Journal of Cardiovascular Disease

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 01, 2022

ORIGINAL RESEARCH

Study of pattern of infections in adult patients presenting as Acute Encephalitis Syndrome in tertiary care centre in Eastern Uttar Pradesh

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ABSTRACT:
Introduction: Acute encephalitis syndrome (AES) is a major health problem in Eastern Uttar Pradesh, India since 1978 with heavy morbidity and mortality. The main cause of such epidemic AES has been an arthropod borne viral infection caused by Japanese encephalitis (JE) virus. However since 2006,there is a change in pattern, with JE positivity progressively decreases in AES cases.
Aims & objectives: To study the pattern of infections in AES in adults.
Methods: Total 200AES casesof age ≥ 18 years, admitted in Medicine department of B.R.D. Medical college, Gorakhpur were studied. It was a prospective study with one month follow up. A detailed demography, clinical features, investigations, complications and outcome was noted.
Results & conclusion: The maximum patients came during September and October. The common presenting symptoms were fever and altered sensorium followed by headache, vomiting, seizures, abdominal pain and loose stools. The most common CNS examination finding was plantar extensor (65%), followed by signs of meningeal irritation (57.5%), brisk DTR (16.5%) and papilledema (11.5%). Extrapyramidal signs (5%), cerebellar signs (4.5%) and hemiparesis (3%) were uncommon presentations. Aspiration pneumonitis was the commonest secondary complication during hospitalization (17%). Full recovery was seen in 72.5% of AES patients. The commonest sequelae was cognitive impairment (5.5%), followed by psychosis (4.5%) and extrapyramidal symptoms (2%). The commonest cause of AES was acute viral (Non JE) encephalitis (57.5%), followed by Japanese encephalitis (29%), acute bacterial meningitis (8.5%) and cerebral malaria (5%). The case fatality rate of AES was 13%.
Keywords: Acute encephalitis syndrome (AES), Japanese encephalitis (JE), Clinical symptoms, Outcome, Case fatality rate, CSF findings.

INTRODUCTION:

Acute encephalitis syndrome (AES) is defined[1] as acute onset of fever (≤ 7 days)and change in mental statuswith or withoutnew onset of seizure (excluding simple febrile seizures), and other early clinical findings may include irritability, somnolence or abnormal behaviour greater than that seen with usual febrile illness.
AES is a major health problem in Eastern Uttar Pradesh in India since 1978[2] as it affects thousands of patients presenting as epidemic mostly in the post monsoon period [3] with heavy morbidity and

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mortality leading to death of several hundreds and even greater number as disabled with sequelae. The main cause of such epidemic AES has been an arthropod borne viral infection caused by Japanese encephalitis (JE) virus. The epidemic of 2005[4] was one of the worst, with highest number of patients of this disease (about 5000) admitted in different institutions of the region. Out of which 1300 died [4]. A massive immunization campaign, using Chinese live attenuated strain SA-14-14-2 was launched in the year 2005 – 2006 [5]. Since 2006 a change in the pattern of cases with AES has been noticed. The JE positivity in serum/CSF has been declining successively.Two distinct patterns of clinical features have been observed in the patients presenting as AES. One group has AES with mainly central nervous system manifestations withpredominantly extrapyramidal involvement. This group presents in the same way as the JE patients used to present. In this group the JE positivity in CSF was higher. The other group has features of encephalitis, but also has other concomitant systemic involvements, particularly the cardiac, renal,hepatic and cutaneous. Clinically, they mimic enterovirus (EV) infections. A special viral research laboratory with the help of National Institute of Virology (NIV), Pune, was established in B.R.D. Medical college, Gorakhpur, having most advanced investigation facility.

The present study was aimed to study the pattern of the various demographic, hospitalization, clinical features, secondary complications and outcome among the AES cases. Any change in the pattern of AES cases was also noted.

METHODS :

Sample :A total of 200 patients presenting as AES formed the study material. These were hospitalized patients in the department of Medicine, Nehru hospital, attached to the B.R.D. Medical college, Gorakhpur. Only patients ≥ 18 years of age were enrolled. The study period was from March 2019 to February 2020. All the 200 patients were subjected to detailed clinical examination and investigations. All the clinical details, progress of the disease and outcome were recorded. It was a prospective study with one month follow up.

Laboratory tests :

Cases of AES were studied for their haematological, biochemical and microbiological parameters.

1. **Blood investigation -** Complete blood count, random blood sugar, renal function tests, liver function tests, serum electrolytes, peripheral smear and rapid diagnostic test for malaria parasite were done.
2. **Urine examination -**Routine and microscopic examination.
3. **CSF examination-**In CSF examination complete cytobiochemical examination was done which includes total leucocyte count, differential count, glucose level, protein level, gram's staining, culture and sensitivity. In immunological examination, IgM ELISA for Japanese Encephalitis virus in CSF was also done (sensitivity and specificity for JE is >95%)[6,7,8].
4. **Chest X-ray (PA view)**
5. **ECG**
6. **IgM ELISA for Japanese encephalitis virus in serum.**

RESULTS:

Demography and hospital stay of AES cases :

A total of 54.5% of cases belonged to less than 30 yrs of age, suggesting the disease has higher incidence in younger population. All age groups were involved, but the number of cases decreases with age. Fifteen cases (7.5%) were of age group more than 60 years. Male : Female ratio was 1.32 : 1.

Although, the cases were seen throughout the year but the incidence peaked to 15% in August, 39% in September and 35% in October. The peak incidence of the disease was from August to October i.e post monsoon period. **(Table 1).**

In 45% of cases, the duration of hospital stay was ≤ 5 days, in 42% of cases it was between 6–10 days and in 9.5% of cases it was between 11-15 days. Duration of stay was more than 15 days in only 3.5%. The mean duration of hospital stay was 6.75 days.

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Patients of AES admitted here mostly from Gorakhpur and its neighbouring districts as well as Bihar and Nepal. The largest number of cases came from Gorakhpur 24.5%, followed by Maharajganj 13%, Deoria 13% and Kushinagar 12.5. AES case also admitted from Bihar (17%) and Nepal (2%).**(Table 2)**.

Clinical features of the AES cases :

The most common presenting symptoms were fever and altered sensorium in 100% cases, followed by headache in 90% and vomiting in 63.5%. Seizures were present in 47% cases, abdominal pain in 17.5%, loose stools in 12.5%, breathlessness in 11.5% and swelling over body in only 7.5%**(Table 3).**

Pyrexia was the predominant feature in 63.5%, followed by tachypnea in 28%, tachycardia in 20.5% and pallor in 16.5%. Icterus and edema were present in only 8% cases each. Shock (4%), cyanosis (3%), bradycardia (2.5%) and lymphadenopathy (2%) were uncommon findings. **(Table 4**).

At the time of admission Glasgow coma scale (GCS) was between 7–10 in 54% of cases. The GCS between 3–6 and >10 was found in 23% cases each. The mean GCS at the time of admission was 8.95. The most common CNS examination finding was plantar extensor, found in 65%, followed by signs of meningeal irritation in 57.5%, brisk deep tendon reflexes (DTR) in 16.5% and papilledema in 11.5%. Extrapyramidal signs (5%), cerebellar signs (4.5%), cranial nerve palsies (4%) and hemiparesis (1.5%)were uncommon presentations of AES cases**(Table 5)**.

Hepatomegaly was the most common finding of abdominal examination found in 12% cases, followed by hepatosplenomegaly (4%) and ascitis (4%). Adventitious breath sounds (crepts/rhonchi) were present in 18% cases, followed by bronchial breath sounds in 4%.Raised JVP was the most common cardiac abnormality found in 4%, followed by muffled heart sounds and gallop rhythm in 2% each.

Investigation of the AES cases :

The haemoglobin of the cases was between 9–12 gm/dl in majority (54%), followed by >12 gm/dl in 34.5%. The mean haemoglobin of the cases was 11.13 gm/dl. Leucocytosis was found in 24.5%. SGPT was raised in 48% of cases. Serum creatinine was raised in 15.5%.

The CSF pleocytosis was seen in 97% of cases, but in majority of them the TLC was between 6–100 cells/mm^2(78.5%). The TLC more than 100 cells/mm^2 was found in only 18.5% cases. In maximum patients the protein was either between 40–100 mg/dl (50%) or normal (29%). The maximum protein found in CSF was 431.5%. Sugar was decreased in only 13.5% and normal in rest of them. Gram positive cocci was found in only 3.5%, while gram negative cocci and bacilli were not found in any case. The CSF examination suggested that the majority of the cases were of acute viral encephalitis.

The IgM for JE positivity was more in serum (23%), than CSF (14.5%). Positivity either in serum or CSF was found in 29% cases and therefore, these 58 (29%) cases were labelled as confirmed cases with Japanese Encephalitis.

On the basis of CSF examination 17 cases (8.5%) were diagnosed as a case of acute bacterial meningitis.Ten cases (5%) were diagnosed as cerebral malaria due to Plasmodium falciparum either on the basis of peripheral smear and rapid diagnostic test for malaria parasite.

Complications during hospital stay andoutcome :

Aspiration pneumonitis was the most common secondary complication during hospitalization, seen in 17% of cases, followed by respiratory failure in 6.5% and psychosis in 5%. Shock (2%), sepsis (2%), upper gastrointestinal bleed (2%), bed sore (2%) and hemiparesis (1%), were uncommon complications during hospitalization**(Table 6)**.

Full recovery was noted in 72.5% of cases. Partial recovery with sequelae was observed in 10.5%. The most common sequelae was cognitive impairment seen in 5.5%, followed by psychosis (4.5%), extrapyramidal symptoms (2%), cranial nerve palsies (1.5%), hemiparesis (1%) and cerebellar ataxia 0.5%).Eight cases (4%) could not be followed because they leave against medical advice (LAMA). Total 26 patients expired, therefore the case fatality rate of AES in our study was 13%. **(Table 7)**.

In our study the most common precipitating cause of death was aspiration pneumonitis seen in 57.69%, followed by respiratory failure(15.38%) and shock 15.38%. Fifty percent patient expired within 3 days of admission and 30.77% cases expired between 4–7 days of admission.

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Pattern of illnesses causing AES in adults :
The most common cause of AES was acute viral (Non JE) encephalitis (57.5%). It was followed by acute viral Japanese encephalitis in 29%. Acute bacterial meningitis and cerebral malaria were responsible for 8.5% and 5% cases respectively**(Table 8)**.

DISCUSSION :

Japanese encephalitis (JE) virus, a flavivirus, represents the most significant aetiology of arboviral encephalitis worldwide. It affects about 50,000 persons per year, with deaths of about 10,000 [9,10]. Approximately 3 billion people currently live in areas endemic for JE, extending from Pakistan to maritime Siberia and Japan. The first epidemic caused by JE was recorded in Japan 1871 and since then it has been occurring there frequently (Kashahara et al, 1836)[11]. The state of Uttar Pradesh has seen a constant focus of JE virus activity every year since 1978. In our study total 200 cases of AES were subjected to detailed clinical examination and investigation.

Demography and hospital stay of AES cases :
A total of 54.5% of cases belonged to less than 30 yrs of age, suggesting the disease has higher incidence in younger population. Younger patients were more affected probably because of lack of cumulative immunity due to natural infection [12]. Male : Female ratio was 1.32 : 1. A male predominance was noted in our study, the reason of this is not clear, but probably social customs of male preference is responsible for this discrepancy.
Although, the cases were seen throughout the year but the incidence peaked from August to October i.e post monsoon period. The incidence of arboviral and enterovirus infections as well as malaria increases in this period [3].
Patients of AES came here mainly from Gorakhpur and its neighbouring districts as well as Bihar and Nepal. This geographical distribution of AES cases is consistent with previous studies of J. Singh [13] and R. Kumar [14].

Clinical features of the AES cases :

The most common presenting symptoms were fever and altered sensorium, followed by headache and vomiting. Other symptoms were seizures, abdominal pain, loose stools, breathlessness and swelling over body. Abdominal pain, loose stools and swelling over body may be due to enterovirus infection. The cause of swelling over body may be due to myocarditis producing congestive heart failure, or due to multiorgan involvement by the virus [15]. Icterus and edema were present in only 8% cases each. Both the later signs may be seen in enterovirus encephalitis and cerebral malaria[16,17]. The clinical features of the AES are consistent with those of other studies[2,13,18,19,20]. Extrapyramidal features were not so common probably because of decrease JE positivity among AES cases.

The more number of patients with adventitious sounds (crepts/rhonchi) may be due to higher incidence of aspiration pneumonitis in AES patients.Raised JVP was the most common cardiac abnormality found in 4%, followed by muffled heart sounds and gallop rhythm in 2% each. All these findings may be due to enterovirus infection causing myocarditis. Out of all the enteroviruses, Coxsackie B virus is most commonly implicated in heart infection [21], other Coxsackie virus serotypes which may cause myocarditis are A 4,9,16 and B (1-5) [22]. Echovirus may also produce myocarditis. In one study, upto 39% of patients infected with coxsackie virus B5 develop cardiac abnormality [23].

Investigation of the AES cases :

SGPT was raised in 48% of cases. Serum creatinine was raised in 15.5%. The deranged liver and renal functions may be due to multiorgan involvement due to enteroviruses [23] and plasmodium falciparum infection[16].The CSF examination suggested that the majority of the cases were of acute viral encephalitis.The IgM for JE positivity was more in serum (23%), than CSF (14.5%). Positivity either in serum or CSF was found in 29% cases and therefore, these 58 (29%) cases were labelled as confirmed cases with Japanese Encephalitis.

Complications during hospital stay and outcome :

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Full recovery was noted in 72.5% of cases. Partial recovery with sequelae was observed in 10.5%. The most common sequelae was cognitive impairment seen in 5.5%, followed by psychosis in 4.5% and extrapyramidal symptoms in 2%.

The case fatality rate of AES in our study was 13%. The overall case fatality rate was 23% in the epidemic of JE in Uttar Pradesh in 1978 [19]. Mortality rate of 31.8% was observed in 1988 outbreak of JE at Gorakhpur [20] .The low mortality rate of AES cases in our study than previous data may be attributed to mass JE vaccination, decreasing the severity of the disease and also our study includes only adult patients, while disease has high mortality in paediatric age group.

Fifty percent patient expired within 3 days of admission and 30.77% cases expired between 4–7 days of admission. It was interesting to note that majority of the deaths occurred in the first 3 days of admission with aspiration pneumonitis as the most common secondary complication, faulty transportation can be one of the reason for this mortality. In previous studies also during the course of the disease, majority of patients who succumb to illness die within first 3 to 4 days [13,24]. Patients who recover fully in 7 to 10 days show good outcome and go home within 10 days. Patients of JE not recovering within 10 days have higher chances of developing neurological deficits, brain damage and have poor outcome [24].

Pattern of illnesses causing AES in adults :

The most common cause of AES was acute viral (Non JE) encephalitis (57.5%). It was followed by acute viral Japanese encephalitis in 29%. Acute bacterial meningitis and cerebral malaria were responsible for 8.5% and 5% cases respectively.

This clearly this shows that our efforts to control AES has to be in a different direction than controlling only Japanese encephalitis. This calls for the separate epidemiologic studies to find out the exact aetiological agent for the Non JE AES and thus planning the preventive measures.

Japanese encephalitis is still a problem in this region and it must not be neglected. A mass vaccination may be carried out for the prevention of JE. The most common illness among AES patients observed in our study was acute viral (Non JE) encephalitis, which requires a clear elucidation with regards to aetiology, clinical presentation, treatment and prevention. Apart from central nervous system findings, these patients have multisystem involvement specially liver, renal and cardiac dysfunction. Clinically they mimic enterovirus infections, but it is still not established. Other main causes of acute encephalitis syndrome were acute bacterial meningitis and cerebral malaria, should never be forgotten as proper and urgent treatment is mandatory in these life threatening situations.

TABLE - 1

Month wise distribution of the AES cases

Month	No. of cases (%)
January	0 (0)
February	3 (1.5)
March	6 (3)
April	10 (5)
May	4(2)
June	1 (0.5)
July	3(1.5)
August	15(7.5)
September	78 (39)
October	70 (35)
November	5(2.5)
December	5(2.5)
Total	200

TABLE – 2

Area wise distribution of the AES cases

Area	No. of cases (%)
Gorakhpur	49 (24.5)
Maharajganj	26 (13)

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Deoria	26 (13)
Kushinagar	25 (12.5)
Santkabir nagar	12 (6)
Siddharth nagar	11 (5.5)
Basti	7 (3.5)
Mau	4 (2)
Balrampur	2 (1)
Bihar	34 (17)
Nepal	4 (2)
Total	200

TABLE – 3
Presenting symptoms of the AES cases

Symptoms	**No. of cases (%)**
Fever	200 (100)
Altered sensorium	200 (100)
Headache	180 (90)
Vomiting	127 (63.5)
Seizures	94 (47)
Abdominal pain	35 (17.5)
Loose stools	25 (12.5)
Breathlessness	23 (11.5)
Swelling of body	15 (7.5)
Cough	6 (3)
Paralysis	4 (2)

TABLE – 4
General examination findings of the AES cases

General exam. Findings	**No. of cases (%)**
Temperature (≥100˚ F)	127 (63.5)
Tachypnea	56 (28)
Tachycardia	41 (20.5)
Pallor	33 (16.5)
Icterus	16 (8)
Edema	16 (8)
Shock	8 (4)
Cyanosis	6 (3)
Bradycardia	5 (2.5)
Clubbing	4 (2)
Lymphadenopathy	4 (2)

TABLE - 5
CNS examination findings of AES cases

CNS examination findings	**No. of cases (%)**
Plantar extensor	130 (65)
Signs of meningeal irritation	115 (57.5)
Brisk DTR	33 (16.5)
Fundus (Papilledema)	23 (11.5)
Pupil (Dilated and sluggish reacting)	22 (11)
Hypertonia	13 (6.5)
Extrapyramidal signs	10 (5)
Cerebellar signs	9 (4.5)
Cranial nerve palsies	8 (4)

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Diminished DTR	8 (4)
Hypotonia	6 (3)
Hemiparesis	3 (1.5)

TABLE - 6
Secondary complications during hospitalization in the AES cases

Secondary complications during hospitalization	**No. of cases (%)**
Aspiration pneumonitis	34 (17)
Respiratory failure	13 (6.5)
Psychosis	10 (5)
Shock	4 (2)
Sepsis	4 (2)
UGI bleed	4 (2)
Bed sore	4 (2)
Hemiparesis	2 (1)
Pericardial effusion	2 (1)
Drug reaction	2 (1)

TABLE – 7
Outcome of the AES cases

Outcome		**No. of cases (%)**
Full recovery		145 (72.5)
Partial recovery (Sequelae)		21 (10.5)
(i)	Cognitive impairment	11 (5.5)
(ii)	Psychosis	9 (4.5)
(iii)	Extrapyramidal symptoms	4 (2)
(iv)	Cranial nerve palsies	3 (1.5)
(v)	Hemiparesis	2 (1)
(vi)	Cerebellar ataxia	1 (0.5)
LAMA		8 (4)
Expired		26 (13)

TABLE – 8
Distribution of various illnesses in the AES cases

Diagnosis	**No. of cases (%)**
Acute viral encephalitis (JE)	58 (29)
Acute viral encephalitis (Non JE)	115 (57.5)
Acute bacterial meningitis	17 (8.5)
Cerebral malaria	10 (5)
Total	200

CONCLUSION :

Patients of AES came throughout the year but the maximum number of patients came during the month of September and October, suggesting the seasonal occurrence of the disease. The patients of almost all age groups suffered from disease, but the disease has higher incidence in younger population. The most common presenting symptoms of AES patients were fever and altered sensorium followed by headache, vomiting and seizures. The common CNS examination finding in AES patients were plantar extensor, signs of meningeal irritation, brisk DTR and papilledema. On abdominal examination hepatomegaly was the most common finding, followed by hepatosplenomegaly and ascitis. In respiratory examination adventitious sounds (crepts/rhonchi) were the most common abnormality followed by bronchial breath sounds. Raised JVP was the most common cardiac abnormality, next being muffled heart sounds and gallop rhythm. SGPT was raised

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in 48% and serum creatinine was raised in 15.5% of patients. The CSF examination suggested that the majority of cases of AES were due to viral encephalitis. Full recovery was seen in 72.5% of AES patients. Partial recovery in 10.5%. The most common sequelae was cognitive impairment, followed by psychosis and extrapyramidal symptoms. The case fatality rate of AES was 13%. The most common cause of AES was acute viral (Non JE) encephalitis (57.5%), followed by acute viral Japanese encephalitis (29%), acute bacterial meningitis (8.5%) and cerebral malaria (5%).

The emergence of epidemics, first JE, then Non JE AES in this area is a cause of concern and all possible reasons for this occurrence should be sought for. A surveillance system for such infection should be developed which should monitor the trends of such infection and further studies should be conducted to ascertain the clinical profile and epidemiological course of the disease, so that standard protocols can be developed and such patients are managed effectively.

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