Original Article

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Paediatrics Section

Clinico-epidemiological Profile and Predictors of Adverse Outcome in Children Admitted with Japanese Encephalitis at a Tertiary Care Hospital in Assam, India: A Retrospective Cohort Study

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ABSTRACT

Introduction: Japanese Encephalitis (JE) is considered one of the leading causes of Acute Encephalitis Syndrome (AES) affecting children and adolescents, particularly in tropical countries. It presents a major challenge for the health sector, particularly in management, due to its unpredictable course and lack of specific treatment. Therefore, adequate data regarding the clinico-epidemiological pattern and the identification of prognostic factors may assist treating physicians in proper triaging and delivering appropriate management.

Aim: To study the clinico-epidemiological profile and predictors of adverse outcomes in children with JE at Assam Medical College and Hospital (AMCH), a tertiary care hospital in Dibrugarh, Assam.

Materials and Methods: A retrospective cohort study was conducted in the Department of Paediatrics at Assam Medical College and Hospital (AMCH) from April 1, 2018, to September 30, 2019. Data from 146 children were collected, including demographic details, clinical signs and symptoms, laboratory parameters, risk factors, and mortality outcomes. Statistical methods used included Odds Ratio (OR), simple proportion test, Chi-square test, and Relative Risk (RR) estimation with 95% confidence intervals.

Results: The most common age group affected was 5-12 years, with a slight male predominance 1.3:1. Among the participants, 31 (21.23%) children were vaccinated against JE. Common clinical presentations included fever (104 cases, 71.23%), seizures (95 cases, 65.06%), vomiting (88 cases, 60.27%), and headache (84 cases, 57.53%). The common complications observed were circulatory shock (31 cases, 21.23%), sepsis (21 cases, 14.38%), dyselectrolytaemia (34 cases, 23.28%), and acute kidney injury (37 cases, 25.34%). Overall mortality was 33 (22.60%). The highest mortality was observed in children with circulatory shock, altered sensorium with a Glasgow Coma Scale (GCS) score of less than 8, and refractory seizures. Of the children, 86 (58.90%) recovered completely, 33 (22.60%) died, and 16 (10.95%) were discharged with neurological sequelae.

Conclusion: The case fatality rate was 22.60%. Vaccination coverage was significantly low among the children. The poor prognostic factors included shock, low GCS, the need for multiple anticonvulsants, ionotropes, hypertonic saline infusion, and ventilatory support. Therefore, this study highlights the need for extensive research and increased JE vaccination efforts in the region.

Keywords: Acute encephalitis syndrome, Circulatory shock, Mortality, Vaccination

INTRODUCTION

Acute Encephalitis Syndrome (AES) is an inflammation of the brain parenchyma characterised by a sudden onset of fever and changes in mental status, such as confusion, disorientation, delirium, coma, and/or new-onset seizures [1,2]. AES, also known as "acute febrile encephalopathy," has a multifactorial etiology, with viruses as the main causative agents. The mortality and morbidity of AES are very high in children, particularly among those aged 5-12 years, likely due to increased mobility, outdoor activities, school attendance, and exposure to paddy fields [3]. It is a worldwide illness that has a serious impact on public health, posing a hazard to nearly half of the world's population [4].

Japanese Encephalitis (JE) is the most prevalent mosquito-borne viral encephalitis in humans, with an estimated 50,000 cases and 10,000-15,000 deaths worldwide annually [5]. In fact, the concept of AES was introduced to facilitate surveillance for JE [6]. The mortality rate from JE ranges from 20% to 30%, with neurological sequelae observed in 30% to 50% of survivors [7]. In India, the northeastern region, particularly upper Assam, experiences recurrent episodes of JE with varying magnitudes from July to October each year [4]. JE is considered endemic in Assam, affecting thousands of people, especially children, with outbreaks primarily occurring during the monsoon season [7]. Factors such as climatic conditions, abundance of potential mosquito vectors, amplifying hosts, agricultural practices, and socio-cultural behaviors may contribute to its endemicity [8]. Several districts in Assam, particularly Dibrugarh, Jorhat, Tinsukia, Dhemaji, North Lakhimpur, and Sibsagar, are currently witnessing an increase in AES (both JE and non-JE) during the monsoon and post-monsoon period, which leads to deaths and neurological sequelae [9]. Most JE infections are asymptomatic, and the ratio of symptomatic to asymptomatic infections ranges from 1 in 300 to 1 in 1000 [10]. There is no cure for JE; treatment is mainly symptomatic, making early diagnosis and intensive supportive care necessary to avoid neurological sequelae. Initially, the JE vaccine was introduced only in a few endemic states in India but was subsequently added to the National Immunisation Schedule (NIS) by 2014 [11].

Few studies conducted in Assam, particularly on JE, have described the clinical profile and risk factors associated with adverse outcomes [10,12-16]. Keeping this background in mind, the present study was undertaken to determine the demographic, clinical, and laboratory

characteristics associated with JE and their prognostic factors in predicting adverse outcomes in children.

MATERIALS AND METHODS

This is a retrospective cohort study conducted in the Department of Paediatrics at Assam Medical College and Hospital (AMCH), focusing on cases admitted over an 18-month period. Data were collected from April 1, 2018, to June 30, 2019, and analysed from July 1 to September 30, 2019. This is a tertiary care center that provides healthcare facilities to several districts in upper Assam, with most patients referred to this hospital from peripheral areas due to a lack of neuroimaging and intensive care facilities.

Inclusion criteria: Children aged 6 months to 12 years admitted with a provisional diagnosis of AES and positive for JE virus IgM antibody in either serum or Cerebrospinal Fluid (CSF) samples during the study period were included in the study.

Exclusion criteria: Children with febrile seizures, non-infective Central Nervous System (CNS) disorders such as epilepsy, head injury, dyselectrolytemia, and vascular disorders, as well as those whose parents did not consent, were excluded from this study.

Study Procedure

A detailed history was taken, including demographic details, to ascertain the endemicity of any particular causative agent. Immunisation history was categorised into three groups: vaccinated, not vaccinated, and unknown. A thorough clinical examination was conducted, and clinical findings were noted.

Clinico-epidemiological data included were sex, clinical features, general examination, specific diagnosis,vitals signs at the time of admission, level of consciousness, respiratory distress,circulatory shock, convulsions and hypoxemia, along with relevant findings from the systemic examination. Neurological status was represented using the GCS/modified GCS scoring system. A GCS score <8 was considered as coma and indicated a criterion for ventilatory support [12]. Hypoxia was defined as SpO_2 <90% in room air without evidence of congenital cyanotic heart disease [13]. Dyselectrolytemia was diagnosed according to the standard definitions for specific electrolytes [14].

The requirements for oxygen, mechanical ventilation, vasoactive medications, and cardiopulmonary resuscitation were noted. Routine blood investigations, including Complete Blood Count (CBC), electrolytes, Capillary Blood Glucose (CBG), and renal function tests, were conducted and analysed. Cerebrospinal Fluid (CSF) analysis was performed after obtaining proper consent from the parents, and samples were sent for cytology and biochemical analysis. Immunoglobulin M (IgM) antibody capture Enzyme-Linked Immunosorbent Assay (ELISA) for JE was conducted for all CSF and serum samples using ELISA kits manufactured by the National Institute of Virology, Pune, India, and supplied by the National Vector Borne Diseases Control Program (NVBDCP), Ministry of Health and Family Welfare, India [1].

For children in whom lumbar puncture was not possible or contradicted, only serum samples were collected and analysed. Management of the children was initiated as per standard unit protocol. Outcomes were recorded as fully recovered, recovered with neurological sequelae, or death. Neurological sequelae were defined by the presence of one or more of the following at the time of discharge: abnormal limb tone and reflexes, weakness of the limbs, extrapyramidal movement disorders, or new or recurrent seizures [17].

STATISTICAL ANALYSIS

Quantitative variables included clinical profiles and outcome patterns. Statistical analyses utilised were Odds Ratios (OR), Chi-square tests, and simple proportion tests. Means, Standard Deviations (SD), percentages, and ranges were used as appropriate to describe continuous variables. The significance of each factor associated with mortality in children admitted to the Pediatric Intensive Care Unit (PICU) was first analysed using univariate analysis. Univariate analysis was performed through the Chi-square test and Relative Risk (RR) estimation with 95% confidence intervals. The level of significance was set at a p-value <0.05. Statistical software used was MedCalc Version 20.026.

RESULTS

A total of 146 children were included in the present study, with a majority (95, 65.06%) being above 5 years, making the predominant age group affected 5 to 12 years, with a male-to-female ratio of 1.3:1. Only 31 (21.23%) children were confirmed to be vaccinated [Table/Fig-1].

Parameters	Numbers (%)
Age 0-5 years	51 (34.93)
Age 5-12 years	95 (65.06)
Male/Female	84 (57.53)/62 (42.46)
Vaccinated	31 (21.23)
Not vaccinated	39 (26.71)
Vaccination status unknown	76 (52.05)

[Table/Fig-1]: Age, gender and vaccination status.

The children with JE exhibited a wide range of clinical features. The majority presented with fever ranging from 100-104°F. The most common neurological manifestation was convulsion (95, 65.06%), followed by vomiting (88, 60.27%), headache (84, 57.53%), and altered sensorium (79, 54.10%) [Table/Fig-2]. Circulatory shock was the most common complication observed in 31 (21.23%), requiring inotropic drugs to maintain perfusion during the course of the disease, followed by systemic sepsis (21, 14.38%) [Table/Fig-3].

Clinical features	No. of patients	Percentage
Fever	104	71.23
Seizure	95	65.06
Vomiting	88	60.27
Headache	84	57.53
Altered sensorium	79	54.10
Diarrhea	14	9.58
Protein energy malnutrition	12	8.21

[Table/Fig-2]: Clinical features among children with JE.

Complications	No. of patients	Percentage
Sepsis	21	14.38
Shock	31	21.23
Pneumonia	5	3.42
Upper gastrointestinal bleed	4	2.73
Hypertension	3	2.05

[Table/Fig-3]: Complications associated in children with JE.

A total of 79 (54.10%) children were found to be anemic. Leucocytosis was observed in 51 (34.93%) of the children, predominantly with lymphocytes. Other laboratory parameters included dyselectrolytemia in 34 (23.28%) and abnormal Renal Function Tests (RFT) in 37 (25.34%). A total of 141 (96.57%) children were diagnosed by serum testing positive for anti-Japanese Encephalitis Virus (JEV) IgM antibodies, and 51 children (34.93%) showed CSF positive for JEV-specific IgM antibodies [Table/Fig-4].

A total of 41 (28.08%) children had refractory generalised seizures, which required multiple anticonvulsant drugs to control the seizures. Twenty-eight children (19.17%) required hypertonic saline to reduce Intracranial Pressure (ICP). Ventilatory support was provided to

Parameters		Number	Percentage
Anaemia	Present	79	54.10
	Absent	67	45.89
Total leucocyte count	<5000 cell/cumm	11	7.53
	5000-11000/cumm	84	57.53
	>11000/cumm	51	34.93
Dyselectrolytemia	Present	34	23.28
	Absent	112	76.71
Abnormal RFT	Present	37	25.34
	Absent	109	74.65
JE Serology	Positive	141	96.57
	Negative	0	0
	Equivocal	5	3.42
CSF for JE	Positive	51	34.93
	Negative	95	65.06

[Table/Fig-4]: Biochemical profile among children with JE.

19 (13.01%) children. An analysis of the association between interventions and mortality revealed that 31 children who presented with shock and required inotropes showed a statistically significant correlation, with a p-value of 0.0007. Those children requiring multiple anticonvulsants and 3% sodium chloride infusion were also statistically significant (p<0.0001 and p=0.0440, respectively).

A total of 19 children with a poor GCS (<8) required supportive ventilation, which was associated with significant mortality (p<0.0001) [Table/Fig-5]. The complications associated with JE included diarrhea, pneumonia, Upper Gastrointestinal (UGI) bleeding, sepsis, and hypertension, which were found to be statistically insignificant. Anemia, dyselectrolytemia, abnormal RFT, and CSF for JE were also statistically insignificant. However, those groups of children with poor GCS <8, shock, and refractory seizures requiring inotropes and multiple anticonvulsants, in addition to 3% sodium chloride infusion for elevated ICP, were found to have a statistically significant association with mortality [Table/Fig-6].

Intervention		Survivor	Non-survivor	95% CI	Odds Ratio (OR)	p-value
Ionotropes	Yes	16	15	1.87-10.67	4.4792	0.0007
	No	86	18			
Ventillation	Yes	5	14	4.60-44.40	14.2947	<0.0001
	No	97	19			
Multiple anticonvulsant	Yes	15	26	7.93-58.46	21.5429	<0.0001
	No	87	7			
3% sodium chloride	Yes	17	11	1.02-6.07	2.5000	0.0440
	No	85	22			

[Table/Fig-5]: Association of intervention with mortality.
*11 children were lost from the study

Upon evaluation of the outcomes, it was observed that the majority, 86 (58.90%), of the children completely recovered, while 16 (10.95%) children had neurological sequelae at discharge. Unfortunately, 33 (22.60%) children died in the hospital during the study period [Table/Fig-7].

DISCUSSION

This study aimed to analyse the clinico-epidemiological profile and factors determining the outcomes of children diagnosed with JE. A total of 146 children were admitted to the Department of Paediatrics, AMCH, over a period of 18 months. This study revealed that JE is one of the leading causes of Acute Encephalitis Syndrome (AES) in the pediatric population, especially in our country.

The majority of the children, 95 (65.06%), were above five years of age, which is consistent with findings from studies conducted by Bhadouriya R et al., Kuntal M et al., and Chakrabarti SK et al., [4,6,11]. In our study, 84 (57.53%) of the affected individuals were males, showing a male preponderance that aligns with Kuntal M et al., [6].

The vaccination status of most children was unknown, with only 31 (21.23%) reporting vaccination. This study also indicated a significant number of JE cases occurring in June, July, August, and September, suggesting the highest incidence during the monsoon and post-monsoon period. This finding is similar to those reported by Kuntal M et al., Ahmed RA et al., [6,7].

The present study showed high-grade fever as the most common presentation, followed by seizures, vomiting, headache, altered sensorium, and diarrhea. This finding is consistent with studies conducted by Bhadouriya R et al., Kuntal M et al., Adhikari A et al., Lo SH et al., and Avabratha KS et al., [4,6,18-20].

In this study, 31 (21.23%) children experienced shock that required inotropes, of which 15 (10.27%) succumbed, a result found to be statistically significant (p=0.0007). Similar findings were observed by Sambasivam E et al., and Kuntal M et al., where those with shock had high mortality rates with significant p-values of 0.030 and 0.0003, respectively [2,6]. [Table/Fig-8] shows the comparison of the present study finding with previous study [2-4,6,11].

A total of 41 (28.08%) children required multiple anticonvulsants to control seizures, and 26 (17.80%) of these children died, yielding a statistically significant result in our study with a p-value <0.0001. This aligns with earlier studies conducted by Soloman T et al., and Sunwoo JS et al., [21,22].

Variables		Survivors	Non-survivors	95% CI	Odds Ratio (OR)	p-value
Age	0-5 (y)	38	13	-	-	0.8263
	5-12 (y)	64	20	-	-	
gender	Males	60	15	-	-	0.1808
	Females	42	18	-	-	
Vaccination status	Vaccinated	22	6	-	-	0.8336
	Not vaccinated	26	10	-	-	
	Unknown	54	17	-	-	
Diarrhoea	Yes	11	3	0.21-3.16	0.8273	0.7818
	No	91	30			
Pneumonia	Yes	4	2	0.27-9.04	1.5806	0.6070
	No	98	31			
Upper gastrointestinal bleed	Yes	3	1	0.10-10.26	1.0313	0.9791
	No	99	32			
Sepsis	Yes	18	2	0.06-1.37	0.3011	0.1211
	No	84	31			

Hypertension	Yes	2	1	0.13-17.80	1.5625	0.7192
	No	100	32			
Anaemia	Yes	62	23	0.63-3.44	1.4839	0.3583
	No	40	10			
Dyselectrolytemia	Yes	29	7	0.26-1.73	0.6777	0.4168
	No	73	26			
Abnormal RFT	Yes	19	8	0.54-3.57	1.3979	0.4846
	No	83	25			
CSF JE	Positive	41	9	0.23-1.32	0.5579	0.1847
	Negative	61	24			
Poor GCS <8	Yes	5	14	4.60-44.40	14.2947	<0.0001
	No	97	19			
Shock	Yes	16	15	1.87-10.67	4.4792	0.0007
	No	86	18			
Multiple anticonvulsants	Yes	15	26	7.93 to 58.46	21.5429	<0.0001
	No	87	7			
3% sodium chloride infusion	Yes	17	11	1.02 to 6.07	2.5000	0.0440
	No	85	22			

[Table/Fig-6]: Parameters predicting adverse outcome.
*11 children were lost from the study

Outcome	No. of patients	Percentage
Recovered completely	86	58.90
Recovered with neurological sequalae	16	10.95
Death	33	22.60

[Table/Fig-7]: Outcome at discharge.
*11 children were lost from the study

and seizures [20]. Kakoti G et al., revealed 21.13% had neurological sequelae at discharge and 14.7% died in the hospital [16].

In the present study, four factors showed a statistically significant association with mortality among children with JE:

1. Children who had shock and required inotropes.
2. Low GCS (<8) necessitating mechanical ventilation.

Parameters	Sushmitha M et al., [3]	Bhadouriya R et al., [4]	Kuntal M et al., [6]	Sambasivam E et al., [2]	Chakrabarti SK et al., [11]	Present study
Place of study	Karnataka	Indore, MP	Wardha, Maharashtra	Chennai, Tamil Nadu	Agartala, Tripura	Dibrugarh, Assam
Year of study	2023	2022	2020	2017	2017-2019	2018-2019
Sample size	56	50	80	30	100	146
Common age group	Infants upto 1 year followed by >5 years	1-5 y	>10 y	1-5 y	9-12 y	5-12 y
Gender	M>F	M>F	M>F	M>F (1.1:1)	M>F (1.1:1)	M>F (1.3:1)
Seasonality	-	Monsoon	Monsoon	-	May-August	Monsoon
Common clinical features	Fever>Altered sensorium>Seizures	Fever, altered sensorium, seizure, vomiting, headache	Fever, altered sensorium, seizure	Fever, seizure	Fever, altered sensorium, seizure, vomiting	Fever, seizure, vomiting, headache
Common sequalae		-	-		Speech impairment, abnormal movements, cranial nerve palsy	Speech impairment, abnormal movements, cranial nerve palsies, extrapyramidal symptoms
Short term outcome	61% discharged, 18% discharged with neurological sequalae,13% expired	-	65% discharged, 23.7% died, 8.7% LAMA, 2.5% referred		57.4% discharged without sequalae, 14.8% discharged with sequalae and 27.7% died	58.90% discharged, 22.60% died and 10.95% discharged with neurological sequalae
Mortality predictors	Low GCS, MV, hyponatremia	Use of ionotropes and MV	Shock, use of ionotropes, MV	MV, shock	-	Circulatory shock, MV, refractory seizures and raised Intracranial Pressure (ICP)

[Table/Fig-8]: Comparison with other studies [2-4,6,11].

Upon evaluating the outcomes of children affected by JE, 86 (58.90%) children recovered completely, while 16 (10.95%) had neurological sequelae at the time of discharge. A total of 33 (22.60%) children died in the hospital during the study period. Children discharged with residual sequelae exhibited speech impairment, cranial nerve palsies, hypotonia, abnormal movements, and paresis. Eleven children could not be followed-up in the study. Chakrabarti S et al., reported that 14.8% were discharged with neurological sequelae, and 27.7% died [11]. Avabratha KS et al., also reported a 40.85% complete recovery rate at discharge, with 47.61% expecting speech disturbances, motor deficits, behavioural disturbances, involuntary movements,

3. Refractory seizures requiring multiple anticonvulsants.
4. Raised ICP requiring 3% sodium chloride infusion.

These factors resulted in higher mortality rates compared to those who were haemodynamically stable.

This study will be beneficial for healthcare providers in triaging and managing patients, which may rationalise the utilisation of limited healthcare resources and improve patient outcomes.

Limitation(s)

Most specific etiological agents of encephalitis remain unknown in this study. Additionally, short-term and long-term neurological

deficits among admitted and discharged children could not be evaluated due to a lack of longitudinal follow-up. The data collected came from a single hospital, and further studies with a larger sample size are required in Assam.

CONCLUSION(S)

This study reveals that children aged 5-12 years are more vulnerable to JE, especially during the monsoon season. The most common clinical presentations were fever, seizures, vomiting, headache, and altered sensorium. The case fatality rate was 22.60%. The presence of shock, poor GCS, the use of inotropes, 3% sodium chloride, multiple anticonvulsants, and the need for supportive ventilation were associated with poor outcomes. Given that there is no specific treatment for JE, it is essential to identify and intervene early on prognostic features indicative of a poor outcome. Although the JE vaccine has been introduced in the National Immunisation Schedule (NIS), issues of vaccine efficacy and coverage still need to be addressed. Effective vaccination coverage, improved vector control strategies, and public awareness are vital in reducing the disease burden of JE.

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