

Original Research Article

Study on acute encephalitis syndrome in children and their correlation with clinical parameters and etiological factors

Maram Nagarjuna Reddy*, Gangadhar Belavadi, Vaka Hari Priyanka

Department of Paediatrics, Narayana medical college, Nellore, Andhra Pradesh, India

Received: 06 October 2019

Revised: 14 October 2019

Accepted: 18 October June 2019

*Correspondence:

Dr. Maram Nagarjuna Reddy,

E-mail: maramnagarjuna@gmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Background: Acute encephalitis is the clinical diagnosis of children with acute onset of symptoms and signs of inflammatory lesions in the brain. It must be diagnosed promptly for saving life and preserving brain functions. Authors objectives was to determine the profile and outcome of children admitted with Acute Encephalitis Syndrome (AES) and to identify etiological factors.

Methods: Study consist of a retrospective analysis of hospital records of children up to 15 years of age admitted with a diagnosis of AES in the pediatric ward, Narayana medical college, Nellore from January 2018 to June 2019.

Results: In a total of 30 patients of AES, clinical features like fever (100%), altered sensorium (100%), convulsion (40%), headache (45%) and neuro deficit (40%) and vomiting (50%). The average Glasgow coma scale at admission was 8. There are 55% of cases in the 5 to 15 yr age group ($p > 0.05$). Both Encephalitis (56.6%) and meningitis (43.3%) were documented significantly more in males as compared to females ($p < 0.01$). Twenty-one cases are discharged, eight expired, and 1 case was referred ($p < 0.001$). JE IgM positive cases contributed to 36.6%, of which eight males and three females recorded between 5-15 years. Male children are more likely to play outdoors where the mosquito vector of the disease is abundant.

Conclusions: JE has significant morbidity and mortality, can be prevented by immunization, and reduced if supportive interventions are provided in time. Preventive measures must be taken for 5-15 years of age group those playing outdoors, going to school or agriculture fields predisposing them to vector mosquito bite.

Keywords: Acute encephalitis syndrome, Meningitis, Mortality, Glasgow coma scale

INTRODUCTION

Acute Encephalitis Syndrome (AES) is a leading cause of mortality and morbidity in children characterized as acute onset of fever and change in the mental status (mental condition, disorientation, delirium, or coma) and new onset of seizures in the person of any age at any time of the year.¹ AES may present with encephalitis, meningoencephalitis, or meningitis and may be caused by viruses, bacteria, mycobacteria, rickettsia, and rarely by toxoplasma. The causative agent of AES varies with both

season and geographical location; it predominantly affects children below 15 years. Based on various surveillance reports and outbreak investigations, Joshi et al, classified history of AES in India into three phases: (a) period before 1975 when a few cases with JE etiology were recorded; (b) between 1975 and 1999 when more JEV cases are reported with frequent outbreaks that resulted in the development of JE endemic regions near the Gangetic plains and in parts of Deccan and Tamil Nadu; (c) between 2000 and 2010, a dramatic change was observed in the AES scenario, which saw the increase in

non-JE outbreaks mostly caused by viruses such as Chandipura virus (CHPV), Nipah virus (NiV), and other enteroviruses.²⁻⁴ Based on the reports, Indian states of Uttar Pradesh (UP), Bihar, Assam, West Bengal, and Tamil Nadu were identified as JE endemic zones. Many cases of AES were recorded in 2014 from the states of UP (3,329 cases, 627 deaths), Assam (2,194 cases, 360 deaths), West Bengal (2,381 cases, 169 deaths), and Bihar (1,385 cases, 355 deaths) (6,7, Indian Express, September 22, 2015).

Japanese B encephalitis (JE) is the major cause in India. Knowing the wide range of causal agents and the rapid rate of neurological deterioration due to pathogenesis, clinicians face the challenge of small window period between diagnosis and treatment. As a step to control JE, the World Health Organization (WHO) is maintaining a set of standards for JE surveillance, which requires identification of patients with AES.⁶⁻⁹

Pediatricians who treat these children should be aware of how to manage a child with suspected encephalitis, as specific antiviral therapy is lifesaving in some diseases, and these should be diagnosed without delay. These guidelines have been developed to aid the pediatrician in the management of children with suspected viral encephalitis, in both sporadic and epidemic settings in India. These guidelines do not cover viral encephalitis in the neonatal period and in immuno-compromised children, Rabies encephalitis, and chronic viral encephalitis such as Sub-acute sclerosing pan-encephalitis (SSPE).

The present study is carried out to evaluate the clinical profile of pediatric AES cases, to determine both prevalence and outcome of meningitis or encephalitis presentation of AES and their correlation.

METHODS

The current study was carried out in children with a diagnosis of AES admitted in the pediatric ward, Narayana Medical College, Nellore, Andhra Pradesh, India. This retrospective study (hospital records) on 30 children up to 15 years of age from January 2018 to June 2019. AES diagnosed according to the WHO case definition.

Case records of each child were analyzed in detail and data recorded for history, examination, investigation, and outcome. Patients were categorized based on predominant clinical-investigational picture suggestive of meningitis or encephalitis.

Inclusion criteria

- All pediatric patients up to 15 years of age, fulfilling the standard WHO case definition of AES, were included in the study.

Exclusion criteria

- Patients presented like AES picture but with clinical-investigational diagnosis confirmative of cerebral malaria, Reye syndrome, or other noninfectious encephalopathy.
- Data on prevalence and clinical parameters were expressed as a percentage, and a student's t-test performed to identify significant change deriving p-value using SPSS version 16.0 software.

Evaluation and management of children suffering from acute Encephalitis syndrome

Step I: Rapid assessment and stabilization.

- Establish and maintain airway: Intubate if GCS score 8, impaired airway reflexes, abnormal respiratory pattern, signs of raised Intracranial pressure, oxygen saturation <92% despite high flow oxygen, and fluid refractory shock
- adequate Ventilation, Oxygenation
- Circulation: Secure IV access, take samples (CBC, Blood sugar, KFT, LFT, electrolytes, blood gas, lactate, PS and RDT for a malarial parasite, serology for viruses), Fluid bolus if in circulatory failure (20 mL/kg NS), inotropes if required
- Identify signs of cerebral herniation or raised ICP
- Temperature: treat fever and hypothermia
- Treat ongoing seizures- Benzodiazepine, followed by a phenytoin loading dose

Step II: Clinical evaluation: History and examination

History and examination

Step III: Investigation/ Samples to be collected

- CSF
- Blood/serum, Urine
- CT/MRI, avoid sedation
- Throat swab, nasopharyngeal swab.

Step IV: Empirical treatment (must be started if CSF cannot be done/report will take time and patient sick)

- Ceftriaxone.
- Acyclovir (use in all suspected sporadic viral encephalitis)
- Artesunate (stop if peripheral smear and RDT are negative)

Step V: Supportive care and treatment.

- Maintain euglycemia, Control fever, Maintain hydration.
- Treat raised intracranial pressure, mild head-end elevation 15-30°.

- Treat seizures; Give anticonvulsant if the history of seizures or if GCS <8, or if the child had features of raised ICT.
- Steroids: Pulse steroids (methylprednisolone or dexamethasone) should be given in children with suspected ADEM.

Step VI: Prevention and treatment of complications and rehabilitation.

- Physiotherapy, posture change, Prevent bed sores, and exposure keratitis.
- Complications: Aspiration pneumonia, nosocomial infections.

Important Points in the History of a Child with AES

- Fever, headache, vomiting, seizures, abnormal posturing
- Altered behavior, cognition, personality changes, altered consciousness
- Prodromal symptoms- flu-like illness, diarrhea
- Rash, vesicles, past history of chicken pox
- Residence of a child: Rural/urban, endemic for cerebral malaria, any epidemic of AES in neighborhood
- History of animal contact, insect bite, dog bite
- Drug or toxin exposure- enquire for the presence of any drugs at home
- Recent history of travel
- History of trauma

- Personal or family history of seizure disorder
- Recent immunizations
- H/o recurrent episodes of encephalopathy: These are characteristic of some inborn errors of metabolism (urea cycle defects, organic acidemias, and fatty acid oxidation defects), but may also be present in migraine, epilepsy, substance abuse, and Munchausen syndrome by proxy
- Other concurrent systemic illness, e.g., jaundice (hepatic failure), pneumonia (hypoxic encephalopathy), diarrhea (dysselectrolytemia), dysentery (shigella encephalopathy)
- Past h/o medical illness: Diabetes, congenital heart disease, chronic kidney or liver disease
- Family h/o previous infant/child deaths
- Pre-morbid developmental and neurological status of the child
- Risk factors for immunodeficiency- HIV risk factors, cancer treatment, steroid/immunosuppressant treatment.

Surveillance of JE is being done by WHO in endemic areas through detection of JE IgM antibodies in acute stage of AES patients either in serum or serum and CSF samples. Confirmation of diagnosis by JE IgM (ELISA) which is processed.

Treatment-Empirical treatment must be started, pending the results of investigations. A broad-spectrum antibiotic such as ceftriaxone must be given, which can be stopped if no evidence of bacterial meningitis is forthcoming.

Table 1: MRI Findings in viral encephalitis and some mimickers.

Etiology	MRI Finding
<i>Herpes simplex encephalitis</i>	Abnormal signal intensity in medial temporal lobe, cingulate gyrus, and orbital surface of frontal lobes
Japanese B encephalitis	Abnormal signal intensity in thalami (87-94%), substantia nigra, and basal ganglia
EV 71	Abnormal signal intensity in the dorsal pons, medulla, midbrain, and dentate nuclei of the cerebellum; gigh-signal lesions can also be found in the anterior horn cells of spinal cord in patients with acute flaccid paralysis
Chandipura virus	Normal
Nipah virus	Focal subcortical and deep white matter and gray matter lesions; small hyperintense lesions in the white matter, cortex, pons and cerebral peduncles have also been seen.
<i>Varicella</i>	Multifocal abnormalities in cortex, associated cerebellitis, vasculitis and vasculopathy
Acute disseminated encephalomyelitis	Multifocal abnormalities in subcortical white matter; involvement of thalami, basal ganglia, and brainstem also seen
West Nile virus	Abnormalities in deep grey matter and brainstem (50%); white matter lesions mimicking demyelination may also be seen; meningeal involvement on contrast enhanced images.

The table shows suggestive MRI findings present in some etiologies of viral encephalitis such as Herpes simplex encephalitis, JE, enterovirus encephalitis. MRI may show non-specific features of viral encephalitis, such as cortical hyperintensities and cerebral edema. MRI is also useful for diagnosing alternative etiologies such as Acute disseminated encephalomyelitis, and antibody-associated encephalopathies.

Acyclovir should be stopped if an alternative diagnosis has been made, or HSV PCR in the CSF is negative and MRI is normal. However, if the CSF PCR for HSV or MRI have been performed very early after symptom onset (within 48 hours), these may be falsely negative. Hence, these studies should be repeated before stopping acyclovir if the clinical suspicion of HSE continues to be high.

Dose and duration of acyclovir in children with encephalitis- 3 months to 12 y (500mg/m² 8 hourly)

>12 yr: 10mg/Kg 8 hourly

Confirmed cases

14-21 days intravenous treatment; Minimum 21 day for those aged 3 mon-12yr.

Where therapy was started empirically, stop acyclovir, if an alternative diagnosis is confirmed, or if HSV PCR in the CSF is negative on two occasions (24-48 hr apart) and MRI imaging does not suggest HSE.

RESULTS

There were 30 cases of AES pediatric patients up to 15 years of age during the study period fulfilling the WHO definition. Male and female patients were 17 and 13 and there was no statistical significance observed between them (Table 2).

Table 2: Distribution of total cases of meningitis/ encephalitis according to sex.

Diagnosis	Total (AES)		
	Male(17)	Female(13)	30
Meningitis	8	5	13(43.3%)
Encephalitis	9	8	17(56.6%)
p value	p<0.015		

Encephalitis and meningitis were documented significantly more in male (p<0.015).

There are 20% of cases in <1 yr age group, 25% of cases in 1 to 5 yr age group and 55% cases in 5 to 15 yr age group (p >0.05) (Table 3).

Table 3: Outcome of encephalitis/ Meningitis (AES) cases.

Diagnosis	Encephalitis (17, 56.6%)	Meningitis (13, 43.3%)	AES (30)
Discharged	10(58.8%)	11(84.6%)	21(70%)
Referred	1(5.8%)	0(0%)	1(3.3%)
Expired	6(35.2%)	2(15.3%)	8(26.6%)
p value	p <0.25	p <0.001	p <0.001

Statistically significance difference in patients of meningitis (p<0.0001) and encephalitis (p<0.03).

Meningitis and encephalitis cases were 13 and 17 respectively. Both Encephalitis and meningitis were documented significantly more in male as compared to female (p<0.01).

Out of total 30 cases of AES, 21 were discharged, 8 expired and 1 case referred. There was statistically significance difference in patients of meningitis (p<0.0001) and encephalitis (p<0.03).

Serology for JE IgM (ELISA) was positive in 11 cases (36.6%) as per documented reports out of 30 total cases of AES. Most of patients (55%) were from rural areas and remaining from urban areas (Table 4).

Among 11 seropositive cases, male patients were 8 (72.7%) as compared to 3 (27.2%) female cases. No JE seropositive case was found in less than 1-year age group, only 2 (18.8%) cases belonged to 1 to 5 years age group and maximum 9 (81.8%) patients were between 5 to 15 years of age.

Table 4: AES cases according to serology for JE IgM.

JE IgM Positive	JE IgM Negative	Total AES (30)	p value
11(36.6%)	19(63.3%)	30	p<0.001

Serology for JE IgM (ELISA) was positive in 11 cases (36.6%) out of 30 total cases of AES.

DISCUSSION

WHO has given clinical case definition of AES so that these cases are subjected for confirmative diagnosis by IgM captured ELISA in blood and or CSF. JE is the single largest cause of viral encephalitis in the world.¹⁰ Clinical profile of AES patients in this study included vomiting, seizures, Glasgow coma scale (GCS) <8, meningeal irritation signs, neurological deficit in respectively.

Gupta N et al, study observed vomiting in 41.4%, seizures in 79.3%, altered sensorium in 51.7%, signs of meningeal irritation in 17.2% and neurological deficit in 34.5% of their cases in the study done in hospitalized patients suspected of JE.¹¹ These findings are comparable with our present study Kumar et al, study described vomiting in 6.5%, meningeal signs in 35.1%, GCS <7 in 44.1%, extrapyramidal features in 31.1% and convulsions in 98.7% in JE epidemic in Eastern Uttar Pradesh.⁵

Prevalence of meningitis and encephalitis was 43.3% and 56.6% respectively among 30 cases of AES. Number of AES patients discharged (70%) was significantly more in meningitis group (p<0.001) as compared to referred (3.3%) or expired (26.6%). High mortality in encephalitis group is consistent with universal observations of more number of deaths in encephalitis including JE.

Out of 30 cases of AES diagnosed as encephalitis 10 were discharged home, 1 case referred, and 6 patients expired ($p < 0.25$). High mortality in this group is consistent with universal observations of a greater number of deaths in encephalitis including JE. Serology for JE IgM (ELISA) was positive in 11 (36.6%) cases as per documented out of 30 total cases of AES. Most of patients (70%) were from rural areas and remaining from urban areas.

In these 11 positive cases, male was 8 as compared to 3 female cases. There was no JE positive case found in less than 1-year age group, and only 2 cases recorded in 1 to 5 years age group and maximum of 9 patients were recorded between 5 to 15 years of age group. It shows that statistically highly significant a smaller number of patients had positive JE IgM than as compared to negative cases of JE IgM ($P < 0.001$). Similar results were also observed in other studies.^{12,13} This may be attributed partly because male children are more likely to go outdoors or to agriculture area where mosquito vector of the disease is abundant. Most often affected children were between 5 to 15 years of age in this present study which is more or less comparable to other studies. This may be correlated to more ambulation in this age group like playing outdoors, going to school or agriculture rice fields predisposing them to vector mosquito bite. In another study, prevalence of JE patients presenting with encephalitis form ranged between 60 to 75% and presenting with meningitis form consisted up to 5 to 10% cases.¹³

Epidemics of JE are documented in Southeast Asia and most of the Indian subcontinent. In 2005, there was a severe epidemic of JE in the Eastern Uttar Pradesh, as well as in the adjoining areas of the neighboring state of Bihar and in Nepal.⁵ The clinical disease presents with a prodromal stage, an acute encephalitic stage with varying grades of coma, convulsions and neurological deficits with high mortality or convalescent stage of recovery often with sequelae.

In this study, there were equal number of the cases were confined to both rural and urban areas and occurred after rainy season. Other studies also documented prevalence of disease during these months.^{11,14} This is because of increase mosquito density during post monsoon period.

Special schools have been set up to help children challenged by clinical sequelae of JE infection (Indian Express, October 19, 2012). Vero cell-derived purified inactivated JE vaccine-JENVAC, was the first vaccine in India that received manufacturing and marketing approvals from the Drug Controller General of India. Minocycline, a second-generation tetracycline was reported from our laboratory to be protective against JE in the animal model.¹⁵ Based on a pre-clinical study, a phase II clinical trial has been completed at the CSM Medical University (King George Medical College). The trial report showed better outcomes with minocycline, especially in those patients who survived the initial day in

hospital although the exact mechanism of action has remained enigmatic.¹⁶

CONCLUSION

JE IgM positive cases were contributed to significant cases in AES in children up to 15 years of age, 5-15 years age group male were found to be more risk for JE and years. JE has significant morbidity and mortality which can be prevented by vaccination or other preventive measures. The mortality can be reduced if supportive interventions are provided in time.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Narain JP, Lal S. Responding to the challenge of acute encephalitis syndrome/JE in India. *J Comm Dis.* 2014;46:1-3.
2. Kumari R, Joshi PL. A review of Japanese encephalitis in Uttar Pradesh, India. *WHO South-East Asia J Public Health.* 2012 Oct 1;1(4):374-95.
3. Sen TK, Dhariwal AC, Jaiswal RK, Lal S, Raina VK, Rastogi A. Epidemiology of acute encephalitis syndrome in India: changing paradigm and implication for control. *J Comm Dis.* 2014 Oct 7;46(1):4-11.
4. Ghosh S, Basu A. Acute encephalitis syndrome in India: the changing scenario. *Annals Neurosci.* 2016 Sep;23(3):131.
5. Kumar R, Tripathi P, Singh S, Bannerji G. Clinical features in children hospitalized during the 2005 epidemic of Japanese encephalitis in Uttar Pradesh, India. *Clin Infect Dis.* 2006 Jul 15;43(2):123-31.
6. Solomon T, Thao TT, Lewthwaite P, Ooi MH, Kneen R, Dung NM, et al. A cohort study to assess the new WHO Japanese encephalitis surveillance standards. *Bulletin World Health Org.* 2008;86:178-86.
7. Narain JP, Bhatia R. The challenge of communicable diseases in the WHO South-East Asia Region. *Bull World Health Organ.* 2010;88:162.
8. Fidan J, Emsley H, Fischer M et al. The incidence of acute encephalitic syndrome in western industrialized and tropical countries. *Virology J.* 2008;5.
9. WHO-recommended standards for surveillance of selected vaccine preventable diseases. Available at: <http://www.who.int/vaccine-documents/DocsPDF/843.pdf>. Assessed 10 Feb 2010).
10. Burke DS, Nisalak A, Ussery MA, Laorakpongse T, Chantavibul S. Kinetics of IgM and IgG responses to Japanese encephalitis virus in human serum and cerebrospinal fluid. *J Infect Dis.* 1985 Jun 1;151(6):1093-9.

11. Gupta N, Chatterjee K, Karmakar S, Jain SK, Venkatesh S, Lal S. Bellary, India achieves negligible case fatality due to Japanese encephalitis despite no vaccination: an outbreak investigation in 2004. *Ind J Pediatr.* 2008 Jan 1;75(1):31-7.
12. Rayamajhi A, Singh R, Prasad R, Khanal B, Singhi S. Clinico-laboratory profile and outcome of Japanese encephalitis in Nepali children. *Annals of tropical paediatrics.* 2006 Dec 1;26(4):293-301.
13. Solomon T. Flavivirus Encephalitis. *N Eng J Med* 2004; 351:370-8.
14. Shresta SR, Awale P, Neupane S, Adhikari N, Yadav BK. Japanese encephalitis in children admitted at Patan hospital. *J Nepal Paediatr Society.* 2009;29(1):17-21.
15. Mishra MK, Basu A. Minocycline neuroprotects, reduces microglial activation, inhibits caspase 3 induction, and viral replication following Japanese encephalitis. *J Neurochem.* 2008 Jun;105(5):1582-95.
16. Kumar R, Basu A, Sinha S, Das M, Tripathi P, Jain A, et al. Role of oral Minocycline in acute encephalitis syndrome in India—a randomized controlled trial. *BMC Infect Dis.* 2015 Dec;16(1):67.

Cite this article as: Reddy MN, Belavadi G, Priyanka VH. Study on acute encephalitis syndrome in children and their correlation with clinical parameters and etiological factors. *Int J Contemp Pediatr* 2019;6:2628-33.