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Clinical Presentation of Neuropsychiatric Systemic Lupus Erythematosus and Demographic and Radiological Characteristics of Patients

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Abstract: Systemic lupus erythematosus (SLE) is a vasculitis that may affect numerous systems such as the kidneys, skin, joints, heart, lungs and nervous system. The purpose of our study is to evaluate patients with SLE in whom central nervous system involvement is monitored. Files of 1028 patients who were followed up with (SLE) diagnosis was examined Demographic, clinical and radiological characteristics were recorded for patients with a final diagnosis of neuropsychiatric systemic lupus erythematosus (NPSLE) with central involvement. Among 1028 patients diagnosed with SLE, 1.07% had NPSLE. Mean age was 37±5.3. 90.9% of the patients (n=10) were female, while 9.1% (n=1) were male. From a clinical aspect, 45.4% complained from hemiparesis, 27.3% from headache, 18.2% from psychiatric complaints and 9.1% complained from impairment of consciousness. From a radiological aspect, 45.4% (n=5) were consistent with subcortical plaque, 36.4% (n=4) with ischemic stroke, 9.1% (n=1) with cerebral venous thrombosis, and 9.1% (n=1) appeared consistent with posterior reversible encephalopathy syndrome (PRES). Mortality rate was 9.1% (n=1). The central involvement type that caused mortality was ischemia. Since magnetic resonance imaging (MRI) is not sufficient for showing microvascular involvement in NPSLE patients, it is possible for NPSLE diagnosis to be delayed despite consistent clinical characteristics. In case of clinical suspicion, other imaging methods should be applied apart from MRI. This is because early diagnosis is an important factor that reduces morbidity and mortality.

Keywords: Systemic Lupus Erythematosus; Central Nervous System; Magnetic Resonance Imaging.

1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that may affect the kidneys, skin, joints, heart, lungs, hematopoietic system and nervous system. SLE mostly affects women between ages 16-55 (1), and the highest age ranges from 45 to 69 in women while it ranges between 40-89 in men (2).
Nervous system involvement is called neuropsychiatric SLE (NPSLE) in SLE (3), and it is observed in 10% to 80% of patients (4). Furthermore, central nervous system (CNS) involvement is associated with high morbidity and mortality (5). NPSLE may affect peripheral and central nervous system. Meanwhile, the incidence of cerebrovascular system involvement varies between 3% and 20% in SLE (6). In NPSLE, neuroinflammation and cerebral ischemia occurs with the effect of genetic, environmental and

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neuroendocrine factors (7). One of the first important assumptions in NPSLE is that impaired blood-brain barrier (BBB) allows autoantibodies and immune peripheral blood components to enter CNS and results in inflammation and damage (8).

The difficulties often encountered by clinicians in the diagnosis and management of NPSLE patients are caused by the variety of clinical manifestations of patients from common and nonspecific characteristics such as headache, cognitive impairments and mood disorders to rare and complicated conditions such as Guillain – Barré syndrome and autonomic dysfunction (9). NPSLE may be presented as a clinically common disease (e.g., psychosis, anxiety or depression) or a focal disease (e.g., stroke or transverse myelitis) (3, 10). The most common magnetic resonance imaging (MRI) anomalies observed in these patients are small subcortical hyperintense lesions and infarctions (11). NPSLE treatment may be applied with corticosteroids alone, or in combination with other immunosuppressive drugs including cyclophosphamide for remission induction or azathioprine for maintenance treatment (12). Early diagnosis and treatment are important since it reduces morbidity and increases the quality of life. Antimalarial drugs (e.g., hydroxychloroquine) are recommended in SLE patients in order to prevent NPSLE (13).

The purpose of this study is to evaluate the clinical presentation, and demographic and radiological characteristics of NPSLE patients followed up in our region.

2. Material and Methods

The data of 1028 patients, who have applied to our center between the dates January 2012- June 2019 and diagnosed with SLE, were examined retrospectively from the hospital's automation system. Clinical characteristics and radiological data of the patients were recorded. Patients under age 18 and patients with missing data in their file have been excluded from the study. Final diagnosis of patients with SLE according to the criteria of American College of Rheumatology were included in the study. From these patients, the clinical results, the age of diagnosis, medical treatments and radiological findings belonging to 11 patients diagnosed with NPSLE were recorded. Patients with headache and psychiatric clinical complaints and normal MRI results were not included in NPSLE patient group. In order to exclude other reasons that may explain the current clinical status, oral contraceptive use, pregnancy status, concomitant infections, familial history of thrombosis, homocysteine levels, antithrombin III, protein C and S deficiency, and gene mutations (methylenetetrahydrofolate reductase, prothrombin II, Factor V Leiden mutation) were recorded. Ethics committee approval was taken for the study (06/17/26.09.2019).

2.1. Statistical analysis

For the statistical analyses SPSS 22.0 was used. Categorical variables are demonstrated in number and percentage. Continuous variables were presented as mean ± standard deviation. Numerical data were checked for normal distribution by Kolmogorov-Smirnov test. $p<0.05$ value was recognized to be statistically significant.

3. Results

Eleven of 1028 SLE patients (1.07%) had NPSLE. Mean age was 37±5.3. The age interval of patients diagnosed with NPSLE was between 22-46, and only one female patient was diagnosed simultaneously with SLE and NPSLE at age 82. 90.9% of the patients (n=10) were female, while 9.1% (n=1) were male. 27.3% (n=3) of patients diagnosed with NPSLE had SLE diagnosis before central involvement, while 72.7% (n=8) was diagnosed with SLE after central involvement. Our patient group consisted of recently diagnosed patients and patients diagnosed in the past with a disease period ranging from 6 months to 5 years. Neurological symptoms, radiological involvement types and concomitant antibody positivity's are presented in Table 1, and clinical data is presented in Table 2. In one of patients, the first neurological attack was ischemic stroke, and the second neurological attack was demyelination syndrome. This patient was diagnosed with SLE and NPSLE after the second attack. The rate of mortality was 9.1% (n=1) in our patients diagnosed with NPSLE, and the mortal type of central involvement was ischemic stroke. With regard to concomitant secondary risk factors, one patient was pregnant. Central involvement of the pregnant patient was ischemic stroke. Other patients did not have any risk factors (oral contraceptive use, concomitant infections, familial history of thrombosis, high homocysteine levels, antithrombin III, protein C and S deficiency, gene mutations) in their etiology apart from SLE. One patient had low complement 3 and 4 (C3, C4) levels, while it was normal in other patients.

4. Discussion

The cases with SLE were 1.07% NPSLE. The female rate was higher. Clinically, most of the cases were hemiparesis. Radiologically, most of the cases were subcortical plaques. The mortality rate was 9.1%.

NPSLE has a wide variety of symptoms ranging from headache, anxiety disorder and mild cognitive impairment to severe neurological manifestations such as transverse myelitis, Guillain Barre Syndrome and ischemic stroke. Diagnosis may be delayed rarely due to variable clinical symptoms. The disease often affects patients of female gender (1). In our study, most of our patients were women, and the distribution of age and gender was similar to literature.

NPSLE is the most common presented with cerebrovascular disease, seizures, acute confusional state and neuropathy (14, 15). Similar to literature, the most common presentation type was cerebrovascular disease. 36.4% of patients had ischemia (one patient had ischemia and demyelination syndrome in different periods), 9.1% had cerebral venous thrombosis and 9.1% had PRES as involvement. Focal NPSLE generally represents localized CNS involvement in the form of venous thrombosis or arterial ischemia. These are considered to constitute about 20% of NPSLE cases (14, 16). This rate was higher in our study with 45.5%, and there was 36.4% arterial ischemia and 9.1% cerebral venous thrombosis. The fact that this rate is higher than the values in literature is attributed to ethnic differences. These patients did not have secondary risk factors, such as contraceptive use, concomitant infections, familial history of thrombosis, high homocysteine levels, antithrombin III, protein C and S deficiency and gene mutations, apart from SLE that could lead to ischemia and venous thrombosis. A patient with multiple arterial ischemia areas in her brain had pregnancy as a risk factor, and the pregnancy resulted in intrauterine death of the fetus. SLE and NPSLE diagnosis was determined simultaneously while determining the etiology of ischemia in this patient who did not have any known systemic disease in the past, and the patient had negative antiphospholipid antibodies. It has been shown in different studies that arterial ischemia and venous thrombosis rate varied between 3% and 43% (15, 17). Arterial ischemia and venous thrombosis mostly depend on thromboembolic phenomena that appear in hypercoagulability conditions associated with SLE and associated with the presence of antiphospholipid antibodies (15, 18, 19). Antiphospholipid antibodies are Lupus Anticoagulant (LA), Anticardiolipin Antibody and Anti β 2-glycoprotein I Antibodies. One of our patients had anticardiolipin antibody positivity and borderline elevated lupus anticoagulant, and this patient had clinical migraine headache and radiological involvement in subcortical plaque form. One of the other two patients with borderline elevated lupus anticoagulant level had clinical cerebral venous thrombosis, and the other patient had ischemic stroke. Other three patients with clinical ischemic stroke had no antiphospholipid antibody positivity. In our study group, 40% of patients with ischemic stroke and venous thrombosis had accompanying antiphospholipid antibody positivity while 60% had no antiphospholipid antibody positivity. This suggests that NPSLE patients have high ischemia risk even in the absence of antiphospholipid antibodies. Increased ANA serum titers are determined in more than 95% of patients (20). Positive dsDNA antibodies are determined between 37%-80% (20) and interpreted as an indicator of disease exacerbation (21). All of our patients diagnosed with NPSLE had positive anti-dsDNA. The patients with subcortical plaque had slightly higher antibody titers while patients applying with clinical stroke had significantly higher antibody titters, and this finding supports the fact that high antibody titers demonstrate disease exacerbation. More than 50% decrease in antibody titers also supports this result in the controls of patients with stroke that were performed 3 months later.

Ischemic (4%-40%) or hemorrhagic (6%-20%) stroke, which are observed in SLE patients as a complication of reversible cerebral vasoconstriction syndrome (RCVS), may result in persistent sequelae, and even death. Non-aneurysmal subarachnoid hemorrhage and posterior reversible encephalopathy syndrome (PRES) are other reported complications (22, 23).

Table 1: Neurological symptoms, radiological involvement patterns and concomitant antibody positivity at the time of diagnosis of NPSLE.

Neurological symptoms %(n)	
Hemiparesis	45.4 (5)
Headache	27.3 (3)
Psychiatric findings	18.2 (2)
Consciousness disturbance	9.1 (1)
Radiological involvement %(n)	
Ischemia	36.4 (4)
Cerebral veneus thrombosis	9.1 (1)
PRES	9.1 (1)
Subcortical plaque	45.4 (5)
Antibody positivity %(n)	
ANA	100 (11)
Anti-dsDNA	100 (11)
P-ANCA	18.2 (2)
SS-A	9.1 (1)
Anticardiolipin antibody	9.1 (1)

PRES: Posterior reversible encephalopathy syndrome, ANA: Antinuclear antibody, p ANCA: perinuclear antineutrophil cytoplasmic antibody, SS-A: Sjogren syndrome antibody.

Table 2: Clinical data of NPSLE patients.

Patient	Gender	AGE		SLE symptom	NPSLE symptom	Antibody positivity	Radiological involvement	Treatment
		SLE	NPSLE					
1	F	41	41	Proteinuria Anemia Lymphopenia Arthritis	Hemiparesis	ANA anti ds-DNA	Subcortical plaques and acute infarct	Hydroxychloroquine, Deltacortril
2	F	46	46	Arthritis Anemia Proteinuria	Headache	ANA anti ds-DNA	Subcortical plaques	Hydroxychloroquine, Azathioprine
3	F	14	19	Proteinuria Arthritis C3-C4 Levels↓	Anxiety	ANA anti ds-DNA	Subcortical plaques	Deltacortril Antidepressant
4	F	37	37	Anemia Proteinuria Arthritis Abortion	Headache	ANA anti ds-DNA SS-A Anticardiolipin antibody Lupus anticoagulant borderline high	Subcortical plaques	Azathioprine
5	F	33	33	Arthritis Photosensitivity	Headache	ANA anti ds-DNA	Subcortical plaques	Hydroxychloroquine
6	F	42	43	Anemia Thrombocytopenia Proteinuria Abortion	Hemiparesis	ANA, anti ds-DNA	Multiple acute infarct	Deltacortril
7	F	20	20	PhotosensitivityAnemia Thrombocytopenia	Hemiparesis Epileptic seizure	ANA anti ds-DNA Lupus anticoagulant borderline high	Cerebral veneus thrombosis	Hydroxychloroquine Azathioprine Warfarin sodium Levetiracetam
8	F	82	82	Discoid rash Photosensitivity Arthritis	Right hemiparesis	ANA anti ds-DNA p-ANCA	Subcortical and periventricular contrast retaining plaques (Demiyelinating syndrome) Acute infarct	Hydroxychloroquine Acetylsalicylic acid
9	M	38	38	PhotosensitivityDiscoid rash Arthritis Anemia Proteinuria	Hemiparesis	ANA anti ds-DNA p-ANCA Lupus anticoagulant borderline high	Subcortical plaques and acute infarct	Rituximab Deltacortril Acetylsalicylic acid
10	F	23	26	Anemia Thrombocytopenia Arthritis Discoid rash	Psychosis	ANA anti ds-DNA	Subcortical plaques	Azathioprine Antidepressant
11	F	22	22	Arthritis Proteinuria	Consciousness disturbance (somnolance)	ANA anti ds-DNA	PRES	Hydroxychloroquine Calcium channel blocker

In SLE patients, it is important to differentiate RCVS from cerebral vasculitis since they have different treatments; and while cerebral vasculitis responds to high dose corticosteroids and aggressive immunosuppression, RCVS responds to calcium channel blockers (24). RVCS is one of the rare clinical manifestations in SLE patients. Similar to literature, we had a patient with a clinical manifestation of PRES in our study.

The most common MRI anomalies observed in these patients are small subcortical hyperintense lesions and infarctions (11). The most common type of radiological involvement was subcortical plaques (45.4%) in our patients, similar to literature.

MRI is especially sensitive in the determination of hemorrhagic and ischemic infarction and transverse myelitis; however, it does not currently have the spatial resolution required for detecting microvascular involvement (it is known that 42% SLE patients with neurological symptoms have microvascular involvement) (25, 26). Most of the neuropsychiatric events associated with SLE appear at the initial of disease or in the first 1-2 years after the diagnosis (12,17). In our study, 27.3% (n=3) of patients diagnosed with NPSLE had SLE diagnosis before central involvement and SLE diagnosis period varied between 1 and 5 years, while 72.7% (n=8) was diagnosed with SLE after central involvement. Eleven of 1028 SLE patients (1.07%) had NPSLE diagnosis. In our SLE patient group, NPSLE rate was lower than the levels in literature (12). The reason of that was considered to be: 1) Headache, mild anxiety disorders and mood disorders were not reported as complaints by some patients, 2) The deficiencies in complaint recording for these patients due to inadequate questioning, 3) MRI being evaluated as normal in complaining patients and the possibility of missing microvascular involvement. MRI is one of the common used imaging methods with a relatively easy access that contributions in diagnosis and differential diagnosis of NPSLE. However, it is not a sufficiently reliable method in determining NPSLE diagnosis since it does not show microvascular lesions. In cases that conventional MRI remains insufficient in determination of the lesion, the use of advanced imaging methods is recommended such as SPECT or PET (12). Since the cost of these tests is higher, they should be used in cases with SLE diagnosis and NPSLE suspicion, in which MRI remained to be insufficient for diagnosis. This is because central involvement is the most important risk factor affecting morbidity and mortality in SLE.

High dose steroids (methylprednisolone) are used in SLE treatment, and an immunosuppressive agent should be included in treatment after the patient goes in remission. There is no standard treatment regimen in NPSLE, and a treatment protocol that is similar to SLE is applied. At least 5 years of immunosuppressive treatment is recommended to SLE patients with neurological involvement (27). Medicines such as steroids, cyclophosphamide, mycophenolate mofetil and azathioprine are used as immunosuppressive agents. The immunosuppressive agent to be selected is evaluated according to the experience of the clinician and the severity of disease. It was shown in a study that a much better response is obtained with cyclophosphamide use in the treatment of patients diagnosed with severe NPSLE compared to the use of methylprednisolone (28). In addition, symptomatic treatments are applied on the patients, in which antiepileptic agents are administered to patients with seizures, and antidepressant and anxiolytic agents are administered to patients with psychiatric complaints. Life-long anticoagulation with warfarin is recommended in all thrombosis cases associated with antiphospholipid antibody. Different combinations were used in our patients in the form of monotherapy and polytherapy according to their clinical status. Although one of the most effective drugs was cyclophosphamide, none of the patients diagnosed with NPSLE used cyclophosphamide in our clinic. As immunosuppressants, deltacortril and azathioprine use were higher in our patients. Hydroxychloroquine was started in 54.5% of our patients who were diagnosed with NPSLE since it has an effect known to reduce central nervous system involvement. Rituximab and deltacortril were used in the male patient with poor clinical status and wide ischemic area, but the patient passed away 2 months after the treatment. In a retrospective study, it was shown that rituximab was efficient and pretty safe in pediatric NPSLE patients (29). There is no sufficient number of studies about rituximab until this date. The death of the only male patient with NPSLE diagnosis suggested that the course of central involvement may be more severe in men compared to female gender. Other patients were clinically stable, and no new neurological attack was observed in their follow-up.

5. Conclusions

Symptoms such as headache and mild mood disorder are common in SLE. In order to avoid missing NPSLE diagnosis in patients with these symptoms who underwent cranial MRI, the use of imaging methods such as PET and SPECT may be important in early diagnosis and treatment since they are more efficient in showing microvascular involvement. It should be considered that patients may rarely present with stroke secondary to RVCS and PRES, and differential diagnosis is important due to the difference in their treatment. Since there is no standard optimization in treatment and no gold standard method for diagnosis yet, it is important for patients to be evaluated by an experienced clinician. There is a need for new studies to be performed with large groups in order to determine a standard in therapy.

Conflict of Interests
All authors declared that there is no conflict of interest
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Author Contributions
FŞ contributed to the conception
and design of the study. FŞ and MC contributed to the collection of the data, statistical analysis, evaluation of the results, and writing of the manuscript. FŞ contributed to revising the work and final approval of the version.
Ethical Approval
Ethics committee approval was taken for the study (06/17/26.09.2019).
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