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RESEARCH PAPER

A clinico-epidemiological study of acute encephalitis syndrome in a tertiary care hospital of Assam, India

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***Background and aims**: India's significant public health problem is Acute encephalitis syndrome (AES). The present study aims to assess the clinico-epidemiological profile of acute encephalitis syndrome in a tertiary care hospital of Assam, India. **Methods**: A single centre prospective observational study was conducted on AES patients admitted to the Department of Medicine in Tezpur Medical College and Hospital, Assam, India. Clinical features, disease outcome, CSF, biochemical and radiological profiles were studied. All cases above 12 years that fulfil the WHO case definition of AES were included. Informed/written consent was obtained before data collection. Prior Ethical clearance was obtained from the Institutional Ethics Committee. Chi-square and Student's t-test was used to determine significance. Statistical analysis was carried out using Statistical Package for the Social Sciences (SPSS) version 20. The p-value < 0.05 is considered significant. **Results**: Majority (67%) of the cases were male and belonged to the age group 30-40 years. A total of 126 patients (58%) tested positive for Japanese Encephalitis (JE). Fever (97%) and altered sensorium (90%) are the main clinical presentation. Most cases were reported from May to July (P <0.05). Out of 218 AES cases, 69 patients (33%) expired, 104 (47%) were recovered entirely, and 29(13%) had neurological sequelae. **Conclusion**: JE is still the primary cause of AES in this country. Early diagnosis, treatment and vaccination might help effective management and prevention of the disease.*

***Keywords**: Acute Encephalitis syndrome, Japanese Encephalitis, Tezpur, Assam*

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INTRODUCTION

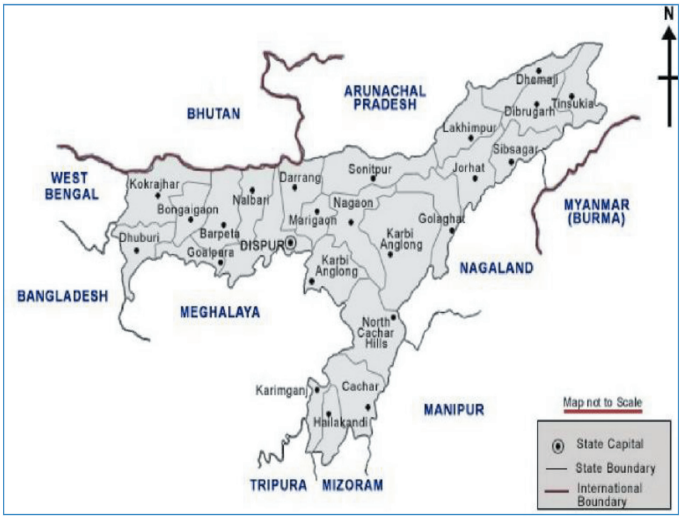
Acute encephalitis syndrome is considered a significant public health problem in India due to the increased morbidity and mortality associated with the disease.[1] As per the World Health Organisation (WHO), the clinical case definition of AES is a person of any age at any time of year with the acute onset of fever and a change in mental statuses such as confusion, disorientation, coma, or inability to talk and new onset of seizures (except simple febrile seizure).[2] An increase in irritability, somnolence, or abnormal behaviour greater than that seen with usual febrile illness are AES's other early clinical findings.[3] The disease most commonly affects children and young adults, although the entire spectrum of age groups can be involved.[1] The average incidence is between 3.5 and 7.4/100,000 patient-years, the incidence being higher in children.[4,5]

Viruses are the main causative agents in AES cases. However, other sources such as bacteria, fungus, parasites,

spirochetes, chemicals, toxins and non-infectious agents have also been reported over the past few decades.[6] Broadly, they can be classified into infective and non-infective agents. Although viruses are the primary cause of AES, aetiology remains unidentified in many cases.[4] The causative agent of AES varies with season and geographical location and predominantly affects populations below 15 years.[5] The type of viruses also markedly differs in different parts of the world. In China, the UK, Norway, Spain, and France, HSV is a common viral agent for AES.[7-11] Whereas Japanese encephalitis virus (JEV) is the primary cause of AES in India (ranging from 5%-35%).[12,13] Herpes simplex virus, Influenza A virus, West Nile virus, Chandipura virus, mumps, measles, dengue, Parvovirus B4, enteroviruses, Epstein-Barr virus and scrub typhus, S. pneumoniae are the other causes of AES in sporadic and outbreak form in India.[14] Nipah and Zika viruses are also causative agents for AES.[1] According to the NVBDCP data, AES cases were reported mainly from Assam, Bihar, Jharkhand, Karnataka, Manipur, Meghalaya, Tripura, Tamil Nadu, and Uttar Pradesh. In India during 2018, 15% of cases of AES were found positive for infection due to JEV.[1]

Although AES cases other than JE continue to be reported throughout the year, there is an overall increase of total AES cases since June, peak during July- August and decline in September-October. All the endemic States except Assam start reporting JE cases from July onwards and attain a peak in September-October. In Assam, the cases start appearing from February, and the peak is in July.[3,15]With a high case fatality rate and frequent residual neuropsychiatric damage in survivors, JE is a significant public health problem. Almost 50,000 cases and 10,000 deaths are reported each year, primarily amongst children.[15]

To study the clinico-epidemiological profile of acute encephalitis syndrome in a tertiary care hospital of Assam, India.



MATERIALS AND METHODS

A single centre prospective observational study was conducted on patients admitted to Tezpur Medical College and Hospital, Assam, India. Clinical features, disease outcome, CSF, biochemical and radiological profiles were studied in AES cases. All cases aged over 12 years, admitted to the Department of Medicine, Tezpur Medical College, who fulfil the WHO case definition of AES, were included in the study.

Based on the case definition, 218 cases were enrolled for the study. Informed consent was obtained from the parents or legal guardians of the participants. Ethical clearance for the study was obtained from the Institutional Ethics Committee. Data on demographic and clinical observations were recorded in a predesigned questionnaire. Case reporting was done in standard Case Investigation Form for clinical and demographic characteristics documentation and Laboratory Request Form as per guidelines set by National Vector Borne Disease Control Programme (NVBDCP), Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India.

All cases satisfying the WHO clinical definition of AES were subjected to Routine blood investigations and NCCT Brain in Emergency Department. After admission in the Medicine ward, lumbar puncture was performed under all aseptic and antiseptic precautions, and CSF (2 ml) was collected. In addition, a serum sample was obtained at the same time. Both serum and CSF samples were kept at 4-8°C if testing is done within 48 h, for short- and long-term storage kept in a deep freezer at –20° and –80°C, respectively. Cerebrospinal fluid (CSF) was analyzed for physical, biochemical, cytological, ADA, HSV, IgM antibodies to JEV (Mac Elisa technique), HSV and West Nile Virus. Testing for scrub typhus (IgM) and Leptospira (ELISA) was done in highly suspicious cases. Serum was analyzed for IgM antibodies to JEV, Dengue (NS1 for symptoms less than 5days, IgM antibodies for signs more than 5 days), Orientiatsutsugamushi (causative agent for Scrub typhus) and Chikungunya. The viral aetiology of Encephalitis was considered either definitive or possible based on the sample type and evidence of viral infection. The presence of viral genome by PCR/RT– PCR / culture of virus or detection of IgM antibodies in CSF was considered “definitive”.

In contrast, the presence of viral genome by PCR/RTPCR from blood samples or detection of IgM antibodies in serum and absence of above viral markers in CSF was considered “possible”. JE Samples were reported as positive or negative, or equivocal. A second serum sample from the patient was obtained 10-14 days after the first sample in the uncertain result. Selected patients were also taken for MRI Brain to

look for active lesions and residual deficits during follow up.

Statistical analysis: The data were statistically analyzed using the Chi-square test for categorical variables and the t-test for continuous variables to determine significance. Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 20. A *p-value* <0.05 is considered significant.

RESULTS

Out of 218 cases taken up for the study, male preponderance with 67% cases was recorded. The highest number of patients (26%) belongs to 30-40 years (**Table 1**). Out of 146 males, 102 (70%) were found to be JE +ve, and 44 (30%) were Non-JE cases, while in the case of females, 24(33 %) were found to be JE +ve, and 48 (67%) were Non-JE cases.

Table 1 Age and gender distribution of AES cases

Age group(years)	Number	Percentage
12-20	39	18
20-30	42	19
30-40	57	26
40-50	34	16
50-60	21	9
>60	25	12
Sex		
Male	146	67%
Female	72	33%

Clinical profile: Most cases presented with fever (97%) and altered sensorium (90%) followed by headache, neck rigidity, vomiting and seizures. Cranial nerve involvement was seen in rare cases, primarily involving third and seventh cranial nerves with 4% of patients (**Table 2**).

Table 2 Clinical features of study participants

CLINICAL FEATURES	NUMBER(n)	PERCENTAGE (%)
Fever	212	97
Altered Mental Status	198	90
Headache	166	76
Vomiting	70	32
Seizures	34	15
Neck Rigidity	113	51
Paralysis	20	9
Cranial nerve injury	10	4

Etiological profile: Of 218 cases included in the study, 126 patients (58%) tested positive for JE. The test was confirmed with IgM antibodies to JEV in CSF or serum. A significant proportion (14%) was also found to be TBM +ve, confirmed by a rise in CSF ADA level and radiologic changes (**Figure 1**).

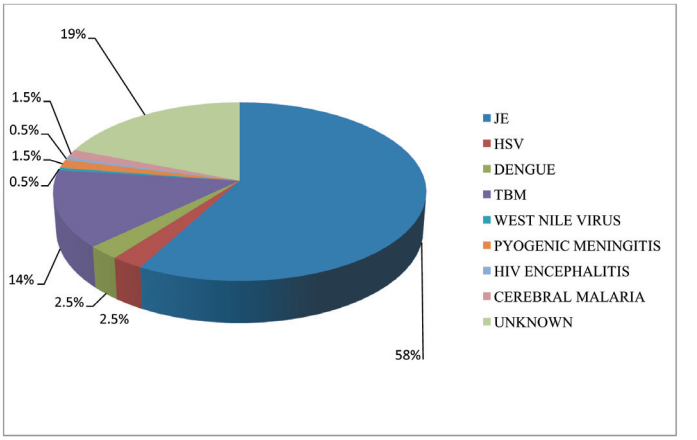


Figure 1 Etiological Profile of AES cases

Seasonal variation and socio-demographic profile: The majority of the cases (77.1%) were reported from May to August, and the association were found to be statistically significant (P <0.05) among viral and non-viral AES cases. Most AES cases were reported from rural areas (76.2%). The association between socioeconomic status and the living condition with viral and non-viral AES cases was found to be statistically insignificant (**Table 3**).

Table 3 Socio-demographic and temporal profile among viral and non-viral AES cases

Socio-demographic and temporal variable	Viral AES (n=138)	Non-Viral AES (n=80)	p-value for x^2
Economic Condition			
Upper	38 (27.5%)	21 (26.2%)	0.96
Middle	53 (38.4%)	32 (40.0%)	
Lower	47 (34.0%)	27 (33.7%)	
Residential Status			
Rural	76 (55.1%)	46 (57.5%)	0.73
Urban	62 (44.9%)	34 (42.5%)	
Season			
January-April	32 (23.2%)	25 (31.3%)	0.02
May-August	77 (55.8%)	29 (36.2%)	
September-December	29 (21.0%)	26 (32.5%)	

Outcome: The clinical outcome was reported for 202 patients. The status of 16 patients (7%) could not be ascertained as the patients leave against medical advice. A total of 69 patients (33%) expired, 104 (47%) were recovered entirely, and 29(13%) had neurological sequelae, which were further evidenced by specific MRI findings (**Figure 2)**.

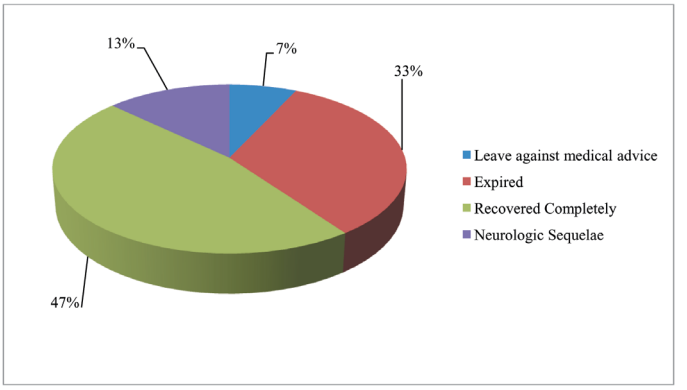


Figure 2 Clinical Outcome of AES cases

Laboratory profile: Out of the 218 AES cases, 138 (63.3%) were confirmed for viral AES. The laboratory profiles of viral and non-viral AES cases are presented in **Table 4**. Significant differences in mean levels of various laboratory parameters were observed among viral and non-viral patients. The lower mean level of total leucocyte count, platelet count and CSF protein was observed in viral AES cases with a p-value <0.05.

Table 4 Laboratory profile of viral and non-viral AES cases

Parameters	Viral AES (mean ±sd)	Non-viral AES (mean ±sd)	P-value for t-test
Hemoglobin(g/dl)	11±3.2	10±2.3	0.015
Total leucocyte count (cumm)	12.9±3.8	13.9±2.8	0.041
Platelet (lakh/cumm)	1.4±0.8	1.6±0.9	0.092
Totalserum bilirubin (mg/dl)	0.8±0.5	1.0.±0.8	0.024
Serum Albumin (g/L)	4.0±0.7	3.5±1.2	<0.001
AST(U/L)	66±15	54±5	<0.001
ALT(U/L)	54±23	45±17	0.003
CSF–cell count (cumm)	86±25.8	79±23.2	0.047
CSF-Sugar (mg/dl)	50±12.6	40±23.7	<0.001
CSF –Protein (mg/dl)	98±13.8	117±22.4	<0.001

DISCUSSION

In our clinical study conducted in a tertiary care hospital of Assam, male preponderance was observed with the male-female ratio of 2:1. Most of the male cases were caused by JE, while no such predominance was found in females. A significant portion of patients (26%) belonged to the age group 30-40 years, in contrast to other similar studies where the prevalence of old age and paediatric age group was more common.[15-17]

The most common clinical presentation was fever (97%) and altered sensorium (90%), followed by headache, neck rigidity, vomiting and seizures. This finding was similar to other clinical studies.[18,19] Change in mental status has been a predominant symptom in the observation of other authors.

Out of multifactorial cases, JE (58%) is the predominant cause of AES in our study, confirmed by CSF or Serum JE specific IgM antibodies. This finding followed previous studies describing both epidemic and sporadic AES cases in different parts of the world.[20,21] In our study, about 19% of the cases remained undiagnosed, which was also similar to a previous study conducted in north east.[22]

Seasonality of the cases was observed during monsoon season, with the highest incidence of cases reported during May to August, and the results were found to be statistically significant (P<0.05). Although more than half of the patients were reported from rural areas, the effect was statistically insignificant. The comparison between socioeconomic status (upper, middle and lower) and the living conditions (rural or urban) was statistically insignificant. In a similar study conducted in northeast India, the peak of cases was recorded between June to August. A predominant rural distribution was reported.[15] While in another study conducted in Odissa, no significant differences in rural predominance were noted.[16]

In our study, out of a total of 218 patients, 69 (33%) expired, 104 (47%) were recovered entirely, and 29 (13%) had neurological sequelae. In a similar study conducted in North-East, a mortality rate of 24% was reported while 51% were stable and discharged.[22]

CONCLUSION

In our clinical study, the findings have been most similar to previous studies conducted on similar subjects. Japanese Encephalitis is still the primary cause of AES in this part of the country, and the most common clinical presentation was fever, altered sensorium and headache. Early diagnosis, treatment, and vaccination are critical to the effective management of such cases.

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Contribution of Authors: We declared that this work was done by the authors named in this article, and the authors will bear all liabilities about claims relating to the content of this article.

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