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Neuropsychiatric Manifestations in Egyptian Systemic Lupus Erythematosus Patients

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Abstract

Background: Neuropsychiatric Systemic lupus erythematosus (NPSLE) is a complex condition that remains poorly understood, and includes heterogeneous manifestations involving both the central and peripheral nervous system, with disabling effects.

Aim of Study: This study was to investigate the frequency and association of NPSLE in a group of Egyptian Systemic lupus erythematosus (SLE) patients.

Patients and Methods: This study retrospectively reviewed the medical records of 198 SLE patients. Ten Neuropsychiatric (NP) manifestations were reported from patient's medical records: Headache, psychosis, seizures, transient ischemic attacks (TIAs), stroke, transverse myelitis, cognitive dysfunction, chorea, cranial neuropathy and peripheral neuropathy. Patients were divided according to the presence or absence of the previously mentioned ten manifestations into two group. The two groups were compared regarding clinical, laboratory, treatment options, Systemic Lupus Erythematosus Disease Activity Index(SLEDAI) and Systemic Lupus International Collaborative clinics/American College of Rheumatology Damage Index (SLICC/ACR DI) indices.

Results: The mean disease duration in our patients was 8.33±6.17 years. Eighty-seven (43.0%) patients had NP manifestations. The most common SLE manifestations were headache (31.8%) followed by epilepsy (9.1%) and psychosis (8.1%). Other NPSLE syndromes observed in the study are peripheral nerve affection (7.1%), cognitive Involvement (4%), stroke (3.5%),TIAs (2.5%). The least common NPSLE manifestation were transverse myelitis, chorea and cranial nerve affection, each (0.5%). SLEDAI at onset, SLEDAI at last visit and SLICC DI were statistically significantly (p<0.001, p<0.001 and p<0.005 respectively). Patients with NPSLE showed higher intravenous pulse methylprednisolone intake (p<0.042) and higher cumulative intravenous methylprednisolone dose (p<0.001).

Conclusion: Frequency of NPSLE in our cohort was (43.0%), headache, seizures and psychosis were the most frequent NP manifestations in the studied patients, patients with NPSLE showed higher SLEDAI both (at onset and in last reported visit), higher SLICC damage index, and higher intake and cumulative dose in pulse methyl prednisolone.

Key Words: *NPSLE manifestation – Egyptian patients – SLEDAI – SLICC – Pulse methyl prednisone.*

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Introduction

SYSTEMIC lupus erythematosus (SLE) is a chronic, systemic autoimmune disease affecting multiple organ systems **[1]**. Neuropsychiatric (NP) involvement is one of the major manifestations of SLE with varying presentations **[2]** and although better understanding of SLE, NP involvement in SLE remains a challenge for clinicians, both at a diagnostic and therapeutic level and is associated with increased morbidity and mortality **[3,4]**.

The prevalence of the NeuropsychiatricSystemic lupus erythematosus (NPSLE) may show wide range from 25-70% in one study **[5]** and to 20-90% in another study **[6]** this wide range may be attributed to overlap with common diseases like anxiety, depression and headache, and to absence of diagnostic gold standards to differentiate between lupus related NPSLE and non-lupus related neurological manifestations, which may be caused by many factors as medications side effects, metabolic disorder and infection **[7,8]**.

In 1999 the American College of Rheumatology (ACR) has classified the symptoms of NPSLE into 19 NP manifestations and these manifestations can be further divided into central [focal and diffuse], peripheral, and autonomic ones. The ACR

has also listed the exclusion criteria to rule out NP event not directly connected to SLE and the co-morbidities to consider as potential confounding causes [9].

Although several studies were conducted on NPSLE, however studies on Egyptian SLE patients are scanty, thus in the current study we aimed to study the frequency of NPSLE in a cohort of Egyptian SLE patients, and to compare patients with NPSLE and those without, regarding different disease parameters.

Patients and Methods

Study was performed in Cairo University Hospitals and some patients were attending Beni Suef University Hospitals from November 2022 to December 2022.

In the current study we retrospectively reviewed medical records of 198 SLE patients fulfilling the Systemic Lupus International Collaborative clinics (SLICC) classification criteria [10]. Our patients were following in Rheumatology Department in Cairo University Hospitals and Beni Suef University Hospitals.

Demographic data, clinical manifestations, routine laboratory investigations and immunological profile were extracted from our patient's medical records. Disease activity was reported from medical records at first visit and in the last visit of each patient by using SLE disease activity was index (SLEDAI) [11], accumulated damage was also reported according to Systemic Lupus International Collaborative clinics/American College of Rheumatology Damage Index (SLICC/ACR DI) [12]. In accordance with the Declaration of Helsinki. The study was performed.

Ten Neuropsychiatric manifestations were reported from patient's medical records: Headache, psychosis, seizures, transient ischemic attacks, stroke, transverse myelitis, Cognitive dysfunction, chorea, cranial neuropathy and peripheral neuropathy, such manifestations were reported based on neurological and psychiatric evaluation when required and based on ACR nomenclature to define major NP manifestations [9]. Patients were divided according to the presence or absence of the previously mentioned ten manifestations into two group; patients with NP manifestations and those without NP manifestations. The two groups were compared regarding clinical, laboratory, treatment, disease activity and damage indices.

Statistical analysis:

The collected data will be tabulated, coded and analyzed using STATISTICA SPss 25 software. Continuous variables will be presented as mean values +/- standard deviation (SD) and categorical variables will be presented as percentages. Non-parametric tests will be used: The Mann-Whitney U test and Spearman's rank correlation coefficient. Differences were considered significant at $p<0.05$.

Results

A total number of 198 patients with SLE with mean age of years 33.2 (±10.03 SD) were included in the current study. The majority of our patients were females 190 (95.95%), with only 8 males (4.04%). Juvenile disease onset was present in 59 patients (29.8%) and the adult onset was present in 139 patients (70.2%). The mean disease duration in was 8.33±6.17 years, details of the demographic features are mentioned in Table (1).

Eighty-seven (43.0%) patients had NP manifestations and 111 patients (56.06%) were without NP manifestations. Clinical characteristics, disease activity and damage indices of SLE patients with and without NPSLE manifestations are shown in Table (1). SLEDAI at onset, SLEDAI at last visit and SLICC DI were statistically significant higher in patients with NPSLE. ($p<0.001$, $p<0.001$ and $p<0.005$ respectively), as shown in Table (1).

The most common SLENP manifestations in our study, was headache (31.8%) followed by epilepsy (9.1%) and psychosis (8.1%). Other NPSLE syndromes observed in the study are peripheral nerve affection (7.1%), cognitive involvement (4%), stroke (3.5%), TIAs (2.5%). The least common NPSLE manifestation were transverse myelitis, chorea and cranial nerve involvement, each (0.5%). (Table 2) (Fig. 1).

Comparison between the patients with and without NPSLE in our study regarding laboratory investigations, immunological profile and medications, showed statistically significant difference regarding intravenous pulse methylprednisolone intake ($p<0.042$) and Cumulativeintravenous pulse methylprednisolone dose ($p<0.001$), details of this comparison are shown in Table (3).

Table (1): Demographic features, clinical characteristics, disease activity and damage indices of SLE patients with and without Neuropsychiatric manifestations.

Variable N (%)	SLE patients (n=198)		*p*-value
	With neuropsychiatric manifestations (n=87)	Without neuropsychiatric manifestations (n=111)	
Female n (%)	82 (94.3%)	108 (97.3%)	
Male n (%)	5 (5.7%)	3 (2.7%)	0.280
Age in years (mean±SD)	32.1±9.7	34.02±10.1	0.193
Duration in years (mean±SD)	8.3±6.6	8.4 ±5.7	0.493
Juvenile disease onset n (%)	31 (35.6%)	28 (25.2%)	0.122
Adult Onset n (%)	56 (64.4%)	83 (74.8%)	0.112
Mucocutaneous manifestations n (%)	83 (95.4%)	98 (88.3%)	0.076
Nephritis n (%)	54 (62.1%)	81 (73.0%)	0.102
Renal failure n (%)	4 (4.6%)	6 (5.4%)	1.000
Arthritis n (%)	55 (63.2%)	79 (71.2%)	0.235
Cardiovascular manifestations n (%)	18 (20.7%)	24 (21.6%)	0.874
Pulmonary manifestations n (%)	52 (59.5%)	56 (50.5%)	0.191
Pulmonary hypertension n (%)	6 (6.9%)	10 (9%)	0.588
Serositis n (%)	50 (57.5%)	50 (45%)	0.083
GIT manifestations n (%)	12 (13.8%)	11 (9.9%)	0.397
Raynaud's phenomenon n (%)	24 (27.6%)	28 (25.2%)	0.764
Thrombotic events n (%)	10 (11.5)	18 (16.2%)	0.344
SLEDAI at onset (mean±SD)	18.4±7.9	14.3±6	<0.001*
SLEDAI at last visit, median (range)	10 (0-30)	4 (0-25)	<0.001*
SLICC DI, median (range)	1 (0-10)	1 (0-7)	<0.005*

SLE: Systemic lupus erythematosus.
GIT: Gastrointestinal tract.
SLEDAI : Systemic lupus erythematosus disease activity index.
SLICC DI: Systemic lupus international collaboration clinic damage index.
N : Number of patients.
SD: Standard deviation.
*Significant differences (p<0.05).

Table (2): Neurological Involvement in our Lupus Cohort.

Type of Neuropsychiatric Involvement	Number and %
Headache	63 (31.8%)
Psychosis	16 (8.1%)
Epilepsy	18 (9.1%)
TIA	5 (2.5%)
Stroke	7 (3.5%)
Transverse Myelitis	1 (0.5%)
Cognitive Involvement	8 (4%)
Chorea	1 (0.5%)
Cranial Nerve affection	1 (0.5%)
Peripheral Nerve affection	14 (7.1%)

TIA: Transient ischemic attacks.

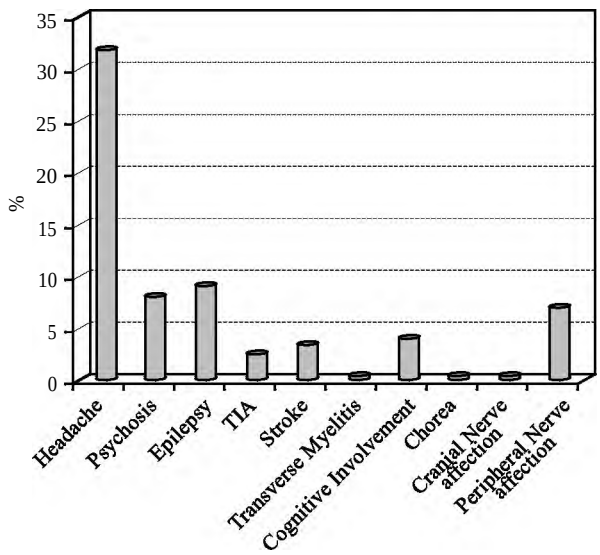

Fig. (1): Frequency of Neuropsychiatric manifestations in our lupus cohort.

Table (3): Laboratory investigations, immunological profile and medications in lupus patients with and without Neuropsychiatric manifestations.

Variable N (%)	SLE patients (n=198)		*p*-value
	With neuropsychiatric manifestations (n=87)	Without neuropsychiatric manifestations (n=111)	
Anemia, n (%)			
Leucopenia, n=197	78 (89.7%)	94 (84.7%)	0.304
Thrombocytopenia	26 (30.2%)	42 (37.8%)	0.265
Consumed C3, n (%) n=184	21 (24.1%)	27 (24.3%)	0.967
Positive ANA, n (%) n=197	40 (48.8%)	54 (52.9%)	0.575
Positive Anti ds DNA, n (%) (n=190)	86 (98.9%)	108 (98.2%)	0.730
Positive aPL, n (%) (total 162)	47 (58.0%)	69 (63.3%)	0.461
Positive APS, n (%) (total 162)	35 (44.9%)	29 (34.5%)	0.178
Medications received	22 (28.2%)	16 (19%)	0.196
Intravenous methylprednisolone intake, n (%)	72 (82.8%)	78 (70.3%)	<.042*
Cumulative intravenous methyprednisolonedose (in grams) median (range)	3 (0-17)	2.5 (0-17.5)	<0.001*
Cyclophosphamide intake, n (%)	46 (52.9%)	55 (49.5%)	0.699
Cumulative cyclophosphamide dose (in gram) median (range)	5.5 (0.8-19.4)	6.9 (1-19.2)	0.771
AZA, n (%)	66 (75.9%)	78 (70.3%)	0.381
MMF, n (%)	13 (14.9%)	22 (19.8%)	0.454
Antimalarial drugs intake, n (%)	83 (95.4%)	104 (93.7%)	0.602

C : Complement.
ANA : Antinuclear antibody.
Anti ds DNA : Anti double stranded deoxyribonucleic acid.
Apl : Antiphospholipid antibodies.
APS : Antiphospholipid syndrome.
AZA: Azathioprine.
MMF: Mycophenolate mofetil.
N: Number of patients.
*Significant differences (p<0.05).

Discussion

Patients with SLE experience a non-specific and diverse range of NP manifestations [13]. NPSLE, which has a mortality rate second only to that of lupus nephritis, is a prominent cause of morbidity in SLE patients [3].

The aim of our study was to investigate the frequency and association of NPSLE in a group of Egyptian Systemic lupus erythematosus (SLE) patients.

The current study was enrolled on 198 SLE patients, 87 patients (43.0%) had NP manifestations, similarly another Egyptian study, found that the NPSLE was present in 50.75% [2].

There is world wide variation in NPSLE prevalence with a significant prevalence heterogeneity between studies [14], which may have explained by different diagnostic standards, geographic and ethnic heterogeneity among study populations [15]. According to the ACR, a diagnosis should be made based on clinical findings and/or electrophysiological studies [16].

In our study the prevalence of NPSLE manifestations was much higher than in Iranian studies, as they reported a prevalence of (21.7%) in one study [17] and (11.3%) in another one [18]. Mok et al. reported the prevalence of NPSLE as 23% in 223 SLE patients [19], also Avčin et al., found that NPSLE prevalence was 25.5% with studying 137 SLE patients [20].

Headache (31.8%) was the most common NPSLE manifestations followed by epilepsy (9.1%) and psychosis (8.1%). Similar to our results, previous reports have identified headache as one of NPSLE most common symptoms [21,22] and the most prevalent NP manifestations being present in 55.9% of SLE patients [25]. Seizures and psychosis were also among the most prevalent presentations [23,24]. On the other hand, cerebral vascular accident (CVA) and cognitive impairment, were the most common NPSLE symptoms in other studies [8,25]. These inconsistencies are caused by the

diverse definition of headache used in various research and the fact that headaches are frequently experienced by people in general, especially women. Just a few previous studies have found a connection between headache and other active lupus clinical features **[25]**.

In the current study SLEDAI at onset, and SLICC DI were statistically significant higher in NPSLE patients, similarly Kakatiand his colleagues in 2017, reported a significant difference between patients with NPSLE and those without NPSLE regarding SLEDAI score **[26]**. Furthermore, patients with SLE presenting with central nervous system (CNS) symptoms, low SLEDAI scores, and abnormal cerebrospinal fluid (CSF) are more suspicious for CNS infections than NPSLE, reflecting that more NPSLE, higher SLEDAI is expected **[27]**. Additionally Podrazilová et al., **[28]** reported that the lesion load in volumetric Magnetic resonance imaging (MRI) was correlated with SLEDAI score in SLE patients, especially those with NPSLE.

Also our results are in accordance with Abdel Sattar and his colleagues, who found that neurological condition can predict organ damage in NPSLE group **[29]**. Also in our study, patients with NPSLE showed statistically significant higher intravenous methylprednisolone intake and higher cumulative intravenous pulse methylprednisolone. Glucocorticoids, especially prednisone, have been the hallmark medication for NPSLE, and is widely used to control mild-severe flares of NPSLE **[30]**, this may explain the higher frequency of pulse methylprednisolone intake in NPSLE group.

In the current study, APL positivity was higher in NPSLE group, however the difference doesn't reach statistical significant, it is to be taken in consideration that APL results was not available for 36 of our patients, and this may impact our results. In the literature there was conflicting reports Govini and colleagues, 2012 concluded that NPSLE involvement in SLE patient was strongly associated with APL **[22]**, on the other hand Hawro et al., **[31]** found that patients with NPSLE and those without it had similar APL characteristics. NPSLE wasn't impacted by variations in APL expression **[32]**.

Limitations: Due to retrospective nature of the study, and some missing data in medical records, we are not able to analyze the 19 NPSLE manifestations identified by ACR, also our analysis of NPSLE association with APL may be impacted by missing APL results in some patients, thus we recommend further cross sectional and prospective studies on Egyptian SLE with NPSLE.

Conclusion:

In this study, NP symptoms were 43.0% prevalent. The most frequent NP symptoms include headache, seizures, and psychosis, and they are related to disease activity. SLE patients with NP manifestations have higher Intravenous methylprednisolone intake, higher SLEDAI score and higher SLICC damage index.

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المظاهر النفسية العصبية في مرضى الذئبة الحمراء المصريين

الخلفية : الذئبة الحمراء الجهازية العصبية (NPSLE). هى حالة معقدة لا تزال غير مفهومة بشكل جيد، وتشمل مظاهر غير متجانسة تشمل كلا من الجهاز العصبى المركزى والمحيطى، مع آثار إعاقة.

الهدف من هذه الدراسة : هو التحقق من تواتر وترابط NPSLE فى مجموعة من مرضى الذئبة الحمراء الجهازية المصرية (SLE).

المرضى والطريقة : قمنا بمراجعة السجلات الطبية بأثر رجعى لـ ١٩٨مريضاً بمرض الذئبة الحمراء. تم الإبلاغ عن عشرة مظاهر عصبية نفسية (NP) من السجلات الطبية للمريض الصداع، والذهان، والنوبات، والنوبات الإقفارية العابرة، والسكتة الدماغية، والتهاب النخاع المستعرض، والضعف الإدراكى، والرقاص، والاعتلال العصبى القحفى، والاعتلال العصبى المحيطى. تم تقسيم المرضى حسب وجود أو عدم وجود المظاهر العشرة المذكورة سابقاً إلى مجموعتين. تمت مقارنة المجموعتين فيما يتعلق بالخيارات السريرية والمخبرية والعلاجية ومؤشر نشاط مرض الذئبة الحمامية الجهازية (SLEDAI) والعيادات التعاونية الدولية الذئبة / الكلية الأمريكية لمؤشر أضرار الروماتيزم (SLICC/ACR DI).

النتائج : كان متوسط مدة المرض لدى مرضانا ٨.٣٣±٦.١٧ سنة. سبعة وثمانون مريضاً (٤٣.٠٪) لديهم مظاهر عصبية نفسية. كانت أكثر مظاهر SLE NP شيوعاً هى الصداع (٣١.٨٪) يليه الصرع (٩.١٪) والذهان (٨.١٪). متلازمات الأخرى NPSLE التى لوحظت فى الدراسة هى عاطفة الأعصاب المحيطية (٧.١٪)، المشاركة المعرفية (٤٪)، السكتة الدماغية (٣.٥٪) ، (٢.٥) TIAs% أقل مظاهر مرض الذئبة الحمراء النفسية شيوعاً هى التهاب النخاع المستعرض والرقاص والتهاب العصب القحفى، كل منها (٠.٥٪). كانت SLEDAI فى البداية، SLEDAI فى الزيارة الأخيرة و SLICC DI ذات دلالة إحصائية (p=0.001، p<0.001 and p=0.005 على التوالى) أظهر المرضى الذين يعانون من NPSLE كمية أعلى من ميثيل بريدنيزولون فى الوريد (p=0.042) وجرعة تراكمية أعلى من ميثيل بريدنيزولون فى الوريد (p<0.001).

استنتاج : كان تواتر الذئبة الحمراء الجهازية العصبية NPSLE فى مجموعتنا (٤٣.٠٪)، وكان الصداع والنوبات والذهان أكثر مظاهر NP شيوعاً فى المرضى الخاضعين للدراسة، وأظهر المرضى الذين يعانون من الذئبة الحمراء الجهازية العصبية NPSLE أعلى SLEDAI على حد سواء (فى البداية وفى آخر زيادة تم الإبلاغ عنها)، مؤشر تلف SLICC أعلى، وزيادة المدخول والجرعة التراكمية فى النبض ميثيل بريدنيزولون.