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Clinical and radiological spectrum of Japanese encephalitis

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ABSTRACT

Introduction: Japanese encephalitis (JE) is mosquito-borne flaviviral encephalitis that remains to be a major health problem in India — it still continues to cause havoc in many parts of the country. We undertook the study to analyze the clinical & radiological spectrum of JE in adults and children.

Method: This prospective study consists of 148 patients with JE. The diagnosis of JE was based on clinical, epidemiological, radiological features and demonstration of JE virus specific IgM in CSF and serum by JE virus immunoglobulin M capture enzyme-linked immunosorbent assay (MAC ELISA). All patients underwent a detailed neurological examination, CSF study & neuroimaging of brain (either CT or MRI or both). All patients were followed-up at regular interval.

Result: Seizures were present in adults (52.88%) and in children (43.18%). Dystonia was more common in children 19 (43.18%) compared to adults 19 (18.2%), and Parkinsonian features were observed in both groups 47 (45.19%) of the adults and 20 (45.45%) of the children. JE-specific IgM antibody was detected in both CSF and serum in 81.7%. In neuroimaging, apart from classical involvement of thalami, basal ganglia & midbrain, prominent involvement of hippocampus and other areas of the cortex was also found in 27 (45.6%) patients. Presence of thalamic lesion in CT/MRI showed significant relationship to the development of dystonia. However, no correlation was found between the neuroimaging features and poor clinical outcome. Twenty three patients (15.5%) died during acute phase of illness. On multivariate logistic regression analysis age, prolonged fever, Glasgow coma scale, recurrent seizures and reflex changes were found to be the predictors of outcome at the time of discharge.

Conclusion: A trend of severe and frequent involvement in younger patients with dystonia and other movement disorders was observed. It should be emphasized that presence of atypical cranial CT/MRI features in JE was not unknown and they need to be differentiated from herpes simplex encephalitis in appropriate clinical setting.

1. Introduction

Japanese encephalitis (JE) is mosquito-borne flaviviral encephalitis that remains to be a major health problem in the Indian subcontinent, Southeast Asia, and the Far East with an estimated 50,000 cases and 15,000 deaths annually. About one third of the patients die and half of the survivors have severe neuropsychiatric sequelae [1]. Infection with JEV is often asymptomatic. The disease progresses through prodromal, encephalitic and convalescent stages. Children under 15 years of age are principally affected in endemic areas. When JEV first affects a nascent population, adults are also affected [2]. Atypical presentations of JE have also been reported which include isolated acute onset abnormal behavior, aseptic meningitis, an acute flaccid paralysis-like illness and hemiplegia [3–5]. In a multivariate analysis of the prognostic predictors for adults and children with JE, the best predictors of outcome were age, Glasgow Coma Scale score, and reflex changes [6]. Poor prognostic predictors reported for children included the presence of high fever, deep coma, a short prodromal stage, abnormalities in tone, & breathing, decerebration, and focal neurological deficit [7–9]. The cranial neuroimaging abnormalities of JE have been described as bilateral thalamic, substantia nigra, basal ganglia, brainstem, cerebellum, cerebral cortical, and white matter lesions [10,11]. Bilateral T2 hyperintense and T1 hypointense to isointense thalamic lesions, especially hemorrhagic lesions have been described as characteristic finding of JE in an appropriate clinical setting. However, there are limited studies addressing the clinical, radiological and serological features of JE from North East India. In this study, we analyzed the clinical and radiological features of JE in adults and children.

2. Patients and methods

2.1. Patients

This study was based on a prospective analysis of 148 patients of JE, diagnosed and treated in Gauhati Medical College Hospital,

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Assam, India from October, 2009 to the end of September, 2011. Informed consent was obtained from all the cases.

The diagnosis of JE was based on the following criteria.

Essential criteria: Patient presenting with acute encephalitic syndrome which is defined as a person of any age, at any time of year with acute onset of fever and a change in mental status and/or new onset of seizures [12].

Supportive criteria:

1. Patients coming from known JE endemic area.
2. Detection of JEV specific IgM in serum and cerebrospinal fluid (CSF) by the IgM Antibody Capture Enzyme-Linked Immunosorbent Assay (MAC ELISA).
3. Thalamic lesions on CT or MRI scans in an appropriate clinical and epidemiological background.

Patients fulfilling the essential criteria and any two of the three supportive criteria were enrolled for the study. Patients who were younger than 14 years were included in the pediatric group; those older than 14 years were included in the adult group. A detailed neurological evaluation was carried out in all the patients. The level of consciousness was assessed by using Glasgow coma scale (GCS). Presence of seizures, behavioral abnormality, focal weakness; wasting and reflex changes were noted in all the patients. Extrapyramidal signs such as rigidity, dystonia, dyskinesia, tremor, and other movement disorders were also noted.

2.2. Diagnosis of infection with JE virus

2.2.1. JE IgM antibody detection

Samples (both serum and CSF) were tested for JE virus-specific IgM antibody on hospital admission, using a MAC ELISA kit developed by Arbovirus Diagnostics, National Institute of Virology, Pune, India. Results were interpreted as per the cut-off point formula given in the kit. All samples with equal to or greater than 50 units were considered as positive for IgM antibody for JEV. CSF was examined in all patients for protein, glucose, cells, bacteria, and fungi.

A cranial computed tomographic (CT) scan was performed using a high-resolution computed tomographic scanner, and 10-mm axial sections were obtained parallel to the orbitomeatal plane. Magnetic resonance imaging (MRI) of the brain was performed using a 2-T scanner operating at 1.5 T (Magnetom Tim Avanto; Erlangen, Germany). T1-weighted (repetition time (TR)/echo time (TE)/excitation = 500 ms/50 ms/3 ms), proton density (TR/TE/excitation = 2000–2500 ms/15–20 ms/1 ms), and T2-weighted (TR/TE/excitation = 4000 ms/80–90 ms/1 ms), SWI, DWI, T1Gd in multiple planes were obtained.

Electroencephalography (EEG) was performed using a 10- to 18-channel EEG with a 10–20 system of electrode placement for 30 min with standard procedure. The EEG was analyzed for background activity, any right-to-left asymmetry, rhythmic activity, and epileptiform discharges [13].

3. Outcome & follow-up

Outcome was classified on discharge and on follow-up at 3rd and 6th months using criteria modified from those of Whitley [14]: 1 = died; 2 = severe sequelae, incompatible with independent living; 3 = moderate sequelae, affecting function; but compatible with independence; 4 = minor sequelae including altered personality or clinical signs not affecting function; 5 = full recovery.

4. Statistical analysis

Baseline patient characteristics were reported using the median or mean ± SD for continuous variables according to their distribution. Normally distributed data were compared using student's *t*-test. Differences between proportions of various clinical, radiological, and laboratory parameters in children and adults were tested using the X^2 test with Yates' correction or Fisher's exact test. For the purpose of the analysis, the grading of the final outcome was defined on the basis of last follow-up. Patients with grade 1 (death) or grade 2 (severe sequelae) were considered to have a poor outcome, whereas patients with grades 3, 4, and 5 (moderate, mild, or no sequelae) were considered to have a good outcome [14]. The univariate analysis was carried out with the single variable such as age, prehospital duration of illness, duration of fever, GCS at the time of presentation, seizures, dystonia, focal neurological deficit, DTR, EEG changes, neuroimaging abnormalities, CSF parameters, etc. and their individual attributes to the outcome. Because we had performed multiple comparisons to look for possible parameters associated with a poor outcome, we considered $p<.05$ to indicate a trend and $p<.01$ to be statistically significant. Variables that were associated with a poor outcome in univariate analyses were examined in stepwise multivariate logistic regression analysis to create a model predictive of a poor outcome with the SPSS version 17.0 (SPSS Inc., Chicago, IL).

5. Results

The algorithm of patient enrollment and the summary findings are shown in Fig. 1. This study comprised of 148 patients, of whom 104 (70.3%) were adult and 44 (29.7%) were pediatric patients. The ratio of adult to pediatric cases was 2.3:1. The mean ages of pediatric and adult cases were 7.2 ± 3.8 years and 42.9 ± 17.6 years, respectively. Out of total 148 patients, 94 were male (adult 63, children 31) and 54 were female (adults 41, children 13) patients. In this study the male to female ratio was 1.7:1. Socioeconomic and demographic profiles of the patients are described in Table 1. The month wise distribution of the cases demonstrates a large number of cases (86%) that occurred between April and November, which coincides with the summer and monsoon seasons in this region, although the disease was seen throughout the year to a lesser degree.

The disease showed a broad spectrum of clinical presentation ranging from a brief illness that lacked specific features, to a protracted course of illness with varying severity. The clinical features of 148 JE cases are shown in Table 2. It was observed that vast majority (81.6%) of JE patients reported to the hospital between 1 and 8 days after the onset. 18.9% of total cases presented beyond 9 days after the onset of illness. However, the surviving cases, reported early (mean 5.19 ± 2.8 days) in comparison to the fatal cases (mean 8.31 ± 3.31 days) ($p = 0.0001$). GCS score ranged between 4 and 15 (mean 10.8 ± 2.32) in adults and between 4 and 12 (mean 9.0 ± 2.19) in children at the time of hospitalization ($p = 0.001$).

History of seizures was reported in 74 (50%) patients; however, the difference was not statistically significant on comparison between adults (52.88%) and children (43.18%) (odds ratio (OR) 0.4836, 95% confidence interval (CI) 0.2454–0.9532, $p = 0.0516$). History of multiple episodes of seizure was present in 25 cases (3 children, 22 adults), among them 18 had poor outcome, compared with 49 of 148 with single or no seizure (OR 0.0081, 95% CI 0.0009–0.0705, $p<.0001$). Most seizures were generalized tonic–clonic (GTCS), 2 children presented with focal seizures with secondary generalization. Seventy two patients had GTCS, of whom two presented with status epilepticus (SE) of convulsive type during the acute phase.

Focal neurological deficit was present in 25 children (56.81%) and 33 adults (31.73%) in the form of quadriplegia (38.81% in children and 28.84% in adults), followed by hemiplegia which was present in 3 children (6.81%) and in 3 adults (2.88%). Monoparesis was observed in five (11.36%) children but none of the adult patient was found to have monoparesis. On comparison of focal neurological deficit between children and adults, the difference was statistically significant, ($p<0.05$). Upper motor neuron (UMN) type of facial nerve palsy was