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Research Article

Evaluation of Neuropsychiatric Manifestations of Systemic Lupus Erythematosus

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Abstract

Background: Neuropsychiatric symptoms are typical consequences in patients with systemic lupus erythematosus (SLE). There is no apparent link between the clinical parameters of SLE patients and the development of neuropsychiatric symptoms.

Objectives: to determine the incidence of neurological manifestations and the risks associated with them in SLE patients.

Methods: This is a case-series study comprised 65 patients who visited the rheumatology Department at Baghdad Teaching Hospital/Medical City between January 2022 and February 2023. All patients' demographic and clinical data, including age, gender, disease duration, type and duration of treatment, general signs of the disease, and neurological and psychiatric manifestations of SLE, were collected. Laboratory data comprised plasma anti-phospholipid antibodies (aPL), anti-double stranded DNA (anti-dsDNA), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). The cognitive dysfunction was assessed using the six-item cognitive impairment test (6CIT).

Results: Out of 65 patients, 34 (52.3%) were found to have at least one neuropsychiatric SLE (NPSLE) manifestation. Headache and depression were the most common NPSLE manifestation encountered in 36 patients (55.4%) followed by psychosis (21.5%), neuropathy (16.9%) and stroke and seizure (13.5%). In multivariate analysis, each of age >35 years (OR= 2.92, 95%CI= 1.12-34.2, p= 0.10), disease duration >5 years (4.45, 95%CI=1.23-28.43, p= 0.001), anti-phospholipid Abs (OR= 4.22, 95%CI= 1.17-89.38, p= 0.036), lupus nephritis (OR= 6.34, 95%CI= 1.27- 64.98, p= 0.029) and 6CIT>3 (OR= 5.83, 95%CI= 1.55-21.87, p= 0.009) are independent predictors for NPSLE in patients with SLE.

Conclusions: Neuropsychiatric manifestations developed in more than half of the SLE cases studied within up to six-year of disease duration. Headache and depression, psychosis and neuropathy are the most common NPSLE manifestations. Older age and longer disease duration are risk factors for development of NPSLE. Clinically, anti-phospholipid antibodies, lupus nephritis and a high score of the six-item cognitive impairment test (>8) are predictors for NPSLE.

Keywords: Cognitive impairment; C-Reactive Protein; Depression; Neuropsychiatric; Systemic Lupus Erythematosus.

Introduction:

SLE is a multisystem autoimmune disease defined by the involvement of nearly every organ in the body, a wide range of clinical symptoms, and many immune-mediated disorders that contribute to multiple organ failure (1). Among the many clinical manifestations of SLE, the neurological system is affected, resulting in a variety of central nervous system (CNS) and peripheral nervous system (PNS) presentations. NPSLE (neuropsychiatric SLE) is a severe complication of SLE characterized by neurological and psychiatric features (2). NPSLE symptoms range from mild to severe and range from localized or isolated to diffuse, peripheral, and/or CNS (3). Diagnosis of NPSLE might be difficult for rheumatologists due to the lack of defined and sensitive laboratory serum or CSF biomarkers, radiographic imaging abnormalities, and other formal criteria in establishing the diagnosis and guiding therapy and management decisions in NPSLE (2). The pathophysiological processes that have been implicated to cause the NPSLE include ischemic process, and autoimmune inflammatory process.

These NP syndromes can be divided into 12 CNS and seven PNS syndromes, and additionally, these were classified into focal neurological syndromes and diffuse neuropsychological syndromes (Table 1) (1).

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Table 1: Clinical syndromes in neuropsychiatric SLE

Syndrome	CNS	(%)	PNS	(%)
Neurological Syndromes	Seizure disorder	7-20	Autonomic disorder	0.08-1.3
	Aseptic meningitis	0.3-2.7	Myasthenia gravis	0.2
	Demyelinated syndromes	0.9-2.7	Polyneuropathy	1.5-5.4
	Myelopathy	0.9-3.9	Cranial neuropathy	1.0
	Headache	12-28	GBS	0.08-1.2
	Cerebrovascular disease	8-15	Mononeuropathy	0.9-6.9
	Movement disorder	0.9	Plexopathy	NR
Psychiatric syndromes	Anxiety disorder	6-40		
	Psychosis	0.6-11		
	Acute confusional state	0.9-7		
	Cognitive dysfunction	6.6-80		
	Mood disorder	7.4-65		

CNS: central nervous system, PNS: peripheral nervous system, GBS: Guillain Barre Syndrome, NR: not reported

The clinical manifestations of NPSLE can range from modest cognitive impairment to acute confusional states, seizure disorders, and psychosis. However, the most common neuropsychiatric manifestations of SLE include headaches, anxiety, mood, and cognitive difficulties. Cerebrovascular disease, neuropathies, acute confusional states, and seizure disorders are the most common presentations of NPSLE, implying many pathogenetic processes in NPSLE that are similar to our current understanding of SLE extracranial manifestations (2). The American College of Rheumatology (ACR) issued a consensus statement defining 19 different NP syndromes. These NP syndromes are classed as 12 CNS and seven PNS syndromes, as well as focal neurological syndromes and diffuse neuropsychological syndromes.

Patients and Methods

Study design and Setting

This is a case-series study of 65 SLE patients who attended the Rheumatology Unit of Baghdad Teaching Hospital/ Medical City between January 2022 and February 2023. SLE was diagnosed using the American College of Rheumatology (ACR) criteria. The Iraqi Council of Medical Specialization approved the research.

Inclusion criteria

Age ≥ 18 years; Fulfillment of the ACR criteria for SLE.

Exclusion criteria: Any other evidence of neurological infections' Diabetes mellitus; Hyperlipidemia, and family history of premature atherosclerosis or other major; risk factors of young adult stroke; Patients with neurological/psychiatric symptoms secondary to other causes, such as hypertension; neurodegenerative disease, or migraine anteceding; SLE symptoms

Data Collection: The following information was gathered from patient files: demographic information including age, gender, duration of the disease, type and length of treatment, general disease manifestations, and neurological and mental manifestations of SLE.

Plasma antiphospholipid antibodies (aPL), plasma levels of anti-double stranded DNA (anti-dsDNA), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were among the laboratory results.

According to the 6-item cognitive impairment test (6CIT), cognitive dysfunction was taken into consideration. The test uses an inverted scoring system, and each question is given a weighted score out of 28. Scores between 0 and 7 are regarded as normal, whereas 8 or more are notable.

The diagnosis of neuropsychic symptoms is based on proper and detailed history intake and full neurological examination.

Data Analysis

Data input was carried out using SPSS version 24 of the Statistical Package for Social Sciences. A normality test was performed on continuously collected data. The mean and standard deviation (SD) were used to convey data with a normal distribution, whereas the median and range were used to express those with an abnormal distribution. The categorical values are expressed as a percentage expressed as a number. Using the t-test for regularly distributed data, the Mann Whitney U test for non-normally distributed data, and the Chi-square (2) test for categorical data, it was determined whether various factors were associated with NPSLE. To identify independent predictors of NPSLE, a binary logistic regression test was utilized. The odds ratio (OR) and corresponding 95% confidence interval (CI) were computed from this test. If p-values were less than 0.05, null hypotheses of no difference were disproved.

Ethics-Related Considerations

Prior to data collection, each patient's signed consent was obtained after being informed of the study's purpose. Every patient had the full, unconditional right to withdraw at any moment. The women were given the assurance that the data would only be utilized for research purposes during the study, and the anonymity of the data was guaranteed.

Results

Demographic characteristics of the Patients: The mean patient's age was 33.3±8.33 years (rang =18-47).

There were 55 (84.6%) females and 10 males (15.4%). The median disease and treatment duration was 5.0 years and 3.5 years, respectively (Table2)

Table (2): Demographic data of SLE patients (n=65)

Variables	Values
Age, years	
Mean±SD	33.3±8.33
Range	18-47
Gender	
Male	10 (15.4%)
Female	55 (84.6%)
Disease duration, years	
Mean±SD	5.1±4.3
Median	4.0
Range	0.1-22
Treatment duration, years	
Mean±SD	4.0±2.84
Median	3.5
Range	0.0-10.0

Clinical characteristics of the Patients

Prednisolone was the most commonly used drug accounting for 64% of the patients followed by HCQ (41.5%), NSAID (35.4%), NSAID (30.8%), rituximab and cyclophosphamide (20% each) and imuran (16.9%). The median CRR and ESR was 6.0 mg/dl and 45.0 mm/h, respectively. Anti-ds DNA and anti-phospholipid antibodies were reported in 23.1% and 24.6% of the patients, respectively, while 27.7% of the patients were suffering from lupus nephritis. The median value of 6CIT was 3.0 (range= 0-24) as shown in table 3

Table 3: Clinical characteristics of patients with SLE (n=65)

Variables	Values
Treatment	
Prednisolone	27 (41.5%)
Hydroxychloroquine	23 (35.4%)
NSAID	20 (30.8%)
Rituximab	13 (20.0%)
Cyclophosphamide	13 (20.0%)
Imuran	11 (16.9%)
Others	6 (9.2%)
C-Reactive protein, mg/dl	
Mean±SD	7.4±5.79
Median	6.0
Range	1-31
Erythrocyte sedimentation rate, mm/h	
Mean±SD	48.6±25.67
Median	45.0
Range	10-127
Anti-dsDNA antibodies	
No	50 (76.9%)
Yes	15 (23.1%)
Anti-phospholipid antibodies	
No	49 (75.4%)
Yes	16 (24.6%)
Lupus nephritis	
No	47 (72.1%)
Yes	18 (27.7%)
Six items cognitive impairment test	
Mean±SD	5.2±6.42
Median	3.0
Range	0.0-24

Incidence of Neuropsychiatric Manifestations: Thirty-four patients (52.3%) were found to have at least one NPSLE manifestation, while the other 31 patients (47.7%) were free from those manifestations (figure 1).

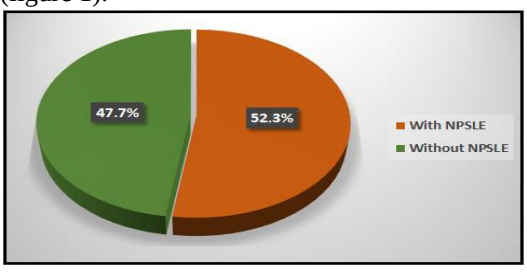

Figure 1: Incidence of NPSLE manifestations in patients with SLE

Types and Frequency of neuropsychiatric Manifestations: Headache and depression was the most common NPSLE manifestation encountered in 36 patients (55.4%) followed by psychosis (21.5%), neuropathy (16.9%) and stroke and seizure (13.5%). Less common manifestation was transverse myelitis (6.2%) as shown in figure 2.

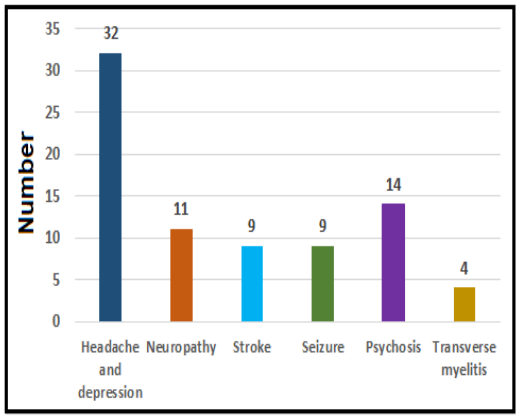

Figure 2: Type and frequency of neuropsychiatric manifestation in patients with SLE. A patient can have more than one NPSLE manifestations.

Association of Demographic factors with the incidence of Neuropsychiatric Manifestations:

Three demographic characteristics were significantly associated with NPSLE. The mean age of patients with NPSLE was 35.7±8.0 years which was higher than that of patients without NPSLE (30.7±8.07 years) with a significant difference. Similarly, patients with NPSLE had longer median disease and treatment duration (6.0 years and 4.5 years, respectively) than those without NPSLE (3.0 years and 2.0 years, respectively) with significant differences (Table 4).

Table 4: Association of demographic factors with the incidence of neuropsychiatric manifestations

Variables	Without NPSLE (N=31)	With NPSLE (N=34)	p-value
Age, years			
Mean±SD	30.7±8.07	35.7±8.0	0.035
Range	19-47	22-47	
Gender			
Male	4 (12.9%)	6 (17.7%)	0.596
Female	27 (87.1%)	28 (82.4%)	
Disease duration, ys			
Median	3.0	6.0	0.005
Range	0.5-10	0.1-22	
Treatment duration, ys	2.0	4.5	0.032
Median	0.0-10	0.15-10.	
Range			

Independent Predictors of NPSLE

Multivariate logistic regression was used to find out the independent predictors for NPSLE. Factors which had p-value of ≤ 0.15 in univariate analysis were further entered into this model. Continuous variables were categorized into binomial variables using a proper cut off value. Each of age >35 years (OR= 2.92, 95%CI= 1.12-34.2, p= 0.10), disease duration >5 years (4.45, 95%CI=1.23-28.43, p= 0.001), anti-phospholipid Abs (OR= 4.22, 95%CI= 1.17-89.38, p= 0.036), lupus nephritis (OR= 6.34, 95%CI= 1.27- 64.98, p= 0.029) and 6CIT>3 (OR= 5.83, 95%CI= 1.55- 21.87, p= 0.009) are independent predictors for NPSLE in patients with SLE (Table 5).

Table 5: Independent Predictors of NPSLE

Variables	Without NPSLE (N=31)	With NPSLE (N=34)	p-value	OR (95%CI)
Age, years				
≤35	17 (70.8%)	9 (34.6%)	0.010	2.92 (1.12-34.2)
>35	7 (29.2%)	17 (65.4%)		
Disease duration, ys				
≤5	22 (91.7%)	12 (45.2%)	0.001	4.45 (1.23-28.43)
>5	2 (8.3%)	14 (53.9%)		
Treatment duration, ys				
≤3.5	15 (62.5%)	12 (45.2%)	0.247	1.27 (0.68-12.5)
>3.5	11 (45.8%)	14 (53.9%)		
Rituximab				
No	18 (75.0%)	10 (38.5%)	0.113	2.11 (0.89-11.82)
Yes	6 (25.0%)	16 (61.5%)		
Cyclophosphamide				
No	22 (91.7%)	17 (65.4%)	0.087	3.15 (1.11-30.56)
Yes	2 (8.3%)	9 (34.6%)		
ESR, mm/h				
≤50	18 (75.0%)	13 (50.0%)	0.073	3.0 (0.9-9.98)
>50	6 (25.0%)	13 (50.0%)		
Anti-phospholipid Abs				
No	23 (95.8%)	18 (69.2%)	0.036	4.22 (1.17-89.38)
Yes	1 (4.2%)	8 (30.8%)		
Lupus nephritis				
No	24 (100.0%)	21 (80.8%)	0.029	6.34 (1.27-64.98)
Yes	0 (0%)	5 (19.2%)		
6CIT				
≤3	20 (83.3%)	12 (45.2%)	0.009	5.83 (1.55-21.87)
>3	4 (16.7%)	14 (53.9%)		

Association of Lupus Nephritis with Neuropsychiatric Manifestations

Three NPSLE manifestations were significantly associated with lupus nephritis. The frequency of headache and depression, psychosis, and seizure among SLE patients was 77.8%, 44.4% and 33.3%, respectively which was much higher than that of patients without lupus nephritis with highly significant differences. On the other hand, 22.2% and 44.4% of patients with lupus nephritis use rituximab and cyclophosphamide, respectively compared with 12.8% and 10.6%, respectively of patients without lupus nephritis with significant differences (Table 6).

Table (6): Association of Lupus Nephritis with Neuropsychiatric Manifestations and Treatment

Variables	Without LN N=47)	With LN (N=18)	p-value
NPSLE manifestations			
Headache and depression	18 (38.3%) 6 (12.8%)	14 (77.8%)	0.004 0.005
Psychosis	8 (17.0%)	8 (44.4%)	0.973
Neuropathy	3 (6.4%)	3 (16.7%)	0.005
Seizure	5 (10.6%)	6 (33.3%)	0.190
Stroke	3 (6.4%)	4 (44.4%)	0.901
Transverse myelitis		1 (5.6%)	
Treatment			
Prednisolone	20 (42.6%)	7 (38.9%)	0.788
Hydroxychloroquine	19 (40.4%)	4 (22.2%)	0.170
NSAID	17 (36.2%)	3 (16.7%)	0.127
Rituximab	6 (12.8%)	4 (22.2%)	0.018
Cyclophosphamide	5 (10.6%)	8 (44.4%)	0.002
Imuran	6 (12.8%)	5 (27.8%)	0.149
Others	4 (8.5%)	2 (11.1%)	0.746

Discussion

The incidence of NPSLE in the current study was 52%, which is fairly high but still falls within the global range (12% to 95%).

This percentage is similar to that previously observed, according to Kakati et al. [4], who evaluated the pattern of neurological involvement in SLE and its association to disease activity and other studies in 52 adult SLE patients from India. A significantly high percentage—92% of the patients—were female. NPSLE cases that were reported accounted for 52.26% of all cases. These patients experienced SLE symptoms for two years before developing NPSLE. Nevertheless, numerous research indicated a lower rate. In a Chinese study, Fan et al. [5] retrospectively evaluated 1,772 SLE patients who were hospitalized and identified 76 patients as having NPSLE, representing a prevalence of 4.3%. The low prevalence may be caused by the exclusion of the majority of NPSLE patients with minor clinical manifestations.

In an Iranian study Borhani Haghighi et al. [6] evaluated the prevalence and characteristics of different neurological and psychiatric presentations in 407 patients. Only 11.3% had neuropsychiatric manifestations. The authors attributed this low rate to the study design which was retrospective, hospital-based study that failed to detect the out patients SLE with neurological manifestations. Bankole et al. [7] studied the connection between socioeconomic and serological factors in the development of NPL and identified the risk factors for the development of NPL in 263 patients. Of those, 82 patients (31.18%) had NPSLE. In a recent meta-analysis, 13 papers totaling 2,003 SLE patients were used in this systematic review and meta-analysis. An estimate of 30.42% (95% CI: 18.26–44.11%) of SLE patients had NP disorders [8]. Using the case criteria provided by the American College of Rheumatology for 19 NPSLE syndromes, Brey et al. [9] assessed the prevalence of NPSLE in a study conducted in the United States. Eighty percent of the patients who were included had one or more NPSLE symptoms.

In a small Finnish study with 46 SLE patients, the diagnosis of NP manifestation was made on the basis of clinical impression after taking into account the patient's medical history, physical exam, evaluation of their medical records, and neuropsychological testing. 42 individuals had at least one NP symptom or sign, representing a 91% incidence rate [10].

This variation between studies could be attributed to a number of variables, the most significant of which are the study design, the length of the illness and the course of treatment, the criteria for the diagnosis of neurological manifestations, the presence of comorbid conditions, and the demographics of the patients who were included.

As for the types of NPSLE manifestations which were found in our study, they were in agreement with the findings of the American study, where 57% of the patients reported having headaches [10]. However, the latter study revealed differing rates for stroke (2%), neuropathy (2%), seizure (16%), anxiety disorder (24%) and psychosis (6.5%).

According to Khan et al.'s study [8], cognitive dysfunctions are the most common symptom of NPSLE (31.51%), followed by headaches (10.22%), seizures (5.96%), psychoses (3.64%), and neuropathies (0.86%).

Previous studies have shown that 28–68% of SLE patients experience headaches [11,12]. Both large series and epidemiological investigations [13,14] have shown that SLE patients experience an increased frequency of cerebrovascular incidents. Premature atherosclerosis, vasculitis, and coagulopathy are a few potential pathomechanisms [13]. (Although these are not addressed in the study but they are presumed mechanisms of the disease pathology).

In contrast to the current analysis, the majority of earlier investigations indicated that seizures were the most common neurological symptom [5-7]. The most common manifestation in the Indian study [4] was cognitive impairment, which was seen in 11 patients (57.89%) and seizure disorder in 8 patients (42.1%). Eight patients (42.1%) had peripheral neuropathy, six (31.57%) had acute confusional condition, and five (26.31%) had headache and depression, respectively. Seizures (63%), headaches (60%), and reduced level of awareness (50%) were the most often seen findings in the Iranian study [6]. In this Iranian study, the three syndromes that were most common were cerebral vascular disease (28.3%), seizure disorder (26.5%), and acute confusional state (19.6%).

These variations between different studies reflect the differences in patients' characteristics, diagnosis criteria and study nature.

These results line well with those from a retrospective cohort of 1,224 patients in Italia [15]. In patients with NPSLE symptoms compared to controls, the mean age of SLE was considerably older (45.914.8 vs. 37.114.0 years), and these patients were also more likely to have more severe illness and hypertension.

In a study conducted in Greece, Karassa et al. [16] examined the risk factors for CNS involvement in SLE in 32 such patients who were individually matched 1: 3 to 96 control SLE patients who had no CNS episodes. According to the study, arterial thrombosis and high titers of IgG anti-aCL antibodies

are two of the hallmarks of antiphospholipid syndrome (APS) as well as being substantially related with CNS involvement.

NPSLE and disease activity were directly associated in the Indian study [4]. The Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score showed a significant difference between individuals with NPSLE and those without NPSLE (32.4216.34 Vs 17.310.6).

In the present study, lupus nephritis was significantly associated with headache, psychosis and seizures. Unfortunately, most available literature did not address this issue. However, lupus nephritis may be an indicator of the severity of SLE and thus the development of neuropsychiatric manifestations.

Conclusions

Neuropsychiatric manifestations developed in more than half of the SLE cases studied within up to six years of disease duration. Headache and depression, psychosis, and neuropathy are the most common NPSLE manifestations. Older age and longer disease duration are risk factors for the development of NPSLE. Clinically, anti-phospholipid antibodies, lupus nephritis, and a high score on the six-item cognitive impairment test (>8) are predictors for NPSLE.

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Conflicts of Interest: None.

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Authors' contributions:

Study conception & design: (Ahmed A. Rasheed, Ghayath A. Shalal, Sadiq M. Hussein). Literature search: (Ahmed A. Rasheed). Data acquisition: (Ahmed A. Rasheed). Data analysis & interpretation: (Ghayath A. Shalal & Sadiq MHussein). Manuscript preparation: (Ahmed A. Rasheed). Manuscript editing & review: (Sadiq MHussein)

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تقييم المظاهر العصبية لمرضى داء الذئبة الحمراء

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الخلاصة
الخلفية: المظاهر العصبية والنفسية هي مضاعفات شائعة في المرضى الذين يعانون من الذئبة الحمامية الجهازية .(SLE) لا توجد علاقة واضحة بين الخصائص السريرية لمرضى الذئبة الحمراء مع تطور المظاهر العصبية والنفسية.
الهدف: تقييم مدى حدوث المظاهر العصبية والمخاطر المرتبطة بها لدى مرضى الذئبة الحمراء
المرضى والطرق المنهجية: هذه مجموعة من الحالات تضم ما مجموعه 65 مريضًا مصابًا بمرض الذئبة الحمراء. تم استخراج البيانات الديموغرافية والسريرية بما في ذلك العمر والجنس ومدة المرض ونوع ومدة العلاج والمظاهر العامة للمرض والمظاهر العصبية والنفسية لمرض الذئبة الحمراء من جميع المرضى. تضمنت البيانات المختبرية الأجسام المضادة للبلازما المضادة للفوسفوليبيد (aPL) ، والحمض النووي المضاد المزدوج-anti) (dsDNA، ومعدل ترسيب كرات الدم الحمراء (ESR) والبروتين التفاعلي .(CRP) تم اعتبار الخلل المعرفي وفقًا لاختبار الضعف الإدراكي المكون من ستة عناصر (6.CIT)
النتائج: من بين 65 مريضًا ، وجد أن 34 (52.3٪) لديهم مظهر واحد على الأقل من مظاهر الذئبة الحمامية العصبية والنفسية .(NPSLE) كان الصداع والاكتئاب أكثر مظاهر NPSLE شيوعًا في 36 مريضًا (55.4٪) يليه الذهان (21.5٪) والاعتلال العصبي (16.9٪) والسكتة الدماغية والنوبة (13.5٪). في التحليل متعدد المتغيرات، كل من عمر أكبر من 35 عامًا(OR = 2.92 ، CI = 1.12-34.2٪95 ، p = 0.10) ، مدة المرض> 5 سنوات (4.45 ، 95٪ CI = 1.23-28.43 ، p = 0.001) ، مضاد - فوسفوليبيد أبس(OR = 4.22 ، CI = 1.17-89.38٪95 ، p = 0.036) ، التهاب الكلية الذئبي(OR = 6.34 ، CI = 1.27- 64.98٪95 ، p = 0.029 و CIT> 3 (OR = 5.836 ، CI = ٪ 95 ، 1.55-21.87 ، p = 0.009) تنبئ مستقل لـ NPSLE في مرضى الذئبة الحمراء
الاستنتاجات: تطورت المظاهر العصبية والنفسية في أكثر من نصف حالات مرض الذئبة الحمراء التي تمت دراستها خلال فترة تصل إلى ست سنوات من مدة المرض. يعد الصداع والاكتئاب والذهان والاعتلال العصبي من أكثر مظاهر NPSLE شيوعًا. يعد التقدم في السن ومدة المرض الأطول من عوامل الخطر لتطور NPSLE. سريريًا، تعتبر الأجسام المضادة للفوسفوليبيد والتهاب الكلية الذئبي والدرجة العالية في اختبار الضعف الإدراكي المكون من ستة عناصر (< 8) من العوامل التي تنبئ بـ NPSLE.