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Status epilepticus in encephalitis: a study of clinical findings, magnetic resonance imaging, and response to antiepileptic drugs

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This study evaluates clinical findings, magnetic resonance imaging (MRI), and response to antiepileptic drugs (AEDs) in encephalitis patients with status epilepticus (SE). Encephalitis patients with SE were included and they were grouped into herpes (HSE), Japanese (JE), dengue, and nonspecific encephalitis on the basis of virological studies. The demographic and clinical details, including SE type and duration, were noted. Cranial MRI and cerebrospinal fluid (CSF) were carried out. Response to first, second, and third AEDs were noted and the patients not responding to the second AED were considered refractory SE. The relationships of the mortality and the refractoriness of SE with various clinical findings, MRI, CSF, and the type of encephalitis were evaluated. Thirty SE patients with encephalitis aged 1 to 64 years were included. Nine patients had JE, 4 HSE, 1 dengue, and 16 nonspecific encephalitis. Generalized convulsive SE was present in 26 and nonconvulsive SE in 4 patients. The mean duration of SE was 21 (0.83 to 72) h. MRI was abnormal in 20 patients. A 46.7% of patients responded to the first AED and 36.7% remained refractory to the second AED. In 26.7% patients, the seizure continued even after the third AED. The response to AED was not related to the clinical, MRI, and laboratory variables. Nine patients died and the mortality was related to gender and Glasgow Coma Scale (GCS) score. In encephalitis with SE, 46.7% patients responded to the fist AED and 36.7% remained refractory to the second AED. One third of patients died, which was related to the depth of coma. *Journal of NeuroVirology* (2008) **14,** 412–417.

Keywords: antiepileptic drug; dengue; encephalitis; herpes; Japanese; mortality; refractory SE; status epilepticus

Introduction

Central nervous system infection is a major cause of seizure, especially in the developing countries where infestations and infections are common. Although the prevalence of herpes simplex encephalitis (HSE) is similar in different geographical areas, the etiology of endemic encephalitides varies. In South East Asia, Japanese encephalitis (JE) occurs in about 50,000 patients annually, of which 30% die and 50% of the survivors have major sequelae (Advisory Committee in Immunization Practices, 1993). Seizure in the acute stage of JE has been reported in 27.8% to 46% and has been reported as a poor prognostic predictor of JE (Misra and Kalita, 2001; Solomon *et al,* 2002). In HSE, seizure is common in the acute stage, occurring in 57% to 62% patients (McGrath *et al,* 1997). Status epilepticus (SE) has been reported as isolated case reports in various viral encephalitis such as HSE (Gunduz *et al,* 2006), JE (Misra and Kalita, 2001; Solomon *et al,* 2002), West Nile encephalitis, and Parvo virus encephalitis (Erol *et al,* 2006). Acute symptomatic SE is more refractory to the antiepileptic drugs (AEDs), with higher mortality (Holtkamp *et al,*

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2005; Mayer *et al,* 2002). The severity, response to AEDs, and outcome may be different in different groups of encephalitides depending on their neurotropism. In the available medical literature, there is no comprehensive study on SE in encephalitis. In this communication, we report encephalitis patients with SE and their clinical, MRI, and electroencephalographic (EEG) findings and response to AEDs.

Results

During the study period, we have managed 191 patients with encephalitis; 68 of them had JE, 51 dengue encephalopathy, 14 HSE, 2 Epstein-Barr virus encephalitis, and 56 nonspecific encephalitis. Thirty-six of these patients with encephalitis had SE. Six patients were excluded because of their incomplete clinical and treatment data. The present study therefore was based on 30 patients. Their age ranged between 1 and 64 (median 24) years and 13 were females. Nine patients were below the age of 13 years and only one was above the age of 60 years. All had encephalitic illness before the onset of status epilepticus. Their Glasgow Coma Scale (GCS) score ranged between 3 and 12 (median 5). High fever ($>104^{\circ}$F) was present in 5 patients. Headache was present in 17, vomiting in 14, hyperventilation in 24, and behavioral abnormalities in 7 patients. None of the patients received quinolones and none had epilepsy in the past. Focal deficit in the form of quadriparesis was present in 12 patients. Muscle tone was increased in 14 and reduced in 3 patients. Tendon reflexes were brisk in 12 and reduced in 9 patients. SE was generalized convulsive in 26 and nonconvulsive in 4 patients. The duration of SE was quite variable ranging between 50 min to 72 h (mean 21 h). Six patients had SE for 6 h or less and remaining 24 had SE for more than 6 h prior to receiving AED. Sixteen patients received phenytoin and 14 valproate as a first-line AED; following which 14 (46.7%) had cessation of SE (phenytoin 50% and valproate 42.8%). Another 5 patients responded following second AED and 11 (36.7%) patients had refractory SE. Third AED in the form of intravenous lorazepam (3), diazepam (3), midazolam (3), or intramuscular paraldehyde (2) was tried but only three more patients responded. In the remaining eight (26.7%) patients, subtle SE continued even after third AED. In these patients carbamazepine (3), gabapentine (2), clobazam (1), and acetazolamide (2) were added. Subtle SE in these patients continued for a period of 36 to 528 (mean 156.7) h. None of these patients received general anesthesia. Following the third AED, two patients developed hypotension and respiratory arrest for which they were artificially ventilated. Twelve patients had recurrence of seizure within 24 h. The recurrence of seizure was more common in refractory SE (10/11) compared to nonrefractory (2/19) patients ($P=.0001$).

At admission, leukocytosis was present in 14 patients, anemia (Hb <12 g/dl) in 24, hyponatremia in 2 (128 meq/L each), and bleeding and coagulation abnormalities in 1, who had dengue. None of the patients had hypo- or hyperglycemia and hypocalcemia. CSF pleocytosis ranged between 10 and 450 (mean 78.5)/mm^3.

Cranial magnetic resonance imaging (MRI) was done in 29 patients and was abnormal in 20 (69%). MRI revealed temporal lobe involvement in all the four patients with HSE (Figure 1). In nine patients with JE, thalamic involvement was present in eight, basal ganglia in three, brainstem in five, and cortical in seven (Figure 2). Seven out of 15 patients with nonspecific encephalitis had MRI abnormality, which included thalamic involvement in three, basal ganglia in one, and cortical in four patients. EEG revealed epileptiform discharges in 9, slowing in 16, asymmetry in 3, and alpha coma in 1 patient.

Nine patients who received phenytoin, valproate, and midazolam died during hospital stay, two of them died during SE due to hypotension and respiratory arrest. Mortality was related to the gender ($P=.04$) and GCS score ($P=.02$). Eight out of 17 males died, whereas only 1 out of 13 females died. The etiology of encephalitis in males and females was not significantly different ($P=.15$). In males, the etiology of encephalitis was JE in seven, HSE in three, nonspecific encephalitis in six, and dengue in one; whereas in females, the etiology was

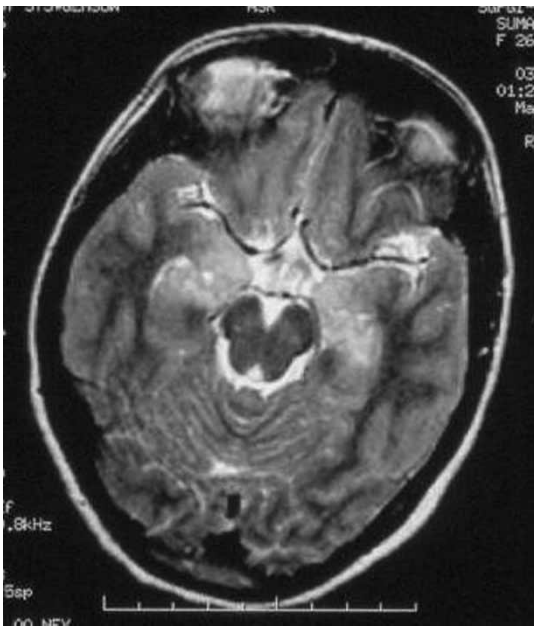

Figure 1 Cranial MRI. T2 sequence of a patient with herpes simplex encephalitis showed hyperintense lesion in both medial temporal lobe. She had generalized convulsive status epilepticus for 68 h and refractory to phenytoin, valproate, and lorazepam and her seizure was controlled after 3 days. She was discharged after 20 days of hospitalization in amnestic state.

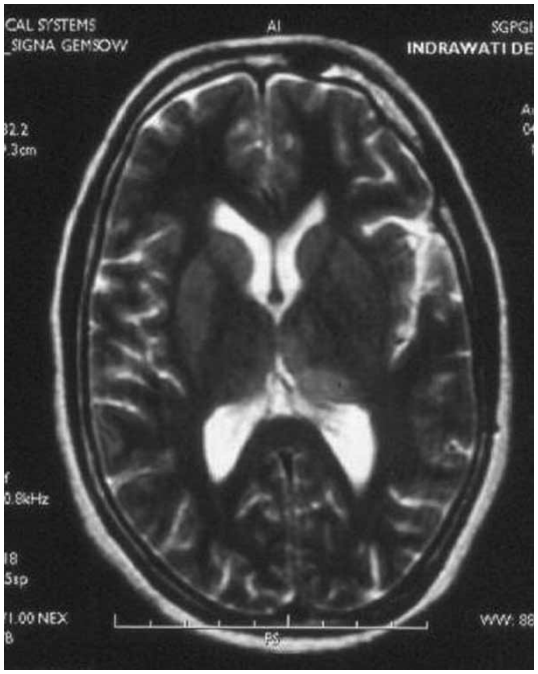

Figure 2 Cranial MRI. T2 sequence of a patient with Japanese encephalitis who had nonconvulsive status epilepticus showed thalamic and basal ganglia hyperintensity. Her seizure discharges disappeared after second antiepileptic drug.

JE in two, HSE in one, and nonspecific encephalitis in 10 patients. Eight male patients died; four had JE, two nonspecific encephalitis, and one each dengue and HSE. None of the clinical, laboratory, EEG, and MRI parameters was significantly related to the mortality. The duration of SE was not related to the mortality ($P = .33$). The details are summarized in Table 1. Refractoriness of SE was also not related to age, type and duration of SE, type of encephalitis, cortical involvement on MRI, and CSF pleocytosis.

Discussion

In the present study on SE in encephalitis, 46.7% patients responded to the first drug and 36.7% were refractory to the second AED. In the literature, 50% to 70% SE patients have been reported to respond to the first AED (Mayer *et al,* 2002; Treiman *et al,* 1998). Acute symptomatic SE, especially due to encephalitis, is more refractory (Holtkamp *et al,* 2005; Mayer *et al,* 2002). In a study on SE, 8 out of 10 patients with encephalitis had refractory SE (Holtkamp *et al,* 2005). This may be due to diffuse or focal encephalitis process involving cerebral cortex. In our study, however, the response to AED was better and the frequency of refractory SE in encephalitis was comparable to the SE as a whole. This may be due to different patient populations; majority of our patients had Japanese or nonspecific encephalitis whereas patients in previous reports were mostly

Table 1 Relation of various clinical findings, MRI, and response to antiepileptic drugs (AEDs) with mortality in encephalitis patients with status epilepticus (SE)

Parameters	Death ($n = 9$)	Survived ($n = 21$)	P
Age			0.27
≤12	3	6	
12–60	5	15	
>60	1	0	
Gender			0.04
Male	8	9	
Female	1	12	
Type of SE			0.29
GCSE	9	17	
NCSE	0	4	
Temperature			1.00
≥104°F	1	4	
<104°F	8	17	
Hyperventilation			0.29
+	8	16	
−	1	5	
Focal deficit			0.42
+	5	7	
−	4	14	
MRI			1.00
Abnormal	6	14	
Normal	2	7	
Diagnosis			0.24
HSE	1	3	
JE	4	5	
Dengue	1	0	
Nonspecific	3	13	
Duration of SE			0.33
≥6 h	6	18	
<6 h	3	3	
Refractory			0.23
+	5	6	
−	4	15	
Malignant			1.00
+	2	6	
−	7	15	
GCS	4.55 ± 1.59	6.67 ± 3.18	0.02

Note. GCSE = generalized convulsive status epilepticus; NCSE = nonconvulsive status epilepticus; HSE = herpes simplex encephalitis; JE = Japanese encephalitis; GCS = Glasgow Coma Scale; CSF = cerebrospinal fluid.

HSE. In JE, predominant subcortical involvement has been reported on MRI (Kalita and Misra, 2000) and pathological studies (Zimmerman HM, 1946; Shankar *et al,* 1983; Falconer *et al,* 1964). In a radiological study, MRI revealed thalamic involvement in 93.5%, basal ganglia in 35.5%, mid brain in 58%, and cortical involvement in 19.3% of patients (Kalita and Misra, 2000). The incidence of seizure is lower in JE (Misra and Kalita, 2001) compared to HSE (McGrath *et al,* 1997). In arbovirus nonendemic area, SE in encephalitis may be mostly due to HSE, which involves highly epileptogenic temporofrontal cortex (Valdlamudi *et al,* 2003; Yafte and Lowenstein, 1993). The definition of refractory SE is controversial; some define it as nonresponsiveness to two and others to three AEDs. In our study, the

lack of response to two AEDs was considered refractory SE.

In 26.7% patients, subtle SE continued even after third AED, in whom oral anticonvulsants were tried. None of these patients received general anesthesia. Twenty percent patients who do not respond even to general anesthesia may develop malignant SE. Encephalitis is identified as a risk factor of malignant SE (Haltkamp *et al,* 2005; Parent and Lowenstein, 1994; Prasad *et al,* 2001).

Extremes of age, duration, acute symptomatic and nonconvulsive SE are the predictors of refractory and malignant SE (Holtkamp *et al,* 2005; Mayer *et al,* 2002; Treiman *et al,* 1998). In the present study, the refractoriness of SE was not related to clinical, type of encephalitis, and MRI findings. Thirty percent of our patients died during hospital stay and death was related to GCS score and male gender. Low GCS score is a well-known predictor of the mortality in HSE (Raschilas *et al,* 2002) and JE (Misra *et al,* 1998). The reported 30 days mortality in SE ranges between 7% and 39% and is higher in acute symptomatic group (Parent *et al,* 1994; Knake *et al,* 2001; Vignatelli *et al,* 2003). The present study is the first study evaluating SE in encephalitis and correlating their response to AED and mortality with various clinical features, MRI, and etiology of encephalitis.

To define control of SE, we have considered clinical cessation of seizure in convulsive SE and EEG cessation of epileptiform discharges in nonconvulsive SE. In encephalitis patients, recovery of consciousness after the cessation of SE does not occur due to the underlying disease process. EEG monitoring was not possible in our patients, which could have detected on-going seizure activity better. Although benzodiazepine has been recommended as a first line antiepileptic drug for status epilepticus, in the present study we have used valproate or phenytoin as the first-line drug as a part of an ongoing trial (Misra *et al,* 2006). The efficacy of phenytoin (50%) and valproate (42.8%) in the present study is comparable to reported efficacy of phenytoin and valproate (Giroud *et al,* 1993; Campistol *et al,* 1999; Treimann *et al,* 1998; Misra *et al,* 2006). In a large study on SE, the efficacy of lorazepam was 64.9%, diazepam 55.8%, phenobarbitone 58.2%, and phenytoin 43.6% (Treimann *et al,* 1998). These studies, however, included patients with diverse etiologies of SE whereas our study is based on patients with encephalitis only. In encephalitis, valproate may be a better option as it has less CNS depressant effect compared to benzodiazepines. All the refractory SE patients had recurrence of seizure within 24 h, suggesting close monitoring of these patients. Similar observation has been reported in our earlier studies (Kalita *et al,* 1003, 2006).

It can be concluded from this study that 46.7% SE patients due to encephalitis respond to the first AED and 36.7% patients remain refractory to the second AED. One third of patients died and death was related to GCS score.

Subjects and methods

Subjects

The patients with encephalitis having status epilepticus during 2002 to 2006 were retrospectively evaluated. The diagnosis of encephalitis was based on fever, altered sensorium with or without focal neurological deficit, in whom malaria, septicemia, bacterial, and fungal meningitis were excluded. Status epilepticus was defined as occurrence of two or more convulsive seizures without full recovery of consciousness between the seizures or continuous convulsive activity lasting for more than 10 min. Nonconvulsive SE was defined when the patients had coma with ictal discharges on EEG with or without subtle convulsive movements, e.g., rhythmic twitching of arm, trunk, leg, or facial muscles, tonic eye movement, or nystagmoid eye jerk (Trieman *et al,* 1998).

Previous history of epilepsy, drug default, intake of seizurogenic drugs (quinolones, antipsychotics, etc.), and head injury were noted. Duration of encephalitic illness and presence of high fever ($>104^{\circ}$F), headache, vomiting, focal deficit, bleeding diathesis, and hypotension were noted. The type of status epilepticus (generalized convulsive and nonconvulsive) and the duration of SE prior to the antiepileptic drugs were recorded. Consciousness was assessed by Glasgow Coma Scale (GCS) score. Presence of papilledema, cranial nerve palsy, and focal deficit in the form of monoplegia, hemiplegia, or quadriplegia were noted. Muscle tone and reflexes were graded into increased, reduced, and normal.

Investigations

Blood counts, hemoglobin, erythrocyte sedimentation rate (ESR), peripheral blood smear for malarial parasite, blood sugar, blood urea nitrogen, serum creatinine, bilirubin, transaminases, sodium, potassium, calcium, albumin, and protein were carried out. Electrocardiogram and radiograph of chest were also done in all. Cranial magnetic resonance imaging (MRI) was done using a 1.5-T (Signa; GE Medical System, Wisconsin, USA) scanner and T1, T2, and FLAIR images were obtained. Twenty-one-channel EEG was carried out after the management of convulsive SE, preferably within 12 h. All the patients with nonconvulsive SE were diagnosed on the basis of EEG. EEG recording was done for 30 min, employing the 10–20 system of electrode placement in both the horizontal and vertical runs using unipolar and bipolar montages. Presence of

epileptiform discharges, slowing, and asymmetry in frequency and voltage were noted.

Cerebrospinal fluid was analyzed for cell, protein, and sugar. For specific virological diagnosis, CSF immuoglobulin G (IgM) enzyme-linked immunosorbent assay (ELISA) for JE, mumps, measles; serum IgM ELISA for dengue; and CSF polymerase chain reaction (PCR) for herpes, Coxsackie, and Epstein-Barr viruses were done. Patients were grouped as nonspecific encephalitis if these tests were negative.

Treatment

As a first-line AED, patients received intravenous phenytoin sodium (20 mg/kg) or sodium valproate (30mg/kg) as a fixed protocol used in our previous randomized control trial. The patients not responding to phenytoin as a first-line AED were infused with valproate and vice versa. This randomized controlled trial evaluating the efficacy and safety of intravenous phenytoin and valproate in SE was duly approved by our Institute Ethics Committee. In this study, sodium valproate was found to be superior to phenytoin in controlling SE (Misra *et al,* 2006). Patients not responding to the second AED were given intravenous lorazepam (0.1 mg/kg), midazolam (0.1 mg/kg), or diazepam (0.15 mg/kg). Occurrence of hypotension, arrhythmia, respiratory dysfunction, and other complications were noted. If SE was not controlled after the third-line AED, oral carbamazepine, gabapentin, and clobazam were used and the patients with convulsive SE were shifted to the intensive care unit for general anesthesia if the intensive care facility was available or affordable. SE was considered refractory if not controlled after second AED. The recurrence of seizure within 24 h in the patients who had responded to initial AED was noted.

The treatment of encephalitis patients was mostly supportive except herpes simplex encephalitis, in which case acyclovir 10 mg/kg 8-hourly was infused intravenously for 14 days. The duration of hospital stay was noted. Outcome was defined as mortality during hospital stay.

Statistical analysis

The response to AED was compared with the various clinical features (age, type, and duration of SE), type of encephalitis, and laboratory, MRI, and EEG abnormalities. The mortality was also correlated with the duration, type, and refractoriness of SE, type of encephalitis, and MRI and EEG abnormalities, employing chi-square, Fisher's exact, and independent *t* tests using SPSS 12 version software.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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