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Prevalence and characteristics of neuropsychiatric involvement in an Egyptian cohort of systemic lupus erythematosus patients: a single-center retrospective cohort

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Abstract

Background: The aim of this study was to retrospectively investigate the prevalence and characteristics of neuropsychiatric (NP) involvement in a cohort of systemic lupus erythematosus (SLE) patients from a single tertiary center.

Results: Of 301 included patients' medical records, the prevalence of NPSLE, that was defined according to the American College of Rheumatology Nomenclature of 1999, was 33.5% (101/301), of whom 10 (9.9%) were males. The mean age at the last visit of patients with NP involvement was 29.1 ± 8.2 years, whereas the mean age at onset was 21.9 ± 7.3 years, and the mean disease duration was 89.8 ± 59.4 months. The most common NP manifestations were psychosis [34/101 (33.7%)], followed by seizures [22/101 (21.8%)]. Compared to those without NPSLE, patients with NP involvement were characterized by having a younger age of onset ($p < 0.001$) had a longer disease duration ($p = 0.02$). Of the cumulative characteristics recorded, NPSLE patients showed a higher prevalence of cutaneous vasculitis ($p = 0.002$), discoid rash ($p = 0.03$), pleurisy and pleural effusion ($p = 0.004$, $p = 0.03$, respectively), pericarditis ($p = 0.007$), thrombocytopenia ($p = 0.04$), and secondary antiphospholipid (APS) ($p = 0.04$); however, there was no difference in any of the included serologic features between the two groups. Patients with NPSLE had a higher median disease activity score [Systemic Lupus Erythematosus Disease Activity Index-2 K (SLEDAI-2 K)] at the disease onset ($p = 0.008$), yet it was comparable to those without NP involvement at the last visit ($p = 0.3$). NPSLE patients demonstrated a higher median damage score ($p < 0.001$) that was assessed according to the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) score. NPSLE patients with secondary APS showed a higher prevalence of cerebrovascular accidents (CVA) ($p < 0.001$), while those without APS developed psychosis more frequently ($p = 0.03$).

Conclusion: Neuropsychiatric SLE patients (33.5%) demonstrated a younger age of onset, higher prevalence of secondary APS and distinct clinical characteristics, and had higher disease damage. APS-positive NPSLE patients had a higher prevalence of CVA, while APS-negative patients showed a higher prevalence of psychosis.

Keywords: Antiphospholipid syndrome, Disease activity, Disease damage, Egyptian, Neuropsychiatric, Systemic lupus erythematosus

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Background

Systemic lupus erythematosus (SLE) is an obscure autoimmune disease characterized by its multisystem affection. Neuropsychiatric systemic lupus erythematosus (NPSLE) is one of the leading causes of morbidity and mortality among patients with SLE [1, 2].

The most widely used classification for NPSLE is the nomenclature developed by the American College of Rheumatology (ACR) in 1999 for 19 NPSLE manifestations that are associated with SLE [3]. Nevertheless, several challenges encounter the management of NPSLE, including the potentially equivocal characteristics of several neuropsychiatric (NP) manifestations that could be attributed to various organic and non-specific manifestations [4].

In this retrospective study, we aimed at describing various neuropsychiatric manifestations in a cohort of patients who sought medical advice at Cairo University hospital.

Methods

We derived information from the medical records of 301 patients who sought medical advice from a sought medical advice at the Rheumatology and Rehabilitation department of Cairo University from December 2017 to January 2019. All patients fulfilled the Systemic Lupus International Collaborating Clinics (SLICC) criteria [5]. The following data were collected from patients' medical records: (1) demographic data: whereby: (i) the age at onset was defined as the age at the development of the initial manifestation(s) and (ii) the disease duration was calculated from the initial manifestation(s) till the last recorded visit. (2) Cumulative clinical manifestations, with secondary antiphospholipid syndrome being diagnosed according to the modified Sapporo criteria [6]. The study was approved by the local Ethics Committee, according to the provisions of the World Medical Association Declaration of Helsinki.

Assessment of disease activity and damage

Disease activity at the onset of the disease and last visit was assessed through the Systemic Lupus Erythematosus Disease Activity Index-2K (SLEDAI-2K) [7]. Disease damage was investigated utilizing the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) [8].

Assessment of neuropsychiatric manifestations

Neuropsychiatric manifestations were defined according to the ACR 1999 nomenclature [3] and in absence of any non-SLE disease. None of the patients with NPSLE had infection, electrolyte imbalance, and/or drug toxicity at the time of development of NP manifestation(s). It is of note that the authors of this study published

preliminary data of this cohort and preliminary data collected as an abstract [9], where several neuropsychiatric manifestations included were not strictly defined according to the ACR nomenclature and thus were subject to inspecificity.

Statistical analysis

Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA). Data was summarized using mean, standard deviation, median, minimum and maximum in quantitative data, and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Mann-Whitney test. *p* values less than 0.05 were considered as statistically significant.

Results

This study included 301 SLE patients, of whom 38 were males (12.6%). The mean age of the cohort was 30.7 ± 9.2 years, whereas the mean age at onset was 24.1 ± 8.3 years. Baseline demographic, clinical, and serologic features are shown in Table 1. The median SLEDAI-2K at onset was 12 [mean \pm SD, 14 ± 8], whereas the median age at the last visit was 4 [mean \pm SD, 6 ± 7]. The median SDI at the last visit was 1 [mean \pm SD, 1 ± 2].

Characteristics of patients with NPSLE

Of our cohort (301 patients), 101 (33.5%) had one or more neuropsychiatric manifestation. The demographic, clinical, and serologic characteristics of patients with NPSLE are shown in Table 2.

Neuropsychiatric involvement was the presenting manifestation in 43/101 (42.6%) patients, whereas it developed after the onset of SLE in 58/101 (57.4%) patients (57.4%), with the median time to occurrence of the NP event being 6 months. The most common NP manifestation was psychosis [34/101 (33.7%)], followed by seizures [22/101 (21.8%)]. The least common NP manifestations were anxiety and movement disorders being present in one (1%) and 2 (2) patients, respectively (Table 3).

Differences between NPSLE and non-NPSLE patients

Upon comparing patients with and without NP involvement, patients with NPSLE were characterized by having a younger age of onset ($p < 0.001$) and had a longer disease duration ($p = 0.02$) (Table 4). Several cumulative clinical characteristics were more prevalent among patients with NP involvement, including cutaneous vasculitis ($p = 0.002$), discoid rash ($p = 0.03$), pleurisy and pleural effusion ($p = 0.004$, $p = 0.03$, respectively), pericarditis ($p = 0.007$), thrombocytopenia ($p = 0.04$), and APS ($p = 0.04$). On the other hand, there was no difference in any of the included serologic features between

Table 1 Baseline demographic, clinical, and serologic characteristics of the cohort (301 patients)*

Demographic characteristics	
Age (years)	Mean ± SD
Age at last visit	30.7 ± 9.2
Age at onset	24.1 ± 8.3
Disease duration (months)	78.8 ± 54.3
Gender	N (%)
Male	38 (12.6)
Female	263 (87.4)
Clinical characteristics	
Fever	125 (41.5)
Weight loss	20 (6.6)
Cutaneous vasculitis	40 (13.3)
Malar rash	192 (63.8)
Photosensitivity	102 (33.9)
Discoid rash	20 (6.6)
Oral ulcers	88 (29.2)
Alopecia	140 (46.5)
Synovitis	210 (69.8)
Serositis	61 (20.3)
Hemolytic anemia	39 (13)
Thrombocytopenia	53 (17.6)
Leukopenia	157 (52.2)
Nephritis	162 (53.8)
Neuropsychiatric	101 (33.5)
APS	45 (15)
Serologic characteristics	
ANA	297 (98.7)
Anti-ds DNA	189 (64.7)
Hypocomplementinemia	183 (61.8)
aPL	99 (32.9)
Comorbidities	
Diabetes mellitus	49 (16.3)
Ischemic heart disease	13 (4.3)
Hypertension	110 (36.5)
Osteoporosis	16 (5.3)

*Unless indicated, data is presented in number and percentage
 APS antiphospholipid syndrome, ANA anti-nuclear antibodies, *Anti-ds DNA* anti-double stranded deoxyribonucleic acid, *aPL* antiphospholipid antibodies

the two groups (Table 4). Interestingly, patients with NPSLE had a higher median SLEDAI-2K score at the disease onset ($p = 0.008$), yet the SLEDAI-2K score at the last visit was comparable between both groups ($p = 0.3$). Moreover, NPSLE patients demonstrated a higher median SDI score at the last visit ($p < 0.001$).

Table 2 Demographic, clinical, and serologic characteristics of neuropsychiatric lupus patients (101 patients)^a

Demographic characteristics	
Age (years)	Mean ± SD
Age at the last visit	29.1 ± 8.2
Age at disease onset	21.9 ± 7.3
Age at the initial NP event	23 ± 8
Disease duration (months)	89.8 ± 59.4
Time to initial NP event	16 (25.4)
Gender	N (%)
Male	10 (9.9)
Female	91 (90.1)
Number of ACR criteria (Mean ± SD)	7 (2)
Cumulative clinical characteristics	
Fever	46 (45.5)
Weight loss	7 (6.9)
Cutaneous vasculitis	22 (21.8)
Malar rash	57 (56.4)
Photosensitivity	33 (32.7)
Discoid rash	11 (10.9)
Oral ulcers	30 (29.7)
Alopecia	48 (47.5)
Synovitis	70 (69.3)
Serositis	30 (29.7)
Hemolytic anemia	10 (9.9)
Thrombocytopenia	24 (23.8)
Leukopenia	50 (49.5)
Nephritis	47 (46.5)
APS	21 (20.8)
Serologic characteristics	
ANA	101 (100)
Anti-ds DNA	61 (62.9)
Hypocomplementinemia	58 (58)
aPL	33 (32.6)

^aUnless indicated, data is presented in number and percentage.
 NP neuropsychiatric, APS antiphospholipid syndrome, ANA anti-nuclear antibodies, *Anti-ds DNA* anti-double stranded deoxyribonucleic acid, *aPL* antiphospholipid antibodies

Evaluation of disease activity in relation to various NP manifestations

We investigated the association of disease activity with the most prevalent NP manifestations reported in our study, psychosis, seizures, and CVA, and cognitive impairment. At baseline, there was no association of the SLEDAI-2K score with any of the aforementioned NP manifestations. On the other hand, the SLEDAI at the last visit was higher among patients with cognitive impairment ($p = 0.02$), with no association between the

Table 3 Characteristics of neuropsychiatric manifestations

	N = 101 (%)
Seizures	22 (21.8)
Psychosis	34 (33.7)
CVA	16 (15.8)
Cognitive dysfunction	15 (14.9)
Polyneuropathy	11 (10.9)
Cranial neuropathy	5 (5)
Mood disorder	4 (4)
Anxiety disorder	1 (1)
Movement disorder	2 (2)
Headache	10 (9.9)
Aseptic meningitis	3 (3)
Acute confusional state	6 (5.9)
CVA cerebrovascular accident	

SLEDAI-2K score at the last visit and any of the other studied NP manifestations (Table 5).

Evaluation of the impact of APS on NPSLE

Patients with NPSLE were further divided into those with and without APS. Interestingly, APS-positive NPSLE patients had a higher number of ACR criteria when compared to APS-negative NPSLE patients ($p = 0.001$). The prevalence of CVA was higher among patients with APS-NPSLE patients ($p < 0.001$); on the other hand, psychosis was more common among patients with APS-negative NPSLE ($p = 0.03$). The median SLEDAI-2K score at the disease onset was significantly higher in the APS-negative NPSLE group ($p = 0.03$), yet both the median SLEDAI-2K and SDI scores at the last visit were comparable between both groups ($p = 0.3$, $p = 0.7$, respectively) (Table 6).

Discussion

The aim of this study was to describe the prevalence and characteristics of various neuropsychiatric manifestations in an Egyptian cohort of SLE patients. The prevalence of NPSLE ranges from 4.3 to 95% [10–15]. This wide variation could be attributed to several factors including race and ethnicity, patients' selection criteria by different centers, and the definitions used to classify NPSLE manifestations. In this study, the prevalence of NPSLE was 33.5%, which although is higher than that detected in a previous Egyptian study [16], is comparable to other Egyptian studies [17, 18].

Neuropsychiatric involvement was the presenting manifestation in 43/101 (42.6%) patients, with the median time to developing NP manifestation(s) being 6 months. NP involvement has been reported to occur

at the onset or within the first year of diagnosis in previous studies [10, 19].

In our study, the most common NP manifestation was psychosis being present in 34/101 patients (33.7%), followed by seizures [22/101 patients (21.8%)]. Similar to our study, psychosis [14] and seizures [11, 14] have been reported among the most common NP manifestations. On the other hand, headache [20], cognitive impairment [15], and CVA [13, 20] were the most prevalent NP manifestations in previous studies.

Interestingly, there were several differences between patients with and without NP involvement. NPSLE patients were characterized by being younger ($p = 0.04$) and further showed an earlier age of onset ($p < 0.001$), and showed a longer disease duration ($p = 0.02$). NPSLE patients were characterized by a having a longer disease duration in a previous study [20]. Despite a comparable prevalence of the investigated serologic features between both groups, several cumulative clinical manifestations were more prevalent among patients SLE with NP involvement, including cutaneous vasculitis ($p = 0.002$), discoid rash ($p = 0.03$), pleurisy ($p = 0.004$), pericarditis ($p = 0.007$), pleural effusion ($p = 0.03$), and thrombocytopenia ($p = 0.04$). On the other hand, clinical and serologic characteristics were comparable between SLE patients with and without NP involvement in a previous study from Portugal [21]. Moreover, apart from thrombocytopenia, there was no difference in other cumulative clinical characteristics between patients with and without NP involvement in a previous Italian study [20], whom unlike our patients, showed a higher prevalence of aPL, yet it is of interest that our NPSLE patients showed a higher prevalence of secondary APS as opposed to SLE without NP involvement ($p = 0.04$).

It is of note that the association of APS with NP involvement in SLE has been demonstrated in several studies [21, 22]. Interestingly, an unexpected and rather surprising finding, NPSLE patients without APS in our study showed a higher prevalence of psychosis ($p = 0.03$); on the other hand, as expected, APS-positive NPSLE patients showed a higher prevalence of CVA ($p < 0.001$). Seizures were more prevalent among APS-negative NPSLE patients in a previous cohort, which showed a comparable prevalence of psychosis and CVA between APS negative and positive NPSLE patients [21].

The importance of assessing NP manifestations in SLE rises from its association with disease activity and hence, subsequent damage. Compared to patients without NP involvement, NPSLE patients in our study showed a higher SLEDAI-2K score at onset ($p = 0.008$). This finding is in agreement with a previous

Table 4 Differences between NPSLE and non-NPSLE patients^a

	Non-NPSLE N = 200 (%)	NPSLE N = 101 (%)	P value*
Demographic characteristics			
<i>Age (years) [Mean (SD)]</i>			
Age at last visit	31.4 (9.6)	29.1 (8.2)	0.04
Age at onset	25.3 (8.6)	21.9 (7.3)	< 0.001
<i>Disease duration (months) [Mean (SD)]</i>	73.2 (50.8)	89.8 (59.4)	0.02
<i>Gender</i>			
Female	172 (86)	91 (90.1)	0.3
Male	28 (14)	10 (9.9)	
Number of ACR criteria [Mean (SD)]	7 (2)	6 (2)	0.1
Clinical characteristics			
Fever	79 (39.5)	46 (45.5)	0.3
Weight loss	13 (6.5)	7 (6.9)	0.8
Cutaneous vasculitis	18 (9)	22 (21.8)	0.002
Malar rash	135 (67.5)	57 (56.4)	0.05
Photosensitivity	69 (34.5)	33 (32.7)	0.7
Discoid rash	9 (4.5)	11 (10.9)	0.03
Oral ulcers	58 (29)	30 (29.7)	0.8
Alopecia	92 (46)	48 (47.5)	0.8
Synovitis	140 (70)	70 (69.3)	0.9
Pleurisy	31 (15.5)	30 (29.7)	0.004
Pleural effusion	22 (11)	20 (19.8)	0.03
Pericarditis	10 (5)	14 (13.9)	0.007
Pericardial effusion	15 (7.5)	12 (11.9)	0.2
Hemolytic anemia	29 (14.5)	10 (9.9)	0.2
Thrombocytopenia	29 (14.5)	24 (23.8)	0.04
Leukopenia	107 (53.5)	50 (49.5)	0.5
Nephritis	115 (57.5)	47 (46.5)	0.07
APS	24 (12)	21 (20.8)	0.04
Serologic characteristics			
ANA	196 (98)	101 (100)	0.1
Anti-ds DNA	128 (65.6)	61 (62.9)	0.6
Hypocomplementemia	125 (63.8)	58 (58)	0.3
aPL	66 (33)	33 (32.7)	0.9
Disease activity and damage Median (Mean ± SD)			
SLEDAI at disease onset	12 (14 ± 8)	13 (16 ± 9)	0.008
SLEDAI at the last visit	7 (6 ± 7)	6 (7 ± 8)	0.3
SDI at the last visit	1 (1 ± 2)	2 (3 ± 2)	< 0.001

^aUnless indicated, data is presented in number and percentage. *Abbreviations:* NPSLE neuropsychiatric systemic lupus erythematosus, APS antiphospholipid syndrome, ANA anti-nuclear antibodies, *Anti-ds DNA* anti-double stranded deoxyribonucleic acid, *aPL* antiphospholipid antibodies

Egyptian study that showed an association of the SLE-DAI-2K score with NP involvement [22]. Moreover, among our NPSLE cohort, patients with cognitive impairment showed a higher SLEDAI-2K score at the

last visit compared to those without ($p = 0.02$). Previous Egyptian studies showed higher SLEDAI-2K scores among patients with depression, anxiety, and dementia [22, 23]. Furthermore, similar to our study,

Table 5 Association between NP manifestations and disease activity throughout the disease

	SLEDAI-2 K at onset [Mean \pm SD (median)]		<i>p</i> value*
	Presence	Absence	
Psychosis	18.5 \pm 9.1 (17)	15.2 \pm 8.3 (12)	0.07
Seizures	17.7 \pm 10.7 (13.5)	15.9 \pm 8.1 (13)	0.6
CVA	15.8 \pm 9.1 (15)	16.4 \pm 8.7 (12)	0.7
Cognitive dysfunction	19.4 \pm 8.2 (21)	15.7 \pm 8.7 (12)	0.1
	SLEDAI-2 K at the last visit [mean \pm SD (median)]		
Psychosis	6.2 \pm 8.7 (4)	6.8 \pm 7.7 (4)	0.5
Seizures	6.5 \pm 9.1 (4)	6.7 \pm 7.8 (4)	0.8
CVA	7.3 \pm 7.2 (4)	6.5 \pm 8.2 (4)	0.3
Cognitive dysfunction	9.4 \pm 8 (7)	6.2 \pm 8 (4)	0.02

*Significant *p* value < 0.05

SLEDAI-2K Systemic Lupus Erythematosus Disease Activity Index-2 K, CVA cerebrovascular accident

Table 6 Differences between APS-positive and APS-Negative NPSLE patients^a

	APS-Negative N = 80 (%)	APS-Positive N = 21 (%)	<i>P</i> value*
Demographic characteristics			
Age (years)			
Age at last visit [Mean (SD)]	28.5 (8.3)	29.3 (8.3)	0.7
Age at onset [Mean (SD)]	20.8 (6.1)	22.2 (7.6)	0.8
Age at initial NP event [Median]	20	20	0.7
Disease duration (months) [Median]	84	84	0.4
Time to initial NP event (months) [Median]	6	5	0.9
Gender			
Female	74 (92.5)	17 (81)	0.1
Male	6 (7.5)	4 (19)	
Number of ACR criteria [Median]	6	8	0.001
NP characteristics			
Seizures	17 (21.3)	5 (23.8)	0.8
Psychosis	31 (38.8)	3 (14.3)	0.03
CVA	7 (8.8)	9 (42.9)	< 0.001
Cognitive dysfunction	12 (15)	3 (14.3)	0.9
Polyneuropathy	9 (11.3)	2 (9.5)	0.8
Cranial neuropathy	3 (3.8)	2 (9.5)	0.2
Mood disorder	2 (2.5)	2 (9.5)	0.1
Anxiety disorder	1 (1.3)	0	1
Movement disorder	2 (2.5)	0	1
Headache	6 (7.5)	5 (23.8)	0.06
Aseptic meningitis	2 (2.5)	1 (4.8)	0.5
Acute confusional state	4 (5)	2 (9.5)	0.6
Disease activity and Damage [Median]			
SLEDAI at disease onset	16	10	0.03
SLEDAI at the last visit	4	4	0.3
SDI at the last visit	2	2	0.7

^aUnless indicated, data is presented in number and percentage. *Abbreviations:* APS antiphospholipid syndrome, NPSLE Neuropsychiatric systemic lupus erythematosus, ACR American College of Rheumatology, CVA cerebrovascular accident, SLEDAI Systemic Lupus Erythematosus Disease Activity Index, SDI Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index

a previous Egyptian report demonstrated a higher SLEDAI-2K score among patients with cognitive impairment [23]. Moreover, patients with NPSLE had a higher SDI score compared to without NP involvement ($p < 0.001$), which is similar to a previous report [24].

Being a retrospective study, some data was missing, which could be considered as the study's main limitation. On the other hand, our study has many strengths including that it involved a large cohort from a tertiary center, and tackled the potential impact of APS on NP involvement in SLE.

Conclusions

The prevalence of NP involvement in our cohort was 33.5%, with the most NP manifestations being psychosis and seizures. NPSLE patients were characterized by a younger age of onset, demonstrated a higher prevalence of several cumulative manifestations including secondary APS, and showed a higher damage score. APS-positive NPSLE patients showed a higher prevalence of CVA, whereas APS-negative NPSLE patients developed psychosis more frequently. Hence, this study highlights the impact of NP involvement on disease activity and damage of SLE, and the potential association of NPSLE with APS.

Abbreviations

ACR: American College of Rheumatology; APS: Antiphospholipid syndrome; CVA: Cerebrovascular accident; NP: Neuropsychiatric; NPSLE: Neuropsychiatric Systemic Lupus Erythematosus; SD: Standard deviation; SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLE: Systemic lupus erythematosus; SLEDAI-2 K: Systemic Lupus Erythematosus Disease Activity Index-2 K; SLICC: Systemic Lupus International Collaborating Clinics criteria

Acknowledgements

None

Authors' contributions

All authors have read and approved the manuscript, with the specific roles stated below: BMM: contributed to data collection from patients' medical records, analysis of data and results that was obtained from the statistician, searching and researching the literature, and main author writing and revising the manuscript. AM: has contributed to data collection and analysis from the patients' medical records, searching and researching the literature, and revising the manuscript. ME: is the main author contributing to the ideation of the research subject, data collection from the medical records, analysis of data and results obtained from the statistician, searching and researching the literature, and participating in manuscript writing and revision.

Funding

Not applicable

Availability of data and materials

Excel sheet, raw data, and statistical results are available whenever needed or asked for.

Ethics approval and consent to participate

The study was approved by the Department's Ethics Committee, according to the provisions of the World Medical Association Declaration of Helsinki. The study included medical records of patients being a retrospective study

and has no serial number as approval was obtained from the Department of Rheumatology and Rehabilitation of Cairo University.

Consent for publication

The study was approved by the local ethical committee of the Rheumatology and Rehabilitation Department of Cairo University; hence, has no serial number. Being a retrospective study, data was derived from medical records of patients.

Competing interests

The author's declare that they have no competing interests.

Received: 30 April 2020 Accepted: 18 May 2020

Published online: 24 August 2020

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