

Seizures in patients with systemic lupus erythematosus

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Abstract

This was a study on 58 neuropsychiatric systemic lupus erythematosus (SLE) patients with epileptic seizures treated in University of Malaya Medical Centre, Kuala Lumpur from 1975 to 1994. The aim of this study was to better characterize seizures in SLE so as to formulate policy on management. Over the same period of time, there were 7 other SLE patients with seizures from secondary causes such as metabolic disturbances and central nervous system (CNS) infections. Thus, seizures in SLE is more frequently due to neurological involvement of the disease itself (ratio = 8.3:1). In 93% of patients, the seizures occurred in the setting of active SLE. Following the convulsion, 69% of the patients took more than 24 hours to regain full consciousness. Non-convulsive status may be an important cause as 4 out of 6 EEGs done when the patients were still stuporous was supportive of the diagnosis. 29.3% of patients developed neuropsychiatric manifestations during or immediately following the seizures. Status epilepticus was common (21%). The mortality in patients with status epilepticus was 25%. Seizures may have a deleterious effect on the brain with active lupus, and contribute to the high morbidity and mortality. Thus, seizures in neuropsychiatric SLE should be treated urgently and aggressively. After a mean follow-up of 3.6 years, two-thirds of the patients who survived the acute illness were seizure-free by 2 months. Most remained seizure-free when anticonvulsants were withdrawn. A third continued to have recurrent seizure requiring long-term anticonvulsant therapy. Therefore, long-term maintenance anticonvulsants are not indicated in the majority of patients.

Key words: seizures, SLE, neuropsychiatric lupus.

INTRODUCTION

Nervous system involvement has been reported in 10 to 75% of patients with systemic lupus erythematosus (SLE) and is reportedly common in the terminal, uncontrolled stages of the disease.¹ Seizures are one of the most common neurological manifestations of SLE and are reported to affect 15 to 35% of SLE patients.² Despite this there have not been studies focusing on seizures alone. We sought to characterize seizures occurring in patients with lupus in terms of the underlying pathogenic mechanisms, seizure type, EEG, laboratory investigations, neuroimaging and clinical outcome.

MATERIALS AND METHODS

Patients with SLE and seizures treated in University of Malaya Medical Centre, Kuala Lumpur from 1975 to 1994 were identified and enrolled in the study. The demographic characteristics, history and progression of the SLE disease, clinical descriptions of seizures and its course, associated neuropsychiatric manifestations, laboratory findings, treatment

and final outcome of these patients were noted. In 50% of the cases, the data were entirely based on the hospital case records. In the other 50%, the author (LGH) was either able to study the patients prospectively, or the findings in case records confirmed and supplemented by interviews.

The diagnosis of SLE was based on the diagnostic criteria defined by the American Rheumatology Association in 1982.³ The diagnosis of seizures was primarily clinical and seizures were defined as being due to neuropsychiatric lupus after exclusion of secondary causes such as azotemia, hypertensive encephalopathy, electrolyte imbalance and CNS infections.

The activity of SLE disease at the time of seizure was assessed by using the Lupus Activity Criteria Count (LACC) proposed by Urowitz et al in 1984.⁴ All patients studied prospectively underwent cerebrospinal fluid (CSF), electroencephalography (EEG) and computed tomography (CT) brain scan examinations. Statistical analyses were carried out using Fisher's Exact test. P values of < 0.05 were

taken as being significant.

RESULTS

A total of 65 SLE patients seen from 1975 to December 1994 were found to have epileptic seizures. 58 patients (89.2%) had no secondary cause for their seizures and were deemed to have seizures due to neuropsychiatric lupus. Seven (10.8%) patients had an underlying secondary cause of seizures i.e. cryptococcal meningitis, azotemia, intracranial haemorrhage, thrombotic thrombocytopenic purpura and preexisting epilepsy. The ratio of neuropsychiatric lupus seizures to secondary seizures was 8.3 : 1. Only data of patients with seizures due to neuropsychiatric seizures were further analysed.

The majority of the study subjects were Chinese (79.3%). There were 56 females and 2 males giving a female to male ratio of 28 : 1. Their ages ranged from 10 to 56 years with a mean of 28.4 years.

The age of the first seizure ranged from 10 to 54 years with a mean of 28.2 years. The time interval from diagnosis of SLE to seizure onset ranged from 0 (presenting symptom) to 15 years (mean 2.7 years). 24.1% of patients presented with seizures. By one year, 58.6% had developed seizures and by 10 years, 93.1% had developed seizures. All patients were followed up for at least one year after the onset of seizures. The mean duration of follow up was 3.6 years.

By the Lupus Activity Criteria Count (LACC), SLE was assessed to be active in 92.8% of patients at the time of seizure onset.

Seizure characteristics

All patients had generalized seizures - 57 patients had generalized tonic-clonic seizures (GTCS) and one patient had generalized tonic seizure. Two patients had in addition, simple partial and complex partial seizures. The convulsive phase of the seizure usually lasted less than 10 minutes.

However, following the ictus, the majority of the patients took a long time to regain full consciousness. Fourteen patients (24.1%) were fully conscious within one hour and four (6.9%) took a few hours to recover whereas 40 patients (68.9%) took >24 hours to regain full consciousness. Twelve patients (20.7%) progressed to status epilepticus. When the patients whose data was entirely based on case notes and those seen prospectively or personally interviewed by the author were analysed separately, the findings remain the same. Following the ictus, 79% in the first group and 62% of the second group took >24 hour to regain full consciousness.

The frequency and course of seizures in patients who survived the acute illness is summarized in table 1. Two-thirds of the patients stopped having seizures after two months post-onset, most of them remaining seizure-free without anticonvulsant therapy. A third of the patients continued to have seizures requiring long-term anticonvulsant therapy. Of the 12 patients who had status epilepticus, three (25%) died within two weeks of the acute illness, while five patients (41.7%) had recurrent seizures on follow-up indicating a poorer prognosis for this group. Four (33.3%) remained seizure-free after recovering from their status epilepticus.

Associated neuropsychiatric manifestations

34 patients (58.6%) had other neuropsychiatric manifestations. In 9 patients (15.5%), it occurred before the onset of seizures. The manifestations were: psychosis (4), altered mentation (4), hemiparesis (1). In 17 patients (29.3%), it occurred during or immediately following the seizures. The manifestations were psychosis (6), hemiparesis (6), psychosis and hemiparesis (3), altered mentation (2). In 8 patients (13.8%), following the seizures, there was a short latency period before the neuropsychiatric manifestations. The manifestations were myelopathy (3), psychosis (2), hemiparesis (2),

TABLE 1: Frequency and course of seizures

<i>Pattern</i>	<i>No. of patients (%) (n = 43)</i>
1 to 3 seizures within 2/52	14 (32.6)
Multiple seizures within 2/7	5 (11.6)
Status epilepticus	9 (20.9)
Seizures occurring for up to 2/12	6 (14.0)
Seizures occurring for years	14 (32.6)

altered mentation (1). All but three patients recovered fully from these neuropsychiatric manifestations; one patient remained hemiparetic, one continued to have psychosis and one patient had both residual hemiparesis and psychosis.

Laboratory investigations

Cerebrospinal fluid (CSF) examination: There was no uniform policy as to the indications for CSF examination. The CSF were done to exclude central nervous system infection and as a confirmatory test for neuropsychiatric lupus. A total of 27 patients had CSF examination carried out and in 16 (59.3%), the CSF was found to be abnormal. Ten (37.1%) showed increased CSF protein levels without other abnormalities (range from 55 to 285 mg/dL); four (14.8%) showed both raised CSF protein and white cell count and two (7.4%) had increased white cell count alone. On the whole, the white cell count was mildly increased only (10 to 55 WBC/ul) and the differential count showed a mixture of both polymorphonuclear leucocytes and lymphocytes with neither cell-type being more predominant.

Electroencephalography (EEG): 33 of the 36 EEG (91.7%) done were abnormal. Table 2 is a summary of the EEG abnormalities found. The frequency and type of abnormality also depended on the timing of EEG in relation to the clinical seizures. Twelve EEGs were carried out within 24 hours of the last seizure, 12 within a week and another 12 more than a week from the last episode of seizure. All 12 EEGs done within 24 hours from the last seizure showed generalized abnormalities. Those done less than one week from the last seizure were abnormal in all but one (91.7%); nine showed generalized abnormalities and two showed focal abnormalities. Ten of the 12 EEGs (83.3%)

done more than one week after the last seizure episode were abnormal, with four showing generalized abnormalities and 6 showing focal abnormalities. EEGs carried out soon after seizures showed a higher frequency of abnormalities with most showing generalized slowing with or without spikes. When the EEG was delayed, the rate of abnormal EEG was lower, with the abnormality mainly focal. EEG was carried out in 6 patients during the prolonged stuporous state post-ictus. In 4 of the EEGs, the changes were supportive of non-convulsive status. In all the 4, the discharges involved temporal and sometimes other areas, it was bilateral in two patients and unilateral in the other two.

C.T. brain scan: C.T. brain scans were done in 24 patients and in 17 (70.8%) they were abnormal. Eight scans showed cerebral atrophy alone, four showed cerebral atrophy and hypodense areas, three showed hypodense lesions alone and two showed cerebral oedema. All patients with status epilepticus who had CT brain scans done had abnormal findings of either cerebral atrophy or infarction or both. However, this was not significant statistically ($p=0.327$).

Treatment

Forty eight patients were treated with anticonvulsants. Of these, nine patients died within 2 months. Twenty-two patients received anticonvulsant for variable periods, the mean duration was 9.8 months. Seventeen were still receiving anticonvulsants at the time of study. All 58 patients were treated with high dose corticosteroids in the form of oral prednisolone 1mg/kg, intravenous hydrocortisone 100mg 6 hourly or intravenous methylprednisolone 1 gram daily for 3 days followed by high dose oral prednisolone.

TABLE 2: EEG abnormalities

<i>EEG abnormality</i>	<i>No. of patients(%) (n = 36)</i>
Gen. slow waves alone	14 (42.4)
Gen. slow waves & spikes	7 (21.2)
Gen. slow waves & focal spikes	4 (12.1)
Focal spikes alone	4 (12.1)
Focal slow waves & spikes	3 (9.0)
Focal slow waves alone	1 (3.0)
Total	33 (91.7)

Mortality

15 patients (25.9%) died within 2 months of seizure-onset. The causes of death were sepsis (53%), renal failure and pulmonary embolism. Status epilepticus was the cause of death in two patients. There was no significant relationship between mortality and age of patient ($p=0.63$) or activity of the SLE ($p=0.395$). The patients were divided into two broad groups, above and below the age of 30 for the Fisher exact test.

DISCUSSION

Seizure is one of the most common neuropsychiatric manifestations of SLE, secondary only to organic brain syndrome and psychiatric disorders. Seizures affects 6 to 26 % of all SLE patients and 10 to 58% of all patients with neuropsychiatric lupus.² The relative importance of primary neuropsychiatric lupus and secondary disorders such as metabolic disturbances and central nervous system infection as the cause of seizures in SLE patients has been uncertain. It has been reported previously that in the majority of cases, seizures were NOT due to primary neuropsychiatric disease.⁵ In the present study however, seizures in 89.2% of the patients were found to be due to primary neuropsychiatric lupus. This is probably partly attributable to different patient populations. On the other hand, the finding that seizures from neuropsychiatric lupus usually occur at the time of active SLE disease is consistent with previous reports.⁶

Seizures may occur at any time during the course of SLE.⁷ De novo presentation with other neurological symptoms was said to be rare.⁸ The present series showed however that it may not uncommonly be the presenting symptom, occurring in 24% of our patients.

Ropes stated that seizure episodes were usually limited although status epilepticus could occur frequently, signaling a preterminal event⁹. In this study, status epilepticus occurred in 20.6%. Three of the 12 patients (25%) who had status epilepticus died within two weeks. In two of the patients, status epilepticus was the cause of death. A large proportion (68.9%) took more than one day to regain full consciousness. Prolonged clouding of consciousness may be due to non-convulsive status. 29.3% of the patients also developed various neuropsychiatric manifestations during or immediately following the seizures. The high prevalence of status epilepticus, with its associated high mortality and the high frequency of other concurrent

neuropsychiatric manifestations may be a reflection of the severity of the cerebral pathology in lupus. On the other hand, seizures itself may have a particularly deleterious effect on the brain with active lupus disease as evidenced by the delay in regaining consciousness post-seizure, the high mortality from status epilepticus and the large number of patients whose neuropsychiatric manifestations occurred during or immediately following the seizures. This may be analogous to cerebrovascular disease, where early seizures have been identified as a risk factor for in-hospital mortality.¹⁰ In a study using positron emission tomography, postapoplectic seizures were associated with more severe brain ischaemia.¹¹

The CSF findings in this study is similar to previous studies which showed that CSF was abnormal in only about 50% of patients with neuropsychiatric lupus.¹² Although the abnormalities are often non-specific, its examination is important to exclude secondary CNS infection. When this possibility is excluded, abnormal CSF is supportive of neuropsychiatric lupus.

EEG abnormalities were found in 54 to 84% of patients with neuropsychiatric lupus.^{2,7} It has been said that the EEG correlates poorly with clinical manifestations and abnormal EEGs may often be seen in patients without CNS manifestations.¹³ Matsukawa et al performed EEGs in 120 SLE patients and found that the frequency of abnormal findings in patients with and without neuropsychiatric lupus was almost the same (88.2% versus 80.0% respectively), although patients with neuropsychiatric lupus had more severe EEG changes.¹⁴ Abnormalities include diffuse theta and delta waves, paroxysmal spike and wave complexes and focal discharges. In another study by Gibson et al, the EEG abnormalities were generalized in 57% of cases and lateralized or focal in 43%.¹⁵ The EEG was abnormal in 91.7% of patients in this study. The timing of the EEG post-seizure appeared to influence the frequency as well as type of abnormalities. All the EEGs done within 24 hours of seizures were abnormal compared to 91.7% and 83.3% of EEGs done within the first week and more than one week respectively. Diffuse EEG changes were more common in EEGs done soon after seizures whereas focal abnormalities were more common in EEGs done later. The abnormal EEG is likely to be due to the underlying lupus pathology, and post-ictal changes. The 6 EEGs done while the patients had prolonged stupor post-ictus, with 4 EEGs

showing changes of non-convulsive status, suggests that non-convulsive status epilepticus may be an important cause for the delay in regaining consciousness following seizures in patients with active neuropsychiatric lupus. This issue should be addressed further in a prospective study.

Brain atrophy, frequently perisulcal, has been reported in 27-71% of CT scan of patients with neuropsychiatric lupus.² Other than cerebral lupus, corticosteroid therapy has been known to cause reversible cerebral atrophy.^{16,17} 50% of CT brain scans of lupus patients with seizures in this study showed cerebral atrophy.

There has been no universal agreement on the treatment of neuropsychiatric lupus with seizures. Most authors recommend that anticonvulsant therapy should be used with steroids in moderate to severe diffuse neuropsychiatric lupus with seizures and anticonvulsants alone without steroids when the neuropsychiatric manifestations are mild.^{2,18} The possibility that seizures in SLE may be able to aggravate cerebral pathology as discussed above suggests seizures should be treated urgently. Loading doses of anticonvulsants e.g. intravenous phenytoin should be given to rapidly achieve therapeutic levels, after which maintenance doses of the medication should be continued and close monitoring the therapeutic response carried out. In view of the possible common occurrence of non-convulsive status causing prolonged stupor, close EEG monitoring should be done particularly for those who has delay in recovering full consciousness. On the other hand, long-term anticonvulsant therapy is probably not necessary in the majority of patients as two-thirds of our patients were seizure-free by two months and most remained seizure free even without anticonvulsants. About a third of our patients, however, did require long-term anticonvulsant therapy to control seizure-recurrence.

Massive doses of corticosteroids was advocated for treatment of neuropsychiatric lupus by Dubois as early as 1974.¹³ Thus far, there have been no controlled clinical trials proving the value of corticosteroids or cytotoxics in the acute treatment of neuropsychiatric lupus. Therefore, treatment remains empirical. Gibson reported that there was no difference in the rate of improvement within three weeks with low, intermediate or high dose of corticosteroids.¹⁵ Nevertheless, most authors still recommend high dose steroids for severe diffuse neuropsychiatric lupus.^{2,18} Apart from corticosteroids, pulsed

cyclophosphamide has been reported to be beneficial in the treatment of diffuse CNS lupus but this has been usually with concomitant high dose of corticosteroids.^{19,20} Azathioprine and cyclosporin A were reported to be ineffective.⁶ Short-term plasmapheresis may be a useful adjunct in managing life-threatening complications of fulminant neuropsychiatric lupus either alone or with corticosteroids and cytotoxic agents.⁶

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