Neurology Asia 2012; 17(4) : 303 – 309

Profile and predictors of symptomatic seizures following acute Japanese and herpes simplex encephalitis

[1]S Rao, [1]S Sinha, [2]V Ravi, [3]S Nagarathna, [4]RD Bharath

Departments of [1]Neurology, [2]Neurovirology, [3]Neuromicrobiology, and [4]Neuroradiology, National Institute of Mental Health and NeuroSciences (NIMHANS), Bangalore, India

Abstract

Background: Acute viral encephalitis often manifests with seizures. Studies from India regarding subsequent remote symptomatic epilepsy following acute viral encephalitis are few. *Objectives:* To describe the incidence, identify the risk factors of acute symptomatic seizures in acute viral encephalitis and analyze the prevalence of seizure recurrence in those patients who had acute symptomatic seizures. *Methods:* This retrospective hospital based cross-sectional study involved 75 patients (age: 27.44 ±18.47 years; Male:Female = 37:38) of acute viral encephalitis viz. herpes simplex encephalitis (HSE: 48) and Japanese encephalitis (JE: 27) with acute symptomatic seizures over a 10 years period. *Results:* Acute symptomatic seizures was noted in 55 patients (73.3%) patients with acute viral encephalitis: HSE: 35 (72.9%) and JE: 20 (74.1%). The types of seizures were: generalized (n=29; 52.7%) and focal (n=26; 47.3%). Status epilepticus was noted in 10 (18.2%) patients ($p<0.001$), while cluster seizures were observed in 9 (16.4%). Some of the risk factors of seizures in HSE were imaging abnormalities and higher CSF cell count. Younger patients of JE had higher risk of having seizures and those with seizures did not improve completely compared to without seizure subgroup. Fifty patients with acute symptomatic seizures received parenteral phenytoin, followed by phenobarbitone (n=5), and 14 (25.5%) required a second AED, which was often carbamazepine. Scalp EEG was abnormal in 36/44 (81.8%) with HSE and in 8/15 patients (53.3%) with JE. Among 23/75 patients with viral encephalitis who were followed up for median of 2 years, 34.8% (n=8) of patients developed unprovoked seizures and the others (n=15) were seizure free.
Conclusions: Acute symptomatic seizures are common in acute viral encephalitis. A significant proportion of the patients with acute viral encephalitis and acute symptomatic seizures developed unprovoked seizures.

INTRODUCTION

Acute symptomatic seizures are defined as seizures occurring in close temporal relation to any central nervous system (CNS) insult secondary to varying etiologies and are associated with an increased risk for subsequent epilepsy.[1-3] An episode of viral encephalitis complicated by early seizures increased the risk of developing a subsequent unprovoked seizure by 22 times and an episode that was not accompanied by early seizures increased this risk by 10 times.[1] Overall, there was 16 times increased risk of developing an unprovoked seizure following viral encephalitis. Most seizure so occurred within the first 5 years following the encephalitic episode though the risk of unprovoked seizures remained elevated until 20 years.

Herpes simplex encephalitis (HSE) is a focal necrotizing encephalitis and therefore patients often manifest with focal neurological deficits in addition to other features of encephalitis. As it commonly involves the temporal and basi-frontal lobes, aphasia, psychiatric manifestations, visual hallucinations and acute symptomatic seizures (40-60%) are common. Two thirds of survivors have significant neuropsychiatric sequelae, including memory impairment (69%), personality and behavioural change (45%), dysphasia (41%) and epilepsy (25%).[4] In patients with acute HSE, seizures were noted in 63% and unprovoked seizures in 24.7% of patients as per a hospital based study from India by Misra *et al*.[5] This might reflect the propensity of HSV to involve the highly epileptogenic mesial temporal lobe region.

Address correspondence to: Dr Sanjib Sinha, Additional Prof of Neurology, NIMHANS Bangalore: 560 029, Karnataka, India, Tel: +91 80 26995150, Fax: +91 80 26564830, E-mail: sanjib_sinha2004@yahoo.co.in

Patients with seizures have a worse outcome compared to those without seizures.[6]

Japanese encephalitis (JE) is the commonest epidemic viral encephalitis, with an estimated 30,000-50,000 cases and 10,000-15,000 deaths annually.[7] About 30% of patients admitted to hospital with JE die, and around half of the survivors have severe neurological sequelae.[8] The classical description of JE sequelae include a dull flat mask-like facies with wide unblinking eyes, tremor, generalized hypertonia, and cogwheel rigidity.[9] Severe cognitive and language impairment, motor dysfunction and seizures are noted in 20% each.[7] The reported frequency of acute symptomatic seizures in JE is highly variable (7-67%).[10] In survivors of JE, Misra *et al* from India reported that 20% have remote symptomatic seizures with an odds ratio of 3.03 of having epilepsy when compared to other encephalitis.[5]

We described the incidence and identified the risk factors of acute symptomatic seizures in acute viral encephalitis (HSE and JE) and analyzed seizure recurrence in those patients with HSE/JE and new onset acute symptomatic seizures from a centre in South India.

METHODS

This retrospective hospital based cross-sectional study involved confirmed patients with acute viral encephalitis (n=75; Male:Female, 37:38; mean age: 27.44±18.47 years) viz. HSE (n=48) and JE (n=27) who were evaluated from January'1999 to December'2008 at a major tertiary care referral centre in south India for neuropsychiatric disorders. This study was approved by the institutional ethics committee. Information regarding patients' details was retrieved from the medical case records, National Institute of Mental Health and NeuroSciences (NIMHANS), Bangalore.

Inclusion criteria

Herpes simplex encephalitis (HSE) was defined as those developing features of encephalitis with fever and a consistent CSF (lymphocytic pleocytosis (<100 cells/co.mm), mild-moderate elevated protein (<100 mg/dl) and normal/mild decrease in glucose) over hours to days and having either (i) CSF- antibody titers (ELISA – IgG 1:625 or more / four fold rise in antibody titres estimated serially) / antigen / PCR studies confirming acute HSE infection, or (ii) Imaging of the brain - CT/ MRI suggestive of acute HSE infection namely signal changes in bilateral medial temporal lobe, orbitofrontal and or the cingulate cortices.

Japanese encephalitis (JE) was defined here as those developing features of encephalitis with fever and a consistent CSF picture (lymphocytic pleocytosis (<100 cells/co.mm), mild-moderate elevated protein (<100 mg/dl) and normal/mild decrease in glucose) and having CSF antibody titers (1:625 titer of IgM by ELISA) against JE virus suggestive of acute infection.

Acute symptomatic seizures, remote symptomatic seizures, status epilepticus, and epilepsy defined as per the ILAE 1989 Commission on Epidemiology and Prognosis – criteria.[11-13] Acute symptomatic seizure was defined as seizures occurring in close temporal relation to any central nervous system (CNS) insult of varying aetiology. Epilepsy was defined as a condition characterized by recurrent (two or more) epileptic seizures, unprovoked by any immediate identified cause. Remote symptomatic seizure was defined as unprovoked seizures owing to a brain damage secondary to a central nervous system infection like HSE and JE. SE was defined a seizure of >30-min duration or a series of epileptic seizures during which consciousness s not regained between the ictal events. The cluster of seizures is defined as 3 attacks of seizures per 24 hours.[14]

The demographic profile, clinical features, seizure details, details of brain imaging of brain, CSF profile, therapeutic details, clinical and seizure outcome at discharge/last follow-up were recorded in a pre-designed computerized spread sheet. The clinical data, including gender, and clinical manifestations between two patient groups (with and without seizures) during the acute symptomatic phase were analyzed by means of the Chi-square test or Fisher's exact test. The mean ages between the two groups and the mean CSF cell count and mean CSF sugar and protein were analyzed by Student's t test. A p value of less than 0.05 was considered significant.

RESULTS

The demographic and major clinical features of 75 patients diagnosed to have acute viral encephalitis (HSE: 48; JE: 27) are mentioned in Table 1. The mean duration of hospital admission was 18.12±11.7 days. Fifty five patients had acute symptomatic seizures. The type of seizures was: generalized 29 (52.7%) and focal 26 (47.3%). Among them, 10 (18.2%) patients had status epilepticus (SE) - secondary generalized: 4; generalized: 6, and 9 (16.4%) had cluster attacks of seizures - secondary generalized: 3; generalized: 6.

Table 1: Demographic and clinical features in patients with acute viral encephalitis

Parameters	Overall VE (n=75)	HSE (n=48)	JE (n=27)
Mean Age (years)	27.44 ±18.47	36.5±16.7	13.6±9.03
Male: Female	37:38	25:23	12:15
Fever	64 (85.3%)	41 (85.4%)	23 (85.2%)
Headache	47 (62.7%)	27 (56.2%)	20 (74.07%)
Vomiting	14 (18.7%)	6 (12.5%)	8 (29.6%)
Seizures GTCS Focal	55 (73.3%) 29 (52.7%) 26 (47.3%)	35 (72.9%) 18 (51.4%) 17 (48.6%)	20 (74.07%) 11 (55%) 9 (45%)
Status epilepticus (Sec Gen: 4; Gen: 6)	10/55 (18.2%)	7/35 (20%) (Sec Gen: 4; Gen: 3)	3/27 (15%) (Gen:3)
Cluster attacks (Sec Gen: 3; Gen: 6)	9 (16.4%)	3 (8.6%) (Sec gen: 2; Gen: 1)	6 (30%) (Sec Gen: 1; Gen:5)
Behavioural abnormalities	33(44%)	32 (66.7%)	1 (3.7%)
Mono/Hemi paresis	20 (26.7%)	12 (25%)	8 (29.6%)
Outcome at discharge Improved Dependent for ADL Dead	 27 (36%) 31 (41.3%) 3 (4%)	 15 (31.25%) 16 (33.3%) 1 (2.1%)	 12 (44.4%) 15 (55.5%) 2 (7.4%)
Specific CT abnormalities	22	10 (20.8%)	12 (44.4%)
Specific MRI abnormalities	36	31 (64.6%)	5 (18.5%)
EEG abnormalities Epileptiform PLEDs Slowing of background activity	44 26 10 32	36 (75%) 24 (50%) 10 (20.8%) 25 (52.1%)	8 (29.6%) 2 (7.4%) 0 7 (25.9%)
CSF mean cell count (cells/cu.mm) Protein (mg/dl) Serology	63.45 ±138.58 73.42 ±52.42 Positive 50/75	74.3±160.3 69.9±51.3 a) CSF HSV antibody (1:625): 17/48 (35.4%) b) CSF HSV PCR: 6/19 (31.6%)	20.4±61.5 68.1±51.1 CSF JE antibody (1:625) 27/27 (100%)
Follow up in patients with acute symptomatic seizure No follow up Less than 6 months 6 months or more	 32 07 16	 20 (41.7%) 5 (10.4%) 12 (25%)	 12 (44.4%) 2 (7.4%) 4 (14.8%)
Remote symptomatic seizures	8/23 (34.8%)	6 (35.3%)	2 (33.3%)

VE: Viral encephalitis; HSE: herpes simplex encephalitis; JE: Japanese encephalitis; GTCS: Generalized tonic clonic seizures; Sec gen: secondary generalized; Gen: Generalized; ADL: Activities of daily living; PLEDs: Periodic lateralized epileptiform discharges

Table 2: Imaging in herpes simplex encephalitis and Japanese encephalitis

Herpes simplex encephalitis	**CT (n=48)**	**MRI (n=42)**
Bilateral medial temporal	15 (31.2%)	25 (59.5%)
Unilateral medial temporal	10 (20.8%)	7 (16.6%)
Orbito-frontal	1 (2.1%)	9 (21.4%)
Diffuse edema	3 (6.3%)	-
Cingulate cortex	-	5 (11.9%)
Normal	20 (41.6%)	4 (9.5%)
Japanese encephalitis	**CT (n=27)**	**MRI (n=13)**
Unilateral thalamus	2 (7.4%)	4 (30.7%)
Bilateral thalamus	9 (33.3%)	2 (15.4%)
Brainstem	3 (11.1%)	2 (15.4%)
Cerebellum	1 (3.7%)	1 (7.7%)
Cortex	5 (18.5%)	-
Striatum	3 (11.1%)	1 (7.7%)
Diffuse edema	12 (44.4%)	1 (7.7%)
Normal	3 (11.1%)	2 (15.4%)

All patients underwent CT scan and 55 patients had undergone MRI of brain. The details are mentioned the Table 2. In patients with HSE (n=48), the CT scan was normal in 20/48 (26.6%) patients, while MRI was normal in only 4/42 patients (9.5%). In patients with JE (n=27), CT was normal in 3/27 (11.1%) and MRI was normal in 2/13 (15.4%) patients. (Figure 1 A-C)

Scalp EEG in 44 patients (89.8%) with HSE was abnormal in 36 (81.8%) and showed slowing of background activity in 25 patients and epileptiform discharges in 24 patients. Periodic lateralized epileptiform discharges (PLEDs) was evident in 10 patients (22.7%). EEG was carried out in 15 patients (55.5%) with JE and was abnormal in 8 patients (53.3%). The abnormalities included slowing of background activity in 7 (46.6%) and paroxysmal activity in 2 (13.3%) patients with JE.

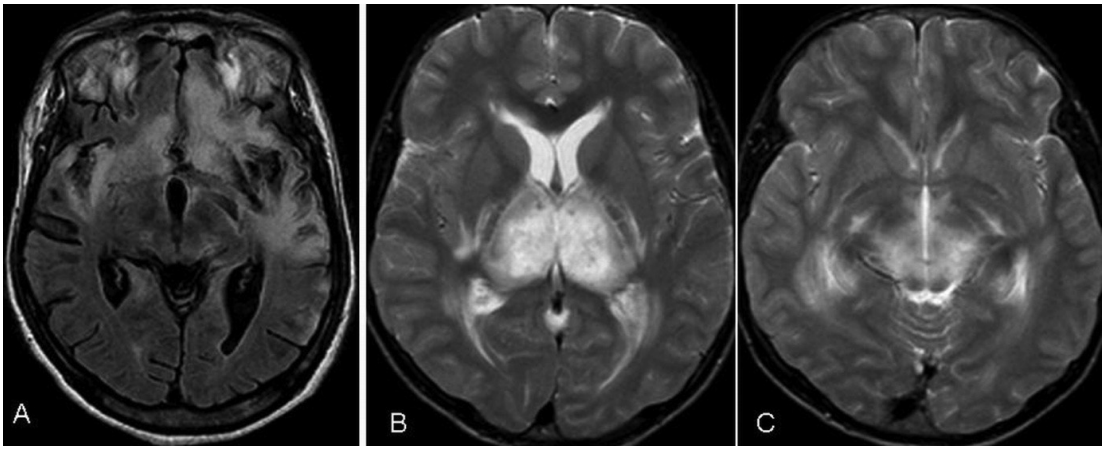

Figure 1A. MRI (axial FLAIR sequence) showing signal changes in the bilateral temporal and orbito-frontal lobes in a patient with herpes simplex encephalitis; Figure 1B,C. MRI (axial T2W image) revealing signal changes in bilateral thalami (B), upper midbrain (C) characteristic of Japanese encephalitis

Acute symptomatic seizures and acute viral encephalitis

A total of 55 patients (73.3%) with acute viral encephalitis had acute symptomatic (provoked) seizures during the acute phase of illness i.e. within 7 days of onset of illness. There were 35 patients (72.9%) with HSE and 20 patients (74.1%) with JE who had acute symptomatic seizures. The comparison between those with and without seizures is presented in Table 3 and none of the parameters were significantly different. On comparing JE with and without acute symptomatic seizures, statistical significant difference included: younger age (p=0.04); and lesser number making improvement without significant disability at discharge (p=0.001) in those with seizures subgroup [Table 3]. Similarly, on comparing HSE with and without acute symptomatic seizures, statistical significant difference included: imaging abnormality (p=0.001); higher CSF cell count (P=0.02) in those in the seizure subgroup [Table 3].

Those with symptomatic seizures were treated with phenytoin (n=50) and phenobarbitone (n=5). Fourteen patients required a second antiepileptic drug which was most frequently carbamazepine (n=11).

Unprovoked seizure in those with acute symptomatic seizures

Three patients with acute viral encephalitis died (with seizures: 2; without seizure: 1). At discharge from hospital, there was significant improvement without any disability in 15 (27.3%) and 12 (60%) patients with and without seizures. Thirty two patients with acute viral encephalitis with acute symptomatic seizures (58.2%) did not come for follow-up. Among the remaining 23 patients (mean follow up: 24±2; median: 24 months; range: 3 – 60 months): seizure free - 15; recurrence of seizures i.e. unprovoked seizures: 8 (HSE: 6; JE: 2) in 34.8%. They were monotherapy (n=5; phenytoin – 4; carbamazepine- 1) and polytherapy (n=3).

Table 3: Comparison of patients of acute viral encephalitis with and without seizures

	Herpes simplex encephalitis (n=48)			**Japanese encephalitis (n=27)**		
Variables	**Without seizures**	**With seizures**	**P**	**Without seizures**	**With seizures**	**P**
n	**13**	**35**		**7**	**20**	
Age (years)	41.8 ±16.4	33.6±15.98	0.14	15.6±4.3	9.8±6.7	**0.04**
Male Female	8 5	17 18	0.52	4 3	11 9	0.33
Altered sensorium	10	33	0.12	7	19	1.00
Behavioral symptoms	9	23	1.0	0	1	1.00
Hemiparesis	5	7	0.26	2	6	1.00
Any imaging abnormality	1	33	**<0.001**	7	19	1.00
EEG abnormality	9	27	0.71	3	5	0.63
PLEDs	1	9	0.25	0	0	NA
Mean CSF cell (cu.mm)	19±21.6	116.4±204.8	**0.02**	59±118.2	32±38.6	0.60
Mean CSF protein (mg/dl)	89.5±71.4	66.4±45.9	0.22	85.3±30.95	69.4±58.95	0.54
Improved without significant disability at discharge	5	10	0.51	7	5	**<0.001**
Dead	1	1	0.47	0	1	1.00
Unprovoked seizure	0	6	0.17	0	2	1.00

PLEDs: Periodic lateralized epileptiform discharges; *P<0.05= statistically significant

DISCUSSION

The clinical feature of patients with infective encephalitis is one of alteration in sensorium with fever. Focal deficits are highly suggestive of focal encephalitis like HSE.[6] During the acute phase of JE, patients frequently present with seizures and behavioral abnormalities. The classic description of JE includes mask-like facies and other features of parkinsonism.[9] These features are more often observed during the convalescent stage of the illness rather than during the initial presentation[15] In this cohort of JE, the duration of hospital stay was short, though seizures and alteration in sensorium were common at presentation, manifestations due to basal ganglionic involvement were less often noted. As high as 92.5% with JE in this study had an abnormal brain imaging viz; thalamic involvement - 41% (bilateral-10 and unilateral-2); basal ganglionic signal changes - 11%; midbrain - 15%; and cerebellum - 7%. These have been reported previously.[5,10,16,17] One fourth of the patients with HSE in this study had CT scan abnormalities in medial temporal structures, orbito-frontal lobes and cingulate cortices; while these were observed in 74% on MRI scan.

Acute symptomatic seizures were detected in almost three quarter of patients with acute encephalitis, and in 65% of the patients with HSE in this study. The frequency of acute symptomatic seizures in acute herpes encephalitis has been reported from 40-60% of the cases.[5,10] The prevalence of 65% in our patients was thus at the high end of the range reported. There are conflicting reports regarding the effect of seizures in the long-term outcome in HSE.[18] In a study by Hsieh *et al*, those with acute seizures were associated with a poor outcome in children.[19] In the present study of 48 patients with HSE, seizures were associated with higher rate of imaging abnormality and greater CSF pleocytosis, suggesting a more severe encephalitis infection, but seizures were not associated with a worse neurological outcome.

Acute symptomatic seizures were noted in 74.1% with JE in this study. The reported seizure frequency in JE mainly from south-east Asia was 7-84.7%.[5,10,20-22] The prevalence of seizures in our study was high but in the range of the previous studies. We have found the associations of seizures with worse neurology outcome in our patients. Solomon *et al*[9] had also observed the association between seizures and poor outcome in their Vietnamese patients with JE. They have further observed that patients with seizures were more likely to have raised CSF opening pressure, and to develop brainstem signs compatible with herniation syndrome; suggesting that in JE, seizures and raised intracranial pressure may be important cause of death. In this study, the CSF pressure was not measured.

Annegers *et al* evaluating the long-term recurrence of seizures in patients with acute CNS infection reported a risk of 6.8% of developing remote symptomatic seizures after 20 years.[23] The twenty-year risk of developing seizure recurrence after viral encephalitis in those with early seizures was 22% and in those without early seizures was 10%. In another study of JE (n=55), remote symptomatic seizures was noted in 18.2% when followed up for a period of 12-18 months.[16] Kim *et al* followed patients with acute symptomatic seizures following CNS infection for >18 months, and found that 41% had uncontrolled remote epilepsy.[24] The only significant variable in their cohort predicting anti-epileptic drug resistance was status epilepticus during the acute infection. Chang *et al* in their study on seizures and acute bacterial meningitis in children, reported the risk factors for development of unprovoked seizures. They recommended administration of AEDs for a longer period, if children had (1) focal neurological deficits or developmental abnormalities; (2) abnormal neuro-imaging during the acute phase of their illness; (3) prolonged duration of seizures before they are controlled; (4) high frequency of seizures before control; (5) consistently abnormal EEG; and (6) focal onset of seizures.[25] In this cohort, among patients with acute viral encephalitis and new onset symptomatic seizures, 34.8% of patients developed unprovoked seizures after median follow up of 2 years. However, close to two thirds of our patients did not come back for follow up.

The strengths of this study are that only patients with definite viral encephalitis were included and every patient had a brain imaging. Some of the major limitations are retrospective study, small sample size, poor measurement of altered sensorium, outcome and inadequate follow-up. The possible reasons of poor follow up could be availability of health care at other centres such as by the primary care and family physicians, lack of finance resources, do not expect further recovery from our care, complete recovery or unreported death in a few.

In conclusion, new onset acute symptomatic seizures were common in our patients with acute HSE and JE. Some of the risk factors of seizures in HSE were imaging abnormalities and higher CSF cell count. In patients of JE, younger age had

higher risk of having seizures and seizures were associated with poorer neurological outcome. A significant proportion of the patients with acute viral encephalitis and acute symptomatic seizures developed unprovoked seizure in follow up.

DISCLOSURE

Conflict of interest: None

Financial support in the form of grants or others: None

REFERENCES

1. Hesdorffer DC, Logroscino G, Cascino G, Annegers JF, Hauser WA. Risk of unprovoked seizure after acute symptomatic seizure: effect of status epilepticus. *Ann Neurol* 1998; 44:908-12.
2. Berg AT, Shinnar S. The risk of seizure recurrence following a first unprovoked seizure: a quantitative review. *Neurology* 1991; 41:965-72.
3. Singh G, Prabhakar S. The association between central nervous system (CNS) infections and epilepsy: epidemiological approaches and microbiological and epileptological perspectives. *Epilepsia* 49 2008; (Suppl 6):2-7.
4. Tyler KL. Update on herpes simplex encephalitis. *Rev Neurol Dis* 2004a; 1:169-178.
5. Misra UK, Tan CT, Kalita J. Viral encephalitis and epilepsy. *Epilepsia* 2008; 49 Suppl 6: 13-8.
6. Tyler KL. Herpes simplex virus infections of the central nervous system: encephalitis and meningitis, including Mollaret's. *Herpes* 2004b; 11(Suppl 2):57-64.
7. Solomon T. Recent advances in Japanese encephalitis. *J Neurovirol* 2003; 9:274-83.
8. 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.
9. Solomon T, Dung NM, Kneen R, *et al*. Seizures and raised intracranial pressure in Vietnamese patients with Japanese encephalitis. *Brain* 2002;125(Pt 5):1084-93.
10. Misra UK, Kalita J. Seizures in Japanese encephalitis. *J Neurol Sci 2001;* 190:57-60.
11. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia* 1989; 30:389-99.
12. Beghi E, Carpio A, Forsgren L, *et al*. Recommendation for a definition of acute symptomatic seizure. *Epilepsia*; 2010; 51(4):671-5.
13. Berg AT, Berkovic SF, Brodie MJ, *et al*. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. *Epilepsia* 2010;51(4):676-85.
14. Haut S, Katz M, Masur J, Lipton R. Seizures in the elderly: Impact on mental status, mood, and sleep. *Epilepsy Behav* 2009; 14(3):540-4.
15. Kumar R, Tripathi P, Singh S, Bannerji G. Clinical features in children hospitalized during the 2005 epidemic of Japanese encephalitis in Uttar Pradesh, India. *Clin Infect Dis* 2006; 43:123-31.
16. Kalita J, Misra UK, Pandey S, Dhole TN. A comparison of clinical and radiological findings in adults and children with Japanese encephalitis. *Arch Neurol* 2003; 60:1760-4.
17. Kalita J, Misra UK. Comparison of CT scan and MRI findings in the diagnosis of Japanese encephalitis. 2000; *J Neurol Sci* 174:3-8.
18. McGrath N, Anderson NE, Croxson MC, Powell KF. Herpes simplex encephalitis treated with acyclovir: diagnosis and long term outcome. *J Neurol Neurosurg Psychiatry* 1997; 63: 321-6.
19. Hsieh WB, Chiu NC, Hu KC, Ho CS, Huang FY. Outcome of herpes simplex encephalitis in children. *J Microbiol Immunol Infect* 2007; 40:34-8.
20. Poneprasert B. Japanese encephalitis in children in northern Thailand. *Southeast Asian J Trop Med Public Health* 1989; 20(4):599-603.
21. Barzaga NG. A review of Japanese encephalitis cases in the Philippines (1972-1985). *Southeast Asian J Trop Med Public Health* 1989;20(4):587-92.
22. Kumar R, Mathur A, Kumar A, Sharma S, Chakraborty S, Chaturvedi UC. Clinical features & prognostic indicators of Japanese encephalitis in children in Lucknow (India). *Indian J Med Res* 1990; 91:321-7.
23. Annegers JF, Hauser WA, Beghi E, Nicolosi A, Kurland LT. The risk of unprovoked seizures after encephalitis and meningitis. *Neurology* 1988; 38:1407-10.
24. Kim MA, Park KM, Kim SE, Oh MK. Acute symptomatic seizures in CNS infection. *Eur J Neurol* 2008; 15:38-41.
25. Chang CJ, Chang HW, Chang WN, *et al*. Seizures complicating infantile and childhood bacterial meningitis. *Pediatr Neurol* 2004; 31:165-71.