Original Article

Neuropsychiatric events attributed to systemic lupus erythematosus: a single center study from Pakistan

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Objective: Neuropsychiatric systemic lupus erythematosus (NPSLE) is a relatively common and potentially serious manifestation of SLE. This study was designed to collect evidence about clinical and demographic characteristics of patients with NPSLE in a Pakistani lupus cohort.

Methodology: This cross-sectional study was conducted at Department of Rheumatology, Pakistan Institute of Medical Sciences, Islamabad, Pakistan between July 2016 and December 2016. Patients fulfilling diagnostic criteria for SLE as defined by ACR were enrolled. For detection of neuropsychiatric involvement the One-Hour Neuropsychological Battery proposed by the ACR was performed. Neuropsychiatric manifestations were classified into major and minor. Relationship of presence and severity of individual neuropsychiatric manifestations to disease duration in years and organ damage using SLICC/ACR-DI was studied.

Results: Out of 100 SLE patients, there were 96 females and 4 males (female to male ratio of 24:1). Mean age of all participants was 30.99 years (range 17-72 years) and average disease duration at the time of enrolment was 3.89 years. Neuropsychiatric manifestations were observed in 84 patients. 20 out of these 84 patients (23.8%) had major neurological manifestations including seizures (13 patients), altered consciousness (10 patients) and cerebro-vascular accident (5 patients). While 7 out of these 84 patients (8.3%) had major psychiatric manifestations including psychosis (5 patients) and depression with suicidal ideation (2 patients). All major neurological manifestations occurred beyond and major psychiatric manifestations occurred within 2 years of diagnosis of SLE. Minor psychiatric manifestations observed included severe anxiety (52 patients), cognitive impairment (43 patients) and mood disorder (25 patients). No statistically significant difference in mean SLICC/ACR-DI score was observed between NPSLE patients and non-NPSLE patients when points received for neurologically related damage were excluded (P=0.10). Neuropsychiatric damage was the most common damage category, followed by renal (25%), pulmonary hypertension (6%), pericarditis (5%), digit loss (4%), venous thrombosis (4%) avascular necrosis (3%), osteomyelitis (2%), muscle weakness (2%) and deforming arthritis (1%).

Conclusions: NPSLE manifestations were seen in 84% of patients, with major neuropsychiatric manifestations in 27% of patients. Headache, seizures and cerebrovascular disease were the most frequent neurological manifestations, while cognitive disorder and severe anxiety being the most common psychiatric manifestations. (Rawal Med J 201;42:306-311)

Keywords: Neuropsychiatric systemic lupus erythematosus, systemic lupus erythematosus, lupus nephritis, lupus cerebritis.

INTRODUCTION

Systemic lupus erythematosus (SLE) is the prototypic autoimmune disease of unknown etiology, characterized by multi-system involvement and production of auto-antibodies.[1] The disease follows a relapsing and remitting course with highly variable clinical features in individual patients ranging from skin and joint involvement to organ threatening and life threatening disease.[2] It usually affects women of reproductive age group, with estimated prevalence of 100 per 100,000 women.[3] Neuropsychiatric systemic lupus erythematosus (NPSLE) is a potentially serious manifestation of SLE characterized by involvement of any aspect of the central or peripheral nervous system, as well as psychiatric disorders.[4] In 1999, the American College of Rheumatology (ACR) categorized these neuropsychiatric manifestations

of SLE into 19 distinct syndromes[5] (Table 1).

The pathogenic mechanisms underlying these manifestations are variable, including small vessel vasculopathy, thrombosis of arteries and veins, atherosclerotic disease, demyelination, or intrathecal production of proinflammatory cytokines.[6] Central nervous system events occur more frequently than peripheral nervous system events.[4] There are several types of histopathologic changes including small vessel vasculopathy, multifocal infarctions, hemorrhage, cortical atrophy and demyelinating lesions; true vasculitis is rare.[7] The diagnosis of NPSLE is mainly clinical,[8] supported when necessary by autoantibody profiles, diagnostic imaging and electrophysiologic studies. Involvement of nervous system is a predictor of poor prognosis with high frequency of flares, longstanding functional impairment and high mortality rate.[9]

The prevalence of NPSLE ranges between 9.5% and 95%.[10] This difference in prevalence is due to difference in frequency and clinical manifestations of the disease among populations of different geographic and ethnic origin.[11] This variability might be attributed to absence of standardized case definitions in assessment of NPSLE. Even by using the ACR case definitions, the prevalence of NPSLE in different regions is estimated to vary from 3795%.[9-11] There is limited data available about prevalence and manifestations of NPSLE in Pakistan. The aim of this study was to collect evidence about clinical and demographic characteristics of patients with NPSLE in a Pakistani lupus cohort.

METHODOLOGY

This prospective, cross-sectional study was undertaken at Department of Rheumatology, Pakistan Institute of Medical Sciences, Islamabad, Pakistan after approval of the study design by hospital Ethics Review Board. After taking written informed consent, all patients (above 16 year of age), fulfilling the diagnostic criteria for SLE as defined by the ACR[5] that presented to the Lupus clinic between July 2016 and Dec 2016 were included in the study. Exclusion criteria included other coexistent connective tissue diseases (e.g. rheumatoid arthritis, systemic sclerosis, polymyositis or Sjögren's syndrome), treatment side effects (e.g., intracranial hemorrhage due to anticoagulation therapy), dysfunction of other internal organs, intracranial infection, other CNS syndromes (e.g. hypertensive encephalopathy) and magnetic resonance imaging (MRI) findings not suggestive of NPSLE.

All patients were assessed by the rheumatologist by taking standard medical history and physical examination. For definition of individual NPSLE items ACR case definitions[5] (Table 1) were used while major and minor neurological and psychiatric symptoms were defined according to classi?cation criteria developed by How et al.[12] For detection of neuropsychiatric involvement the One-Hour Neuropsychological Battery proposed by the ACR was performed.[13] Subsequent investigations were performed and consultations from neurologist and psychiatrist were sought only if clinically warranted.

Recorded data included demographic features (such as age, gender, date of visit), clinical data (age, presenting features, ACR diagnostic criteria and autoantibody profile at time of diagnosis, duration of SLE and treatment taken since diagnosis including glucocorticoids and cytostatic drugs, disease activity and neurological and psychiatric manifestations as well as involvement of other systems) and relevant laboratory investigations (including antiphospholipid antibodies, CSF RE, EEG and brain imaging if performed). Organ damage was determined according to the SLICC/ACR?DI.[14]

Descriptive statistics and logistic regression analysis were performed for statistical assessment. Relationship of presence and severity of individual neuropsychiatric manifestations to disease duration in years and organ damage using SLICC/ACR-DI was studied by logistic regression. ODDS ratio and 95% confidence interval were used to present the strength of association. Level of significance was taken as <0.05. All data were analyzed using SPSS version 18.

RESULTS

Demographic characteristics: Of 100 patients, 96

were female (96%) and 4 (4%) were male with a female to male ratio of 24:1. Mean age of all participants was 30.99 years (range of 1772 years). Average duration of disease at the time of enrollment in study was 3.89 years.

Prevalence of neuropsychiatric systemic lupus erythematosus manifestations: Neuropsychiatric manifestations were observed in 84 (84%) patients. Major neurological manifestations occurred in 20 out of these 84 patients (23.8%). The most common major neurological manifestations observed included seizures, altered consciousness and cerebro-vascular accident. Most common minor neurological manifestation was headache, which was observed in 34(40.47%) patients. Among patients with headache and paresthesias, without any objective finding (Table 2). In 52.9% cases (18 out of 34 patients) these minor neurological manifestations occurred within 1 year of diagnosis of SLE.

Major psychiatric manifestations were observed in 7 out of these 84 patients (8.3%). These included psychosis and depression with suicidal ideation. All major psychiatric manifestations occurred within 2 years of diagnosis of SLE. Minor psychiatric manifestations were observed in 61 out of these 84 patients (72.6%). These included severe anxiety, cognitive impairment and mood disorders (Table 2). In 42.6% cases (26 out of 61 patients) these minor psychiatric manifestations occurred within 1 year of diagnosis of SLE.

Table 1. American College of Rheumatology classification of neuropsychiatric manifestations of SLE.

Central Nervous System	Peripheral Nervous System
Aseptic meningitis	Guillain-Barre syndrome
Cerebrovascular disease	Autonomic disorder
Demyelinating syndrome	Mononeuropathy, single/multiplex
Headache	Myasthenia gravis
Movement disorder	Cranial neuropathy
Myelopathy	Plexopathy
Seizure	Polyneuropathy
Acute confusional state	
Anxiety disorder	
Cognitive dysfunction	
Mood disorder	
Psychosis	

Table 2. Prevalence of Neuropsychiatric Manifestations (n=100).

Clinical manifestations	Number of Patients
Major neurological	
Seizures	13
General disturbances/altered consciousness	10
Cerebrovascular accident	5
Transverse myetilis	1
Acute disseminated encephalomyelitis	1
Aseptic meningitis	1
Mononeuritis multiplex	1
Cranial neuropathy	1
Polyneuropathy	1
Minor neurological	
Headache	34
Paresthesias (no Objective finding)	19
Major psychiatric	
Psychosis	5
Depression with suicidal ideation	2
Minor psychiatric	
Anxiety	52
Cognitive impairment	43
Mood disorder	25

Anti-phospholipid antibodies: Among the total 100 patients, work up for APLAS was done in 10 patients (5 patients positive for lupus anti-coagulant, 3 patients positive for anti-cardiolipin antibody and 2 patients were triple positive). Seizures were observed in 40% (4 out of 10) patients with secondary antiphospholipid syndrome. Half of these patients (5 out of 10) had headache and minor psychiatric manifestations while 1 patient had no neuropsychiatric manifestation.

Organ damage: The mean SLICC/ACR-DI score for the NPSLE patients was 2.1 compared with 0.7 for the non-NPSLE patients (P<0.001). However, when SLICC/ACR-DI points received for neurologically related damage were excluded, there was no signi?cant difference between the two groups (P=0.10). Neuropsychiatric damage was the most common damage category, followed by renal (25%), pulmonary hypertension (6%), pericarditis (5%), digit loss (4%), venous thrombosis (4%) avascular necrosis (3%), osteomyelitis (2%), muscle weakness (2%) and deforming arthritis (1%).

Mortality: During the study, 1 male who presented

with generalized tonic clonic seizures and right sided hemiparesis (infarcts in left thalamic and left central semiovale region on initial MRI) died after 5 days of presentation. Cause of death was suspected bleed (had aneurysm involving junction of M1/M2 segment of left middle cerebral artery).

DISCUSSION

This study was designed to collect evidence about clinical and demographic characteristics of patients with NPSLE in Pakistani population. The prevalence of NPSLE manifestations in our study was 84%, with major neurological and psychiatric manifestations observed in 27% of lupus patients. Previous studies reported wide variation in prevalence of NPSLE.[9] The main reasons behind this variation are different diagnostic criteria used to classify NPSLE as well as geographic and ethnic variation among different populations.[9]-11 In previous studies from neighboring countries, neuropsychiatric manifestations were observed in 11.3% of Iranian, 35.82% of Chinese and 78% of Indian lupus patients.[15-17] The data from large lupus cohorts worldwide suggest prevalence rates of approximately 30-40% for NPSLE.[11]

In our study, headache, seizures and CVD were the most frequent neurological manifestations. Prevalence of these headache types in SLE patients is similar to normal population.[18] There are no criteria available to distinguish headache secondary to high disease activity in lupus patients from headache secondary to drugs like hydroxy-chloroquine, stress or other co-morbidities.

Our study had prevalence of seizure as 13% that is in the range of reported prevalence in SLE patients (651%).[19] 40% of our patients with secondary antiphospholipid syndrome had seizures. However, the work up for antiphospholipid syndrome was done only in a very small subset of our patients due to financial constraints. The prevalence of CVD (5%) was also similar to previous reports (215%).[20]

Neurocognitive impairment (NCI) is common and clinically most challenging manifestation of all SLE. It is characterized by significant deficit in simple or complex attention, reasoning, executive skills, memory, visual-spatial processing, language, and psychomotor speed.[5] It's detection requires administration of an extensive neuropsychiatric testing battery, which is difficult to perform and time consuming. The pathogenesis of cognitive impairment in SLE patients is poorly understood. Available data suggests that demographic factors, such as ethnicity, are not predictive of NCI in patients with SLE. Furthermore, NCI can develop in the apparent absence of SLE disease activity or other manifestations of neuropsychiatric SLE.[21] In this study, the prevalence of cognitive impairment was 43%, almost in the range of previous reports.[22]

The prevalence of psychiatric disorders in our study was 68% (major psychiatric manifestations in 7%) The reported prevalence has varied from 17% to 75%.[23] This variation may be due to difference in ways and expertise in neuropsychologic testing. Severe anxiety was observed in 52% of our SLE patients.

Development of 70% of major neurological manifestations in our study occurred beyond 2 years of diagnosis of SLE. This is in contrast to previously available data which reports that a high percentage of patients develop NPSLE early in the disease course, with a total of 55% within 1 year of SLE diagnosis.[24] Neuropsychiatric damage was the most common damage category in our lupus cohort followed by renal, pulmonary hypertension, pericarditis and digit loss.

Our study has some limitations that should be considered. We studied prevalence of neuropsychiatric manifestations in a referral clinic population. Some of these manifestations like cognitive impairment and anxiety can be better studied if compared to matched controls (healthy adults/patients with other auto-immune diseases). It would be interesting to study the relationship of auto-antibodies to individual neuro-psychiatric manifestations, which could not be done in our study due to financial constraints. Further research is warranted to analyze potential risk factors contributing to the development and severity of NPSLE and study long term functional impairment and survival of these patients.

CONCLUSION

We found NPSLE manifestations in 84% of patients, with major neuropsychiatric

manifestations in 27% of patients. Headache, seizures and CVD were the most frequent neurological manifestations, while cognitive disorder and severe anxiety being the most common psychiatric manifestations.

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