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Original Article

# Neuropsychiatric Manifestations in Systemic Lupus Erythematosus Patients at a Tertiary Hospital in Peru

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## Abstract

**Background:** Systemic lupus erythematosus is a prevalent autoimmune disease that affects multiples systems, exerting its most incapacitating and life-threatening impact through neuropsychiatric involvement. According to the American College of Rheumatology (ACR), 19 neuropsychiatric syndromes types of SLE are classified into categories encompassing the central and peripheral nervous systems. This study aimed to investigate the frequency of neuropsychiatric manifestations in systemic lupus erythematosus patients admitted to Hospital Cayetano Heredia in Lima, Peru, between 2008 and 2019.

**Methods:** A retrospective observational study was conducted, entailing the review of 240 medical records of patients diagnosed with systemic lupus erythematosus during the specified period, based on the Systemic Lupus International Collaborating Clinics (SLICC) 2012 criteria. Among these records, 55 patients presented neuropsychiatric systemic lupus erythematosus (NPSLE). Data were collected using standardized form and entered into Microsoft Excel 2019 database. Statistical analysis was performed using Stata v16.

**Results:** The frequency of neuropsychiatric compromise in systemic lupus erythematosus patients was found to be 22.91%. Among the 55 systemic lupus erythematosus patients, 40 demonstrated involvement of the central nervous system (72.72%), 2 exhibited involvement of the peripheral nervous system (3.63%), and 13 displayed involvement in both the central nervous system and peripheral nervous system (23.63%). The most prevalent psychiatric disorder observed was a major depressive disorder, with a prevalence rate of 30.9%.

**Conclusion:** The study revealed a frequency of 22.91% for neuropsychiatric involvement in systemic lupus erythematosuspatients at Cayetano Heredia Hospital between 2008 and 2019, with central nervous system manifestations prevailing. Furthermore, the findings suggest that NPSLE commonly manifested after the diagnosis of systemic lupus erythematosus.

**Keywords:** Systemic erythematosus lupus, neuropsychiatric compromise, neurolupus, central nervous system symptoms, peripheral nervous system symptoms

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## Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that varies in prevalence and incidence by age, ethnicity, gender, genetics, etc.[1] Epidemiological data have been evaluated at a global level with a prevalence of 9 to 241 per 100 000 person-years and an incidence of 0.3-23.2 per 100 000 person-years.[2]

Systemic lupus erythematosus can present, per se, compromise of the central and peripheral nervous system (neurolupus) encompassing neurological and psychiatric manifestations, due to this they will be referred to as SLE with neuropsychiatric symptoms (NPSLE).[3] It is known that, in terms of prevalence, 14%-80% of patients develop NPSLE; either in the first 2 years after the diagnosis of SLE or debuting with these symptoms.[4] In addition, active SLE or antiphospholipid antibodies with high titers are considered risk factors for presenting neuropsychiatric manifestations.[5]

According to the American College of Rheumatology (ACR), the manifestations are classified into 19 neuropsychiatric syndromes, of which 12 are related to the central nervous system (CNS) and 7 to the peripheral system.[6] Regarding the frequency of these, the most common are headache (20%-40%), seizures (7%-10%),[7] acute confusional state (7%), cognitive dysfunction (80%),[8] psychosis (3%-5%) (normally at the beginning of the disease and with rapid remission if treated), cerebrovascular disease (2%-8%),[9] depression (79%), and anxiety (80.6%).[10]

In Peru, there is no recent data on neurological and psychiatric involvement in SLE; therefore, it is important to evaluate these manifestations, with timely diagnosis and treatment. The main objective of this study is to determine the frequency of neuropsychiatric manifestation in SLE in Cayetano Heredia Hospital between 2008 and 2019.

## Material and Methods

### Study Design

An observational, descriptive, and retrospective study was conducted with convenience sampling, in which 240 paper medical records of patients diagnosed with SLE who were admitted to the Cayetano Heredia Hospital (Lima, Peru) between 2008 and 2019 were reviewed. Although we reviewed medical records for patients, an individual informed consent was not needed for this study.

These patients were selected based on the SLE diagnostic criteria (SLICC 2012). Of which, we selected 55 records with neuropsychiatric manifestations according to the ACR nomenclature and case definitions for the 19 neuropsychiatric lupus syndromes. Those each case definitions provided inclusion and exclusion criteria for differential diagnosis in NPSLE. Also, reported signs and symptoms, laboratory test, and imaging tests were considered for proper evaluation.[6] Besides, all psychiatric and neurological diagnoses were made by a psychiatrist and neurologist, respectively.

A data collection sheet was designed to synthesize the information from the medical records. This information obtained was entered through a Google Form into an electronic database in Microsoft Excel 2019, to which only the researchers had access.

### Main Points

- **Research motivation:** The lack of information regarding the neuropsychiatric component of lupus in Peru was our first motivation to conduct this research.
- **Main findings:** Headache, depression, and seizures are the 3 most common neuropsychiatric manifestations of lupus.
- **Implications:** With these results, we conclude that these manifestations are present at some frequency, and an early diagnosis must be performed to treat them correctly.

### Statistical Analysis

Sociodemographic and clinical variables were expressed in frequencies and percentages. Measures of central tendency were used for quantitative variables. Statistical analysis was performed in Stata Statistical Software (Release 16. College Station, TX: StataCorp LLC).

### Ethics

This study obtained the approval of the Institutional Research Ethics Committee of the Universidad Peruana Cayetano Herediaand the Research Committee of Hospital Cayetano Heredia (SIDISI: 103437). Personal information was coded and only the investigators could access the database. There was no harm in conducting this study as no patient was directly involved.

## Results

We collected 240 medical records from patients diagnosed with SLE. Of these, 55 had SLE and neuropsychiatric compromise, representing a frequency of 22.91%. Of these patients, 53 were women (96.36%) and 2 were men (3.64%). The average age was 31.62 years (Figure 1). Regarding the level of education, we found 1 with incomplete primary education (1.8%), 3 with complete primary education (5.5%), 5 with incomplete secondary education (9.1%), 37 with complete secondary education (67.3%), 5 with incomplete superior education (9.1%), and 4 with superior technician (7.3%).

The clinical manifestations of the patients were divided according to the classification of the American College of Rheumatology (ACR 1999) into the CNS and peripheral nervous system (PNS) involvement (Table 1). Of the 55 patients included, 40 (72.72%) had CNS involvement, 2 (3.63%) had PNS involvement, and 13 (23.63%) had both CNS and PNS involvement.

Within the CNS manifestations, 34 patients presented headache (61.81%), 17 mood disorders (30.9%), 8 seizure disorders (14.54%), 5 cerebrovascular disease (9.09%), 5 anxiety disorders (9.09%), 4 psychosis (7.27%), 4 acute confusional state (7.27%), 1 myelopathy (1.81%), and 1 movement disorder (1.81%).

Regarding the manifestations in SNP, 10 patients presented polyneuropathies (18.18%), 4 cranial neuropathies (7.27%), 1 plexopathy (1.81%), 1 mononeuropathy (1.81%), 1 autonomic neuropathy (1.81%), and 1 aseptic meningitis (1.81%) (Table 1)

Finally, cognitive dysfunction, demyelinating syndromes, myasthenia gravis, and Guillain–Barré syndrome were not observed in this study.

The onset of neuropsychiatric manifestations before and after the SLE diagnosis, on average,

**Table 1.** Neuropsychiatric Manifestations (NPSLE)

| | n | % |
|---|---|---|
| Central nervous system | | |
| Headache | 34 | (61.81) |
| Mood disorders | 17 | (30.90) |
| Seizures | 8 | (14.54) |
| Cerebrovascular disease | 5 | (9.09) |
| Anxiety disorders | 5 | (9.09) |
| Psychosis | 4 | (7.27) |
| Acute confusional state | 4 | (7.27) |
| Myelopathy | 1 | (1.81) |
| Aseptic meningitis | 1 | (1.81) |
| Movement disorder | 1 | (1.81) |
| Peripheral nervous system | | |
| Polyneuropathy | 10 | (18.18) |
| Cranial neuropathy | 4 | (7.27) |
| Plexopathy | 1 | (1.81) |
| Mononeuropathy | 1 | (1.81) |
| Autonomic neuropathy | 1 | (1.81) |

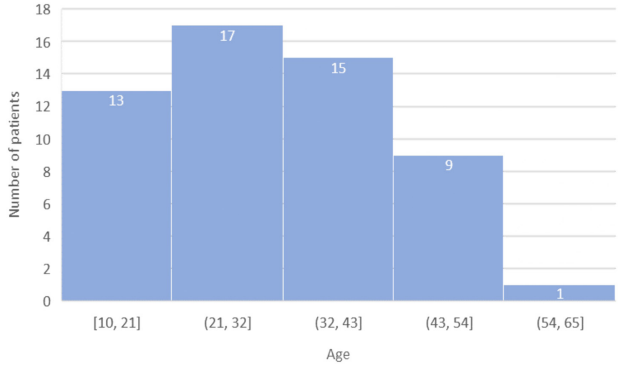


**Figure 1.** Range of ages of NPSLE patients.

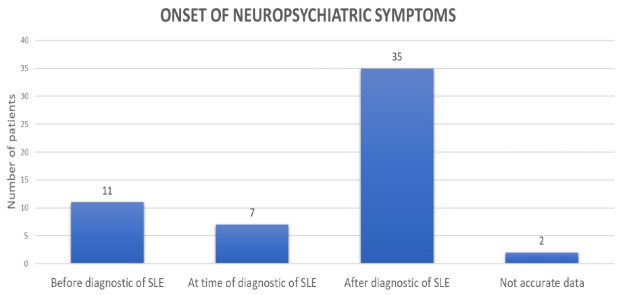


**Figure 2.** Onset of NPSLE symptoms.

were 1 year 8 months and 4 years 8 months, respectively. In our study, we found 11 patients with manifestations before diagnosis, 7 patients during diagnosis, and 35 patients after SLE diagnosis. In 2 patients, it was not possible to determine the onset of these syndromes (Figure 2).

The immunological criteria considered were the positive results for the following antibodies: 42 positive for antinuclear antibodies (ANA); 34 double-stranded DNA antibodies (anti-dsDNA); 14 anti-Smith antibodies (anti-Sm); 12 anti-sn-ribonucleoprotein (sn-RNP); 4 antiphospholipid (AAF); 9 anti-Ro (SSA); 7 anti-ribosomal P antibodies (anti-P); and 4 anti-La (SSB). The frequencies between positive antibody results and some type of neuropsychiatric compromise are represented in Figure 3 and Figure 4.

## Discussion

The main objective of this study was to determine the frequency of neuropsychiatric manifestations in patients with SLE at Hospital Cayetano Heredia between 2008 and 2019, which was 22.91%. Comparing our results with other studies in Latin America, we observed similar trends. Studies from Colombia and Brazil reported frequencies of 26.2%[11] and close to 26%,[12] respectively. However, a study conducted in Greece found a much lower prevalence of 4.3% of the same manifestations.[13] Notably, a thesis from Lima, Peru, in 1983 described 24% of neurological compromises in a tertiary-care hospital.[14]

Regarding CNS involvement, headache was the most common symptom, accounting for 61.81% of cases. Our findings are consistent with a study from Brazil, which reported a prevalence of 75.7% for headaches, with 66.1% being migraine-type headaches.[15] Similarly, an Egyptian study showed a prevalence of 54.4%.[16] Remarkably, in a 2004 meta-analysis on the characteristics of lupus headache, the authors concluded that these are nonspecific, lacking significant association with specific headache types or NPSLE.[17]

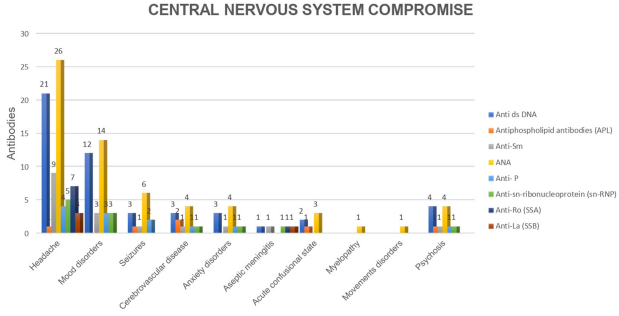


**Figure 3.** Comparison of antibodies and central nervous system symptoms.

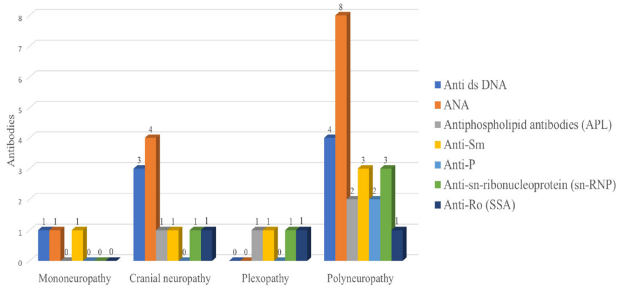


**Figure 4.** Comparison of antibodies and peripheral nervous system symptoms.

We found 8 patients with seizure disorders (14.54%), mainly with tonic–clonic characteristics, who had been diagnosed around the onset of SLE. These findings differed with a cohort study that reported seizures occurring up to 9 years after SLE onset and their association with organ damage and reduced quality of life.[18] In our study, we were unable to measure organ damage nor life quality. Additionally, a multicenter study in the United States reported a prevalence of 6.7% for seizures in SLE, with an early onset in the presence of type-IV lupus nephritis or psychosis.[19] Seizures in patients with SLE are also linked to the presence of anticardiolipin and anti-beta 2 glycoprotein I antibodies.[20] In our sample, not all patients who had seizures underwent the study of these markers.

The risk of cerebrovascular accident (CVA) in SLE is high and represents one of the most frequent and deadly complications.[21] In our study, we found 5 patients (9.09%) who had stroke, with 1 patient experiencing the onset of the disease. An observational study in Mexico reported a prevalence of 3.1% for strokes in SLE, with occurrences documented from early to late stages of the disease, up to 10 years after diagnosis.[22] The presence of antiphospholipid antibodies has been significantly associated with cerebrovascular events, as supported by previous research.[23]

Certain infrequent manifestations in NPSLE include acute confusional state or delirium, we describe 4 cases (7.27%), which were presented together with other neuropsychiatric symptoms such as headache, depression, psychosis, and stroke. A cohort study reported a delirium prevalence of 17% among SLE patients, besides it was suggested the use of immunological markers such as Interleukin 6 or 8 (IL-6 or IL-8) to attribute delirium to SLE.[24]

From the most infrequent neurological manifestations, we reported a case of transverse myelopathy (TM) (1.81%). Previous studies have shown similar frequencies, with one study reporting a TM frequency of 2% in a population of 600 SLE patients;[25] besides, a case series reported 15 lupus patients with TM between 1994 and 2007.[26] We also described a case of movement disorder (1.81%), this was a patient who debuted with chorea 7 years before the diagnosis of SLE. This syndrome may be related to the presence of antiphospholipid antibodies but few cases are reported in the literature to explore more about the physiopathology.[27] In addition, we identified a case of aseptic meningitis (1.81%) at the onset of SLE. However, the

underlying mechanisms of these manifestations in SLE remain poorly understood.

In our study, major depressive disorder (MDD) was the most common psychiatric disorder, affecting 30.90% of patients, followed by generalized anxiety disorder (GAD) in 9.09%. These results differ slightly from a systematic review of 59 studies, mainly from North America, Europe, and Asia, which reported higher frequencies for MDD (24%) and GAD (37%); this probably differs from our results by the sample size.[28] In our study, the next most frequent disorder was psychosis with 4 patients (7.27%), the disorder onset was before and after the diagnosis of SLE. Our results are similar with an international cohort study in Mexico, Canada, the United States, Europe, and Asia that reported a frequency of 1.53% of psychosis with an onset of 1 year before and 3 years after the SLE diagnosis.[29]

We found 10 patients (18.18%) with polyneuropathy, including paresthesias, numbness, dysesthesias, and burning sensations, among others. Polyneuropathies due to SLE are nonspecific and are diagnoses of exclusion. A Spanish cohort of patients with SLE reported a higher prevalence of 36.6% for polyneuropathies,[30] whereas a retrospective study in Italy identified 68% of PNS involvement attributable to SLE, with 39.2% representing patients with polyneuropathy.[31]

We describe 4 patients (7.27%) with cranial neuropathies, 3 of whom had involvement of the second cranial nerve (optic neuritis), and the last with a palsy of the fourth cranial nerve. Consistent with our findings, a case series of Asian patients, they reported 8 patients with various cranial nerve compromises especially optic and oculomotor nerves.[32] Although, according to the 1999 ACR case definitions, NPSLE may affect the twelve cranial nerves, even though there has been few cases reported.

The occurrence of Mononeuropathy, autonomic neuropathy, and Plexopathy was relatively rare on our study, with each representing 1.81% of cases. A case–control study in China reported similar rates of mononeuropathies (13.9%) and autonomic neuropathies (2.5%), but no cases of plexopathies were observed.[33]

Regarding laboratory investigations, of the 55 patients diagnosed with NPSLE, 52 patients (92.85%) were tested for at least 1 type of antibody at the time of NPSLE diagnosis. Positive anti-Sm antibodies were found in 14 patients, while 34 patients had positive anti-dsDNA antibodies. The presence of these antibodies may be related to SLE.[34] We also identified 7 patients with positive anti-RibP antibodies, which has been previously associated to NPSLE in the CNS, particularly with depression and psychosis.[35]

In our study, we demonstrated a frequency of 22.91% of patients exhibiting neuropsychiatric manifestations in systemic lupus erythematosus in Cayetano Heredia Hospital. Being CNS involvement more common than the PNS. Within the CNS syndromes, headache (61.81%) was the most frequent manifestation, and the most severe ones were seizures (14.54%), and cerebrovascular disease (9.09%). Within the PNS syndromes, polyneuropathy (18.18%) was the most common manifestation. Depression was the most frequent psychiatric syndrome in our study, which is why greater emphasis is needed on the diagnosis and treatment of this disease. The onset of the most frequent neuropsychiatric manifestations was after the diagnosis of SLE.

In summary, we observed similarities and differences in the prevalence of certain manifestations when compared to other studies from various regions, highlighting the multifaceted nature of NPSLE. Larger multicenter studies would provide a more comprehensive understanding of NPSLE across different populations. Finally, assessing diverse parameters such as SLE disease activity index (SLEDAI), specific antibody tests, cerebrospinal fluid analyses, and imaging studies, among others, are crucial for early diagnosis and tailored treatment approaches, ultimately improving the quality of life for patients with this complex and challenging condition.

**Ethics Committee Approval:** This study was approved by Institutional Research Ethics Committee of Universidad Peruana Cayetano Heredia (Approval No: 103437, Date: August 19, 2019).

**Informed Consent:** N/A.

**Peer-review:** Externally peer-reviewed.

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**Declaration of Interests:** The authors have no conflict of interest to declare.

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