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Original Research Article

Clinico-Etiological Profile and Predictors of Outcome in Acute Encephalitis Syndrome

Abhilash Dhariwal[1*], Ritu Rakholia[2], Vineeta Rawat[3]

[1]Junior Resident III, Department of Paediatrics, Government Medical College, Haldwani, Nainital, India

[2]Professor and Head, Department of Paediatrics, Government Medical College, Haldwani, Nainital, India

[3]Professor and Head, Department of Microbiology, Department of Paediatrics, Government Medical College, Haldwani, Nainital, India

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Corresponding author: Abhilash Dhariwal
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Abstract

Background: Acute encephalitis syndrome (AES) is a disease that has emerged rapidly in twenty first century with significant mortality, morbidity and various sensory-motor sequelae. Acute inflammation of brain parenchyma presents, with varied clinical presentation, have numerous aetiologies which remains unknown in majority of cases and it provides very short window period for the clinician to diagnose and treat the disease empirically and hence prevention is also of utmost importance.

Materials and Methods: All patients (<16 years of age) diagnosed with AES, presenting to a tertiary care hospital in Kumaun region of Uttarakhand, India from January 2021 to June 2022 were included in this hospital based prospective study.

Result: The varied clinical presentation was observed. Almost all the patients had fever and altered sensorium, half of the patients had symptoms of raised intra cranial pressure, signs of meningeal irritation, seizures and other organ system involvement. Major aetiologies identified were scrub typhus (25%), tuberculosis (14.7%), JE (11.8%), Dengue encephalitis (2.9%), Enteroviral encephalitis (2.9%), COVID-19 (1.5%), varicella (1.5%), unknown in 39.73% and mortality was 25%. Patients requiring ionotropic and ventilatory support had worst outcome.

Conclusion: Early diagnosis and regional aetiology based empirical therapy are beneficial for better outcome of this dreaded disease. Apart from that prevention in the form of JE immunisation should be made a part of national immunisation schedule in Uttarakhand.

Keywords: AES, Acute Encephalitis Syndrome, Japanese Encephalitis, Etiology, Outcome

Introduction

World Health Organisation defines acute encephalitis syndrome (AES) as a person of any age, at any time of year, with the acute onset of fever and a change in mental status and/or new onset of seizures. [1]

This definition thus leads to clubbing of different aetiologies, many of them with specific treatment and others, mostly neurotropic viruses-based encephalitis which have no specific treatment to be clubbed together. The aetiologies of acute encephalitis syndrome (AES) are divided

into three broad groups: infective, post-infective (ADEM) and autoimmune. Among infections various viruses are the common causes, Japanese Encephalitis being the commonest, has the highest mortality with poor outcome and neurological sequelae in survivors.

Following a large outbreak of AES in 2005, which accounted for 5737 cases and 1344 deaths, the Government of India introduced vaccination for Japanese encephalitis virus (JEV) in highly affected regions, and the National Vector Borne Disease Control Programme (NVBDCP) initiated sentinel surveillance for acute encephalitis syndrome. [2] Since 2005, the overall incidence of acute encephalitis syndrome in India has not decreased, with 10867–13672 cases reported each year to the NVBDCP between 2014 and 2017. Among reported cases of acute encephalitis syndrome, only 14–18% are associated with JEV infection and the aetiology of most cases in India remain unknown. [3] During 2016, 11,651 case and 1301 deaths were reported to the National Vector Borne Diseases Control Programme (NVBDCP), with a CFR of around 11 per cent. Most deaths were from Uttar Pradesh, followed by West Bengal, Assam and Bihar. [4]

This catastrophic illness needs aggressive approach in diagnosis and, management to prevent mortality and reduce morbidity. In order to study, the new emerging infectious aetiological distribution and ascertain the predictors of outcome of encephalitis in the Kumaun region of Uttarakhand, the current investigation was carried out**.**

Materials and Methods

This study was conducted in a tertiary care hospital from January 2021 to Sep 2022. It was an Institution based prospective study. All children below 16 years of age admitted in Paediatric ICU and ward of tertiary care hospital, Haldwani, Uttarakhand, fulfilling the WHO definition of Acute encephalitis Syndrome (AES) were included.

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Children >16 years, suffering from encephalopathy due to hepatic failure/ Uraemia, febrile convulsions, metabolic disorders, seizure disorder and children of parents not giving written informed consent or children(>9years) not giving assent were not included in the study.

Corelative Parameters

All consecutive children fulfilling the inclusion criteria and giving consent were included in the study. A detailed history and clinical examination with special reference to the following parameters was taken.

Demographic Variables

Patients' age, sex, body weight, height, body mass index, lymph node enlargement were noted. Detailed history of symptoms including fever with duration, abnormal body movements (focal or generalised) was recorded. A thorough examination including CNS examination- presence of meningeal signs, cranial nerve palsy. Sensorium was periodically assessed by GCS scores and documented. History of contact with tuberculosis, Vaccination history specially against Japanese encephalitis syndrome and tuberculosis. Examination of the patients for presence of eschar, presence of scar mark of BCG vaccination, presence of rash, fundus examination and detailed central nervous examination was done and documented.

Clinico-Laboratory Evaluation

The following laboratory parameters were evaluated. Haematological: ESR, WBC, Neutrophil, Lymphocyte and Platelets Count & Haemoglobin level. Cerebro spinal fluid (CSF) examination for microprotein, sugar, total and differential cell count (TLC, DLC) culture, gram and Acid-Fast Bacilli (AFB) staining. For viral aetiology, Polymerase chain Reaction

(PCR) for Herpes and enterovirus, adenovirus, or Enzyme Linked Immuno Sorbent Assay (ELISA) was sent for confirmation. CSF cartridge based nucleic acid amplification test was sent if Tubercular meningitis is suspected. CSF was collected in sterile containers and reverse cold chain was maintained for viral investigations. (CSF sample and serum for virology investigations was collected under aseptic precautions and CSF was transported on ice at -70Degree till processing)

IgM Elisa for scrub typhus, Mac Elisa for JE, Ns1 Ag and IgM ELISA for dengue. Malaria card test and peripheral smear to rule out cerebral malaria.

Kidney and liver function tests were done to look for derangements, Chest Xray was done if needed. Blood and CSF cultures were sent to rule out bacterial pathology, CNS imaging (MRI brain contrast enhanced when possible and CT if MRI was not possible) was done.

Management: -All confirmed cases of Acute encephalitis Syndrome were managed by intravenous fluids, supportive management including stabilizing vitals and maintaining airway, breathing circulation, anticonvulsants, antipyretics, antimicrobial agents, mechanical ventilation as per standard protocol for AES, tubercular meningitis, scrub meningoencephalitis or suspected aetiology.

The patients were observed during the hospital stay, any complication, need for ionotropic support, ventilation and outcome was documented.

Results

We studied 68 children below 16 years of age admitted to pediatric ICU of tertiary care hospital fulfilling the WHO definition of Acute Encephalitis Syndrome. In our study mean age was 7.29 years (RANGE: 1 to 15 years). There were 45.6% males (31) and 54.4% females (37).

In the present study nearly, all patients presented with fever. Half of the patients presented with seizures. Mental status showed altered sensorium in 62(91.2%) and loss of consciousness in 6(8.8%). Meningeal signs were seen in majority (60%) Neck pain was present in half of the patients. Kernig's sign was present in 41(60%) and absent in 27(40%). Brudzinski's sign was present in 41(60%) and absent in 27(40%). Comorbidities were seen in 12(17.64%) and absent in 56(82.36%). Table 1

Table 1-Clinical Profile of Children presenting with Acute Encephalitis Syndrome

SYMPTOM AND SIGNS	FREQUENCY (n/%)
FEVER	(66) / 97.1%
ALTERED SENSORIUM	(62) / 91.2%
UNCONSIOUSNESS	(6) / 8.8%
SEIZURES	(35) / 51.5%
VOMITING	(29) / 42.6%
NECK PAIN	(34) / 50%
OTHER SYMPTOMS (ABDOMINAL PAIN, LOOSE STOOLS, COUGH, BREATHING DIFFICULTY)	(24) / 35.3%
KERNIG'S SIGN	(41) / 60.3%
BRUDZINSKI	(41) / 60.3%
COMORBIDITIES (ASPIRATION PNEUMONIA, DIC, SEIZURE DISORDER, HEPATITIS A, DISSEMINATED TB)	(12) / 17.6%

We were able to establish an etiological diagnosis in 61.2% patients presenting with clinical syndrome of AES. Etiology was *Mycobacterium tuberculosis* in 10(14.70%), scrub typhus in 17(25%), Japanese Encephalitis (JE) in 8(11.76%), dengue in 2(2.94%), varicella zoster in 1(1.4%), enteroviral encephalitis in 2 (2.94%) and Sars Cov-2 in 1(1.4%). We could not identify the etiology in 39.7%. Table 2.

Table 2: Etiology of Children presenting with Acute Encephalitis Syndrome

ETIOLOGY	(n) / %
SCRUB TYPHUS	(17) / 25%
TUBERCULOSIS	(10) / 14.7%
JAPANESE ENCEPHALITIS	(8) / 11.8%
DENGUE ENCEPHALITIS	(2) / 2.9%
ENTEROVIRAL ENCEPHALITIS	(2) / 2.9%
VARICELLA	(1) / 1.5%
COVID -19	(1) / 1.5%
UNKNOWN	(27) / 39.8%

In our results, shock needing ionotropic support was present in 26(38.23%) and absent in 42(61.77%). Ventilatory support was required in 26(38.23%) and absent in 42(61.77%) for respiratory failure due to aspiration pneumonia or low GCS (<9) to secure the airway.

In the present study43, (62.3%) patients survived, 17 (25%) patients died and 8(11.76%) left against medical advice (LAMA).

In our study there was correlation of etiology and death. Maximum deaths (50%) occurred in JE (50%mortality). Tubercular meningitis presenting as AES also had a high mortality of 40%. We had a single child with Sars Cov 2 encephalitis, who could not be salvaged though the incidence of AES in Sars cov2 was very low. Scrub typhus meningoencephalitis, and enteroviral encephalitis had a good prognosis and with institution of timely management could survive (Table 3).

Table 3: Table showing outcome of children based on etiology

Etiology	Outcome				Total	P value
		LAMA	Discharge	Death		
Tuberculosis	Count	1	5	4	10	0.071
	%	10.0%	50.0%	40.0%	100.0%	
Scrub typhus	Count	0	17	0	17	
	%	.0%	100.0%	.0%	100.0%	
JE	Count	1	3	4	8	
	%	12.5%	37.5%	50.0%	100.0%	
Dengue	Count	0	2	0	2	
	%	.0%	100.0%	.0%	100.0%	
Enterovirus encephalitis	Count	0	2	0	2	
	%	0%	100%	0%	100%	
COVID- 19	Count	0	0	1	1	
	%	.0%	.0%	100.0%	100.0%	
Varicella	Count	0	1	0	1	
	%	.0%	100.0%	.0%	100.0%	
No	Count	6	13	8	27	
	%	20.22%	48.14%	29.62%	100.0%	
Total	Count	8	43	17	68	
	%	11.8%	63.2%	25.0%	100.0%	

Discussion

Encephalitis is challenging to manage given the diversity of clinical and epidemiologic features. More than 100 infectious species have been identified as causative agents of meningoencephalitis, with a burgeoning of new infectious and autoimmune etiologies in the last decade. Despite advances in diagnosis, more than 50% of encephalitis cases remain cryptogenic, posing additional management challenges. Viral encephalitis is a worldwide disease that has a substantial impact on public health, posing a hazard to nearly half of the world's population. Whereas herpes simplex encephalitis (HSE) is sporadic, Japanese B encephalitis is widespread (JE). Guidelines for management of encephalitis emphasize the role of targeted disease treatment with antimicrobial agents and anti-inflammatory treatment, as well as supportive care.

The present study was Clinico etiological profile and predictors of outcome in acute encephalitis syndrome conducted among 68 children below 16 years of age admitted to pediatric ICU of tertiary care hospital fulfilling the WHO definition of Acute Encephalitis Syndrome.

We were able to establish an etiological diagnosis in 61.2% patients presenting with clinical syndrome of AES. Etiology was scrub typhus in 25%, *Mycobacterium tuberculosis* in 14.70%, Japanese Encephalitis (JE) in 11.76%, dengue in 2.94%, varicella zoster in 1.4%, enteroviral encephalitis in 2.94% and Sars Cov-2 in 1.4%. We could not identify the etiology in 39.7%. Earlier studies have identified aetiologies of AES include Japanese encephalitis virus (5–20%), Enterovirus (0.1–33%), Orientia tsutsugamushi (45–60%) and other viral (0.2–4.2%), bacterial (0–5%) and Rickettsia (0.5–2%) causes. [5] Chandrayan P et al in 2019 studied the demographical profile, aetiology and clinical parameters of AES in a tertiary referral centre of Uttarakhand as data from this newly created state is lacking. They studied 111 adult AES patients and found tuberculous meningo-encephalitis was the most common aetiology (22.5 %) of AES followed by scrub typhus (19.8 %). [6]

In the present study mortality was 25%. Total 43(62.3)% patients survived, and 8(11.76%) left against medical advice (LAMA). There was correlation of etiology and death. Maximum deaths (50%) occurred in JE cases. Tubercular meningoencephalitis. Scrub meningo encephalitis, and Enteroviral encephalitis had better prognosis. Earlier studies have shown a reduction in case fatality rate from 33% during 1980-1984 to 12.6% during 2015-2019. AES incidence was 9 (2019) and 7 (2020) cases per million populations respectively and CFR was 5.8% (2019) and 5% (2020). [7]

Maximum mortality was seen in JE cases. Our results showed that there was significant difference in mean value of GCS score, hemoglobin and serum sodium in survivors and dead patients. The presence of low GCS, use of inotropic support and need for mechanical ventilation were noted to be higher in the viral group of AES and were associated with poor outcome. AES is a clinical syndrome based on clinical signs and symptoms but diverse etiology. Conventionally AES was assumed to be due to neurotropic viruses especially arbo viruses with no specific treatment and high mortality It however mimics several non-viral (scrub meningoencephalitis, TBM) and treatable viral(varicella)etiology. Each child must be thoroughly investigated to find specific etiology promptly and aggressively managed to salvage life and preserve neurologic function Early diagnosis and treatment of AES patients and attempts to detect exact etiology could improve their outcomes

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