

## Original Research Article

# A clinico-epidemiological study of acute encephalitis syndrome with multi organ dysfunction

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## ABSTRACT

**Background:** Acute Encephalitis Syndrome (AES) is a pressing public health problem in Eastern Uttar Pradesh, India. Japanese Encephalitis (JE), which has been endemic in this region, has shown a declining trend. AES not due to JE (Non JE) constitutes more than 75% of all cases and is associated with non-neurological clinical manifestations also. The etiology of Non JE AES is still unknown. We studied the clinic-epidemiological profile of AES, and compared Non JE AES to JE.

**Methods:** This study was done in a tertiary care hospital in children 1-15 years. Clinical features, CSF analysis, biochemical tests, radiological features and outcome were studied in AES cases.

**Results:** Out of 505 patients, 27 had an identifiable non-viral etiology. JE was a cause in 31/478(6.48%) patients. The remaining 447 patients were labeled as Non JE AES. Headache at presentation (25.8% vs. 10.7%) and hypertonia (22.6% vs. 9.8%) were significantly higher in JE patients. Swelling over the body (21.25% vs 3.2%) and hypotonia (25.7% vs. 3.2%) were significantly more common in Non JE AES. Although cardiac involvement and multi-organ involvement was more in Non JE AES, the difference was not statistically significant. Overall mortality was 32.42%.

**Conclusions:** JE is no longer an important cause of AES in this region. Swelling over the body, floppiness and multi organ involvement are predominant features of Non JE AES. Although many infectious diseases can present with similar features, a viral etiology seems most likely. Further efforts are needed to identify etiology.

**Keywords:** Acute encephalitis syndrome, Encephalitis, Myocarditis, Multi-organ dysfunction

## INTRODUCTION

Encephalitis is a leading cause of morbidity and mortality not only in India, but worldwide. Of the pathogens reported to cause encephalitis, the majority are viruses. However in a substantial proportion of cases the etiology remains unknown.<sup>1</sup> Seasonal outbreaks of Japanese Encephalitis/Acute Encephalitis Syndrome (AES) that have been occurring with striking regularity in this and adjoining areas lead to substantial mortality.<sup>2-4</sup> Our hospital is the sole tertiary care hospital for a population

of approximately 50 million and the annual admission rate for AES in this hospital is 2000-2500 patients/year, which is nearly 95% of the reported cases of AES from this region. Although Japanese encephalitis virus (JEV) was the key etiological agent for AES in this region, during 2008-2012 the positivity of IgM ELISA for JE was less than 10%.<sup>5</sup> Etiology for most of the remaining cases, labeled broadly as non JE AES, is unknown. The manifestations in these are also different from that of JE. Evidence of myocarditis and enterovirus infection has been found in recent studies in few of this case.<sup>6-9</sup> The

present study was conducted to describe the clinico-epidemiological patterns of Non JE AES in comparison to AES due to JE. The clinic epidemiological pattern will be helpful in planning a testing algorithm to look for possible etiologies.

## METHODS

AES cases between 1-15 years of age, admitted in the pediatric wards were included. Acute encephalitis syndrome was defined as a person with the acute onset of fever (<15 days) and a change in mental status (including symptoms such as confusion, disorientation coma, or inability to talk) and/or new onset seizures (excluding simple febrile seizures). Patients showing an increase in irritability, somnolence or abnormal behavior greater than that seen with usual febrile illness were also included as per WHO definition.<sup>9</sup> All patients with a known neurological illness, any congenital anomaly or patients with a previous diagnosis of AES were excluded.

### Study procedure

Out of all cases of AES admitted to a pediatric ward on alternate days (thrice a week), every third patient fulfilling the inclusion criteria was enrolled. The study was done from April 2012 to March 2014. The Institutional ethics committee approved the study and informed consent was obtained before enrollment by the patients who were investigated and treated as per institutional protocols by their physician.

### Investigations undertaken

Apart from a detailed history and examination, the patients were tested for Typhoid (Typhi Check Standard Diagnostic USA), Malaria (MERISCREEN Malaria Pf/Pv Ab: Meril Diagnostics) and Dengue (Standard Diagnostic USA). Other investigations performed in all cases were hematological (haemoglobin, total and differential leucocyte count) random blood sugar, arterial blood gases, renal function test (blood urea, serum creatinine), liver function test (SGOT, SGPT, serum bilirubin, PT and APTT) and CPK-MB in the institutional lab. Troponin I was done using QDx Trop I (DiaSys system- detection limit >0.3ng/ml). CSF examination was performed on the day of admission in all patients wherever patient's general condition permitted a lumbar puncture. CSF for biochemistry and microbiological examination was sent to the Departmental side lab as soon as possible. A part of the CSF and sera samples were tested for presence of IgM antibodies against JE (anti JE IgM MAC ELISA). ECG and Echocardiography was performed in cases with suspected myocarditis. CT scan was performed in cases stable for transportation and MRI was performed at discharge or follow-up.

### Data analysis

The JE and Non JE groups were compared in terms of their clinical features and investigations. Categorical data

in both groups was compared using Fisher exact test (2 tailed t test). Variables were considered significant if the two-tailed p value was <0.05. Mean and standard deviations were used to depict continuous data.

## RESULTS

Out of total 505 patients enrolled, 12 were positive for malaria, 7 were positive for IgM antibodies against typhoid, and 8 had positive bacterial blood cultures. Further analysis was done on the remaining 478 patients. Out of these 31 were IgM positive for JE and the rest were termed non-JE AES (n=447). IgM for Dengue was done in 150 cases and all were negative.

Majority of the cases belonged to a low socioeconomic status (n=445, 88%), went for open field defecation (n=418, 83%) and gave history of living in close proximity to animals (n=201, 40%). Shallow (n=280, 55%) and deep (n=114, 23%) hand pumps were the commonest source of drinking water. Parents of 90 (18.8%) children gave a definite history of JE vaccination, 133 (27.8%) were not vaccinated while the vaccine status was unknown in the remaining 53.3% children. Of the 505 children, 145 (28%) were referred from primary or secondary public health facilities and 198 (39%) referred by private practitioners. There was no prior medical contact in 162 (32%) who came directly to our institute. Only 18% availed the ambulance facility and the rest came in private vehicles.

### Clinical presentation

The mean duration of illness before hospitalization was 7.59 days (SD=4.2 days). Besides fever, other complaints with which patient presented are listed in Table 1. Headache was a significant complaint among JE positive patients whereas edema was significant in Non JE patients. Edema was mainly periorbital. The rash seen in these patients was reddish, macular, all over the body including palms and soles.

### Clinical examination and investigations

Neurological: Findings are listed in Table 2. There was no significant difference in the clinical findings. Nearly one-third patients had a low Glasgow Coma Score at admission. Movement disorders developed during hospital stay and were choreoathetoid in character. The only significant difference was in the muscle tone with hypertonia significantly more in JE and hypotonia in non JE AES. CSF was collected in 377 patients. CSF findings are described in Table 3. Mild CSF pleocytosis with normal to mild increase in protein levels are suggestive of a viral etiology. CT scan was performed in 220 patients during the acute phase of illness (<7 days). CT scans showed features of meningitis in 18 (8.2%). Cerebral edema 29, early hydrocephalus 9, frontal hypodensities 2, cerebral atrophy 31 and granuloma 12 were also reported. No difference was found in both groups. MRI was performed in the follow up phase in 115 patients and in

54 no abnormality was detected. The common abnormalities detected on MRI were: meningitis in 19,

encephalitis in 15, leuco-encephalitis in Nine and acute demyelinating encephalomyelitis in Three patients.

**Table 1: Demographic details of AES patients and clinical history on admission.**

Variables	AES patients (n=478)	JE (n=31)	Non JE AES (n=447)
Median Age (IQR)	5 (3,8)	5 (3,8)	5 (3,8)
Male to female ratio	1.16:1	1:1	1.18:1
<b>Symptoms</b>			
Fever(>39°C)	335 (70.1)	22 (71.0)	313 (70.0)
Fever <3 days	68 (14.2)	2 (6.5)	66 (14.8)
Seizures/convulsion	257 (53.8)	20 (64.5)	237 (53.0)
Altered sensorium	235 (49.2)	15 (48.4)	220 (49.2)
Irritability	76 (15.9)	4 (12.9)	72 (16.1)
Headache	56 (11.7)	8 (25.8)	48 (10.74)*
Increased somnolence	44 (9.2)	3 (9.7)	41 (9.2)
Behavioural abnormality	17 (3.6)	1 (3.2)	16 (3.6)
Psychosis /hallucinations	12 (2.5)	0 (0.0)	12 (2.7)
Coma	38 (8.0)	2 (6.5)	36 (8.1)
Focal Neurological deficit	10 (2.1)	0 (0.0)	10 (2.2)
Vomiting	187 (39.1)	14 (45.2)	173 (38.7)
Swelling all over the body	96 (20.1)	1 (3.2)	95 (21.25)*
Loose motion / abdominal pain	70 (14.6)	6 (19.4)	64 (14.3)
Jaundice	9 (1.9)	0 (0.0)	9 (2.0)

**Table 2: Findings on general and systemic examination among AES patients.**

	AES patients (n=478)	JE (n=31)	Non JE AES (n=447)
<b>General examination</b>			
Tachypnea <sup>#</sup>	283 (59.2)	20 (64.5)	263 (58.8)
Tachycardia <sup>##</sup>	241 (50.4)	15 (48.4)	226 (50.6)
Edema	113 (23.6)	2 (6.5)	111 (24.8)*
Pallor	37 (7.7)	5 (16.1)	32 (7.2)
Rash	22 (4.6)	1 (3.2)	21 (4.7)
Icterus	11 (2.3)	1 (3.2)	10 (2.2)
Lymphadenopathy	8 (1.7)	0 (0.0)	8 (1.8)
<b>CNS examination</b>			
GCS≤7	147 (30.8)	11 (35.5)	136 (30.4)
Plantar Extensor	322 (67.4)	24 (77.4)	298 (66.7)
Hypotonia	116 (24.3)	1 (3.2)	115 (25.7)
Hypertonia	51 (10.7)	7 (22.6)	44 (9.8)
Abnormal Movements	15 (3.1)	0 (0.0)	15 (3.4)
Neck Rigidity	14 (2.9)	1 (3.2)	13 (2.9)
Kerning Sign	12 (2.5)	1 (3.2)	11 (2.5)
<b>Cardiovascular system</b>			
Hypotension	165 (34.5)	10 (32.3)	155 (34.7)
Congestive heart failure	76 (16.1)	2 (6.4)	74 (16.6)
Gallop rhythm	21 (4.4)	0 (0.0)	21 (4.7)
<b>Abdomen examination</b>			
Splenomegaly	142 (29.7)	5 (16.1)	137 (30.6)
Hepatomegaly	200 (41.8)	11 (35.5)	189 (42.3)

(Figures in bracket are percentages). <sup>#</sup>- Tachycardia-Heart rate- 1-4y=>125/min, 5-9y>115/min, 10-15y>110/min. <sup>##</sup>-Tachypnea-Respiratory rate- 1-4 years= >40/min, 5-9 years= >20/min, 10-15 years= >15/min.

Encephalitis was evidenced by the presence of hyperintensities in the cortical and subcortical areas involving the brain stem, cerebellar areas, deep nuclei and early hydrocephalus. Cardiovascular: Congestive heart failure was clinically defined by the triad of

tachycardia, tachypnea and hepatomegaly. Although not significant, there was a trend of CHF being more common in non JE AES. CPK-MB elevation (>24IU) was seen in nearly 40% cases.

**Table 3: Abnormalities in haematological and biochemical parameters among AES patients.**

	AES patients	JE	JE negative AES
Hematology	n= 469	n=31	n=438
HB < 10mg/dl	258 (55.0)	13 (41.9)	153 (34.9)
TLC > 15000cell/mm <sup>3</sup>	166 (35.4)	13 (41.9)	153 (34.9)
Platelets <50000	58 (12.4)	4 (12.9)	54 (12.3)
CSF	n=377	n=23	n=354
Color (Clear)	377 (100.0)	23 (100.0)	354 (100.0)
Protein (40-100mg/dl)	216 (57.3)	13 (56.5)	203 (57.3)
Cells (5-300cell/mm <sup>3</sup> )	344 (91.3)	20 (87.0)	324 (91.5)
Serum	No positive/No. tested	No. positive/ No. tested	No. positive/No. tested
RBS <40 mg/dl	16/355 (4.5)	1/25 (4.0)	15/330 (4.6)
Serum Na <120meq/dl	23/391 (5.9)	1/24 (4.2)	22/367 (6.0)
Serum K <2.5meq/dl	8/391 (2.1)	1/24 (4.2)	7/367 (1.9)
Azotemia (Urea>40mg/dl)	97/394 (24.6)	5/23 (21.7)	92/371 (24.8)
Inc. Creatinine mg/dl <sup>#</sup>	174/394 (44.2)	9/23 (39.1)	165/371 (44.5)
SGOT > 40IU/dl	288/450 (64.0)	18/30 (60.0)	270/420 (64.3)
SGPT > 40 IU/dl	312/450 (69.3)	20/30 (66.7)	292/420 (69.5)
Serum Bil ↑	83/276 (30.1)	5/21 (23.8)	78/255 (30.6)
PT INR >1.5	76/351 (21.7)	8/20 (40.0)	68/331 (20.5)
Trop I positive	32/141 (22.7)	1/15 (6.7)	31/126 (24.6)
CPK-MB >24U/L	141/348 (40.5)	7/18 (38.9)	134/330 (40.6)

Serum creatinine = 1-5 years: >0.5mg/dl; 5-10 years >1mg/dl; 10 years> 1.4 mg/dl

ECG, done in 141 cases revealed sinus tachycardia (29/141, 20.5%), low voltages (10/141, 7.6%), conduction defects (3/141, 2.1%) and T wave inversion in various leads (32/141, 22.7%) (Low voltage complex was taken when the QRS amplitude is <5mm in all limb leads and <10mm in all precordial leads).

2D Echocardiogram was done in 113 non JE AES cases with either features of CHF, raised CPK-MB or persistent hypotension. The common findings were decreased ejection fraction (17, 14.5%), increased left ventricular thickness (23, 20.4%) decreased fractional shortening (10, 8.5%) and regional wall motion abnormalities (30, 26.5%). Cardiac MRI was performed in five patients at follow up (i.e after one month) and patchy centromyocardial delayed enhancement in the mid-inferior segment suggestive of myocarditis was reported in one case and pericarditis reported in one case.

### Others

Thrombocytopenia was not commonly seen. Deranged renal functions were not uncommon and renal biopsy done in one patient showed lymphocytic infiltration.

Transaminitis was not associated with a significant rise in serum bilirubin levels.

Out of the total, 131 (27.4%) patients had respiratory failure either at admission or during their hospital stay and required ventilatory support. Chest X-ray showed cardiomegaly (57/297, 19.2%) and pulmonary edema in 15.2% (45/297) cases. Interstitial pneumonia was also a feature in 26% (78/297) cases and resolved by the 3rd week. These were seen equally in both the groups.

### Outcome

Full recovery was seen in 298 (62.3%) patients, 155 (32.4%) expired and outcome could not be ascertained in 25 (5.2%) as they refused continued hospital stay. In the JE group mortality was slightly higher (35.48%) as compared to Non JE (32.21%) but difference was non-significant.

### DISCUSSION

This study showed a very low JE positivity among AES cases. Although there is no data on the epidemiology of

AES in India, individual studies have shown varying positivity for JE, ranging from 31% to 80%.<sup>10</sup> most studies were done before JE vaccination was included in the routine immunization by the Government of India. Mass JE vaccination was done in the year 2010 in this and surrounding districts. Along with this there have been intense public education programs, residual mosquito spray and free distribution of insecticide-impregnated mosquito nets. There has also been introduction and breeding of Gambusia fish, a larvicidal fish, in water logged fields. The decrease in positivity for JE in this area could be a collective influence of all these efforts, because vaccination status in our study population is very low.<sup>11</sup> a similar low positivity has been shown in a study in Tamil Nadu.<sup>12</sup> A mutation in the JE virus and decreased virulence has been postulated as one of the possible reasons.

We had aimed at finding differences in clinic epidemiological patterns of JE and non JE encephalitis. The epidemiological features were similar in both the groups with no geographical difference in the distribution of cases. Both groups also had near similar neurological presentations with headache and hypertonia being more common in JE and hypotonia in non JE. JE virus has a predilection for the basal ganglia and hypertonia is a documented feature.<sup>13</sup> Hypotonia has been shown to be a feature of brain stem involvement, and has been documented in Nipah and Enterovirus.<sup>14,15</sup> Neurological signs in acute encephalitis do not usually help in reliably identifying the underlying etiology.<sup>11</sup> Neuroimaging has not been helpful in differentiating between the two, both in the acute phase as well as at follow up. Localizing features like involvement of basal ganglia, thalamus etc which have been documented in Japanese encephalitis in previous studies, were not found in the study population.<sup>13</sup> Non JE encephalitis patients had more edema and a multi organ involvement characterised by mild transaminitis, deranged renal functions and evidence of myocarditis.

Myocarditis was suggested by presence of increased CPK MB, Troponin I positivity, ECG and Echocardioc findings. CPK MB and troponin I have been considered to be sensitive markers of myocarditis in many studies in the past.<sup>16</sup> Echocardiographic findings similar to our study have also been documented by others.<sup>17</sup> Myocardial biopsy is the gold standard for diagnosis of myocarditis but has its limitations. Cardiac MRI has emerged as a sensitive and specific noninvasive tool for diagnosis of myocarditis.<sup>18</sup> Cardiac MRI suggestive of myocarditis was present in two of our cases. The use of cardiac MRI as a diagnostic tool is limited by financial constraints in our study and could be done only in five patients.

Edema could be attributed to either heart failure due to myocarditis or to an abnormal cytokine activation that produces a severe inflammatory response, leading to leaky capillaries.<sup>19</sup> Most patients in the study group had features of a multi-organ involvement. This kind of

multi-organ involvement where patients are affected in large numbers have been reported in many infections like Rickettsial infections, scrub typhus, leptospirosis and viral illnesses like enterovirus, Dengue, etc.<sup>19-23</sup> In India, scrub typhus is an emerging infection and has been reported from many states.<sup>24</sup> Although patients have a similar presentation but absence of an eschar and non-clustering of cases do not support the possibility. Leptospirosis is another emerging infection with multisystem involvement. However, there is a significant hepatic involvement with high Serum Bilirubin levels, albuminuria, conjunctival suffusion and meningism. These features, which are used in a score for diagnosis of leptospira, were absent in the study population.<sup>25</sup> Apart from the epidemiological profile, the widespread use of antibiotics for fever in the periphery and non-responsiveness of these rather treatable conditions makes their possibility less likely.

Other common viruses having similar presentations like HSV, mumps, measles usually are sporadic and epidemics of this volume have not been reported with any of these. Dengue outbreaks in India have been recently on the surge and might have a multisystem involvement but none of those tested for the illness were positive.

Enteroviruses have been postulated as potential causative agents of AES.<sup>10</sup> In the year 2006, National Institute of Virology demonstrated enterovirus (EV) in CSF of 66/306 (21.6%) of AES patients by RTPCR.<sup>3</sup> Sequencing and phylogenetic analyses of PCR products from 59 (89.3%) of 66 specimens showed similarity with EV-89 and EV-76 sequences. A similar study published from a tertiary care teaching hospital of Lucknow revealed the predominance of various enteroviruses. Enterovirus infections worldwide have shown a presentation with multiorgan dysfunction.<sup>13</sup> the poor sanitation and lack of safe drinking water in our study population, epidemiologically favours water borne infection. Enterovirus has however not been demonstrated consistently and because of its ubiquitous nature and widespread prevalence even in healthy individuals, its etiological role has been questioned. A predominantly multi organ dysfunction can be caused by both viral and non-viral etiologies. It may also result as a manifestation of severe systemic inflammatory response syndrome. Studies aimed at identifying etiologies causing MODS may be able to identify the causative agent and help in planning preventive measures, as mortality in AES still remains high.

## CONCLUSION

Incidence of JE has reduced considerably and Non JE encephalitis is the major cause of encephalitis in this region with a high mortality. Non JE encephalitis presents predominantly with edema and hypotonia which can help us distinguish it from JE. Multi-organ involvement and a prominent cardiac involvement in the



form of myocarditis is feature of this encephalitis. These features may help in identifying etiology.

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