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Clinical Profile Of Japanese Encephalitis In Children In A Tertiary Care Hospital, Imphal: A Cross Sectional Study.

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Abstract:
Background:*Acute encephalitis syndrome is defined clinically as a person of any age, at any time of year with the acute onset of fever and a change in mental status and or new onset of seizures.*
Objective: *The aim of the study is to assess the clinical profile of japanese encephalitis (je) in children admitted for acute encephalitis syndrome.*
Materials and methods: *The total study participants 86, were selected by convenience sampling method who are admitted in the paediatric ward for acute encephalitis syndrome, enrolled in the study depending on the fulfilment of the eligibility criteria. A detailed history, general physical and systemic examination was done with baseline investigation and investigations such as je serology, imaging studies, lumbar puncture for csf analysis was done to arrive at the diagnosis.*
Results: *among study participants the demographic characteristics showed male predominance. Most of the cases were reported in >6-12 years of age. Majority of the patients had fever (100%) and seizures (41.1%) as the most common presenting symptoms followed by altered sensorium (35.3%) and headache (29.4%). The blood investigation showed predominantly lymphocytic leucocytosis, anemia and thrombocytopenia. All the positive cases expressed anti-je igm antibodies in both serum and csf. The csf cell count showed lymphocytic predominance with normal sugar level. The gcs score was >10 in majority of the cases. The mri showed findings suggestive of je in 76.5% cases.*
Conclusion: *Among the study participants, males were most commonly affected, who were from rural areas belonging to lower socio-economic class. The most common clinical features were fever, seizures, altered sensorium and the predominant age group affected was >6 to 12 years of age. Leucocytosis, hyponatremia and anemia were the most commonly encountered laboratory findings. Significant mri findings and recovery with sequelae were seen among the study population who were not vaccinated against japanese encephalitis.*
Keywords: *Japanese encephalitis, acute encephalitis syndrome, encephalitis, paediatric febrile illness, febrile seizure.*

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I. Introduction

Acute Encephalitis Syndrome is defined clinically as a person of any age, at any time of year with the 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 of seizures (excluding simple febrile seizures).[1] Japanese encephalitis (JE) is a mosquito borne encephalitis caused by a group B arbovirus (Flavivirus) and transmitted by culex mosquito[2] (Culex tritaeniorhynchus summarosus).[3] It is a zoonotic disease, Pigs serve as an amplifying host.[3]

JE is the leading cause of viral encephalitis in Asia and occurs in almost 24 Asian and Western Pacific countries. It is increasingly reported from Bangladesh, India, Nepal, Pakistan, Thailand and Vietnam. Transmission is seasonal and mainly related to rainy season in Southeast Asia region. The annual incidence of

clinical disease varies both across and within countries, ranging from <10 to >100 per 100000 population. The vast majority of cases occur among children less than 15 years of age.[2]

The disease principally occurs in rural agricultural areas where vector mosquitoes breed in the close proximity with pigs, wading birds and ducks. The natural transmission cycle involves multiple mosquito species from genus Culex whereas pigs, birds and bats are the susceptible reservoir hosts. Humans as well as equines are considered as dead-end host since the viremia in peripheral blood is low and transient. The most important vector Culex tritaeniorhynchus is associated with agricultural practices like rice cultivation or irrigated crop fields. Domestic pigs serve as key virus-amplifying host as they develop high viral as well as and long-lasting viremia after natural infection with JE virus and facilitate transmission to humans living in their close proximity.

After a 4 to 14 day incubation period, cases typically progress through the following four stages: prodromal illness (2-3 days), acute stage (3-4 days), subacute stage (7-10 days) and convalescence (4-7 weeks). The onset may be characterized by an abrupt onset of fever, headache, respiratory symptoms, anorexia, nausea, abdominal pain, vomiting and sensory changes including psychotic episodes. Grand mal seizures are seen in 10-24% of children with JE. The etiologic diagnosis of JE is established by testing acute-phase serum collected early in the illness for the presence of virus-specific IgM antibodies. There is no specific treatment for JE. The treatment is intensive supportive care, including control of seizures. Patient fatality rates for JE are 24–42% and are highest in children 5-9 year of age and in adults older than 65 years of age. The frequency of sequelae is 5–70%and is directly related to the age of the patient and severity of disease. Sequelae are most common in patients younger than 10 years at the onset of disease. The more common sequelae are mental deterioration, severe emotional instability, personality changes, motor abnormalities, and speech disturbances.

Vaccination is recommended for travellers planning visits >1 month to rural areas of Asia, where the disease is endemic, especially areas of rice or pig farming. The vaccine is administered as 3 primary doses at days 0,7,28. In India, single dose cell culture based live attenuated vaccine (SA-14-14-2) forms an integral part of Universal Immunization Programme in 83 endemic districts targeting children in age group from 1-15 years. Vector control includes aerial or ground fogging with ultra-low volume (ULV) insecticides (eg: malathion, fenitrothion). The spraying should cover the vegetation around the houses, breeding sites and animal shelters in the affected villages. Uninfected villages falling within 2-3km radius of the infected village should also receive spraying as a preventive measure.[2]

II. Materials And Methods

A cross sectional study was conducted in the Department of Paediatrics in collaboration with Department of Microbiology, Regional institute of medical sciences (RIMS), Imphal, Manipur from January 2021 to November 2022 consisting of 86 children totally. The permission of the Research Ethics Board, RIMS, Imphal, Manipur was obtained before initiating the study. Informed written consent were taken from all patients.

Study Design: Prospective cross sectional study

Study Location: This was a tertiary care teaching hospital based study done in the Department of Paediatrics at Regional institute of medical sciences (RIMS), Imphal, Manipur.

Study Duration: January 2021 to November 2022

Sample Size: 86 patients

Sample size calculation: The total calculated sample size was 86 by using the percentage of altered sensorium (83.58%) and marginal error of 8% from the study conducted by Kakoti et al[4].

Subjects and selection method: The study population was drawn from consecutive convenient sampling of children who were admitted in the Paediatric ward, RIMS, Imphal

Inclusion criteria:

Children from the age group of 1 to 12 years admitted in the paediatric ward

Children who presented with fever or history of fever and at least one of the following signs and symptoms: reduced level of consciousness (e.g., lethargy, drowsiness, or coma), severe headache, neck stiffness, limb paralysis and seizure (except for simple febrile seizure)[8]

Exclusion criteria: Patients with acute encephalitis syndrome (AES) like presentations but with clinically and investigation proven malaria, associated with other chronic illness and other non-infectious encephalopathy including rabies, trauma, animal or tick bite.[2]

Procedure methodology:

Prior to the study, ethics approval was taken from Research Ethics Board (REB). A written and informed consent was obtained in the language well understood by the parents/legal guardian before the participants were admitted into Paediatric ward and were enrolled in the study depending on the fulfilment of the eligibility criteria. A detailed history, general physical, systemic examination findings at the time of study was recorded on pro-forma. Baseline investigations including complete blood count, kidney and liver function tests, urine routine and culture were done initially. Subsequently investigations such as JE serology, Imaging studies, Lumbar puncture for CSF analysis were done to arrive at the diagnosis. Under aseptic conditions, venous blood sample was collected in sterile vials (EDTA vial, plain vial) appropriate for the blood investigations included in the study. Under strict aseptic precautions, 1ml of CSF was collected in four vials for CSF analysis through lumbar puncture using 22-gauge LP needle. The detection of JE specific IgM antibody was done by IgM enzyme linked immunosorbent assay (IgM ELISA).

Statistical analysis:

Data analysis was done using SPSS version 21.0 (IBM, INC.ARMONK, NY, USA). Descriptive statistics like frequency, percentage, mean, standard deviation was used to summarise the findings. Chi square test was applied to see the association between dependent variables and independent variables. A p-value of <0.05 was taken significant at 95% confidence interval.

III. Results

The age distribution among participants 45% were in the age group of 1-6 years, 54% were in the age group of >6-12 years. Among them 61% were males and 39% were females with M:F ratio of 1.52. That majority of the participants 42 (49%) were from upper lower class while 37 (43%) were from lower middle class, 5 (6%) were from upper middle class and 2 (2%) were from lower class according to modified Kuppuswamy socioeconomic scale. The geographical distribution of the participants, majority of them (69%) were from rural areas.

Figure 1: Signs and Symptoms

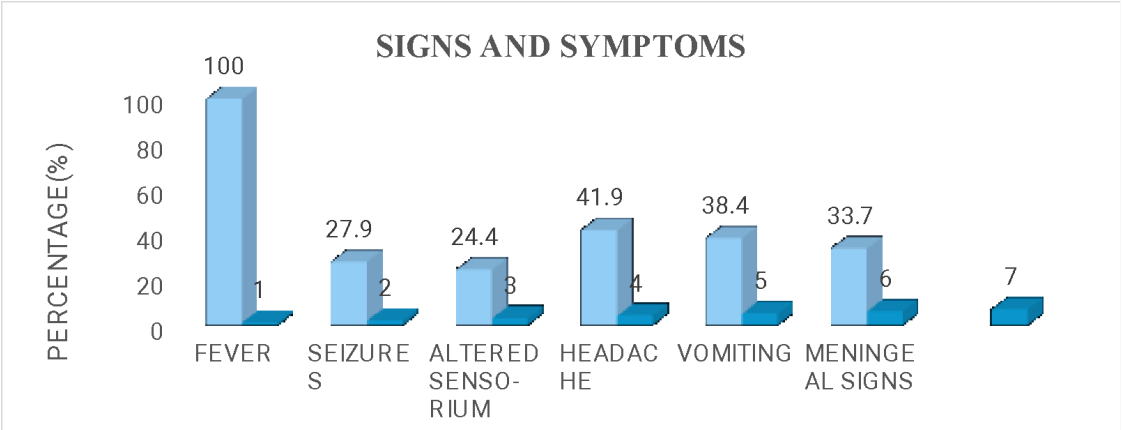


Figure 1 shows the clinical findings of the study population admitted for AES, the most common presenting complaints were fever 100% and headache 41.9% followed by vomiting 38.4%, 33.7% of them had positive meningeal signs.

Table 1: CSF Analysis

CSF ANALYSIS	INTERPRETATION	FREQUENCY(N)	PERCENTAGE (%)
PROTEIN	Normal (20-40 mg%)	67	77.9
	Elevated(>40mg%)	19	22.1
	Low(<20mg%)	0	0
SUGAR	Normal (40-80mg%)	78	90.8

	Elevated(>80mg%)	1	1.1
	Low (<40 mg%)	7	8.1
TOTAL CELL COUNT	Normal (0-5 cells/cumm)	64	74.4
	Neutrophilic pleocytosis (>5 cells/cumm)	6	7
	Lymphocytic pleocytosis	16	18.6
CSF CULTURE (Bacteria)	Positive	3	3.5
	Negative	83	96.5

Table 1 denotes the CSF findings of patients with AES where CSF protein was elevated in 19 cases (22.1%); CSF sugar was normal in 79 cases (91.1%); total cell count was showing lymphocytic pleocytosis in 16 cases (18.6%), neutrophilic pleocytosis in 6 cases (18.6%) and CSF culture was positive in 3 cases (3.5%).

Figure 2: Complete Blood Profile

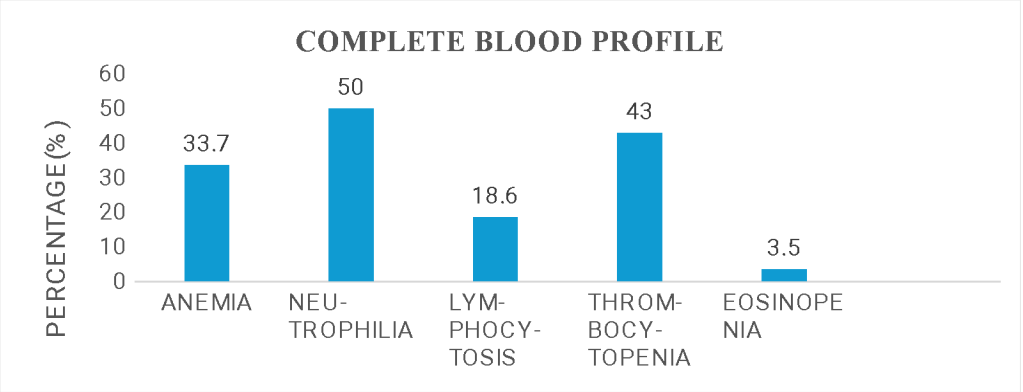


Figure 2 shows the complete blood profile findings of the study participants, out of which 50% had neutrophilia, 43% had thrombocytopenia, 33.7% had anaemia, 18.6% had lymphocytosis, 3.5% had eosinopenia.

The serological findings observed were 23% deranged KFT, 21% deranged LFT (20% hyponatremia, 13% hypoglycemia, 8% hypokalemia, 6% hypernatremia, 3% hyperglycemia, 1% hyperkalemia). The urine analysis findings showed that the urine culture was positive in 13%, microscopic hematuria was seen in 2% and 1% had proteinuria.Among the participants the chest Xray showed normal findings in 59% cases, abnormal findings in 41% cases.

Figure 3: Differential diagnosis of participants

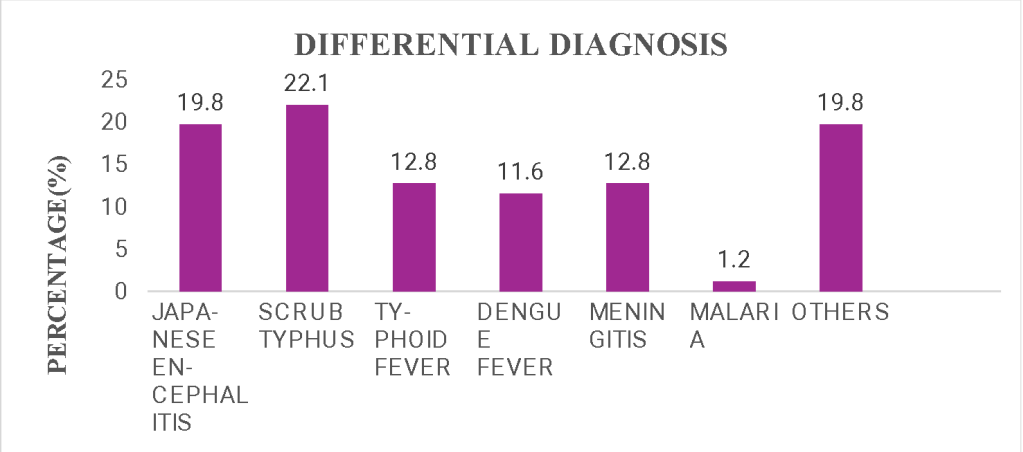


Figure 3 depicts that 19.8% had Japanese Encephalitis among those who were admitted for AES and the various other differential diagnosis seen.

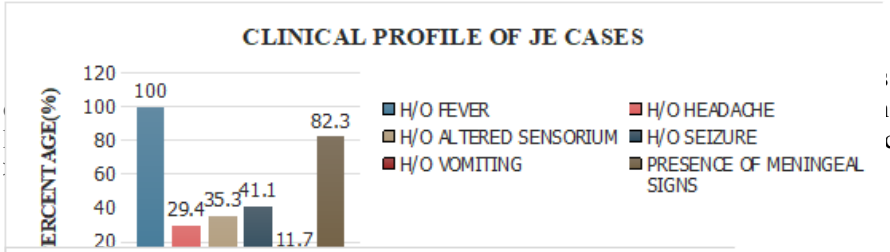
Among the total study participants (86), *17 cases of Japanese Encephalitis (JE) were detected*. Out of those 17 cases, 3(18%) cases were from 1-6 years of age and *14(82%) cases from > 6-12 years of age*. Among those *13(77%) were males* and 4(23%) were females. *More cases were reported from the rural population 12(71)* when compared to urban 5(29%). The JE vaccination has a huge impact on disease occurrence. *In our study all the diagnosed JE cases were unvaccinated children* and all of them did not have any previous history of JE among them and their siblings. *Most of the cases 10(59%) belonged to upper lower class family status*.

Table 2: Association between the age of the participants and Japanese encephalitis

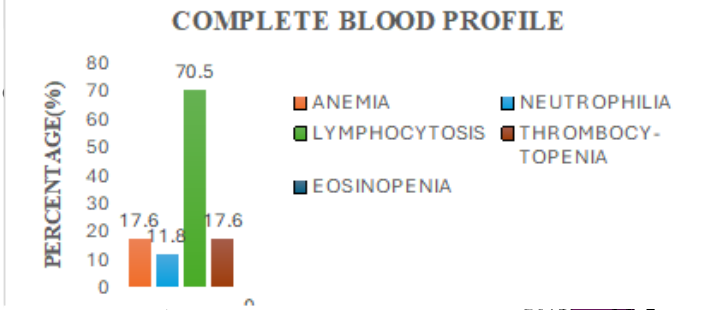
Age	JE positive	JE negative	p value
1-6 years	3 (7.5%)	37 (92.5%)	0.008
>6-12 years	14 (30.4%)	32(69.6%)	
Total	17 (19.8%)	69(80.2%)	

Table 2 depicts the age distribution of the JE patients; out of the total 17 JE cases, 3 (18%) were from 1-6 years of age and 14 (82%) were from >6-12 years of age.

Figure 4: Clinical profile of JE cases



fever (100%) was the most
s, 41.1% had seizures, 35.3%
cases 64.7% had a GCS score



seen among the JE cases, out of the total
openia, 11.8% had neutrophilia.

E cases:

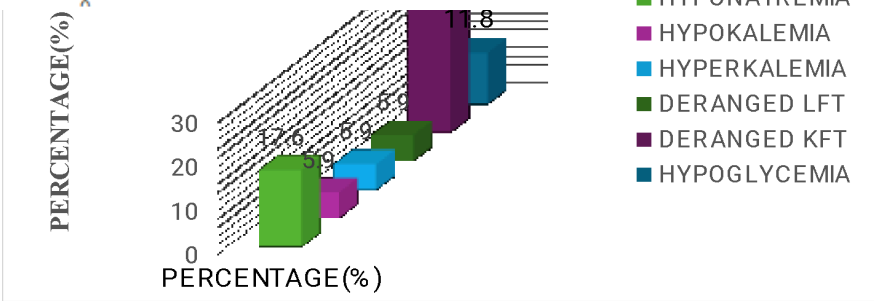


Figure 6 depicts the serological findings seen among the JE cases which shows deranged KFT (29.4%) as the most commonly seen finding.

We found that among all positive JE cases deranged renal function test (29.4%) as the most commonly seen findings in serological profile. All 17 cases of JE were sterile for blood culture results. From the urine analysis among JE positive cases we found that 94.1% had normal examination findings 5.9% had urinary tract infections and 88.3% had sterile urine culture findings. Chest Xray showed normal findings in 12(70.5%) cases and abnormal finding in 5(29.5%) cases. Among all JE positive participants 76% showed MRI findings which suggestive of Japanese Encephalitis.*100% of the total JE cases (17) tested positive for serum anti-JE IgM antibody and CSF anti-JE IgM antibody.*

Table 3: CSF analysis:

CSF ANALYSIS		FREQUENCY(N)	PERCENTAGE (%)

CSF PROTEIN	Normal	5	29.4
	Elevated	12	70.6
CSF SUGAR	Normal	16	94.2
	Elevated	1	5.8
TOTAL CELL COUNT	Normal	1	5.9
	High	16	94.1
CSF CULTURE	Sterile	17	100
	Positive	0	0

Table 3 depicts the CSF analysis of the JE cases, among them 12 cases (70.6%) had elevated CSF protein levels, 16 cases (94.2%) had normal CSF sugar levels, 16 cases (94.1%) had elevated total cell count with lymphocytic predominance and CSF culture was sterile for all 17 cases (100%). The mean CSF protein level was $57.3^{\pm}$ 19.6 (mean$^{\pm}$ standard deviation) and the mean CSF sugar level was $62.02^{\pm}$ 61.9 (mean$^{\pm}$ standard deviation).

IV. **Discussion**

This is a hospital based prospective cross-sectional study conducted in the Paediatric department in collaboration with the department of Microbiology, RIMS, Imphal from January 2020 to November 2022. During the study period, total of 86 children from 1-12 years of age with acute encephalitis syndrome (AES) fulfilling WHO definition, were enrolled to determine the clinical profile of Japanese encephalitis (JE) who tested positive for Japanese encephalitis. Out of 86 cases, 17 (19.7%) cases tested positive for Japanese encephalitis. A study carried out by Medhi et al[7] reported a similar finding that among 196 cases admitted for AES, 31 (15.8%) cases tested positive for JE.

Considering the demographic characteristics of the study, out of 17 JE cases, 13 (76.5%) cases were males and 4 (23.5%) cases were females showing a male preponderance among JE cases. In a study conducted by Dongol et al[5] similar findings were seen. Most of the JE positive cases were in the age group of >6 to 12 years of age. This is similar to the studies conducted by Panyang et al[1] and Khinchi et al[6] whose findings included that the predominant affected age group was 5 to 12 years and 5 to 15 years respectively.

Majority of JE cases, 12 (70.5%) were from rural areas and belonged to lower socio-economic class (94.1%) according to modified Kuppuswamy classification. Most of the previous studies also concluded with a similar finding[4,7,8]. This correlated well with the earlier studies where the patients were children of farmers or farm labourers of low socio-economic group residing in rural areas[4,9]. This may be due to favourable epidemiological factors like presence of water-logged paddy fields supporting profuse breeding of vector mosquitoes, piggeries in close proximity to residence, non-use of bed nets and outdoor playing habits of children[4]. Out of 17 cases, none of them were vaccinated with JE vaccine. A similar finding was reported in a study conducted by Avabratha et al[10] on Japanese encephalitis in children in Bellary, Karnataka.

Following a detailed history, physical examination with baseline and confirmatory investigations were done among the study participants. The present study denotes that majority of the patients had fever (100%) and seizures (41.1%) as the most common presenting symptoms followed by altered sensorium (35.3%) and headache (29.4%). These findings were similar to that of the studies conducted by Panyang et al[1], Yasodhara et al[11], Paswan et al[12].

Initial investigations like complete blood profile, liver and kidney function test, serum electrolytes, blood glucose, urinalysis, blood culture, chest x-ray was done. From those, lymphocytic leucocytosis (7.5%), anemia (17.6%) and thrombocytopenia (17.6%) were the common findings seen in complete blood profile. Furthermore, deranged liver function test (29.4%), hyponatremia (17.6%), hypoglycemia (11.8%), hypokalemia (5.9%) were the other findings seen in the serological study. These findings are similar to that of the study conducted by Chakrabarti at al[13]. Following these, confirmatory tests like JE serology, lumber puncture for CSF analysis and MRI brain. All 17 (100%) cases tested positive for both serum anti-JE IgM and CSF anti-JE IgM. Rayamajhi et al[14] in their study reported a similar finding that 50 (86.2%) cases tested positive for both serum anti-JE IgM and CSF anti-JE IgM.

Elevated CSF cell count with lymphocytic predominance was reported in 94.1% cases, elevated CSF protein with mean value of 57.3 mg/dL was seen in 70.6% cases, normal CSF sugar with mean value of 62.02 mg/dL was seen in 94.2% cases, CSF culture was sterile in all 17 JE cases (100%). Similar findings were reported in the previous studies[15,10,16,8,13] conducted. Blood culture was sterile in 100% of cases. In the present study, 13 (76.5%) cases showed MRI findings which were suggestive of JE. This is similar to the study conducted by Chakrabarti et al[13] in which 66.66% were having MRI findings suggestive of JE.

The GCS score was >10 in 64.7% cases, <8 in 29.5% of cases, 8-10 in 5.8% cases. Overall outcome of JE cases in the current study shows that 64.7% cases had complete recovery while 35.3% cases recovered with sequelae. This correlated with the study conducted by Kakoti et al[4] which reported that GCS score was ≤8 in 26.92% cases and 63.9% cases recovered completely. There was no mortality recorded in the present study

which is in contrast to the study conducted by Chakrabarti et al [20] which showed significant mortality in 44.4% of JE cases.

Hence from the study, it shows that Japanese encephalitis is a major cause of acute encephalitis syndrome in the paediatric population. The study also determines the socio-demographic and clinical profile of Japanese encephalitis along with the common clinical presentations and predominant age group affected which would be an aid to the paediatricians in the evaluation and management of children with acute encephalitis syndrome. The limitations of the study is that it is a single centre based study and does not provide any information regarding the long-term neurological outcome of patients after discharge which is due to the lack of longitudinal follow up in the study. There-fore further studies with a larger sample size on a multicentric level with long term longitudinal follow up would help in better understanding and management of the neurological sequelae of Japanese encephalitis.

V. Conclusion

This cross-sectional study enrolled 86 children admitted for acute encephalitis syndrome from 1 to 12 years of age. A detailed history, physical examination and staged investigations were done in the study population. Males were most commonly affected, who were from rural areas belonging to lower socio-economic class. The most common clinical features were fever, seizures, altered sensorium and the predominant age group affected was >6 to 12 years of age. Leucocytosis, hyponatremia and anaemia were the most commonly encountered laboratory findings. Significant MRI findings and recovery with sequelae were seen among the study population who were not vaccinated against Japanese encephalitis. Hence these observations of the study indicate the need for further extensive studies and scaling up of JE vaccination.

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