Cross-sectional Study

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Central neurological manifestations in a sample of Syrian patients with systemic lupus erythematosus: cross-sectional study

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Introduction: The authors aimed to study systemic lupus erythematosus (SLE) central neurological patterns and their correlations with the disease activity.

Patients and methods: The authors' retrospective observational study was carried out on admitted SLE patients. The patients' demographic data, clinical examinations, laboratory tests, imaging studies, and systemic lupus erythematosus disease activity index (SLEDAI) were recorded.

Results: Thirty-six SLE patients had neurological manifestations from 203 patients, but 8 patients were excluded. 90.2% were females. The age of neuro-lupus manifestation was 24.1 + 2.9 years. Neurological manifestations were the initial presentation in 25% of patients. General seizures were the frequent manifestation. SLEDAI was 29.51 ± 18.43, while it was 18.3 ± 9.2 among patients without neuropsychiatric systemic lupus erythematosus (NPSLE). Twenty-five percent of patients had pleocytosis on cerebrospinal fluid (CSF) analysis. Small lesions were seen in 57.1% of patients on brain MRIs, and large lesions were observed in 10.6%. These findings were compatible with the disease activity.

Discussion: Central nervous system involvement ranged between 10 and 80%, and much more with active disease. The frequent finding was general seizures. Psychosis and cognitive impairment were relatively frequent. Adult NPSLE manifestations had developed before or around the time of SLE diagnosis and within the first year after diagnosis. These manifestations were directly correlated to the disease activity. Abnormality in CSF is characterized by slight pleocytosis, and elevation of protein with normal fructose. MRI is the neuroimaging test of choice for NPSLE in clinical practice.

Conclusion: Central neurological involvement in SLE was seen early in the course of the disease, and correlating to the disease activity.

Keywords: cognitive impairment, neurological manifestation, neuro-lupus, SLE

Introduction

Systemic lupus erythematosus (SLE) is a systemic connective tissue disease, that predominates in women, Asian and Hispanic populations[1].

Neurologic symptoms occur in 6–91%, either before the diagnosis of SLE or during its course[2–5], even without serologic activity or disease clinical presentations[6]. This wide range of prevalence is due to variable presentations, using different study designs, different criteria, and different methods for screening[4,7]. It involves both central and peripheral nervous system[5].

The neuro-manifestations of SLE is classified into primary, which is related to the direct involvement of the neuro system, and secondary, which is related to the disease complications and/or its treatment[4]. The American College of Rheumatology (ACR) has formulated the definition of neuro-lupus[8].

HIGHLIGHTS

- Systemic lupus erythematosus (SLE) primarily affects women, Asian, and Hispanic populations.
- Neurologic symptoms can occur in SLE cases and are classified as primary or secondary involvement.
- Sixty percent of Syrian SLE patients experienced neuro-lupus manifestations.
- The most common symptoms of neuro-lupus were headaches, seizures, and cognitive disorders.
- Patients with neuro-lupus had higher SLE disease activity scores, and a significant association was found between neuropsychiatric symptoms and anti-dsDNA antibodies.

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Studies have found that the frequent presentations were headaches, seizures, cerebrovascular diseases, cranial neuropathies, movement disorders, psychosis, cognitive disorders, and others[9,10].

The pathological etiologies are still obscure. Autoantibody production, micro-angiopathy, intrathecal production of pro-inflammatory cytokines, and premature atherosclerosis play a role[4,5,11].

This retrospective cohort study took place to evaluate the frequency and characteristics of these manifestations, in a sample of Syrian SLE patients and correlate them with the disease activity since there have been no studies of NPSLE in Syria.

Patients and methods

Our retrospective observational study took place from January.2015 to January. 2022. The hospital files of 203 SLE patients were examined.

Inclusion criteria included SLE patients, diagnosed according to the ACR criteria[12], and the presence of SLE-related neurological symptoms, after signing the informed consent[8].

Exclusion criteria included SLE patients with strokes, intravenous drug abuse, neurological infections, and encephalopathies due to other causes, diabetes mellitus, hyperlipidemia, and electrolyte disturbances.

We divided our cohort of patients into two groups. Group A including patients with neuropsychiatric manifestations, and Group B including those without neuropsychiatric manifestations.

Demographic data, disease duration, clinical, labotorial, and imaging findings of the disease were collected and analyzed.

Neuropsychiatric manifestations were reported from patients medical records, including: Headaches, psychosis, seizures, transient ischemic attacks, strokes, transverse myelitis, Cognitive dysfunctions, chorea, cranial neuropathies and peripheral neuropathies, based on ACR definition of neuro-SLE[8].

Laboratory tests included: Complete blood count, erythrocyte sedimentation rate, C-reactive protein, urea, creatinine, and liver enzymes. All analyzed within 1 h after the collection of samples.

Immune profile included: Complement (C3, and 4), ANA, Anti-Smith, anti-ds DNA, Lupus Anticoagulant, anti-cardiolipin, anti-β2-glycoprotein 1 antibodies.

Urinalysis and 24 h proteinuria analysis, were performed. Cerebrospinal fluid analysis was performed, when necessary.

Nerve conduction studies, electromyography, and electroencephalography if necessary were also performed. Conduction velocity of action potential in meters per second was the used criteria.

MRI of the brain was done using (3 Tesla) Siemens machine, in addition to MR angiography when necessary.

The disease activity index of the SLEDAI contained 20 variables, and was used to evaluate the disease activity. Patients were classified as: high (20), moderate (10–20), and mild/in remission (<10)[13].

Statistical analysis

Statistical Package for Social Sciences (SPSS) software version 23, and Excel2010 were used. Data were presented as mean standard deviations and percentiles. The *t*-student test, χ^2 test, and Fisher's exact test were utilized. The Kolmogorov–Smirnov was used to verify the normality of variables distribution. *P* valueless than 0.05 was considered statically significant.

Our study is compatible with the STROCCS guidelines of the annals of medicine and surgery journal[14].

Results

As shown in Table 1, this study included 203 patients with SLE. Thirty-six (17.73%) of SLE patients) had neurological manifestations, and 167 patients without NPSLE. Eight patients were excluded from neuropsychiatric systemic lupus erythematosus; due to the presence of uremic encephalopathy resulting from renal involvement by SLE (4 patients), hypertension-induced intracranial hemorrhage (2 patients), meningitis (2 patients), and the remaining were 28 patients. In 8 out of 28 patients (25%), neurological manifestations were the initial presentation of SLE.

The mean age of group A was 27.4 ± 7.7 (18–50), while it was 28.4 ± 8.5 (18–52) years in group B. In group A, 26 (90.2%) were females, and 2 (7.1%) were males, while in group B, 155 (92.81%)were females, and12 (7.1%) were males. The mean duration of the disease was 5.9 ± 3.8 years in group A, and 6.1 ± 3.5 years in group B.

In patients of group A, malar rash was present in 78.5% ($n=22$), photosensitivity in 64.2% ($n=18$). Serositis in 53.2% ($n=15$) patients, arthralgia was noted in almost all patients 92.7% ($n=26$), articular arthritis was noted in 53.2% ($n=15$) patients, hematological disorders in 42.5% ($n=12$), renal involvement in 82.1% ($n=23$), cardiac manifestations in 6 (21.42%), pulmonary manifestations in 4 (14.28%), thrombotic event in 5 (17.85%), fatigue in 18 (28%) patients, and fever in 28% ($n=18$) patients. While in group B, the malar rash was present in 78.44% ($n=131$), photosensitivity in 59.88% ($n=100$). Arthralgia was noted in almost all patients 98.20%

Table 1

Comparison between the studied groups according to demographic data

Variable	Patients with neuropsychiatric manifestations (group A) ($n=28$)	Patients without neuropsychiatric manifestations (group B) ($n=167$)	*P*
Age in years (mean ± SD)	27.4 ± 7.7 (18–50)	28.4 ± 8.5 (18–52)	NS
Sex, *N* (%)			
Female	26 (90.2)	155 (92.81)	NS
Male	2 (7.1)	12 (7.1)	
Educational level, *N* (%)			
Bachelor, or less	18 (64.28)	35 (20.95)	NS
University	8 (28.57)	132 (79.04)	**<0.05**
Marital status, *N* (%)			
Single	10 (35.71)	54 (32.33)	NS
Married	18 (64.28)	113 (67.66)	NS
Work			
Employed	18 (64.28)	100 (59.88)	NS
Unemployed	10 (35.71)	67 (40.11)	NS
Menstrual period			
Normal	14 (50)	126 (75.44)	**<0.05**
Abnormal	14 (50)	41 (24.55)	**<0.05**
Disease duration	5.9 ± 3.8	6.1 ± 3.5	NS

Statistically significant P values are in bold.
NS, not specified.

Table 2

The neuro-manifestations of SLE

Manifestation	Frequency (percentage), *N* (%)
Headache	8 (28.57)
Seizure	6 (21.42)
Cognitive dysfunction	3 (10.7)
Psychosis	3 (10.7)
Cranial neuropathy	3 (10.7)
Peripheral neuropathy	2 (7.14)
Stroke	2 (7.14)
Aseptic meningitis	1 (3.57)

($n=164$), articular arthritis was noted in 50.89% ($n=85$) patients, hematological disorders in 47.90% ($n=80$), renal involvement in 52.09% ($n=87$), and fever in 28.74% ($n=48$) patients. Renal involvement was significantly higher in group A patients compared to group B patients ($P<0.05$).

SLEDAI was 20.1 ± 8.2 in group A patients and 13.9 ± 6.9 ($P<0.05$) in group B patients.

Headaches had the highest percentage 28.57%, then seizures 21.42%, cognitive dysfunction 10.7%, and finally psychosis 10.7% (Table 2).

Generalized seizures in 5 out of 6 patients (83.33%), and 5 out of 28 patients (17.85%) were the most frequent type of seizures. One patient had a partial seizure in the form of epilepsy partials' continuing to involve the facial muscles.

Persistent headache, not relieved by narcotics was present in 5 (17.85%) patients.

Cognitive impairment assessment of group A, by using the mean Mini-Mental State Examination (MMSE)[15] score was 28.79 ± 1.98, while it was 19.71 ± 6.12($P<0.05$) in group B patients.

Out of 28 patients studied, 25 (89.28%) had normal cognitive function with an MMSE score between 24 and 30. Two patients (7.1%) had mild cognitive impairment, with a score between 18 and 23, while one (3.57%) had severe cognitive impairment. (Table 3).

Laboratory findings at the presentation

As shown in Table 4, results of complete blood picture were compared between both groups, with an evaluation of different laboratory abnormalities found in patients of SLE as anemia, leukopenia, lymphopenia, neutropenia and thrombocytopenia and there was no significant difference between both groups. However, regarding immunological profile, group A patients had lower C3 and C4 levels, and more lupus anticoagulant level, ACL level, and β 2 GP 1 level.

Cerebral spinal fluid (CSF) analysis

CSF was performed and analyzed in 8 patients from group A. Fifty-eight percent of the CSF analysis were completely normal, 25% revealed pleocytosis, 18% showed increased protein content, and 2% showed decreased glucose levels (Table 4).

Table 3

MMSE score

Score	Patients	Percentage (%)
24–30	25	89.28
18–23	2	7.14
0–17	1	3.57

MMSE, Mini-Mental State Examination.

Table 4

Laboratory findings at the presentation of both groups

Laboratory parameter	NPSLE patients (group A) (28), *N* (%)	SLE patients (group B) (167), *N* (%)	*P*
ANA	27 (96.42)	155 (92.8)	NS
Anti-ds DNA	20 (71.42)	100 (59.88)	**<0.05**
Anti-smith	4 (14.28)	27 (16.16)	NS
C3	9 (32.14)	90 (53.89)	**<0.05**
C4	7 (25)	82 (49.10)	
Leukopenia	10 (35.71)	54 (32.33)	NS
Lymphopenia	6 (21.42)	42 (25.14)	NS
Thrombocytopenia	4 (14.28)	18 (10.77)	NS
Lupus anticoagulant	4 (14.28%)	6 (4.7%)	**<0.05**
ACL			
Ig M	5 (17.85)	7 (4.19%)	**<0.05**
Ig G	5 (17.85)	7 (4.19%)	**<0.05**
Anti β 2 GP 1			
Ig M	2 (7.4%)	1 (0.59%)	**<0.05**
Ig G	2 (7.4%)	1 (0.59%)	**<0.05**

Statistically significant P values are in bold.

ACL anti-cardiolipin; ANA antinuclear antibody; Anti β 2 GP 1 anti β 2 glycoprotein I; Anti-dsDNA anti-double stranded DNA antibodies; C3, complement 3; C4, complement 4; NPSLE, neuropsychiatric systemic lupus erythematosus; NS, not specified; SLE, systemic lupus erythematosus.

Brain images in NPSLE patients

Among the 28 available brain MRIs, small lesions were seen in 16 (57.1%) brain MRIs, and large lesions were observed in two (10.6%) MRIs. All abnormal MRIs revealed hyperintense lesions in T2-weighted images, but only in 14 (50%), MRIs were corresponding hypointense lesions in T1-weighted images. These characteristics were compatible with ischemic/demyelinating lesions. Twelve patients had high disease activity (SLEDAI ≥ 20). Nerve conduction studies and electromyography revealed a myogenic pattern in 3 (10.7%) patients; there was myositis and a neurogenic pattern with conduction block in the patient with the Guillain–Barre syndrome.

A treatment comparison between the two groups is revealed in Table 5.

Table 5

Treatment of both groups.

Drug	NPSLE patients (group A), *N* (%)	SLE patients (group B), *N* (%)	*P*
Corticosteroids			
<10 mg/day	7 (25)	42 (25.14)	**<0.05**
10–20	10 (35.71)	82 (49.1)	
20–30	8 (28.57)	26 (15.56)	
>40	3 (10.71)	17 (10.17)	
Methyleprednisolone	15 (53.57)	84 (50.29)	
Hydroxychloroquine	24 (85.71)	142 (85.02)	
Azathioprine	12 (42.85)	80 (47.90)	
Cyclophosphamide	7 (25)	47 (28.14)	
Mycophenolate mofetil	5 (17.85)	34 (20.35)	
Rituximab	4 (14.28)	4 (2.3)	**<0.05**

Statistically significant P values are in bold.

NPSLE, neuropsychiatric systemic lupus erythematosus; SLE, systemic lupus erythematosus.

Table 6

The different neurological published articles

Study features	Present study	Robert *et al.*[27]	Brey *et al.*[28]	Sanna *et al.*[29]	Khare *et al.*[30]
No. patients included in the study	52	50	128	323	35
Nervous system involvement, *N* (%)	19 (36.54)	39 (78)	102 (80)	185 (57.3)	35 (100)
Cognitive dysfunction, *N* (%)	11 (57.89)	7 (17.95)		35 (10.8)	3 (9)
Seizure, *N* (%)	8 (42.1)	8 (20.51)	21 (16)	27 (8.3)	23 (66)
Acute confusional state, *N* (%)	6 (31.57)	6 (16.2)		12 (3.7)	7 (20)
Headache, *N* (%)	5 (26.31)	20 (55.6)	73 (57)	78 (24)	2 (6)
Depression, *N* (%)	5 (26.1)		37 (28)		
Psychosis, *N* (%)	4 (21.05)	6 (16.2)	6 (5)	25 (7.7)	3 (9)
Polyneuropathy, *N* (%)	4 (21.05)		29 (22)		2 (6)
Cerebrovascular accident, *N* (%)	NS	6 (16.2)	2 (2)	47 (14.5)	2 (6)
Movement disorder, *N* (%)	NS	8 (20.51)	1 (1)		

NS, not specified.

Discussion

Nervous system involvement in SLE is frequent, serious, potentially treatable, and affects both central nervous system (CNS) and peripheral nervous system (PNS). Central involvement can present as aseptic meningitis, cerebrovascular accidents, headaches, psychosis, and many others. It usually occurs during the active disease[1,2].

CNS involvement ranged between 10 and 80% (3), according to studies, as in our one (17.73%). In this present study, headaches were the frequent presentation followed by seizures, decreased level of consciousness, and weakness. This is compatible with some other studies[16,17]. Meanwhile, seizures were a frequent neurological feature in other studies that had occurred during the disease course alone or with another neurological manifestation[1,18].

The frequency of headaches among SLE patients is (28–68%), and it was 66%, which is compatible with studies[15,19].

Studies have registered the frequency of cerebrovascular accidents among SLE patients[20]. The frequency of a cerebrovascular disease in our study was 35.6%, while it was less than that in the studies of to Futrell and Milikan[21]. This may have been due to their small-sized patients sample (105), and the study of risk factors for stroke.

Acute meningitis and cranial nerve palsy are rare[22], as in our case. The use of non-steroidal anti-inflammatory treatment may cause meningitis as a side effect[1]. We had one patient with this manifestation.

In our study, psychosis and cognitive impairment were the frequent presentations.

Psychosis and depression are frequent. Psychosis must be differentiated from corticosteroid-induced psychosis[4]. Cognitive impairment occurs frequently due to the diagnostic criteria used[1]. Cognitive impairment was 10.7% in our series, and this is in contrast with other results[23,24]. These variable differences may be due to criteria selection, geographic region, and ethnicity.

In 8 patients (25%), neurological symptoms were the initial presentation of SLE, moreover, it may be developed earlier and in younger patients. Our results are compatible with some studies[1,5].

SLEDAI score was significantly higher in patients with group A compared to those of group B. In addition, the neurological manifestations were directly correlated to the disease activity[24], such as in our study.

CSF findings in neuro-lupus are pleocytosis, elevated protein, and normal sugar level[1], as 25% of our patients had elevated white blood cells.

MRI is the best neuro-imagining tool for detecting NPSLE[25]. Our results showed that small lesions were found in 57.1%, and large ones were seen in 10.6%. Abnormal MRIs revealed hypodense lesions in T1-weighted images, and hyperdense lesions in T2-weighted images, which is compatible with previous reports[1,25].

EEG abnormalities were observed in patients with clinical neuro-lupus, but it may be an indicator for subclinical neuro-lupus[1]. In our study, electromyography revealed a myogenic pattern in 3 (10.7%) patients; there was myositis and a neurogenic pattern, with conduction block in the patient with the Guillain–Barre syndrome, like some other previous studies[1,26].

The limitation to our study was the small sample size enrolled in one center, when compared to the different neurological published articles (Table 6).

Ethical approval/declaration of Helsinki

Approval of Ethical Board (NS: 2321) was credited, and in accordance with the Declaration of Helsinki, the study was performed.

Consent

Written informed consent was obtained from the patients for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

M.K.: supervision, writing—review and editing. B.A.: conceptualization, writing—original draft , writing—review and editing. N.K.: data curation, writing—review and editing. K.R.: writing—review and editing. N.R.: writing—review and editing. L.A.D.: data curation, writing. F.A.A.: resources, review.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

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