Journal of the Neurological Sciences 366 (2016) 110–115

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Can we differentiate between herpes simplex encephalitis and Japanese encephalitis?

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ARTICLE INFO

Article history:
Received 1 April 2016
Received in revised form 2 May 2016
Accepted 10 May 2016
Available online 11 May 2016

Keywords:
Encephalitis
Herpes simplex encephalitis
Japanese encephalitis
MRI
EEG
Outcome

ABSTRACT

Background: Herpes simplex encephalitis (HSE) occurs without regional and seasonal predilections. HSE is important to differentiate from arboviral encephalitis in endemic areas because of therapeutic potential of HSE. This study evaluates clinical features, MRI and laboratory findings which may help in differentiating HSE from Japanese encephalitis (JE).

Methods: Confirmed patients with JE and HSE in last 10 years were included. The presenting clinical symptoms including demographic information, seizure, behavioral abnormality, focal weakness and movement disorders were noted. Cranial MRI was done and location and nature of signal alteration were noted. Electroencephalography (EEG), cerebrospinal fluid (CSF), blood counts and serum chemistry were done. Outcome was measured by modified Rankin Scale (mRS). Death, functional outcome and neurological sequelae were noted at 3, 6 and 12 months follow up, and compared between HSE and JE. Outcome was categorized as poor (mRS; >2) and good (mRS ≤ 2).

Results: 97 patients with JE and 40 HSE were included. JE patients were younger than HSE and occurred in post monsoon period whereas HSE occurred throughout the year. Seizure (86% vs 40%) and behavioral abnormality (48% vs 10%) were commoner in HSE; whereas movement disorders (76% vs 0%) and focal reflex loss (42% vs 10%) were commoner in JE. CSF findings and laboratory parameters were similar in both the groups. Thalamic involvement in JE and temporal involvement in HSE were specific markers of respective encephalitis. Delta slowing on EEG was more frequent in JE than HSE. 20% JE and 30% HSE died in the hospital, and at 1 year follow up JE patients showed better outcome compared to HSE (48% vs 24%). Memory loss (72% vs 22%) was the predominant sequelae in HSE.

Conclusion: Seizure and behavioral abnormality are common features in HSE whereas focal reflex loss is commoner in JE. In a patient with acute encephalitis, thalamic lesion suggests JE and temporal lobe involvement HSE. Long term outcome in JE is better compared to HSE.

1. Introduction

Herpes simplex encephalitis (HSE) is the most common cause of sporadic encephalitis in the world, while *Arboviruses* are the most common cause of endemic encephalitis. The incidence of HSE is 1–3/million population and it constitutes 5–10% of viral encephalitis in the USA [1,2]. In South-East Asia, Japanese encephalitis (JE) is the most common endemic encephalitis. It is endemic in 24 countries with an incidence of 1.8/100,000 population and 5.4/100,000 children. 50% of JE patients die and half the survivors have severe neurological sequelae [3]. Some patients with HSE present during an epidemic of viral encephalitis, and they need to be diagnosed and treated at the earliest for good outcome. Acyclovir, due to its therapeutic potential in HSE, is empirically used in the majority of patients presenting as 'encephalitis' [4,5]. Empirical acyclovir therapy is not cost effective, especially in resource-poor countries. Moreover one may miss other treatable encephalitis as the proportion of HSE patients may be much lower compared to arboviral encephalitides in these areas. The outcome and sequelae of HSE and JE are also different, because different areas of the brain are involved in the two encephalitides [6–9]. It is therefore important to analyze the differences in clinical profiles and investigations of the two encephalitides, which may assist in cost-effective management.

2. Subjects and methods

In the present study, we compare the clinical, laboratory and MRI findings in HSE and JE as well as their outcome and sequelae at 1 year.

2.1. Patient selection and evaluation

In a hospital-based retrospective review, confirmed cases of HSE and JE were retrieved from a prospectively maintained encephalitis registry.

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http://dx.doi.org/10.1016/j.jns.2016.05.017
0022-510X/

Patients were diagnosed as acute encephalitis based on the presence of fever, altered sensorium and cerebrospinal fluid (CSF) pleocytosis, with or without focal neurological deficits or seizure [10]. HSE and JE were diagnosed by HSE DNA detection using PCR, and JE IgM ELISA in the CSF respectively.

2.2. Clinical evaluation

Demographic details of patients including age, gender, residence and occupation were noted. Duration of illness, duration of fever and altered sensorium were recorded. The presence of seizures, status epilepticus, behavioral abnormalities, focal weakness, movement disorders and signs of raised intracranial pressure [(ICP) (hyperventilation, pupillary abnormality and extensor posturing)] were noted. Consciousness was assessed by the Glasgow Coma Scale (GCS). A Mini Mental State Examination (MMSE) was done in the follow-up period in patients who could cooperate. Movement disorders were categorized into dystonia, tremor, chorea, athetosis, parkinsonian syndrome and myoclonus, and were graded into mild, moderate, severe and very severe [11].

2.3. Investigations

All the patients underwent routine blood counts and serum chemistry. Cerebrospinal fluid findings (cells, protein and sugar) were also recorded. Cranial MRI was done using 3T MRI scanner (Signa GE medical system, Wisconsin, USA). T1, T2 and FLAIR images were obtained, and the signal abnormalities and their locations were noted. Electroencephalography was done soon after admission using the 10–20 system of electrode placement. Background activity, right to left asymmetry in frequency and voltage and epileptiform discharges were noted.

2.4. Treatment and sequelae

The patients with HSE received intravenous acyclovir 10 mg/kg for 2 weeks. All patients received supportive care with maintenance of fluid, nutrition and electrolytes. Patients with seizures received antiepileptic drugs (carbamazepine, levetiracetam or sodium valproate), and those with status epilepticus (SE) were treated with intravenous lorazepam, levetiracetam or sodium valproate. Temperature was controlled with paracetamol or tepid sponging, and raised intracranial pressure was treated with intravenous bolus of 20% mannitol. The patients with respiratory failure were intubated and mechanically ventilated.

2.5. Outcome

The occurrence of death and its predictors were evaluated. Functional outcomes were assessed at 3, 6 and 12 months. These were categorized into poor (mRS 3,4,5) and good outcomes (mRS 0,1,2) [12].

Sequelae were noted at 3, 6 and 12 months. Cognitive functions were evaluated by screening MMSE. The occurrence of new seizures, recurrence and refractoriness of seizures were noted. Movement disorders were also noted and severity was graded on a 0–4 scale (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = markedly severe). The distribution and severity of focal deficits and speech abnormalities were also assessed.

2.6. Statistical analysis

Clinical features, MRI and laboratory findings at the time of presentation were compared using the Chi square test for categorical variables and the independent *t*-test or Mann-Whitney *U* test for continuous variables. Mortality, functional outcome and sequelae between the patients with HSE and JE were compared using Chi square test. The statistical analysis was done using SPSS version 16, and a variable having p-value ; <0.05 was considered significant.

3. Results

3.1. Patient population

97 patients with JE and 40 with HSE were admitted between 2004 and 2014, and were included in the present study. Their age ranged between 1 and 78 (median 25) years, 31 were children (<15 years) and 52 (38%) were females.

3.2. Demography

The number of JE patients was declining over last one decade (Fig. 1). Patients with JE were younger (29.0 ± 20.6 vs 38.0 ± 16.9 years, $p = 0.02$) compared to HSE. Children (30% vs 5%, $p = 0.001$; Fig. 2) and males (69 vs 35%, $p = 0.01$) were more commonly affected with JE compared to HSE, but there was no difference in their urban or rural living.

3.3. Seasonal variation

There was prominent clustering of JE in the post-monsoon period; 77% patients with JE were admitted between August and October, while HSE occurred throughout the year (Fig. 3).

3.4. Presenting features

Patients with HSE had more frequent seizures (83% vs 46%, $p < 0.001$), status epilepticus (48% vs 18%, $p = 0.001$) and behavioral abnormalities on admission compared with JE (63% vs 35%, $p = 0.004$). On the other hand, patients with JE had more frequent movement disorders (76% vs 0%, $p < 0.001$), focal deficit (68% vs 50%, $p = 0.05$) and focal reflex loss (42% vs 10%, $p < 0.001$) (Table 1).

3.5. Laboratory findings

There were no significant differences in the two groups with respect to routine blood counts and serum chemistry, including CK level. CSF cells (86.5 ± 140.3 vs 120.0 ± 164.5/mm^3, $p = 0.22$), glucose (79.14 ± 31.71 vs 71.39 ± 26.88, $p = 0.26$) and protein levels (76.9 ± 47.4 vs 79.7 ± 43.1 mg/dl, $p = 0.98$).

3.6. MRI findings

Most of the patients with HSE had bilateral temporal (31/40; 77.5%), insular (12/40; 30%) and basifrontal (24/40; 60%) cortical involvement. Patients with JE had predominant thalamic (bilateral in 73/97; 75.3%) which were unilateral in 7. In JE patients, putamen was involved in 32

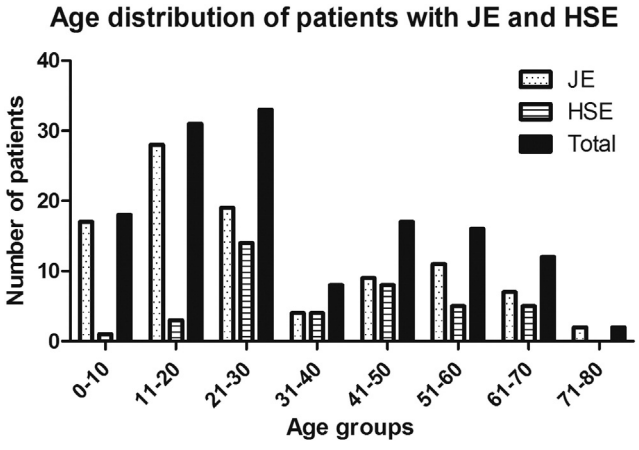

Fig. 1. Bar diagram shows a declining trend of Japanese encephalitis in the elderly.