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Original Article

Paediatrics Section

Clinical Profile and Outcome of Children with Acute Central Nervous System (CNS) Infection from a Tertiary Care Centre in the Present Vaccination Era

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ABSTRACT

Introduction: Meningitis is a common tropical infection which causes significant morbidity and mortality in children. Vaccination is available now-a-days for *Haemophilus influenza* and pneumococcus which are the common infection causing meningitis. Profile of acute Central Nervous System (CNS) infection in children varies with time to time as it depends on the organism, age, seasonal period, outbreaks, immunisation and place.

Aim: To study the clinical, microbiological, radiological profile and outcome of children with acute CNS infection in a tertiary care centre in the present vaccination era.

Materials and Methods: This prospective observational study was done in the Department of Paediatrics, Government Dharmapuri Medical College Hospital, Tamil Nadu, India, from December 2018 to June 2020. Total 50 children from one month to 12 years with features of acute CNS infection were included in the study. Clinical features, Cerebrospinal Fluid (CSF) and serology findings, Computed Tomography (CT) scan findings and outcome were taken for analysis. The data were entered in Microsoft Excel software and analysed using Statistical Package for the Social Sciences (SPSS) version 23.0.

Results: During the study period, 50 children were diagnosed with acute CNS infection. A total of 37 (74%) children were less than 3 years and 31 (62%) male children were commonly affected. Fever 42 (84%), seizures 46 (92%) and altered sensorium 31 (62%) were the common symptoms. Status epilepticus 40 (87%), shock 18 (36%), respiratory distress 16 (32%) were common findings. In CSF, elevated cell count, reduced sugar, elevated protein were seen in 21 (42%), 14 (28%) and 27 (54%), respectively. Pneumococcus 3 (6%), Japanese Encephalitis (JE) 8 (16%), dengue 5 (10%), herpes 4 (8%), scrub typhus (aetiological agent *Orientia tsutsugamushi*) 2 (4%) were the common aetiological agents for CNS infection. CT brain was abnormal in 8 (16%) children. Nine children died (18%) and rest 41 (82%) recovered.

Conclusion: In the present vaccination era, viruses and tropical fevers- JE, dengue, herpes and scrub typhus were common causes for acute CNS infection in children. Common clinical features were status epilepticus, fever, altered sensorium, respiratory distress and shock. Initial stabilisation of physiological status, specific management and JE vaccination are mandatory to improve the outcome in CNS infection.

Keywords: Dengue encephalitis, Meningoencephalitis, Japanese encephalitis, Seizures, Tropical infection

INTRODUCTION

Meningitis is a severe infection causing significant morbidity and mortality in children. The characteristic triad of meningitis contains fever, altered sensorium and neck stiffness. Bacteria and viruses are the common causes of CNS infection in India. The common bacterial organisms causing CNS infection in children are *Neisseria meningitidis* (*N. meningitidis*) *Haemophilus influenzae* (*H. influenzae)* type b (Hib) and *Streptococcus pneumoniae* (*S. pneumoniae*) [1]. Pneumococcal meningitis is instigated by *S. pneumoniae*, a gram positive coccus and is the most common bacterial cause of meningitis. Meningococcal meningitis is caused by gram negative diplococcus-*N. meningitidis*. *H. influenzae* type B causes significant meningitis in underdeveloped countries, incomplete vaccinated individuals, and immunosuppressive children. Most bacterial meningitis children improve completely if suitable antibiotic therapy is started on time [2]. Global causes of viral meningitis include enterovirus, herpes, mumps, measles, JE and Human Immunodeficiency Virus (HIV). Enterovirus is the utmost common cause of viral meningitis. The prevalence of acute encephalitis in western countries is 7.4 per 100,000 population per year. In tropical countries like India it is 6.4 per 100,000 per year [3].

The clinical features of CNS infection in children are fever, poor feeding, headache, shock, various cutaneous signs such as petechiae and purpura, reduced level of consciousness, irritability, acute confusion, neck stiffness, photophobia, lethargy and generalised or focal seizures [2]. In developing countries, *S. pneumoniae* and *H. influenzae* type B are the common organisms causing significant mortality and morbidity due to acute CNS infection. *S. pneumoniae* was the common aetiological agent of community acquired CNS infection in Eastern India and Southern India, as reported in previous studies [4,5]. These aetiological profiles are changing after the widespread use of vaccination in many parts of the world.

Government of India included Pentavalent vaccine (DPT+HepB+Hib) in the Universal Immunisation Programme (UIP) in the year 2012 across the country and in a phased manner entire country was covered by 2017 [6]. Pneumococcal vaccine has been given to many children in our country by private practitioners as per Indian Academy of Paediatrics (IAP) immunisation schedule. Pneumococcal vaccine was introduced in India's UIP in a phased manner from June 2017 [7]. After introduction of vaccines, meningitis due to *H. influenzae* type B and *S. pneumoniae* were significantly reduced in developed countries [1,2]. So, there is an urgent need to study the

profile of bacterial meningitis as it depends on the organism, age, seasonal period, outbreaks, immunisation and place. Identifying the organism and treating the cause is crucial for the survival and intact neurological recovery of the child in acute CNS infection. So, the aim of present study was to study the clinical, microbiological and radiological profile and outcome of children with acute CNS infection in a tertiary care centre in the present vaccination era.

MATERIALS AND METHODS

A prospective observational study was done in the Department of Paediatrics, Government Dharmapuri Medical College Hospital, Dharmapuri, Tamil Nadu, India, from December 2018 to June 2020. This study was approved by the Institutional Human Ethics Committee (IEC) (IEC No.5/2018, Dt.17.11.2018).

Inclusion criteria: All children from one month to 12 years of age presenting with signs and symptoms of acute CNS infection like fever, altered sensorium, seizures, meningeal signs and bulging fontanelle were included in this study. Study included all the children referred from both urban and rural areas of nearby six districts, covering all the seasonal outbreaks including tropical fevers like dengue and scrub typhus, along with routine organisms causing CNS infection.

Exclusion criteria: Children <1 month of age and >12 years of age, simple and complex febrile seizure, partially treated acute CNS infection cases and seizure disorder were excluded from the study.

All the children with features suggestive of acute CNS infection during the study period were included in the study. Vaccination details of all the children were obtained. Initial clinical presentation, laboratory, radiological findings and outcome of these children were taken for analysis.

Study Procedure

The children admitted with clinical features of acute CNS infection were enrolled after obtaining informed/written consent from parent/guardian. Routine investigations like complete blood count (normal haemoglobin 11.5-14.5 g/dL, leukocyte count 4000-12000 cells/mm^3), blood sugar (normal 60-100 mg/dL), serum calcium (normal 8.8 - 10.8 mg/dL), serum electrolytes (normal sodium 134-143 mmol/L, potassium 3.3-4.6 mmol/L) and blood culture were sent for all cases [8]. Immunisation and contact history were obtained.

Children presenting with meningeal signs-neck stiffness, Kernig sign (flexion of the hip 90° with subsequent pain with extension of the leg) and Brudzinski sign (involuntary flexion of the knees and hips after passive flexion of the neck with supine) were also noted [2]. Glasgow Coma Scale (GCS) {which consists of eye opening (total points 4), verbal response (total points 5), motor response (total points 6)} scores were also noted to assess the children with an altered level of consciousness [2].

Lumbar puncture was done for all suspected cases after stabilisation. Cerebrospinal Fluid (CSF) was tested for cells (<5, 75 lymphocytes), glucose (normal >50 or 75% of serum glucose), protein (normal 20-45 mg/dL) [2], gram stain, bacterial culture, sensitivity pattern and Polymerase Chain Reaction (PCR). CSF IgM Enzyme-Linked Immunosorbent Assay (ELISA) for JE, dengue and scrub typhus and serological test like IgM ELISA for JE, dengue and scrub typhus were done in needed cases. Supportive radiological investigations like chest X-ray, CT brain, abdominal ultrasound, Magnetic Resonance Imaging (MRI) brain were done wherever required and findings were noted.

STATISTICAL ANALYSIS

Data was entered in microsoft excel software and analysed using SPSS version 23.0. Distribution of different parameters was mentioned as percentages.

RESULTS

During the study period, 50 children were admitted with features of acute CNS infection with male preponderance 31 (62%). A 22 (44%) children were in the age group of three months to three years, 15 (30%) children were in the age group of 1-3 months and 13 (26%) children were in the age group of 3-12 years. All the children were completely vaccinated for *H. influenzae* B (hib) and no child received pneumococcal or JE vaccine in this study group.

Demographic and clinical features are shown in [Table/Fig-1]. A 22 (44%) children were in the age group of three months to three years, 15 (30%) children were in the age group of 1-3 months and 13 (26%) children were in the age group of 3-12 years. Seizures, fever and altered sensorium were the common presentations seen in 46 (92%), 42 (84%) and 31 (62%) children, respectively. Many children with CNS infection presented with fever (84%) and seizures (92%) in present study. Status epilepticus was the common type of seizure seen in 40 (87%) of 46 seizure cases.

Variables	n (%)
Age	
1-3 months	15 (30)
>3 months - 3 years	22 (44)
>3 years - 12 years	13 (26)
Sex	
Male	31 (62)
Female	19 (38)
Symptoms	
Seizures	46 (92)
Fever	42 (84)
Altered sensorium	31 (62)
Irritability	24 (48)
Vomitting	19 (38)
Shock	18 (36)
Respiratory distress	16 (32)
Meningeal signs	7 (14)
Glasgow Coma Scale (GCS) <6	6 (12)
Bulging fontanel	4 (8)
Headache	3 (6)
Kernig sign	1 (2)
Brudzinski sign	1 (2)
Types of seizures (n=46)	
Status epilepticus	40 (87)
Non convulsive status epilepticus	4 (8.7)
Focal seizures	2 (4.3)

[Table/Fig-1]: Demographic and clinical features of acute CNS infection in children (n=50).

Meningeal signs were seen in only 7 (14%) children. Kernig and Brudzinski signs were seen in one children each. GCS was less than 6 in 6 (12%) children. Shock and respiratory distress were seen in 18 (36%) and 16 (32%) children, respectively. Due to delayed presentation, many children presented with respiratory distress (32%) [Table/Fig-1]. Blood and CSF laboratory values are shown in [Table/Fig-2].

Parameters	n (%)
Blood	
Anaemia	34 (68)
Leucocytosis	18 (36)
Hypoglycaemia	9 (18)
Hypocalcaemia	15 (30)
Hyponatraemia	12 (24)
CSF	
Elevated cell count	21 (42)
Predominant neutrophil	10 (47.6)
Predominant lymphocyte	11 (52.4)
Reduced sugar	14 (28)
Elevated protein	27 (54)

[Table/Fig-2]: Laboratory values of acute CNS infection in children.

Microbiological and radiological profile shown in [Table/Fig-3]. Pneumococcus was isolated in 3 (6%) children. IgM ELISA in CSF was positive for JE in 8 (16%) children. Dengue was the aetiological agent in 5 (10%) children who presented with severe thrombocytopenia (<20000/mm^3) and IgM ELISA for dengue was positive. CSF-PCR was positive for herpes in 4 (8%) children. The other common tropical fever scrub typhus (aetiological agent-*Orientia tsutsugamushi*) with characteristic eschar presented with CNS manifestation in 2 (4%) children.

Profile	n (%)	Diagnosis
Organism		
Japanese encephalitis virus	8 (16)	IgM ELISA
Dengue virus	5 (10)	IgM ELISA
Herpes simplex virus	4 (8)	Polymerase chain reaction
S. pneumoniae	3 (6)	CSF culture
Orientia tsutsugamushi (Scrub typhus)	2 (4)	IgM ELISA
CT Brain findings		Disease
B/l Thalamic hypodensities	2 (4)	Japanese encephalitis
Temporal lobe changes	2 (4)	Herpes simplex encephalitis
Subdural haemorrhage	2 (4)	Organism not identified.
Hydrocephalus	1 (2)	Organism not identified.
Gangliocapsular hypodensities	1 (2)	Organism not identified.
Normal	42 (84)	-

[Table/Fig-3]: Microbiological and radiological profile of acute CNS infection in children (n=50).

The CT brain was abnormal in 8 (16%) cases and normal in 42 (84%) cases. Bilateral thalamic hypodensities was seen in JE and temporal lobe changes were seen in HSV causing meningitis. In this study, 9 (18%) children died and rest recovered completely.

DISCUSSION

In this present vaccination era, clinical and microbiological patterns of CNS infection are changing from time to time worldwide. So, analysing the clinical and microbiological profile of acute CNS infection in children is very important, because it is still an important public health problem causing high morbidity and mortality in children. In this study, 22 (44%) children were in the age group three months to three years with male preponderance. Another study conducted at the Vijayanagar Institute of Medical Sciences, Bellary states that higher proportion of subjects were toddlers (30.1%), followed by pre school children (26.5%). Of them males were 88 (64.7%) and females were 44 (32.3%) [9]. In this study, seizures was the most common symptom presenting in 46 (92%) cases followed by fever in 42 (84%) patients, altered sensorium was seen in 31 (62%) patients and vomiting in 19 (38%) cases. In a study by Chinchankar N et al., 96% had fever and 98% had altered sensorium [10]. In Farag HF et al., study seizures were seen in 64.9% of cases and in Thomas M et al., study 38.7% children were presented with seizures, which was less compared to this study [11,12]. CNS infection is an important cause of epilepsy in developing countries. Status epilepticus was the common type of seizure seen in 87% (40/46) of seizure cases in this study. Prolonged seizures cause airway compromise and increases the respiratory distress which will have very important impact in the outcome of the children affected with CNS infection. Also, proper management of status epilepticus and raised Intra Cranial Tension (ICT) which is very much essential to save the life of child as well as intact neurological survival.

Among the 50 CSF samples collected, cell count was elevated in 42% of children-out of which 47.6% was neutrophil predominant and 52.4% was lymphocyte predominant. In CSF, reduced sugar and elevated protein were seen only in 28% and 54%, respectively in this study. In another study by Ramadevi GV et al., 60% cases had reduced sugar and 90% had elevated CSF protein [13]. In this study, the children were treated with emperical intravenous (i.v.) antibiotics and supportive measures in emergency room, as majority of the cases came with status epilepticus, respiratory distress and shock. Because of this, CSF examination was done after stabilisation of the children, which will have impact on the CSF results.

In a study done at Nil Ratan Sircar medical college, West Bengal in 2015, 50% cases were diagnosed by *S. pneumoniae,* followed by *N. meningitidis* and *Staphylococcus aureus* [4]. *S. pneumoniae* was the most common aetiological agent of community acquired meningitis in Mani R, et al., study conducted at National Institute of Mental Health and Neuro Sciences, Bengaluru in 2007 [5]. Pneumococcus (6%) was the common bacteria causing acute CNS infection in children in this study. Japanese encephalitis (16%), dengue (10%) and herpes (8%) were the common viruses causing CNS infection in this study. Scrub typhus manifested as CNS infection in 4% of children in this study.

In this study, the JE cases presented with fever, altered sensorium, and seizures. CT brain showed bilateral thalamic involvement. During seasonal periods, dengue encephalitis cases were also presented with fever, thrombocytopenia, Generalised Tonic Clonic Seizures (GTCS), altered sensorium and CT brain showed bilateral thalamic involvement. IgM ELISA for dengue was positive in those cases. The other common tropical fever scrub typhus presented with prolonged fever, thrombocytopenia with altered sensorium with characteristic eschar at hidden places, where IgM ELISA for scrub typhus was positive. After doxycycline treatment both children improved dramatically. In a study by Kakoti G et al., 30% of the children were confirmed with JE [14]. Similar study carried out in Cuddalore district, Tamil Nadu, also reported 29.3% patients affected with JE [15]. In another study conducted by Khinchi Y et al., serology for JE IgM (ELISA) was positive in 11 cases out of 61 total Acute Encephalitic Syndrome (AES) cases as per documented reports received from World Health Organisation (WHO) field office [16]. In De S et al., study in children, they concluded that out of 24 cases of AES, 6 (25%) patients were JE and 18 (75%) patients were non JE [17]. In studies done by Ali H et al., Rathore SK et al., and Jain P, et al.,) JE virus and HSV were the common organisms causing CNS infection [4,18,19]. AES including JE was reported

Study	Publication year	Place	Causative organisms for acute CNS infections
Ali H et al., [4] (n=50)	2019	West Bengal, Eastern India	Viral: Japanese encephalitis- 39.2%, Herpes simplex virus- 35.72%, Varicella zoster virus- 10.7% Bacterial: *S. pneumoniae*- 4 (50%), *N. meningitidis*- 1 (12.5%), *S. aureus*- 1 (12.5%)
Mani R et al., [5] (n=385)	2007	NIMHANS, Bangalore	Bacterial: *S. pneumoniae*- 238 (61.8%), *H. influenzae*- 7 (1.8%), *N. meningitidis*- 4 (1%), *Streptococcus*- 9 (2.3%), *S. aureus*- 7 (1.8%)
Kamble S and Raghvendra B, [9] (n=136)	2016	Bellary, Karnataka	Acute encephalitis syndrome- viral aetiology (Japanese Encephalitis and Dengue): 115 (84.5%) Other agents (Pyogenic, TB and varicella): 13 (9.5%) Unknown: 8 (5.8%)
Chinchankar N et al., [10] (n=547)	2002	Pune, Maharastra	*S. pneumoniae*- 39%, *H. influenzae*- 26%, Others- 35%
Farag HF et al., [11] (n=310)	2005	Egypt	*H. influenzae*- 21%, *S. pneumoniae*- 13.4%, *N. meningitidis*- 14.27%
Thomas M et al., [12] (n=62)	2020	Kerala	*S. pneumoniae*- 1 (1.6%), *N. meningitidis*- 1 (1.6%), Angiostrongylus cantonensis- 1 (1.6%), Herpes simplex virus - 1 (1.6%)
Ramadevi GV et al., [13] (n=32)	2015	Kurnool, Andhra Pradesh	*S. pneumoniae*- 8 (25%), Coagulase positive *S. aureus*- 3 (9.35%), Coagulase negative *S. aureus*- 5 (15.63%), *N. meningitidis*- 3 (9.38%), *Klebsiella*- 4 (12.5%), Others- 9 (28.13)
Kabilan L et al., [15] (n=58)	2004	Cuddalore, Tamilnadu	Japanese encephalitis- 17 (29.3%)
Khinchi Y et al., [16] (n=61)	2010	Nepal	Japanese encephalitis- 11 (18%)
De S et al., [17] (n=24)	2015	West Bengal	Japanese encephalitis- 6 (25%), Non Japanese encephalitis- 18 (75%)
Rathore SK et al., [18] (n=526)	2014	Odisha, Eastern India	Hepes simplex virus- 16.1%, measles- 2.6%, Japanese encephalitis- 1.5%, Dengue- 0.57%, Varicella zoster virus- 0.38%, Enterovirus- 0.19%
Present study	2022	Tamil Nadu	Japanese encephalitis virus- 8 (16%), Dengue virus- 5 (10%) Herpes simplex virus- 4 (8%), *S. pneumoniae*- 3 (6%) *Orientia tsutsugamushi* (Scrub typhus)- 2 (4%)

[Table/Fig-4]: Comparison of causative organisms for acute CNS infection with various studies [4,5,9-13,15-18].

in many states like Assam, Bihar, Karnataka, Tamil Nadu and Uttar Pradesh as mentioned in Borah J et al., [20]. Various studies showing causative organisms for acute CNS infections are tabulated in [Table/Fig-4] [4,5,9-13,15-18].

Japanese encephalitis is the mosquito borne disease primarily affects children. This is the important cause of CNS infection in Asia due to viral aetiology. JE is a dangerous disease causing high morbidity and mortality with a case fatality rate as high as 30% and 30-50% of significant permanent neurologic or behavioural sequelae [1]. IgM ELISA is diagnostic for JE but it is unavailable even in many tertiary care centres in our country. For JE, specific antiviral drug is not available till now and those children are managed with only supportive care. Herpes simplex virus is the another important agent causing significant meningoencephalitis all over the world [1], where injection acyclovir is very much helpful. Tropical fevers like dengue and scrub typhus were the aetiological agents for CNS infection, reported in studies by Khan SA et al., Behera B et al., Kar A et al., Vasanthapuram R et al., and Pal S et al., [21-25].

After introduction of Hib vaccine and pneumococcal vaccine, morbidity and mortality caused by *H. influenzae* and *Streptococcal pneumonia* causing CNS infection in children are significantly reduced [7]. In this study, all the children were completely vaccinated for *H. influenzae* B (hib) and no child received pneumococcal or JE vaccine in this study group. Though, pneumococcal vaccine has been administered in the private hospitals, it is being administered in government hospitals from July, 2021 in Tamil Nadu [26]. Whereas, above reports and this study showed that recent CNS infection in children was caused by mainly JE virus, herpes virus and tropical fevers like dengue and scrub typhus. Identifying the above organisms help in specific management which will improve the recovery. Injection doxycycline or azithromycin will be life saving in scrub typhus encephalitis, if diagnosed earlier. Same as injection acyclovir will be helpful in Herpes encephalitis. In this study, CT Brain was evaluated in all patients and it was normal in 42 (84%) children. CT brain was abnormal in only 8 (16%) children. CT scan may be useful in JE and HSV encephalitis which have specific CT scan findings [2,27,28]. In this study, 9 (18%) children died and rest recovered and discharged. The case fatality rate in CNS infections is 30% and neurological disabilities acquire in 1/3rd of survivors [29]. Even in developed nations with best available facilities, case fatality rate is around 10%. Approximately one third of the mortalities occurred during first 48 hours reflecting the critical condition of the children at admission [2]. It is around 18% in this study which is influenced by multiple factors like late arrivals, presented with prolonged status epilepticus, respiratory distress and shock.

Many children presented with shock and respiratory distress because of late arrival from distant places influenced the outcome. Initial management of airway, breathing, circulation and disability is very important for favourable outcome. Also, treatment of seizures and raised intracranial pressure is mandatory for survival [30,31].

As most of the CNS infection cases required ventilator support, they later developed secondary sepsis (24%) and pneumonia (10%) in spite of improved from primary CNS insult. So, identification of organism, initial management of physiological status, specific therapy, ventilator care, nursing care and nutritional supportive care are very much essential for successful outcome in children affected

with CNS infection [30,31]. Along with JE and herpes, dengue encephalitis and scrub typhus encephalitis are emerging aetiologies of acute CNS infection. These aetiologies should be kept in mind during seasonal periods [32].

Limitation(s)

In this study, majority of the cases presented with shock and respiratory distress, lumbar puncture could be done only after stabilisation of the patient. Because of this, positive culture report could not be obtained. Only 22 (44%) samples showed positive for organisms. CSF sterilisation can occur within first two to four hours of administration of antibiotics. Advanced technology like multiplex PCR for both bacteria and viruses and ELISA could not be done in all cases. Unavailability of PCR and IgM ELISA in many tertiary care centres led to difficulty in identification of organisms, resulting in under treatment and poor outcome in children.

CONCLUSION(S)

Fever, status epilepticus, altered sensorium, respiratory distress and shock were the common presentations in children with acute CNS infection. CT brain was abnormal mainly in JE and HSV cases. In the present vaccination era, Tropical fevers (Dengue, scrub typhus) and viruses (JE, HSV) cause more serious CNS infections than usual bacterial causes. High index of suspicion, initial stabilisation of physiological status, specific treatment and supportive care will improve the outcome in children. The recommendation of present study is making available of advanced investigations like multiplex PCR for viruses and bacteria and IgM ELISA in CSF in all centers to pinpoint the diagnosis, which helps in management of acute CNS infection. JE vaccine should be included in UIP which will prevent the severe JE in children.

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