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CLINICO-ETIOLOGICAL PROFILE OF ACUTE ENCEPHALITIS SYNDROME IN CHILDREN: A RETROSPECTIVE STUDY FROM A TERTIARY CARE CENTRE IN MUMBAI, INDIA

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ABSTRACT

Introduction: Acute Encephalitis Syndrome (AES) poses a significant public health challenge in India, with diverse etiologies varying by region and season. Despite its impact, data from western India, particularly Maharashtra, remains sparse. This study aimed to evaluate the clinical and etiological profile of pediatric AES cases in a tertiary care hospital in Mumbai. **Methods:** A retrospective, cross-sectional study was conducted at a tertiary care teaching hospital in Mumbai from February 2018 to February 2023. Data from 57 pediatric patients (1 month–12 years) fulfilling the International Encephalitis Consortium's AES criteria were analyzed. Clinical, laboratory, radiological, and etiological data were extracted using a standardized proforma. Cases were classified as definite, probable, or possible AES. Descriptive statistics were applied, and chi-square tests were used to assess associations, with significance set at $p<0.05$. **Results:** Among 57 AES patients, 57.9% were female. Among the causes, infective causes predominated with viral encephalitis was the most common etiology (59.6%). HSV, Dengue virus, and JEV were the common viruses implicated. Tuberculous (14%) and autoimmune (10.7%) etiologies were also notable. MRI findings varied by etiology, with meningeal enhancement in bacterial cases and infarcts/hemorrhages in viral cases. **Conclusion:** This study highlights viral encephalitis as the predominant cause of AES in western India, with tuberculosis and autoimmune encephalitis also contributing significantly. The high proportion of undiagnosed viral cases underscores the need for enhanced virological testing and national referral networks. Improved diagnostic infrastructure and surveillance are essential for timely diagnosis, targeted therapy, and reduced morbidity and mortality.

KEYWORDS : Encephalitis, AES, Meningoencephalitis, Acute encephalitis, neuro-infections

INTRODUCTION:

Acute Encephalitis Syndrome (AES) is clinically defined as an acute onset of fever accompanied by a change in mental status (such as confusion, disorientation, coma, or inability to talk) and/or new-onset seizures (excluding simple febrile seizures) in individuals of any age and at any time of the year, as per World Health Organization (WHO) [1]. AES incidence varies globally and is influenced by factors such as geographical area, age and surveillance. A comprehensive review by Jmor et al reported that the incidence of AES ranges between 3.5 and 7.4 per 100,000 person-years [2]. AES continues to pose a significant public health challenge in India, with its prevalence varying across different states and over time. Between 2010 and 2016, India reported over 60,000 AES cases, with case fatality rates (CFR) ranging from 11% to 33% (3,4,5). In India, infectious agents remain the leading cause for AES, with the most common causes being Japanese Encephalitis virus (JEV), ricketssial infections, tuberculosis, Dengue virus, Enteroviruses, Herpes viruses and Chandipura virus [6]. Due to high case fatality and constantly changing epidemiology of AES, it becomes imperative to study the evolving clinico-etiological profile of this entity. Moreover, there exists sparse recent literature on AES from western India, especially from the state of Maharashtra. Hence, we conducted this study with the objective to determine the clinico-etiological profile of AES cases presenting to a tertiary care hospital in Mumbai.

MATERIALS AND METHODS:

The study was a retrospective, cross-sectional, single centre study. Institutional Ethics Committee (EC-92/2022) approval was obtained. (ECWaiver of consent and assent was obtained since the study only involved retrospective chart review. The study was conducted at a tertiary care teaching hospital in Mumbai. The study included data of all AES patients admitted to the pediatric ward or PICU of the hospital, in the last five years, i.e. during the period between February 2018 to February 2023. A convenient sampling technique was used. After preliminary review of the hospital records over the last 5 years, 57 cases were identified. A case of AES was defined as a person of any age, at any time of year with the acute onset of fever (>38°C) in the preceding 7 days 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), as per the latest case definition of the International Encephalitis Consortium consensus guidelines [7]. All children aged between 1 month to 12 years fulfilling the definition of AES were included in the study. Encephalopathy secondary to traumatic brain Injury (TBI), proven metabolic encephalopathies and space occupying lesions (SOLs) were excluded from the study. Admission records and discharge records of patients with a diagnosis of AES at admission were reviewed and data including demography, clinical findings, fundoscopy, blood reports including complete hemogram, blood sugar, renal and liver function tests, electrolytes, cerebrospinal fluid (CSF) analysis, Electro-encephalography (EEG) and neuro imaging, etc. were obtained in a pre-designed case record proforma.

Cases were classified into definite, probable and possible AES as per the WHO and the International Encephalitis Consortium consensus guidelines, 2013 [1,7]. Normal CSF values for proteins, sugars and cells were defined as per accepted normative data in infants and paediatrics [8]. Sero-negative or possible autoimmune encephalitis (AE) was defined as per clinical definition provided by *Graus et al* in 2016 [9]. Encephalitis of presumed viral etiology and presumed bacterial encephalitis were diagnosed based on accepted definitions [10,11]

Statistical Analysis:

Data was descriptively analysed using mean, median and interquartile range (IQR) for continuous variables and frequency and proportion for categorical variables. Chi-square test was used to check association between clinico- etiological profile and radiological features. A 2 tailed $p<0.05$ was considered to be statistically significant. Statistical analysis was performed by appropriate statistical tests using Microsoft Excel (v29) and IBM SPSS v28 (statistical package for social sciences) software.

RESULTS:

A total of 57 children were enrolled in the study. In our study, 57.9% of the total patients were female with a male/female ratio of 0.72. The mean age of our cohort of patients was 4.4 years (±2.8 years). Among the patients, 40.3% were classified as having definite AES, while 50.8% and 8% of total patients were classified as having probable AES and possible AES, respectively.

Out of total patients, 8.8% of children had a history of travel to areas known to be endemic for viral encephalitis. Positive tuberculosis contact was found in 10.5% of total patients. In our cohort of patients, 5/57 (8.8%) had history of recent infections – such as otitis media (2/5,

40%), varicella infection (2/5, 40%) and diarrheal disease (1/5, 20%). Around 70% of children were completely immunized while 22.8% and 7% were partially or unimmunized respectively. Co-morbidities at time of presentation included pre-existing neuro-developmental delay (3.5%) and malnutrition (5.3%).

Most common symptoms seen in AES patients were fever (100%), altered sensorium (100%), seizures (100%), vomiting (57.9%), headache (19.3%), focal neurological deficits (17.5%), blurring of vision (12.3%), rashes (10.5%) and ataxia (7%). Seizures were generalized in onset in 71.9% of patients and focal in the rest (28.1%). Focal deficits were in the form of hemiplegia in 87.7% of patients and monoplegia in the rest (12.3%).

The demographic and clinical profile of patients are described in Table 1. Serological tests helped identify dengue infection causing encephalitis in 6 patients (10.5%) and leptospirosis in 1 patient. Eight patients had suspected CNS tuberculosis (14%). Out of these, one patient was diagnosed based on CSF positivity by the Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA, USA), 3 patients based on sputum positivity and 4 patients based on strong clinico-radiological evidence. CSF culture was positive for *Klebsiella Pneumoniae in* 1 patient. CSF viral PCR was positive in 8 cases.

The most common etiology for AES in our cohort was found to be infective (87.7%). Out of these, viral, tubercular and bacterial causes accounted for 68%, 16% and 14% respectively. The etiological profile of all AES cases is enlisted in Table 2. Common MRI changes in AES patients included signal intensity changes (66.7%), meningeal enhancement (33.3%), diffusion restriction (31.6%), infarcts (31.6%) and hydrocephalus (10.5%).

On analysing association of clinical parameters with etiological cause, there was found to be statistically significant association between enhancement and exudates on MRI and bacterial etiology (p=0.001). Presence of infarction, haemorrhage was significantly associated with viral etiology (p=0.047) and hydrocephalus, with bacterial etiology of encephalitis (p<0.0001). There was found to be no other significant correlation of etiology with other demographic or clinical parameters.

DISCUSSION:

AES remains a major public health concern in India with significant regional variations. Causative agents of AES vary by region, with JEV being a predominant cause in eastern and north-eastern states where paddy fields and high mosquito density create ideal conditions for its transmission. [3] In contrast, in states like Bihar and Uttar Pradesh, non-JEV causes such as scrub typhus, enteroviruses, and toxins (e.g., from litchi consumption in Muzaffarpur) have been linked to outbreaks [4,5]. This diverse etiology of AES across India complicates diagnosis and treatment and makes region-specific surveillance and interventions necessary for mitigating the burden of AES.

In our study, we found a female preponderance in AES patients in contrast to the increased incidence in male children as noted in other similar studies [12]. In our study, the most common etiology of AES at our centre was infective which accounted for 87.7% of all cases. Among these, viral etiology was predominant with the most common viruses implicated being HSV (10.5%), Dengue virus (10.5%) and JEV (5.2%). Other studies have also shown that viruses predominate over bacterial causes and remain the most common etiological agents, with HSV and JEV being particularly common [13]. The National Vector Borne Disease Control Programme (NVBDCP) has played a key role in preventing and managing Japanese Encephalitis by implementing JE vaccination campaigns in endemic areas, strengthening vector control measures like fogging and larval source reduction, and improving early case detection through surveillance programs [14]. Additionally, initiatives such as clean water access, sanitation improvements, and enhanced pediatric care facilities aim to reduce the burden of AES, particularly in vulnerable regions [14]. Despite these efforts, gaps remain in diagnostic capacities and timely treatment, highlighting the need for continued investment in public health infrastructure and research to combat this life-threatening syndrome effectively.

However, 26.3% of AES cases were classified as 'viral encephalitis with unknown cause' which included cases which had clinical, radiological and CSF analysis features highly suggestive of viral encephalitis despite no isolation of the viral agent on CSF culture, PCR studies or blood serology with no alternate diagnosis. This could be attributed to the fact that PCR testing for extended spectrum of uncommon viruses is often unavailable in clinical settings, especially in resource-constrained settings. Moreover, since isolation of rarer viruses does not directly impact treatment due to lack of targeted therapies, patients are often unwilling to incur out-of-pocket expenses in extensive diagnostic tests. Further, referral systems must be established linking tertiary care hospitals with existing state or central neurovirology laboratories to enable further testing of such samples, which will help in enhancing surveillance and enable early detection of possible outbreaks.

Fourteen percentage of all AES cases were attributed to a tubercular etiology. This stresses that tuberculosis remains an important cause in India with substantial morbidity and mortality [15] and hence should be strongly suspected in AES cases with a history of tuberculosis contact. The National Tuberculosis Elimination Programme (NTEP) has been proactive in addressing TB-related encephalitis by providing free diagnostics and quality-assured drugs, financial through the Nikshay Poshan Yojana (NPY) to support patient nutrition [16]. Despite these efforts, challenges persist in the early detection and management of neuro-tuberculosis, necessitating continued investment in healthcare infrastructure and research to mitigate the burden of TB-related encephalitis in India. A bacterial etiology was seen only in 12.2% of total patients. Serological tests often proved to be useful markers in identifying bacterial pathogens.

An increasing incidence of autoimmune encephalitis is further re-shaping the global trends in AES [17]. Our study reported an autoimmune etiology in 10.7% of the patients. Autoimmune encephalitis (AE) has emerged as a significant cause of encephalitis second only in frequency to viral or post-infectious causes globally, as well as in India [17,18]. A prospective study from North-western India involving 42 patients found that anti-NMDAR encephalitis constituted 57% of AE cases, followed by anti-leucine-rich glioma inactivated-1 (anti-LGI1) encephalitis at 11.9% [18]. In our study, only 1 patient had tested positive for Anti-NMDAR antibodies, whereas four others were classified as seronegative AE. AE often has a relapsing or progressive course and hence we repeated testing for antibodies may help identify more cases. It is also imperative to identify seronegative AE as early corticosteroid therapy helps in symptomatic improvement.

In our study, MRI served as an important diagnostic tool which helped in differentiating between viral, tubercular and bacterial etiologies of AES. Meningeal enhancement and hydrocephalus helped identify a bacterial etiology whereas infarcts and haemorrhages were more commonly seen in viral etiologies. CSF served as an important differentiating test since 77.2% showed CSF pleocytosis. EEG abnormalities were seen in 36.8% of the cohort and was key in appropriate management of convulsions.

Our study had few limitations such as small sample size, lack of testing facilities for rarer viruses and an inherent referral bias. Due to our inability to have long term follow-up of these patients, we could not garner data on further evolution of the disease process or development of neuro-developmental sequalae. However, our study emphasizes the ever-evolving natural trends in AES and stresses the need for ongoing epidemiological surveillance. It also stresses on the rising prevalence of AE in India and need for complete and thorough evaluation in AES cases to establish a definitive etiology. In conclusion, effective nation-wide linkage systems can effectively help ongoing research reach the clinician, truly bridging the lab to bedside discordance.

CONCLUSION:

This study from a Mumbai tertiary center highlights the predominantly infectious nature of pediatric acute encephalitis syndrome, with viral agents leading, followed by tubercular and bacterial causes, and an emerging role of autoimmune encephalitis. Neuroimaging and CSF analysis proved vital in differentiating etiologies, emphasizing the urgent need for expanded diagnostic capabilities, stronger laboratory linkages, and continuous surveillance to guide region-specific strategies and improve outcomes in western India.

Table 1. Clinico-demographic Profile Of Patients With AES.

Clinical parameters	Number (Percentages)
A. Demographic Features:	
1. Age:	

<1 year	11 (19.3%)
1-5 years	22 (38.6%)
> 5years	24 (42.1%)
2. Recent infections	**5 (8.7%)**
Otitis media	2/5 (40%)
Varicella	2/5(40%)
Diarrheal illness	1/5(20%)
3.Malnutrition	**3 (5.3%)**
4. Immunization:	
Completely immunized	40 (70.2%)
Partially immunized	13 (22.8%)
Unimmunized	4 (7%)
B. Clinical Features:	
1. Examination findings:	
GCS < 8	22 (38.6%)
Features of raised ICP	24 (42.1%)
Cranial nerve involvement	7 (12.3%)
Involuntary movements	7 (12.3%)
Tone abnormalities	26 (45.6%)
Papilledema	14 (24.6%)
2. Laboratory investigations:	
Anemia	26 (45.6%)
Leukocytosis	10 (17.5%)
Thrombocytopenia	8 (14%)
Transaminitis	6 (10.6%)
Azotemia/AKI	6 (10.6%)
3. CSF abnormalities:	
CSF pleocytosis	44 (77.2%)
CSF hypoglycorrhacia	24 (42.1%)
Elevated CSF proteins	32 (56.1%)
4. EEG abnormalities:	
Generalised slowing	11 (19.3%)
Epileptiform discharges	3 (5.3%)
Periodic sharp waves	7 (12.3%)
5. MRI abnormalities:	
Hydrocephalus	6 (10.5%)
Diffusion Restriction	18 (31.6%)
Infarcts	18 (31.6%)
Meningeal enhancement/exudates	19 (33.3%)'
Signal intensity changes	38 (66.7%)
Normal MRI	2 (3.5%)

(GCS= Glasgow Coma Scale, ICP= Intracranial Pressure, CSF= Cerebro spinal fluid, MRI = Magnetic resonance Imaging)

Table 2. Etiological Profile Of Patients With AES.

Etiology of AES (n=57)		**Frequency (n)**	**Percentage (%)**
1. Infective:		**50**	**87.7**
a. Viral		**34**	**59.6**
	Japanese Encephalitis	3	5.3
	HHV7	1	1.75
	HSV	6	10.5
	Dengue	6	10.5
	Influenza	2	3.5
	Varicella	1	1.75
	Viral encephalitis of unknown cause	15	26.3
b. Tubercular:	**8**	**14.0**	
c. Bacterial:	**7**	**12.2**	
	Klebsiella	1	1.75
	Listeria	1	1.75
	Leptospirosis	1	1.75
	Pneumococcus	1	1.75
	Presumed bacterial meningo-encephalitis	3	5.3
d. Parasitic (Malarial)	**1**	**1.75**	
B. Non-Infective:	**7**	**12.3**	
Demyelinating Disease	NMOSD	1	1.75
Autoimmune Encephalitis	Anti-NMDAR encephalitis	1	1.75
	Seronegative AE	4	7.0
	FIRES	1	1.75
Total	**57**	**100.0**	

(AES= Acute encephalitis syndrome, HSV= Herpes Simplex virus, HHV = Human herpes virus, NMOSD = Neuromyelitis Optica spectrum disorders, NMDAR= Anti-N-Methyl-D-Asparate Receptor Antibody)

Table 3. Association Between Age, Gender And Outcome Of Patients With Underlying Etiology Of AES

Parameter		**Etiology**			**p value**
		Viral (%)	**Bacterial (%)**	**Autoimmune (%)**	
Age	**<1 year**	1 (9.1)	6 (54.5)	4 (36.4)	0.299
	1-5 years	9 (40.9)	8 (36.4)	5 (22.7)	
	>5 years	11 (45.8)	9 (37.5)	4 (16.7)	
Gender	**Male**	6 (25.0)	12 (50.0)	6 (25.0)	0.270
	Female	15 (45.5)	11 (33.3)	7 (21.2)	
Outcome	**Recovery**	12 (35.3)	5 (33.3)	4 (66.7)	0.075
	Morbidity	18 (52.9)	4 (26.7)	0 (0.0)	
	Death	4 (11.8)	6 (40.0)	2 (33.3)	
MR Changes	**Normal MRI**	2 (5.9)	0 (0.0)	0 (0.0)	0.705
	Brain Signal Changes	25 (73.5)	6 (40.0)	6 (100.0)	0.330
	Enhancement / Exudates	6 (17.6)	11 (73.3)	1 (16.7)	**0.001***
	Infarct/ Bleed	13 (38.2)	2 (13.3)	1 (16.7)	**0.047***
	Diffuse Restriction	12 (35.3)	3 (20.0)	3 (50.0)	0.390
	Hydrocephalus	0 (0.0)	6 (40.0)	0 (0.0)	**<0.0001***

**(Chi-square test, P <0.05 = significant)*
(MRI= Magnetic Resonance Imaging)

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Clinical Trial Number: Not Applicable

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