Subclinical neuropsychiatric dysfunctions in female patients with systemic lupus erythematosus

Caroline S. Morad^a, Howaida E. Mansour^a, Soha E. Ibrahim^b, Khaled A. Ahmad^c, Shaimaa G. Arafa^a

^aInternal Medicine Department, Rheumatology Division, ^bRheumatology and Rehabilitation Department, ^cRadiodiagnosis Department, Ain Shams University, Egypt

Correspondence to Caroline S. Morad, MD, Internal Medicine Department, Rheumatology Division, Ain Shams University, Egypt, ORCID ID: 0000-0002-5482-0632. Tel: +201221107474; e-mail: carolinesamy@yahoo.com

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Objective

To examine for presence of subclinical neuropsychiatric lupus and cerebral atherosclerosis and their correlation with MRI/magnetic resonance angiography (MRA) findings and disease activity and to find if these radiological changes compared with laboratory parameters could be predictive of the early NP affection aiming for early management of these dysfunctions.

Patients and methods

Thirty adult female patients with systemic lupus erythematosus (SLE) were enrolled, with assessment of SLE disease activity using Systemic Lupus Erythematosus Disease Activity Index; psychometric evaluations using the Modified Mini-Mental State Examination to assess for cognitive dysfunction; Hamilton Depression Rating Scale and Hamilton Anxiety Scale to assess for depression and anxiety, respectively; and brain MRI/MRA to detect any changes in subclinical cases.

Results

The mean age was 31.7 years. Twelve (40%) patients had positive antiphospholipid (aPL) antibodies with or without clinically evident antiphospholipid syndrome, 22 (73.33%) had different NP manifestations, 13 (43.3%) depression, 15 (50%) anxiety, and 16 (53.3%) cognitive dysfunction. All patients with depression and anxiety and 87.5% of patients with dementia showed abnormalities on MRI. All patients with positive aPL showed abnormalities on MRI, whereas abnormalities on MRI were found in only eight patients with SLE with negative aPL (100 vs. 44.4%). There was a significant correlation between SLE disease activity and both NP manifestations and abnormalities on MRI/MRA, and also between aPL antibodies and NP manifestations. Abnormalities on MRI included discrete white matter lesions, cortical atrophy, and gross infarctions.

Conclusion

Significant number of patients with SLE without overt NP manifestations had subclinical cerebrovascular and cognitive dysfunctions, depression, and anxiety by simple bedside questionnaires. SLE disease activity positively correlates with NP manifestations. The presence of aPL antibodies is a strong risk factor for developing NP SLE. Several distinct brain MRI patterns were observed in patients with active NP SLE, suggestive of different pathogenic mechanisms.

Keywords:

antiphospholipid syndrome, anxiety, cognitive dysfunction, depression, MRI, systemic lupus erythematosus

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Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease where autoantibodies result in tissue injury [1]. Up to 50% of patients with SLE experience neurological involvement throughout the course of the disease [2]. In ~40% of cases, neuropsychiatric (NP) manifestations are because of the disease itself. Other causes of NP manifestations are infections, metabolic disorders, and adverse effects of drugs [3].

Overt NP symptoms are usually clinically obvious. However, subtle changes such as mild cognitive dysfunction are often unnoticed. Neuropsychiatric systemic lupus erythematosus (NPSL) can occur any time during the course of the disease or may even precede its onset. Furthermore, NPSL can present during the active or quiescent phase of SLE [4].

NP manifestations result in impaired quality of life and high morbidity and mortality [5]. As no specific tests or biomarkers are available for establishing a diagnosis, the attribution of NP manifestations to SLE continues

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to be a challenge and is made after ruling out secondary causes of NP manifestations [6].

Nineteen NP syndromes have been identified by the American College of Rheumatology and have been further divided into central and peripheral nervous system manifestations [7]. Central nervous system (CNS) manifestations are more common than peripheral and are further classified into diffuse or focal [8]. NPSL may be the first or presenting manifestation of SLE. Patients may present with single or multiple events. Its prevalence ranges from 21 to 95% [5,7].

In primary NPSL, potential pathogenic mechanisms include blood-brain barrier disruption, direct action of intrathecal inflammatory cytokines, antiphospholipid (aPL) antibodies causing accelerated atherosclerosis, and thrombotic vasculopathy [3]. In addition, autoantibodies may bind to neurons causing neuronal dysfunction and apoptosis [8,9].

In this study, our aim was to search for the presence of subclinical NPSL manifestations and their correlation – if any – to brain MRI findings and SLE disease activity and also to find if the radiological changes compared with the laboratory parameters could be predictive of the early NP affection, aiming for early management of these dysfunctions.

Patients and methods

In this cross-sectional observational study, 30 patients with SLE fulfilling the updated ACR classification criteria for SLE [10] and not known to have NPSL were recruited from the rheumatology outpatient clinic and Inpatient Department of Ain Shams University Hospitals.

All participants gave written informed consent to participate in the study, which was approved by our local ethical committee.

Patients were subjected to full medical history and examination including measurement of SLE disease activity by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score [11].

Psychometric evaluations were performed in all patients with SLE who were asymptomatic regarding NP disease using Mini-Mental State Examination (MMSE) for the presence of cognitive dysfunction [12]. Hamilton Depression Rating Scale (HAM-D) [13], and Hamilton Anxiety Scale (HAM-A) [14] were used for assessment of depression and anxiety, respectively.

Laboratory assessment

It included complete blood count, erythrocyte sedimentation rate, C-reactive protein, complete urine analysis, protein/creatinine ratio, serum creatinine clearance, aspartate aminotransferase, alanine aminotransferase, prothrombin time, partial thromboplastin time, international normalized ratio, antinuclear antibodies, anti-double-stranded DNA antibodies, lupus anticoagulant, and anticardiolipin antibodies (IgM and IgG).

Imaging

MRI and magnetic resonance angiography (MRA) of the brain were done at the Radiodiagnosis Department of Ain Shams University Hospital using Philips achieva 1.5 Tesla (Philips) to examine for the presence of signs of cerebral vacuities, atherosclerotic cerebral vessels, vascular narrowing, infarctions, or hemorrhage.

Statistical analysis of the data

Data were analyzed using IBM SPSS software package, version 20.0 (IBM). Qualitative data were described using number and percent. Quantitative data were described using mean and SD. Comparison between different groups regarding categorical variables was tested using χ^2 -test. When more than 20% of the cells had expected count less than 5, correction for χ^2 was conducted using Fisher's exact test or Monte Carlo correction. The distributions of quantitative variables were tested for normality. For normal data distribution, parametric tests were applied. If the data were abnormally distributed, nonparametric tests were used. For normally distributed data, comparison between two independent populations was done using independent t-test. For abnormally distributed data, comparison between two independent populations was done using Mann-Whitney U-test, whereas Kruskal-Wallis *H*-test was used to compare between different groups. Correlations were assessed using Spearman's coefficient. Significance test results are quoted as two-tailed probabilities. Significance of the obtained results was judged at the 5% level, where P value of up to 0.05 was considered significant, and Pvalue of more than 0.05 was nonsignificant.

Results

This study was conducted on 30 female patients with SLE, and their ages ranged from 22 to 40 years, with a mean of 31.77±5.33 years. Patients were considered positive for NPSL by having at least one of the three main NP manifestations: anxiety, depression, and/or dementia. Twenty-two patients with SLE were found to have NPSL. Overall,

13 (43.3%) patients were found to have depression, 15 (50%) patients had anxiety, and 16 (53.3%) patients had dementia. Of the 22 patients, eight had the three manifestations simultaneously, six had two combined manifestations, and eight had only one manifestation.

Positive aPL antibodies were found in 12 (40%) patients with SLE, of whom 10 had depression (83.3%), nine (75%) had anxiety, and eight (66.67%) had dementia.

Abnormal MRI findings were present in 20 (66.67%) patients with SLE of whom 13 (100%) had depression, 15 (100%) had anxiety, and 14 (87.5%) had dementia. MRI abnormalities included discrete white matter lesions (60%), cortical atrophy (25%), and gross infarctions (15%).

Abnormal MRA findings were found in seven (23.3%) patients with SLE. Of these seven patients, six (43.3%) had depression, four (26.7%) had anxiety, and three (20%) had dementia. MRA revealed vascular affection of one or more large intracranial vessels in 27.27% of patients with NPSL.

The comparisons between patients with SLE with and without depression, anxiety, and dementia regarding MRI findings are presented in Table 1 and regarding MRA findings are presented in Table 2.

Concerning patients with SLE with positive aPL antibodies, 12 (100%) patients had different MRI abnormalities, whereas abnormalities on MRI were found in only eight patients with SLE with negative aPL (100 vs. 44.4%) (P<0.001). There was no statistically significant difference between patients with SLE with and without aPL antibodies regarding MRA findings (P=0.053).

There was a statistically significant association between aPL antibodies and depression, as 83.33% of patients with depression had positive aPL antibodies whereas depression was only present in three (16.6%) of 18 patients SLE with negative aPL antibodies (P<0.05), with a statistically significant higher mean HAM-D among patients with positive aPL antibodies than in those with SLE with negative aPL antibodies (18.7 vs. 13.16) (P<0.001).

In addition, there was a statistically significant association between aPL and anxiety, as 75% of patients with anxiety had positive aPL antibodies, whereas only 33% of patients with negative aPL antibodies had anxiety (P<0.05), with a statistically significant higher mean HAM-A among patients with positive aPL antibodies than in patients with SLE with negative aPL antibodies (21.3 vs. 14.6) (P=0.003).

There was no statistically significant difference between aPL antibodies positive and negative patients regarding dementia (P>0.05) (Table 3). However, there was a statistically significant lower mean MMSE among patients with positive aPL antibodies than that in patients with SLE with negative aPL antibodies (23.167 vs. 2.1) (P=0.011).

Table 1 Comparison between patients with systemic lupus erythematosus with and without depression, anxiety, and dementia regarding MRI findings

MRI	SLE (<i>n</i> =30)						
	Depression		Anxiety		Dementia		
	Positive	Negative	Positive	Negative	Positive	Negative	
Total [n (%)]	13 (43.3)	17 (56.7)	15 (50)	15 (50)	16 (53)	14 (47)	
Abnormal [<i>n/N</i> (%)]	13/13 (100)	7/17 (41.1)	15/15 (100)	5/15 (33.3)	14/16 (87)	6/14 (42.9)	
χ^2	15.15		15		7.013		
P-value	<0.001		<0.001		0.008		

SLE, systemic lupus erythematosus. Bold values are significant for P<0.05.

Table 2 Comparison between patients with systemic lupus erythematosus with and without depression, anxiety, and dementia regarding magnetic resonance angiography findings

MRA	SLE (<i>n</i> =30)						
	Depression		Anxiety		Dementia		
	Positive	Negative	Positive	Negative	Positive	Negative	
Total [n (%)]	13 (43.3)	17 (56.7)	15 (50)	15 (50)	16 (53)	14 (47)	
Abnormal [n/N (%)]	6/13 (46)	1/17 (6)	4/15 (26.7)	3/15 (20)	3/16 (18.8)	4/14 (28.6)	
χ^2	7.045		0.187		0.402		
P-value	0.008		0.666		0.526		

MRA, magnetic resonance angiography; SLE, systemic lupus erythematosus. Bold values are significant for P<0.05.

NPSL manifestations	SLE (n=30) [<i>n/N</i> (%)]		
	aF	PL		
	Positive	Negative		
Total [n (%)]	12 (40)	18 (60)	χ^2	P-value
Depression	10/12 (83.3)	3/18 (16.7)	13.032	<0.001
Anxiety	9/12 (75)	6/18 (33.3)	5.000	0.025
Dementia	8/12 (66.67)	8/18 (44.4)	1.429	0.232

Table 3 Comparison between patients with systemic lupus erythematosus with and without antiphospholipid antibodies antibodies regarding, depression, anxiety, and dementia

aPL, antiphospholipid antibodies; NPSL, neuropsychiatric lupus; SLE, systemic lupus erythematosus. Bold values are significant for P<0.05.

On comparing patients with SLE with and without NPSL with the other studied parameters, there was a statistically significant difference regarding SLEDAI, MRI findings, and positive aPL antibodies, as *P* value was less than 0.001.

There was a highly statistically significant positive correlation between HAM-D and each of HAM-A and SLEDAI (r=0.746 and 0.793, respectively; P<0.001). However, there was a statistically significant negative correlation between HAM-D and each of MMSE and age (r=-0.428 and -0.369, respectively; P<0.05).

There was a statistically significant positive correlation between HAM-A and SLEDAI (r=0.708; P<0.001) (Fig. 1). However, there was a statistically significant negative correlation between MMSE and each of HAM-A and SLEDAI (r=-0.526 and -0.708, respectively; P=0.003) (Figs 2 and 3).

Discussion

Up to 50% of patients with SLE experience NP manifestations during the course of their disease, but many might have subclinical NPSL. The pathogenesis of NPSL is multifactorial and involves several inflammatory cytokines, autoantibodies, and immune complexes [15]. NPSL carries a high frequency of flares, in addition to being a major cause of long-standing functional impairment as well as being associated with increased mortality rate [16].

In the present study, there was a statistically significant number of patients with SLE (n=22) having different NP manifestations (73.33%) (P<0.05).

Our results agree with a previous study carried by Shehata *et al.* [17] on 26 patients with SLE who underwent psychological assessment. They reported that 14 (53.8%) patients had different NP manifestations. Our results also agree with both Nery *et al.* [18], who found that among 71 patients





Correlation between Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and Hamilton Anxiety Scale (HAM-A).





Correlation between Modified Mini-Mental State Examination (MMSE) and Hamilton Anxiety Scale (HAM-A).

with SLE, 42 (59.2%) patients had NPSL, and Unterman *et al.* [19], who reported that NP syndromes were estimated to exist in more than half of the studied patients with SLE, making it one of the most common and significant manifestations of SLE. Figure 3





Moreover, our study agrees with a previous study done by Ainiala *et al.* [20] on 46 (91%) patients with SLE who found that the prevalence of NP manifestations among them were significantly high.

Among the SLE psychiatric disorders in our study, we found that 13 (43.3%) cases had depression, 15 (50%) cases had anxiety, and 16 (53.3%) patients had cognitive impairment in the form of dementia.

Our results agree with the study done by Nery *et al.* [18] who found that of 71 patients with SLE evaluated for presence of NP manifestations, 35 (49.2%) cases presented with depression and 37 (52.1%) cases presented with anxiety disorders. In addition, Shehata *et al.* [17] found that of 26 patients with SLE, 15 (57.7%) cases had depression and 17 (65.4%) cases had anxiety, and they also noted significant cognitive impairment in patients with NPSL.

In our study, there was a statistically significant higher mean HAM-D among patients with anxiety than in patients without SLE without anxiety (17.7 vs. 13.067), (P<0.001), and they also had a statistically significant lower mean MMSE (23.267 vs. 25.4) (P=0.009).

There was also a statistically significant lower mean MMSE among patients with depression than in patients with SLE without depression (23.15 vs. 25.2) (P<0.01).

Our study agrees with a previous study done by Kheirandish *et al.* [21] on 166 patients with SLE evaluated for the presence of anxiety and depression and found that 105 (63.3%) patients had combined

anxiety-depression. Our results also agree with a previous study done by Cavaco *et al.* [22] on 85 patients with SLE and found that patients with depression (28 patients) more frequently had impairment in their cognitive functions than controls or patients without NPSL.

In our study, 66% of our patients with SLE were found to have different abnormalities on MRI examination. Most abnormalities on MRI were in the form of discrete white matter lesions in periventricular, cortical/subcortical junction and frontal lobe tissues (60%), cortical atrophy (25%), and gross infarctions (15%), and these results agree with Arinuma *et al.* [23], who found the same abnormalities in patients with NPSL evaluated by brain MRI. Furthermore, there was a higher percentage of abnormal MRI findings (90.9%) among patients with SLE with NPSL than in patients with SLE without NPSL (0%) (*P*<0.001).

There was a statistically significant higher mean HAM-D score among patients with abnormal MRI findings than that in patients with SLE with normal MRI findings (17.750 vs. 10.7) (P<0.001). Moreover, there was a statistically significant higher mean HAM-A score among patients with abnormal MRI findings than in patients with SLE with normal MRI findings (20.800 vs. 10.3) (P<0.001), and there was a statistically significant lower mean MMSE score among patients with abnormal MRI findings that in patients with SLE with normal MRI findings than that in patients with SLE with normal MRI findings than that in patients with SLE with normal MRI findings (23.400 vs. 26.2) (P=0.008).

In our study, we found that all patients with SLE with depression (n=13) were found to have different MRI abnormalities (100%), whereas MRI abnormalities were found in only seven patients with SLE without depression (100 vs. 41.1%) (P<0.001).

In the same way, patients with SLE with anxiety (n=15) were found to have different MRI abnormalities (100%), whereas MRI abnormalities were found in only five patients with SLE without anxiety (100 vs. 33.3%) (P<0.001).

Most of our patients with SLE with dementia (n=16) were found to have different abnormalities on MRI (87.5%), whereas abnormalities on MRI were found in only six patients with SLE without dementia (87.5 vs. 42.9%) (P=0.008).

Our study agrees with a previous study done by Ainiala *et al.* [20] on 46 patients with SLE patients that found abnormalities on MRI (mainly cerebral atrophy) were

more common in patients with SLE with NP manifestations than those without NP manifestations. Our study also agrees with a previous study done by Arinuma *et al.* [23] on 53 patients with diffuse NPSL who were evaluated by brain MRI scans. In their study, they found that as many as 25 of 53 patients with SLE with NP manifestations (47.2%) had abnormal MRI findings. Our study also agrees with a previous study done by Jennings *et al.* [24] on 116 patients with NPSL who underwent MRI brain study, and 66% were found to have abnormal MRI findings.

All patients with SLE with positive aPL (n=12) were found to have different MRI abnormalities (100%), whereas MRI abnormalities were found in only eight patients with SLE with negative aPL (100 vs. 44.4%) (P<0.001). In a previous study by Toubi *et al.* [25] 53 patients with SLE were positive for aPL antibodies. When those 53 patients with SLE underwent MRI brain study, 33 (62%) patients showed abnormal findings.

In the present study, when our patients with NPSL were evaluated by MRA of the brain, it revealed vascular affection of one or more large intracranial vessels in the form of vascular beading and attenuation, and these findings were positive in six (27.27%) of 22 patients with NPSL. The affected vessels were posterior cerebral circulation (83.3%), anterior cerebral circulation (50%), internal carotid artery (16.67%), and vertebral arteries (16.67%). Our results agree with a previous study done by Shehata *et al.* [26] on 26 patients with SLE. Psychometric assessment and transcranial duplex were used to evaluate the intracranial vessels, and there was a significant affection of most studied intracranial vessels in patients with SLE with NP manifestation.

In our study, we found that 46% of patients with SLE with depression (n=13) were found to have different MRA abnormalities, whereas MRA abnormalities were found in only one patient with SLE without depression (46 vs. 6%) (P=0.008), with a statistically significant higher mean HAM-D among patients with abnormal MRA findings than that in patients with SLE with normal MRA findings (17.7 vs. 14.7) (P=0.019).

Additionally, we found a statistically significant association between presence of positive aPL antibodies in serum of patients with SLE and NP manifestations, as there was a higher percentage of positive aPL antibodies (54.5%) among patients with NPSL than those without NPSL (0%) (P=0.002).

There was a statistically significant correlation between aPL antibodies and both depression and anxiety. Furthermore, there was a statistically significant lower mean MMSE among patients with positive aPL antibodies than that in patients with SLE with negative aPL antibodies. These findings were in agreement with both Syuto et al. [27], who found that the prevalence of aPL antibodies was significantly higher in patients with SLE with NP features than those without NP features, and Karassa et al. [28], whose results showed that CNS involvement was significantly associated with the antiphospholipid syndrome. Our study also matched a previous study done by Sanna et al. [29] on 323 patients with SLE who were evaluated for presence of NP manifestations, where 185 (57.3%) patients had NP manifestations at any time during follow-up, and the presence of aPL antibodies was significantly associated with NP manifestations (P < 0.001).

In our study, we found a statistically significant correlation between SLE disease activity measured by SLEDAI and NP manifestations (P<0.05), with a statistically significant higher mean SLEDAI among patients with depression than that in patients with SLE without depression (57.69 vs. 30.059) (P<0.001), a statistically significant higher mean SLEDAI among patients with anxiety than that in patients with SLE without anxiety (55.3 vs. 28.7) (P<0.001), and a significantly higher mean SLEDAI among patients with dementia than that in patients with SLE without dementia (49.68 vs. 33.2), (P=0.035).

These results agree with Shehata *et al.* [17] who found that SLE disease activity is positively correlated with cognitive impairment, depression, and anxiety in patients with NPSL. Our results also agree with Nery *et al.* [30] who found that patients with SLE presented with depression had a greater severity of SLE disease activity compared with those without depression. This also agrees with a previous study done by Jonsen *et al.* [16] on 117 patients with SLE and found that patients with SLE with NP manifestations [44 (38%) of 117] had a high rate of organ damage (SLICC/ACR damage index) (P<0.001).

Our results showed statistically significant correlation between abnormal MRI findings and SLE disease activity measured by SLEDAI, as there was a higher mean SLEDAI among patients with abnormal MRI findings (53.8) than that in patients with SLE with normal MRI finding (18.5) (P<0.001), and these results agree with a study done by Toledano *et al.* [31] who found presence of association between certain disease activity features (measured by SLEDAI) and presence of abnormal pattern on brain MRI of the studied patients with NPSL.

Our results also agree with a study done by Ainiala *et al.* [20] on 43 patients with SLE who were subjected to neuropsychological assessment and brain MRI study. SLE activity was assessed by the SLICC damage index, and all the abnormal MRI parameters correlated significantly with the SLICC index and all the measured MRI parameters were statistically significantly higher in patients with NPSL than those without NPSL.

Our results showed statistically significant correlation between abnormalities on MRA and SLE disease activity measured by SLEDAI as there was a higher mean SLEDAI among patients with abnormal MRA findings (59.8) than that in patients with SLE with normal MRA finding (36.8) (P<0.001).

In our study, we found that patients with one subclinical NP manifestation had mild MRI/MRA changes as atrophic changes. However, patients with combined two or three subclinical NP manifestations showed more affection as ischemic white matter lesions and gross infarcts.

From our results, we conclude that a significant number of patients without SLE without overt NP manifestations might have subclinical cerebrovascular and cognitive dysfunctions, depression, and anxiety, and this can be detected by simple bedside questionnaires. Moreover, the presence of aPL antibodies is a strong risk factor for developing NPSL. We therefore recommend doing MRI/MRA for patients with SLE with positive MMSE, HAM-A, or HAM-D for early detection and management of NP complications.

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Conflicts of interest

There are no conflicts of interest.

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