European Journal of Molecular & Clinical Medicine (EJMCM)
ISSN: 2515-8260 Volume 08, Issue 04, 2021

Original research article

A Prospective Cohort Study on the Long-Term Morbidity and Functional Outcomes of Japanese Encephalitis in Children

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Abstract

Aim: Long-Term Morbidity and Functional Outcome of Japanese Encephalitis in Children.

Methods: A prospective study was conducted in the Department of Pediatrics, Shri Krishna Medical College and Hospital, Muzaffarpur, Bihar, India. Children aged up to 12 years admitted with acute encephalitis syndrome (AES) were subjected to laboratory tests for detection of JE. Anti-JE IgM antibody capture (MAC) ELISA was performed on cerebrospinal fluid and serum samples using ELISA kit. Diagnosis of JE was confirmed by detection of anti-JE IgM antibody in cerebrospinal fluid (CSF), or both in CSF and serum samples. Patients with positive results were included in this study. Background demographic and relevant clinical data and results of various laboratory investigations including magnetic resonance imaging (MRI) of brain were noted. Discharged patients were followed up for two years at out-patient department and detailed clinical examination was done to document clinical status.

Results: A total of 300 children with features of AES were screened, and 100 (33.33%) children (55% boys) were diagnosed with laboratory confirmed JE during the study period. Anti-JE IgM was detected in both CSF and serum in 80 children, and in only CSF in another 20 children. 20 cases (20%) died during the hospital stay. At the time of discharge, 30 children (30%) had severe sequelae, 9 (9%) had moderate sequelae, 10 (10%) developed minor sequelae, and 32 children (32%) showed full recovery as per LOS. Motor deficit was noted in 40 children (50%) at discharge; quadriparesis in 25, hemiparesis in 8, and monoparesis in 2 child. EEG was performed in 50 children, 35 (70%) were abnormal. Till the end of the study, 20 children (20%) were on AED. Among cases under follow-up, 60 children were school-going. Poor scholastic performance was observed in 10 (20%) children in the long term; another 10 of them became drop-outs due to motor deficits, behavioral problems and apprehension of seizures.

Conclusion: Considering high mortality and long term morbidities, preventive aspects of the disease need to be prioritized.

Keywords: Seizures, EEG, Japanese Encephalitis

Introduction

Japanese encephalitis (JE) is a mosquito-borne disease and the leading cause of viral encephalitis in Asia. Children bear the greatest burden of JE disease, as most adults have developed immunity to infection. In Indonesia, surveillance studies have recently confirmed JE to be an endemic human disease across the country.[1,2]

The impact of JE results from the acute hospitalization — which is often lengthy — as well as from death and long-term sequelae of disease. A fatal outcome occurs in about 10—30% of patients.[3-5] Disability rates of up to 50% are commonly reported, and rates of 70% or higher have been documented.[6-8] Disability in a household member has a significant impact on the family, and the economic burden of disability is well recognized.[9,10]
A simple assessment tool to measure the extent of disability after JE has recently been developed and validated.[11] The Liverpool Outcome Score enables a rapid appraisal of the practical level of disability. A key purpose of the tool is to predict the likelihood that a child will be able to live independently. It is suitable for use by a range of health professionals, requires minimum training, and does not require any equipment for implementation; thus, it is suitable for use in developing country settings where specialized equipment is not always readily available.

Sequelae at hospital discharge have been reported by clinicians in 31—37% of Indonesian children after JE disease, and death reported in 10-16%.[1,2] There is little information on the extent of disabilities, and no published literature on subsequent follow-up of children after discharge, so no information on persistence of sequelae or death post-discharge is available. Assessment of disability at least 3—6 months after hospital discharge has been shown to predict long-term status.[12]

Material and methods
A prospective study was conducted in the Department of Pediatrics, Shri Krishna Medical College and Hospital, Muzaffarpur, Bihar, India from April 2019 to July 2021, after taking the approval of the protocol review committee and institutional ethics committee. After taking informed consent detailed history was taken from the patient.

Methodology
Children aged up to 12 years admitted with acute encephalitis syndrome (AES) were subjected to laboratory tests for detection of JE. Anti-JE IgM antibody capture (MAC) ELISA was performed on cerebrospinal fluid and serum samples using ELISA kit . Diagnosis of JE was confirmed by detection of anti- JE IgM antibody in cerebrospinal fluid (CSF), or both in CSF and serum samples. Patients with positive results were included in this study. They were managed as per standard guideline including empirical broad spectrum antibiotics and acyclovir, maintenances of fluid, electrolyte, acid-base balance and euglycemia, management of raised intracranial pressure, control of seizures, management of nosocomial infection and other complications, and rehabilitation therapy.[13] Background demographic and relevant clinical data and results of various laboratory investigations including magnetic resonance imaging (MRI) of brain were noted. Discharged patients were followed up for two-and-a-half years at out-patient department and detailed clinical examination was done to document clinical status. They were provided with symptomatic and supportive management during these visits. EEG was performed in children with history of seizures either during hospital stay or during follow-up. After documentation of full recovery, patients were kept under telephonic follow-up till the end of the study. The Liverpool Outcome Score (LOS) [14,15] previously validated in Indian children [16], was used in the present study for functional grading of disability at discharge and during follow-up. It assesses motor, cognition, self-care and behavior using ten questions to parents or caregivers, and observation of response to five simple motor tasks given to the child. Outcome grading was assigned based on minimum score obtained in any of the domains. Based on score obtained, LOS classifies outcome as full recovery, minor sequelae, moderate sequelae, severe sequelae, and death.

Statistical analysis
Descriptive statistics were used. Data were analyzed using IBM Statistical Package for Social Sciences version 21.0

Results
A total of 300 children with features of AES were screened, and 100 (33.33%) children (55% boys) were diagnosed with laboratory confirmed JE during the study period.

Table 1: prevalence of AES

Total no of children	AES	%
300	100	33.33

Table 2: gender distribution

Gender	No.	%
Male	55	55
Female	45	45

Anti-JE IgM was detected in both CSF and serum in 80 children, and in only CSF in another 20 children.

Table 3: Age distribution of children

Age in years	No.	%
Below 1 years	5	5
1-5 years	40	40
5-12	55	55

5 children were below 1 year of age, 40 between 1-5 years and the rest between 5-12 years age group; median (IQR) age of study population was 6.5 year 5 month. Most common clinical features were fever (*n*=100, 100%), altered sensorium (*n*=90, 90%), seizures (*n*=65, 65%), signs of meningeal irritation (*n*=48, 48%) and headache (*n*=37, 37%). Glasgow Coma Scale of 8 or less was observed among 21 children (21%) at admission. Median (IQR) duration of symptoms before admission and duration of hospitalization was 4 (2,6) days and 15.9 (12, 23.2) days, respectively. MRI of brain could be performed in 50 children, of which 35 (35%) were abnormal. Common sites of involvement were thalamus (*n*=40, 80%), basal ganglia (*n*=30, 60%), cortex (*n*=23, 46%), brainstem (*n*=15, 30%), medial temporal lobe (*n*=12 24%) and cerebellum (*n*=4, 8%). Hemorrhagic lesion was found in 5 children (10%) in addition to involvement of other parts of brain; 2 had cerebral hemorrhage and 1 had subdural hemorrhage. 20 cases (20%) died during the hospital stay.
At the time of discharge, 30 children (30%) had severe sequelae, 9 (9%) had moderate sequelae, 10 (10%) developed minor sequelae, and 32 children (32%) showed full recovery as per LOS.

Motor deficit was noted in 40 children (50%) at discharge; quadriparesis in 25, hemiparesis in 8, and monoparesis in 2 child. With rehabilitation therapy, satisfactory motor improvement was noted in majority of children (70%) within the first year of follow-up. Behavioral abnormalities evolved fully at 1 month of discharge and were noted among 32 children; predominant features were excessive anger (*n*=22), irritability (*n*=12), aggressiveness (*n*=8), sudden bouts of unexplained cry or laughter (*n*=5), and irrelevant talking (*n*=2). 6 children were unable to recognize family members initially, and the problem persisted in one of them. At the end of follow-up, abnormal behavior persisted in 13(26%) children.

In the acute phase of the disease, 65 children presented with seizures, mostly of generalized tonic clonic type; 30 of them needed two or more anti-epileptic drugs (AEDs). EEG was performed in 50 children, 35 (70%) were abnormal. These children were having recurrent seizures and AED was continued during follow- up. Among 12 children receiving AEDs at 2 years, therapy was stopped in six as they were seizure free with normal EEG, but 5 children had relapse of seizures after stoppage of drugs, and therapy was restarted. Till the end of the study, 20 children (20%) were on AED.

Among cases under follow-up, 60 children were school-going. Poor scholastic performance was observed in 10 (20%) children in the long term; another 10 of them became drop-outs due to motor deficits, behavioral problems and apprehension of seizures. Dystonia was noted in 20 children (25%) at the time of discharge, which improved substantially within first 6-9 months. 3 children showed persistence of language problem, 2 with motor aphasia and another with global aphasia. Feeding problems were seen predominantly in first 6 months of follow-up; mostly due to motor deficit, in- coordination and abnormal behavior.

Table 4: Morbidity Profile in Children with Japanese Encephalitis at Various Stages of Follow-up

Morbidity	At discharge (n=80)	6 mo (n=65)	1 y (n=50)	2 y (n=50)
Motor deficit	40 (50)	16 (24.62)	10 (20)	10 (20)
Abnormal behavior[s]	-	32 (49.23)	21 (42)	13 (26)
Epilepsy	32 (40)	22(33.85)	16 (32)	10(20)
Poor scholastic performance	-	19 (29.23)	10 (20)	10 (20)
Incoordination	24 (30)	3(4.62)	3 (6)	3 (6)
Feeding problems	24 (30)	4(6.15)	4 (8)	4 (8)
Dystonia	20 (25)	8 (12.31)	3 (6)	3 (6)
Dysarthria	12 (15)	3(4.62)	3 (6)	3 (6)
Language difficulty	16 (20)	3(4.62)	3 (6)	3 (6)
Urinary incontinence	8 (10)	3(4.62)	3 (6)	3 (6)

All values in no. (%). Evaluation started at [a]1 mo or [b]3 mo of discharge.

Discussion

In the present study, 100 children diagnosed with Japanese encephalitis were evaluated by Liverpool Outcome Score which showed mortality at the time of discharge, 30 children (30%) had severe sequelae, 9 (9%) had moderate sequelae, 10 (10%) developed minor sequelae, and 32 children (32%) showed full recovery as per LOS. Previous studies have reported a wide range of mortality (8-25%) and severe sequelae (11-25%) with Japanese encephalitis.[17-22] Subjective nature, and therefore lack of uniformity of classification, and varying duration of follow-up may be responsible for wide range of sequelae noted in different studies. The various morbidities observed in our cohort are in agreement with previous studies.[19-21] The extent of improvement among different morbidities varied in our study population. Few patients with poor clinical and radiological features showed unexpected remarkable improvement during follow-up. Whereas some survivors with severe sequelae showed improvement of different morbidities; nevertheless they could not be placed at better functional grading as some other domains did not improve. In addition, residual neuro-psychiatric problems prevented a significant proportion of children from returning to normal life.

Only few studies have described long term outcome of Japanese encephalitis affected children beyond 1 year, most probably due to remote residence of patients causing difficulty in follow-up.[17,18] Improvement of morbidities was noted mostly within initial 9-12 months of follow up, and there was no noteworthy additional improvement afterwards. Previous studies also shown majority of improvements within initial 6-12 months for most of the Japanese encephalitis survivors and neurological status at initial months of discharge was predictive of long term outcome.[17,18] Some authors noted neurological deterioration (microcephaly and hyper- active behavior) several years after discharge in some survivors and suggested the need for long term follow up.[18] However, we did not observe worsening of neuro- psychiatric status in any child till the end of follow up.

Conclusion: Considering high mortality and long term morbidities, preventive aspects of the disease need to be prioritized.

Reference

1. Ompusunggu S, Hills S, Sembiring Maha M, Moniaga V, Susilarini NK, Widjaya A, et al. Confirmation of Japanese encephalitis as an endemic human disease through sentinel surveillance in Indo- nesia. Am J Trop Med Hyg 2008;79:963—70.
2. Kari K, Liu W, Gautama K, Mammen MP, Clemens JD, Nisalak A, et al. A hospital-based surveillance for Japanese encephalitis in Bali, Indonesia. BMC Med 2006;4:8.
3. Solomon T, Dung NM, Kneen R, Thao le TT, Gainsborough M, Nisalak A, et al. Seizures and raised intracranial pressure in Vietnamese patients with Japanese encephalitis. Brain 2002;125(Pt 5):1084— 93.
4. Burke DS, Lorsomrudee W, Leake CJ, Hoke CH, Nisalak A, Chongswasdi V, et al. Fatal outcome in Japanese encephalitis. Am J Trop Med Hyg 1985;34:1203—10.
5. Schneider RJ, Firestone MH, Edelman R, Chieowanich P, Pornpi- bul R. Clinical sequelae after Japanese encephalitis: a one year follow-up study in Thailand. Southeast Asian J Trop Med Public Health 1974;5:560—8.
6. Kalayanarooj S. Japanese encephalitis: clinical manifestations, outcome and management. Southeast Asian J Trop Med Public Health 1995;26(Suppl 3):9—10.
7. Goto A. A long duration follow-up study of encephalitis Japonica. Folia Psychiatr Neurol Jpn 1964;17:326—34.
8. Matsunaga Y, Yabe S, Taniguchi K, Nakayama M, Kurane I. Current status of Japanese encephalitis in Japan. Kansenshogaku Zasshi 1999;73:97—103.
9. Suraratdecha C, Jacobson J, Sivalenka S, Narahari D. A cost- effectiveness analysis of strategies for controlling Japanese encephalitis in Andhra Pradesh, India. J Pharm Fin Econ Policy 2006;15:21—40.
10. Ding D, Hong Z, Zhao SJ, Clemens JD, Zhou B, Wang B, et al. Long- term disability from acute childhood Japanese encephalitis in Shanghai, China. Am J Trop Med Hyg 2007;77:528—33.
11. World Health Organization Regional Office for the Western Paci- fic. Meeting report. Third biregional meeting on control of Japanese encephalitis. Ho Chi Minh City, Viet Nam, April 26- 27, 2007.
12. Ooi MH, Lewthwaite P, Lai BF, Mohan A, Clear D, Lim L, et al. The epidemiology, clinical features, and long-term prognosis of Japanese encephalitis in Central Sarawak, Malaysia, 1997— 2005. Clin Infect Dis 2008;47:458—68.
13. Sharma S, Mishra D, Aneja S, Expert Group on Encephalitis, Indian Academy of Pediatrics. Consensus Guidelines on Evaluation and Management of Suspected Acute Viral Encephalitis in Children in India. Indian Pediatr. 2012;49:897-910.

14. University of Liverpool Brain Infections Group. Liverpool Outcome Score for Assessing Children at Discharge. Accessed October 10, 2020.
15. University of Liverpool Brain Infections Group. Liverpool Outcome Score for Assessing Children at Follow–up. Accessed October 10, 2020. Available from: https://vac cineresources.org/details.php?i=677.
16. Lewthwaite P, Begum A, Ooi MH, et al. Disability after encephalitis: Development and validation of a new outcome score. Bull World Health Organ. 2010;88:584-92.
17. Baruah HC, Biswas D, Patgiri D, et al. Clinical outcome and neurological sequelae in serologically confirmed cases of Japanese encephalitis patients in Assam, India. Indian Pediatr. 2002;39:1143-8.
18. Ooi MH, Lewthwaite P, Lai BF, et al. The epidemiology, clinical features, and long-term prognosis of Japanese encephalitis in central Sarawak, Malaysia, 1997-2005. Clin Infect Dis. 2008;47:458-68
19. Basumatary LJ, Raja D, Bhuyan D, et al. Clinical and radiological spectrum of Japanese encephalitis. J Neurol Sci. 2013;325:15-21.
20. Kakoti G, Dutta P, Ram Das B, et al. Clinical profile and outcome of Japanese encephalitis in children admitted with acute encephalitis syndrome. Biomed Res Int. 2013;2013: 152656.
21. Maha MS, Moniaga VA, Hills SL, et al. Outcome and extent of disability following Japanese encephalitis in Indonesian children. Int J Infect Dis. 2009;13:e389-93.
22. Verma A, Tripathi P, Rai N, et al. Long-term outcomes and socioeconomic impact of japanese encephalitis and acute encephalitis syndrome in Uttar Pradesh, India. Int J Infect. 2017; 4:e1560

Received:10-08-2021. Revised:28-08-2021. Accepted:19-09-2021