Original Article

Clinico-epidemiological characteristics of hospitalized acute encephalitis syndrome children and their correlation with case fatality rate

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Abstract

Background: Acute Encephalitis Syndrome (AES) in children contributes considerable morbidity and mortality in endemic region. A study was conducted to see the clinico-epidemiological characteristics of hospitalized AES children and to find out if there is any correlation of clinico-epidemiological factors with case fatality rate (CFR). **Methods:** This hospital-based observational prospective study was conducted in a tertiary care teaching hospital of Assam, India from 16th May, 2019 to 15th May, 2020. We enrolled clinically diagnosed 140 hospitalized AES children consecutively as per WHO case definition. Cerebrospinal fluid and serum samples were tested for JEV-specific IgM antibodies. **Results:** Out of 140 AES children 84 (60%) were male and 5–12 years age group had the highest 79 (56.4%) number of cases. Primarily cases were from rural areas 132 (94.3%). In addition to fever, major clinical manifestations were seizures 114 (81.4%), altered sensorium 128 (91.4%), meningeal signs 62 (44.3%), and <8 GCS 42 (30%). CFR was 27.7%. Significantly high CFR was seen among AES children with GCS <8 (*P*-value 0.0001) and presence of meningeal signs (*P*-value 0.0007). A higher proportion of non-survivors 55.6% were non JE AES. Monthly incidence of AES/Death showed a peak in the month of July. **Conclusion:** AES in children is a significant public health problem in the study area with high CFR. Presence of GCS <8 and meningeal irritation are the important predictors of mortality in AES children. Preponderance of non-JE AES case fatality in children warrant further exploration and appropriate public health interventions.

Keywords: Acute encephalitis syndrome, case fatality rate, children, morbidity, non-JE

Introduction

Acute Encephalitis Syndrome (AES) mortality in children remains a significant health care concern in India, as the rates continue to rise despite of best investment to improve child health. AES is defined as the acute onset of fever and a change in mental status (including symptoms such as confusion, disorientation, coma, or inability to talk) and/or new onset of seizures (excluding simple febrile seizures) in a person of any age at any time of year.[1]

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The first major AES outbreak was reported from Eastern India (Bankura, West Bengal) in 1973.[2,3] Since then epidemics of AES have occurred in different parts of India with striking regularity. There have been 57,432 AES cases and 5,963 deaths occurred in between 2014 and 2018. In the year 2019 alone, 14995 AES cases and 710 deaths were reported from 21 Indian states with a case fatality rate near to 5%. The states mostly affected were Assam, West Bengal, Uttar Pradesh, Bihar, Odisha, Jharkhand, Manipur, Tamil-Nadu. Among them, Assam alone contributed 2,652 cases with over all case fatality rate (CFR) 13.3%.[4]

Every year the AES outbreak shows a seasonal trend with a high CFR, causing heavy toll of human life affecting mostly

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the children below 15 years of age.[5] Viruses are the main causative agents in AES cases, although other sources such as bacteria, fungus, parasites, spirochetes, chemicals, toxins, and non-infectious agents have also been reported over the past few decades.[6] In recent times, despite of remarkable advancement in virology, the technology to detect these agents is expensive and often limited to reference laboratories, making specific diagnosis difficult at peripheral facility.[7,8]

Presently in India AES surveillance has mostly concentrated only on finding out Japanese encephalitis virus (JEV) infection. It is obvious that AES cases have not been limited to only JE etiology.[9] In this changed perspective of wide range of causal agents and the rapid rate of neurological impairment because of CNS infection, clinicians face the challenge of a small window period between diagnosis and treatment,[9,10] resulting high CFR specially in pediatric age group.

Therefore, it is crucial to characterize the clinico-epidemiological features of AES in children and their correlation with the mortality. This will enable to advocate for its appropriate management and formulating programmatic intervention.

Objectives

To study the clinico-epidemiological characteristics of hospitalized AES in children and to see their correlation with case fatality rate.

Materials and Methods

Settings

Present study was conducted in pediatric ward of Jorhat Medical College and Hospital (JMCH), Jorhat, Assam during the period 16th May, 2019 to 15th May, 2020. JMCH is a tertiary care health institute among the seven public sector medical colleges of Assam. Usually people residing in districts of Upper Assam and neighboring state like Nagaland seek the health care services from this institute.

Inclusion criteria

- All hospitalized AES children as per WHO case definition
- Children between 1 month and 12 years of age whose parents/Legally Acceptable Representatives (LAR) willing to sign written informed consent

Exclusion criteria

- Children with history of simple febrile seizure[1]
- Children having generalized seizure without fever

Case enrollment

For the present study, 140 hospitalized AES children aged 1 month to 12 years were consecutively recruited who fulfilled the WHO case definition of AES. Written Informed consent was obtained from the parents/LAR before enrolment of the participants and biological sample collections. Children below 1 month were not included in this study. Clinically WHO has defined AES as a case of fever or recent history of fever with change in mental status (including confusion, disorientation, coma, or inability to talk) and/or new onset of seizures (excluding simple febrile seizures). Other early clinical findings could include an increase in irritability, somnolence, or abnormal behavior greater than that seen with usual febrile illness.[1]

All the AES cases were clinically examined on the day of admission with the help of a WHO standard Case Investigation Form (CIF). The outcome of each AES children were noted till the hospital discharge or at the time of death whichever was earlier. Information regarding DAMA cases were recorded and excluded from the outcome analysis.

Sample collection and lab testing

From the eligible study participants 2 ml of blood samples were collected. Lumber puncture were carried out routinely for collection of CSF by the attending pediatricians as a part of clinical care. A portion of the CSF sample kept separately and then transferred under cold chain to State Reference Laboratory, JMCH. Blood samples were kept at 4°C overnight and sera were separated. Both serum and CSF were then stored at −80°C for further analysis. Other relevant data were noted from the bed head tickets of the patient. Study participants were classified as JE and Non-JE cases after doing Mac ELISA for detection of JE specific IgM antibody in CSF and or Serum.

Statistical analysis

Descriptive statistical methods were used to present the clinico-epidemiological characteristics. All statistical analysis were performed with the use of Statistical Package for Social Sciences (SPSS) software, IBM SPSS - version 20. Chi-square tests with Yates correction were performed to test for differences in proportions of categorical variables. *P* values of less than 0.05 were considered as statistically to be significant.

Ethics

Ethical approval was obtained from the Institutional Ethics Committee involving Human participants of Jorhat Medical College and Hospital, Assam, India. Administrative clearance was obtained from the Institute Head to carry out the research project under Women Scientist Scheme, Department of Health Research, Government of India.

Results

Clinico-epidemiological characteristics of AES cases

We observed that among the enrolled 140 AES patients male were affected more 84 (60%) in comparisons to female 56 (40%). The maximum numbers of AES patients 79 (56.4%) were recorded in 5–12 years age group. Predominantly cases were resided in rural areas 132 (94.3%) and by religion they were mostly Hindu 126 (90%). Out of the total 140 AES cases, 94 (72.3%) survived

at the time of discharge, 36 (27.7%) died during hospital stay, and 10 (7.1%) discharged against medical advice (DAMA).

It was noticed that most of the AES patients were hospitalized 131 (93.6%) within 7 days of onset of illness. Next to fever seizures were the most common clinical manifestation 114 (81.4%) during or before hospitalization. Most of the children had altered sensorium 128 (91.4%) and meningeal signs in 62 (44.3%) cases. We calculated the Glasgow Coma Scale (GCS) score of the AES patients and recorded that 42 (30%) had GCS score below 8.

We performed Mac ELISA to know how many of the AES cases were Japanese Encephalitis (JE) and found that of the total cases 53 (37.9%) were JE positive either in CSF or Serum or both [Table 1].

Clinico-epidemiological features of AES non-survivors

In our study 10 AES cases were discharged against medical advice. We followed 130 AES cases till the time of their hospital stay and found that out of the total 130 AES patients 36 died at hospital.

Of the total 36 deaths 23 (63.9%) were male while 13 (36.1%) were female and maximum were belong to age groups of 5–12 years followed by <1 years 11 (30.6%). We observed that most of the patients 34 (94.4%) died were hospitalized within 7 days of onset of fever. Table 2 shows the Clinical characteristics of all the AES death cases. Majority of the death cases presented with seizures 31 (86.1%), altered sensorium 35 (97.2%), and 3-8 GCS score in 25 (69.2%).

Etiology of AES death revealed that 16 (44.4%) of the AES were because of JE and 20 (55.6%) were Non-JE AES [Figure 1].

Monthly incidence of AES/Deaths

Over the period of 12 months it was demonstrated that the AES patients were admitted throughout the year. Similarly, death of AES cases were recorded in all the months of the year except November, 2019 [Figure 2]. We recorded high admission and CFR during the rainy season with a peak in the month of July in our study period.

Geographic distribution of AES/Deaths

District wise distribution of 140 AES cases showed that highest numbers 71 (50.7%) of AES cases were hospitalized from Jorhat district followed by Golaghat 42 (30%), Majuli 16 (1.4%), Sivasagar 8 (5.7%), and Lakhimpur 3 (2.1%).

Of the total 36 AES deaths highest mortality were occurred from Golaghat district 15 (41.6%). On the other hand mortality recorded was from Jorhat 13 (36.1%), Majuli 4 (11.1%), Sivasagar 3 (8.3%), and Lakhimpur 1 (2.8%).

Table 1: Demographic and clinical characteristics of AES cases

Variables	Total AES patients (*n*=140)	Percentage
Demographic characteristics		
Age group		
< 1 year	28	20%
1-5 years	33	23.6%
5-12 years	79	56.4%
Sex		
Male	84	60%
Female	56	40%
Settings		
Urban	8	5.7%
Rural	132	94.3%
Religion		
Hindu	126	90
Islam	14	10%
Others	0	0
Outcome of AES children		
Survivor	94	72.3%
Non-survivor (CFR)	36	27.7%
DAMA	10	7.1%
Clinical characteristics of AES		
Duration of Illness prior to admission		
<7 days	131	93.6%
≥7 days	9	6.4%
Seizure		
Yes	114	81.4%
No	26	18.6%
Change in mental status		
Yes	128	91.4%
No	12	8.6%
GCS		
3-8	42	30%
>8	98	70%
Meningeal signs		
Present	62	44.3%
Absent	78	55.7%
Laboratory results		
JE	53	37.9%
Non-JE AES	87	62.1%

Correlation of clinico-epidemiological features with fatality

The CFR rate was 27.6% till hospital stay. We calculated age specific CFR and found that CFR was 11/27 (40.7%) for <1 years age, 7/30 (23.3%) for 1–5 years age group, and 18/73 (24.7%) for the age 5–12 years. It was revealed that there was no significant association of CFR with age groups, sex, and settings. Similarly clinical variables like duration of illness before admission, presence of seizure, and change in mental status were not associated with AES case fatality. Contrary to these we observed that CFR was noticeably high among AES children when the GCS score was less than 8 or there was presence of meningeal signs [Table 3]. Our observations were found to be statistically extremely significant (*P*-value 0.0001, Chi-square 34.96 with 1 d.f and *P* value 0.0007, Chi square 11.627 with 1 d.f).

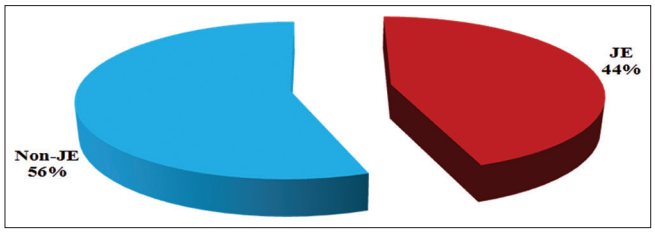

Figure 1: AES Death according to aetiology

Table 2: Clinico-demographic characteristics of non-survivor of AES cases

Variables	Total Fatal patients (*n*=36)	Percentage
Gender		
Male	23	63.9%
Female	13	36.1%
Age in years		
<1	11	30.6%
1-5	7	19.4%
5-12	18	50%
Settings		
Urban	1	2.8%
Rural	35	97.2%
Duration of Illness before admission		
<7 days	34	94.4%
>7 days	2	5.6%
Seizure		
Yes	31	86.1%
No	5	13.9%
Altered sensorium		
Yes	35	97.2%
No	1	2.8%
GCS		
>8	11	30.6%
<8	25	69.4%
Laboratory results		
JE	16	44.4%
Non-JE	20	55.6%

Discussion

The present study revealed that AES in children is a significant public health problem in the study area. In our study, majority of the AES children were male and age groups mainly affected were 5–12 years. Similar observations were also made in earlier studies,[11-14] while in other study there was equal proportion of cases in both the sexes[15] and most of the AES cases were from 1 to 5 years of age group documented.[16] Children between 5 and 12 years are more ambulatory and adore playing out door along with their buddies. Many a time children of this age group are engaged in securing the necessities of life being they are belong to low socioeconomic section of the society. These make them more vulnerable to CNS infection of varied arthropod born etiology.[14] In conformity to our findings many earlier study showed most of the AES cases were from rural origin.[14,16]

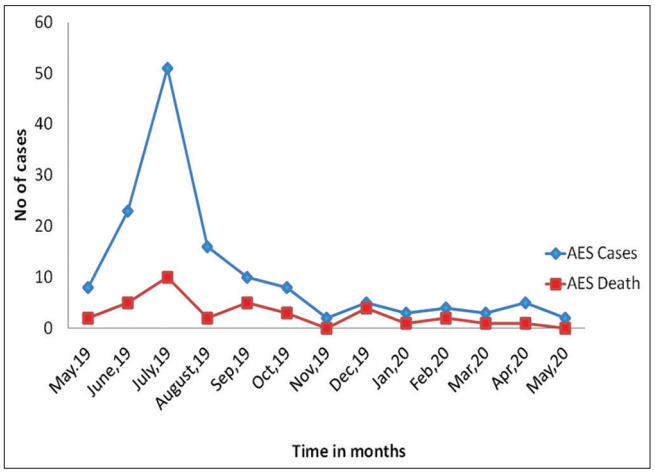

Figure 2: Monthly incidence showed a peak in july among AES/Death during the study period

Among the clinical findings apart from fever, seizure, and altered mental status were the most commonly noticed clinical manifestations. At the time of admission many cases had signs of meningeal irritation and GCS score <8. Our findings are consistent with earlier studies.[5,17]

JE-specific IgM Mac ELISA showed that 37.9% AES cases were because of JE. India is known to be endemic for JE since long including Assam state because of prevailing conducive anthropogenic and ecological environment that favors in circulation of JE virus transmission. Our earlier study confirmed that similar proportion of AES cases were JE positive in upper Assam districts.[14] Kabilan *et al.*, 2004 also recorded the similar finding.[15] In contrast, the non-JEV proportion of AES cases alarmingly high and overridden AES because of JEV in the study area. New viral agents such as Chandipura and Nipah virus, and other viruses such as HSV, VZV, Dengue, Enteroviruses, West Nile Virus, Chikungunya and Parvovirus B4 have been reported in different parts of the India.[5,6,10,18] Therefore, in this changed circumstances it is paramount important to conduct further explorative research to throw more light on the etiological diagnosis of AES cases in the study area. This will help in developing appropriate intervention strategies for prevention and control of AES.[18]

The CFR among the hospitalized AES cases was very high (27.6%). The age specific CFR was highest in children below 1 year of age and male were more fatal. Children with GCS <8 and presence of meningeal irritation had significantly high fatality rate. In conformity to our findings Rayamajhi *et al.*, 2007, Klein *et al.*, Kakoti *et al.*, 2016 also observed the same.[14,19,20] This may be explained that children below 1 year of age living in endemic area are relatively less immune to various etiological agents causing AES in comparison to higher age groups. However, why males are more fatal to his matching part needs further explorative studies.

From our findings it may be conferred that GCS <8 and presence of meningeal signs may be taken as one of the predictors of

Table 3: Correlation of Clinico-epidemiological variables with non-survivors AES children (*n*=36)

Variables	AES children, *n*=130	Fatal (%), *n*=36	Non Fatal (%), *n*=94	Significance
Age (years)				
<1	27	11 (40.7)	16 (59.3)	NS
1-5	30	7 (23.3)	23 (76.7)	
5-12	73	18 (24.7)	55 (75.3)	
Gender				
Male	80	23 (28.7)	57 (71.3)	NS
Female	50	13 (26)	37 (74)	
Settings				
Urban	8	1 (12.5)	7 (87.5)	NS
Rural	122	35 (28.7)	87 (71.3)	
Duration of Illness prior to admission				
<7 days	122	34 (27.9)	88 (72.1)	NS
≥7 days	8	2 (25)	6 (75)	
Seizure				
Yes	114	31 (27.2)	91 (79.8)	NS
No	16	5 (31.3)	11 (68.7)	
Change in Mental status				
Yes	121	35 (28.9)	86 (71.1)	NS
No	9	1 (11.1)	8 (88.9)	
GCS				
3-8	40	25 (62.5)	15 (37.5)	S
>8	90	11 (12.2)	79 (87.8)	
Meningeal signs				
Present	59	25 (42.4)	34 (57.6)	S
Absent	71	11 (15.5)	60 (84.5)	

NS: Not significant, S: Significant at 95% level

mortality in evaluating out come in hospitalized AES children. We could not establish any association of mortality with clinical parameters like seizure, duration of illness, and change in mental status.

Our study revealed high admission of AES cases and their fatality during rainy season with a pick in July. These findings are comparable with the findings of previous studies.[14,17,19,21,22] Conversely in another study conducted by Kamble and Raghabendra[16] seasonal occurrence of AES cases was peak in post monsoon period (October–February). The hot and humid climate of the year is characterized by water-logging, filling up of the perennial tributaries, paddy fields and increased agriculture activities in rural areas. These conditions are attributable to enhance vector densities leading proportionately increased hospitalization of AES cases.[23]

District wise distribution of AES cases confirmed that all the adjoining districts of study site Jorhat are endemic to AES with a highest CFR in Golaghat.

From the findings of the current study it may be stated that the practitioners working in primary health care need to play an important role in planning, organizing, and implementation of various strategies for prevention and control of AES in children. Primary care physician are to be trained extensively so as to make them skilled to do early diagnosis based on clinical findings and to manage AES cases at primary health care facility in early phase of the disease. Further on the basis of mortality predictors physician should able to diagnose timely the complicated AES cases to refer them higher set up for specialized care. Linking primary care physician in community awareness building in regard to preventive measures and well-timed reporting of fever cases to disease surveillance system for appropriate actions will boost the AES containment programme.

Summary

1. The current hospital based observational prospective study was conducted in a tertiary care teaching hospital of Assam, India during the period 16th May, 2019 to 15th May, 2020 to understand the clinico-epidemiological characteristics of hospitalized AES children and to know if there is any correlation of clinico-epidemiological factors with case fatality rate (CFR).
2. As per WHO AES case definition a total of 140 hospitalized children clinically diagnosed as AES were recruited consecutively.
3. Cerebrospinal fluid and serum samples were tested for JEV-specific IgM antibodies.
4. Out of 140 AES children 84 (60%) were male and 5–12 years age group had the highest numbers 79 (56.4%) of cases. Principally cases were from rural areas 132 (94.3%).
5. Along with fever other major clinical manifestations recorded were seizures 114 (81.4%), altered sensorium 128 (91.4%), meningeal signs 62 (44.3%) and <8 GCS 42 (30%).
6. Overall CFR was 27.7%. Significantly higher CFR was observed among AES children with GCS <8 (*P*-value 0.0001) and those

who had signs of meningeal irritation (*P*-value 0.0007).
7. Among the non-survivors a higher proportion 55.6% was non-JE AES.
8. Monthly incidence of AES/Death showed a peak in the month of July.

Highlight

AES in children is a significant public health burden in the study area with high CFR. Non-JE etiology shares major load of AES cases in children. We revealed the presence of GCS <8 and meningeal irritation as the important predictors of AES mortality in children.

Conclusion

The present study revealed morbidity and mortality of AES in children as a significant public health problem in this part of the country. Non-JE etiology contributes to the major burden of AES demands further extensive study to find out the underlying causes. Children less than 1 year of age are more vulnerable to fatality and disease transmission is mostly climate dependent with a peak in July. Extremely significant association of fatality of AES in children with GCS 3 to 8 and meningeal irritation have established as the important mortality predictors. This will help clinicians in predicting outcome in resource limited set up.

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Conflicts of interest

There are no conflicts of interest.

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