

# Profile of Acute Encephalitis Syndrome Patients from South India

Rache Suma, M. Netravathi<sup>1</sup>, Gopalkrishna Gururaj, Priya Treasa Thomas<sup>2</sup>, Bhagteshwar Singh<sup>3</sup>, Tom Solomon<sup>4,5</sup>, Anita Desai<sup>6</sup>, Ravi Vasanthapuram<sup>6</sup>, Pradeep S. Banandur

Departments of Epidemiology, <sup>1</sup>Neurology, <sup>2</sup>Psychiatric Social Work and <sup>6</sup>Neurovirology NIMHANS, Bengaluru, Karnataka, India, <sup>3</sup>Clinical Research Fellow, Institute of Infection, Veterinary and Ecological Sciences, University of Liverpool, <sup>4</sup>Health Protection Research Unit in Emerging and Zoonotic Infections, National Institute of Health Research, University of Liverpool, <sup>5</sup>The Walton Centre, Liverpool, UK

## Abstract

**Introduction:** Encephalitis is a major public health problem worldwide that causes huge emotional and economic loss to humanity. Encephalitis, being a serious illness, affects people of all ages. The aim is to describe the sociodemographic, clinical, etiological, and neuroimaging profile among 101 acute encephalitis syndrome (AES) patients visiting a tertiary neuro-specialty care hospital in India. **Methods:** Record review of medical records of all patients attending neurology emergency and outpatient services at NIMHANS Hospital, diagnosed with AES in 2019, was conducted. Data were collected using standardized data collection forms for all cases in the study. Descriptive analyses (mean and standard deviation for continuous variables and proportions for categorical variables) were conducted. The Chi-square test/Fisher's exact test was used for the comparison of independent groups for categorical variables, and *t*-test for comparing means for continuous variables. **Results:** About 42.6% of AES patients had viral etiology, while in 57.4%, etiology was not ascertained. Common presenting symptoms were fever (96%), altered sensorium (64.4%), seizures (70.3%), headache (42.6%), and vomiting (27.7%). Herpes simplex was the most common (21.8%) identified viral encephalitis, followed by chikungunya (5%), arboviruses (chikungunya and dengue) (4%), Japanese encephalitis (4%), rabies (3%), dengue (1%), and varicella virus (1%). About 40% of AES patients showed cerebrospinal fluid pleocytosis (44%), increased protein (39.6%), abnormal computed tomography brain (44.6%), and magnetic resonance imaging abnormalities (41.6%). **Conclusion:** The study highlights the need to ascertain etiology and importance of evidence-based management of AES patients. A better understanding of opportunities and limitations in the management and implementation of standard laboratory and diagnostic algorithms can favor better diagnosis and management of AES.

**Keywords:** Acute encephalitis syndrome, neurology, tertiary care

## INTRODUCTION

Acute encephalitis syndrome (AES) is a major public health problem. Alarmingly, three billion people live in countries endemic to Japanese encephalitis (JE),<sup>[1-5]</sup> a major cause of AES. Further, its constantly evolving epidemiology makes management challenging.

Gaps exist in relation to its profile, presentation, and etiology in tertiary care centers in India. The profile of AES patients in tertiary centers is different, possibly due to delayed care-seeking, empirical therapy, and disease progression. In this study, we report sociodemographic, clinical, and etiological profiles of AES patients at a large neuro-specialty center in India over a 1-year period and the gaps involved in their care.

## METHODS

We performed a retrospective hospital-based review of physical and electronic case records of AES patients attending NIMHANS between January 1, 2019, and December 31, 2019. All case records meeting the WHO case definition for AES<sup>[3,4]</sup> were included. Briefly, any person of any age, at any time of year, with acute onset of fever and a change

**Address for correspondence:** Dr. Pradeep S. Banandur, #211, Department of Epidemiology, 2<sup>nd</sup> Floor, Dr. M. V. Govindaswamy Building, NIMHANS, Bengaluru - 560 029, Karnataka, India. E-mail: doctorpradeepbs@gmail.com

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**How to cite this article:** Suma R, Netravathi M, Gururaj G, Thomas PT, Singh B, Solomon T, *et al.* Profile of acute encephalitis syndrome patients from South India. *J Global Infect Dis* 2023;15:156-65.

**Received:** 27 January 2023

**Revised:** 18 July 2023

**Accepted:** 23 August 2023

**Published:** 30 November 2023

### Access this article online

Quick Response Code:



Website:  
www.jgid.org

DOI:  
10.4103/jgid.jgid\_19\_23

in mental status (including symptoms such as confusion, disorientation, coma, or inability to talk) and/or new onset of seizures (excluding simple febrile seizures) were included in the study. Neonates, people with preexisting indwelling ventricular devices (e.g., extraventricular drains and ventriculoperitoneal shunts) or other implants in contact with meninges or brain (e.g., deep brain stimulation), people having undergone neurosurgical procedures within the preceding 12 months of visiting NIMHANS, children diagnosed with simple febrile seizures and all patients with confirmed noninfectious etiology (autoimmune encephalitis) were excluded. Complete case records under the International Classification of Diseases (ICD-10) classification codes of G02\*, G02.0\*, G04, G04.0, G04.8, G04.9, G05\*, G05.0\*, G05.1\* were retrieved from the medical records department (MRD). These codes consisted of suspected or confirmed diagnoses of acute encephalitis, meningitis, myelitis, and encephalomyelitis due to infectious causes.

A specifically developed digitized clinical case pro forma based on standard neurological examination evaluation followed by neurologists was used [Supplementary File S1] to capture and enter data from all eligible case records. It included sociodemographic characteristics, clinical signs and symptoms, etiological investigations, imaging features, treatment profiles, and outcomes of subjects.

### Ethical consideration

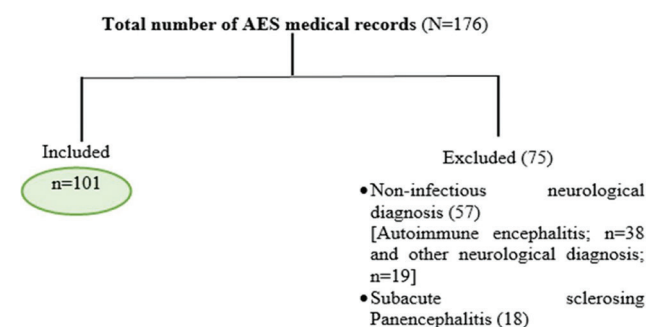
The study was approved by the Institutional Ethics Committee at NIMHANS, Bengaluru, vide letter number NO. NIMH/DO/IEC (BS and NS DIV) 2019–2020 Dated January 31, 2020.

### Statistical analysis

Descriptive analyses (mean and standard deviation for continuous variables and proportions for categorical variables) were conducted using Microsoft Excel 2016 for Windows. The Chi-square test/Fisher's exact test was used for the comparison of independent groups for categorical variables and *t*-test for comparing means for continuous variables.

## RESULTS

A total of 176 eligible records were retrieved from MRD [Figure 1]. Among these, 57 (30%) records had alternative



**Figure 1:** Flowchart depicting the sampling framework of the study

diagnosis and were excluded. These were autoimmune encephalitis ( $n = 38$ ) and neurological diagnoses other than encephalitis ( $n = 19$ ), such as demyelination ( $n = 13$ ), acute disseminated encephalomyelitis ( $n = 3$ ), spinal dysmorphism ( $n = 2$ ), and radiculopathy ( $n = 1$ ). Eighteen (10.2%) records of subacute sclerosing panencephalitis were excluded. Thus, a total of 101 records were included for analysis in the study.

### Sociodemographic findings of acute encephalitis syndrome patients

Out of 101 AES patients, majority were men (62.4%), adults aged 17–59 years (61.38%), and from rural areas (64.4%). Among them, 43 (42.6%) had viral etiology, while 58 (57.4%) had no known etiology [Table 1]. The sociodemographic profile of AES patients with unknown etiology was similar to those with viral etiology.

### Clinical features

Common symptoms observed among AES patients were fever (97/101; 96.04%), seizures (71/101; 70.3%), altered sensorium (65/101; 64.4%), headache (43/101; 42.6%), and impaired cognition (34/101; 33.7%). Although statistically insignificant, more than half of the patients presented with a combination of fever and altered sensorium (59/101; 58.4%). Symptom combinations, namely fever and altered sensorium (27/43; 62.8%); fever, headache, and altered sensorium (13/43; 30.2%), were more frequently noted among AES patients with viral etiology compared to those with unknown etiology (32/58; 55.2%). Seizures and vomiting were observed more frequently among AES patients with unknown etiology (45/58; 77.6%) than those with viral etiology (26/43; 60.5%). Combinations of fever and headache; and impaired cognition and hallucinations were observed more commonly in AES patients with unknown etiology (29/58; 61.7%; and 10/58; 17.3%). The classical triad of fever, seizures, and altered sensorium was seen in less than half of AES patients with (17/43; 39.5%) or without (26/58; 44.8%) known etiology [Table 2]. Two patients, each with herpes simplex virus (HSV) encephalitis and unknown etiology presented without fever, possibly due to care givers ignorance or being treated with medications for headache. Aerophobia and hydrophobia were exclusively seen in rabies encephalitis patients [Supplementary Table 1]. Overall, analysis of individual symptoms or in combination was similar among both AES patients with confirmed viral etiology and those with unknown etiology.

### Neurological examination findings [Table 3]

Overall, the most common clinical neurological finding was an impaired Glasgow Coma Scale response (77/101; 76.2%), followed by abnormal plantar reflex response (58; 57.4%), dysarthria (34/101; 33.7%), meningeal signs (30/101; 29.7%), and cranial nerve signs (18/101; 17.8%), respectively. AES patients with viral etiology had a significantly higher proportion of disorientation to time (39.5% vs. 15.5%), place (37.2% vs. 15.5%), and person (37.2% vs. 15.5%)

**Table 1: Sociodemographic characteristics of patients with acute encephalitis syndrome, comparing patients with viral versus unknown etiology (n=101)**

	AES patients with viral etiology (n=43; 42.57), n (%)	AES patients with unknown etiology (n=58; 57.42%), n (%)	Total AES patients (n=101; 100%), n (%)	P (Chi-square or t-test) comparing
Age (years)*	27.97 (19.1)	31.55 (20.2)	30.02 (19.7)	0.370
≤16	12 (28)	16 (27.6)	28 (27.7)	0.906
17–59	27 (62.8)	35 (60.3)	62 (61.4)	
≥60	4 (9.3)	7 (12.1)	11 (10.9)	
Gender				
Male	29 (67.4)	34 (58.6)	63 (62.4)	0.411 <sup>F</sup>
Female	14 (32.6)	24 (41.4)	38 (37.6)	
Occupation				
Waged workers	19 (44.2)	28 (48.3)	47 (46.5)	0.874
Farmers	9 (21)	10 (17.2)	19 (18.8)	
Others <sup>#</sup>	15 (34.9)	20 (34.5)	35 (34.7)	
Education				
Illiterate	7 (16.3)	12 (20.7)	19 (18.8)	0.265
Primary level completed	26 (60.5)	30 (51.7)	56 (55.4)	
Above primary level	10 (23.3)	16 (27.6)	26 (25.7)	
Religion				
Hindu	30 (69.8)	50 (86.2)	80 (79.2)	0.130
Muslims	11 (25.6)	7 (12.1)	18 (17.8)	
Others	2 (4.7)	1 (1.7)	3 (3)	
Marital status				
Married	19 (44.2)	39 (53.5)	58 (57.4)	0.255
Unmarried	24 (55.8)	25 (43.1)	49 (48.5)	
Widowed	0	2 (3.5)	2 (2)	
Type of location				
Rural	26 (60.5)	39 (67.2)	65 (64.4)	0.532 <sup>F</sup>
Urban	17 (39.5)	19 (32.8)	36 (35.6)	
Region in India				
North	1 (2.3)	1 (1.7)	2 (2)	0.530
North-East	1 (2.3)	1 (1.7)	2 (2)	
South	27 (62.8)	42 (72.4)	69 (68.3)	
East	14 (32.5)	14 (24.1)	28 (27.7)	
West	0	0	0	
Referral pathway				
Direct	12 (27.9)	20 (34.5)	32 (31.7)	0.493
General Practitioner	5 (11.6)	8 (13.8)	13 (12.9)	
Neurologist	1 (2.3)	2 (3.5)	3 (3)	
Others	16 (37.2)	12 (20.7)	28 (27.7)	
Not documented	9 (20.9)	16 (27.6)	25 (24.8)	

\*Mean (SD), <sup>#</sup>Others include drivers, employees of both private and government institutions and those reported to be involved in any kind of business,

<sup>F</sup>Fisher's exact test. SD: Standard deviation, AES: Acute encephalitis syndrome

compared to AES patients with unknown etiology. Although not significant, AES patients with viral etiology appeared to have a higher proportion of behavioral changes (30.23% vs. 22.41%), psychosis (18.60% vs. 5.17%), and cranial nerve involvement (48.83% vs. 25.86%) compared to AES with unknown etiology. Combinations of higher mental function abnormalities such as hallucinations with psychosis and behavioral changes with hallucinations, were exclusively seen among HSV encephalitis patients (among the AES patients with known viral etiology). Multiple cranial nerve involvement was noted in JE and HSV patients, while single cranial nerve

involvement was noted in AES patients with other viral etiologies [Supplementary Table 2].

#### Haematological, biochemical, neuroimaging, and cerebrospinal fluid findings of patients with acute encephalitis syndrome [Table 4]

Hematology was done in 82.17% of AES patients, which revealed neutrophilia (45/101; 44.55%), anemia (31/101; 30.7%), and increased ESR (29/101; 28.7%) overall. Comparison of hematological findings revealed significantly higher neutrophilia (24/43; 55.8% vs. 21/58; 36.2%;

**Table 2: Symptoms experienced by patients with acute encephalitis syndrome (n=101)**

	AES patients with viral etiology (n=43; 42.6%), n (%)	AES patients with unknown etiology (n=58; 57.4%), n (%)	Total AES patients (n=101; 100%), n (%)	P value for Chi-square/t-test
Symptoms				
Fever	41 (97.7)	56 (96.6)	97 (96)	0.581 <sup>F</sup>
Altered sensorium	29 (67.4)	36 (62.1)	65 (64.4)	0.445 <sup>F</sup>
Seizures	27 (62.8)	45 (77.6)	72 (71.3)	0.16
Generalized seizures	8 (18.6)	15 (25.9)	23 (22.8)	0.94
Partial seizures	4 (9.3)	3 (5.2)	7 (6.9)	0.47
Myoclonic seizures	1 (2.3)	0	1 (1)	0.43 <sup>F</sup>
Others	0	1 (1.7)	1 (1)	1.00 <sup>F</sup>
Type of seizure not documented	14 (32.5)	26 (57.8)	40 (39.6)	0.80
Absent	16 (37.2)	13 (22.4)	29 (28.7)	0.16
Headache	18 (41.9)	25 (43.1)	43 (42.6)	0.93
Vomiting	11 (25.6)	17 (29.3)	28 (27.7)	0.85
Impaired cognition	15 (34.9)	19 (32.8)	34 (33.7)	0.99
Hallucinations	9 (20.9)	13 (22.4)	22 (21.8)	0.94
Involuntary micturition	9 (20.9)	7 (12.1)	16 (15.8)	0.35
Diplopia	3 (7)	4 (7)	7 (6.9)	0.32
Photophobia	0	2 (3.5)	2 (2)	0.65 <sup>F</sup>
Giddiness	2 (4.7)	2 (3.5)	4 (4)	0.99 <sup>F</sup>
Aerophobia	1 (2.3)	0	1 (1)	0.85 <sup>F</sup>
Hydrophobia	1 (2.3)	0	1 (1)	0.85 <sup>F</sup>
Combinations of symptoms				
Fever and altered sensorium	27 (62.8)	32 (55.2)	59 (58.4)	0.85 <sup>F</sup>
Altered sensorium and seizures	18 (41.9)	26 (44.8)	44 (43.6)	0.92 <sup>F</sup>
Fever, headache and seizures	18 (41.9)	24 (41.4)	42 (41.6)	0.92 <sup>F</sup>
Fever and headache	16 (40)	29 (61.7)	42 (41.6)	0.28
Fever, altered sensorium and seizures	17 (39.5)	26 (44.8)	43 (42.6)	0.74
Altered sensorium and impaired cognition	12 (27.9)	16 (27.6)	28 (27.7)	0.85
Headache and altered sensorium	12 (27.9)	15 (25.9)	27 (26.7)	0.99
Fever, headache and altered sensorium	13 (30.2)	14 (24.1)	27 (26.7)	0.64
Impaired cognition and Hallucinations	5 (11.6)	10 (17.2)	15 (14.9)	0.61
Vomiting and diarrhoea	1 (2.3)	1 (1.7)	2 (2)	1.00 <sup>F</sup>

<sup>F</sup>Fisher's exact test. AES: Acute encephalitis syndrome

$P = 0.022$ ) and lymphocytopenia (13/43; 30.2% vs. 14/58; 24.1%,  $P = 0.033$ ) in AES patients with viral etiology. The biochemical assessment was done in 79.2% of AES patients. Increased liver enzymes (29/101; 28.7%), serum creatinine, and hyponatremia were the major biochemical abnormalities noted. However, hyponatremia (27.9% vs. 13.8%) was more often noted in AES patients with viral etiology, while hyperbilirubinemia (8.6% vs. 0), increased serum creatinine (25.9% vs. 7%) and hyperkalemia (15.5% vs. 4.7%) were observed more often amongst those with unknown etiology. Cerebrospinal fluid (CSF) analysis was done polymerase chain reaction technique in 81.9% of AES patients. CSF pleocytosis (46/101; 45.5%) and increased CSF protein (40/101, 39.6%) were common abnormalities noted in AES patients and there was no difference between AES patients with or without known etiology.

Neuroimaging was done in 91.1% of AES patients. Computed tomography (CT) was done in 74.3%, and magnetic resonance imaging (MRI) in 68.3% of patients. Parenchymal changes

were observed in CT (44/101; 43.6%) and MRI brain (42/101; 41.6%). AES patients with viral etiology had a higher proportion of abnormalities in MRI (24/43; 55.8% vs. 18/58; 31%), while AES patients of unknown etiology showed more CT brain abnormalities than those with known viral etiology (27/58; 46.6% vs. 17/43; 39.5%) [Supplementary Table 3]. Representative MRI images of AES patients with viral etiology are presented in Figure 2.

### Etiological profile of acute encephalitis syndrome patients

Etiology in 57.43% of the patients was unknown [Figure 3 and Supplementary Table 4]. Among viral AES patients, HSV was detected in 22 (51.6%) patients, followed by chikungunya encephalitis virus (6, 14%), JE (6, 14%), chikungunya-dengue dual infection encephalitis (4, 9.3%), rabies encephalitis (3, 7%), dengue encephalitis (1, 2.3%), and varicella encephalitis virus (1, 2.3%). Four patients presented with acute necrotizing encephalopathy (ANE); of these, two had JE, one had chikungunya encephalitis, and one patient had encephalitis with unknown etiology.

**Table 3: Neurological examination findings of patients with acute encephalitis syndrome (n=101)**

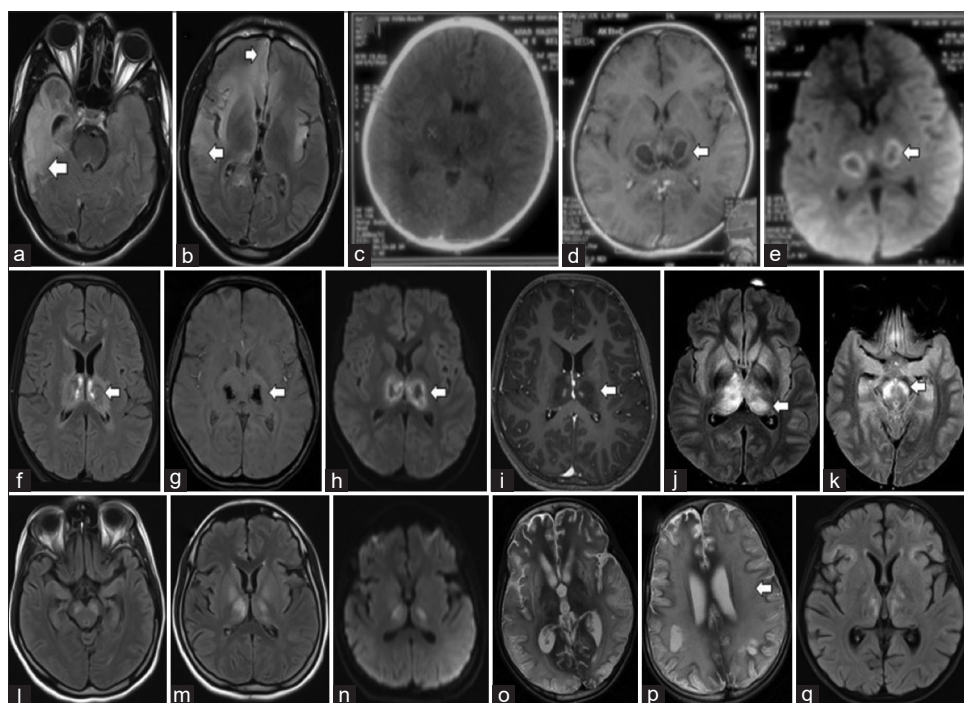
Neurological signs	AES patients with viral etiology (n=43; 42.6%), n (%)	AES patients with unknown etiology (n=58; 57.4%), n (%)	Total AES patients (n=101; 100%), n (%)	P value for Chi-square/t-test
Higher mental functions				
GCS recorded	36 (83.7)	41 (70.7)	77 (76.2)	0.266
Normal response	16 (37.2)	12 (20.7)	28 (27.7)	0.25
Impaired response	16 (37.2)	22 (37.9)	38 (37.6)	0.56
Completely absent	4 (9.3)	8 (13.8)	12 (11.9)	0.48
Not documented	7 (15.07)	16 (27.6)	23 (22.8)	
Dysarthria	16 (37.2)	18 (31.0)	34 (33.7)	0.66
Disorientation to place	17 (39.5)	9 (15.5)	26 (25.7)	0.01
Disorientation to time	16 (37.2)	9 (15.5)	25 (24.8)	0.02
Disorientation to person	16 (37.2)	9 (15.5)	25 (24.8)	0.02
Behavioral changes	13 (30.2)	13 (22.4)	26 (25.7)	0.51
Hallucinations	9 (20.9)	12 (20.7)	21 (20.8)	0.83
Psychosis	8 (18.6)	3 (5.2)	11 (10.9)	0.069
Combination of neurological signs				
Dysarthria and Hallucinations	5 (11.6)	6 (10.5)	11 (10.9)	1.00 <sup>F</sup>
Meningeal signs and behavioral changes	4 (9.3)	5 (8.6)	9 (8.9)	1.00 <sup>F</sup>
Behavioral changes and Hallucinations	1 (2.3)	5 (8.6)	6 (5.9)	0.37 <sup>F</sup>
Hallucinations and psychosis	2 (4.7)	1 (1.7)	3 (3)	0.77 <sup>F</sup>
Cranial nerves involvement				
II	9 (20.9)	9 (15.5)	18 (17.8)	0.66
II	2 (4.7)	0	2 (2)	0.45
III, IV, VI	4 (9.3)	6 (10.3)	10 (9.9)	0.63
V	1 (2.3)	2 (3.4)	3 (3)	0.99
VII	6 (14)	4 (6.9)	10 (9.9)	0.63 <sup>F</sup>
VIII	1 (2.3)	2 (3.4)	3 (3)	0.99
IX, X, XI	1 (2.3)	1 (1.7)	3 (3)	0.99
XII	1 (2.3)	0	1 (1)	0.99 <sup>F</sup>
Tone				
Abnormal	8 (18.6)	20 (34.5)	28 (27.7)	0.03
Normal	34 (79.1)	32 (55.2)	66 (65.3)	
Not documented	1 (2.3)	6 (10.4)	7 (6.9)	
Abnormal tone	8 (18.6)	20 (34.5)	28 (27.7)	
Hypotonia	2 (4.6)	5 (8.6)	7 (6.9)	0.99 <sup>F</sup>
Spasticity	3 (7)	10 (17.2)	13 (12.9)	0.99 <sup>F</sup>
Rigidity	3 (7)	5 (8.6)	8 (7.9)	0.99 <sup>F</sup>
Power				
Abnormal	8 (18.6)	21 (35.2)	29 (28.7)	0.10
Grade 5 (normal)	32 (74.4)	35 (60.3)	67 (66.3)	
Not documented	2 (4.7)	2 (3.4)	4 (4)	
Abnormal power	8 (18.6)	21 (36.2)	29 (28.7)	
Grade 4	1 (2.3)	6 (10.3)	7 (6.9)	
Grade 1, 2, 3	6 (14)	10 (17.2)	16 (15.8)	
Grade 0	1 (2.3)	5 (8.6)	6 (5.9)	
DTRs				
Normal	24 (55.8)	36 (62.1)	60 (59.4)	0.56
Abnormal	16 (37.2)	17 (29.3)	33 (32.7)	
Sluggish	2 (4.7)	7 (12.07)	9 (8.91)	0.14 <sup>F</sup>
Brisk/exaggerated	14 (32.6)	10 (17.2)	24 (23.8)	
Absence of DTRs	0	5 (8.6)	5 (5)	
Not documented	3 (7)	0	4 (4)	
Plantar reflexes				
Flexor				0.01
Bilateral	26 (60.5)	17 (29.3)	43 (42.6)	

Contd...

Table 3: Contd...

Neurological signs	AES patients with viral etiology (n=43; 42.6%), n (%)	AES patients with unknown etiology (n=58; 57.4%), n (%)	Total AES patients (n=101; 100%), n (%)	P value for Chi-square/t-test
Unilateral Extensor	8 (18.6)	8 (13.8)	16 (15.8)	
Bilateral Extensor	7 (16.3)	16 (27.6)	23 (22.8)	
Unilateral Equivocal	0	4 (6.9)	4 (4)	
Withdrawal	0	3 (5.2)	3 (3)	
Loss of sensation	2 (4.7)	10 (17.2)	12 (11.9)	0.634 <sup>F</sup>
Movement disorders	1 (2.3)	2 (3.4)	4 (4)	
Tremors	3 (7)	5 (8.6)	8 (7.9)	
Dystonia	1 (2.3)	1 (1.7)	2 (2)	0.94 <sup>F</sup>
Chorea	1 (2.3)	1 (1.7)	2 (2)	
Meningeal signs	1 (2.3)	3 (5.2)	4 (4)	
Abnormal gait	14 (32.6)	16 (27.6)	30 (29.7)	0.74
	3 (7)	2 (3.4)	5 (5)	0.08

<sup>F</sup>Fisher's exact test. GCS: Glasgow Coma Scale, NT: Not tested, DTRs: Deep tendon reflexes, AES: Acute encephalitis syndrome



**Figure 2:** Magnetic resonance imaging (MRI) brain findings. (a and b) Patient-2, 24 years/male; herpes simplex virus encephalitis showing flair axial images showing hyperintensities of the right temporal, bilateral frontal and insula (arrow). (c-e) Patient-4, 6 years/male, Japanese encephalitis (JE)-acute necrotizing encephalopathy of children (ANEC) showing axial images of computed tomography (c), MRI-flair (d) and diffusion weighted (e) images showing central hypo-intensity with diffusion restricting peripheral hyperintensity in the thalamus (arrow) suggestive of ANEC. (f-i) Patient-8, 13 years/female, ANEC showing flair (f), gradient (g), Diffusion (h), T1 contrast (i) showing central hypo-intensity in the center with diffusion restricting peripheral hyperintensity and patchy contrast enhancement in the center in the thalamus (arrow) suggestive of ANEC. (j and k) Patient-10, 26 years/male, JE showing flair (j and k) hyperintensities in the thalamus, midbrain (arrow). (l-n) Patient-13, 30 years/female, JE showing flair (l and m) and diffusion (n) hyperintensities in the thalamus, midbrain (arrow). (o and p) Patient-15, 11 years/male, rabies encephalitis flair hyperintensities of the white matter (arrow) with diffuse cerebral atrophy. (q) Patient-16, 8 years/female, chikungunya encephalitis showing flair hyperintensities in the bilateral thalamus, insula and frontal region

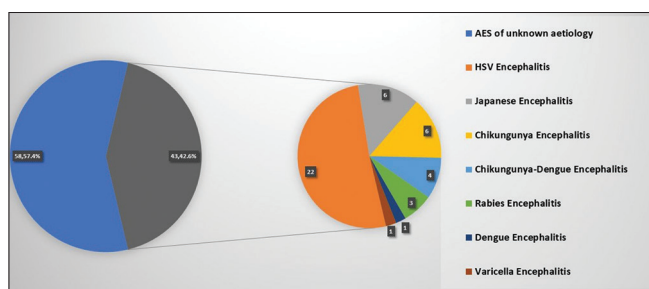
Nearly half of AES patients presented (49/101; 48.5%) to the hospital during early (January and February) and late part of the year (November and December). Number of patients presenting to the hospital was highest in December (19/101;

18.8%). AES patients with viral etiology, reported mostly from July to December (31/43; 72.1%), while those with unknown etiology reported throughout the year (Data not shown). Among patients with known viral etiology, patients of HSV

**Table 4: Neuroimaging, hematological, biochemical and cerebrospinal fluid findings of patients with acute encephalitis syndrome (n=101)**

	AES patients with viral etiology (n=43; 42.6%)	AES patients with unknown etiology (n=58; 57.4%)	Total AES patients (n=101; 100%), n (%)	Chi-square/ t-test
Neuroimaging			92 (91.1)	
CT brain findings		75 (74.3)		
Normal	14 (32.6)	17 (29.3)	31 (41.3)	0.27
Abnormal	17 (39.5)	27 (46.6)	44 (58.7)	
Diffuse cerebral oedema	9 (20.9)	10 (17.2)	19 (25.3)	
Parenchymal hypodensity	13 (30.2)	10 (17.2)	23 (30.7)	
Cerebral atrophy	1 (2.3)	1 (1.7)	2 (2.7)	
Not available	6 (14)	20 (34.5)	26 (25.7)	
MRI findings		69 (68.3)		
Normal	12 (27.9)	15 (25.9)	27 (26.7)	0.74
Abnormalities	24 (55.8)	18 (31)	42 (41.6)	
Diffuse cerebral oedema	2 (4.7)	0	2 (2)	
Parenchymal hyperintensity	20 (46.5)	14 (24.1)	34 (33.7)	
Diffuse meningeal enhancement	1 (2.3)	1 (1.7)	2 (2)	
Cerebral atrophy	1 (2.3)	3 (5.2)	4 (2)	
Not available	7 (16.3)	25 (43.1)	32 (31.7)	
Hematology			83 (82.17)	
Anaemia (<11 g/dL)	14 (32.6)	17 (29.3)	31 (30.7)	0.70
Leukocytosis (>11,000/mm <sup>3</sup> )	12 (27.9)	15 (25.9)	27 (26.7)	0.79
Neutrophilia (>7.5×10 <sup>9</sup> /L)	24 (55.8)	21 (36.2)	45 (44.6)	0.022
Lymphocytopenia (<1000 lymphocytes/μL of blood)	13 (30.2)	14 (24.1)	27 (26.7)	0.033
Thrombocytopenia (<150,000/μL)	7 (16.3)	7 (12.1)	14 (13.9)	0.926
Increased ESR (<20 mm/h)	12 (27.9)	17 (29.3)	29 (28.7)	0.986
Biochemistry			80 (79.20)	
Increased RBS (>130 mg/dL)	5 (11.6)	6 (10.3)	11 (10.9)	0.950
Hyperbilirubinemia (>1.2 mg/dL)	0	5 (8.62)	5 (4.95)	0.140
Increased SGOT (>48 U/L of serum)	12 (27.90)	17 (29.31)	29 (28.71)	0.765
Increased SGPT (>56 U/L of serum)	15 (34.88)	14 (24.13)	29 (28.71)	0.179
Increased serum creatinine (1.35 mg/dL)	3 (6.97)	15 (25.86)	19 (18.81)	0.052
Hyponatremia (<135 mEq/L)	12 (27.90)	8 (13.79)	20 (19.80)	0.227
Hypokalemia (<3.5 mmol/L)	2 (4.65)	4 (6.89)	6 (5.94)	0.318
Hyperkalemia (>5.1 mmol/L)	2 (4.65)	9 (15.51)	11 (10.89)	
CSF findings			82 (81.18)	
CSF pleocytosis (>5 cells)	22 (51.16)	24 (41.37)	46 (45.54)	0.691
Increased CSF protein (>60 mg/100 mL)	18 (41.86)	22 (37.93)	40 (39.6)	0.833

CSF: Cerebrospinal fluid, SGOT: Serum glutamic-oxaloacetic transaminase, SGPT: Serum glutamic pyruvic transaminase, RBS: Random blood sugar, AES: Acute encephalitis syndrome



**Figure 3:** Etiological profile of acute encephalitis syndrome patients visiting NIMHANS in 2019 (n = 101)

encephalitis presented to the hospital throughout the year, while those with arboviral etiology were seen in the postmonsoon

period (July-December and January and February). Among etiological tests, virological tests were performed in 60 (59.4%) and it was positive in 43 (71.7%). Bacterial tests for other micro-organisms were performed in 79 (78.2%) and it was positive in 9 (11.4%) patients. Acyclovir was provided as a presumptive treatment to 13 (22.4%) of the patients with unknown etiology. None of them were diagnosed with HSV encephalitis. While acyclovir was not administered to the remaining 45 (77.5%) patients. The mean duration of hospital stay [Table 5] for AES patients was about 9 days (standard deviation = 10.48 days, range 2–28 days). Majority of AES patients stayed for >5 days in the hospital (62/101; 61.38%). About three-quarters of those with viral etiology (32/43; 74.41%) and half of those with unknown etiology they had

**Table 5: Duration of hospital stay and outcome of patients with acute encephalitis syndrome (n=101)**

Characteristic	Viral AES (n=43; 42.57%), n (%)	Unknown etiology (n=58; 57.42%)	Total AES patients (n=101; 100%)	Chi-square/t-test
Duration of hospital stay				
<5 days	11 (25.58)	26 (44.82)	37 (36.63)	0.05
≥5 days	32 (74.41)	30 (51.72)	62 (61.38)	
Mean duration*	8.83 (7.36)	8.67 (12.31)	8.91 (10.48)	0.934
NA	0	2 (3.45)	2 (1.98)	
Condition at the time of discharge				0.07
Improved/recovered	30 (69.76)	24 (41.37)	54 (53.46)	
Status quo	7 (16.28)	16 (27.59)	23 (22.77)	
Not documented	6 (13.95)	18 (31.03)	24 (23.76)	

\*Mean and SD, FFisher's exact test. NA: Not available, AES: Acute encephalitis syndrome

stayed for > 5 days (30/58; 51.72%) [Supplementary Table 5]. Majority of AES patients had improved (54/101; 53.46%) at the time of discharge.

## DISCUSSION

This is a comprehensive analysis of sociodemographic, clinical, etiological, laboratory profiles and treatment characteristics of AES patients admitted to a tertiary care neuro-specialty center in India in 2019. Individual symptoms of fever, seizures, altered sensorium, and headache were the most commonly observed AES symptoms. The classical triad of fever, seizures, and altered sensorium was observed in less than half of all AES patients. Fever, headache, and altered sensorium were mostly seen in AES patients with viral etiology, while impaired cognition and hallucinations were mostly seen in AES patients with unknown etiology. Although less common amongst AES patients with viral etiology, combinations of higher mental function abnormalities like hallucinations with psychosis and behavioral changes with hallucinations were exclusively seen in patients with HSV encephalitis. Disorientation to time, place, and person was significantly observed among AES patients with viral etiology.

Most sociodemographic features of AES patients noted in our study were similar to those reported in earlier studies except for their age and occupation.<sup>[3,6-10]</sup> Although AES patients are known to commonly affect children,<sup>[3,6,7,11,12]</sup> majority here were adults, which forms the biggest strength of this study addressing the profile of AES in adults from a tertiary neurology center. The study site is located next to a tertiary care children's hospital. It is likely that most pediatric AES patients sought care at the children's hospital. In our study, most patients were waged workers, as against farmers reported in other studies.<sup>[2,3,6,8]</sup> Given that there are only three categories for occupation-related data that are usually collected during registration (paid workers, farmers, and others), it is probable that there is overlap between waged workers and farmers that cannot be studied.

Most clinical features of AES patients were similar to other studies<sup>[5,13]</sup> with some marked differences. The classical triad of fever, seizures, and altered sensorium was observed in only 42.6%. Clinical features such as coma, paralysis, headache,

tremors, and vomiting were observed less often than other studies.<sup>[14]</sup> Commonly reported alterations in higher mental functions, such as abnormal speech, behavioral changes, and psychosis<sup>[15-17]</sup> were noted only in one-third of our patients. While the involvement of 3<sup>rd</sup>, 4<sup>th</sup>, and 6<sup>th</sup> cranial nerves is known,<sup>[3,13,15,18-22]</sup> involvement of multiple cranial nerves (facial and lower cranial nerves) was a unique finding in our study. These differences in presentation are likely to contribute to delays in the diagnosis of AES in primary and secondary care facilities.

This is one of the first studies to provide important insights into the diagnosis and management of AES at a tertiary care hospital in India. In comparison, this study gives a more detailed and comprehensive report on clinical findings, sociodemographic features, and imaging parameters.<sup>[23]</sup> We utilized the standard WHO definition of AES and well-defined inclusion and exclusion criteria on a large sample. In addition to sociodemographic and clinical features, analysis of a range of investigations (hematological, biochemical, virological, and imaging) was conducted, while other studies have been limited to analysis of etiological profile and treatment outcomes.<sup>[6,13,22,24-29]</sup> However, there was an opportunity to understand clinical management gaps by comparing patients for outcomes. Nonavailability of follow-up data limits exploring this opportunity in our study.

Etiological confirmation of AES in this study is similar to other studies reported in India.<sup>[29-33]</sup> However, 58% of AES patients had no confirmed etiology. This high proportion can be minimized through modifications in current clinical practice, the inclusion of newer pathogens amongst the battery of tests, and conducting relevant and timely (due to the fact that viremia and viruses in CSF can be detected only for a short time) serological assessments. Data on time to CSF testing from onset could have thrown light on possible viral AES being rendered nonviral or unknown etiology AES due to the longer duration of time between onset and CSF testing. In current clinical practice, few bacterial tests were not performed; the etiologies classified as viral and nonviral in the current study are based on limited virological testing. Further, the decision on testing, MRI and electro encephalogram was made based on the affordability of



patients and the availability of resources to achieve a diagnosis. A stepwise approach in pathogen search from common to uncommon and adding a few more bacterial tests may provide better yield. The scenario of etiology of AES in India has been evolving.<sup>[4,34]</sup> Pathogens such as *Orientia tsutsugamushi*, *Leptospira*, enteroviruses, measles, and *Chandipura viruses* are becoming increasingly prevalent in India.<sup>[4,34]</sup> Improving the battery of tests to include these pathogens might reduce the proportion of AES patients with unknown etiology. Conducting serological tests amongst all suspected AES patients will also improve etiological confirmation.

This study had certain limitations. The case record review adopted limits generalizability. Standardization of recording and documentation of medical records is needed. It was observed that certain information such as travel history, contact with animals, tick bites, types of seizures, treatment outcome, and referral information were either incomplete or not documented [Tables 1-4]. However, the information within the clinical records can be considered complete as they are maintained by trained neurologists. The comparisons made in our study did not yield any significant differences. The small numbers and probable overlap of patients with unknown etiology actually having viral etiologies might be the reason for such lack of significance. Increasing the battery of tests and comparing the same might throw more light on this hypothesis. This also highlights the fact that all suspected acute encephalitis cases (viral or nonviral) could be ascertained if all the AES cases are subjected to standardized viral, microbiological testing and imaging protocols. However, even though the comparisons made are not significant, the results provide perspectives regarding the pattern of AES, epidemiological, demographical, and seasonal patterns of AES, and limited but valuable information regarding viral etiologies.

Based on our findings, we recommend the exploration of syndromic approach to diagnosis for early initiation of treatment and reduction in complications of AES. Increasing the battery of tests based on local epidemiological situations with a diagnostic algorithm is recommended. At a tertiary care center, with limited time and beds, it is challenging for neurologists to thoroughly evaluate AES patients and perform all possible tests. This may result in delayed treatment. However, care at such centers can be improved by bridging gaps by (i) obtaining a comprehensive clinical case history including recent and remote travel, animal, ticks, and insect exposure, (ii) both serum and CSF analysis for possible etiologies, and (iii) increasing the battery of tests and establishing a standard diagnostic algorithm that incorporates testing for common and rare infections (viruses, bacteria, spirochetes, and parasites), and autoimmune etiologies.

## CONCLUSION

In summary, this study has important implications for evidence-based treatment and management of AES in tertiary care settings. A uniform laboratory and diagnostic criteria

and an understanding of the opportunities and limitations for managing AES cases in tertiary care centers can reduce AES mortality and morbidity. A common model of care package across levels of health care needs to be developed and implemented to efficiently manage AES patients in India.

## Research quality and ethics statement

The authors followed applicable EQUATOR Network (<http://www.equator-network.org/>) guidelines, notably the CARE guideline, during the conduct of this analysis and report. Further, the ethical approval for this study was obtained from the Institutional Ethics Committee of the National Institute of Mental Health and Neuro Sciences, India.

## Declaration of patient consent

The authors declare that they have obtained consent from patients. Patients have given their consent for their images and other clinical information to be reported in the journal. Patients understand that their names will not be published and due efforts will be made to conceal their identity but anonymity cannot be guaranteed.

## Financial support and sponsorship

This work was supported by the UK National Institute for Health Research (NIHR) Global Health Research Group on Brain Infections (Grant No. 17/63/110).

## Conflicts of interest

There are no conflicts of interest.

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**Supplementary Table 1: Symptom characteristics of patients with acute encephalitis syndrome (n=101)**

Symptoms	HSV, n (%)	JE, n (%)	Chikungunya, n (%)	Dengue, n (%)	Dengue + chikungunya, n (%)	Rabies, n (%)	Varicella, n (%)	Viral/AES, n (%)	Unknown etiology, n (%)	Total AES patients, n (%)
Fever	20 (90.90)	6 (100)	6 (100)	1 (100)	4 (100)	3 (100)	1 (100)	41 (97.67)	56 (96.55)	97 (96.04)
Altered sensorium	15 (68.18)	3 (50.00)	5 (83.33)	1 (100)	3 (75.00)	1 (33.33)	1 (100)	29 (67.44)	36 (62.07)	65 (64.35)
Seizures	13 (59.09)	4 (66.66)	4 (66.66)	0	2 (50.00)	3 (100)	1 (100)	27 (62.79)	45 (77.59)	72 (71.28)
Generalized seizures	5 (22.72)	2 (33.33)	0	0	1 (25.00)	0	0	8 (18.60)	15 (25.86)	23 (22.77)
Partial seizures	1 (4.54)	1 (16.67)	2 (33.33)	0	0	0	0	4 (9.30)	3 (5.17)	7 (6.93)
Myoclonic seizures	1 (4.54)	0	0	0	0	0	0	1 (2.33)	0	1 (0.99)
Others	0	0	0	0	0	0	0	0	1 (1.72)	1 (0.99)
Type of seizure not documented	6 (27.27)	1 (16.67)	2 (33.33)	0	1 (25.00)	3 (100)	1 (100)	14 (32.55)	26 (57.77)	40 (39.60)
Absent	9 (40.90)	2 (33.33)	2 (33.33)	1 (100)	2 (50.00)	0	0	16 (37.20)	13 (22.41)	28 (27.72)
Headache	10 (45.45)	2 (33.33)	3 (50.00)	0	1 (25.00)	1 (33.33)	1 (100)	18 (41.86)	25 (43.10)	43 (42.57)
Vomiting	7 (31.81)	1 (16.67)	2 (33.33)	0	1 (25.00)	0	0	11 (25.58)	17 (29.31)	28 (27.72)
Impaired cognition	9 (40.90)	3 (50.00)	1 (16.67)	0	1 (25.00)	0	1 (100)	15 (34.88)	19 (32.76)	34 (33.66)
Hallucinations	6 (27.27)	1 (16.67)	2 (33.33)	0	1 (25.00)	0	0	9 (20.93)	13 (22.41)	22 (21.78)
Involuntary micturition	7 (31.81)	0	1 (16.67)	0	1 (25.00)	0	0	9 (20.93)	7 (12.07)	16 (15.84)
Diplopia	2 (9.09)	0	0	0	1 (25.00)	0	0	3 (6.98)	4 (6.90)	7 (6.93)
Photophobia	0	0	0	0	0	0	0	0	2 (3.45)	2 (1.98)
Giddiness	1 (4.54)	0	0	0	0	0	0	2 (4.65)	2 (3.45)	4 (3.96)
Aerophobia	0	0	0	0	0	1 (33.33)	0	1 (2.33)	0	1 (0.99)
Hydrophobia	0	0	0	0	0	1 (33.33)	0	1 (2.33)	0	1 (0.99)
Combination of symptoms										
Fever and altered sensorium	15 (68.18)	2 (33.33)	4 (66.67)	1 (100)	3 (75.00)	1 (33.33)	1 (100)	27 (62.79)	32 (55.17)	59 (58.42)
Altered sensorium and seizures	9 (40.91)	1 (16.67)	2 (33.33)	0	2 (50.00)	1 (33.33)	1 (100)	18 (41.86)	26 (44.83)	44 (43.56)
Fever, headache and seizures	9 (40.91)	2 (33.33)	2 (33.33)	0	1 (25.00)	1 (33.33)	1 (100)	18 (41.86)	24 (41.37)	42 (41.58)
Fever and headache	9 (40.91)	2 (33.33)	2 (33.33)	0	1 (25.00)	1 (33.33)	1 (100)	16 (40.00)	29 (61.70)	42 (41.58)
Fever, altered sensorium, and seizures	9 (40.91)	2 (33.33)	2 (33.33)	0	2 (50.00)	1 (33.33)	1 (100)	17 (39.53)	26 (44.82)	43 (42.57)
Altered sensorium and impaired cognition	6 (27.27)	2 (33.33)	1 (16.67)	0	1 (25.00)	0	1 (100)	12 (27.91)	16 (27.59)	28 (27.72)
Headache and altered sensorium	7 (31.82)	1 (16.67)	1 (16.67)	0	0	1 (33.33)	1 (100)	12 (27.91)	15 (25.86)	27 (26.73)
Fever, headache and altered sensorium	6 (27.27)	1 (16.67)	2 (33.33)	0	0	1 (25.00)	1 (100)	13 (30.23)	14 (24.13)	27 (26.73)
Impaired cognition and hallucinations	3 (13.64)	1 (16.67)	1 (16.67)	0	0	0	0	5 (11.62)	10 (17.24)	15 (14.85)
Vomiting and diarrhea	1 (4.55)	0	0	0	0	0	0	1 (2.33)	1 (1.72)	2 (1.98)
History of										
Dog bite	0	0	0	0	0	3 (100)	0	3 (7.50)	0	3 (2.97)
Joint pains	2 (9.09)	0	0	0	0	1 (25.00)	0	3 (7.50)	0	4 (3.96)
Diarrhea	3 (13.63)	0	0	0	1 (25.00)	0	0	4 (10.00)	1 (2.12)	5 (4.95)
Weight loss	0	0	0	0	0	0	0	0	1 (2.12)	1 (0.99)
Total	22 (51.56)	6 (13.95)	6 (13.95)	1 (2.32)	4 (9.30)	3 (6.97)	1 (2.32)	43 (42.57)	58 (57.42)	101 (100)

HSV: Herpes simplex virus, JE: Japanese encephalitis, AES: Acute encephalitis syndrome

**Supplementary Table 2: Clinical examination findings of patients with acute encephalitis syndrome (n=101)**

Signs	HSV, n (%)	JE, n (%)	Chikungunya, n (%)	Dengue, n (%)	Dengue + chikungunya, n (%)	Rabies, n (%)	Varicella, n (%)	Viral AES, n (%)	Unknown etiology, n (%)	Total AES patients, n (%)
Higher mental functions										
GCS	22 (100)	5 (83.33)	5 (83.33)	1 (100)	2 (50.00)	2 (66.66)	1 (100)	36 (83.72)	41 (70.68)	77 (76.23)
Impaired response	10 (45.45)	3 (50.00)	2 (33.33)	0	1 (25.00)	0	0	16 (37.21)	21 (36.20)	37 (36.63)
Normal response	7 (31.81)	2 (33.33)	3 (50.00)	0	1 (25.00)	2 (66.66)	1 (100)	16 (37.21)	12 (20.69)	28 (27.72)
Completely absent	3 (13.63)	0	0	1 (100)	0	0	0	4 (9.30)	8 (13.79)	12 (11.88)
CNBT	2 (9.09)	0	0	0	0	0	0	2 (3.45)	2 (3.44)	4 (3.96)
Not documented	0	1 (16.67)	1 (16.67)	0	2 (50.00)	1 (33)	0	5 (11.62)	14 (24.13)	19 (18.81)
Dysarthria	8 (36.36)	3 (50.00)	3 (50.00)	0	2 (50.00)	2 (66.66)	0	18 (31.03)	34 (33.66)	34 (33.66)
Disorientation to place	9 (40.90)	4 (66.67)	3 (50.00)	1 (100)	0	0	0	17 (39.53)	9 (15.52)	26 (25.74)
Disorientation to time	8 (36.36)	4 (66.67)	3 (50.00)	1 (100)	0	0	0	16 (37.21)	9 (15.52)	25 (24.75)
Disorientation to person	8 (36.36)	4 (66.67)	3 (50.00)	1 (100)	0	0	0	16 (37.21)	9 (15.52)	25 (24.75)
Behavioral changes	10 (45.45)	0	2 (33.33)	0	1 (25.00)	0	0	13 (30.23)	13 (22.41)	26 (25.74)
Hallucinations	6 (27.27)	1 (16.67)	2 (33.33)	0	0	0	0	9 (20.93)	12 (20.69)	21 (20.79)
Psychosis	7 (31.81)	0	1 (16.67)	0	0	0	0	8 (18.60)	3 (5.17)	11 (10.89)
Dysarthria and hallucinations	3 (13.63)	1 (16.67)	1 (16.67)	0	0	0	0	5 (11.63)	6 (10.54)	11 (10.89)
Meningeal signs and behavioral changes	3 (13.63)	0	1 (16.67)	0	0	0	0	4 (9.30)	5 (8.62)	9 (8.91)
Behavioural changes and hallucinations	1 (4.54)	0	0	0	0	0	0	1 (2.33)	5 (8.62)	6 (5.94)
Hallucinations and psychosis	2 (9.09)	0	0	0	0	0	0	2 (4.65)	1 (1.72)	3 (2.97)
Cranial nerves involvement	5 (22.72)	2 (50.00)	0	0	1 (25.00)	1 (33.33)	0	9 (20.93)	9 (15.51)	18 (17.82)
II	1 (4.54)	1 (16.67)	0	0	0	0	0	2 (4.66)	3 (5.17)	5 (4.95)
III, IV, VI	3 (13.63)	0	0	0	0	1 (33.33)	0	4 (9.30)	6 (10.34)	10 (9.90)
V	1 (4.54)	0	0	0	0	0	0	1 (2.33)	4 (6.89)	5 (4.95)
VII	3 (13.63)	1 (16.67)	0	0	1 (25.00)	1 (33.33)	0	6 (13.95)	7 (12.06)	13 (12.87)
VIII	1 (4.54)	0	0	0	0	0	0	1 (2.33)	5 (8.62)	6 (5.94)
IX, X, XI	1 (4.54)	0	0	0	0	0	0	1 (2.33)	4 (6.89)	5 (4.95)
XII	1 (4.54)	0	0	0	0	0	0	1 (2.33)	3 (5.17)	4 (3.96)
Dystonia	3 (13.63)	3 (50.00)	0	0	1 (25.00)	1 (33.33)	0	8 (18.60)	20 (34.48)	28 (27.72)
Hypotonia	0	2 (33.33)	0	0	0	0	0	2 (4.65)	5 (8.62)	7 (6.93)
Spasticity	2 (9.09)	0	0	0	0	1 (33.33)	0	3 (6.98)	10 (17.24)	13 (12.87)
Rigidity	1 (4.54)	1 (16.67)	0	0	1 (25.00)	0	0	3 (6.98)	5 (8.63)	8 (7.92)
Normal	18 (38.29)	3 (50.00)	6 (100)	1 (100)	3 (75.00)	2 (66.66)	1 (100)	34 (79.07)	32 (55.17)	66 (65.34)
Not documented	1 (4.54)	0	0	0	0	0	0	1 (2.33)	4 (6.94)	5 (4.95)
CNBT	0	0	0	0	0	0	0	0	2 (3.45)	2 (1.98)
Abnormal power	4 (18.18)	3 (50.00)	0	0	0	1 (33.33)	0	8 (18.60)	21 (36.20)	29 (28.71)
Grade 0	0	1 (16.67)	0	0	0	0	0	1 (2.32)	5 (8.62)	6 (5.94)
Grade 1,2,3	3 (13.63)	2 (33.33)	0	0	0	1 (33.33)	0	6 (13.95)	10 (17.24)	16 (15.84)
Grade 4	1 (4.54)	0	0	0	0	0	0	1 (2.32)	6 (10.34)	7 (6.93)

Contd...

**Supplementary Table 2: Contd...**

Signs	HSV, n (%)	JE, n (%)	Chikungunya, n (%)	Dengue, n (%)	Dengue + chikungunya, n (%)	Rabies, n (%)	Varicella, n (%)	Viral AES, n (%)	Unknown etiology, n (%)	Total AES patients, n (%)
Grade 5	18 (38.29)	2 (33.33)	6 (100)	1 (100)	4 (100)	1 (33.33)	1 (100)	32 (74.41)	35 (60.34)	67 (66.33)
Not documented	0	0	0	0	0	1 (33.34)	0	1 (2.32)	1 (1.72)	2 (1.98)
CNBT	0	1 (16.67)	0	0	0	0	0	1 (2.32)	1 (1.72)	2 (1.98)
Total	22 (51.56)	6 (13.95)	6 (13.95)	1 (2.32)	4 (9.30)	3 (6.97)	1 (2.32)	43 (42.57)	58 (57.42)	101 (100)
Abnormal deep tendon reflexes	3 (13.63)	1 (16.67)	6 (100)	0	1 (25.00)	3 (100)	0	16 (37.20)	17 (29.31)	33 (32.67)
Sluggish	0	0	1 (16.67)	0	1 (25.00)	0	0	2 (4.65)	7 (12.07)	9 (8.91)
Brisk/exaggerated	3 (13.63)	1 (16.67)	5 (83.33)	0	0	3 (100)	0	14 (32.55)	10 (17.24)	24 (23.76)
Normal	17 (36.17)	4 (66.67)	0	1 (100)	3 (75.00)	0	1 (100)	24 (55.81)	36 (62.07)	60 (59.40)
Not documented	2 (9.09)	0	0	0	0	0	0	2 (4.65)	0	2 (1.98)
CNBT	0	1 (16.67)	0	0	0	0	0	1 (2.32)	0	2 (1.98)
Absent	0	0	0	0	0	0	0	0	5 (8.62)	5 (4.95)
Abnormal plantar reflexes										
Flexor	8 (36.36)	2 (33.33)	3 (50.00)	1 (100)	1 (25.00)	2 (66.66)	0	17 (39.53)	41 (70.68)	58 (57.42)
Bilateral	14 (63.63)	4 (66.66)	3 (50.00)	0	3 (75.00)	1 (33.33)	1 (100)	26 (60.46)	17 (29.31)	43 (42.57)
Unilateral	5 (22.72)	0	2 (33.33)	0	1 (25.00)	0	0	8 (18.60)	8 (13.79)	16 (15.84)
Extensor										
Bilateral	2 (9.09)	2 (33.33)	0	1 (100)	0	2 (66.66)	0	7 (16.27)	16 (27.58)	23 (22.77)
Unilateral	0	0	0	0	0	0	0	0	4 (6.89)	4 (3.96)
Equivocal	0	0	0	0	0	0	0	0	3 (5.17)	3 (2.97)
Withdrawal	1 (4.54)	0	1 (16.67)	0	0	0	0	2 (4.65)	10 (17.24)	12 (11.88)
Loss of sensation	0	1 (16.67)	0	0	0	0	0	1 (2.33)	2 (3.44)	4 (3.96)
Movement disorders	1 (4.54)	1 (16.67)	0	0	0	0	0	2 (4.65)	5 (8.62)	7 (6.93)
Tremors	0	0	0	0	0	0	0	0	3 (5.17)	3 (2.97)
Dystonia	0	1 (16.67)	0	0	0	0	0	1 (2.33)	1 (1.72)	2 (1.98)
Chorea	1 (4.54)	0	0	0	0	0	0	1 (2.33)	1 (1.72)	2 (1.98)
Meningeal signs	8 (36.36)	3 (50.00)	2 (33.33)	0	0	1 (33.33)	0	14 (32.56)	16 (27.59)	30 (29.70)
Abnormal gait	1 (4.54)	1 (16.67)	0	0	0	0	0	3 (6.97)	2 (3.44)	5 (4.95)
Total	22 (51.56)	6 (13.95)	6 (13.95)	1 (2.32)	4 (9.30)	3 (6.97)	1 (2.32)	43 (42.57)	58 (57.42)	101 (100)

GCS: Glasgow Coma Scale, CNBT: Could not be tested, HSV: Herpes simplex virus, JE: Japanese encephalitis, AES: Acute encephalitis syndrome

**Supplementary Table 3: Neuroimaging, hematological, biochemical, and cerebrospinal fluid findings of patients with acute encephalitis syndrome (n=101)**

	HSV, n (%)	JE, n (%)	Chikungunya, n (%)	Dengue, n (%)	Dengue + chikungunya, n (%)	Rabies, n (%)	Varicella, n (%)	Viral AES, n (%)	Unknown etiology, n (%)	Total AES patients n (%)
Neuroimaging					83 (82.17)					
CT brain findings					95 (94.05)					
Diffuse cerebral edema	7 (31.81)	1 (16.67)	0	1 (100)	0	1 (33.33)	0	10 (23.25)	11 (18.96)	21 (20.79)
Cerebral atrophy	0	1 (16.67)	0	0	0	0	0	1 (2.33)	1 (1.72)	2 (1.98)
Parenchymal hypodensity	8 (36.36)	2 (33.33)	3 (50.00)	0	2 (50.00)	1 (33.34)	0	16 (37.20)	15 (25.86)	31 (30.69)
Not available	0	0	0	0	0	1 (33.33)	0	1 (2.33)	5 (8.62)	6 (5.94)
Normal	7 (31.81)	2 (33.33)	3 (50.00)	0	2 (50.00)	0	1 (100)	15 (34.88)	26 (44.82)	41 (40.59)
MRI findings					88 (87.12)					
Diffuse cerebral edema	3 (13.63)	0	0	0	0	1 (33.33)	0	4 (9.30)	0	4 (3.96)
Cerebral atrophy	1 (4.54)	0	0	0	1 (25.00)	0	0	2 (4.65)	4 (6.89)	6 (5.94)
Parenchymal hyperintensity	9 (40.90)	5 (83.33)	3 (50.00)	0	1 (25.00)	2 (66.67)	0	20 (46.51)	20 (34.48)	40 (39.60)
Diffuse meningeal enhancement	0	0	0	0	1 (25.00)	0	0	1 (2.33)	3 (5.17)	4 (3.96)
Not available	1 (4.54)	0	0	0	0	0	0	1 (2.33)	12 (20.68)	13 (12.87)
Normal	8 (36.36)	1 (25.00)	3 (50.00)	1 (100)	1 (25.00)	0	1 (100)	15 (34.88)	19 (32.75)	34 (33.66)
Hematology										
Anemia	6 (27.27)	3 (50.00)	2 (33.33)	0	1 (25.00)	2 (66.66)	0	14 (32.55)	17 (29.31)	31 (30.69)
Leukocytosis	4 (18.18)	2 (50.00)	4 (66.66)	0	1 (25.00)	1 (33.33)	0	12 (27.90)	15 (25.86)	27 (26.73)
Neutrophilia	12 (54.54)	4 (66.66)	4 (66.66)	1 (100)	1 (25.00)	2 (66.66)	0	24 (55.81)	21 (36.20)	45 (44.55)
Lymphocytopenia	5 (22.72)	3 (50.00)	3 (50.00)	0	1 (25.00)	1 (33.33)	0	13 (30.23)	14 (24.13)	27 (26.73)
Thrombocytopenia	4 (18.18)	0	1 (16.67)	0	0	1 (33.33)	1 (100)	7 (16.27)	7 (12.06)	14 (13.86)
Increased ESR	4 (18.18)	3 (50.00)	4 (66.66)	0	0	1 (33.33)	0	12 (27.90)	17 (29.31)	29 (28.71)
Biochemistry										
Increased RBS <sup>#</sup>	1 (4.54)	1 (16.67)	1 (16.67)	0	1 (25.00)	0	1 (100)	5 (11.62)	6 (10.34)	11 (10.89)
Hyponatremia	7 (31.81)	2 (33.33)	2 (33.33)	1 (100)	0	0	0	12 (27.90)	8 (13.79)	20 (19.80)
Hypokalemia	1 (4.54)	0	1 (16.67)	0	0	0	0	2 (4.65)	4 (6.89)	6 (5.94)
Hyperkalemia	1 (4.54)	1 (16.67)	0	0	0	0	0	2 (4.65)	9 (15.51)	11 (10.89)
Increased serum chloride	2 (9.09)	1 (16.67)	0	0	0	1 (33.33)	0	4 (9.30)	6 (10.34)	10 (9.90)
Decreased serum chloride	3 (13.63)	2 (33.33)	2 (33.33)	1 (100)	0	0	0	8 (18.60)	7 (12.06)	15 (14.85)
Hyperbilirubinemia	0	0	0	0	0	0	0	0	5 (8.62)	5 (4.95)
Increased <sup>#</sup> SGOT	6 (27.27)	2 (33.33)	2 (33.33)	0	0	1 (33.33)	1 (100)	12 (27.90)	17 (29.31)	29 (28.71)
Increased <sup>#</sup> SGPT	7 (31.81)	3 (50.00)	3 (50.00)	0	0	1 (33.33)	1 (100)	15 (34.88)	14 (24.13)	29 (28.71)
Increased serum creatinine	1 (4.54)	0	1 (16.67)	0	0	1 (33.33)	1 (100)	3 (6.97)	15 (25.86)	19 (18.81)
Decreased serum creatinine	1 (4.54)	1 (16.67)	1 (20.00)	0	0	0	0	2 (4.65)	5 (8.62)	6 (5.94)
CSF abnormalities										
CSF pleocytosis	15 (68.18)	1 (16.67)	2 (33.33)	1 (100)	1 (25.00)	2 (66.66)	0	22 (51.16)	24 (41.37)	46 (45.54)
Increased CSF protein	10 (45.45)	3 (50.00)	2 (33.33)	0	1 (25.00)	2 (66.66)	0	18 (41.86)	22 (37.93)	40 (39.6)
Total	22 (51.56)	6 (13.95)	6 (13.95)	1 (2.32)	4 (9.30)	3 (6.97)	1 (2.32)	43 (42.57)	58 (57.42)	101 (100)

CSF: Cerebrospinal fluid, SGOT: Serum glutamic oxalobacetic transaminase, SGPT: Serum glutamic pyruvic transaminase, HSV: Herpes simplex virus, JE: Japanese encephalitis, AES: Acute encephalitis syndrome, RBS: Random blood sugar

**Supplementary Table 4: Sociodemographic characteristics of patients with acute encephalitis syndrome-2019 (n=101)**

	HSV, n (%)	JE, n (%)	Chikungunya, n (%)	Dengue, n (%)	Dengue + Chikungunya, n (%)	Rabies, n (%)	Varicella, n (%)	Viral AES, n (%)	Unknown etiology, n (%)	Total AES patients, n (%)
Age (years)*	31.59 (18.91)	17.16 (15.23)	23.66 (17.61)	23	21.25 (18.51)	47.66 (19.09)	12	27.97 (19.06)	31.55 (20.20)	30.02 (19.71)
Age groups (years)										
≤16	3 (13.63)	2 (33.33)	3 (50.00)	0	2 (50.00)	1 (33.33)	1 (100)	12 (27.91)	16 (27.59)	28 (27.72)
17-59	17 (77.27)	4 (66.67)	3 (50.00)	1 (100)	2 (50.00)	0	0	27 (62.79)	7 (12.07)	62 (61.38)
≥60	2 (9.09)	0	0	0	0	2 (66.66)	0	4 (9.30)	35 (60.34)	11 (10.89)
Gender										
Male	15 (68.18)	5 (83.33)	1 (16.67)	1 (100)	3 (75.00)	3 (100)	1 (100)	29 (67.44)	34 (58.62)	63 (62.38)
Female	7 (31.81)	1 (16.67)	5 (83.33)	0	1 (25.00)	0	0	14 (32.56)	24 (41.38)	38 (37.62)
Occupation of the patient/caretaker										
Waged workers	10 (45.45)	5 (83.33)	2 (33.33)	0	1 (25.00)	1 (33.33)	0	19 (44.19)	28 (48.28)	47 (46.53)
Farmers	4 (18.18)	1 (16.67)	1 (16.67)	0	2 (50.00)	1 (33.33)	0	9 (20.93)	10 (17.24)	19 (18.81)
Others#	8 (36.36)	0	3 (50.00)	1 (100)	1 (25.00)	1 (33.33)	1 (100)	15 (34.88)	20 (34.48)	35 (34.65)
Yearly family income										
INR 0-19,999	6 (27.27)	1 (16.67)	2 (33.33)	0	1 (25.00)	0	0	10 (25.00)	16 (27.58)	26 (25.74)
INR 20,000-39,999	9 (40.90)	3 (50.00)	3 (50.00)	0	3 (75.00)	3 (100)	1 (100)	22 (53.48)	24 (41.37)	46 (45.54)
INR≥40,000	7 (31.81)	2 (33.33)	1 (16.67)	1 (100)	0	0	0	11 (22.50)	18 (31.03)	29 (28.71)
Education										
Illiterate	2 (9.09)	3 (50.00)	0	0	2 (50.00)	0	0	7 (16.28)	12 (20.68)	19 (18.81)
Primary level completed	13 (59.09)	2 (33.33)	6 (100)	0	1 (25.00)	3 (100)	1 (100)	26 (60.47)	30 (51.72)	56 (55.44)
Above primary level	7 (31.81)	1 (16.67)	0	1 (100)	1 (25.00)	0	0	10 (23.25)	16 (27.58)	26 (25.74)
Religion										
Hindu	14 (63.63)	5 (83.33)	3 (50.00)	0	4 (100)	3 (100)	1 (100)	30 (69.77)	50 (86.21)	80 (79.21)
Muslims	7 (31.81)	1 (16.67)	2 (33.33)	1 (100)	0	0	0	11 (25.58)	7 (12.07)	18 (17.82)
Others	1 (4.54)	0	1 (16.67)	0	0	0	0	2 (4.65)	1 (1.72)	3 (2.97)
Marital status										
Married	11 (50.00)	1 (16.67)	2 (33.33)	1 (100)	2 (50.00)	2 (66.66)	0	19 (44.19)	39 (53.45)	58 (57.42)
Unmarried	11 (50.00)	5 (83.33)	4 (66.67)	0	2 (50.00)	1 (33.33)	1 (100)	24 (55.81)	25 (43.10)	49 (48.51)
Widowed	0	0	0	0	0	0	0	0	2 (3.45)	2 (1.98)
Type of location										
Rural	12 (54.54)	4 (66.67)	3 (50.00)	1 (100)	3 (75.00)	3 (100)	0	26 (60.47)	39 (67.24)	65 (64.36)
Urban	10 (45.45)	2 (33.33)	3 (50.00)	0	1 (25.00)	0	1 (100)	17 (39.53)	19 (32.76)	36 (35.64)
State										
Andhra Pradesh	5 (22.72)	1 (16.67)	0	0	0	0	0	6 (13.95)	5 (8.62)	11 (10.89)
Bihar	3 (13.63)	0	0	0	0	0	0	3 (6.98)	4 (6.90)	7 (6.93)
Jharkhand	0	0	0	1 (100)	0	0	0	1 (2.33)	1 (1.72)	2 (1.98)
Karnataka	5 (22.72)	3 (50.00)	4 (66.67)	0	2 (50.00)	2 (66.66)	0	16 (37.21)	33 (56.90)	49 (48.51)
Kerala	1 (4.54)	0	0	0	0	1 (33.33)	0	2 (4.65)	0	2 (1.98)

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**Supplementary Table 4: Contid...**

	HSV, n (%)	JE, n (%)	Chikungunya, n (%)	Dengue, n (%)	Dengue + Chikungunya, n (%)	Rabies, n (%)	Varicella, n (%)	Viral AES, n (%)	Unknown etiology, n (%)	Total AES patients, n (%)
Odisha	2 (9.09)	0	0	0	0	0	0	2 (4.65)	2 (3.45)	4 (3.96)
Sikkim	0	0	0	0	0	0	0	0	1 (1.72)	1 (0.99)
Tamil Nadu	1 (4.54)	0	1 (16.66)	0	2 (50.00)	0	0	6 (9.30)	2 (3.45)	6 (5.94)
Tripura	1 (4.54)	0	0	0	0	0	0	1 (2.33)	0	1 (0.99)
Uttar Pradesh	1 (4.54)	0	0	0	0	0	0	1 (2.33)	1 (1.72)	2 (1.98)
West Bengal	3 (13.63)	2 (33.33)	1 (16.67)	0	0	0	1 (100)	16 (16.28)	9 (15.52)	16 (15.84)
Referral pathway										
Direct	6 (27.27)	1 (16.67)	1 (16.67)	1 (100)	2 (50.00)	1 (33.33)	0	12 (27.91)	20 (34.48)	32 (31.68)
General practitioner	3 (13.63)	1 (16.67)	1 (16.67)	0	0	0	0	5 (11.63)	8 (13.79)	13 (12.87)
Neurologist	1 (4.54)	0	0	0	0	0	0	1 (2.33)	2 (3.45)	3 (2.97)
Others	7 (31.81)	3 (50.00)	4 (66.67)	0	0	1 (33.33)	1 (100)	16 (37.21)	12 (20.69)	28 (27.72)
Not documented	5 (22.72)	1 (16.67)	0	0	2 (50.00)	1 (33.33)	0	9 (20.93)	16 (27.59)	25 (24.75)
Total	22 (51.56)	6 (13.95)	6 (13.95)	1 (2.32)	4 (9.30)	3 (6.97)	1 (2.32)	43 (42.57)	58 (57.42)	101 (100)

\*Mean (SD), \*Others include drivers, employees of both private and government institutions, and those reported to be involved in any kind of business. SD: Standard deviation, HSV: Herpes simplex virus, JE: Japanese encephalitis, AES: Acute encephalitis syndrome

**Supplementary Table 5: Duration of hospital stay and outcome of patients with acute encephalitis syndrome (n=101)**

Characteristic	HSV, n (%)	JE, n (%)	Chikungunya, n (%)	Dengue, n (%)	Dengue + chikungunya, n (%)	Rabies, n (%)	Varicella, n (%)	Viral AES, n (%)	Unknown etiology, n (%)	Total AES patients, n (%)
Duration of hospital stay* (days)	8 (9)	19 (8)	10 (9)	7	7 (9)	4 (12)	6	8.83 (7.28)	8.98 (12.30)	8.91 (10.48)
<1	1 (4.54)	1 (16.67)	0	0	0	1 (33.33)	0	3 (6.97)	9 (15.58)	12 (11.88)
1-2	2 (9.09)	0	0	0	2 (50.00)	0	0	4 (9.30)	15 (25.86)	19 (18.81)
3-4	3 (13.63)	0	1 (16.67)	0	0	0	0	4 (9.30)	2 (3.45)	6 (5.94)
>5	16 (72.72)	5 (83.33)	5 (83.33)	1 (100)	2 (50.00)	2 (66.66)	1 (100)	32 (74.41)	30 (51.72)	62 (61.38)
NA	0	0	0	0	0	0	0	0	2 (3.45)	2 (1.98)
Outcome										
Improved/recovered	16 (72.72)	5 (83.33)	5 (83.33)	1 (100)	2 (50.00)	0	1 (100)	30 (69.76)	24 (41.37)	54 (53.46)
Unchanged	3 (13.63)	1 (16.67)	1 (16.67)	0	1 (25.00)	1 (33.33)	0	7 (16.28)	16 (27.59)	23 (22.77)
Not documented	3 (13.63)	0	0	0	1 (25.00)	2 (66.66)	0	6 (13.95)	18 (31.03)	24 (23.76)
Total	22 (51.56)	6 (13.95)	6 (13.95)	1 (2.32)	4 (9.30)	3 (6.97)	1 (2.32)	43 (42.57)	58 (57.42)	101 (100)

\*Mean and SD. NA: Not available. HSV: Herpes simplex virus, JE: Japanese encephalitis, AES: Acute encephalitis syndrome, SD: Standard deviation