

# Clinico-etiological Profile and Predictors of Outcome in Acute Encephalitis Syndrome in Adult

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## Abstract

**Introduction:** Acute encephalitis syndrome (AES) is a group of diseases having clinically similar neurologic manifestation caused by viruses, bacteria, fungi, parasites, spirochetes, or chemical/toxins, etc.

**Aims:** Present study has tried to establish etiology, clinical presentation, prognostic factors, and outcome in adult AES patients.

**Materials and Methods:** A prospective study was done on 200 patients of AES admitted to Nehru Chikitsalaya of B.R.D Medical College, Gorakhpur from July 2013 to June 2014. Clinical history, general examination, detailed central nervous system (CNS) examination, cardiovascular system examination, respiratory system examination, and blood investigations were performed for all the patients. An outcome was measured on the basis of modified Rankin scale.

**Results:** Out of 200 patients 96 (48%) were male, and 104 (52%) were female. About half of the patients 98 (49%) were from the age between 15 and 30 years. A total 172 (86%) patients were admitted to the hospital between August and October. The most common presenting symptoms were fever and altered sensorium. CNS examination of AES cases revealed that at the time of admission Glasgow coma scale (GCS) was  $\leq 7$  in 31 (15.5%) of cases and GCS  $> 7$  in 169 (84.5%) cases. Hepatomegaly was the most common finding on abdominal examination. In the majority of the cases, hemoglobin was between 9 and 12 g/dl. Outcome observations revealed that complete recovery was seen in 136 cases (68%).

**Conclusion:** Disease has a higher incidence in the younger population. Japanese encephalitis was most common in 40 (20%) patients followed by enterovirus encephalitis. Most of the patients recovered as an outcome.

**Key words:** Etiology, Acute encephalitis syndrome, Japanese encephalitis, Uttar Pradesh

## INTRODUCTION

Encephalitis is an acute inflammatory process that affects brain parenchyma, presents as a diffuse and/or a focal neuropsychological dysfunction and is almost always accompanied by inflammation of adjacent meninges. Children, elderly, and immunocompromised persons are most commonly affected.<sup>1</sup>

The incidence of viral encephalitis is 3.5-7.4/100,000 persons per year.<sup>2</sup> Herpes simplex encephalitis is the

most common cause of sporadic encephalitis in western countries; the overall incidence is 0.2/100,000 (neonatal Herpes simplex virus (HSV) infection occurs in 2-3 per 10,000 live births). Arboviruses are the most common cause of episodic encephalitis with reported incidence similar to that of HSV Japanese encephalitis (JE), occurring in Japan, southeast Asia, China, and India, are the most common viral encephalitis outside the United States, affecting around 50,000 people per year acute encephalitis syndrome (AES) is reported mainly from Assam, Bihar, Karnataka, Uttar Pradesh, and Tamil Nadu which contributes approximately 80% of cases. North-eastern Uttar Pradesh has been experiencing regular epidemics of encephalitis since 1978.<sup>2</sup> The case fatality and morbidity are very high. The state of Uttar Pradesh has experienced periodic AES outbreaks since 1978, but following a major outbreak in 2006, the annual caseload has exceeded 3,000 patients, three times the level prior to that year.<sup>3</sup> The state has accounted for almost half (over 20,000) of cases and 3,560 deaths since

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2008.<sup>4</sup> Only 8.1% of the cases have been confirmed for JE, and the state has annually hosted a variety of investigative teams.<sup>5</sup> It has been suggested that shallow wells pumping up contaminated drinking water are a major problem. However, making any conclusions about what is causing AES outbreaks in Uttar Pradesh is hampered by poor patient record systems.<sup>6</sup>

JE is considered as a main viral etiology of patients with AES. Infection with JE virus may cause febrile illness, meningitis, myelitis, or encephalitis and is clinically indistinguishable from other causes of an AES.<sup>7</sup> Children and young adults are usually the most frequently affected groups.<sup>1</sup>

This study is conducted to identify the etiological pattern of AES and to study clinical differences among the adult patients admitted in the Department of Medicine, B.R.D. Medical College. To establish prognostic factors and outcomes in a patient of AES is also the secondary endpoint of this study.

## MATERIALS AND METHODS

A prospective study was done on 200 patients of AES admitted to Nehru Chikitsalaya of B.R.D Medical College, Gorakhpur from July 2013 to June 2014.

Patients of any age, at any time of year with an acute onset of fever and a change in mental status (including symptoms such as confusion, disorientation, coma, or inability to talk) and/or new onset seizures (excluding simple febrile seizures), increase in irritability, somnolence, or abnormal behavior greater than that seen with usual febrile illness were included in the study.

Clinical history including duration of fever, headache, vomiting, altered sensorium, seizures, paralysis, cough, breathlessness, chest and abdominal pain, diarrhea, swelling of body, and gastrointestinal bleeding was recorded for all patients.

The general examination including pulse, blood pressure, respiratory rate, temperature, pallor, icterus, cyanosis, clubbing, edema, lymphadenopathy, and state of hydration was also done on all patients.

A detailed central nervous system (CNS) examination was carried out with special emphasis on the state of higher centers, level of consciousness, signs of meningeal irritation, involvement of cranial nerves, sensory, motor examinations, superficial and deep tendon reflexes, cerebellar signs, involuntary movements, gait of the patients, and fundus examination.

In cardiovascular system examination, tachycardia, peripheral circulatory failure, gallop rhythm, features of congestive heart failure, heart murmurs, and heart sounds (muffled or loud) were done. Abdominal examination including hepatomegaly, splenomegaly, hepatosplenomegaly, and ascites was performed. In respiratory system examination including types of breath sounds, adventitious breath sounds (crepts/rhonchi), and respiratory failure was also recorded for all patients.

Blood investigations including hemoglobin, total leucocyte count (TLC), differential leucocyte count, platelet count, general blood picture, random blood sugar, renal function tests, liver function tests, serum electrolytes, and rapid diagnostic test for malaria parasite were done by standard methodology. Blood culture was also done in selected cases.

Other examination including urine, cerebrospinal fluid (CSF), chest X-ray (posterior-anterior view), electrocardiogram, immunoglobulin (IgM) enzyme-linked immunosorbent assay for JE virus and enterovirus (EV) in serum and CSF, IgM, and NS1 antigen for dengue virus, computed tomography scan and magnetic resonance imaging brain, real time-polymerase chain reaction (PCR) assay for quantitation of the viral RNA from the specimens were also done.

The outcome was measured on the basis of modified Rankin scale. The scale runs from 0 to 6, running from perfect health without symptoms to death. Rankin scale is as follows:

0 - No symptoms, 1 - No significant disability, able to carry out all usual activities, despite some symptoms, 2 - Mild disability, able to look after own affairs without assistance, but unable to carry out all previous activities, 3 - Moderate disability, requires some help, but able to walk unassisted, 4 - Moderately severe disability, unable to attend to own bodily needs without assistance, and unable to walk unassisted, 5 - Severe disability, requires constant nursing care and attention, bedridden, incontinent, and 6 - Dead.

In statistical analysis, multiple logistic regressions were applied to know about prognostic factors of the outcome.

## RESULTS

Out of 200 patients, 96 (48%) were male, and 104 (52%) were female. About half of the patients 98 (49%) were from the age between 15 and 30 years. Only 24 (12%) patients had age more than 60 years.

Month wise distribution of patients admitted to hospital showed that a total 172 (86%) patients were admitted to the hospital between August and October.

Duration of stay in the hospital showed that 184 (92%) patients had to stay in the hospital for <10 days. Only 2 (1%) patients had a hospital stay of >15 days.

Area wise distribution of AES cases revealed that 171 (85.5%) patients were from Uttar Pradesh area from districts of Gorakhpur and Basti division, 22 (11%) were from Bihar, and 1 (0.5%) was from Nepal. Only 6(3%) belonged to other districts of Mau, Ballia, and Balrampur.

The most common presenting symptoms were fever and altered sensorium, which was present in all cases (100%) followed by vomiting in 137 (68.5%), headache 131 (65.5%), and seizures in 104 (52%).

Pyrexia was the predominant feature in 164 cases (82%) followed by tachycardia in 154 (77%) and pallor in 49 (24.5%). Icterus was present in 23 (12.5%) and shock in 20 (10%).

CNS examination of AES cases revealed that at the time of admission Glasgow Coma Scale (GCS) was  $\leq 7$  in 31 (15.5%) of cases and GCS >7 in 169 (84.5%) cases, signs of meningeal irritation was present in 119 (59.5%) patients and cranial nerve palsy present in 3 (1.5%) patients, dilated sluggish reacting pupil was seen in 10 (5%) patients. The tone was normal in 116 (58%) patients, increased in 48 (24%) patients, and decreased in 36 (18%) patients. The deep tendon reflex exam was increased in 33 patients (16.5%) and decreased in 46 (23%) patients. Plantar was extensor in 100 cases (50%) and mute in 26 (13%). Papilledema was present in 15 (7.5%). Extrapyrimal and cerebellar signs were found in only 5 (2.5%) and 6 (3%) cases, respectively while hemiparesis in only 5 (2.5%) cases.

Findings of other systemic examination of AES cases showed that hepatomegaly was the most common finding on abdominal examination found in 6 (3%) cases followed by splenomegaly in 5 (2.5%) and ascites in 2 (1%). Adventitious sounds (crepts/rhonchi) were present in 29 cases (14.5%), ventilator support was required in 10 (5%), and bronchial breath sounds in 3 (1.5%). Raised jugular venous pressure (JVP) was the most common cardiac abnormality found in 3 cases (1.5%) followed by muffled heart sounds and gallop rhythm in 2 (1%). In JE positive group, none had a cardiac abnormality.

Hematological and biochemical investigations showed that in the majority of the cases hemoglobin was between 9 and 12 g/dl 102 (51%) cases followed by >12 in 52 (26%). Leukocytosis was found in 98 cases (49%). Serum glutamic pyruvic transaminase was raised in 142 cases (71%). Serum creatinine was raised in 46 cases (23%).

Evaluation of CSF found that CSF protein level was between 40 and 100 mg/dl present in 95 cases (47.5%) and more than 100 in only 68 (34%). Sugar was decreased in only 25 cases (12.5%) and normal in rest of them. Gram-positive cocci were not seen in any of the samples. Protein <40 and sugar >40 was present in 19 (9.5%) patients which suggested of viral encephalitis. CSF protein was between 40 and 100 mg% and sugar >40 mg% found in 42% of the patients which suggested that patient may be partially treated acute bacterial meningitis or tubercular or viral meningitis. Protein >40 and sugar <40 was present in 11% of cases which suggested acute bacterial meningitis.

In JE patients, most common CSF finding was protein between 40 and 100 mg% and sugar >40 24 (60%). Only in 11 (27.5%) patients, CSF protein was >100 and sugar in normal range. In EV positive patients, most common CSF finding was CSF protein >100 and sugar >40 in 9 (64.3%) patients only in 3 (21.4%) patients, CSF protein was 40-100 and sugar >40 mg%.

Virological analysis of CSF and serum showed that out of total cases (200) studied, 40 cases (20%) were found to be JE positive. IgM for JE positivity was found in CSF was (9%) and serum (15%). 14 (7%) cases were found to be EV positive. 2 patient (1%) had HSV positive in CSF by PCR and 2 patient (1) were Dengue positive.

In 59% of cases, etiology could not be known. Out of all known etiologies (41%) AES, JE was most common seen in (20%) followed by EV encephalitis 14 (7%) and rest 14% were of tuberculosis meningitis, acute bacterial meningitis, cerebral malaria, HSV encephalitis, or dengue virus encephalitis.

Outcome observations revealed that complete recovery was seen in 136 cases (68%). 34 (17%) cases of AES expired while 15% were discharged with sequelae. Out of 34 patients, who expired etiology of AES was uncertain in 20 cases (58.8 %) and 6 (17.6%) patients were JE positive, while rest 3 (8.8%) patients each had acute bacterial meningitis and cerebral malaria only 1 (2.9%) EV positive patients expired out of 14 patients.

Out of 200 patients, 26 (13%) had aspiration pneumonitis followed by shock 20 (10%), ventilatory support was required in 10 (5%) cases while sequelae was seen in 7 (3.5%) and psychosis in 3 (1.5%) cases (Tables 1 and 2).

## DISCUSSION

North-eastern Uttar Pradesh has drawn national and international attention due to continuing epidemics of AES

**Table 1: CNS examination findings of JE and non-JE cases\***

CNS examination findings	Number of cases	JE positive (n=40)	Non-JE viral (n=18)	Non-JE unknown and other (n=142)
GCS				
<7	31 (15.5)	3 (7.5)	2	26
7-12	169 (84.5)	37 (92.5)	16	116
>12	0	0	0	0
Signs of meningeal irritation (NR/KS/both)	119 (59.5)	28 (70)	8	83
Cranial nerve palsies	3 (1.5)	0	0	3
Pupil				
NS/NR	150 (75)	32 (80)	16	102
SS/SR	40 (20)	6 (15)	1	37
Dilated/SR	10 (5)	2 (5)	1	7
Fundus (papilledema)	15 (7.5)	2 (5)	1	12
Cranium and spine deformity	0 (0)	0	0	0
Tone				
Normal	116 (58)	19 (47.5)	15	82
Increased	48 (24)	18 (45)	1	29
Decreased	36 (18)	3 (7.5)	2	31
Hemiparesis	5 (2.5)	1 (2.5)	0	4
DTR				
Normal	121 (60.5)	22 (55)	14	85
Increased	33 (16.5)	14 (35)	2	17
Decreased	46 (23)	4 (10)	2	40
Plantar				
Extensor	100 (50)	16 (40)	10	74
Flexor	50 (25)	13 (32.5)	4	37
Mute	26 (13)	4 (10)	3	19
Withdrawal	24 (12)	7 (17.5)	1	16
Cerebellar signs	6 (3)	2 (2.5)	1	3
Extrapyramidal signs	5 (2.5)	4 (10)	0	1

\*Data is expressed as no of patients (%). JE: Japanese encephalitis, DTR: Deep tendon reflex exam, GCS: Glasgow coma scale, CNS: Central nervous system

**Table 2: Relation of blood and CSF parameters with outcome**

Outcome	TLC/mm <sup>3</sup>	Platelet lac/mm <sup>3</sup>	Serum creatinine mg%	SGPT IU/DL	CSF protine in mg%	CSF sugar in mg%	CSF TLC
mRS 0	11199	1.6	1.2	73	109	65	124
mRS 1	12500	1.6	1.1	138	102	62	84
mRS 2	11500	1.75	0.8	40	68	30	159
mRS 3	9200	1.7	0.92	67	57	63	68
mRS 4	11400	1.5	0.89	113	156	51	126
mRS 5	8333	1.3	1.1	47	180	52	66
mRS 6	14800	1.3	1.5	90	137	64	122
LAMA	13100	2.1	1.2	71	193	53	290
REFER	7271	1.28	1.9	66	120	65	147
Total (average)	11797	1.5	1.3	79	116	64	206

\*Data are expressed as average. TLC: Total leucocyte count, SGPT: Serum glutamic pyruvic transaminase, CSF: Cerebrospinal fluid

and its changing pattern. Moreover, it has a wide socio-political implication. Mostly, AES affects children though significant numbers of adults are also affected. Several epidemics of AES has occurred since 1978,<sup>2</sup>

which has drawn massive public and political attention, Despite all the efforts, the epidemics are regularly occurring causing heavy mortality and morbidity.

### Demography

A total of 200 consecutively admitted cases of AES in the Department of Medicine, BRD Medical College Gorakhpur were included in this study. Mean age of

patients was 37 years (range 16-80 years). Age of 45% of cases was <30 years of age suggesting that the disease mostly affected the younger population. Younger patients were more affected most probably because of lack of cumulative immunity due to natural infection.<sup>8</sup> In our study, 48% patients were male, and 52% patients were female. Male: female ratio was 1:1.08.

Although the cases were seen throughout the year, the incidence peaked in the month of October (34.5%). The peak incidence of the disease was from August to October, i.e., post monsoon period suggesting the seasonal occurrence of the disease. It is well-known fact that the

incidence of arboviral and EV infections increases in this period.

The average duration of hospital stay was 5.7 days. In 62.5% of cases, the duration of hospital stay was  $\leq 5$  days and in 29.5% of cases, it was between 6 and 10 days. Duration of stay was more than 15 days in only 1%. The majority of patients were from Uttar Pradesh. Gorakhpur division accounted for 68.5% cases followed by Basti division (17%) and adjoining regions of Bihar and Nepal. Only 6 (3%) patients belonged to other districts/regions of Uttar Pradesh like Mau, Ballia, and Balrampur.

### Clinical Features

The most common presenting symptoms were fever and altered sensorium which was present in all cases (100%) cases, followed by in vomiting 68.5% and headache in 65.5%. Abdominal pain was present in 7.5% patients, loose stools in 4.5%, breathlessness in 4%, and swelling over the body in only 3%. Abdominal pain, loose stools, and swelling over body are more common in EV infection. The cause of swelling over the body may be due to myocarditis producing congestive heart failure or due to multiorgan involvement by the virus. Pyrexia (temperature  $>100$  F) was the predominant feature in 82%, followed tachycardia in 77% patients and pallor in 24.5%. Icterus and edema were present in 11.5% and 3% of cases, respectively. Both these signs is usually seen in EV encephalitis and cerebral malaria.<sup>9</sup> At the time of admission, GCS was  $\leq 7$  in 31 (15.5%) of cases in which 3 patients had JE encephalitis while 28 patients had non-JE encephalitis. Signs of meningeal irritation were present in 119 (59.5%) patients. Response were present in 30 (28%) and 42 (39.3%) subjects, respectively. In our study, papilledema was seen in 15 (7.5%) cases only. The extrapyramidal sign was present in 5 (2.5%) patients out of which 4 patients had JE while cerebellar signs were found in only 6 (3%) cases. Hemiparesis was found in only 5 (2.5%) cases out of which only 1 patient had JE. Focal neurological deficits at presentation were present in only 10 (9.3%) cases.

Hepatomegaly was the most common finding on abdominal examination found in 6 cases (3%) followed by splenomegaly in 5 (2.5%) and ascites in 2 (1%). None of the patients in JE positive group had positive abdominal examination finding. Adventitious sounds (crepts/rhonchi) were present in 29 cases (14.5%) followed by the requirement of ventilator support in 10 (5%) and bronchial breath sounds in 3 (1.5%). The patients with adventitious sounds may be due to a higher incidence of complication like aspiration pneumonitis.

Raised JVP was the most common cardiac abnormality found in 3 cases (1.5%), followed by muffled heart sounds

and gallop rhythm in 2 each (1%). In JE positive group, none of the patients had positive cardiac examination finding.

All these findings may be due to EV infection causing myocarditis. Out of all, the EVs, Coxsackie B virus is most commonly implicated in heart infection.<sup>10</sup>

### Etiology

JE accounted for 40 (20%), EV encephalitis 14 (7%), tubercular meningitis 11 (5.5%), septic meningitis 7 (3.5%), cerebral malaria 6 (3%), HSV encephalitis 2 (1%), and dengue encephalitis in 2 (1%) patients of AES. In 118 (59%) cases, cause of AES could not be ascertained. Clearly, in more than half of the cases, the etiology could not be known. This calls for separate epidemiological and microbiological studies to find out the exact etiological agent for the unknown agent's causing AES and thus planning the preventive measures.

The cause of viral encephalitis was established as JE in 19 (17.7%) patients and herpetic encephalitis in 4 (3.7%) patients. Pyogenic meningitis was the second most common diagnosis responsible for 45 (42%) cases. Cerebral malaria was documented in 8 (7.5%) children and tubercular meningitis in 4 (3.7%) children presenting as acute febrile encephalopathy. Typhoid fever was a cause of encephalopathy in one subject. In our study, the predominance of viral etiology over bacterial meningitis may be due to more prevalence of vector borne and water borne diseases in our study population.

### Outcome

The outcome was measured on the basis of modified ranking scale (mRS) poor outcome were taken as mRS 4, mRS 5, and mRS 6. A good outcome is taken as mRS 0-mRS 3. Most of the patients 136 (68%) belongs to mRS 0 which was fully recovered, 41 patients had poor outcome (mRS 4, mRS 5, and mRS 6) out of which 34 (17%) patient has been expired (mRS 6) and 7 (3.5%) patient had morbidity (mRS 4 and mRS 5).

In our study, case fatality rate was 17%. Etiology wise mortality showed that out of 34 patient who expired, 20 (58.8%) patients were of unknown etiology, 6 (17.6%) patients had JE, 1 (2.9%) patient in each were suffering from EV encephalitis, and tubercular meningitis while 3 (8.8%) patient each belonged to septic meningitis and cerebral malaria group. It suggested that mortality is more in septic meningitis, cerebral malaria, and patients in which etiology is uncertain. The average duration of stay was more in mRS 4 and mRS 5 group. It may be due to because these patients had severe morbidity. Out of 31 patients who had low GCS ( $<7$ ), 28 (90.3%) belonged to mRS 6 group. It was observed that low GCS associated with poor outcome.

TLC was markedly raised (average - 14800 cells/mm<sup>3</sup>) in mRS 6 group which suggests that high TLC may be correlated with poor outcome. Other blood and CSF parameter did not show many differences in between expired patients and survivors.

In the univariate analysis, we assessed all potential variables including clinical features, demographic parameters, blood and CSF examination, etiologies of AES, and complications for their association with poor outcome.

On univariate correlation, the presence of seizure, low GCS, high TLC, aspiration pneumonia, and requirement of ventilator support, and low platelet count was statistically significantly associated with poor outcome in AES Patients. In multivariate analysis, we assessed parameter which found to be significant on univariate analysis with poor outcome.

On multivariate analysis, low GCS, high TLC, aspiration pneumonia, and respiratory failure had statistically significant correlation with poor outcome, but seizure and low platelet count which had significant correlation on univariate analysis found no significant on multivariate analysis.

## CONCLUSION

The patients of almost all the age groups suffered from disease. Mean age was 37.7 years. Almost half of the patients (49%) were between 15 and 30 years of age, suggesting the disease has a higher incidence in the younger population. A maximum number of patients came during the month of August-October, suggesting the seasonal occurrence of the disease. The most common presenting symptoms of AES patients were fever and altered sensorium followed by vomiting, headache, and seizures. The most common finding of a general examination of AES patients was pyrexia followed by tachycardia and pallor. Most of the patients presented with signs of meningeal irritation and raised intracranial tension. In 118 (59%) patients, etiology of AES could not be ascertained. Out of known agents, JE was most common in 40 (20%) patients followed by EV encephalitis in 14 (7%) patients than tubercular meningitis, septic meningitis, cerebral malaria, HSV encephalitis, and dengue virus encephalitis. On univariate correlation, the presence of seizure, low GCS, high TLC, aspiration pneumonia, requirement of ventilator support and low

platelet count was statistically significantly associated with poor outcome in AES Patients.

On multivariate analysis, low GCS, high TLC, aspiration pneumonia, and respiratory failure had statistically significant correlation with poor outcome. In spite of best of our effort and limited resources, etiologies of more than 50% AES cases could not be ascertained. Further research and analysis are required to analyze AES cases due to unknown agents. Out of known etiologies of AES, JE (vector borne), EV encephalitis (water borne), and cerebral malaria (vector borne) are preventable. So, the burden of the disease could possibly be reduced by educating people and preventive measures.

Aspiration pneumonia (13%) was the most common complication in AES patients followed by respiratory failure (5%). As these complications may be prevented so early hospitalization, proper positioning, and general care of patients could possibly help in reducing morbidity and mortality. New strategies for pathogen identification and continued analysis of exposures and clinical features could help us improve our ability to diagnose, treat, and prevent AES.

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