

Original Research Article

Comparative study of pattern of infections in adult patients presenting as Acute Japanese Encephalitis and Acute Non Japanese Viral Encephalitis in tertiary care centre in Eastern Uttar Pradesh

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Abstract

Introduction : Acute encephalitis syndrome (AES) caused by Japanese encephalitis (JE) virus is a major health problem in Eastern Uttar Pradesh in India since 1978. In last 10 years a change in pattern of AES has been noticed, with two distinct patterns. One group has AES with extrapyramidal involvement and higher JE virus positivity, while the other has concomitant systemic involvement, mimicking enterovirus infection with low JE virus positivity. **Aim & objectives :** To compare the pattern of infections in adult patients presenting as Acute JE and Acute Non JE in a tertiary care centre in Eastern Uttar Pradesh. **Methods :** Fifty eight patients of JE were compared with the 115 patients with Non JE viral encephalitis for demography, clinical features, investigations, complications and outcome. It was a prospective study with one month follow up. **Results & Conclusion :** Cases of JE came mostly from August to October, while cases of Non JE came throughout the year. Abdominal pain, loose stools, swelling of body and breathlessness were more common in Non JE patients. Hepatomegaly, icterus, ascitis and raised JVP were more common in Non JE patients. Non JE cases have multisystem involvement like renal, hepatic and cardiac. Cerebellar signs, extrapyramidal signs, brisk DTR, hypertonia and hemiparesis were predominant in JE. Full recovery was achieved in 68.96% in JE and 74.78% in Non JE. Partial recovery with sequelae was seen in 13.79% in JE and 11.30% in Non JE. The case fatality rate was 13.79% in JE and 10.43% in Non JE.

Keywords : Acute encephalitis syndrome (AES), Japanese encephalitis (JE), Outcome, Case fatality rate, CSF findings.

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Introduction

Acute encephalitis syndrome (AES) is defined [1] as acute onset of fever (≤ 7 days) and change in mental status with or without new 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. The most common cause of AES in Eastern Uttar Pradesh (U.P.) has been a mosquito-borne viral infection caused by Japanese encephalitis (JE) virus. Eastern Uttar Pradesh draws national and international attention due to continuing epidemic of acute viral encephalitis and its changing picture temporally. It has a wide socio-political implication. Most of the patients with acute encephalitis syndrome (AES) are children, though a significant number are adults as well. Several epidemics of

AES recurring since 1978 [2], have drawn massive public and political attention, but despite all the efforts, the epidemics are regularly occurring with heavy mortality and morbidity. The most severe epidemic so far has been of 2005 [3], with lot of hue and cry in the public. This forced a massive vaccination in the whole of Eastern UP in the year 2005-2006 [4] and surprisingly, the number of patients of AES still kept on pouring. Significantly it was observed that the JE positivity declined continuously and a large number of patients (70–80%) did not show JE infection. Many of these patients had multisystem involvement particularly cardiac, renal, and hepatic and clinically they were similar to enterovirus infection. However despite all the efforts enterovirus positivity could not be established conclusively in all the patients and epidemiologic studies have also failed to demonstrate the reasons of their emergence. 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. This viral research centre worked in collaboration with Central for Disease Control (CDC) – Atlanta, United States of America. NIV Centre at

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Gorakhpur has claimed the isolation of EV - 86, EV - 76, and Cocksackie B-5 viruses in some AES patients. The maximum number of the patients (about 70-80%) with AES belong to paediatric age group and most studies have been done in these patients. In our hospital adult patients account for the approximately 25% of AES. The study was aimed to compare the pattern of the various demographic, hospitalization, clinical features, secondary complications and outcome among the Japanese encephalitis (JE) and Non Japanese encephalitis (Non JE) cases.

Methods

Patients : A total of 200 patients with 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 for study. The study period was from March 2019 to February 2020. All the 200 patients were subjected to detailed clinical examination and investigations. It was a prospective study with one month of follow up. All the clinical details, progress of the disease and outcome were recorded. Out of 200 AES cases, 58 were diagnosed as Acute Japanese encephalitis (JE), 115 as Acute Non Japanese viral encephalitis (Non JE), 17 as acute bacterial meningitis and 10 as cerebral malaria. We compare 58 JE cases with 115 Non JE cases based on demography, hospital stay, clinical features, investigations, complications and outcome. Laboratory investigations: Cases of AES were studied for their haematological, biochemical and microbiological parameters.

1. Blood investigations - Complete blood count, random blood sugar, renal function tests, liver function tests, serum electrolytes, and 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 cytochemical examination was done which includes total leucocyte count, differential count, glucose level, protein level, gram staining, culture and sensitivity. In immunological examination, IgM ELISA for Japanese Encephalitis virus in CSF was also done (sensitivity and specificity for JE is $>95\%$) [5-7].

4. Chest X-ray (PA view)

5. ECG

6. IgM ELISA for Japanese encephalitis virus in serum.

Results

Demography and hospital stay of the JE and Non JE cases :

The age of presentation of the cases in Non JE was less than in JE, both in males ($z=3.023$) and females ($z=2.407$) and was statistically significant. The mean age of presentation in Non JE cases was 31.28 yrs, while it was 41.5 yrs for JE ($z=3.940$). Male : Female ratio in Non JE cases was 1.25 : 1, while it was 1.52 : 1 for JE. In JE 94.82% cases were seen in the month of August, September and October, while it was 79.12% for Non JE (Table - 1). Non JE cases came throughout the year with a peak in the month of September and October, while JE cases came mostly in the month of August, September and October. In most of the cases, duration of hospitalization was ≤ 5 days in both JE (44.82%) and Non JE (45.21%), followed by 6-10 days in both groups. Duration of stay was more than 15 days in only 3.45% of JE and 3.48% of Non JE. There was no statistical significant difference between two groups ($z=0.045$). The largest number of JE cases came from Gorakhpur (20.69%), followed by Deoria (13.8) and Kushinagar (12.06%). The largest number of Non JE cases came from Gorakhpur (26.08%), followed by Maharajanjanj (17.39%) and Deoria (14.78%) (Table - 2).

Clinical features of the JE and Non JE cases : The most common presenting symptoms were fever (100%) and altered sensorium (100%), in both groups, followed by headache in 89.65% in JE and 89.56% in Non JE. Seizures were present in 46.55% of JE and 50.43% of Non JE. Abdominal pain ($z=2.898$), loose stools ($z=3.657$), breathlessness ($z=2.250$) and swelling of body ($z=2.120$) were more prominent feature in Non JE (statistically significant)

(Table - 3). Temperature $\geq 100^\circ\text{F}$ was predominant feature in both groups 62.06% in JE and 60% in Non JE, followed by tachypnea 24.13% in JE and 17.82% in Non JE. Icterus (7.82% in Non JE and nil in JE, $z=2.188$) and edema (8.69% in Non JE and 1.72% in JE, $z=2.120$) were significantly more common finding in Non JE cases (Table - 4). At the time of admission GCS was found to be between 7-10 in majority of cases 53.44% in JE and 51.30% in Non JE. GCS greater than 10 was found in 27.58% in JE and 22.61% in Non JE. GCS between 3-6 was found in 18.96% in JE and 26.08% in Non JE cases. There was no significant difference between the two groups ($z=1.083$). The commonest CNS finding was plantar extensor seen in 62.6% of Non JE and 68.96% of JE, next common being signs of meningeal irritation 65.51% in JE and 50.53% in Non JE (not significant). Cerebellar signs ($z=3.613$), extrapyramidal signs ($z=2.010$), brisk DTR ($z=2.195$), hypertonia ($z=2.163$) and hemiparesis ($z=2.002$) were statistically predominant in JE cases (Table - 5). Hepatomegaly ($z=2.022$) and ascitis (2.042) were more common in Non JE cases. Raised JVP, muffled heart sounds, gallop rhythm and murmur were all more common in Non JE cases, out of which predominance of raised JVP was significant ($z=2.042$) (Table - 6).

Investigation of the JE and Non JE cases : There was no statistical significant difference between two groups in haemoglobin, total leucocyte count and serum creatinine. However raised SGPT was found in 54.78% in Non JE cases as compared to 31.04% in JE cases ($z=2.955$). Raised SGPT was significantly more common in Non JE cases. CSF pleocytosis was found in 96.55% of JE cases and 99.13% of Non JE, however cells were less than 100 in majority in both groups. In maximum patients the protein was either between 40-100 mg/dl (56.90% in JE and 65.52% in Non JE) or normal (27.59% in JE and 29.56% in Non JE). The maximum protein in CSF in JE was 180 mg/dl, while it was 258.7 in Non JE. Sugar was normal in 91.38% cases of JE and 93.05% of Non JE. There was no significant difference in CSF findings of TLC, DLC, protein, sugar & gram staining. The CSF findings in both the groups were consistent with that of acute viral encephalitis.

Complications during hospital stay and outcome in the JE and Non JE cases: Aspiration pneumonitis was the most frequent secondary complication during hospitalization in JE (24.13%) and Non JE (14.78%). Next being respiratory failure (8.62%) among JE, while it was psychosis (6.95%) among Non JE. Nevertheless no significant difference was observed between the two groups for any complication. Full recovery was achieved in 68.96% in JE and 74.78% in Non JE. Partial recovery with sequelae was seen in 13.79% in JE and 11.30% in Non JE. The most common sequelae was cognitive impairment found in 10.34% in JE and it was psychosis seen in 6.08% in Non JE (statistically insignificant). The significant difference in outcome was predominance of extrapyramidal signs ($z=2.120$), cerebellar ataxia ($z=2.002$) and hemiparesis ($z=2.002$) in JE (Table - 7). Total 8 patients of JE expired, while 12 patients of Non JE expired. Therefore the case fatality rate in our study was 13.44% in JE and 10.43% in Non JE. Clinically it was conceived that the most common precipitating cause of death was aspiration pneumonitis in both groups 62.5% in JE and 58.33% in Non JE. However there was no significant difference between two groups for the precipitating cause of death.

Discussion

JE has been considered to be the leading cause of AES in Asia 8.9 with over 50000 cases and 10000 deaths reported each year [10]. The history of AES in India has paralleled that of JE, with the virus first being reported from southern India (Vellore, Tamil Nadu) in 1955 [11]. Various subsequent studies confirmed that most AES in India are due to JE, which has been considered as the only major cause of AES in India. However, several recent studies have reported that novel viruses such as enteroviruses [12,13] may account for AES in the regions endemic for JE. This change may reflect either a true epidemiological effect or the use of improved diagnostic

tests for non-JEV aetiologies[14]. In the present study we compare the pattern of infection in JE and Non JE cases. There are very few previous comparative study of JE and Non JE cases and also the causative organism of Non JE cases is not known, so it is very difficult to compare our results. Enteroviruses have multisystem involvement and have similar clinical presentation like that of Non JE cases, so we took previous studies of enteroviruses for comparison in place of Non JE cases.

Demography and hospital stay of JE and Non JE cases : In our study JE cases were seen mostly in the months of August, September and October, while Non JE cases came throughout the year with a peak in the month of September and October. In previous studies by Mathur A et al (1978), Parida M et al (2005) and Rashmi et al (2005) [15]. JE cases were admitted mostly in the post monsoon period from August to September, due to increased prevalence of the vector mosquitoes. Culex mosquitoes breed abundantly in the paddy fields covered with stagnant water during the rainy season. Cases of enteroviruses came throughout the year with the peak in post monsoon period was also seen in previous studies by Jain S et al (2014) [16]. The largest number of JE and Non JE cases came from Gorakhpur, followed by nearby districts. Gorakhpur and neighbouring districts like Deoria, Kushinagar, Maharajganj, Siddharth nagar, Santkabir nagar had always been affected in epidemics of Japanese encephalitis as demonstrated by previous studies of Mathur A et al (1978)[2], Rashmi et al (2005)[15] and Roop Kumari et al (2012)[17]

Clinical features of the JE and Non JE cases : The most common presenting symptoms were fever and altered sensorium, followed by headache in both the groups. Abdominal pain, loose stools, breathlessness and swelling of body were more prominent feature in Non JE 18. This can be explained if Non JE infections were due to enteroviruses. In previous study by Pallansch et al (2001) [18] the enteroviruses were commonly associated with multi organ involvement like liver, kidney, cardiac and gastrointestinal tract. In our study temperature $\geq 100^{\circ}\text{F}$ was predominant feature in both groups, followed by tachypnea. Icterus and edema were more common finding in Non JE cases. In one study done in USA, enterovirus produced clinical signs of hepatitis such as jaundice, lethargy, and hepatomegaly with raised transaminases[19]. Lower GCS (<6) at the time of presentation is associated with higher mortality and more chances of partial recovery with sequelae. It is consistent with previous studies of Rashmi et al [15] and Parida M et al [3] during the JE epidemic in 2005. The commonest CNS finding was plantar extensor, next being signs of meningeal irritation in both the groups. Cerebellar signs, extrapyramidal signs, brisk DTR, hypertonia and hemiparesis were statistically predominant in JE cases. These findings are consistent with many previous studies of JE epidemics like Rathi AK et al [20] and Mathur A et al [2]. In JE cases extrapyramidal signs in 30-35%, cranial nerve palsies in 10-20% and cerebellar signs in about 10% cases are seen. These findings are less

common in enterovirus encephalitis. Hepatomegaly and ascitis were more common in Non JE cases. Raised JVP, muffled heart sounds, gallop rhythm and murmur were all more common in Non JE cases. Enterovirus infection causes 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). Echovirus may also produce myocarditis. In one study, upto 39% of patients infected with coxsackie virus B5 develop cardiac abnormality [22]. Investigation of the JE and Non JE cases : There was no statistical significant difference between two groups in haemoglobin, total leucocyte count and serum creatinine. However raised SGPT was significantly more common in Non JE cases, can be explained because of hepatitis seen in enteroviruses. There was no significant difference in CSF findings of TLC, DLC, protein, sugar & gram staining. The CSF findings in both the groups were consistent with that of acute viral encephalitis. CSF examination findings are similar to previous studies of AES epidemics in this region.

Complications during hospital stay and outcome in JE and Non JE cases: Aspiration pneumonia was the most frequent secondary complication during hospitalization in both the group, followed by respiratory failure in JE and psychosis in Non JE. It was similar to study of Rathi AK et al [20] in which aspiration pneumonia was the most common secondary complication of AES cases. Full recovery was achieved in 68.96% in JE and 74.78% in Non JE. Partial recovery with sequelae was seen in 13.79% in JE and 11.30% in Non JE. The most common sequelae was cognitive impairment found in 10.34% in JE and it was psychosis seen in 6.08% in Non JE. The significant difference in outcome was predominance of extrapyramidal signs, cerebellar ataxia and hemiparesis in JE. This outcome was similar to previous studies of Mathur A et al [2], Rashmi Kumar et al [15] and Rathi AK et al [20]. The case fatality rate in our study was 13.79% in JE and 10.43% in Non JE. The overall case fatality rate was 23% in the epidemic of JE in Uttar Pradesh in 1978 [21,22]. It was 26% in Karnataka in 1989, mortality being higher in the younger age groups and increased with increasing duration of illness before hospitalization and depended on the level of consciousness at the time of admission [23]. Mortality rate of 31.8% was observed in 1988 outbreak of JE at Gorakhpur [20]. The low mortality rate of JE 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. The mortality rate of Coxsackie B4 virus is 9.8% and poliomyelitis is 5-10%, i.e. comparable to Non JE cases in our study [24]. Thus our study delineates following pointers towards differentiation of AES due to JE and Non JE (Table – 8). We have taken only those parameters which were statistically significant. However a detailed multivariate analysis is required to get a clear differentiation

Table 1: Month wise distribution of the cases

Month	No. of JE cases(%)	No. of Non JE cases (%)	Z value
January	0 (0)	0 (0)	0
February	1 (1.72)	1 (0.87)	0.496
March	0 (0)	3 (2.60)	1.240
April	0 (0)	8 (6.96)	2.056
May	0 (0)	4 (3.48)	1.437
June	0 (0)	0 (0)	0
July	0 (0)	3 (2.60)	1.240
August	8 (13.79)	6 (5.21)	1.952
September	22 (37.93)	49 (42.61)	0.590
October	25 (43.10)	36 (31.30)	1.533
November	2 (3.46)	2 (1.74)	0.706
December	0 (0)	3 (2.60)	1.240
Total	58	115	

Table 2:Area wise distribution of cases

Area	No. of JE cases (%)	No. of Non JE cases (%)	Z value
Gorakhpur	12 (20.69)	30 (26.08)	0.781
Maharajganj	3 (5.17)	20 (17.39)	2.234
Deoria	8 (13.80)	17 (14.78)	0.174
Kushinagar	7 (12.06)	15 (13.04)	0.181
Santkabinagar	3 (5.17)	7 (6.08)	0.243
Siddharth nagar	4 (6.89)	3 (2.60)	1.351
Basti	2 (3.44)	4 (3.48)	0.010
Mau	4 (6.89)	0 (0)	2.849
Balrampur	1 (1.72)	1 (0.87)	0.496
Bihar	14 (24.13)	15 (13.04)	1.844
Nepal	0 (0)	1 (0.87)	0.712
Total	58	115	

Table 3:Presenting Symptoms Of The Cases

Symptoms	No. of JE cases (%)	No. of Non JE cases (%)	Z value
Fever	58 (100)	115 (100)	0
Altered sensorium	58 (100)	115 (100)	0
Headache	52 (89.65)	103 (89.56)	0.018
Vomiting	32 (55.17)	71 (61.74)	0.830
Seizures	27 (46.55)	58 (50.43)	0.482
Paralysis	2 (3.44)	0 (0)	2.002
Breathlessness	2 (3.44)	17 (14.78)	2.250
Abdominal pain	3 (5.17)	26 (22.60)	2.898
Loose stools	0 (0)	23 (20)	3.657
Swelling of body	1 (1.72)	10 (8.69)	2.120
Cough	2 (3.44)	4 (3.47)	0.010

Table 4:General Examination Findings Of The Cases

General exam. Findings	No. of JE cases (%)	No. of Non JE cases (%)	Z value
Temperature ($\geq 100^{\circ}$ F)	36 (62.06)	69 (60)	0.263
Tachypnea	14 (24.13)	32 (27.82)	0.518
Tachycardia	11 (18.96)	22 (19.13)	0.026
Pallor	8 (13.79)	18 (15.65)	0.323
Bradycardia	3 (5.17)	1 (0.87)	1.770
Shock	1 (1.72)	1 (0.87)	0.496
Icterus	0 (0)	9 (7.82)	2.188
Edema	1 (1.72)	10 (8.69)	2.120
Lymphadenopathy	0 (0)	0 (0)	0
Cyanosis	1 (1.72)	2 (1.73)	0.071
Clubbing	1 (1.72)	1 (0.87)	0.496

Table 5:CNS Examination Findings Of JE And Non JE Cases

CNS examination findings	No. of JE cases (%)	No. of Non JE cases (%)	Z value
Plantar extensor	40 (68.96)	72 (62.60)	0.826
Signs of meningeal irritation	38 (65.51)	58 (50.43)	1.884
Brisk DTR	14 (24.13)	13 (11.30)	2.195
Pupil (Dilated and sluggish reacting)	5 (8.62)	16 (13.91)	1.006
Fundus (Papilledema)	8 (13.79)	12 (10.43)	0.652
Hypertonia	6 (10.34)	3 (2.60)	2.163
Cerebellar signs	8 (13.79)	1 (0.87)	3.613
Extrapyramidal signs	7 (12.06)	4 (3.47)	2.010

Cranial nerve palsies	3 (5.17)	4 (3.47)	0.533
Hypotonia	2 (3.44)	3 (2.60)	0.311
Hemiparesis	2 (3.44)	0 (0)	2.002
Diminished DTR	2 (3.44)	5 (4.34)	0.283

Table 6: Findings of other systemic examination of cases

Abdominal examination	No. of JE cases (%)	No. of Non JE cases (%)	Z value
Hepatomegaly	3 (5.17)	18 (15.65)	2.022
Splenomegaly	1 (1.72)	2 (1.73)	0.007
Hepatosplenomegaly	1 (1.72)	2 (1.73)	0.007
Ascitis	0	7 (6.08)	2.042
Respiratory system examination	No. of cases (JE)	No. of cases (Non JE)	
Bronchial breath sounds	0 (0)	2 (1.73)	1.010
Adventitious sounds (crepts/rhonchi)	10 (17.24)	20 (17.39)	0.008
CVS examination	No. of cases (JE)	No. of cases (Non JE)	
Raised JVP	0 (0)	7 (6.08)	2.042
Muffled heart sounds	0 (0)	2 (1.73)	1.010
Gallop rhythm	0 (0)	2 (1.73)	1.010
Murmur	0 (0)	2 (1.73)	1.010

Table 7: outcome of the cases

Outcome	No. of JE cases (%)	No. of Non JE cases (%)	Z value
Full recovery	40 (68.96)	86 (74.78)	0.812
Partial recovery (sequelae)	8 (13.79)	13 (11.30)	0.473
(i) Cognitive impairment	6 (10.34)	5 (4.34)	1.526
(ii) Psychosis	2 (3.44)	7 (6.08)	0.737
(iii) Extrapramidal symptoms	5 (8.62)	1 (0.86)	2.122
(iv) Cerebellar ataxia	2 (3.44)	0 (0)	2.002
(v) Hemiparesis	2 (3.44)	0 (0)	2.002
(vi) Cranial nerve palsies	0 (0)	3 (2.61)	1.240
LAMA	2 (3.44)	4 (3.48)	0.010
Expired	8 (13.44)	12 (10.43)	0.652

Table 8: Statistically Significant Variables Differentiating JE Infection From Non JE In Adults

Pointers to infection	JE	Non JE
Symptoms	Nil	Abdominal pain, loose stools, swelling of body and breathlessness
Sign	Cerebellar sign, extrapyramidal signs, brisk DTR, hypertonia and hemiparesis	Icterus, Edema, Hepatomegaly, Ascitis, Raised JVP
Investigation	Nil	Raised SGPT

Conclusion

Cases of JE came mostly in the months of August, September and October. Cases of Non JE came throughout the year but the maximum number of patients came during the month of September and October. Abdominal pain, loose stools, swelling of body and breathlessness were more common in Non JE cases. Icterus was more common in Non JE cases. Cerebellar signs, extrapyramidal signs, brisk DTR, hypertonia and hemiparesis were statistically predominant in JE patients. Hepatomegaly, ascitis and raised JVP were significantly more common in Non JE patients. Raised SGPT was more common in Non JE cases. Full recovery was achieved in 68.96% in JE and 74.78% in Non JE. Partial recovery with sequelae was seen in 13.79% in JE and 11.30% in Non JE. The most common sequelae was cognitive impairment found in 10.34% in JE and it was

psychosis seen in 6.08% in Non JE. The significant difference in sequelae were predominance of cerebellar signs, extrapyramidal signs and hemiparesis in JE. The case fatality rate was 13.79% in JE and 10.43% in Non JE. 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. Clinically Non JE cases are similar to enteroviruses, but it is yet to be established. Better diagnostic tests to link an agent to encephalitis are needed in this field. New strategies for pathogen identification and continued analysis of

exposures and clinical features should also help us improve our ability to diagnose, treat and prevent encephalitis.

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