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Clinicoepidemiological profile and outcome among children with acute encephalitis syndrome from Central India

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ABSTRACT

Background: Acute encephalitis syndrome (AES) is defined as the acute onset of fever and a change in mental status and/or new onset of seizures (excluding simple febrile seizures) in a person of any age at any time of the year. **Aims and Objectives:** The objectives of the study were as follows: (a) To study clinicoepidemiological profile and outcome among children with AES admitted at M.Y.H. Hospital and MGM Medical College, Indore, M.P., and (b) to study prognostic factors associated with bad outcomes. **Materials and Methods:** This prospective observational study was conducted over 12 months (July 2019–August 2020) at the pediatric department of our hospital. Inclusion criteria: Inpatient children aged 6 months–14 years meeting the case definitions of acute encephalitis syndrome. Exclusion criteria: Simple febrile seizures. **Results:** Out of 50 AES cases, majority were between 1 and 5 years of age (40%). There were more males 31 (62%) than 19 (38%) females. Most of the cases were reported during the monsoon period 29 (58%) followed by post-monsoon 13 (26%) and pre-monsoon 8 (16%). Out of 50 cases, all had fever and altered sensorium, 37 (74%) had convulsions, 14 (28%) had vomiting, and 9 (18%) had headache. Out of 50 cases, 42 (84%) had viral etiology including 7 (14%) of dengue encephalitis and 1 (2%) of case of human immunodeficiency virus encephalitis. Only 5 (10%) cases had bacterial etiology. Those who needed inotropes and mechanical ventilation showed significant mortality. **Conclusion:** The peak of AES cases occurred during the monsoon period. A higher proportion of such cases had viral etiology on cerebrospinal fluid analysis. Use of inotropes and mechanical ventilation was identified to be associated with significant mortality.

Key words: Acute encephalitis syndrome; Clinical features; Mortality

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INTRODUCTION

AES also known as acute febrile encephalopathy, viral encephalitis, infectious encephalitis, and brain fever was created to help with surveillance for Japanese encephalitis (JE), mosquito-borne viral encephalitis.[1] Viral encephalitis is a worldwide disease that has a substantial impact on public health, posing a hazard to nearly half of the world's population.[2] Whereas herpes simplex encephalitis (HSE) is sporadic, Japanese B encephalitis is widespread (JE). The etiological agents are diverse, and clinicians treating such children are frequently constrained by the lack of diagnostic tests for the majority of them. In developed countries, 50–60% of survivors of viral encephalitis with clear etiologies had a poor prognosis after long-term follow-up.[3-7]

At present, pathogen detection for viral encephalitis is not widely used for clinical diagnosis and treatment in India; the diagnosis is largely based on clinical data and auxiliary examination of patients.[8,9] Furthermore, research suggests that only 30–40% of encephalitis cases can be pathogenically diagnosed.[10,11] Moreover, the prognosis for more than half of the viral encephalitis pathogenically diagnosed cases was poor.[12] In India except for Jammu and Kashmir, Himachal Pradesh, and Uttaranchal, nearly, all states have reported JE. The northeast part of India has

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been experiencing recurrent episodes of JE with different magnitude from July to October every year.[13,14]

The etiological agents are varied and clinicians treating such children are frequently constrained by the lack of diagnostic tests for the majority of these agents. Our country's smaller clinics have several gaps in knowledge, a shortage of diagnostic facilities, and challenges in caring for critically ill children. Hence, a study was conducted to determine the clinical profile and outcomes of AES in hospitalized children. These data will be beneficial to the clinician to diagnose and treat these patients early and improve their outcomes. The ultimate goal is to prevent disease occurrence through early diagnosis, effective control measures, and high vaccine coverage.

Aims and objectives

(a) To study clinicoepidemiological profile and outcome among children with AES admitted at M.Y.H. Hospital and MGM Medical College, Indore, M.P., and
(b) To study prognostic factors associated with bad outcomes.

MATERIALS AND METHODS

This prospective observational study was conducted at a tertiary care hospital in Central India. The study was conducted over a period of 12 months (July 2020–August 2021) after final clearance from the Institutional Ethics Committee. The study was done based on various diagnostic reports and case history sheets, including neuroimaging, cerebrospinal fluid examination, and various blood investigations of the patients of AES.

Inclusion criteria

Children aged 6 months–14 years of age admitted with a provisional diagnosis of acute encephalitis syndrome in the department of pediatrics in tertiary care hospital in Central India during the study period were included in the study.

Exclusion criteria

Simple febrile seizures were excluded from the study.

Methodology

The detailed history and examination of each patient were recorded. Investigations of serum (complete blood counts, peripheral smear for malarial parasite, NS1 antigen, and human immunodeficiency virus [HIV] ELISA based as per history and examination) and cerebrospinal fluid (CSF) (routine examination, culture, and CBNAAT) were done. Neuroimaging was done wherever possible.

Data analysis

The above data were analyzed according to etiology, clinical presentation, and immediate outcome. Data were entered into Excel sheet and analyzed using SPSS program. The collected data were analyzed using various statistical methods, including the Mann–Whitney U-test and independent t-tests.

RESULTS

Majority of the cases presented with fever, altered sensorium, convulsion, neck stiffness, headache, vomiting, and diarrhea. The presence of diarrhea, low Glasgow Coma Scale (GCS) (<8), use of inotropic support, and need for mechanical ventilation were noted to be higher in the viral AES group. Neck stiffness, vomiting, and headache were noted more in the non-viral group of AES (Table 1).

There was a significantly higher level of median total lymphocyte count (TLC) ($P<0.001$), polymorphs ($P=0.001$), and protein ($P=0.020$) in children with non-viral AES as compared with viral AES. Viral AES showed significantly higher level lymphocyte ($P=0.002$) as well. However, there was no significant difference in median glucose level between viral and non-viral AES (Table 2).

Out of 50 cases, 42 (84%) cases had viral etiology including 7 (14%) cases of dengue encephalitis and 1 (2%) case of HIV encephalitis. Besides this, 5 (10%) cases were having bacterial etiology, 2 (4%) cases were having cerebral malaria as etiology, and 1 (2%) case with tubercular meningoencephalitis as etiology. Out of 50 cases, neuroimaging was done for 15 patients, in which the majority had normal findings on neuroimaging, 5 (10%) showed features of encephalitis. In all cases of dengue encephalitis along with fever and cerebral involvement, anti-dengue IgM, NS1 was positive (Table 3).

The correlation of various variables to an outcome was studied. Those patients who had shock and need of inotropes showed significant mortality ($P=0.001$). Moreover, patients who needed mechanical ventilation showed significant mortality rate ($P=0.001$). Out of 25 patients put on mechanical ventilation, 19 died which were statistically significant with $P=0.001$. Patients having GCS<8 on admission also had significantly higher mortality ($P=0.001$) (Table 4).

DISCUSSION

In the present study, we have analyzed the clinical profile and factors associated with mortality in AES patients. It demonstrates that viruses are the leading cause of encephalitis in children. Most of the patients were 1–5 years of age (40%); the majority being males 31 (62%). Similar results were also found in studies done by Kakoti et al., and Sudhir and Prasad.[15,16]

Table 1: Clinical features of children with AES

Clinical features	Overall (=50)		Viral AES (=42)		Non-viral AES (=8)		OR (95% CI)	P-value
	Count	N	Count	N%	Count	N%		
Fever	50	100	42	100	8	100	NA	NA
Altered sensorium	50	100	42	100	8	100	NA	NA
Convulsion	37	74	33	78.57	4	50	3.67 (0.76–17.61)	0.104
Shock and need of inotropes	26	52	24	57.1	2	25	4 (0.72–22.18)	0.113
Need of mechanical ventilation	25	50	23	54.7	2	25	3.63 (0.65–20.11)	0.14
GCS<8	24	48	22	52.38	2	25	3.3 (0.60–18.26)	0.171
Neck stiffness	18	36	13	34	5	62.5	0.26 (0.05–1.3)	0.102
Vomiting	14	28	11	26.9	3	37.5	0.59 (0.12–2.89)	0.517
Headache	9	18	6	14.2	3	37.5	0.21 (0.037–1.18)	0.07
Diarrhea	12	24	11	26.1	1	12.5	2.48 (0.27–22.54)	0.419
Coagulopathy	9	18	7	20	2	13	0.6 (0.1–3.61)	0.577
Rash	4	8	4	9.5	0	0	1.98 (0.1–40.50)	0.655
Paresis	3	6	2	4.7	1	12.5	0.35 (0.03–4.4)	0.416
Cranial nerve palsy	2	4	1	2.38	1	12.25	1 (0.02–50.40)	1

AES: Acute encephalitis syndrome, GCS: Glasgow Coma Scale

Table 2: Characteristics of different parameters of CSF fluids

Parameter	Overall	Viral AES (n=42)	Non-viral AES (n=8)	P-value
TLC (cells/cubic mm)*	5 (3)	5 (2.75)	117.50 (485.75)	<0.001
Polymorphs (cells/cubic mm)	10 (18.25)	10 (10)	90 (27.50)	0.001
Lymphocytes (cells/cubic mm)	90 (19.50)	90 (10)	10 (20)	0.002
Protein (mg/dL)	64.80 (5.35)	64.40 (3.95)	82.30 (12.30)	0.020
Glucose (mg/dL)	42.80 (5.45)	42.80 (4.40)	42.70 (4.55)	0.408

* Mann–Whitney U-test. Non-parametric data were represented as median. TLC: Total lymphocyte count, AES: Acute encephalitis syndrome, CSF: Cerebrospinal fluid

Table 3: Etiology identified in various AES patients

AES etiology	Number (n=50)	% of total
Viral (other than dengue and HIV)	34	68%
HIV encephalitis	1	2%
Dengue encephalitis	7	14%
Cerebral malaria	2	4%
Pyogenic	5	10%
Tubercular meningoencephalitis	1	2%

AES: Acute encephalitis syndrome, HIV: Human immunodeficiency virus

In our study, most of the cases were reported during the monsoon period 29 (58%) followed by post-monsoon 13 (26%) and pre-monsoon 8 (16%). During monsoon and post-monsoon season, there is an increase in the number of mosquito breeding sites; thus, it increases dengue, malaria, and other vector-borne encephalitis. Similar results were found in a study by Kamble et al.[17]

Out of 50 cases, all had fever and altered sensorium, 37 (74%) had convulsions, 14 (28%) had vomiting, and 9 (18%) had headache. Similar findings were noted in a study done by Anuradha S K et al. It showed that majority patients had fever (97.6%)and altered sensorium (80.5 %); while 70% cases had seizures.[18] In the present study, blood investigations for different parameters showed that mean Hb is 10.58±1.88 g/dL, total leukocyte count with a mean of 13315.4±7169.03 cells/cubic mm, platelet count 1.5±1.06 lac/cubic mm, total serum protein 5.17±0.51, serum albumin 3.26±0.29, median of SGPT 52 IU/l, and SGOT 48.50 IU/l.

CSF examination was done in all patients. There was a significantly higher level of median TLC (P<0.001), polymorphs (P=0.033), and protein (P=0.011) in children with non-viral AES as compared with viral AES. Moreover, there was a significantly higher level lymphocyte (P=0.002) in viral AES. However, there was no significant difference in median glucose level between viral and non-viral AES (P=0.463). In a study by Rose and Condon on the diagnosis of pyogenic meningitis, low glucose values in CSF were observed in 70% and raised protein levels in 90% of cases. Raised protein values have a better diagnostic value than low glucose levels in this study.[19] No CSF culture was positive in our study. Various reasons for the low yield of bacteria on culture are prior antibiotic therapy, delay in transport of specimens to the laboratory, non-availability of special media for specific pathogens, and lack of 24 h facility for processing CSF samples.

In the present study, out of 50 cases, 42 (84%) had viral etiology, including 7 (14%) of dengue encephalitis and 1 (2%) of a case of HIV encephalitis. Besides this, 5 (10%) cases had bacterial etiology, 2 (4%) cases were diagnosed with cerebral malaria, and 1 (2%) case was diagnosed with tubercular meningoencephalitis.

Table 4: Factors associated with mortality among viral AES cases

Factors	Discharge (n=22)	Died (n=19)	OR (95% CI)	P-value*
Seizure	18	19	0.10 (0.005–2.1)	0.140
Low GCS<8	5	19	0.008 (0.0004–0.16)	0.001
Coagulopathy	3	4	0.59 (0.11–3.06)	0.531
Shock and need of inotropes	5	19	0.008 (0.0004–0.16)	0.001
Need of mechanical ventilation	6	19	0.008 (0.0004–0.16)	0.001

*Chi-square test. AES: Acute encephalitis syndrome, GCS: Glasgow Coma Scale, OR: Odds ratio, CI: Confidence interval.

In all cases of dengue encephalitis, along with fever and cerebral involvement, NS1 was positive. Serum NS1 and anti-dengue IgM play a key role in the early diagnosis of dengue virus infection and encephalitis, as shown by Manthalkar et al.[20] In this study, we had only one case of HIV presenting as AES. Imaging revealed cerebral atrophy and diagnosis was confirmed by ELISA.

In our study, two cases of cerebral malaria were admitted with the clinical picture of AES. CSF analysis and imaging were normal in these cases and a simple peripheral smear examination revealed the diagnosis. Smear was positive for mixed infection of *Plasmodium vivax* and *Plasmodium falciparum*. In the patients of AES, residing in the malaria-endemic area, the presence of anemia with splenomegaly is important clues toward diagnosing cerebral malaria. These children were treated with artemisinin combination therapy (ACT), other supportive measures, and a dramatic improvement was observed within 36 h. All efforts must be made to diagnose cerebral malaria by repeatedly examining peripheral smears and using rapid diagnostic (RDT) tests in cases where there is a high index of suspicion.

Out of 50 cases, neuroimaging was done for 15 patients, in which the majority had normal findings on neuroimaging, 5 (33%) showed features of encephalitis. Out of five cases, three cases showed diffuse cerebral edema, one case showed leptomeningeal enhancement, and one case revealed cerebral atrophy. In the present study, those patients who had shock and need of inotropes showed significant mortality (P=0.001). Similar results were found by Sambasivam et al., where those having shock had higher mortality, with a significant P=0.010.[21] In the present study, out of 50 children of AES admitted to pediatric intensive care unit (PICU), 22 (44%) were discharged, 19 (38%) succumbed, and 9 (18%) left against medical advice (LAMA). In a study from Assam by Kakoti et al., they observed 63.9% of patients recovered completely till discharge, 14.7% expired.[15]

Along with the clinical profile, we have tried to analyze the factors determining the outcome of patients admitted to PICU with features of AES. We found that three factors had a statistically significant association with mortality. Patients who had shock and needed inotropic support, low GCS (<8), and required mechanical ventilation showed a greater mortality rate than those who were hemodynamically stable. Similar results were found in a study done by Sambasivam et al. They found two factors to have a statistically significant association with mortality: Shock and use of inotropes and hyponatremia had more mortality than those who were hemodynamically stable.[21]

Limitations of the study

Most of the specific etiological agents of encephalitis remain unknown in this study due to the higher cost of viral markers in CSF and serum. Follow-up is lacking in our study which may be of help in finding out long-term neurological deficit and other sequelae in AES patients.

CONCLUSION

This study reveals that children of age group 1–5 years are more vulnerable to AES especially in monsoon season. The presence of low GCS (<8), use of inotropic support, and need for mechanical ventilation were noted to be higher in the viral group of AES and were associated with poor outcome. Because most AES cases do not have a specific treatment; identifying and correcting prognostic features of poor outcomes, understanding the importance of supportive management in improving outcomes, and identifying novel effective treatments for treating AES are all-important future strategies for improving outcomes among AES patients. Early diagnosis and treatment of AES patients and attempts to detect exact etiology could improve their outcomes.

REFERENCES

1. Hamid JS, Meaney C, Crowcroft NS, Granerod J, Beyene J and UK Health Protection Agency Aetiology of Encephalitis Study Group. Potential risk factors associated with human encephalitis: Application of canonical correlation analysis. BMC Med Res Methodol. 2011;11:120.
   https://doi.org/10.1186/1471-2288-11-120
2. Arciniegas DB and Anderson CA. Viral encephalitis: Neuropsychiatric and neurobehavioral aspects. Curr Psychiatry Rep. 2004;6(5):372-379.
   https://doi.org/10.1007/s11920-004-0024-x
3. McGrath N, Anderson NE, Croxson MC and Powell KF. Herpes simplex encephalitis treated with acyclovir: Diagnosis and long-term outcome. J Neurol Neurosurg Psychiatry. 1997;63(3):

321-326.

https://doi.org/10.1136/jnnp.63.3.321

4. Utley TF, Ogden JA, Gibb A, McGrath N and Anderson NE. The long-term neuropsychological outcome of herpes simplex encephalitis in a series of unselected survivors. Neuropsychiatry Neuropsychol Behav Neurol. 1997;10(3):180-189.
5. Raschilas F, Wolff M, Delatour F, Chaffaut C, De Broucker T, Chevret S, et al. Outcome of and prognostic factors for herpes simplex encephalitis in adult patients: results of a multicenter study. Clinic Infect Disease. 2002;35(3):254-260.

   https://doi.org/10.1086/341405
6. Erlanger TE, Weiss S, Keiser J, Utzinger J and Wiedenmayer K. Past, present, and future of Japanese encephalitis. Emerg Infect Dis. 2009;15(1):1-7.

   https://doi.org/10.3201/eid1501.080311
7. Solomon T. Control of Japanese encephalitis-within our grasp? N Engl J Med. 2006;355(9):869-871.

   https://doi.org/10.1056/nejmp058263
8. Solomon T, Hart IJ and Beeching NJ. Viral encephalitis: A clinician's guide. Pract Neurol. 2007;7(5):288-305.

   https://doi.org/10.1136/jnnp.2007.129098
9. Whitley RJ and Kimberlin DW. Viral encephalitis. Pediatr Rev. 1999;20(6):192-198.

   https://doi.org/10.1542/pir.20-6-192
10. Wang WS and Liu CP. The clinical presentation, diagnosis, treatment, and outcome of encephalitis: Five years of experience at a medical center in Northern Taiwan. Int J Gerontol. 2011;5(1):9-12.

    https://doi.org/10.1016/j.ijge.2011.01.002
11. Wang L, Hu W, Magalhaes RJ, Bi P, Ding F, Sun H, et al. The role of environmental factors in the spatial distribution of Japanese encephalitis in mainland China. Environ Int. 2014;73:1-9.

    https://doi.org/10.1016/j.envint.2014.07.004
12. Zhao L, Zhou M, Wang B, Guo J, Chen N and He L. Clinical characteristics and outcome of clinically diagnosed viral encephalitis in southwest China. Neurol Sci. 2015;36(12):2191-2197.

    https://doi.org/10.1007/s10072-015-2333-8
13. Arunachalam N and Rajendran R. Studies on Japanese Encephalitis in Kurnool District, Andhra Pradesh. CRME Annual Report.

    https://doi.org/10.1603/033.046.0331
14. Dutta P, Khan SA, Khan AM, Borah J, Sarmah CK and Mahanta J. The effect of insecticide-treated mosquito nets (ITMNs) on Japanese encephalitis virus seroconversion in pigs and humans. Am J Trop Med Hyg. 2011;84(3):466-472.

    https://doi.org/10.4269/ajtmh.2011.10-0270
15. Kakoti G and Das BR. Clinico-epidemiological characteristics of hospitalized acute encephalitis syndrome children and their correlation with case fatality rate. J Family Med Prim Care. 2020;9(12):5948-5953.

    https://doi.org/10.4103/jfmpc.jfmpc_1645_20
16. Sudhir SK and 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.

    https://doi.org/10.18410/jebmh/2018/5
17. Kamble S and 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.

    https://doi.org/10.18203/2394-6040.ijcmph20163902
18. Anuradha SK, Surekha YA, Sathyanarayan MS, Suresh S, Satish P, Mariraj J, Krishna S, Ravikumar R. Epidemiological aspects of Japanese encephalitis in Bellary, Karnataka, India. Int J Biol Med Res. 2011;2(3):691-5.
19. Rose FC and Condon J. The diagnosis of pyogenic meningitis postgraduate. Med J. 1967;43(499):376-378.

    https://doi.org/10.1136/pgmj.43.499.376
20. Manthalkar PS and Peerapur BV. Utility of NS1 antigen for diagnosis of dengue virus infection. J Krishna Inst Med Sci Univ. 2017;6(1):72-75.
21. Sambasivam E, Muthaiyan J, Mohan S, Ayyavoo AM and Jayachandran G. Clinical profile and predictors of outcome in children admitted to PICU with acute encephalitis syndrome. Int J Contemp Pediat. 2017;4(4):1214-1217.

    https://doi.org/10.18203/2349-3291.ijcp20172512

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RB- Prepared the first draft of manuscript, **HJ-** Concept and design of the study, **DC-** Interpreted the results and reviewed the manuscript preparation, and **AB-** Preparation and revision of manuscript.

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