Frequency of Different Neuropsychiatric Manifestations of Systemic Lupus Erythematosus at a Tertiary Care Hospital in Pakistan

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ABSTRACT

Objective: To determine the frequency of different neuropsychiatric manifestations of systemic lupus erythematosus

Study Design: Cross-sectional study.

Place and Duration of Study: Division of Rheumatology Lady Reading Hospital, Peshawar Pakistan, from Sep 2020 to Feb 2021.

Methodology: 31 patients who fulfilled the 2019 ACR/EULAR criteria for SLE diagnosis were included in the study. Different features of neuropsychiatric manifestations of systemic lupus erythematosus were recorded on a proforma.

Results: Our study sample included 27 females and four males. Most of the patients were young, with a mean age of 23.12 ± 10.74 years. All patients had positive Anti-nuclear antibodies (100%), while anti-double standard DNA antibody was found in 21 patients (67. 74%). Seizures were the most common neuropsychiatric feature, i.e., found in 18 patients (58%), followed by headache (25.8%), acute confusional state (25.8%) and CNS demyelinating disease (19.3%).

Conclusion: We found that seizures, headache and acute confusional state were the most common neuropsychiatric manifestations of systemic lupus erythematosus.

Keywords: Anti ds DNA, Demyelinating disease, Neuropsychiatric systemic lupus erythematosus, Seizures.

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INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disorder characterized by multisystem inflammation, protean clinical manifestations, and a relapsing and remitting course.[1] SLE has affected more than 1.5 million people in the United States alone.[2] Globally, the annual incidence of SLE has ranged from approximately 1-10 per 100,000 populations, while the prevalence of SLE has been estimated to range from approximately 5.8 to 130 per 100,000 populations.[3] SLE predominantly affects the female gender with a male to female ratio of 9 to 1.[4]

SLE is a chronic disease affecting various body organs with different proportions. Thus, it carries a variable prognosis.[5] Depending upon the organ involved, and some patients may have a relatively benign disease while others may have life-threatening manifestations. The disease can sometimes progress from mild disease activity to near-fatal disease within the same individual if not managed according.[6]

SLE is a multisystem disorder that can present a wide range of symptoms. Some of the common organs systems involved are the skin, joints, kidneys, blood and serosa, leading to the features which include, but are not limited to are, malar rash, oral ulcers, alopecia, pleural effusion, proteinuria, acute kidney injury, low platelets count, hemolytic anaemia and high temperature.[7]

Like other organs, SLE can affect the central and peripheral nervous system, called the neuropsychiatric lupus erythematosus (NPSLE). NPSLE is characterized by a variety of neurological manifestations which are frequently overlooked despite being associated with increased mortality and morbidity.[8,9] In one study conducted in China, some of the manifestations together with their percentage incidence included; cognitive dysfunction occurred in 42.1%, headache in 31.2%, acute confusional disorder in 16.8%, cerebro-vascular disease in 12.3%, mood disorder in 10.8%, seizures in 8.9%, anxiety in 6.7%, psychoses in 6.5%, movement disorders in 2.3%.[10]

The primary purpose of our study was to determine the frequency of different manifestations of NPSLE. Since no study has been conducted in our setup, this study will provide important data about the pattern presentation and neurological manifestations in SLE patients.

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METHODOLOGY

This cross-sectional study was conducted at the Rheumatology Division of Lady Reading Hospital, Peshawar Pakistan, from September 2020 to February 2021. Thirty-one patients were included in the study through the non-probability consecutive sample. The sample size was calculated using 6.25%[10] the frequency of different manifestations of NPSLE among SLE patients using the margin of error of 9% and confidence level of 95% through the WHO sample size calculator. The diagnostic criteria were based on ACR/EULAR 2019 criteria for SLE. NPSLE features were defined according to ACR nomenclature and case definitions for neuropsychiatric lupus syndrome.[11]

Inclusion Criteria: Patients of age range 10 to 70 years, fulfilling the diagnostic criteria of SLE were included in the study.

Exclusion Criteria: Patients with septic meningitis and encephalitis, multiple sclerosis; metabolic disorders; and CNS tumours were excluded from the study.

Ethical approval was obtained (ERC/IERB: 02-1/LRH/MTI, dated: 06/01/2020) from the Hospital Ethical Committee of LRH, and data was collected from all the diagnosed NPSLE patients admitted under the Rheumatology division of LRH. Informed consent was taken from the patient or his/her next kin. A detailed history was taken, a complete physical examination was performed, and all patients' records, including MRI findings/all other investigative findings, were noted and recorded on a predesigned pro forma. Then the frequency of every manifestation was calculated among the total cases of diagnosed NPSLE included in the study. Strict exclusion criteria were followed to control confounding.

Statistical Package for Social Sciences (SPSS) version 23.0 was used for the data analysis. Quantitative variables like age were described as mean and standard deviation. Categorical variables like gender and different manifestations were described as fre-quency and percentages. Finally, the chi-square test or Fischer exact test was applied to determine the difference between different NPSLE manifestations by age and gender, and the *p*-value ≤0.05 was considered significant.

RESULTS

This study included 31 patients with NPSLE at the Rheumatology Division of Lady Reading Hospital, Peshawar. There were 27 females (87%) and 4 (12.9%) male patients (Table-I). Most of the patients were young, with a mean age of 23.12 ± 10.74. The youngest patient was 11 years, while the oldest patient was 60 years (Table-I).

Table-I: Basic Demographics.

Demographics	Values
Females	27 (87%)
Males	4 (12.9%)
Minimum Age	11 Years
Maximum Age	60 Years
Mean Age ± SD	23.12 ± 10.74 Years

All patients had positive ANA (100%). Anti-DsDNA was found in 21 patients (67.7%), while Anti-Ro/SSA antibody was found in 8 patients (25.8%) (Table-II).

Table-II: Different auto antibodies (n=31).

Antibodies	Total Number
ANA	31 (100%)
Anti-Ds DNA	21 (67.7%)
Anti-Ro/SSA Antibody	8 (25.8%)
Anti-Nucleosome	3 (9.7%)
Anti La/SSB	3 (9.7%)
Anti-RNP	2 (6.5%)
Anti-Smith	1 (3.2%)
Anti-Histone	1 (3.2%)

In our study, seizures were the most common NPSLE feature, i.e., found in 18 patients (58.1%), followed by headache in 8 patients (25.8%), the acute confusional state in 8 patients (25.8%), demyelinating disease in 6 patients (19.3%), stroke in 4 patients (12.9%), dural sinus thrombosis, cranial nerve palsy and myelitis; each was found in 3 patients (9.7%), and CNS vasculitis, Meningoencephalitis and depression; each was found in 2 patients (6.4%). Other CNS manifestations, including Chorea, posterior reversible encephalopathy syndrome (PRES syndrome), and Psychosis, were found in 3 patients (9.7%) (Table-III).

Table-III: Different neuropsychiatric manifestations.

Manifestations	Total Number
Seizures	18 (58.1%)
Headache	8 (25.8%)
Acute Confusional State	8 (25.8%)
Demyelinating Disease	6 (19.3%)
Stroke	4 (12.9%)
Dural Sinus Thrombosis	3 (9.7%)
Cranial Nerve Palsy	3 (9.7%)
Myelitis	3 (9.7%)
CNS Vasculitis	2 (6.4%)
Meningoencephalitis	2 (6.4%)
Depression	2 (6.4%)
Others	3 (9.7%)

All the patients, 31 (100%) were positive for ANA, and Anti-dsDNA antibodies were the second most common antibodies found in our patients, 21 (67.7%), followed by Anti-Ro/SSA in 8 patients (25.8%), Anti-La/SSB and Anti-nucleosome each was found in 3 (9.7%), and Anti-RNP was found in 2 patients (6.5%) (Table-II). Anti-dsDNA was the only Extractable Nuclear Antigen Antibodies (ENA) found in all 4 (100%) male patients, and it was also the most common ENA in females with 17 (63%) (Table-IV).

Table-IV: Different auto antibodies in patients (n=31).

Antibodies	Male (n=4)	Female (n=27)
ANA	4	27
Anti-dsDNA	4 (100%)	17 (63%)
Anti Ro/SSA antibody	-	8 (30%)
Anti-Nucleosome	-	3 (11.1%)
Anti La/SSB	-	3 (11.1%)
Anti RNP Antibody	-	2 (7.4%)
Anti-Smith	-	1 (3.7%)
Anti-Histone	-	1 (3.7%)

While all other auto antibodies were found only in female patients, which were including Anti-Ro/SSA antibody in 8 female patients (30%), Anti-La/SSB and Anti-nucleosome; each was found in 3 female patients (11.1%), Anti-RNP was found in 2 female patients (7.4%), and Anti-smith and Anti-histone; each was found in 1 female patient (3.7%) (Table-V). Though seizures were the most feature in both males and females, we observed that stroke and cranial nerve palsy were more common in males, statistically signi-ficant (p=0.03).

Table-V: Different neuropsychiatric manifestations.

Manifestations	Male (n=4)	Female (n=27)	*p*-value
Seizures	3 (75%)	15 (55.5%)	0.72
Headache	1 (25%)	7 (25.9%)	0 .96
Acute Confusional State	-	8 (30%)	0.20
Demyelinating Disease	-	6 (22.2%)	0.24
CVA	2 (50%)	2 (7.4%)	0.003
Dural Sinus Thrombosis	-	3 (11.1%)	0.48
Cranial Nerve Palsy	2 (50%)	1 (3.7%)	0.003
Myelitis	1 (25%)	2 (7.4%)	0.26
CNS Vaculitis	-	2 (7.4%)	0.69
Meningoencephalitis	-	2 (7.4%)	0.7
Depression	-	2 (7.4%)	0.57
Others	-	3 (11.1%)	-

DISCUSSION

We studied 31 patients with SLE and found that seizures were the most common CNS manifestation occurring in 58% of the patients. Other common manifestations were headaches and acute confusional states occurring in 8 patients, accounting for 25.8% of all patients.

Our cohort comprised predominantly females accounting for 87% of all patients in our study. It has been a fact that SLE occurs more in females compared to males, with a ratio of 9 to one. Similarly, CNS manifestations are also more common in females.[12] Moreover, SLE occurs most commonly in the young population,[13] which is also in accordance with this study as most of the study population was young (mean age= 23.12 ± 10.7 years).

In this study, we observed that seizures were the most common NPSLE feature (58%), and in all cases, the generalized tonic-clonic seizure was observed. Another study conducted in India has also reported our finding, which recorded seizures occurring in 58% of the patients.[14] In addition, they observed that lupus headache was the 2nd most common clinical feature (40%), which was also in accordance with our study; however, in this study, the frequency was slightly lower (28.1%). Moreover, they reported stroke, anxiety and mood disorder occurring in 20%, 18% and 30%, respectively, which is higher than our study.

Kakati *et al*, 15 also studied 52 patients for different CNS manifestations of SLE in northeast India. Their cohort also comprised majorly of female patients (92%), which was in accordance with our study. In their study, cognitive impairment and seizures were the most common CNS manifestations, with seizures occurring in up to 42.1% of the patients. In another study conducted in Mexico,[16] seizures in SLE were reported in 51% of the patients. The most common type of seizure in both studies was generalized tonic-clonic seizures. In our study, seizures also occurred in 58%, and generalized tonic-clonic was the most common type of seizure.

The literature review showed a verity of auto-antibodies positivity in NPSLE patients regarding the autoantibodies profile. Pradhan *et al*, observed,[14] that Anti-Rib-P antibodies and anti-neuronal antibodies were the most common autoantibodies found in NP-SLE patients, while one study reported that anti-dsDNA is the most common auto-antibody present in 88.6% of the patients.[16] Anti-dsDNA was also the most frequently found auto-antibody (67.7%) in this study. When stratified by gender, we observed that Anti dsDNA was present in all male patients with NP-SLE.

We observed that the Anti Ro antibody was the 2nd most common antibody found in patients with features of NP–SLE. This was a unique finding since Anti Ro antibody is strongly associated with Sjogren syndrome,[17] and no association with NP-SLE has been described in the literature.

The exact pathophysiology of neuropsychiatric SLE is unknown; however, it is believed to be multifactorial due to its diverse presentation. It is believed that neuronal injury occurs either directly through antibodies mediated receptor activation or through disruption of the blood supply to the neurons through various cytokines and immune complex-mediated pathways. Indeed, micro vasculopathy has been the most common finding seen in patients with NPSLE.[18-21]

American College of Rheumatology in 2001 proposed a revised criterion for NPSLE in which they have described 19 different clinical entities.[11] In a systemic review published in 2011, 5057 SLE patients were studied for different clinical features. They observed that neuro-psychiatric features were seen in 1439 (28.5%) SLE patients, with 2.2 to 94.7%.[22] They observed the following NPSLE manifestations in descending order: headache (12.2%), mood disorders (7.4%), seizures (7.0%), cognitive dysfunction (6.6%), and cerebrovascular disease (5.0%). Other syndromes occurred in less than 5% of the cohorts.[22]

Our study was not without limitations. First, our sample size was small, i.e., 31 patients. However, SLE is a rare disease, and CNS manifestations occur in only 28–35% of patients. Therefore, we did not perform detailed investigations of all patients, including antiphospholipid antibodies.

CONCLUSION

Neurological manifestations are not uncommon in SLE and possess high mortality and morbidity. Apart from seizures, other common manifestations are subtle, including headaches and cognitive decline. Therefore, there should be a high index of suspicion and evaluation by clinical, neuroimaging and neurophysiological tests so that NPSLE can be diagnosed early.

Conflict of Interest: None.

Author's Contribution

NU: Supervision, data collection, analysis, SA: Originol idea of the study, SHM: Manuscript writing, statistical analysis, SK: Proof reading, final approval, IH:, SU: Data collection.

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