



RESEARCH ARTICLE

CLINICAL PROFILE AND PREDICTORS OF MORTALITY OF JAPANESE ENCEPHALITIS IN CHILDREN ADMITTED WITH ACUTE ENCEPHALITIS SYNDROME

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ABSTRACT

Background: Japanese encephalitis (JE) is the most prevalent and significant vector-borne viral encephalitis in human, with an estimated 30,000 to 50,000 of cases and 10,000 - 15,000 deaths annually worldwide. Mortality of JE is about 20% to 30% and 30–50% result in permanent neuropsychiatric sequelae.

Aims and objectives: To determine the clinical profile and for a better understanding predictors of mortality of JE in children hospitalized with AES cases.

Materials and methods: All cases admitted with symptoms suggestive of AES were included in the study. A detailed history was taken and investigations like CBG, CBC, electrolytes, peripheral smear were analyzed. Neuroimaging done was analyzed and abnormal findings documented. CSF analysis was done after taking consent from the parents. CSF was sent for cytology, biochemical analysis, AFB and gram stain. Viral analysis was done in CSF, which included antibodies for JE. The outcome of the patients was recorded at the time of discharge.

Results: Most common age group was 5 – 12 years. There was no significant difference in death among the infants or older children. Male to female ratio was 1.13:1. Common presentations were fever 64 (100%), seizures 52 (80.25%), dysglycemia 22 (34.37%) and found statistically insignificant with mortality. Twenty three JE patients (35.93%) presented with GCS<8, the mortality was significantly high (P<0.001). Those group of patients who had shock and required inotropes and the group of patients who had hyponatremia 21(32.81%), the mortality was significantly high (P <0.001 and p = 0.0017 respectively). Outcome at discharge was recorded for 64 patients. Among the 64 confirmed JE patients, 37(57.81%) were recovered completely, while 14 (21.8%) cases had neurological sequelae at the time of discharge. 13 (20.32%) patient died in the hospital

Conclusion: The case fatality rate was observed 20.31% mortality due to JE in children admitted with AES. In the present study, Predictors of mortality in JE patients were GCS <8, hyponatremia, shock and use of inotrope significantly associated with mortality.

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INTRODUCTION

Encephalitis is defined as inflammation of the brain parenchyma and is usually a result of viral infections (Forbes, 2017). Japanese encephalitis (JE) is the most prevalent and significant vector-borne viral encephalitis in human, with an estimated 30,000 to 50,000 of cases and 10,000 - 15,000 deaths annually worldwide (Potula, 2003; <http://www.cdc.gov/japaneseencephalitis/qa/index.html> and http://www.who.int/immunization/topics/Japanese_encephalitis/en/index.html). Mortality of JE is about 20% to 30% and 30–50% result in permanent neuropsychiatric sequelae (<http://www.cdc.gov/japaneseencephalitis/qa/index.html>) (http://www.who.int/immunization/topics/Japanese_encephalitis/en/index.html).

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Children are more commonly affected. Most of the JE infections are asymptomatic, and the ratio of symptomatic to asymptomatic infections ranges from 1 in 300 to 1 in 1000 (Halstead, 1962 and Huang, 1982). In India, nearly all states have reported JE cases except that of Jammu & Kashmir, Himachal Pradesh, and Uttaranchal (Arunachalam, 2009). The Northeastern region of India, particularly Assam has been experiencing recurrent episodes of JE with different magnitudes from July to October every year (Dutta, 2011). JE is characterized by fever, reduced consciousness, seizures and focal neurological signs, can cause aseptic meningitis or a poliomyelitis-like acute flaccid paralysis (Kumar, 1990). Treatment of JE is symptomatic and intensive supportive care is important to avoid neurological sequelae (Halstead, 2007). This study was carried out to determine the clinical profile and for a better understanding predictors of mortality of JE in children hospitalized with AES cases which may help in early diagnosis and initiate prompt supportive care.

MATERIALS AND METHODS

This study was prospective study carried out in the Department of Pediatrics, Silchar Medical College and Hospital, Silchar, Assam, over a period of 2 years from January 2015 to December 2016. Age group included was from 1 month to 12 years. All cases admitted with symptoms suggestive of AES were included in the study. According to the World Health Organization (WHO) clinical case definition, Acute Encephalitis Syndrome (AES) is defined as the acute-onset of fever with change in mental status including symptoms such as confusion, disorientation, coma or inability to talk and/or often with new onset of seizures (Excluding simple febrile convulsion) in a person of any age at any time of the year (Solomon, 2008). This is a tertiary care hospital and provides health care services to several districts like Hailakandi, Karimganj etc and neighboring state Manipur and Tripura. Most patients are referred to this apex level institute from periphery for better supportive care and treatment. A detailed history was taken and relevant factors in history were documented. Demographic details were taken into consideration to find out the endemicity of any particular etiological agent. Thorough clinical examination was done and clinical findings were noted. All enrolled cases were worked up with the help of a predesigned and pretested proforma. Immunization status was recorded in the proforma. Blood investigations like CBG, CBC, electrolytes, peripheral smear were analyzed. Neuroimaging done was analyzed and abnormal findings documented. CSF analysis was done after taking consent from the parents. CSF was sent for cytology, biochemical analysis, AFB and gram stain. Viral analysis was done in CSF, which included antibodies for JE.

JE virus specific IgM antibodies were detected by IgM antibody capture-enzyme-linked immunosorbent assay kits obtained from the National Institute of Virology (NIV), Pune, India. The test was standardized and reported by NIV in 1984 (Gadkari, 1984). The JE IgM kit contains all ready to use reagents and has also been evaluated by Centers for Disease Control (CDC), Fort Collins, CO, the USA for its performance. Using the United States' CDC results as the reference standard, the NIV kit had sensitivity in CSF 75%, Serum 71%, and specificity 96% in CSF and 77% in Serum (Khan, 2011). Reports of CSF samples analyzed for physical, chemical, and cytological examination and other relevant investigations are done at the time of admission were recorded from the bed head tickets of the patient. The outcome of the patients was recorded at the time of discharge. Few patients were released from the hospital against medical advice and their condition could not be assessed. They were disqualified from the outcome analysis. The outcome was defined as recovered completely, recovered with neurological sequelae, and death. Neurological sequelae were defined by the presence of one or more of the following at discharge; impaired consciousness, weakness (monoparesis, hemiparesis, and quadriplegia), focal or generalized abnormal limb tone (hypertonia and hypotonia), focal or generalized abnormal limb reflexes (hyperreflexia and hyporeflexia), diagnosis of new onset or recurrent seizures, or new or recurrent extra pyramidal movement disorders (Solomon, 2002).

Statistical Analysis: Results were presented in the form of percentages, mean \pm SD. The statistical association was analyzed with the help of chi-square test and Fisher's exact test whichever was applicable.

RESULTS

Demographic Characteristics: During the study period of two years, the total number of admissions in the department of pediatrics was 8368, out of 4021 patient were admitted in 2015 and 4347 patient in 2016. 26 JE cases out of 115 AES were admitted in 2015 and 38 JE cases out of 153 AES admitted in 2016. The total number of clinically diagnosed Acute Encephalitis Syndrome (AES) patients was 278, as per WHO criteria. Thus, the overall percentage of acute encephalitis cases among all admissions was 3.32%. Of these 64 cases (23.02%) were JE and 214 patients (76.98%) were non-JE. The JE cases were confirmed following detection of JEV specific IgM antibody either in CSF or serum. Among the JE positive patients, 16 were diagnosed by only serum testing positive for anti-JEV IgM antibodies and 6 were identified following detection of anti-JEV IgM antibodies in CSF only. In 42 AES patients both serum and CSF were positive for JEV specific IgM antibody. Among the JE positive cases, 34 (53.12%) were male and 30 (46.57%) were female. The predominant age group affected was 5 to 12 years (Table 1) and the youngest child affected was 6 months old. Majority of the patients (90.62%) were from the rural area and belonged to low socioeconomic group (79%). Most of the children (93.75%) were not vaccinated against JE. Vaccination status of 4.68% children was not known. However, only 1.56% of the caregiver could confirm that their children were vaccinated against JE.

Table 1. The demographic profile of JE patients

Parameter	Number of patients (n=64)	Percentage (%)
Age in years		
<1	4	6.25
1 to 5	24	37.5
>5	38	59.37
Sex		
Male	34	53.12
Female	30	46.57
Setting		
Urban	6	9.37
Rural	58	90.62

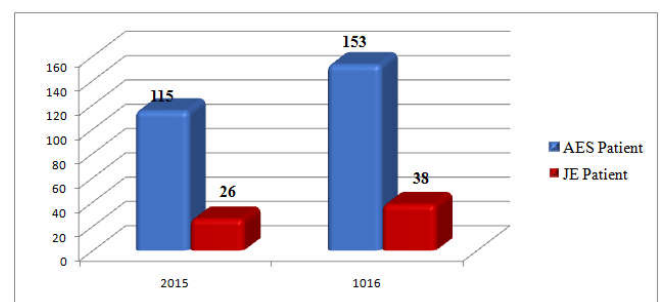


Fig. 1. Proportion of JE patients (year wise)

Clinical Profile: The clinical profile of JE positive patients was presented in Patients with JE were presenting vivid signs of AES. The most common presenting symptoms recorded were moderate to high-grade fever (100%), altered sensorium (84.37%), seizures (81.25%), headache (40.26%), and vomiting (34.37%). Signs of meningeal irritation were present in 34.37% of cases. Around 35.93% of JE patients had Glasgow coma scale (GCS) within 3 to 8. All the JE patients were presented to the hospital between 1 to 10 days from the onset of illness (Table 2).

Table 2. Clinical profile of children with JE (n = 64)

Features	Number	Percentage (%)
Fever	64	100
Altered sensorium	54	84.37
Headache	26	40.26
Irritable	4	6.66
Vomiting	22	34.37
Abnormal behavior	4	6.25
Diarrhea	5	7.81
Seizure	52	81.25
Glasgow coma scale (GCS) \leq 8	23	35.93
Signs of meningeal irritation	22	34.37
Shock and inotrope use	21	32.81

Table 3. Biochemical profile of children with JE (n=64)

Parameter	Number	Percentage (%)
CBG on admission		
<60mg/dl	2	3.12
60 – 150mg/dl	40	62.5
>150mg/dl	22	34.37
Serum sodium		
<135meq/l	21	32.81
135 – 145meq/l	37	57.81
>145meq/l	6	9.37
Total leucocyte count		
<5000cell/cumm	0	0
5000 – 11000/cumm	25	39.06
>11000/cumm	39	60.93
CSF cell count		
>5 cell/mm ³	37	57.81
CSF protein concentration		
>40mg/dl	28	43.75

Table 4. Outcome of children with JE at the time of discharge

Outcome	JE patients (n=64)	Percentage (%)
Recovered completely	37	57.81
Recovered with neurological sequelae	14	21.87
Death	13	20.31

Table 5. Comparison of variables between death and survivors in children with JE

Variables	Group	Death(%)	Survivors (%)	P value
Age	Less than 1 year	1(1.5)	1(1.5)	P=0.25
	1 to 5 years	7(10.9)	19(29.6)	
	More than 5 years	5(7.8)	31(48.4)	
Sex	Male	7(10.9)	27(42.2)	P=0.95
	Female	6(9.3)	24(37.5)	
Seizure	Yes	11(17.18)	38(59.37)	P=0.16
	No	2(3.1)	13(20.3)	
CBG on admission	<60mg/dl	0	1(1.5)	P=0.47
	60 – 150mg/dl	7(10.9)	33(51.5)	
	>150mg/dl	6(9.3)	17(26.5)	
Serum sodium	<135meq/l	9(14)	12(18.7)	P=0.0017*
	135 – 145meq/l	3(4.6)	34(53.1)	
	>145meq/l	1(1.5)	5(7.8)	
Total leucocyte count	<5000cell/cumm	0	0	P=0.18
	5000-11000/cumm	3(4.6)	22(34.3)	
	>11000/cumm	10(15.6)	29(45.3)	
GCS	<8	10(15.6)	13(20.3)	P<0.001*
Meningeal signs	Positive	4(6.2)	18(28.1)	P=0.09
CSF cell count	>5 cell/mm ³	6(9.3)	28(59.3)	P=0.57
CSF protein concentration	>40mg/dl	7(10.9)	30(46.8)	P=0.74
Shock and inotrope use	Yes	12(18.7)	9(14)	P<0.001*
	No	1(1.5)	42(65.6)	

*Pvalue<0.05 significant. CBG- Capillary blood sugar

Biochemical profile: The CSF WBC counts of the 64 patients ranged from 1.0/mm³ to 672.0/mm³ (39.69 ± 79.86). Elevated levels of WBC (>5/mm³) were found in 39 (60.93%) patients and predominantly lymphocytic in nature. The mean CSF protein and glucose level were 54.0 ± 24.3mg/dL and 49 ± 14.2mg/dL, respectively. Of these 29 (45.3%) had elevated (>40mg/dL) level of protein (Table 3).

The outcome of JE Patients: Outcome at discharge was recorded for 64 patients. Among the 64 confirmed JE patients, 37(57.81%) were recovered completely, while 14 (21.8%) cases had neurological sequelae at the time of discharge. 13 (20.32%) patient died in the hospital (Table 4). Analysis of the results shows that; most common age group was 5 – 12 years. There was no significant difference in death among the infants

or older children. Male to female ratio was 1.13:1. Common presentations were fever 64 (100%), seizures 52 (80.25%), dysglycemia 22 (34.37%) and found statistically significant with mortality. Twenty three JE patients (35.93%) presented with GCS < 8, the mortality was significantly high ($P < 0.001$). Those group of patients who had shock and required inotropes and the group of patients who had hyponatremia 21 (32.81%), the mortality was significantly high ($P < 0.001$ and $p = 0.0017$ respectively). Hyponatremia did not seem to influence the mortality significantly. Presences of meningeal signs were not found to be associated with fatal outcome. Similarly, no significant association was observed between high cell counts, an elevated level of protein in CSF, and children fatality (Table 5).

DISCUSSION

In the present study, we have tried to analyze the clinical profile and factors determining the predictors of mortality in JE patients. This study demonstrates that JE is one of the leading forms of viral encephalitis of children in this part of the country. Around 23% of hospitalized children with AES were diagnosed as confirmed JE. A similar study done by Gilati et al. (2013), reported 30% patients with JE in hospitalized AES children, Pankaj P et al. (2016) reported 34.2% and Jain A et al. (2015) also reported JEV 16%. In our study, children mostly affected were from rural areas (90%). The age group mainly affected was 5 to 12 years comprising 56.25% which is similar to that of other studies (Kakoti et al., 2013; De et al., 2015; Khinchi et al., 2010). Majority of the affected children were not vaccinated (93.75%). A male preponderance was seen in our study which was similar to various earlier studies (Gitali Kakoti, 2013; Pankaj, 2016; Jain, 2015; Kumar, 2006 and Samanta, 2015). Among the clinical presentation, fever (100%), altered sensorium (54%), seizures (52%), headache (26%), and vomiting (22%) were the most common symptoms observed in this study. In children, similar manifestations were also noted in earlier studies (Gitali Kakoti, 2013; Chen, 2009 and Avabratha, 2012). Signs of meningeal irritation were observed in 22 (34.37%) patients. Similar observations were made by different researchers in earlier studies (Gitali Kakoti, 2013; Gourie-Devi, 1984 and Potula, 2003). Elevated cell count (> 5 cell/mm³) in CSF was noted in 57.81% of patients with lymphocytic predominance and elevated CSF protein level (> 40 mg/dL) was recorded in 43.75% in JE cases. However, in a study done by Avabratha et al. (Avabratha, 2012) observed elevated cell count in 45.06% and protein in 74.67% study patients and Kakoti et al. (Gitali Kakoti, 2013), also found that cell count 77% and protein in 52.5% study patients.

In the present study, 21.85% JE patients had neurological sequelae at the time of discharge, neurological sequelae in JE are the common observation (Avabratha, 2012 and Wu, 1999). Mortality of JE in the present study was 20.31%, mortality of JE reported by Kakoti et al (14.7%), De et al (29.2%) Khinchi et al (27.2%), Pankaj P et al (16%). In present study mortality was significantly associated with GCS < 8, hyponatremia and shock. Similar association was also noted in other different studies (Gitali Kakoti, 2013; Kumar, 2006; Avabratha, 2012; Burke, 1985). We could not establish any association of mortality with the meningeal signs and elevated level of CSF cell count and CSF protein. A similar finding was noted by kakoti et al (Gitali Kakoti, 2013), while Avabratha et

al (Avabratha, 2012), revealed an association between mortality and meningeal signs.

Limitations

The etiology of non-JE cases is not apparent from the study. The study does not give any information on the extent of short term and long term neurological deficits among the admitted and discharged patients. This is obvious due to lack of longitudinal follow up in the study. The data was collected from a single hospital. Further, studies with large sample size are needed in Assam.

Conclusion

Acute Encephalitic Syndrome is a major public health problem in Assam. The yearly seasonal occurrence of both Japanese and Non – JE encephalitic diseases are associated with significant mortality and morbidity in terms of long-term neurological sequelae. The most common clinical presentations were fever, altered sensorium, seizure, headache, vomiting and signs of meningeal irritation. The case fatality rate was observed 20.31% mortality due to JE in children admitted with AES. In the present study, Predictors of mortality in JE patients were GCS < 8, hyponatremia, shock and use of inotrope significantly associated with mortality. Though JE vaccine has been introduced in the National Immunization Schedule (NIS), vaccine efficacy and coverage are issues that need to be addressed as effective vaccination combined with improved vector control strategies and public awareness will be helpful in reducing the disease burden of Japanese Encephalitis.

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