

Neurological Study of Patients with Systemic Lupus Erythematosus

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Abstract

Background: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease of unknown etiology affecting multiple organ systems including the joints, skin, heart, lungs, kidneys and the nervous system.

Aim of Work: Is to study the neurological manifestations in patients with systemic lupus erythematosus attending Tanta University Hospitals over 6 months.

Patients and Methods: Cross sectional study was carried out on 60 patients with SLE diagnosed according to American College of Rheumatology criteria attending Tanta University Hospitals during six months.

Results: Mean age was 46.7 ± 12.1 . Fifty two patients were females and 8 patients were males. This study found that 43 patients showed neurological manifestations, headache was the most common representing 51.7% followed by cognitive impairment 46.7% and cerebrovascular stroke 13%. 6 patients complicated by seizures in whom 3 patients were focal. Focal slowing was the most common EEG abnormalities while white matter hyper intensity lesions were the most common MRI brain abnormalities.

Conclusion: Neurological manifestations are frequent in SLE patients. Headache is the most common neurological manifestation followed by cognitive impairment.

Key Words: SLE, Neurological manifestations – Headache.

Introduction

SYSTEMIC lupus erythematosus (SLE) is a chronic autoimmune disease of unknown etiology affecting multiple organ systems including the joints, skin, heart, lungs, kidneys and the nervous system [1].

Neuropsychiatric systemic lupus erythematosus (NPSLE) is a clinical feature of SLE which is characterized by neurological syndromes of the central, peripheral and autonomic nervous system as well as psychiatric disorders [2]. NPSLE syndromes range from diffuse CNS disorders (acute

confusional state, psychosis and anxiety) to focal CNS syndromes (seizures, cerebrovascular disease and chorea) and peripheral nervous system disorders (polyneuropathies, mononeuropathies, autonomic disorder and plexopathy) [3].

Seizure is one of the diagnostic criteria for SLE. It can occur around the onset of the disease. In SLE patients; generalized tonic-clonic seizures are most common but simple and complex partial seizures can occur [4]. Patients with SLE are at increased risk of stroke, cerebrovascular disease affects between 2% and 15% of patients with SLE. Acute ischemic stroke is the most common form. Headache is rather a common complaint that can be associated with the disease. Most common types of headache are migraine with or without aura, tension headache and idiopathic intracranial hypertension [5].

Chorea is the best documented movement disorder in SLE and has been associated with antiphospholipid antibody. Most frequent cranial neuropathies involves the 8th, 3rd, 6th and less common 5th, 7th nerves. Optic neuropathy includes inflammatory optic neuritis & ischemic thrombotic optic neuropathy [6]. SLE patients have mild to moderate degree of cognitive dysfunction with an overall benign course [7]. The cognitive deficits common in SLE include difficulties in the domains of verbal visual-spatial functioning and executive function [8].

Patients and Methods

This study was conducted in the Neuropsychiatry department and internal medicine department, Tanta University Hospitals on sixty patients with SLE over six months starting from February 2017. All Patients were above 18 years old with systemic lupus erythematosus diagnosed according to the American College of Rheumatology Criteria, Each patient was subjected to full history taking, full

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neurological examination including assessment of cognitive function using the Montreal Cognitive Assessment scale (MoCA) [9]. Patients with cerebrovascular stroke were assessed by Modified Rankin Disability Scale [10]. Also SLEDAI score was done to all patients. Routine lab investigations were done for all patients including complete blood picture, international normalized ratio, liver & renal functions and lipid profile, in addition to further lab investigations, including ESR, ANA and Anti-dsDNA. MRI brain were done to all patients with cerebrovascular stroke, headache and cognitively impaired individuals. Cerebral MRV was ordered for only two patients as their MRI brain revealed hemorrhagic infarction and delta signs MRI cervical spine was done to only one patient presented by myelopathy. EEG was done for all patients. Nerve conduction and Electromyography studies for both upper and lower limbs were indicated if there was a possibility of neuropathy or myopathy.

Results

The total number of cases was 60 patients with mean age 46.7±12.1 ranging from 22-68 years with female sex predominance representing 86.7% in comparison to male 13.3%. The most common educational level was high education which was representing 38.3% followed by preparatory 20%, secondary 18.3%, primary 16.7% and illiterate 6.7%. The mean disease duration was 5.10±4.26 ranging from 1-6 years (Table 1).

Table (1): Socio-demographic characteristics of the studied patients.

Demographic data	Number of cases (No.=60)	
<i>Age (in years):</i>		
Mean ± SD	46.7±12.1	
Range	22-68	
	No.	%
<i>Sex:</i>		
Male	8	(13.3%)
Female	52	(86.7%)
<i>Educational level:</i>		
Illiterate	4	6.7%
Primary	10	16.7%
Preparatory	12	20.0%
Secondary	11	18.3%
High education	23	38.3%
<i>Disease duration (inyears):</i>		
Mean ± SD	5.10±4.26	
Range	1-16	

The most common educational level is high education representing 38.3% followed by preparatory 20%, secondary 18.3%, primary 16.7% and illiterate 6.7%. Fig. (1).

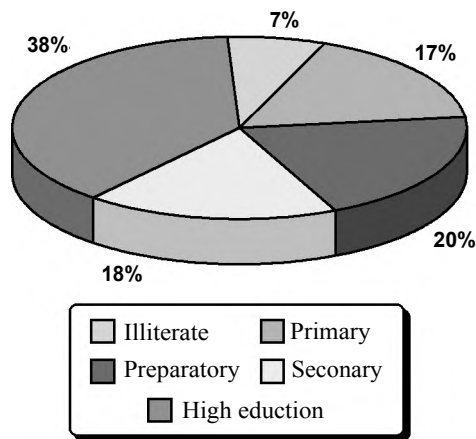


Fig. (1): Educational level of the studied patients.

Photosensitivity was the most common clinical presentations representing (76%) followed by neurological (71.7%), immunological (70%), oral ulcers (55%), renal disorder (50%), malar rash (40%), arthritis (36%), hematological (31%), serositis (25%), discoid rash (3%). Mean SLEDAI score was 9.92±6.62 ranging from 2 to 30. Table (2).

Table (2): Clinical presentations of SLE according to ACR in the studied patients.

Clinical presentation	Number of cases (No.=60)	
	No.	%
Malar rash	24	40
Discoid rash	2	3
Photosensitivity	46	76
Oral ulcers	33	55
Arthritis	22	36
Renal disorder	30	50
Hematological	19	31
Immunological	42	70
Neurological	43	71.7
Serositis	15	25
<i>SLEDAI Score:</i>		
Mean ± SD	9.92±6.62	
Range	2-30	

Headache was the most common neurological presentations representing 51.7% followed by cognitive impairment 46.7%, cerebrovascular 13.3%, seizures 10%, neuropathy 10% and myelopathy 1.7%. Fig. (2).

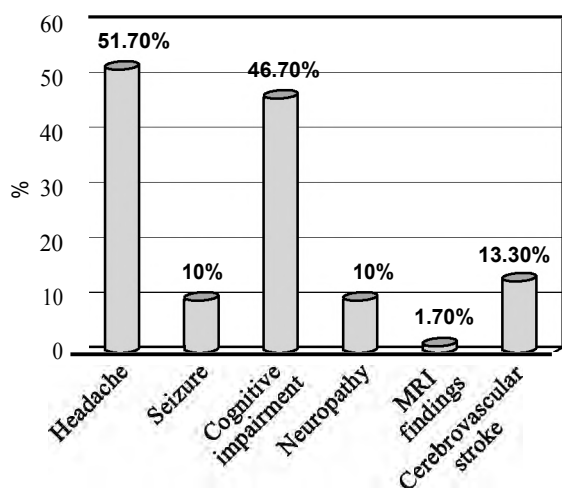


Fig. (2): Neurological presentations of the studied patients.

Migraine with aura was the commonest headache type representing 45.2% followed by tension headache 25.8%, migraine without aura 22.8% and headache with unspecified character 6.4%. Table (3).

Table (3): Headache characteristics of the studied patients.

Headache character	Number of cases (No.=3 1)	
	No.	%
Migraine with aura	14	45.2
Tension headache	8	25.8
Migraine without aura	7	22.6
Unspecified character	2	6.4

There was association between headache and disease duration, hypertension, hematological disorder, cognitive impairment, Cerebrovascular stroke and MRI findings with significant predictor risk factor affecting headache. Table (4).

Table (4): Multivariate regression analysis of factors affecting headache.

Significant predictor variables	t	p-value	Confidence interval
<i>Demographic data:</i>			
Age (years)	0.73	0.43	0.20–0.55
Sex	1.001	0.28	0.013–0.075
Disease duration	9.7	0.003*	0.25–0.96
<i>Risk factors:</i>			
Diabetes mellitus	2.25	0.45	0.01–0.86
Hypertension	2.43	0.001*	0.05–0.93
<i>SLE manifestations:</i>			
Arthritis	0.89	0.43	0.20–0.55
Renal disorder	1.001	0.28	0.013–0.075
Hematological disorder	9.7	0.023*	0.25–0.96
Immunological disorder	2.25	0.45	0.01–0.86
<i>Neurological presentation & radiological finding:</i>			
Seizures	1.001	0.028*	0.13–0.095
Cognitive impairment	9.7	0.003*	0.25–0.96
Neuropathy	2.25	0.45	0.01–0.86
Cerebrovascular stroke	2.43	0.033*	0.05–0.9
MRI findings	10.96	0.001*	0.07–0.44

Focal fits were the commonest type of seizure representing 50% followed by generalized tonic-clonic 33% and focal with secondary generalization 17% Table (5).

Table (5): Seizure type among the studied patients.

Seizure type	Number of cases (No.=6)	
	No.	%
Focal	3	50
Generalized tonic-clonic	2	33
Focal with secondary generalization	1	17

There was an association between seizures and disease duration, diabetes mellitus, headache, cognitive impairment, cerebrovascular and MRI findings with significant predictor risk factor affecting seizures Table (6).

Table (6): Multivariate regression analysis of factors affecting seizures.

Significant predictor variables	t	p-value	Confidence interval
<i>Demographic data:</i>			
Age (years)	0.73	0.55	0.020–1.55
Sex	1.001	0.28	0.013–0.075
Disease duration	9.7	0.003*	0.25–0.96
<i>Risk factors:</i>			
Hypertension	2.25	0.45	–0.01–0.86
Diabetes mellitus	2.43	0.001*	0.05–0.93
<i>SLE manifestations:</i>			
Arthritis	0.89	0.43	–0.20–0.55
Renal disorder	1.001	0.28	0.013–0.075
Hematological disorder	9.7	0.23	0.25–1.96
Immunological disorder	2.25	0.45	–0.01–0.86
<i>Neurological presentation & radiological finding:</i>			
Seizures	1.001	0.028*	0.13–0.095
Cognitive impairment	9.7	0.003*	0.25–0.96
Neuropathy	2.25	0.45	–0.01–0.86
Cerebrovascular stroke	2.43	0.033*	0.05–0.9
MRI findings	10.96	0.001*	0.007–0.44

Visuospatial/executive was the commonest domain of cognition that affected in the studied patients 42.9% followed by Memory 32.1%, Attention 21.2%, Language 17.9%, Naming 10.7%, Abstraction 10.7%, Delayed recall 10.7% and Orientation 8.3% Fig. (3).

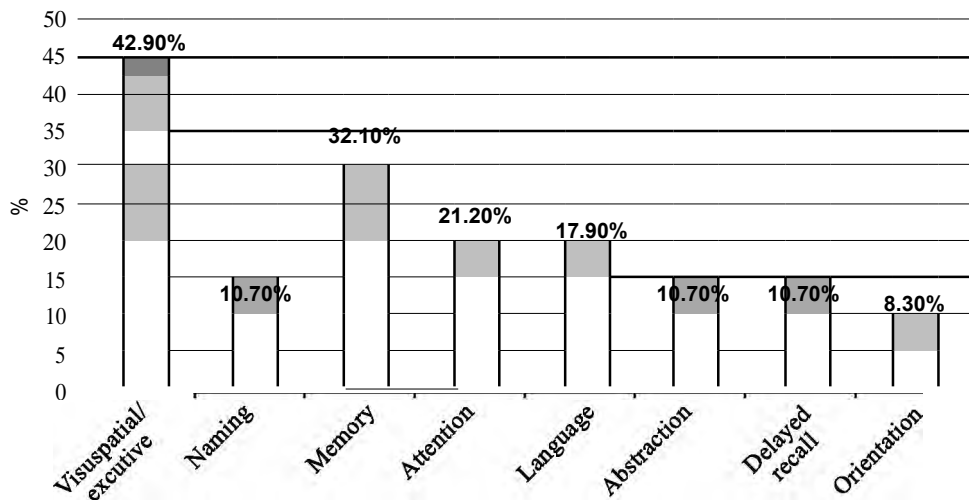


Fig. (3): Affected cognitive Domains among the Studied Patients

Eight patients complicated by cerebrovascular stroke representing 13% of all patients in whom 2 patients (25%) presented by sinus thrombosis and 6 patients (75%) presented by arterial ischemic stroke 3 of whom were large and 3 were lacunar. 6 patients (75%) presented by side weakness while 2 (25%) patients presented by headache and only 1 patient (12.5%) presented by language disturbance. the modified Rankin scale mean was 3 ± 2 ranging from 0 to 6 Table (7).

Table (7): Cerebrovascular stroke among studied patients.

Cerebrovascular stroke	Number of cases (No.=8)	
	No.	%
<i>Type of stroke:</i>		
• Sinus thrombosis	2	25
• Ischemic(arterial)	6	75
Lacunar	3	50
Large	3	50
<i>Clinical picture of cerebrovascular stroke:</i>		
• Side weakness	6	75
• Language disturbance	1	12.5
• Headache	2	25
<i>Modified Rankin scale:</i>		
Min. – Max.	0–6	
Mean \pm SD.	3+2	

There was an association between cerebrovascular stroke and age, disease duration, hypertension, headache, seizure, cognitive impairment and MRI findings with significant predictor risk factor Table (8).

Table (8): Multivariate regression analysis of factors affecting cerebrovascular stroke.

Significant predictor variables	t	p-value	Confidence interval
<i>Demographic data:</i>			
Age (years)	1.31	0.043*	0.20–0.55
Sex	1.20	0.26	0.013–0.075
Disease duration	9.75	0.003*	0.25 - 0.96
<i>Risk factors:</i>			
Hypertension	2.25	0.047*	0.01–0.56
Diabetes mellitus	2.43	0.001*	0.05–0.93
<i>SLE Manifestations:</i>			
Arthritis	0.89	0.98	0.20–1.19
Renal disorder	1.05	0.25	0.013–1.07
Hematological disorder	1.32	0.33	0.25–0.96
Immunological disorder	2.95	0.85	0.01–1.86
<i>Neurological presentation & radiological finding:</i>			
Headache	2.65	0.045*	0.13–0.095
Seizure	9.2	0.026*	0.25–0.96
Neuropathy	1.25	0.45	0.01–0.86
Cognitive impairment	2.32	0.03*	0.05–0.9
MRI findings	11.2	0.001*	0.07–0.44

EEG was normal in 55% of patients and 45% was showing abnormalities. The most common abnormalities was focal slowing representing 28.3% followed by Generalized spike sharp waves representing 10%, Focal spike sharp waves 8.3% and Focal spike slow wave with 2ry generalization representing 5%. There was more than one abnormality in many EEG Table (9).

Table (9): EEG characteristics among the studied patients.

EEG character	Number of cases (No.=60)	
	No.	%
Normal	33	55.0
<i>Abnormal:</i>	27	45
• Generalized spike sharp waves	6	10.0
• Focal slowing	17	28.3
• Focal spike sharp waves	5	8.3
• Focal spike slow wave with 2ry generalization	3	5.0

The MRI brain was abnormal in about 30 patients (84.4%) in relation to the normal 16.6%. The most common abnormalities was white matter hyperintensity lesions 47.2% followed by infarction 19.4% and cortical atrophy 16.6% Table (10).

Table (10): MRI findings among the studied patients.

MRI Findings	Number of cases (n=36)	
	No.	%
Normal	6	16.6
<i>Abnormal:</i>	30	84.4
• White matter hyper intensity	17	47.2
• Cortical atrophy	6	16.6
• Infarction	7	19.4

Nerve conduction was done to 6 patients in which 2 patients showed sensorimotor axonal polyneuropathy (50%), and 1 patient showed entrapment neuropathy median nerve (16%). However, nerve conduction of 2 patients (33.3%) was normal Table (11).

Table (11): Neurophysiological study results in the studied patients.

Diagnosis	Number of cases (n=6)	
	No.	%
<i>NCS:</i>		
Sensorimotor axonal polyneuropathy	3	50
Entrapment neuropathy median nerve	1	16.7
Normal	2	33.3

MRI brain was done for 36 patients with different neurological manifestations. MRI brain of 31 patients with headache revealed that 5 patients (16%) has normal imaging while 26 patients (83.8%) had abnormal findings in comparison to 5 patients without headache whom 20% had normal imaging and 80% had abnormal, MRI brain of 28 patients with cognitive impairment showing that only 2 patient has normal imaging while 26 patients

(92.8%) had abnormal findings also MRI brain of patients with seizures revealed that 33% had normal imaging while 66.6% had abnormal imaging. All patients with cerebrovascular stroke had abnormal imaging Table (12).

Table (12): Relation between neurological manifestations and MRI findings.

Presence of neurological manifestations	(No=36)	
	Normal MRI	Abnormal MRI
<i>Headache:</i>		
Yes (n=31)	5 (16.1%)	26 (83.8%)
No (n=5)	1 (20%)	4 (80%)
X ²		0.65
p		0.41
<i>Cognitive impairment:</i>		
Yes (n=28)	2 (7.14%)	26 (92.85%)
No (n=8)	4 (50%)	4 (50%)
X ²		9.61
p		0.002*
<i>Seizure:</i>		
Yes (n=6)	2 (33.3 %)	4 (66.6%)
No (n=30)	4 (13.3%)	26 (86.6%)
X ²		0.65
p		0.82
<i>Cerebrovascular Stroke:</i>		
Yes (n=8)	0 (0.0%)	8 (100%)
No (n=28)	6 (21.4%)	22 (78.5%)
X ²		4.04
p		0.039*

Table (13): Comparison between symptomatic and asymptomatic patients regarding SLEDAI score among the studied patients.

	Number of cases (n=60)	
	Symptomatic (n=43)	Asymptomatic (n=17)
<i>SLEDAI score:</i>		
Mean ± SD	18.5±2.6	6.5±2.3
Range	13–30	2–15
t-test (p-value)	5.9 (0.001)*	

There was a significant difference between symptomatic and asymptomatic patient regarding SLEDAI score, $p=0.001$.

Discussion

In 1999, American college of Rheumatology (ACR) developed the nomenclature and case definitions for the 19 NPSLE syndromes. With respect to validation, these case definitions provided a satisfactory detection rate of 91% for NPSLE;

however, the specificity was only 46%. Jeong et al., 2014 [11].

This study found that SLE was more common in female than male with 86.7% in female and 13.3% in male. This result is similar to Ainilia et al., [12], in which the prevalence was 84% in female and is near to the result of Hafez et al., [13], which was 93%. The mean disease duration of SLE in this study was 5.10 ± 4.26 ranging from 1 to 16 years which is similar to Appenzeller et al., [14] in which disease duration mean was 5.54 ± 4.87 . But this result was inconsistent with the mean disease duration in Sibbitt et al., [15] study in which the mean was 7.82 ± 6.1 this difference could be explained by different age group as that study was conducted at pediatric age group.

The most common SLE clinical presentations in this study was cutaneous manifestations in the form of photosensitivity 76% which is consistent with study Foering et al., [16] in which photosensitivity was representing 81% however Khedr et al., [17] reported a lower prevalence 33%. This discrepancy can be explained by disparity in number of patients in each study.

In the current study, the frequency of nervous system involvement was about 71% which is similar to the reported prevalence in Afeltra et al., [18], study which was 72% and near to the frequency in the study of Hafez et al., 2007 [13] and Ainilia et al., [12] which was 80% and 91% respectively.

In contrary to this result the frequency detected by Zhou et al., [19] and Flower et al., [20] was about 12.2% and 15% respectively. This variation may be due to different populations and regions (including race, socioeconomic status) and study methodology.

The most frequent neurological manifestations in this study were headache (51.7%) cognitive impairment (46.7%) and cerebrovascular stroke (13%). In fact, the frequency of headache in the current study was similar to the prevalence in the general population according to Stovener et al., 2007 [21] study which was 55%. Also, some researchers believed that headache was frequent in the general population and was usually unrelated to SLE. Wang et al., [22].

In this study 14 patients of 31 patients with headache was complaining of migraine with aura and 8 patients reported tension headache. Migraine without aura was reported in 7 patients with headache while 2 patients were complaining of headache with unspecified character. Disease duration is

considered to be a risk factor for headache in this study with significant *p*-value which is consistent with the findings of study Chiewthanakul et al., [23] and inconsistent with Abdel-Sattar et al., [24] in which disease duration was not a risk factor for development of headache in SLE patients.

In the current study cognitive impairment was reported in 28 patients representing 46.7%. Visuospatial/executive functions and memory are the most affected cognitive domains with frequency of 20% and 15% of cognitively affected patients. This results were near to the reported prevalence of cognitive impairment in study of Alfeltra et al., [18] and Brey et al., [25] which was 52.5% and 41.4% respectively but there was a lower prevalence in Mok et al., [26] and Schenatto et al., [27] reaching 3.5% and 3.4% respectively. This variation may be due to different methods used for cognitive assessment and also for the educational level of selected patients.

In this study, 8 patients were complicated by cerebrovascular stroke in whom 6 patients presented by arterial ischemic stroke and 2 patients presented by sinus thrombosis but hemorrhagic stroke was not reported in this study. This frequency is consistent with Yu et al., [28] and Sibbitt et al., [15] studies with frequency of 13.5% and 12% respectively but there was lower prevalence reported in Abdel Nasser et al., [29] and Brey et al., [25] 3.1% and 1.6 respectively. The explanation for this discrepancy may be wide variations of number of studied patients and also duration of each study.

In this study, nerve conduction was done only for symptomatic patients in whom 3 patients were complaining of persistent numbness and distal weakness of both hands, their nerve conduction revealed sensorimotor axonal polyneuropathy. One patient was complaining of persistent left hand numbness, nerve conduction revealed left median nerve entrapment neuropathy. Other two patients were complaining of numbness of both hands but their nerve conduction was normal.

This result is near to the reported prevalence of neuropathy in Alfeltra et al., [18] and Brey et al., [25] studies which was 13.1% and 15.6% respectively but other studies recorded a higher prevalence for example Ainilia et al., [12], reported 28%. But Abdel Nasser et al., [29], Did not report any case with peripheral neuropathy. This variation may be due to different methodology and number of studied patients and duration of each study.

In this study, EEG was done for all cases. EEG interpretations was showing 55% patients had

normal EEG and 45% had abnormal EEG. This results is similar to Gora et al., [30] in which the abnormal EEG was seen in 49.3%. Other studies reported a higher EEG abnormality for example Kheder et al., [17] and Matsukawa et al., [31] reported 71% and 90% respectively. On the other hand, Omdal et al., [32] recorded a prevalence of 33%. This wide variations could be explained by different number of studied patients and methodology.

The most common MRI brain abnormality in this study was white matter changes representing 47.2% of all abnormalities followed by infarction representing 19.4% and cortical atrophy 16.6%. Also we found significant association between MRI brain abnormality and cognitive impairment also with cerebrovascular stroke which is consistent with Appenzeller et al., [14] and Ainlia et al., [12] studies that found association between MRI brain abnormalities, cognitive impairment and cerebrovascular disease respectively.

Generalized SLE activity is a major risk factor for SLE related neuropsychiatric events. SLEDAI is a validated model for the overall evaluation of disease activity in SLE patients and can be of great use in treatment. Wang et al., [33]. In this study, SLEDAI score mean was about 18.5 ± 2.6 in patients with neurological complications denoting disease activity in comparison to others without any neurological complications. This results are in accordance with previous study Abdel Sattar et al., [24] which found more organ damage in the NPSLE group, which was, as expected, due to neurological disease.

Conclusion: Neurological complications are frequent in SLE patients. Headache, cognitive impairment and cerebrovascular disease are the most common neurological complications. SLEDAI score is high in patients with neurological complications denoting disease activity. Sensorimotor axonal polyneuropathy are the most common type of peripheral neuropathy in SLE. White matter hyperintensity lesions are the most common MRI brain abnormality in SLE.

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Conflicts of interest:

No conflicts of interest declared.

Authors' Contributions:

All authors had equal role in design, work, statistical analysis and manuscript writing. All authors have approved the final article work.

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دراسة عصبية لمرضى الذئبة الحمراء

مرض الذئبة الحمراء هو مرض مناعي مزمن يسبب أجهزة الجسم المختلفة بما في ذلك الجهاز العصبي سواء المركزي أو الطرفي أو اللا إرادي ويؤثر هذا المرض على الجهاز العصبي في صور متعددة منها الصداع سواء نصفى أو التوتري وكذلك السكتات الدماغية الحادة كما أنه قد يؤدي إلى التشنجات الصرعية والتي تعتبر من سمات هذا المرض وأحد معايير تشخيصية.

الهدف من الدراسة: دراسة الأعراض العصبية في مرضى الذئبة الحمراء المتردين على مستشفيات جامعة طنطا خلال ستة أشهر.

المرضى وطرق البحث: قد أجرى هذا البحث على مرضى الذئبة الحمراء المتردين على مستشفيات جامعة طنطا خلال ستة أشهر ابتداء من فبراير ٢٠١٧ سواء يعانون من أعراض عصبية أو عدمه. وتم تشخيص مرض الذئبة الحمراء طبقاً للمعايير التي وضعتها الكلية الأمريكية لأمراض الروماتيزم.

وقد تم إجراء الفحوصات التالية للمرضى المشاركين بالبحث: التاريخ المرضي والفحص الأكلينيكي الشامل وأبحاث معملية منها صورة دم كاملة ووظائف كلى وسرعة ترسيب وأختبار الأجسام المضادة للنواة وكذلك أختبار الأجسام المضادة للحمض النووي ثنائي النوعية. وتم عمل رسم المخ لجميع المرضى وكذلك رسم عصب للمرضى المشتبه بإصابتهم بالتهابات بالأعصاب الطرفية وتم عمل رنين مغناطيسي على المخ للمرضى الذين يعانون من سكتات دماغية أو تشنجات صرعية أو صداع مزمن وكذلك عمل أختبار للوظائف لمعرفة يسمي مونتريال سكور.

الاستنتاج: ٧١٪ من الحالات قد أصيبوا بمضاعفات بالجهاز العصبي سواء المركزي أو الطرفي حيث كان الصداع هو أكثر المضاعفات العصبية يليها إختلال الوظائف المعرفية ثم السكتات الدماغية ووجد أن الصداع النصفى هو أكثر أنواع الصداع شيوعاً يليه الصداع التوتري وكان إحتلال الوظائف المرئية المكانية والذاكرة هي أكثر الاضطرابات المعرفية شيوعاً كما أن السكتات الدماغية الأحتشائية هي أكثر أنواع السكتات الدماغية شيوعاً.

التوصيات: نحن نوصى بضرورة عمل التحاليل اللازمة والتصوير الطبى للاكتشاف المبكر للأعراض العصبية في المرضى المصابون بمرض الذئبة الحمراء وذلك لأخذ العلاج اللازم ومنع تكرار حدوثها.