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Clinical Profile of Acute Encephalitis Syndrome in Children with Special Reference to Japanese Encephalitis in a Tertiary Care Teaching Hospital of Upper Assam

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Abstract
Background: *The north eastern region of India is an endemic area for viral encephalitis that clinically presents as acute encephalitis syndrome (AES). The Japanese Encephalitis (JE) is an acute mosquito-borne viral disease and the most important causative agent of AES in this region, resulting in considerable morbidity and mortality every year. JE is endemic in Assam with outbreaks every year during the monsoons.*
Aims: *This study was conducted to study the clinical profile of pediatric Acute Encephalitic Syndrome with special reference to Japanese Encephalitis admitted to the department of Pediatrics, Jorhat Medical College and Hospital.*
Study Design: *Retrospective record-based hospital study in the Department of Pediatrics, Jorhat Medical College and Hospital, Jorhat for 2 years (1st January 2014 to 31st December 2015).*
Methods And Materials: *All admitted cases age between 2months to 12 years fulfilling WHO clinical criteria of AES admitted in Pediatric Ward during study period were included in the study. Other cause of fever, altered sensorium with or without seizure and febrile seizure cases were excluded from the study. Clinical & pathological profile, outcome were analyzed from patient bed head tickets.*
Results: *The mean age at presentation of AES in children was 6.5 years (range 2 month-12 years) with a male: female ratio of 1:1.2. The maximum number of cases presented during the monsoon months of July and August. JE virus was the commonest causative agent accounting for 34.56% of all cases. Case fatality rate for JE was 51.78% and the majority of deaths were observed in the age group of 5 to 12 years.*
Conclusion: *Acute Encephalitic Syndrome is a major public health problem in Assam. The yearly seasonal occurrence of both Japanese and Non – JE encephalitic diseases is associated with significant mortality and morbidity in terms of long term neurological sequeale. Japanese Encephalitis accounts for a majority of cases of AES in this region. Though JE vaccine has been introduced in the National Immunization Schedule (NIS), effective vaccination combined with improved vector control strategies and public awareness will be helpful in reducing the disease burden of Japanese Encephalitis.*
Keywords: *Encephalitis, Japanese; Encephalitis, Viral; Japanese Encephalitis Vaccines.*

INTRODUCTION

Encephalitis defined as inflammation of the brain parenchyma and is usually as a result of viral infections [1]. 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 [2].

AES is caused by a wide range of viruses, bacteria, fungus, parasites, spirochetes, chemicals and toxins. It may be sporadic like herpes simplex encephalitis (HSE), or epidemic such as Japanese B encephalitis (JE). Although AES has multi-factorial etiology with Japanese encephalitis (JE) and Dengue predominating in South-East Asia [3], JE is endemic in Assam with outbreaks every year during monsoons [4]. Viral encephalitis is an important cause of mortality and morbidity in children. The disease typically has an acute onset with fever and progresses rapidly with or without seizures. In many cases, it may lead to death in a matter of hours especially children below the age of 10 years [5].

According to NVBDCP, GOI report(year 2014), India witnessed 10,834 cases of AES, with Uttar Pradesh recording the highest with 3,329 cases, followed by Assam with 2,194 and 1,716 deaths nationally due AES. Assam had the highest Japanese Encephalitis cases at 761, and 165 deaths out of 292 deaths nationally in 2014. Usually one-third of JE patients die and half of all survivors develop severe neurological sequeale [6, 7, 8].

The detection of JE virus specific IgM antibody from serum or cerebrospinal fluid (CSF) by IgM captive-enzyme linked immune sorbent assay (IgM-Captive ELISA) has been accepted as the standard for serological diagnosis [9]. The presence of JE virus-specific IgM in CSF is considered to be a sign of JE virus infection of the central nervous system. CSF is the preferred sample for diagnosis of JE because if anti JE IgM is detected in the CSF this confirms infection of the central nervous system with JEV [10].

This study was carried out to examine the demographic, clinical profile, laboratory characte-ristics and outcome of children hospitalized with AES which may help in early diagnosis and initiating prompt supportive care.

MATERIALS AND METHODS

This study was record based retrospective descriptive study of 2 years duration. The study included pediatric patients of the age group of 2 months to 12 years admitted from January 2014 to December 2015 in the Department of Pediatrics, Jorhat Medical College and Hospital (JMCH), Jorhat, Assam, India satisfying the WHO clinical case definition of AES. This is a tertiary level hospital and provides health care services to nearby districts including neighboring state of Nagaland. Most patients are referred to this apex level institute from periphery because of lack of neuro-imaging and intensive care facilities in the periphery. Data for the study was retrieved from patient bed head tickets and also from Institutional AES case reporting database. Data extracted from the records included age, sex, demographic profile, JE positivity, vaccination status/outcome.

As per WHO guidelines, AES is defined as acute onset of fever and a change in mental status, including symptoms such as confusion, disorientation, or inability to talk and/or new onset of seizures excluding febrile convulsions; in a person of any age at any time of the year." [10] OR "a person of any age, at any time of year with the acute onset of fever and a change in mental status (including symptoms such as confusion, disorientation, come, or inability to talk) AND/OR new onset of seizures (excluding simple febrile seizures). Other early clinical findings may include an increase in irritability, somnolence or abnormal behavior greater than that seen with usual febrile illness [11]". All AES cases were reported using standard case investigation and laboratory request forms as per guidelines of the

National Vector Borne Diseases Control Program (NVBDCP), Ministry of Health and Family Welfare, India [12].

A total of 162 cases were included in the study. Cerebrospinal fluid (CSF) and serum samples were collected from the patients after obtaining informed and written consent from the guardians. Only serum samples were collected from patients in whom a lumbar puncture was not possible or contraindicated.

Samples were collected in sterile vials and immediately transported to the laboratory of the Department of Microbiology, JMCH, Jorhat. All the samples were tested by the NIV JE IgM Capture ELISA Kit supplied by NVBDCP at RMRC, Lahoal, Dibrugarh and Department of Microbiology, JMCH, Jorhat. CSF cytological and biochemical analysis and other pathological tests were done at Pathology and Biochemistry Department of JMCH.

Inclusion Criteria All pediatric patients up to 12 years of age brought to Jorhat Medical College and fulfilling the standard WHO case definition of AES as mentioned above were included in the study.

Exclusion Criteria This included patients presented like AES picture, but with clinico-investigational diagnosis confirmative of cerebral malaria, Reye syndrome or other non-infectious encephalopathy.

RESULTS AND OBSERVATIONS

During the study period of two years, the total number of admissions was 7585, with 3414 in 2014 and 3271 in 2015. The total number of clinically diagnosed Acute Encephalitis Syndrome (AES) patients was 162, as per WHO criteria. Thus, the overall percentage of acute encephalitis cases among all admissions was 2.13%. Of these 162 cases, 18 patients had equivocal results.

The JE cases were confirmed following detection of JEV specific IgM antibody either in CSF or serum. All the samples were found to be negative for the presence of IgM antibody against other flaviviruses, namely, Dengue and West Nile prevalent in this region. Among the JE positive patients 14 were diagnosed by only serum positivity for anti-JEV IgM antibodies and 17 were identified following detection of anti-JE IgM antibodies in CSF. In 25 AES patients both serum and CSF were positive for JE specific IgM antibody. Among the JE positive cases 25 (44.6%) were male and 31 (55.3%) were female (Table 1).

Table no 1: Gender Distribution of AES Cases (JE and Non-JE)

Sex	AES					
	JE	%	Non JE	%	Total	%
Male	25	44.6	71	66.9	96	59.2
Female	31	55.3	35	33.0	66	40.7
Total	56	100	106	100	162	100

The male-to-female ratio was 1:1.2.The predominant age group affected was 5 to 12 years with 105 (64.8%) AES cases (Table 2).

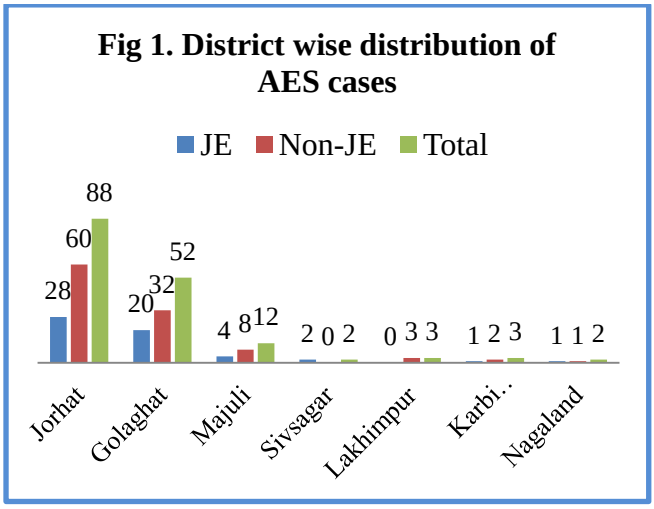
No JE positive result was observed under one year age group. The majority of AES cases were reported from Jorhat 88 cases (56.6%) followed by Golaghat 52 (32%) and Majuli (7.40%). The remaining 4.93% of cases were referred from the districts of Sivasagar, Lakhimpur and Karbi Anglong (Table 3, Fig 1). Also, the nearby state of Nagaland accounted for 1.23% of AES cases.

Table no 2: Age wise distribution of AES Cases (JE and Non-JE)

Age in Years	AES					
	JE	%	Non JE	%	Total	%
0-1	0	0	13	12.2	13	8.02
1-5	15	26.7	29	27.3	44	27.1
>5	41	73.2	64	60.3	105	64.8
Total	56	100	106	100	162	100

Table no 3: District wise distribution of AES Cases (JE and Non-JE)

District	AES					
	JE	%	Non-JE	%	Total	%
Jorhat	28	50.1	60	56.6	88	54.3
Golaghat	20	35.7	32	30.1	52	32.0
Majuli	4	7.14	8	7.54	12	7.40
Sivasagar	2	3.57	0	0	2	1.23
Lakhimpur	0	0	3	2.83	3	1.85
Karbi Anglong	1	1.78	2	0	3	1.85
Nagaland	1	1.78	1	0	2	1.23



Highest AES cases 89 (54%) observed in the ethnic community, out of which 27(48.2%) JE positive cases were observed. Patients from tea garden community accounted for 34.5% of all AES cases and 44.6% of all JE positive cases (Table no 4).

Table no 4. Community wise distribution of AES Cases (JE and Non-JE)

Communities	AES					
	JE	%	Non JE	%	Total	%
Ethnic	27	48.2	62	58.4	89	54.9
Tea Garden	25	44.6	31	29.2	56	34.5
Others	4	7.14	14	13.2	18	11.1
Total	56	100	106	100	162	100

Table 5 shows the religion wise distribution of AES Cases. It is evident that out of 162 cases, 156 AES are from the Hindu community and no JE positive result was observed in other communities. All JE positive results (100%) are from the Hindu community.

Table no 5. Religion wise distribution of AES Cases (JE and Non-JE)

Religion	AES					
	JE	%	Non JE	%	Total	%
Hindu	56	100	100	94.3	156	96.2
Muslim	0	0	6	5.66	6	5.66
Christian	0	0	0	0	0	0
Others	0	0	0	0	0	0
Total	56	100	106	100	162	100

Analysis of the vaccination status of the cases showed a poor percentage (36.4%) of JE vaccination among these cases admitted with AES. This is despite the efforts by the government to incorporate JE vaccination into the Routine Immunization Programme. Even among the patients who were found to be JE positive, JE vaccination was confirmed on history in 17 (30.3%) cases (Table 6).

It is evident that a larger number of AES (as well as JE) cases presented during the monsoon months of July and August during the study period. Occurrence of AES cases during the consecutive two years of study, 2014 and 2015 are showed in Figure no 2.

Table no 6: JE Vaccination Status among AES Cases

Vaccinated against JEV	AES					
	JE	%	Non JE	%	Total	%
Vaccinated	17	30.3	42	39.6	59	36.4
Not vaccinated	28	50	48	45.2	76	46.9
Unknown	11	19.6	16	15.0	27	16.6
total	56	100	106	100	162	100

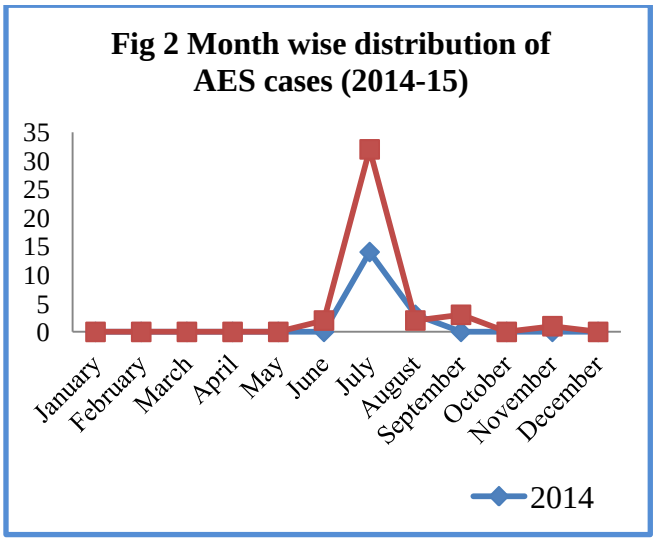


Table no 7. Year wise distribution of AES Cases (JE and Non-JE)

Year	AES					
	JE	%	Non JE	%	Total	%
2014	18	32.1	57	53.7	75	46.2
2015	38	67.8	49	46.2	87	53.7
Total	56	100	106	100	162	100

Table 7 shows the year-wise distribution of AES cases during the two years of study, 2014 and 2015. JE positivity in 2014 was 24.0% (18 out of

75 AES cases), while it was 43.6% (38 cases out of 87) in 2015.

In this study mean duration of hospital stay found to be 14 days and maximum number of both JE positive(33, 58.9%) and JE negative(51, 48.1%) AES cases needed hospitalization for 7 to 14 days. (Table 8)

The outcome analysis shows that out of 162 AES cases 105 (64.8%) were discharged, 33 (20.3%) died, 22 (13.5%) left against medical advice and 2 (1.23%) were referred to higher centre. Out of the 33 deaths, maximum number of deaths were found in the months of July (15, i.e. 45.4%) and August (5, i.e. 15.1%). Overall, 9 (27.2%) of all AES deaths were due to JE. Of all patients diagnosed to be JE positive, the mortality was 16.0 % (i.e. 9 out of 56 JE positive cases) (Table 9).

Table no 8: Duration of hospital stay of AES cases

Duration of stay	AES				total	
	JE		Non-JE			
	No.	%	No.	%	No.	%
<7 days	17	30.3	42	39.6	59	36.4
7-14 days	33	58.9	51	48.1	84	51.8
>14 days	6	10.7	13	12.2	19	11.7
Total	56	100	106	100	162	100

Table no 9: Outcome of AES cases: JE and Non JE

outcome	AES				total	
	JE		Non-JE			
	No.	%	No.	%	No.	%
Died	9	16.0	24	22.6	33	20.3
Discharged	38	67.8	67	63.2	105	64.8
LAMA	9	16.0	13	12.2	22	13.5
Referred	0	0	2	0	2	1.23
Total	56	100	106	100	162	100

From the study it is evident that after JE, meningitis is the most important infective cause of AES in this region. There were total of 7 (5.6 %) cases of meningitis among the AES cases. Among JE positive cases, Neurocysticercosis is observed to be the most common associated co-morbidity but along with Neurocysticercosis other conditi-ons like Hydrocephalus, Cerebral infarction, and Tuberculoma were almost equally distributed among Non-JE AES cases (Table 10).

Fever is the universal presentation but headache and altered sensorium was more common in JE (66%, 75%) than in non-JE AES (52.8%, 66.9%). Similar observation was noted for presence of meningeal signs and AFP. But shock and visual problems were more seen among non-JE AES cases.

Occurrence of AES is more among in the well nourished children in this study. (Table 11)

Table no 10: Other associated co-morbidities

Co-morbidities	AES				total	
	JE		Non-JE			
	No.	%	No.	%	No.	%
Neurocysticercosis	3	6.38	2	2.5	5	4
Hydrocephalus	0	0	2	2.5	2	1.6
Cerebral infarction	0	0	2	2.5	2	1.6
Tuberculoma	0	0	2	2.5	2	1.6
Meningitis	1	2.1	6	7.69	7	5.6

Table no 11: Nutritional profile: distribution of nutritional status among AES cases according to IAP classification

Nutrition	AES				Total	
	JE		Non-JE			
	No.	%	No.	%	No.	%
Normal	22	39.2	38	35.8	60	37.0
IAP Gr I	13	23.2	30	28.3	43	26.5
IAP Gr II	10	17.8	18	16.9	28	17.2
IAP Gr III	8	14.2	12	11.3	20	12.3
IAP Gr IV	3	5.3	8	7.54	11	6.72
Total	56	100	106	100	162	100

The analysis of hematological parameters shows that the mean hemoglobin level is 10.5gm%; mean leukocyte count is 3250/mm3 in JE and 15,400/mm3 in non JE AES cases. In JE AES cases, cerebrospinal fluid analysis shows a mean leukocyte count of 81/mm3, mean sugar of 58mg/dl and mean protein level of 81.5mg%. In non JE AES cases, CSF shows a mean leukocyte count of 48.5/mm3, mean sugar of 61mg/dl and a mean protein of 77.5mg/dl

DISCUSSION

In the present study JE comprises 34.2% of AES cases which is similar to that reported by Kakoti and Dutta et al [13] from Dibrugarh (30%) and Kabilan et al from Tamilnadu (29.3%) [14]. Kushwaha et al reported a lower incidence of JE AES (7-15%) from Gorakhpur, UP [15].

The gender distribution of AES cases shows a male: female ratio of 1.45:1 with a slight female preponderance for JE positive cases (M: F 1:1.2). Roy et al from Kolkata reported a M: F ratio of 1.8:1[16].

The most common affected age group is 5-12 years comprising 64.8% (n=105) of cases which is similar to that of other studies (Kakoti, Dutta et al [13], Khinchi et al [17], De et al [18]). However Roy et al from Kolkata reported 71.4% cases in the 1mon- 7 years age group.

The peak period of occurrence was the month of July (55% of total cases) which is similar to that reported by Mohan et al from Guwahati [19]. However Yashodhara P et al from Guntur, AP reported the peak season from September-October (53.3% of cases).

The study shows a low 36.4% vaccination against JE among the admitted AES cases which is higher than that reported by Kakoti and Dutta et al (19.5%).

Fever (100%), seizure (82.7%), altered sensorium (69.2%), headache (57.4%) and meningeal signs (53.7%) are the common clinical manifestations of this study which is similar to that reported by others. Yashodhara et al reported a higher incidence of meningeal signs (77.1%) while Kushwaha et al reported a lower incidence (25-35%).Shock on presentation was more common in non JE (38.6%) compared to JE cases (21.4%) which is higher than that reported by others (Kushwaha et al 4.5%). Acute bacterial meningitis (ABM) was seen in 5.6% of patients in the present study while Khinchi et al reported a much higher incidence of 47.5% ABM among AES patients in Nepal.

The analysis of CSF among JE cases shows a mean TC of 81/mm3, protein 81.5mg/dl and glucose 58mg/dl as compared to that reported by Kakoti and Dutta et al (CSF TC 42.63±82.11, Protein 57± 27.2mg/dl and Glucose 45.6± 12.4mg/dl).

The overall mortality of AES in the present study is 20.3% with JE comprising 27.2% of total deaths. The mortality among JE cases is 16% (9/56 cases). This is lower than that reported by De et al (29.2%), Khinchi et al (27.2%), and Patgiri et al (29.9%) [20].

LIMITATIONS

The present study has the inherent limitation of being a retrospective study. The detailed epidemiological background of the enrolled subjects is not known. The etiology among 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.

CONCLUSION

Acute Encephalitic Syndrome is a major public health problem in Assam. The yearly seasonal occurrence of both Japanese and Non – JE encephalitic diseases is associated with significant mortality and morbidity in terms of long term neurological sequeale. The high incidence of shock in the present study suggest delayed referral and lack of pre- transport stabilization of AES cases referred to Jorhat Medical College from the peripheral health facilities. 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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