Original Article

Neuropsychiatric manifestations in patients with systemic lupus erythematosus: A study from Iran

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Abstract

Background: Neuropsychiatric systemic lupus erythematosus (NPSLE) is a serious and well-known complication of systemic lupus erythematosus (SLE). There is limited evidence about the prevalence of NPSLE and its manifestations in Iran. The aim of this study was to study clinical and demographic characteristics of patients with NPSLE in an Iranian population.

Materials and Methods: This was a cross-sectional study that was undertaken in two referral Clinics of Neurological and Rheumatological Disorders in Alzahra Hospital, Isfahan, Iran. Between March 2004 and June 2010, medical records of registered patients with SLE were examined. NPSLE was characterized using the American College of Rheumatology case definitions. Descriptive statistics and logistic regression were performed for statistical assessment.

Results: Among 556 patients with SLE, 121 (21.7%) patients were diagnosed as NPSLE and enrolled in the study. Of whom, 94 patients were female (77.7%) and 27 patients were male (22.3%) with a female to male ratio of 3.48:1. The most common NPSLE manifestations were headache (38.8%), cerebrovascular disease (CVD) (38.8%) and seizure (26.4%). Thirty-nine patients have psychiatric disorders. Among them, 32 patients (26.4%) have periods of psychosis and mood disorder was found in 6 patients (5%).

Conclusions: We identified NPSLE manifestations in 21.7% of patients; headache and CVD were the most frequent neurological manifestations. Continued studies into the pathogenesis of neurological involvement in patients with SLE are warranted.

Key Words: American College of Rheumatology, neuropsychiatric systemic lupus erythematosus, prevalence, systemic lupus erythematosus

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease of unknown etiology, affecting multiple organ systems, including the joints, skin, heart, lungs, kidneys, and nervous system.[1] Neuropsychiatric systemic lupus erythematosus (NPSLE) is a clinical feature of SLE, which is characterized by neurological syndromes of the central, peripheral, and autonomic nervous system, as well as psychiatric disorders.[2] This severe complication is a significant cause of morbidity and mortality that can adversely affect patients'

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quality of life and their ability to work, resulting in substantial direct and indirect costs.[3]

The diagnosis of NPSLE is largely clinical and lacks a biologic or radiographic marker for the disease.[4] In 1999, the American College of Rheumatology (ACR) developed case definitions for 19 NPSLE syndromes to standardize definitions, diagnostic criteria, and diagnostic testing of this disorder[5] [Table 1]. NPSLE manifestations consists of 19 NPSLE syndromes, namely aseptic meningitis, cerebrovascular disease (CVD), demyelinating syndrome (e.g., multiple sclerosis) headache, movement disorder, myelopathy, seizure disorder, acute confusional state, anxiety disorder, cognitive dysfunction, mood disorder, psychosis, Guillain-Barré syndrome, autonomic neuropathy, mononeuropathy (single/multiplex), myasthenia gravis, cranial neuropathy, plexopathy, and polyneuropathy.

The prevalence of NPSLE varies between 9.5% and 95% based on the literature, subject selection and the diagnostic criteria.[6] The frequency and clinical manifestations of the disease show geographic and ethnic variation among populations.[7] For example, in a Chinese study, the prevalence of NPSLE manifestations was reported as only as 19%[8] in comparison to the prevalence estimate of 37% in a Canadian study.[9] Some authors proposed that much of the variability in these estimates might be attributable to the absence of standardized case definitions in the assessment of NPSLE; though, using the ACR case definitions, results have yielded a wide range of prevalence estimates (37–95%) in different geographic areas.[10-13]

However, there is limited evidence about the prevalence of NPSLE and its manifestations in Iran. In a retrospective hospital-based study in Fars province, NPSLE was observed in 11.3% of SLE patients.[14] However, in another study of Tehran, the neuropsychiatric involvement was present in 23.4% of patients.[15]

These conflicting results and the high frequency and potential severity of NPSLE prompted us to study the clinical and demographic characteristics of patients with NPSLE in an Iranian population.

MATERIALS AND METHODS

This was a retrospective cross-sectional study that was undertaken in two referral Clinics of Neurological and Rheumatological Disorders in Alzahra Hospital, Isfahan, Iran.

The study examined registered patients since 20 March 2004 to 20 June 2010. All patients fulfilling the criteria for SLE as defined by the ACR[5] included. Exclusion criteria were other coexistent connective tissue diseases, such as rheumatoid arthritis, mixed

Table 1: Frequency of the observed neuropsychiatric manifestations of SLE in comparison to international studies

NPSLE manifestations	Our study *n*=556 (%)	Ainiala (2001) *n*=46 (%)	Mok (2001) *n*=518 (%)	Brey (2002) *n*=128 (%)	Kasitanon (2002) *n*=390 (%)	Chiewthanakul (2012) *n*=738 (%)	Akbarian (2010) *n*=2280 (%)	Hanly (2008) *n*=890 (%)
General prevalence	21.7	91	19	80	23	13	23.4	30.4
Aseptic meningitis	0.8	2	1	-	-	1.0	2.1	0.3
Cerebrovascular disease	38.8	15	19	2	2.0	22.3	28.3	2.6
Demyelinating syndrome	7.4	2	1.5	-	-	-	2.1	0.0
Headache	38.8	54	4	57	-	1.9	2.1	19.2
Movement disorder chorea	3.3	2	2	1	-	-	4.3	0.3
Myelopathy	5.7	-	8	-	6.1	7.8		0.6
Seizure disorders	26.4	9	28	16	54.1	31.1	26.5	3.4
Acute confusional state	-	7	14	-	11.2	-	19.6	1.8
Anxiety disorders	8	13	1.5	24	-	-		2.9
Cognitive dysfunction	11.6	80	-	79	-	-	2.1	2.9
Mood disorders	5	44	6	23	-	1.0		7.5
Psychoses	26.4	-	11	5	13.3	22.3	6.5	1.0
Guillain–Barre syndrome	-	-	-	-	-	1.0	2.1	0.0
Autonomic disorder	2.5	-	-	-	-	-		0.1
Mononeuropathy, single/multiple	5.8	-	1.5	8	-	1.0		1.1
Myasthenia gravis	8.2	2	-	-	-	-		0.0
Neuropathy, cranial	16.5	7	3	2	-	1.0		0.8
Plexopathy	5.7	-	-	-	-	-		0.0
Polyneuropathy	5	28	1	22	5.1	9.7		1.1

NPSLE: Neuropsychiatric systemic lupus erythematosus, SLE: Systemic lupus erythematosus

connective tissue disease, Sjögren's syndrome, or progressive systemic sclerosis. Other exclusion criteria includes: Treatment side-effects (e.g., intracranial hemorrhage due to anticoagulation therapy), dysfunction of other internal organs, intracranial infection, other CNS syndromes (coma in stroke patients and hypertensive encephalopathy) and other non-NPSLE magnetic resonance imaging (MRI) findings.

Registered data included demographic features (such as sex, age at diagnosis and date of the first visit) and clinical data (time of onset, duration of SLE and neurological and psychiatric manifestations). Patients' follow-up visits were every 1–3 months depending on the severity of the disease included a standard medical history, physical examination, and cognitive testing.

Screening of all NPSLE was based on the clinical assessment together with MRI. Subsequent investigations were performed only if clinically warranted.

All descriptive statistics are presented as means and standard deviations (SDs) for quantitative variables, and as relative frequencies and percentages for categorical variables.

The effect of NPSLE damage on mortality was studied by logistic regression. Odds ratio and 95% confidence interval were used to present the strength of association ($P < 0.05$). Analyses were performed using SPSS 18.0 statistical software (SPSS Inc., Chicago, IL, USA).

The design of the study was approved in Ethics Committee of Vice Chancellor for Research, Azad Najaf Abad University. We requested participants' permission to review their medical records. All participants consented.

RESULTS

Demographic characteristics

Among 556 patients with SLE, 121 (21.7%) patients met the inclusion criteria and enrolled in the study. The mean age of all participants was 33.9 (SD: 14.1) years with a range of 18–67 years. Of whom, 94 patients were female (77.7%) and 27 patients were male (22.3%) with a female to male ratio of 3.48:1.

The mean follow-up time was 48.62 (SD: 34.57) months. The mean age at onset of NPSLE manifestations was 33.77 (SD: 13.56) years.

Prevalence of neuropsychiatric systemic lupus erythematosus manifestations

The most common NPSLE manifestations were headache (38.8%), CVD (38.8%) and seizure (26.4%). Among patients with headache, 40 patients (33.1%) had migraine type and 7 (5.7%) diagnosed as tension like headache. Headache was the only neurological manifestation in 14 (11.6%) patients.

Cranial neuropathy and myasthenia gravis were seen in 20 (16.5%) and 10 (8.2%) of patients, respectively. Cognitive disorders were diagnosed in 14 patients (11.6%). Thirty-nine patients have psychiatric disorders. Among them, 32 patients (26.4%) have periods of psychosis and mood disorder was found in 6 patients (5%). Other neurological manifestations include sensorineural hearing loss (5.8%), peripheral neuropathy (5%), transverse myelopathy (5.7%) and autonomic neuropathy (2.5%).

The least common NPSLE manifestation was aseptic meningitis (0.8%). The prevalence of other manifestations is presented in Table 1.

The most common change on MRI was small punctate focal lesions in subcortical white matter found in 35% of NPSLE patients, followed by cortical atrophy, periventricular white matter changes and major infarcts.

During our study, 6 patients died due to neurological involvement. Most of these patients were female and had an onset of disease before the age of 25 years.

Logistic regression analysis revealed that neither CVD (adjusted odds ratio, 1.03 [0.57–1.84]; $P = 0.91$) nor cognitive disorders (adjusted odds ratio, 1.01 [0.28–3.32]; $P = 0.68$) were associated with mortality, after adjustment of age, sex and duration of SLE.

DISCUSSION

The aim of this study was to study clinical and demographic characteristics of patients with NPSLE in an Iranian population. The prevalence of NPSLE manifestations in our study was 21.7% that is similar to the results of other studies. Mok *et al*. examined 223 patients with SLE and reported the prevalence of NPSLE as 23%.[16] With studying 137 SLE patients, Avčin *et al*. found that the prevalence of neuropsychiatric manifestations was seen in 25.5% of patients.[17]

However, wide heterogeneity of prevalence exists between different studies.[18] The main results of this variation are different diagnostic criteria and

geographic and ethnic variation among populations.[19] In a large study from Iran, 23.4% of patients have neuropsychiatric disease.[15] In another study in Shiraz University, the NPSLE prevalence was lower (11.3%) that could be because of the retrospective, hospital-based nature of this study, which failed to detect the cases of NPSLE that did not require hospitalization.[14]

In our study, like in many other studies, headache and CVD were the most frequent neurological manifestations.[20-22] A systematic review concluded that the prevalence of all headaches types, predominantly tension-type headache and migraine, is similar to SLE patients and the normal population.[23] In another meta-analysis study, the prevalence of headache using random-effects model was 37.0%, which is similar to the results of our study (38.8%).[18] Unfortunately, there is lack of a standard protocol to establish whether if it is associated to NPSLE or happened as a separate neurological syndrome or other features such as medication, stress reaction or co-morbid syndromes.

The prevalence of CVD was higher than previous reports (2–15%).[24] It may be due to the underlying mechanisms of CVD in SLE, which include bleeding, thrombosis, hypertension, and thrombocytopenia.[10] Our study reported the prevalence of seizure as 26% that is in the range of reported prevalence in SLE patients (6–51%).[11]

Cognitive dysfunction was described by the ACR as "significant deficits in any or all of the following cognitive functions: Simple or complex attention, reasoning, executive skills, memory, visual-spatial processing, language, and psychomotor speed."[5] In this study, the prevalence of this disorder was lower in comparison to previous reports (17–66%).[25] A study on determinants of cognitive function in SLE patients showed that demographic variables account for much of the variation in cognitive performance in different populations.[26]

The prevalence of psychiatric disorders in our study was 32.3. The reported prevalence of psychiatric manifestations in patients with SLE has varied from 17% to 75%.[27] This wide range may be due to different rates of neuropsychologic testing.[18]

In this study, the least common NPSLE manifestations were aseptic meningitis (0.8%) which is in line with the results of previous studies in Finland[10] and Italy.[28]

The pathogenesis of NPSLE is incompletely understood although it has been referred to autoantibody-mediated neuronal dysfunction, vasculopathy, and coagulopathy and numerous autoantibodies and cytokines have been suggested as possible mediators.[29,30] Our study did not measure these mediators, and future studies are recommended to measure these important factors and its association with prevalence and prognosis of NPSLE manifestations.

Our study, while having much strength, involved some limitations that should be considered. The cross-sectional design of this study limits its generalizability. More research, particularly longitudinal, is warranted to direct the incidence of NPSLE manifestations and survival of these patients. Furthermore, participants were from a referral clinic population, and there is no general population reference data to compare. Further research may be helpful to determine the relative prevalence of each syndrome in comparison to matched controls, including patients with other autoimmune diseases or healthy subjects.

CONCLUSION

We identified NPSLE manifestations in 21.7% of patients and headache and CVD were the most frequent neurological manifestations. Continued studies into the pathogenesis of neurological involvement in patients with SLE are warranted.

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Conflicts of interest

There are no conflicts of interest.

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