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PREDICTORS OF MORTALITY IN JAPANESE ENCEPHALITIS.

Medicine

Bhaskar K. Nath1 Assistant Professor, Medicine, Silchar Medical College & Hospital
Abhishrut P. Jog Post-Graduate Resident, Medicine, Silchar Medical College & Hospital
Prithwiraj Bhattacharjee Professor and Head of Department, Medicine, Silchar Medical College & Hospital
Polok Das Assistant Professor, Medicine, Silchar Medical College & Hospital

ABSTRACT

Introduction- Japanese Encephalitis (JE) is a mosquito-borne viral infection of the central nervous system. Mortality rate is about 30 %. The study assesses the significance of the clinical and biochemical parameters in predicting the mortality in JE.
Materials- Over a period of 3 years, from 2013 to 2015, a total of 81 patients were diagnosed with JE. The cases were followed up for 1 year regarding mortality.
Observations- Loss to follow up- 9. There were 20 deaths (27.7%). The parameters of Seizures, GCS< 8 and hyponatremia, were present in 73.68%, 76.47% and 57.89% of expired patients respectively. Statistical analysis using Pearson $\chi 2$ testing, suggested significant association with mortality in patients having any or all of these three abnormalities.
Conclusions- The parameters of seizures, GCS<8 and hyponatremia are strong predictors of mortality in JE, individually or together.

KEYWORDS:

Japanese encephalitis, Mortality, Seizures, Hyponatremia

Introduction:
Japanese encephalitis (JE) is a mosquito-borne viral encephalitis disease found worldwide. It is mainly prevalent in Asian, Western Pacific countries, and in northern Australia **(Erlanger TE, 2009).** Over 3 billion individuals live in JE epidemic and endemic countries. The fatality rate in JE cases ranges from 20%–30%, with neuro-psychiatric sequelae seen in 30%–50% of survivors **(Campbell GL, 2011) .**

JE is caused by infection with Japanese encephalitis virus (JEV). It belongs to genus Flavivirus **(Solomon T, 2004).** JEV has a single-stranded, positive-sense RNA genome of 11 kb in length. It contains seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) and three structural proteins: nucleocapsid or core protein (C), non-glycosylated membrane protein (M), and glycosylated envelope protein (E) **(Chambers, 1990) .**

The most important vector is the Culex mosquito especially Culex. Tritaeniorhynchus. The vertebrate amplifying hosts are pigs and wading birds **(Vaughn DW, 1992) .**

The clinical syndrome caused by the virus include a nonspecific febrile illness, febrile seizures, aseptic meningitis, encephalitis, and a poliomyelitis-like illness **(Vaughn DW, 1992).**

Over the years a few factors have been found to have a bearing on the outcome for JE patients. These include BMI, anemia, consciousness, seizure activity, perfusion status, CSF cell count, age etc. **(Mong, 2008) (Kalita J, 2003) (Misra UK, 1998) (Luo D, 1995) (Baruah HC, 2002) (Solomon 2000) .**

Silchar Medical College and Hospital is the only referral hospital in the southern part of Assam, and serves neighbouring states including Mizoram, North Tripura, West Manipur and South Meghalaya. It caters to many JE patients, particularly in the months of May to August. A study on this particular subject has not been conducted in these parts before. Knowledge about the predictors of mortality in JE patients will provide important prognostic information and may lead to further interventional studies.

AIMS AND OBJECTIVES:
To assess the significance of clinical and biochemical parameters in predicting the mortality of patients with JE

MATERIALS AND METHODS

Study setting:
The present study was conducted in the Department of Medicine, Silchar Medical College and Hospital, Silchar, Assam.

Period of Study:
The present study was conducted from 1st January 2013 to 31st December 2015, for a period of 3 years

Sample Size:
A total of 81 patients admitted in the Department of Medicine during the study period were included for the study after fulfilment of the inclusion and exclusion criteria.

Study Design:
The study was a hospital based prospective observational study.

Methodology:
All the patients presenting with the symptoms of fever and altered consciousness were evaluated. After emergent stabilization of the patients, Lumbar Puncture of all patients was done. CSF samples were studied with Gram's stain, ZN stain, protein and glucose, total and differential cell count and Japanese Encephalitis IgM capture ELISA. Those patients who tested positive in the ELISA were enrolled in the study

Based on the patients' sensorium, an explanation about the study objectives and methodology was provided, either to the patients or to their close relatives. A written and informed consent was obtained from either the patient or the relative, for patients who fulfilled the inclusion and exclusion criteria.

A detailed clinical history and physical examination was done in all cases. Complete Blood Count, Peripheral Blood Smear for malarial parasite, Random Blood Sugar, Liver Function Tests, Kidney Function Tests, Blood Culture, Urine microscopy and Culture, funduscopy and Chest Radiographs were done in all cases,

In selected cases, Nervous System imaging in the form of CT Brain or MRI Brain with or without MRI spine, was done.

The patients were followed up daily in the hospital. The patients who were discharged were followed up in the Out-patient department, with home visits or telephonically at monthly intervals for a period of one year. Mortality data was thus collected.

All relevant data was noted in a pre-designed proforma.

Inclusion Criteria:
1) Age greater than 15 years.
2) All patients who tested positive for the JE IgM ELISA

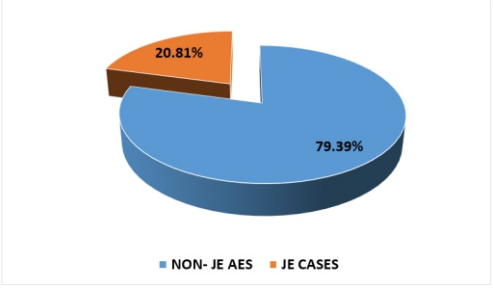
Exclusion Criteria:
1) Patients with concomitant illness such as tuberculosis, malignancy, HIV-AIDS, malaria, typhoid.
2) Post-traumatic or Post-neurosurgical patients.
3) Unwilling patients or relatives.

Statistical analysis:
The data collected, were compiled, tabulated and analysed in terms of descriptive statistics using SPSS version 17.0 software. Continuous variables were presented as mean ± SD and categorical variables were expressed as frequencies and percentages. Categorical data between the groups were compared using Pearson Chi square test. A p value < 0.05 was considered as statistically significant.

RESULTS AND OBSERVATIONS:
In the study period, the total number of cases admitted in the Medicine ward with complaints of fever and altered consciousness (Acute Encephalitis Syndrome- AES) were 393. Out of these a total of 81 patients tested positive for JE IgM ELISA. Thus, the incidence of JE in this period was 20.61%

TABLE 1: INCIDENCE OF NON-JE AES vs JE IN THE STUDY

CASES	NUMBER	PERCENTAGE
NON-JE AES	312	79.39%
JE	81	20.61%
TOTAL	**393**	**100%**

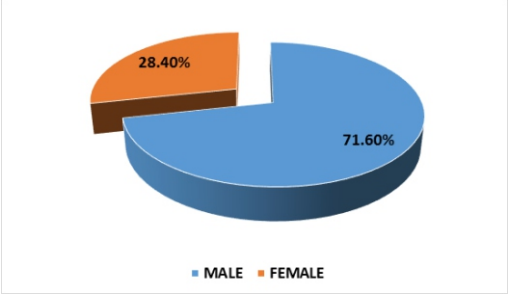


GRAPH 1- PIE DIAGRAM OF THE INCIDENCE OF NON-JE AES vs. JE

Out of the 81 cases, 58 (71.60%) cases were male, whereas 23 (28.40%) cases were female.

TABLE 2: SEX DISTRIBUTION OF THE JE CASES

SEX	NUMBER	PERCENTAGE
MALE	58	71.60%
FEMALE	23	28.40%
TOTAL	81	100%

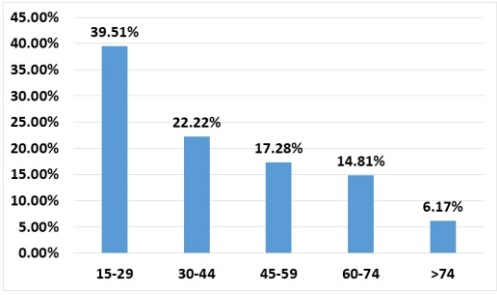


GRAPH 2 : PIE DIAGRAM OF THE SEX DISTRIBUTION OF JE CASES.

Out of 81 cases, majority of the cases were in the age group of 15 to 29 years (32), followed by 30 to 44 years (18), 45 to 59 years (14), 60 to 74 years (12) and then above 74 (5).

TABLE 3: AGE DISTRIBUTION OF JE CASES.

AGE GROUP	NUMBER	PERCENTAGE
15-29	32	39.51%
30-44	18	22.22%
45-59	14	17.28%
60-74	12	14.81%
>74	5	6.17%
TOTAL	**81**	**100%**

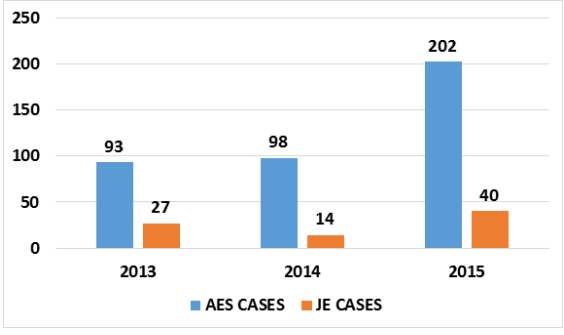


GRAPH 3: BAR GRAPH OF AGE DISTRIBUTION OF JE CASES.

The total number of AES cases were 93, 98 and 202 whereas the total number of JE cases were 27, 14 and 40 in the years 2013, 2014 and 2015 respectively.

TABLE 4: PROPORTION OF JE CASES YEAR-WISE

YEAR	NUMBER OF AES CASES	NUMBER OF JE CASES	PERCENTAGE OF JE CASES IN YEARLY AES CASES	PERCENTAGE OF JE CASES IN TOTAL AES CASES
2013	93	27	29.03%	33.33%
2014	98	14	14.28%	17.28%
2015	202	40	19.80%	49.38%
TOTAL	**393**	**81**		**100%**

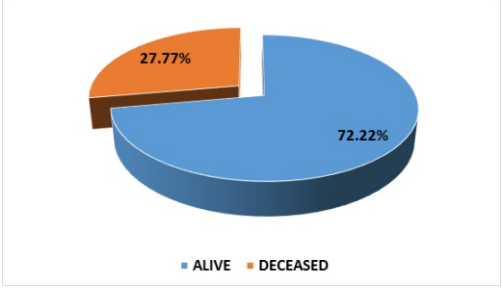


GRAPH 4: BAR DIAGRAM OF YEAR-WISE PROPORTION OF JE CASES

Out of the 81 JE patients, 9 patients could not be contacted or were irregularly traceable. Thus, the data about mortality could be gathered in 72 cases. Mortality was found to be 27.77%.

TABLE 5: MORTALITY OF JE PATIENTS

CASES	NUMBER	PERCENTAGE
ALIVE	52	72.22%
DECEASED	20	27.77%
TOTAL	**72**	**100%**

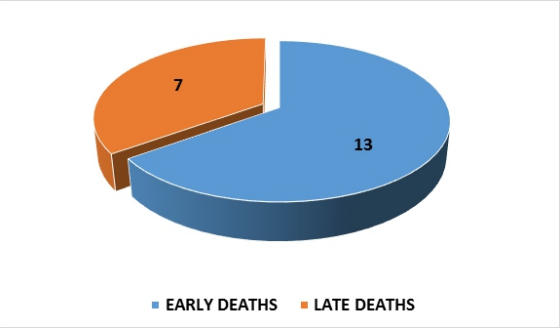


GRAPH 5: PIE DIAGRAM OF MORTALITY OF JE PATIENTS

Out of the 20 deaths, 13 deaths occurred in the first month (early death), whereas 7 deaths occurred between the second and twelfth months (late death). 9 of the 13 early deaths occurred in the hospital.

TABLE 6: PROPORTION OF EARLY AND LATE MOR TALITY

DEATHS	NUMBER	PERCENTAGE
EARLY	13 (9 + 4)	65%
LATE	7	35%
TOTAL	**20**	**100%**

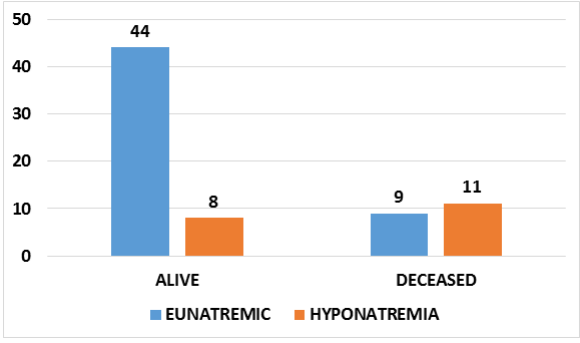


GRAPH 6: PIE DIAGRAM OF THE PROPORTION OF EARLY AND LATE DEATHS.

Out of all patients, hyponatremia was found in 19 patients. 8 out of these 19 patients survived whereas 11 patients expired within the next year.

TABLE 7: PROPORTION OF CASES WITH RESPECT TO SODIUM LEVELS

	HYPONATREMIC CASES	EUNATREMIC CASES
ALIVE	8 (42.10%)	44 (83.02%)
DECEASED	11 (57.89%)	9 (16.98%)
TOTAL	**19 (100%)**	**53 (100%)**

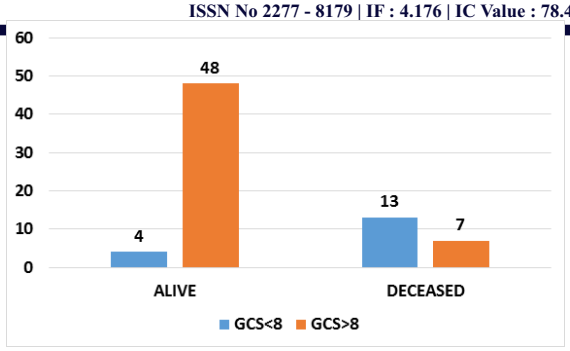


GRAPH 7: BAR DIAGRAM SHOWING THE PROPORTION JE CASES WITH RESPECT TO SODIUM LEVELS.

Out of all the patients, a total of 17 patients had a GCS of less than 8, either at presentation or during their hospital stay. Out of these 17 patients 4 patients survived, whereas 13 patients expired over the course of the next year.

TABLE 8: PROPORTION OF JE CASES WITH RESPECT TO GCS

	CASES WITH GCS < 8	CASES WITH GCS > 8
ALIVE	4 (23.53%)	48 (87.27%)
DECEASED	13 (76.47%)	7 (12.73%)
TOTAL	**17 (100%)**	**55 (100%)**

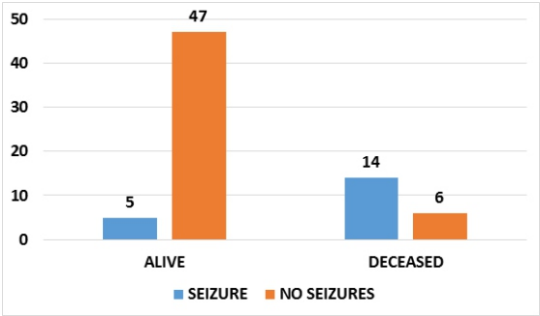


GRAPH 8: BAR DIAGRAM SHOWING PROPORTION OF CASES WITH RESPECT TO GCS

Out of all the patients, 19 patients had seizures, either at presentation or during hospital stay. 5 out of these 19 patients, survived, whereas 14 of these 19, expired within the next one year.

TABLE 9: PROPORTION OF JE CASES WITH RESPECT TO SEIZURE OCCURRENCE.

	SEIZURES PRESENT	NO SEIZURES
ALIVE	5 (26.32%)	47 (88.68%)
DECEASED	14 (73.68%)	6 (11.32%)
TOTAL	**19 (100%)**	**53 (100%)**

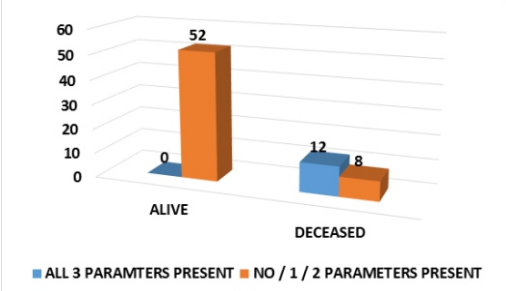


GRAPH 9: BAR DIAGRAM OF JE CASES WITH RESPECT TO SEIZURE OCCURRENCE.

Out of all the patients, all three parameters, i.e. hyponatremia, GCS< 8 and seizures were present in 8 cases. None of these 8 cases survived.

TABLE 10: PROPORTION OF PATIENTS WITH RESPECT TO PRESENCE OF ALL THREE PARAMETERS (HYPONATREMIA + GCS<8 + SEIZURES)

	HYPONATREMIA, GCS<8 AND SEIZURES PRESENT (ALL 3 PARAMETERS PRESENT)	NO / 1 / 2 PARAMETER S PRESENT
ALIVE	0	52
DECEASED	8	12
TOTAL	**8 (100%)**	**64 (100%)**



GRAPH 10 : BAR DIAGRAM SHOWING PROPORTION OF PATIENTS WITH RESPECT TO PRESENCE OF ALL THREETHREE PARAMETERS (HYPONATREMIA + GCS<8 + SEIZURES)

DISCUSSION:

1) Demographic features

a) Age

In the present study majority of the cases were in the age group of 15 to 29 years (39.51%), followed by 30 to 44 years (22.22%). Thus more than half the cases were young adults and adoloscents.

This is in accord with the analysis of **Wang et al (Wang, 2015)** that showed that majority of the cases in India are among children and adoloscents.

b) Sex

In the present study, majority of the patients were male (71.60%) whereas females were 28.40%
In the study by **Misra et al (Misra, 1998),** too, majority of the cases were males (58.97%) and 41.03% were females.

2) Mortality

In the present study mortality was 27.77%.
Mortality rates in various other studies were as follows: 20.5% in **Baruah et al (Baruah, 2002),** 16.21% in **Kalita et al (Kalita J, 2003),** 14.2% in **Misra et al (Misra UK, 1998).**

The average case fatality rate of JE in India is around 35.1% **(Wang, 2015).**

Thus, the current study, has a mortality rate below the national average but greater than a few other case series.

3) Seizures

In the present study, the occurrence of seizures was significantly associated with an increase in mortality ($p < 0.05$).

Solomon et al (Solomon T, 2004), in their study in Vietnam on JE patients, note that occurrence of seizures (witnessed or recorded) is associated with increased mortality and poor neurological outcomes. A significant association between seizures and mortality has also been noted in the study conducted by **Mong et al (Mong, 2008)** in Malaysia between 1997 and 2005.

4) Low GCS

In the present study, a GCS < 8 was significantly associated with an elevated mortality ($p<0.05$)

This finding corroborates with the finding of Solomon et al **(Solomon T, 2004).** In their study, coma was defined as a GCS <11 in adults. They found a significant association between such comatose patients and mortality.

Low GCS was a strong predictor of 3 month mortality in the study conducted by **Luo et al (Luo D, 1995)** in the Henan province in China. Coma or low GCS as a predictor of mortality has also been found significant in the studies conducted by **Misra et al (Misra UK, 1998)** and **Mong et al (Mong, 2008).**

5) Hyponatremia

In the present study, a serum sodium level less than 135 meq/l was significantly associated with increased mortality at the end of 1 year.

This finding is in accord with the study of **Mong et al (Mong, 2008)** in Malaysia, where hyponatremia was a significant predictor of mortality.

CONCLUSIONS-

The parameters of seizures, GCS<8 and hyponatremia are strong predictors of mortality in patients of JE, individually or together. Presence of any of these findings should alert the clinician to an increased likelihood of death in such patients, and the need of prompt corrective measures.

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