ORIGINAL ARTICLE

Acute Encephalitis Syndrome in Children and Adolescents: A Five-Year Descriptive Study From South India

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ABSTRACT

Objective: Acute encephalitis syndrome (AES) in children results in significant neurocognitive deficits or mortality. It is pertinent to study the AES patterns periodically to identify the changes in the etiological trends and outcomes. Our objective was to find the etiological agents of AES, mode of diagnosis, treatment given, and outcomes.

Methods: We reviewed the electronic records of children aged 1 month to 15 years who were admitted with AES in our centre from January 2015 to December 2019. We analyzed the the clinical, laboratory, and radiological profile of these children and adolescents in relation to their outcome. Poor outcome was defined as death, discharge against medical advice with neurological deficits, or Glasgow Outcome Score Extended (GOS-E) d≤ 5 at the time of discharge.

Results: Among 250 patients admitted with AES during the study period, a definitive etiological diagnosis was established in 56.4% of children (30.4% viral, 22% bacterial). Scrub typhus (11.2%) and dengue (9%) were the two most common underlying illnesses. Serology helped in clinching the diagnosis in 30% of children. A surge in AES cases in the post-monsoon season was observed in our cohort. Third-generation cephalosporin drugs (85.7%) and acyclovir (77.7%) were the most commonly used empiric antimicrobial drugs. About one-third of children (n = 80) had a poor outcome. GCS ≤ 8 at presentation and requirement for invasive ventilation were found to be significant predictors of poor outcome.

Conclusion: A definitive diagnosis was obtained in about half of the children with AES. Viral (30.4%) and rickettsial infections (22%) were the common etiologies identified. Poor outcome was observed in 32 % of patients.

Keywords: *Acute encephalitis syndrome, Children, Glasgow Outcome Score - Extended*

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INTRODUCTION

Acute Encephalitis Syndrome (AES) is defined by the World Health Organization (WHO) as "a syndrome in a person of any age, at any time of year, with 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)". Other clinical symptoms include increased irritability, somnolence, or abnormal behaviour unexplained by a usual febrile illness [1]. Encephalitis involves inflammation of the cerebral cortex, which may be due to infection or immune-mediated. The etiologies of AES are numerous and the Japanese encephalitis (JE) virus has been reported as the single most important virus causing AES (5-35%) in India. The common bacterial agents are *Orientia tsutsugamushi*, which causes scrub typhus, and *Streptococcus pneumoniae*. In the majority of AES cases, the etiology remains unknown [2].

Though AES is not a common problem among children, the presentation is acute and often associated with poor outcomes contributing to significant morbidity and mortality [3]. The mortality rate in children with AES in India has reduced considerably after the widespread use of JE vaccination, adequate vector control measures, and improvements in the field of health and sanitation [4]. The case fatality rate in JE-related AES was 11.2%, compared to 30-40% in the previous decades [5] . Several studies have shown that the long-term neurological sequelae in children with AES may be as high as 60-80% [6,7].

Identifying AES in children and timely management is pertinent to help prevent catastrophic sequelae. Hence, our

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study objectives were to identify the etiological agents, diagnostic methods, treatment options, and outcomes of children and adolescents with AES admitted in a tertiary care hospital over 5 years.

METHODS

We reviewed the electronic medical records of children aged one month to 15 years admitted between January 2015 to December 2019 to the Department of Pediatrics or Pediatric Neurology at Christian Medical College, Vellore, India, with a diagnosis of AES as per the WHO definition [1]. We used search terms: "encephalitis", "cerebritis", "encephalopathy", "meningoencephalitis" to identify children fulfilling the case definition of AES. We excluded children with brain tumours, epilepsy, brain/ vascular malformations, intracranial bleeding, poisoning, toxin- or drug-related encephalopathy, underlying systemic disorders causing encephalopathy such as uremic or hepatic encephalopathy, steroid psychosis, hypothyroidism (myxoedema coma), neurometabolic disorders and rheumatological disorders such as CNS lupus and vasculitis.

Data were extracted onto a case record form to capture the demographic, clinical, laboratory, treatment, and outcome details. Aseptic meningitis was defined as the presence of clinical signs and symptoms of meningitis, with sterile cerebrospinal fluid (CSF) bacterial cultures and CSF pleocytosis of more than five cells/mm^3 [8]. Pyogenic meningitis was defined as the presence of meningitis with a positive CSF bacterial culture, or the presence of bacterial antigens detected on latex agglutination test. The outcome was assessed in terms of mortality and neurological status at the time of discharge and a follow-up after six months. It was grouped into three categories: complete recovery, discharged against medical advice (DAMA) or dead. Good outcome was defined as complete recovery, discharged against medical advice (DAMA) without any deficits or Glasgow Outcome Score Extended (GOS-E) > 5 (child can get back to normal life with/ without minimal difficulty). Poor outcome was defined as death, DAMA with neurological deficits, or GOS-E <5 (child will be restricted to home or further debilitated) at the time of discharge. Neurological deficit was defined as disorders of the central and peripheral nervous system, which can cause functional or intellectual disability [9]

Statistical analysis: Data were analyzed using the Statistical Package for Social Sciences for Windows (SPSS version 22.0, Chicago, IL). Descriptive statistics were used for the representation of frequency, mean, and standard deviation (SD). Data not following normal distribution were represented as median and interquartile range (IQR). Categorical variables between the two groups were compared with the χ^2 test and Fisher's exact test, whereas continuous variables were compared using the Kruskal–Wallis or Mann–Whitney U test. Factors such as age, undernourishment, immunosuppression, Glasgow Coma Scale (GCS) on admission, duration of mechanical ventilation and etiology of AES were analysed by logistic regression for their effect on outcomes. *P* value < 0.05 was considered significant.

RESULTS

Out of 1224 electronic data of children shortlisted using the key search terms, 250 children fulfilled the AES diagnostic criteria during the 5-year study period and were included for analysis.

Children with AES were admitted from various states across India; Tamil Nadu (*n* = 160, 64%), Andhra Pradesh (*n* = 71, 28.4%), West Bengal (*n* = 6, 2.4%), Karnataka (*n* = 3, 1.2%), Odisha (*n* = 3, 1.2%), Jharkhand (*n* = 3, 1.2%), Kerala (*n* = 2, 0.8%), Chhattisgarh (*n* = 1, 0.4%), Assam (*n* = 1, 0.4%) and Meghalaya (*n* = 1, 0.4%). There was significantly a greater number of AES cases per month in the postmonsoon period, between October to February (range: 23-33/month), compared to the other months (range: 15-23/month) (*P* = 0.014). The seasonal pattern of AES with common etiological agents in our cohort is shown in **Fig. 1**.

There were 37 infants (14.8%), 92 (36.8%) between 1-5 years, and the rest 121 (48.4%) aged 6-15 years. The proportion of children with good neurological outcome was 19 (51.3%) in less than 1 year, 63 (68.4%) in 1-5 years and 83 (68.5%) in 6-15 years of age. The common presentating symptoms included fever (100%), seizures (74.7%), altered sensorium (74.3%), vomiting (56.6%), headache (34.7%), and altered behaviour (23.8%).

The etiology of children with AES was determined using multiple modalities. CSF analyses were available in 187 (74.8%) children. Aseptic meningitis was seen in

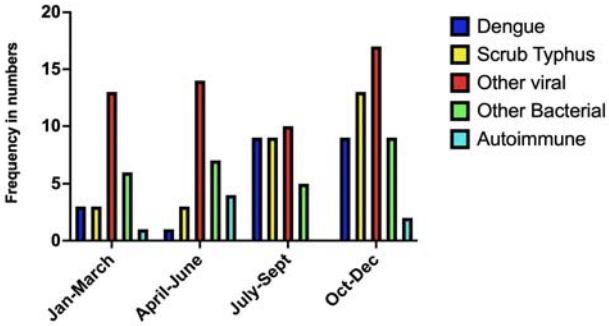

Fig. 1 Seasonal variation in etiological agents causing acute encephalitis syndrome among children

Table I Tests for Etological Diagnosis in Acute Encephalitis Syndrome

Etological Agent	*Diagnostic Modality*	*Diagnostic Yield n (%)*
Bacterial		55 (22)
Rickettsioses	Scrub typhus (IgM+ Weil Felix OX K)	28 (11.2)
	Spotted fever (IgM+ Weil Felix OX 2/OX 19)	5 (2)
S. pneumoniae	CSF Latex agglutination and blood culture	5 (2)
Salmonella (*Salmonella typhi* and C2)	Blood culture	2 (0.8)
	Widal test (Paratyphoid and typhoid- 1 each)	2 (0.8)
Klebsiella spp.	Blood culture	4 (1.6)
Enterococcus	CSF culture	1 (0.4)
	Blood culture	1 (0.4)
H. influenzae type B	CSF culture	1 (0.4)
	Blood culture	1 (0.4)
Neisseria meningitidis	Blood culture	1 (0.4)
Mycoplasma pneumoniae	Cold agglutinin	1 (0.4)
Staphylococcus aureus	Blood culture	1 (0.4)
Acinetobacter spp.	Blood culture	1 (0.4)
Nonfermenting gram-negative bacilli (NFGNB)	CSF culture	1 (0.4)
Viral		75 (30)
Dengue	Serology	22 (9)
Epstein Barr virus	CSF PCR	11 (4.4)
	Serology	1 (0.4)
Herpes Simplex virus	CSF PCR	9 (3.6)
	Serology	1 (0.4)
Influenza A virus	Nasopharyngeal swab	7 (3)
Mumps virus	Serology	6 (2.4)
Varicella Zoster virus	CSF PCR	4 (1.6)
	Blood PCR	1 (0.4)
Influenza B virus	Nasopharyngeal swab	4 (1.6)
Cytomegalovirus	CSF PCR	3 (1.2)
Enterovirus	CSF PCR	1 (0.4)
	Nasopharyngeal swab	1 (0.4)
Measles virus	Serology	1 (0.4)
Parainfluenza virus	Nasopharyngeal swab	1 (0.4)
Boca virus	Nasopharyngeal swab	1 (0.4)
Chikungunya virus	Serology	1 (0.4)
Fungal		
Candida	Blood culture	1 (0.4)
Parasite		
Cysticercosis	CSF Antigen	1 (0.4)
Autoimmune		
Anti-NMDA receptor	CSF/Serum antibodies	8 (3.2)
None		110 (44)

CSF Cerebrospinal fluid, NMDA N-methyl-D-aspartic acid, PCR Polymerase chain reaction

49.2% and pyogenic meningitis in 1.2%. CSF latex agglutination or viral PCR was positive in 34 (16%) of these children. Other diagnostic methods used were serology, which aided in diagnosing 30% of cases, for dengue, scrub typhus, other rickettsial infections, measles, mumps, Epstein Barr virus, Herpes simplex virus (HSV), spotted fever rickettsioses, chikungunya, and cysticercal antibody. Nasopharyngeal (NP) swabs for multiple viruses were sent in 40 children and was positive in 17 (42.5%) cases.

Definitive etiological diagnosis was established in 56.4% of these children (30.4% viral, 22 % bacterial). The two most common etiologies identified in our cohort were scrub typhus (11.2%) and dengue (9%). Description of the etiological profile in children and adolescents with AES including the diagnostic modalities is presented in **Table I**. Amongst infants, HSV was the most common etiological agent identified along with dengue (13.5%).

MRI of the brain was performed in 108 (43.2%) children; white matter hyper-intensities were the most common finding observed in 88 children (81.4%). EEG was performed in 126 (50.4%) children and was normal in 72 cases (50.4%). Only one out of the 10 children with HSV-related AES had periodic lateralised epileptiform discharges (PLEDs).

Antimicrobial therapy was administered to all patients. All children with rickettsioses (13.2%) had received doxycycline and had a good outcome at discharge. Other treatment modalities used were anti-edema drugs, immunomodulation with steroids or IVIG, anti-seizure medications, and general supportive care.. The majority of children in our study recovered without any deficits (n = 133, 53.2%), 36 (14.4%) were DAMA and 36 (14.4%) died. Good outcomes were seen in 68% (170) and bad outcomes in 32% (n = 80) of children. Among the two most common etiologies, the good outcome was seen in all children who had scrub typhus (n = 28), whereas in children with dengue, almost half (n = 10, 45%) had a bad outcome. Factors such as age, immunosuppression, GCS on admission , invasive ventilation and etiology of AES were analysed for their effect on outcome in children with AES. On univariate and multivariate analysis, GCS ≤ 8 on admission [OR 3.38 (95%CI 1.54,7.43), P = 0.002] and need for invasive ventilation [OR 17.48 (95%CI 8.1, 37.8), P < 0.0001] were significant predictors of poor outcomes (**Table II**).

DISCUSSION

Our study showed that a definitive etiological diagnosis was established in 56.4% of children with AES, with viral etiology being the most common (30.4 %). This was found to be higher than most other Indian studies, where more than 50% of children with AES had no identifiable etiology [10]. The California Encephalitis Project identified the etiology of AES in only 16% of cases and viral etiology was the most common (11%) [11]. **Table III** presents the yield of diagnostic tests from other Indian studies on AES [10,12,13,18-24]. Scrub typhus (11.2%) and dengue (9%) were the most common causes of AES in our study, which was similar to a prospective study conducted in the three high burden states of Uttar Pradesh, Assam and West Bengal, where scrub typhus was identified in 10.5% and dengue in 5% of AES cases [12].

Among the various host factors, infants were identified to be the most vulnerable population. This finding is in contrast to a study reported from Assam, where children aged 5-12 years were found to be at risk for AES [13]. An Australian multicentre prospective cohort study also showed that AES was more common in younger children (median age of 1.7 years) [14]. There was an increase in the number of AES patients during the postmonsoon season which was similar to a surveillance study done in Uttar Pradesh, where there was an increase in AES cases during the monsoons [15]. This seasonality can be used to prepare the health care services to be geared towards handling the increased number of AES cases. Since dengue and scrub typhus are the most common causes of AES, public education and preventive measures can be instituted to decrease AES cases.

MRI brain showing non-specific white matter hyper-intensities was the most common finding in our study (81.5 %). An Israeli retrospective study showed that neuro-

Table II Predictors of Poor Outcome in Children With Acute Encephalitis Syndrome

Parameter	*OR (95% CI)*	*P value*	*Adjusted OR*	*95% CI*	*P value*
Age	0.97 (0.92, 1.03)	0.32	-	-	-
Immunosuppression	1.47 (0.45, 4.78)	0.52	-	-	-
GCS ≤ 8	11 (5.6, 21.43)	< 0.0001	3.38	1.54-7.43	0.002
Invasive Ventilation	26.9 (12.9, 55.9)	< 0.0001	17.48	8.1-37.8	< 0.0001
Aetiology of AES	1.04 (0.95, 1.14)	0.38	-	-	-

CI Confidence interval, GCS Glasgow coma score, OR Odds ratio

Table III Diagnostic Yield in Various Studies From India on Acute Encephalitis Syndrome

Authors	*States represented*	*Study period*	*Sample size*	*Age group*	*Diagnosis*
Damodar et al [18]	Karnataka	2019-2022	376	1 mo -18 y	23%
Kakoti et al [13]	Assam	2019-2020	140	1 mo -12 y	37.9%
Tandale et al [10]	Maharashtra, Telangana	2018-2020	278	All ages	41.4%
Murhekar et al [19]	Uttar Pradesh	2016	407	All ages	65.4%
Tandale et al [20]	Maharashtra	2015-2016	280	< 15 y	22.1%
Goel et al [21]	Delhi	2015	50	1 mo -12 y	22%
Vasanthapuram et al [12]	Uttar Pradesh, West Bengal, Assam	2014-2017	10,107	All ages	49.2%
Medhi et al [22]	Assam	2012-2014	1707	All ages	46.8%
Tripathy et al [23]	Orissa	2012-2013	834	6 mo - 5 y	16.3%
Beig et al [24]	Uttar Pradesh	2004-2006	87	6 mo -12 y	21.8%

imaging was abnormal in 39% of children with AES at presentation [16]. Although PLEDs are considered specific for HSV, out of 10 children who had HSV-related AES only one had PLED. An etiology was established in 17.5% of our cases based on CSF analysis and 30.1% based on serological tests.

Considering the therapeutic response to doxycycline in rickettsiosis, it would be prudent to add empiric treatment for the same with doxycycline and/or azithromycin, especially during the peak season, till a definite alternate diagnosis is established. In a recent study in adults with scrub typhus infection [17] combination therapy with doxycycline and azithromycin, was more effective in preventing morality/ complications than either of the drugs used alone.

Our study has several limitations. Being a retrospective study, a structured etiological diagnostic algorithm was not followed in all cases and it is possible that etiological diagnosis would have been missed in a few cases. Children who were discharged against medical advice were not followed up and their final outcome was not ascertained. MRI brain scans were not done in 56.8% of children, which is a major limitation, considering the importance of neuroimaging in AES. Being a tertiary hospital-based study, the findings of this study cannot be extrapolated to general population. However, the findings of this study are important and add knowledge to this condition with high morbidity and mortality which is not well studied among children.

In conclusion, a definite etiological diagnosis for AES was obtained in a majority (56.4%) of the children in our study. Dengue and scrub typhus were the most common etiological agents of AES. Unfavorable outcome was seen in 32% of children, with low GCS ≤ 8 at presentation and the need for mechanical ventilation being the significant predictors.

Ethics clearance: Institutional Ethics Committee, No. 13145, dated July 08, 2020.

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WHAT THIS STUDY ADDS?

- Scrub typhus and dengue are the commonest cause of acute encephalitis syndrome in our study.
- Serological tests can aid in establishing the diagnosis in a third of cases with AES.
- Good outcome was seen in 68% children in our study.

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