the present study, CSF cultures and blood cultures proved to be more sensitive over conventional methods like gram staining, though a gold standard, cultures require days to weeks, trained medical personnel and equipped laboratory. Hence it is thus advised to start the patient with empirical therapy with antibiotics with a good coverage for gram positive and gram-negative organisms till the reports for culture and sensitivity are waited.

In present study, CSF culture analysis revealed MRCONS and Pseudomonas were the predominant species isolated in the cases with meningoencephalitis in 42% (n=3) and 28% (n=2) culture positive cases. Results of present study were not in line with other pediatric age group studies.^{18,19} Vaccine strategies are being encouraged across the country, inclusion of Hemophilus influenzae type b (Hib) vaccine in the national immunization schedule had increased the coverage for the same, the availability and prescription for Pneumococcal vaccine has also increased in the recent times, evolving trends in the causative agents for bacterial meningitis are hence warranted. Present study was limited as latex agglutination test was not done for the detection for causative agents in pyogenic meningitis and PCR for complete virologic screening was not available for detection of causative agents for viral meningoencephalitis.

All the cases were managed conservatively with intravenous fluids and antipyretics along with cold sponging. cases that presented with status epilepticus and hence were treated with intravenous lorazepam and antiepileptic's like phenytoin sodium and sodium valproate were used for the seizure control according to the AIIMS protocols for status epilepticus.²⁰ The cases were managed for raised ICT, coma, sepsis and electrolyte disturbances including hyponatremia were managed. Relevant investigations were undertaken to rule out other causes of fever with seizures. diagnosis was established with the help of CSF analysis and other relevant hematological and radiological investigations. 16% (n=11) cases with CNS infection had fulminant course and succumbed to illness in the hospital stay.

The overall case fatality rate in present study for the cases with meningoencephalitis was 16% and was comparably higher than other studies.⁹ Maximum mortality (33%, n=3) was seen with cases which presented in acute encephalitis syndrome cause? JE/unknown agent and other cases were discharged after 10-21 days on antiepileptic's after full course with antibiotics with standard treatment protocols.

Follow-up after one month was analyzed, complete recovery was seen in 57% (n=38) cases of CNS infection with none of the patient developing seizure within the

one month. 28% (n=19) cases with meningoencephalitis prevailed with neurological deficits. Cases that presented with acute encephalitis syndrome cause? JE/ unknown agent had mortality as high as 33%(n=3) and prevailed with neurologic deficits in rest of the cases, which hampered their outcome.

CONCLUSION

In view of high number of serious infective etiologies early diagnosis and treatment is required, hence recommend admission and observation for each child presenting with fever with seizures. Clinical signs of meningitis are not always reliable, and a laboratory support is required to reach early diagnosis hence, all children with fever with seizures be thoroughly examined by cerebrospinal fluid analysis and biochemical and haematological tests, whenever meningitis is suspected. Pseudomonas and MRCONS were the major pathogens responsible for the bacterial meningitis among the paediatric age groups, evolving trends in the causative agents of bacterial meningitis are warranted and hence antibiotic management should be planned intensively while culture reports are awaited. Cluster of cases with meningoencephalitis were found in rainy season hence suggested possible etiologies are JE/ scrub/ enterovirus. mortality as well as morbidity was high in cases with acute encephalitis syndrome cause? JE/unknown etiology in this era for modern medicine hence vector control strategies be encouraged and more detailed diagnostic studies to identify the culprit viruses responsible for meningoencephalitis are required.

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