Neuropsychiatric lupus erythematosus in a cohort of Egyptian patients

Salma M. Ragab1* and Amira M. Ibrahim2

Abstract

Background: The neuropsychiatric lupus erythematosus (NPSLE) is a severe complication of systemic lupus erythematosus (SLE) that is characterized by a variety of neurological manifestations involving both central and peripheral nervous system with variable mechanisms. This study aimed to investigate the frequency of NPSLE and its relation to other clinical and laboratory findings in SLE patients.

Results: We retrieved the medical records of 134 SLE patients during the study period; of them, 68 patients (50.7%) had NPSLE. Headache (55.9%) was the most frequent NPSLE manifestation followed by seizures (54.4%), psychosis was the third most frequent one with a percentage of 41.2. The demographic data didn't differ in patients with and without NPSLE. NPSLE patients had lower complement 3 (C3) ($p = 0.025$) and C4 ($p = 0.008$) levels, more lupus anticoagulant level ($p = 0.033$) and more frequency of antiphospholipid syndrome ($p = 0.030$). There was no statistical difference regarding the drug intake or other laboratory findings. Disease activity and damage indices didn't differ in both groups.

Conclusion: The prevalence of NPSLE in this study was 50.7%. Headache, seizures and psychosis were the most frequent neuropsychiatric manifestations in the studied patients. SLE patients with neuropsychiatric manifestations had lower complement levels, higher lupus anticoagulant antibodies and antiphospholipid syndrome.

Keywords: Neuropsychiatric lupus erythematosus, Antiphospholipid syndrome, Complement, Lupus anticoagulant

Background

Systemic lupus erythematosus (SLE) is an inflammatory autoimmune disease with multi organ affection. One of the most severe manifestations in SLE is neuropsychiatric involvement, which is commonly associated with a poor prognosis [1]. In fact, neuropsychiatric systemic lupus erythematosus (NPSLE) is a leading cause of morbidity in SLE patients, with mortality rate second only to lupus nephritis [2].

The prevalence of NPSLE ranges from 12.2 to 94.7% for SLE patients. This wide range is likely due to different study designs regarding follow-up duration and methods of screening. Also, the high variability of NPSLE presentations, the lack of specificity of many symptoms (such as headache and mild cognitive impairment) as well as difficulties in attributing NPSLE manifestations to SLE or non SLE pathologies making it difficult to estimate the precise incidence of NPSLE [3–5].

The American College of Rheumatology (ACR) in 1999 has identified 19 neuropsychiatric syndromes that can be categorized into central and peripheral nervous systems manifestations. Despite the fact that this definition involves signs with undefined physiological and pathological mechanisms, it assists physicians in determining neurological involvement in SLE [6]. In 2014, some authors developed and validated a new algorithm based on the American College of Rheumatology (ACR) definitions that involves evaluating the patient’s lupus behavior, imaging techniques, and cerebrospinal fluid analysis to identify true NPSLE [7].
Two different pathophysiologic pathways are postulated to contribute to NPSLE: the inflammatory, related to a pro-inflammatory and/or autoimmune-mediated cause and the thrombotic/ischemic pathway, associated with vascular occlusion, hemorrhage and microangiopathy. Both ischemic and inflammatory NPSLE have been included in the term primary NPSLE. Moreover, secondary NPSLE refers to SLE patients with symptoms linked to the medication for SLE or to SLE-related organ damage [2, 8–12].

Although autoantibodies are one of the most powerful tools for the diagnosis of NPSLE, not all of them are characterized by high specificity and sensitivity for the NPSLE. Antinuclear antibodies (ANA) or anti-double stranded DNA (anti-dsDNA) antibodies can be found in every patient with SLE and not only in those with NPSLE. The frequency of other antibodies in NPSLE, such as anti-SSA/Ro, anti-SSB/La, anti-Sm or anti-nuclear ribonucleoprotein, varies widely among the different studies. Lupus anticoagulant is a group of autoantibodies frequently found among patients with NPSLE, that usually associated with focal symptoms. Anti-aquaporin 4 antibodies cause astrocyte toxicity, mainly in the white matter structures of the spinal cord and optic nerve, so they are thought to underlie the pathogenesis of neuromyelitis optica [13].

Since there have been few systematic studies of NPSLE in Egypt, in this retrospective study we aimed at describing the various neuropsychiatric manifestations in a cohort of Egyptian patients and its relation to different demographic, clinical and laboratory characteristics.

**Methods**

**Aim, study design and patients**

This study aimed to investigate the frequency of NPSLE and its relation to other clinical and laboratory parameters in SLE patients.

In this retrospective study, the medical records of SLE patients who sought medical advice at the Neuropsychiatry and Rheumatology departments—from July 2018 to March 2021—were revised. All patients fulfilled the Systemic Lupus International Collaborating Clinics (SLICC) criteria [14]. NPSLE were diagnosed according to the ACR 1999 categories [6]. Patients with Diabetes mellitus or any primary neurological disease that was diagnosed before SLE diagnosis were excluded.

**Data collection**

The following data was retrieved from the records of all patients: demographics characteristics including age, age of onset and disease duration, detailed medical history about different manifestations of neuropsychiatric lupus and different drug therapy, general medical examination and thorough neurological examination. SLE Disease Activity Index (SLEDAI) [15] and SLICC Damage Index score [16] were calculated for all patients. Laboratory investigations including: Complete blood picture and immunological profile: Complement 3 (C3), Complement 4 (C4), ANA, anti-dsDNA, anti-cardiolipin, Lupus Anticoagulant, anti-β2-glycoprotein 1 (anti β 2 GP 1) and Anti-Smith antibodies, were all reported. We divided our cohort of patients into two groups, Group 1 including NPSLE (patients with one or more neuropsychiatric manifestations) and Group 2 including non-NPSLE.

**Statistical analysis**

Data was analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). The Kolmogorov–Smirnov was used to verify the normality of distribution of variables, Comparisons between groups for categorical variables were assessed using Chi-square test (Fisher or Monte Carlo). Student t test was used to compare two groups for normally distributed quantitative variables. Significance of the obtained results was judged at the 5% level.

**Results**

**Characteristics of the study population**

As shown in Table 1, this study included 134 patients with SLE. 68 patients (50.75%) had one or NPSLE manifestations. The mean age of the NPSLE group was 27.4 ± 7.7, while it was 28.2 ± 8.9 years in the non-NPSLE group. In the NPSLE group, the frequency of males and females was 7.4% (n = 5) and 92.6% (n = 63),

| Demographic data | Group I (with NPSLE) (n = 68) | Group II (without NPSLE) (n = 66) | p |
|------------------|-------------------------------|----------------------------------|---|
| Sex              |                               |                                  |   |
| Male             | 5 (7.4%)                      | 8 (12.1%)                        | 0.351 |
| Female           | 63 (92.6%)                    | 58 (87.9%)                       |   |
| Age              |                               |                                  |   |
| Median (Min.–Max.) | 26 (16–53)                  | 25.5 (16–56)                     | 0.796 |
| Mean ± SD        | 27.4 ± 7.7                    | 28.2 ± 8.9                       |   |
| Age of onset     |                               |                                  |   |
| Median (Min.–Max.) | 20 (8–45)                    | 19.5 (7–46)                      | 0.583 |
| Mean ± SD        | 21.3 ± 7.4                    | 21.4 ± 9.6                       |   |
| Duration         |                               |                                  |   |
| Median (Min.–Max.) | 5.5 (1–18)                   | 6 (1–16)                         | 0.318 |
| Mean ± SD        | 6 ± 3.8                       | 6.8 ± 4.4                        |   |
respectively. The mean age of onset was 21.3 ± 7.4. The mean duration of the disease was 6 ± 3.8 years.

**Characteristics of patients with NPSLE**

Headache (55.9%) was the most frequent NPSLE manifestation followed by seizures (54.4%), psychosis was the third most frequent one with a percentage of 41.2. The least common NP manifestation was chorea. Acute Inflammatory Demyelinating Polyneuropathy (AIDP) and acute confusional state being present in one (1.5%), 2 (2.9%) and 3 (4.4%) patients, respectively (Table 2).

**Differences between both groups regarding laboratory and immunological results**

As shown in Table 3, results of complete blood picture were compared between both groups with 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, NPSLE patients had lower C3 and C4 levels and more lupus anticoagulant level.

**Impact on disease activity and damage indices, association with antiphospholipid antibody syndrome and drug intake**

As illustrated in Tables 4 and 5, there was no significant difference of SLICC damage index or SLE-DAI between NPSLE group and non NPSLE group. Antiphospholipid syndrome has higher association with NPSLE as compared to non NPSLE patients (25%, 10.6%, respectively) \( p > 0.03 \), as shown in Table 4. No difference in the drug intake in both groups.

**Table 2** Distribution of the studied patients according to NPSLE in group I patients \( n = 68 \)

| NPL                           | Percent |
|-------------------------------|---------|
| Headache                      | 38 (55.9%) |
| Seizures                      | 37 (54.4%) |
| Psychosis                     | 28 (41.2%) |
| Cerebrovascular disease       | 22 (32.4%) |
| Peripheral neuropathy         | 16 (23.5%) |
| Cognitive                     | 13 (19.1%) |
| Cranial neuropathy            | 5 (7.4%) |
| Acute confusional State       | 3 (4.4%) |
| AIDP                          | 2 (2.9%) |
| Chorea                        | 1 (1.5%) |

AIDP: acute inflammatory demyelinating polyradiculoneuropathy

**Table 3** Comparison between the studied groups according to laboratory results

|                | Group I \( n = 68 \) | Group II \( n = 66 \) | \( p \) |
|----------------|----------------------|-----------------------|-------|
| ANA            | 67 (98.5%)           | 63 (95.5%)            | 0.362 |
| Anti-DNA       | 42 (61.8%)           | 44 (66.7%)            | 0.554 |
| C3 Dec         | 23 (33.8%)           | 35 (53%)              | 0.025* |
| C4 Dec         | 18 (26.5%)           | 32 (48.5%)            | 0.008* |
| ACL IgG        | 11 (16.2%)           | 5 (7.6%)              | 0.125 |
| ACL IgM        | 11 (16.2%)           | 5 (7.6%)              | 0.125 |
| Lupus anticoagulant | 8 (11.8%)        | 1 (1.5%)              | \( \chi^2 p = 0.033^* \) |
| Anti β 2 GP 1 IgG | 1 (1.5%)         | 0 (0%)                | \( \chi^2 p = 1.000 \) |
| Anti β 2 GP 1 IgM | 1 (1.5%)           | 0 (0%)                | \( \chi^2 p = 1.000 \) |
| Anti-Smith     | 2 (2.9%)             | 2 (3%)                | \( \chi^2 p = 1.000 \) |
| Anemia         | 49 (72.1%)           | 43 (65.2%)            | 0.389 |
| Leucopenia     | 24 (35.3%)           | 20 (30.3%)            | 0.539 |
| Lymphopenia    | 17 (25%)             | 16 (24.2%)            | 0.919 |
| Neutropenia    | 5 (7.4%)             | 4 (6.1%)              | 1.000 |
| Thrombopenia   | 12 (17.6%)           | 8 (12.1%)             | 0.369 |
| Proteinuria    | 39 (57.4%)           | 41 (62.1%)            | 0.574 |

Anti-diDNA: Anti-double stranded DNA antibodies, ANA: antinuclear antibody. C3: Complement 3, C4: Anticardiolipin. \( \chi^2 \): Chi square test; FE: Fisher Exact.

|                | Group I \( n = 68 \) | Group II \( n = 66 \) | \( p \) |
|----------------|----------------------|-----------------------|-------|
| SLICC calculated |                      |                       |       |
| Median (Min.–Max.) | 2 (0–6)              | 1 (0–6)               |       |
| Mean ± SD        | 1.9 ± 1.7            | 1.4 ± 1.3             | 0.067 |
| SLEDAI          |                      |                       |       |
| Median (Min.–Max.) | 4 (0–37)            | 4 (0–29)              |       |
| Mean ± SD        | 7.4 ± 9.6            | 6.3 ± 7.5             | 0.952 |
| Antiphospholipid syndrome |        |                      |       |
| Median (Min.–Max.) | 17 (25%)            | 7 (10.6%)             | 0.030* |

SLICC: Systemic Lupus International Collaborating Clinics Damage Index score. SLEDAI: SLE Disease Activity Index

**Discussion**

The present study, using the ACR definitions, detected the presence of 10 of the 19 syndromes: 7 central and 3 peripheral nervous system syndromes. The NPSLE was present in 50.75% of the studied patients. Previous study conducted on 770 Egyptian patients showed that NPSLE was present in 44.3% [17]. The prevalence of NPSLE ranges from 12.2 to 94.7% for SLE patients [3, 4] which is obviously a wide range due to the high
variability of NPSLE presentations, the lack of specificity of many symptoms (such as headache and mild cognitive impairment) as well as difficulties in attributing NPSLE manifestations to SLE or non-SLE pathologies. The most common clinical manifestations in the current study were headache which reported in 38/68 patients, followed by seizures (37/68) and psychosis (28/68). Similar to this study, headache has previously been reported as the most prevalent manifestations of NPSLE [18, 19].

Also, previous studies showed that seizures [20, 21] and psychosis [20] were among the most common presentations. On the other hand, CVA [12, 22] and cognitive impairment [23] were the most NPSLE manifestations in other previous studies.

In this study, headache was the most prevalent neuropsychiatric manifestations, being present in 55.9% of SLE patients. The relation between SLE and headache is debatable. Some studies have discovered a higher, but highly variable, prevalence of headache in people with SLE (ranging from 24 to 72%) [24]. Others, including the results of a meta-analysis of several studies, also found no rise in the incidence of headache in SLE patients relative to control groups [25]. The discrepancies are due, in part, to the lack of uniform headache definition in several studies and the fact that headache is a common occurrence in the general population, especially among women. Just a few previous studies have found a connection between headache and other active lupus clinical features [26, 27]. Obviously, many confounding factors may be related to the headache whether related or not to SLE.

The results of this study showed that seizures occurred in 54.4% of patients. A recent Egyptian study reported that seizure was the most common presentation in NPSLE patients with a prevalence of 43.3% [28]. SLE patients have a higher risk of seizures than the general population, according to previous reports [29, 30].

Seizures were the most common NPSLE manifestation in SLICC study [31]. The definite cause of seizures in SLE is unknown but it might be due to systemic inflammation, focal microvascular brain trauma, direct autoantibody effects on neuronal networks, or a combination of these factors [32, 33].

Regarding psychosis, the prevalence of psychosis has been reported to range between 0 and 17.1% using the ACR case description for psychosis [34, 35]. The following criteria are included in the ACR case definition for psychosis [6]: (1) delusions or hallucinations without insight; (2) causing clinical distress or impairment in social, occupational, or other relevant areas of functioning; (3) disturbance should not occur exclusively during delirium; and (4) not better accounted for by another mental disorder. Episodes of psychosis that occurred during the enrollment window or reported previously by patients were recorded. In the current work, psychosis was reported in 41% of NPSLE patient group. Other recent studies report psychosis as a rare NSSLE event [36, 37]. Similar to this finding, another Egyptian study in 2020 reported psychosis as the most prevalent NPSLE [38]. This high prevalence among our patients as patients of African descent were also more likely to develop psychosis than other race/ethnicity [39]. In addition, the use of large dosages of steroids in patients with SLE is thought to cause psychological problems and the neuropsychiatric symptoms appear shortly after starting steroid treatment, making it difficult to distinguish from steroid psychosis [40]. Apart from psychosis, major depression is one of the most common psychiatric illnesses seen in individuals with SLE, with prevalence rates ranging from 16 to 60% (which is subsequently greater than the general population [41, 42]. Higher prevalence of major depression was found among Egyptian SLE (64%) which was related to disease activity, not to steroids or duration of illness [43]. Depression worsens fatigue, discomfort, and psychological distress in SLE patients, as well as lowering adherence to drugs, resulting in a considerable reduction in quality of life [44].

Focal NPSLE is a form of NPSLE that affects only one part of the brain and is caused by venous thrombosis or arterial ischemia. Similar to this study which reported cerebrovascular disorders in 22% of patients, the incidence of focal NPSLE cases are thought to account for about 20% of all cases [45, 46], but reported rates range from 3 to 43% in other studies [47, 48]. These are primarily caused by thromboembolic events that occur as a part of SLE-related hypercoagulable states and are strongly linked to the existence of antiphospholipid antibodies [49].

The average incidence of peripheral neuropathy (PN) in studied sample (23.5%) was higher than that reported.

### Table 5
Comparison between the studied groups according to drugs

| Drugs                     | Group I (n = 68) | Group II (n = 66) | p   |
|---------------------------|-----------------|------------------|-----|
| Steroids (mg/day)         |                 |                  |     |
| <20                       | 23 (33.8%)      | 18 (27.3%)       | 0.705 |
| 20–40                     | 38 (55.9%)      | 40 (60.6%)       |     |
| >40                       | 7 (10.3%)       | 8 (12.1%)        |     |
| Pulse steroid             | 35 (51.5%)      | 30 (45.5%)       | 0.486 |
| Anti-malarials            | 59 (86.8%)      | 54 (81.8%)       | 0.431 |
| Azathioprine              | 50 (73.5%)      | 49 (74.2%)       | 0.925 |
| Mycophenolate mofetil     | 8 (11.8%)       | 6 (9.1%)         | 0.613 |
| Cyclophosphamide          | 21 (30.9%)      | 20 (30.3%)       | 0.942 |

χ²: Chi square test

p: p value for comparing between the studied groups
by Oomtia et al. (5.9%) [50] and Hanly et al. (7.6%) [51] and that reported in the other two major cohort studies (14.7% and 17.7%) [52, 53]. Hanly and colleagues in the international inception cohort study classified all PNs as not attributable to SLE if there was no electrophysiologic confirmation [29, 51]. The ACR, on the other hand, recommends that the diagnosis be based on clinical findings and/or electrophysiological testing [6]. The justification of the high prevalence of PN is that PN in the current study was diagnosed according to ACR criteria for diagnosis and confirmed by electrophysiological study which might detect earlier cases before manifest clinical complaint. Also the process of attribution of neurologic events to SLE or not is not always an easy task. PN can also manifest as complications of other organ involvement in SLE (renal failure, liver failure), nutritional deficiency, or even as drug side effects (steroid-induced diabetes, antimalarial drugs, azathioprine) [52].

There were no differences between patients with and without NPSLE involvement according to the demographic data. NPSLE can occur at any time during the disease course and it can be even the first presentation. There is a limited evidence to support an association between demographic characteristics and NPSLE [54]. This is in contrast to a recent Egyptian study that found NPSLE patients were characterized by being younger with an earlier age of onset of lupus [38].

In the current work, a statistical significant difference of C3 \( (p=0.025) \) and C4 \( (p=0.008) \) levels, lupus anticoagulant level \( (p=0.033) \) and antiphospholipid syndrome \( (p=0.030) \), was found between the studied groups. This goes in accordance with Magro-Checa et al. [55] and partially with Medhat et al. [38] regarding antiphospholipid syndrome and other studies regarding complement levels [56, 57].

Complement activation is an important mechanism of tissue injury in neural tissue ischemia. Platelets bearing the complement-activation product C4d are a well-known link between cerebrovascular inflammation, thrombosis and NPSLE. An increase in deposition of complement-activation products on platelets is related to the presence of antiphospholipid antibodies, and it has been postulated as an important mechanism in antiphospholipid mediated thrombosis in SLE [56–58]. A rise in complement-activation products in serum of antiphospholipid antibodies positive patients has been related with the development of NPSLE [58]. Antiphospholipid antibodies, anti-ribosomal-P antibodies, and anti-NMDA antibodies are all closely associated to the neuropsychiatric manifestation in SLE [59]. A relatively recent study discovered that brain exposure to antibodies is caused by aberrant blood–cerebrospinal fluid barrier (BCSFB) function in the choroid plexus and significant intrathecal lymphocyte infiltration is likely to occur via the BCSFB, which is accompanied by epithelial hyperpermeability to antibodies [60].

In this study, there was no statistical difference regarding the drug intake or other laboratory findings. SLICC and SLEDAI didn’t differ in both groups. SLE, being a multisystem disease affecting almost all body systems can explain these findings. While the NPSLE manifestations can affect the disease activity and damage scores, many other systemic affection have also comparable effect on them. This is in contrast to previous studies [38, 58].

Being a retrospective study, some data needed more verification, which could be considered as the study’s main limitation. On the other hand, this study involved a large cohort from a tertiary center involving patients from two different specialty clinics and providing high variability of disease presentations.

Conclusion

The prevalence of Neuropsychiatric manifestations in this study was 50.7%. Headache, seizures and psychosis are the most frequent neuropsychiatric manifestations in the studied patients. SLE patients with neuropsychiatric manifestations have lower complement levels, higher lupus anticoagulant antibodies and antiphospholipid syndrome. SLE patients with low complement levels and antiphospholipid syndrome should be regularly assessed for early diagnosis of NPSLE. Patients of SLE should have regular neuropsychiatric evaluation regardless the disease activity or damage scores.

Abbreviations

ACR: American College of Rheumatology; AIDP: Acute inflammatory demyelinating polyneuropathy; C3: Complement 3; C4: Complement 4; ANA: Antinuclear antibody; Anti-dsDNA: Anti-double strand DNA; Anti β 2 GP 1: Anti-beta-2 glycoprotein 1 antibody; BCSFB: Blood–cerebrospinal fluid barrier; SLE: Systemic lupus erythematosus; NPSLE: Neuropsychiatric systemic lupus erythematosus; SLICC: Systemic Lupus International Collaborating Clinics; SLEDAI: SLE Disease Activity Index.

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Authors’ contributions

All authors have contributed to designing the study, collecting and analyzing, interpretation of data, and preparing and revising the manuscript. Design of the study: SR, AI. Recruitment of patients: SR, AI. Data collection: SR, AI. Randomizing: SR, AI. Assessment: SR, AI. Statistical analysis and data interpretation: SR, AI. Manuscript preparation: SR, AI. Manuscript revision: SR, AI. All authors read and approved the final manuscript.

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Availability of data and materials

Available.
Declarations

Ethics approval and consent to participate
We confirm none of the present study’s procedures had violated the principles stated by the latest version of declaration of Helsinki. The protocol of the present study was registered by the local ethics committee of Kafrelsheikh University. Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
1 Neuropsychiatry Department, Faculty of Medicine, Kafrelsheikh University, Kaf El Sheikh, Egypt
2 Physical Medicine, Rheumatology and Rehabilitation Department, Faculty of Medicine, Kafrelsheikh University, Kaf El Sheikh, Egypt.

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