ORIGINAL ARTICLE

Clinical Profile and Predictor of Adverse Outcome in Children with Acute Encephalitis Syndrome: A Cross-Sectional Study

Mohanshyam Kuntal[1], Keerti Swarnkar[1]*

[1]Department of Paediatrics, Jawaharlal Nehru Medical College, Sawangi (M), Wardha 442001 (Maharashtra) India

Abstract

Background: Acute Encephalitis Syndrome (AES) is defined as a person of any age at any time of year, with the acute onset of fever and a change in mental status such as confusion, disorientation, coma or inability to talk and/or new onset of seizures (excluding simple febrile seizure). Most cases of AES are due to viral encephalitis, which is more prevalent in South East Asia. *Aim and Objectives:* to study clinical profile and risk factors for adverse outcome of AES in children in Acharya Vinoba Bhave Rural Hospital (AVBRH). *Material and Methods:* This cross-sectional, observational study was conducted in children with AES admitted in Pediatric Intensive Care Unit (PICU) of AVBRH over period of 2 years (August 2017- July 2019). Data collection were done by using predesigned, structured proforma and analyzed by using SPSS version 22. *Results:* Of the 80 cases enrolled in the study 31.25% were between 10-15 years. In this study male to female ratio was 1.5. Mostly subjects were residing in rural area (54.1%), with a common presentation of fever (100%), altered sensorium (73.7%) and convulsion (71.25%). Mortality was observed in 23.7% cases out of which 40(50%) had viral etiology (other than dengue), 21(26.25%) had dengue, 5(6.2%) had malaria. Those who presented with shock and required mechanical ventilation and had deranged Liver Function Test (LFT) profile have statistically significant correlation with mortality. *Conclusion:* Majority of cases were in the age group 10-15 years, with male predominance. Deranged LFT, presence of shock significantly associated with mortality among children with AES. Viral encephalitis is an important cause of AES.

Keywords: Acute Encephalitis Syndrome, Viral encephalitis, Dengue, Shock

Introduction:

According to World Health Organization (WHO) clinically a case of Acute Encephalitis Syndrome (AES) is defined as a person of any age at any time of year, with the acute onset of fever and a change in mental status such as confusion, disorientation, coma or inability to talk and/or new onset of seizures (excluding simple febrile seizure) [1]. Worldwide annual incidence of acute encephalitis reported to be ranging between 3.5-7.5 cases per 100,000 persons and approximately 10.5 to 13.8 per 100,000 children [2]. Many different pathogens have been recognized as causative agent for encephalitis, most important being the viral agents. Herpes simplex virus-1, enteroviruses and arboviruses have increased in frequency and occur in younger age groups [3, 4].

AES is known as 'acute febrile encephalopathy', 'viral encephalitis', 'infectious encephalitis', and 'brain fever', the concept of AES was introduced to facilitate surveillance for Japanese Encephalitis (JE), a mosquito borne viral encephalitis [5]. Enteroviruses account for 85 to 95% of all cases of encephalitis, but the arboviruses and herpes simplex virus are also important etiologic agents. Other rare causes are mumps, lymphocytic chorioencephalitis virus, herpes zoster, human

herpes virus type 6, and influenza [6]. JE is a leading cause of viral encephalitis. It is a disease of major public health importance because of its epidemic potential and high case fatality rate. Outbreaks of JE usually coincide with monsoons and post monsoon period when the vector density is high (Ministry of Health and Family Welfare, 2009). The ultimate objective is to prevent the disease occurrence by early diagnosis, implementation of effective control measures, high vaccine coverage with strong and active surveillance system [5-7].

The etiological agents are varied, and physicians treating such children often feel limited by the lack of availability of diagnostic testing for most of these agents. There are numerous lacunae in our knowledge, problems in epidemiological investigations, lack of diagnostic facilities, as well as difficulties in managing these critically ill children in smaller centers in our country.

Therefore, study was conducted to assess clinical profile of AES and to assess risk factors for adverse outcome of AES in children.

Material and Methods:

A Cross-sectional, observational study was done between August 2017-July 2019 at Pediatrics departments in Acharya Vinoba Bhave Rural Hospital (AVBRH), Sawangi, Wardha. Children between age 1 month to 15 years with the acute onset of fever and a change in mental status such as confusion, disorientation, coma or inability to talk and/or new onset of seizures (excluding simple febrile seizure) were included in study. Those with febrile seizures, toxic encephalopathy and children with Central Nervous System (CNS) malformations and other major congenital anomalies predisposing to CNS infections, e.g. spinal bifida, pilonidal sinus, CSF rhinorrhoea, meningocele etc. were excluded. For patients fulfilling inclusion criteria, detailed history and clinical examination were done. All cases were investigated for baseline investigations as well as some specific investigations [Cerebrospinal Fluid (CSF) analysis, dengue serology, radiological investigation] as per clinical presentation. Patient's clinical course, treatment and outcome were noted. The SPSS 22 software was used for all statistical analyses. The descriptive variables were presented in percentages, means and standard deviations. Various variables were compared using Chi-square test or Fischer exact test. A *p*-value less than 0.05 was considered significant. Sample size calculated with alpha value of 0.0500, power of 0.9000 and alternative p of 0.2500, total 80 cases were estimated.

Results:

Demographic profile of acute encephalitis syndrome patients

Table 1 indicates that among 80 AES cases most of them were above 10 years of age (31.25%). Majority of them were males 48(60%), and 32(40%) were females. Majority of them were Hindu 70(87.5%), followed by 09(11.25%) were Muslim. Most of them were from joint family 75(93.75%), agriculture 54(67.5%) is main occupation of parents of them. Most of them belongs to lower socioeconomic status 61(76.25%), 13(16.25%) from middle SES; and 14(17.5%) out of 80 children had potential breeding site at their residing area. Most of the cases were reported during monsoon period 47(58.7%), followed by post-monsoon 18(22.5%) and pre-monsoon 15(18.5%).

Table 1: Demographic Profile of Acute Encephalitis Syndrome Patients

Variables	Frequency (n)	Percentage (%)
Religion		
Hindu	70	87.50
Muslim	09	11.25
Other	01	01.25
Type of Family		
Joint	75	93.75
Nuclear	05	06.25
Parents occupation		
Agriculturist	54	67.50
Business	07	08.70
Labourer	18	22.50
Unemployed	01	01.25
Socioeconomic status		
Upper	06	07.50
Middle	13	16.25
Lower	61	76.25
Potential breeding Site		
Present	14	17.50
Absent	66	82.50

Clinical manifestation of acute encephalitis syndrome patients

Table 2 depicts that out of 80 cases , all had fever; 59 (73.7%) had altered sensorium ; 57 (71.25%) had convulsion; 20 (25%) had headache; 32 (40%) had vomiting. On fundus examination 26 (32.5%) showed papilledema (Table 2). CSF study was done in 38, in which 27 (33.75%) had viral picture, 3 (3.75%) had pyogenic picture, 4(5%) had tuberculosis picture while 4(5%) had normal findings. In 42(52.5%) patients, CSF analysis was not done because they were having severe thrombocytopenia, DIC or critically ill.

Etiology of acute encephalitis syndrome

Table 3 depicts that out of 80 cases 40 (50%) had viral etiology, 21 (26.25%) had dengue, 5 (6.25%) had malaria, 3 (3.75%) bacterial etiology, 4 (5%) had tuberculosis, 5 (6.25%) had other causes. out of 80 AES patients neuroimaging was done for 29(36.25%) patients, in which majority had normal finding on neuroimaging, 7(8.75%) showed Encephalitis features while 4(5%) showed other features like Acute Disseminated Encephalomyelitis (ADEM) in 3(3.75%), 1(1.25%) Neurocysticercosis (NCC).

In all cases of dengue encephalitis along with fever and cerebral involvement, anti-dengue IgM, NS1 were positive. Dengue encephalopathy cases were not included.

Table 2: Distribution of AES Patient according to Clinical Features

Clinical features	Frequency (n)	Percentage (%)
Fever	80	100.00
Altered sensorium	59	73.75
Convulsion	57	71.25
Headache	20	25.00
Excessive cry	03	03.75
Altered behaviour	18	22.50
Vomiting	32	40.00
Neurodeficit	03	03.75
Extrapyramidal features	02	02.50
Cranial nerve palsy	03	03.75
Fundoscopy Normal Papilledema	 54 26	 67.50 32.50
Other system abnormality: CVS RS Abdomen	 04 04 05	 05.00 05.00 06.20

Table 3: Distribution of AES Patients according to Etiology

AES Etiology	Number (n)	Percentage (%)
Viral etiology (other than dengue)	40	50.00
Pyogenic	03	03.75
Tuberculosis	04	05.00
Dengue encephalitis	21	26.20
Cerebral malaria	05	06.25
Other	05	06.25
Not known	02	02.50
Total	80	100.00

Predictors of adverse outcome

Table 4 shows correlation of various variables to the outcome. Those patients who had shock and need inotropes showed significant mortality (p-value: 0.017). Also those who required mechanical ventilation had significant mortality, out of 21 patients put on mechanical ventilation 14 died which was statistically significant with p -value 0.000. Those patient had deranged Liver Function

Table 4: Logistic Regression Analysis of Variables Affecting the Outcome

Risk factors	Group	Death	Survivors	*P*
Age	<1yr 1-5yrs 5-10yrs >10 yrs	04 01 05 09	14 16 15 16	0.377
Sex	Male Female	12 07	36 25	0.740
RBS on admission	<60 (mg/dl) 60-150 (mg/dl) >145 (mg/dl)	02 17 00	01 580 02	0.155
Serum Na	<135 (meq/l) 135-145 (meq/l) >145 (meq/l)	06 13 00	19 49 06	0.354
TLC	<4000 (cells/cumm) 4000-11000 (cells/cumm) >11000 (cells/cumm)	02 10 07	12 35 14	0.072
Sr. creatinine Normal Deranged	 <1.5 times of baseline >1.5 times of baseline	 14 05	 51 10	0.125
LFT (SGPT) Normal Deranged	 <45 (U/L) >45 (U/L)	 09 10	 37 26	0.034
GCS on admission	<8 >8	08 11	10 51	0.119
Shock and ionotropes need	Yes No	03 16	32 29	0.017
Mechanical ventilation need	Yes No	14 05	07 54	< 0.001
Length of hospital stay	<7 days 7-21days >21 days	07 12 00	23 29 09	0.159

Test (LFT) profile also had significant higher mortality (p- value: 0.034). GCS on admission, leucocytes counts, serum sodium concentration and duration of hospital stay had no influence on outcome. Out of 80 children of AES admitted in Pediatric Intensive Care Unit (PICU) 52(65%) were discharge, 19(23.7%) were succumbed, 7(8.7%) were got Discharge against Medical Advice (DAMA), 2(2.5%) were referred to Government Medical College Nagpur because of their unaffordability to long duration of ICU stay for ventilator care.

Discussion:

In the present study most of cases 25 (31.25%) of AES occurred in more than 10 years of age group and between 5 to 10 years were 20 (25%). Similar results also found in studies done by Kakoti *et al*. [8] and Kamble *et al*. [9] whereas Sudhir *et al*. [10] studied 92 cases where he found 70.6% were 1-5 years. In the present study, there is male preponderance which is in concordance with study done by Sudhir *et al*. [10].

In this present study out of 80 cases, 61(76.25%) belongs to lower SES, 13(16.25%) from middle SES, 6(7.5%) were from upper SES. Similar results were found in Kamble *et al*. [9]. Beig *et al*. [11] in U.P. also found that majority of AES cases that is 73.6% were from lower SES. Because of overcrowding in lower SES, poor maintenance of hygiene the transmission of viral and vector borne disease are more common.

In the present study, more than half of patients i.e. 47(58.75%) of AES were admitted during monsoon period that means between July to October followed by 18(22.5%) in post-monsoon period and least in pre-monsoon period i.e.15(18.75%). During monsoon and post-monsoon season, there is increase in number of mosquito breeding site thus it leads to increase in dengue, malaria and other vector born encephalitis. Similar results were found in studies by Kamble *et al*. [9] and Sarkar *et al*. [12]. Study by Sudhir *et al*. [10] showed highest number of AES cases i.e. 68.47% and were admitted in the month of June. However, contrary to this study, study by Yashodhara *et al*. [13] found that 71.42% of encephalitis cases occurred in winter season means post monsoon season.

In the present study, the main presentation was fever present in all patients 80(100%), altered sensorium in 59(73.75%), convulsion in 57(71.2%) while 32(40%) had vomiting, 20(25%) had headache. 3(3.75%) patients had both neurodeficit and cranial nerve palsy, 2(2.5%) had extrapyramidal features. On fundus examination 26(32.5%) had papilloedema, while 54 had normal findings on fundus examinations. Similar findings were done in studies by Kakoti *et al*. [8] and Anuradha *et al*. [14]. Khinchi *et al*. [15] showed all patients had fever and altered sensorium, 90% had seizures.

In the present study, on blood investigations for different parameters showed mean of Hb 10.3 ± 2.2 g/dl, total leucocyte count with mean of 9212.5 ± 5185.774 cells/cumm, RBS with mean 98.48 ± 21.84 mg/dl, SGPT with mean 106.46 ±172.29 U/L. CSF examination done in about half of patients wherever possible. Mean CSF cell counts were 21.62 ± 65.79 cells/cumm, CSF sugar and protein were 25.6 ± 23.37 mg/dl and 14.96 ± 23.37 mg/dl respectively. Similar findings were also seen in study done by Kakoti *et al*. [8] and Sambasivam *et al*. [16].

In the present study, among 80 children admitted in our PICU, 40 (50%) patients had viral etiology

followed by 21(26.25%) patients had dengue encephalitis, 5(6.25%) patients had cerebral malaria 4(5%) had tubercular meningitis 3(3.75%) had pyogenic meningitis while 3(3.75%) had ADEM, 1 had neurocysticercosis, 1 had listeriosis and 2 other in whom etiology not known. Similar results were found in study done by Kamble *et al*. [9] showed out of 136 cases of AES, 84.5% had viral etiology, and 9.5% had other agents like pyogenic, tuberculosis. Thakur *et al*. [17] found that etiology of encephalitis include 27% viral and 47.6% were of unknown etiology. In studies done by Jain *et al*. [18] and Jain *et al*. [19] JE and dengue encephalitis were important etiologies.

As JE is endemic in Andhra Pradesh, Assam, Bihar, Uttar Pradesh and West Bengal, it is the most common cause of AES in these regions. In other region, Enterovirus may be an important cause. In regions where dengue and malaria are endemic there dengue encephalitis and cerebral malaria are more common respectively. Serum NS1 and anti-dengue IgM plays important role in early diagnosis of dengue virus infection and encephalitis as shown by Manthalkar *et al*. [20].

In the present study, out of 80 patients admitted in PICU, 47(58.75%) patients had shock, out of which 16(34%) were succumbed, which was statistically significant in our study ($p = 0.030$). Similar results were found by Sambasivam *et al*. [16] where those having shock had higher mortality, with significant p- value 0.010.

In present study, out of 80 children of AES admitted in PICU, 52(65%) were discharge, 19(23.7%) were succumbed, 7(8.7%) took DAMA, 2(2.5%) referred. Present results is in concordance with previous observation in a hospital based study on AES by DuBray *et al*., [21] where 67.4% of cases discharged with full recovery. Study done by Khinchi *et al*. [15] in Nepal found 40.6% encephalitis patients were discharged and 34.3% were expired. Kakoti *et al*. [8] study in Assam showed 63.9% patients were completely recovered on discharge, 14.7% expired.

In the present study, along with clinical profile, we have tried to analyse the factors determining the outcome of patients admitted to PICU with AES features. Death is higher in age group >10 years of age. In our study we found that three factors have statistical significant association with mortality. Hemodynamic status of patient, those who were having shock and on inotropic support had abnormal LFT and those who required mechanical ventilation had more mortality as compared to those who were hemodynamically stable and had normal liver function test. Similar results were found in a study done by Sambasivam *et al*. [16]. They found two factors have statistically significant association with mortality, one is shock and use of inotropes and another those who had hyponatremia have more mortality then those who are hemodynamically stable.

Most of the specific etiological agent of encephalitis is remained unknown, due to higher cost of viral marker in CSF and serum. Follow up is lacking in our study which may be of help to find out long term neurological deficit and other sequelae in AES patients.

Conclusion:

AES is an important cause of morbidity and mortality especially during monsoon and post monsoon period. Fever, altered sensorium and convulsion were the important presenting features in AES cases. Viral encephalitis along with dengue encephalitis are important causes of AES. Early stabilization and institution of supportive

measures including mechanical ventilation are the cornerstones of management. Investigations are aimed at recognition of etiological agents specially to whom specific treatment are available as Antimalarial drugs for cerebral malaria, antibiotics for pyogenic meningitis, antitubercular drug for tubercular meningitis, steroid for ADEM and to find out things which may adversely affect the outcome. Those who were having shock and on inotropic support, had abnormal LFT and those who required mechanical ventilation have more mortality.

References

1. World Health Organisation. Acute Encephalitis Syndrome. Japanese encephalitis surveillance standards. January 2006. From WHO-recommended standards for surveillance of selected vaccine-preventable diseases. WHO/V&B/03.01. Available from: http://www. who. int/vaccines-documents/DocsPDF06/843.pdf.
2. Kneen R, Michael BD, Menson E, Mehta B, Easton A, Hemingway C, *et al*. Management of suspected viral encephalitis in children - Association of British Neurologists and British Pediatric Allergy Immunology and Infection Group National Guidelines. *J Infect* 2012; 64(5):449-77.
3. Hollidge BS, González-Scarano F, Soldan SS. Arboviral encephalitides: transmission, emergence, and pathogenesis. *J Neuroimmune Pharmacol* 2010; 5(3):428-42.
4. Rayamajhi A, Ansari I, Ledger E, Bista KP, Impoinvil DE, Nightingale S, *et al*. Clinical and prognostic features among children with acute encephalitis syndrome in Nepal; a retrospective study. *BMC Infect Dis* 2011; 11(1):294.
5. Hamid JS, Meaney C, Crowcroft NS, Granerod J, Beyene J. Potential risk factors associated with human encephalitis: application of canonical correlation analysis. *BMC Med Res Method* 2011; 11(1):120.
6. Rotbart HA, Webster AD, Pleconaril Treatment Registry Group. Treatment of potentially life-threatening enterovirus infections with pleconaril. *Clin Infect Dis* 2001; 32(2):228-35.
7. Kumar R, Mathur A, Singh KB, Sitholey P, Prasad M, Shukla R, *et al*. Clinical sequelae of Japanese encephalitis in children. *Indian J Med Res* 1993; 97:9-13.
8. Kakoti G, Dutta P, Ram Das B, Borah J, Mahanta J. Clinical profile and outcome of Japanese encephalitis in children admitted with acute encephalitis syndrome. *BioMed Res Int* 2013; 2013.
9. Kamble S, Raghvendra B. A clinico-epidemiological profile of acute encephalitis syndrome in children of Bellary, Karnataka, India. *Int J Comm Med Public Health* 2016; 3(11):2997-3002.
10. Sudhir SK, Prasad MS. Acute Encephalitis Syndrome (AES) associated with sociocultural and environmental risk factors in infants/children of Muzaffarpur, Bihar-hospital-based, prospective study. J Evid Based Med Health 2018; 5(1): 23-26.
11. Beig FK, Malik A, Rizvi M, Acharya D, Khare S. Etiology and clinico-epidemiological profile of acute viral encephalitis in children of western Uttar Pradesh, India. *Int J Infect Dis* 2010; 14(2):e141-6.
12. Sarkar A, Taraphdar D, Mukhopadhyay SK, Chakrabarti S, Chatterjee S. Molecular evidence for the occurrence of Japanese encephalitis virus genotype I and III infection associated with acute encephalitis in patients of West Bengal, India, 2010. *Virol J* 2012; 9(1):271.
13. Yashodhara P, Madhavi N. Clinical profile and outcome of viral encephalitis in pediatric department in Government General Hospital, Guntur. *Int J Sci Res* 2015; 4(1):2142-6
14. Anuradha SK, Surekha YA, Sathyanarayan MS, Suresh S, Satish P, Mariraj J, *et al*. Epidemiological aspects of Japanese encephalitis in Bellary, Karnataka, India. *Int J Biol Med Res* 2011; 2(3):691-5.
15. Khinchi YR, Kumar A, Yadav S. Study of acute encephalitis syndrome in children. *J Coll Med Sci Nepal* 2010; 6(1):7-13.
16. Sambasivam E, Muthaiyan J, Mohan S, Ayyavoo AM, Jayachandran G. Clinical profile and predictors of outcome in children admitted to PICU with acute encephalitis syndrome. *Int J Contemp Pediat* 2017; 4(4):1214-7.
17. Thakur KT, Motta M, Asemota AO, Kirsch HL, Benavides DR, Schneider EB, *et al*. Predictors of outcome in acute encephalitis. *Neurology* 2013; 81(9):793-800.

18. Jain P, Jain A, Kumar A, Prakash S, Khan DN, Singh KP, *et al*. Epidemiology and etiology of acute encephalitis syndrome in North India. *Japanese J Infect Dis* 2014; 67(3):197-203.
19. Jain A, Prakash S, Khan DN, Garg RK, Kumar R, Bhagat A, *et al*. Aetiology of acute encephalitis syndrome in Uttar Pradesh, India from 2014 to 2016. *J Vector Borne Dis* 2017; 54(4): 311.
20. Manthalkar P S, Peerapur B V. Utility of NS1 antigen for diagnosis of dengue virus infection. *J Krishna Inst Med Sci Univ* 2017; 6(1): 72-75.
21. DuBray K, Anglemyer A, LaBeaud AD, Flori H, Bloch K, San Joaquin K, Messenger S, Preas C, Sheriff H, Glaser C. Epidemiology, outcomes and predictors of recovery in childhood encephalitis: a hospital-based study. *Pediat Infect Dis J* 2013; 32(8):839-44.

[*]***Author for Correspondence:*** *Dr. Keerti Swarnkar, Department of Paediatrics, Jawaharlal Nehru Medical College, Sawangi (M), Wardha 442001, Maharashtra, India*
Email: drkeerti1978@gmail.com Cell: 9921613920