

# Subclinical cerebrovascular cognitive function, and mood changes in patients with systemic lupus erythematosus

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**Objective:** To estimate the prevalence of neuropsychiatric disorders, cerebral atherosclerosis in patients with systemic lupus erythematosus (SLE) and explore the relation between transcranial duplex findings of different intracranial vessels with neuropsychiatric affect, and Systemic lupus erythematosus disease activity index (SLEDAI).

**Methods:** Twenty-six consecutive SLE patients were evaluated for neurological and psychiatric disorders. Another 26 subjects matched with respect to age, sex, education, and socioeconomic status formed the control group. SLE disease activity was assessed by the SLEDAI. For each participant, a complete medical history was obtained and clinical, laboratory, and neurophysiological examinations, magnetic resonance imaging of the brain, transcranial duplex for intracranial vessels, and psychometric evaluations were performed. For the psychometric evaluation, we used the Modified Mini-mental State Examination and Cognitive Assessment Scale Inventory to assess cognitive function, and Hamilton Depression Rating Scale and Hamilton Anxiety Scale to assess symptoms of depression and anxiety.

**Results:** Anxiety in 65.4% is the most prevalent manifestation followed by depression in 57.7%, headache in 38.5%, peripheral neuropathy in 26.9%, seizures in 23.1%, psychosis in 19.2%, radiculopathy and dementia in 15.4% for each, myositis in 11.5%, and stroke in 7.7%. There was a significant increased mean velocity and decreased pulsatility index of most studied intracranial vessels in both patient groups than in the control group. There was significant negative correlation between SLEDAI and transcranial Doppler findings in the pulsatility index of medial circumflex artery and procoagulant activity.

**Conclusion:** Neurological disorders, cognitive impairment, depression, anxiety, psychosis and cerebrovascular changes detected by transcranial Doppler ultrasound are common in SLE.

**Keywords:** SLE, SLEDAI, cognitive function, depression, anxiety, neurological disorders, TCD, cerebrovascular changes

## Introduction

Systemic lupus erythematosus (SLE) is a multisystem disease with a spectrum of clinical manifestations and variable course characterized by exacerbation and remission.<sup>1</sup> Involvement of the nervous system by SLE is one of the most profound manifestations of the disease and encompasses a wide variety of neurological and psychiatric features.<sup>2</sup>

In recent years several studies have indicated that a leading cause of morbidity and mortality in SLE patients is represented by an increased occurrence of cerebrovascular diseases secondary to accelerated atherosclerosis.<sup>3</sup> The prevalence of cognitive dysfunction in SLE patients varies from 20% to 80%.<sup>4-8</sup>

The mechanism is due in part to a combination of chronic inflammatory and immune mechanisms characterized by altered lipoprotein metabolism leading to formation

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of proinflammatory and prooxidative lipids and immune response.<sup>4-6</sup> Contributory factors include increased levels of oxidized lipids (such as oxidized low-density lipoprotein [LDL] and proinflammatory high-density lipoprotein [HDL]), upregulation of adhesion molecules, and upregulation of cytokines such as monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interferon- $\gamma$  (IFN- $\gamma$ ), interleukin-1 (IL-1), and IL-12. Auto-antibodies to oxidized lipids and immune complexes may also play a role in the development of atherosclerosis in SLE.<sup>7</sup> Magnetic resonance angiography (MRA) or transcranial Doppler ultrasound (TCD) confirm thrombotic lesions of extracranial or intracranial vessels. In the presence of a clear stroke with positive antinuclear antibody (ANA) and anti-DNA binding studies, a presumptive diagnosis of lupus cerebritis may be considered, even in the absence of positive imaging studies, provided that other causes of stroke have been reasonably excluded in the patient with SLE who has risk factors for conventional small-vessel cerebrovascular disease (eg, diabetes, hypertension).<sup>8</sup> In addition, microembolic signals have also been reported in systemic diseases which typically involve small cerebral vessels such as SLE, which could be detected by TCD. TCD is a sensitive, real-time monitor of cerebral blood flow velocity (CBFV) and emboli.<sup>9</sup> The present study was conducted to clarify issues regarding 1) the prevalence of neuropsychiatric disorders in a randomly selected group of SLE patients with or without manifest neuropsychiatric symptoms, 2) the early appearance of cerebrovascular changes in SLE patients by usage of transcranial duplex imaging to assist internal cerebral blood vessels. In addition, to determine the relation between transcranial duplex findings of different intracranial vessels with systemic, neuropsychiatric symptoms cognitive function and Systemic Lupus Erythematosus Disease Activity Index (SLEDAI).

## Patients and methods

Twenty-six consecutive SLE patients (22 female and 4 male) aged 18–40 years were selected from the outpatient clinics and inpatient departments of rheumatology and neurology and psychiatry at Al-Azhar (Assiut) and Assiut university hospitals. All patients met the diagnostic criteria according to American College of Rheumatology (ACR) classification criteria for the diagnosis of SLE.<sup>10</sup> Rheumatologic evaluation was completed using the SLEDAI.<sup>11</sup> SLEDAI measures the current status of SLE disease activity according to clinical and laboratory manifestations. SLE disease activity is defined as the reversible manifestations of the underlying inflammatory process.<sup>11</sup> The SLEDAI consists

of 24 weighted attributes, which are grouped into nine organ system domains (weighting in parentheses): central nervous system (8), vascular (8), renal (4), musculoskeletal (4), serosal (2), dermal (2), immunologic (2), constitutional (1), and hematologic (1). SLEDAI is a reliable and valid instrument for measuring the clinical state of SLE patients.<sup>12</sup> Exclusion criteria included: 1) aged below 18 years or more than 40 years; 2) pre-existing clinical cardiovascular or cerebrovascular events (angina, myocardial infarction, transient ischemic attack, or stroke); 3) history of psychosis or other neurological diseases involving the central nervous system that interfere with cooperation of patient; 4) brain ischemia due to cardiorespiratory arrest; 5) other systemic diseases, or taking drugs known to involve the central nervous system (such as renal and liver diseases, AIDS, and endocrinal); 6) cancer discovered in the previous five years; and 7) patients with primary vasculitis. Medications at time of the study included nonsteroidal anti-inflammatory drugs in 18 cases, prednisone (10–20 mg/d) in all cases and immunosuppressive drugs (hydroxychloroquine, azathioprine, methotrexate, cyclophosphamide) in 17 cases.

Twenty-six healthy individuals with age, sex, number of years education and socioeconomic status<sup>13</sup> matching were selected as a control group. The patient group was subdivided into two subgroups according to ACR nomenclature for neuropsychiatric SLE (NPSLE),<sup>14</sup> which provided case definitions for 19 neuropsychiatric syndromes in SLE, including the presence of cognitive dysfunction as a separate syndrome. NPSLE patients were those with overt neurological manifestation in their history documented by examination and investigations (n = 14). Nonneuropsychiatric patients (nSLE) were those who did not complain of any neurological illness, but neurological findings were detected by examination and investigations (n = 12).

The regional ethical committee of Assiut University and Al-Azhar (Assiut) Hospitals approved this study. All subjects gave their informed consent for participation.

## Methods

### Clinical evaluation

All subjects underwent a structured interview, physical examination, neurological and magnetic resonance imaging (MRI) of the brain and neurophysiologic studies. Traditional vascular risk factors were assessed in all subjects as follows: presence or absence of hypertension (as defined by a blood pressure of at least 140/90 mm Hg or use of antihypertensive medications), diabetes, and smoking status. Age at onset, duration of illness and therapeutic history were recorded in SLE patients.

## Neuropsychiatric assessment

Cognitive Abilities Screening Instruments (CASI) consists of 25 test items and provides quantitative assessment on attention, concentration, orientation, memories for past knowledge and present input, language abilities, drawing and writing abilities, list-generating ability, abstract thinking and judgment.<sup>15</sup> The CASI is more comprehensive than most screening tests of cognitive abilities and can be used to screen for dementia. The cut off equals less than 67 points for dementia according to Ross and colleagues.<sup>16</sup> The Modified Mini-Mental State Examination (MMSE) is a widely used scale to screen for dementia.<sup>17</sup> As most of the subjects of the present study were illiterate, the two points testing reading and writing were excluded, and the full score was calculated as 28 instead of 30 points. The lower value for regarding a subject as dementia suspect was 21 instead of 23 points.<sup>18</sup> In the present study, dementia was diagnosed if the clinical presentation fulfilled criteria of dementia as well as when the subject scored  $\leq 21$  on MMSE and  $\leq 67$  points on CASI according to Khedr and colleagues.<sup>19</sup> The Hamilton Depression Rating Scale is a widely used and reliable scale, although not specific to elderly.<sup>20</sup> The cut off point of depression in this scale is 17 or more according to Michele and Bolino.<sup>21</sup> Since then, numerous authors have investigated the dimensionality of the scale and demonstrated that it is multidimensional.<sup>22</sup> The Hamilton Anxiety Scale lists 14 symptom types. The total score can range from 0 to 56. A total score of 18 or more means anxiety.<sup>23</sup>

## Laboratory tests

Venous blood was obtained from all subjects by puncture of an antecubital vein at 8 AM after an overnight fast. Samples of complete blood count (CBC) using automated cell counter, blood urea and serum creatinine by spectrophotometric method using Stat Fax<sup>®</sup> (Awareness Technology, Dubai, United Arab Emirates) were taken. Normal ranges are blood urea 15–45 mg/dL and serum creatinine  $< 1.5$  mg/dL.<sup>24</sup> Liver function tests were applied by using Stat Fax. Normal ranges are aspartate aminotransferase (AST; SGOT) 0–35 U/L and alanine aminotransferase (ALT; SGPT) 0–35 U/L.<sup>25</sup> Fasting blood glucose was done for patients with Stat Fax. In addition, complete urine analysis by microscopic examination, and 24-hour collection of urine protein is done by Stat Fax. Disease activity indexes such as erythrocyte sedimentation rate (ESR) were obtained using the Western green tubes method and are considered normal when less than 10 mm/hour, anti-nuclear (ANA) and antidouble stranded DNA (anti-dsDNA) obtained using the ELISA method.<sup>26</sup>

## Imaging studies

All subjects underwent MRI of the brain and transcranial duplex (TCD). Transcranial duplex was performed with a Nicolet Bravo model 460 SNF0000001544 with 2 mHz probe (Neurocare, Madison, WI), which provides a direct and noninvasive assessment of subclinical vascular changes. Transcranial duplex examinations were performed at the Department of Neurology and Psychiatry, Clinical Neurophysiology Unit, Assiut University Hospital. Right anterior cerebral artery (ACA) via trans-temporal window and the depth of insinuation was recorded between 60–90 mm with the subject's head in neutral position. Right middle cerebral artery (MCA) was measured via transtemporal window and the depth of insinuation was between 30–60 mm with the subject's head in neutral position. Right posterior cerebral artery (PCA) was assessed via trans-temporal window and the depth of insinuation was between 60–80 mm with the subject's head in neutral position. Right vertebral artery (VA) was measured via sub-occipital window and the depth of insinuation was between 60–90 mm with the subject's head in neutral position. Right basilar artery (BA) was measured via suboccipital window and the depth of insinuation was between 80–120 mm with the subject's head in neutral position. Systolic mean flow velocity (MV) and pulsatility index (PI) were recorded so that PI is equal to the peak velocity minus the end-diastolic velocity, divided by the mean velocity.<sup>27</sup> PI normally ranges between 0.5–1.1.<sup>28</sup>

## Statistics

Data obtained from this study were fed into a computer. Descriptive statistics such as mean, standard deviation, and percentages were calculated using SPSS software (version 16 for Windows; SPSS Inc, Chicago, IL). Results were analyzed using an independent-sample *t*-test that did not assume equal variances. One-way analysis of variance (ANOVA) was followed by a post hoc test (LSD) and Chi-squared test. A series of Pearson correlation coefficients were used to examine the relation between parameters of transcranial duplex findings and SLEDAI. The depression, anxiety, and cognitive functions of all patient groups were calculated. The level of significance was  $P < 0.05$ .

## Results

Details of demographic data, systemic examination, and laboratory data are illustrated in Tables 1 and 2. There were nonsignificant differences between cases and control in age, sex, education, and socioeconomic status. Arthralgia was the most common systemic finding in SLE patients.

**Table 1** Demographic data of patients and control group

Item	Control (N = 26)	Cases (N = 26)	P value
Age (Mean ± SD)	25.9 ± 8.9	24.9 ± 7.6	0.65
Sex			
Male (n%)	2 (7.7%)	2 (7.7%)	0.383
Female (n%)	24 (92.3%)	24 (92.3%)	
Number of educated years (Mean ± SD)	3.7 ± 0.55	3.8 ± 0.02	0.93
Socioeconomic status (Mean ± SD)	12.6 ± 2	12.05 ± 1.6	0.33

**Notes:** Unless otherwise indicated, data are expressed as mean ± standard deviation (SD) when normally distributed.

ANA is positive in 92% and Anti-ds DNA antibody is positive in 80%. Overt neurological manifestations were observed in 14 patients (53.8%; Table 3). Anxiety in 17 (65.4%; 10 in NPSLE and 7 in nSLE) is the most prevalent manifestation followed by depression in 15 (57.7%; 10 in NPSLE and 5 in nSLE), headache in 10 cases (38.5% NPSLE),

**Table 2** Patient clinical, laboratory, and radiological data

Clinical data	Control (N = 26)	Data recorded (N = 26)	P value
Systemic manifestations (fever, fatigue, malaise, anorexia, and weight loss)	0 (0%)	22 (88%)	–
Cutaneous			
Malar rash	0	24 (92.3%)	–
Photosensitivity		25 (96.2%)	–
Arthralgia	0	26 (100%)	–
Arthritis	0	23 (88.5%)	–
Renal	0 (0%)	17 (65.4%)	–
Gastrointestinal findings	0 (0%)	7 (26.9%)	–
Cardiovascular system findings	0 (0%)	9 (34.6%)	–
Pulmonary findings	0 (0%)	3 (11.5%)	–
ANA (+ve)	0 (0%)	24 (92.3%)	–
Anti ds DNA antibody (+ve)	0 (0%)	21 (80.8%)	–
Significant proteinuria (>0.5 g/d or 3+) or cellular casts	0 (0%)	20 (76.9%)	–
Hematologic disorder			
Anemia	4 (15.4%)	26 (100%)	–
Thrombocytopenia	0 (0%)	3 (11.5%)	–
Leucopenia	0 (0%)	9 (34.6%)	–
ESR	5 (19.2%)	20 (76.9%)	–
MRI brain	0 (0%)	0 (0%)	–

**Notes:** Data are expressed as number (percent).

**Abbreviations:** ANA, Antinuclear antibody; Anti ds (DNA), double-stranded DNA; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging.

peripheral neuropathy in 7 cases (26.9%), seizures in 6 cases (23.1%), psychosis in 5 cases (19.2%), radiculopathy and dementia in 4 cases (15.4%; 3 in NPSLE and 1 in nSLE) for each, myositis in 3 cases (11.5%), and then stroke in 2 cases (7.7%). There was a significant increased mean velocity and decreased pulsatility index of most studied intracranial vessels in both patient groups than in the control group. In addition, these changes were more apparent in NPSLE than nSLE groups as illustrated in Table 4. To examine the relation between TCD findings of different intracranial vessels and depression, anxiety, cognitive functions and SLEDAI of all patients group (Tables 5 and 6), a series of correlation coefficients were calculated. No significant association was identified between TCD mean velocities and SLEDDAI. However, there were significant negative correlations between SLEDAI and TCD findings in the pulsatility index of MCA and PCA. In addition, significant correlations were noted between some of these intracranial vessels and depression, anxiety, and fluency.

Examples of abnormal TCD of intracranial vessels are illustrated in Figures 1 and 2.

## Discussion

SLE is a chronic autoimmune disease characterized by multisystem involvement with a broad spectrum of clinical manifestations. Neurological and psychiatric manifestations occur in up to two thirds of patients with ranges from 20% to 80%.<sup>29</sup> In the present study, 53.8% SLE patients had overt neurological manifestations either in central nervous system (ie, seizures, headache, stroke, and dementia), psychiatric (psychosis, depression, and anxiety) or in peripheral nervous system (ie, radiculopathy, myositis, and peripheral neuropathy). These results matched a previous study by Nery and colleagues<sup>30</sup> on 71 SLE patients and reported that 42 patients (59.2%) had NPSLE. Given the plethora of neuropsychiatric manifestations reported in SLE patients, it is unlikely that there is a single pathogenic mechanism. Neuropsychiatric events in SLE may be caused by a primary manifestation of the disease, secondary complications of the disease, or a therapeutic side effect or coincidental problem unrelated to lupus.<sup>31</sup> In addition, Hanly<sup>31</sup> suggested the mechanism of involvement of neurological manifestation in SLE may be due to vascular abnormalities (noninflammatory vasculopathy, vasculitis, thrombosis), autoantibodies (antineuronal antibodies, antiribosomal P antibodies, antiphospholipids antibodies) and inflammatory mediators (IL-2, -6, -8, and -10, INF- $\beta$ , TNF- $\beta$ , matrix metalloproteinase-9 MMP-9).

**Table 3** Neuropsychiatric manifestations and Daily Activity Index of studied groups

Item	Control (n = 26)	nSLE (n = 12)	NPSLE (n = 14)	P1	P2	P3
Neurological manifestation						
Seizures	–	–	6 (42.9%)	–	–	–
Headache	–	–	10 (71.4%)	–	–	–
Stroke	–	–	2 (14.3%)	–	–	–
Radiculopathy	–	–	4 (28.6%)	–	–	–
Myositis	–	–	3 (21.4%)	–	–	–
Peripheral neuropathy	–	–	7 (50%)	–	–	–
Psychosis	–	–	5 (35.7%)	–	–	0.00
Depression	–	5 (41.6%)	10 (71.4%)	–	–	0.001
Anxiety	–	7 (58.3%)	10 (71.4%)	–	–	NS
Dementia	–	1 (8.3%)	3 (21.4%)	–	–	–
MMSE score	28.15 ± 1.9	26.75 ± 3.3	25.0 ± 5.8	NS	0.010	NS
CASI						
Long term memory	9.5 ± 1.0	8.3 ± 2.2	7.8 ± 2.1	0.045	0.003	NS
Short term memory	9.9 ± 1.8	8.6 ± 2.2	6.4 ± 3.1	NS	0.000	0.026
Attention	8.1 ± 0.74	7.3 ± 0.8	7.1 ± 0.9	0.01	0.001	NS
Mental manipulation/concentration	8.3 ± 2.1	7.0 ± 2.8	5.1 ± 3.1	NS	0.000	NS
Orientation	16.2 ± 3.3	15.9 ± 3.2	15.9 ± 3.2	NS	NS	NS
Drawing	8.1 ± 2.8	8.9 ± 1.7	7.1 ± 3.4	NS	NS	NS
Abstract thinking and judgment	8.8 ± 2.9	7.9 ± 2.6	6.8 ± 2.9	NS	0.024	NS
Fluency with four-legged animals	9.7 ± .6	9.1 ± 1.9	7.3 ± 3.2	NS	0.037	NS
Language	7.8 ± 2.0	7.7 ± 1.7	7.2 ± 1.7	NS	NS	NS
CASI Total score	86.6 ± 9.6	79.5 ± 15.4	70.1 ± 18.2	NS	0.001	NS
Hamilton Depression Scale	6.0 ± 0.6	13.5 ± 8.41	18.64 ± 10.03	0.004	0.000	NS
Hamilton Anxiety Scale	7.5 ± 8.3	18.8 ± 8.4	21.93 ± 10.03	0.002	0.000	NS
Daily Activity Index	–	12.5 ± 3.41	22.3 ± 3.7	–	–	0.000

**Notes:** Unless otherwise indicated, data are expressed as mean ± standard deviation when normally distributed.

**Abbreviations:** NPSLE, neuropsychiatric SLE; nSLE, nonneuropsychiatric patients; NS, nonsignificant; SLE, systemic lupus erythematosus; CASI, Cognitive Abilities Screening Instruments; P1, control vs. asymptomatic; P2, control vs. symptomatic; P3, asymptomatic vs. symptomatic.

In the present study, significant cognitive impairment was noted in patients with or without neuropsychiatric manifestations than in the control group. This impairment was more apparent in long-term memory, short-term memory, mental manipulation, concentration, attention, abstract thinking and judgment, four-legged animal fluency test, and total scores of MMSE and CASI. These results matched those by Fisk and colleagues<sup>32</sup> who identified two patterns of memory dysfunction in SLE patients: impaired remote memory appears to be associated with a history of past central nervous system involvement (suggesting the presence of a residual neurological deficit), while impaired immediate memory and concentration implies increased disease activity that may represent transient and diffuse central nervous system effects.<sup>32</sup> In addition, cognitive impairment was significantly more frequent in

NPSLE than in nSLE (short term memory) at the time of neuropsychological testing. These data confirmed previous data by Carbotte and colleagues<sup>33</sup> and Monastero and colleagues<sup>29</sup> who found a greater prevalence of cognitive impairment in NPSLE than nSLE. On the other hand, the possibility exists that the absence of a specific 'SLE-pattern' of cognitive impairment reflects the clinical heterogeneity of the disease. These deficits are not specific to one brain region or one neuropsychological process, and may reflect both multifocal and diffuse brain diseases. Monastero and colleagues<sup>29</sup> suggested that a frontotemporoparietal dysfunction may account for the cognitive deficits found in patients with SLE. Positron emission tomography/single photon emission computed tomography (PET/SPECT) studies<sup>34</sup> revealed a hypoperfusion in the frontal, temporal, and parietal lobes mainly in NPSLE patients.



**Table 4** Intracranial vessels with neuropsychiatric symptoms in patients and control

Item	Control N = 20 (Mean ± SD)	nSLE (n = 12) 44% (Mean ± SD)	NPSLE (n = 14) 56% (Mean ± SD)	P1	P2	P3
MCA						
MV (cm/s)	53.04 ± 9.24	55.04 ± 10.54	62.28 ± 12.25	NS	0.010	NS
PI	0.66 ± 0.1	0.80 ± 0.22	0.63 ± 0.05	0.005	N.S	0.002
ACA						
MV (cm/s)	41.15 ± 24.92 (4.89)	52.34 ± 11.62	52.44 ± 10.96	NS	NS	NS
PI	0.67 ± 0.13	0.67 ± 0.14	0.61 ± 0.13	NS	NS	NS
PCA						
MV (cm/s)	48.81 ± 11.26	46.69 ± 8.34	53.67 ± 12.33	NS	NS	NS
PI	0.61 ± 0.15	0.68 ± 0.12	0.57 ± 0.09	NS	NS	0.035
VA						
MV (cm/s)	34.54 ± 17.61	44.67 ± 7.52	46.16 ± 6.04	0.036	0.012	NS
PI	0.58 ± 0.08	0.63 ± 0.15	0.53 ± 0.06	NS	NS	0.020
BA						
MV (cm/s)	42.88 ± 5.05	40.15 ± 30.69 (8.86   14)	48.49 ± 4.95	NS	NS	NS
PI	0.63 ± 0.09	0.64 ± 0.11	0.57 ± 0.089	NS	NS	NS

**Notes:** Data are expressed as mean ± standard deviations. \*The mean difference is significant at the 0.05 level.

**Abbreviations:** NPSLE, neuropsychiatric SLE; nSLE, nonneuropsychiatric patients; ACA, anterior cerebral artery; BA, basilar artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; PI, pulsatility index; SLE, systemic lupus erythematosus; MV, mean velocity (cm/s); NS, nonsignificant; P1, control vs asymptomatic; P2, control vs symptomatic; P3, asymptomatic vs symptomatic.

Among the psychiatric disorders in this study, 15 (57.7%) cases have a depression and 17 cases have an anxiety (65.4%) by clinical assessment and using Hamilton Depression and Anxiety Scales. These results match a study by Nery and colleagues<sup>30</sup> where 35 cases out of 71 (49.2%) presented with major depression and 37 cases (52.1%) presented with anxiety disorders. Several factors might explain these high prevalence rates, and they include the stress of having a chronic disease and the high doses of corticosteroids commonly used in treatment.<sup>35</sup> On the other hand, there is intriguing evidence suggesting that some patients

with SLE may have organic forms of depression caused by autoimmune lesions in the central nervous system. For instance, the antiribosomal P antibody is highly associated with both lupus psychosis and severe depression.<sup>35</sup> Furthermore, neuropsychiatric disorders due to SLE activity, such as seizures, strokes, aseptic meningitis, delirium, and psychosis, may also be associated with concomitant depressive symptoms.<sup>35</sup> Nery and colleagues<sup>30</sup> hypothesized that the high prevalence of some anxiety disorders could be linked to feelings of embarrassment experienced in public by some

**Table 5** Correlation between transcranial duplex TCD (PI) findings and systemic lupus erythematosus disease activity index

Item	R	P value
MCA	-0.414	0.035*
ACA	-0.079	N.S
PCA	-0.449	0.021*
VA	-0.342	N.S
BA	-0.344	N.S

**Notes:** \*Correlation is significant at the 0.05 level (2-tailed).

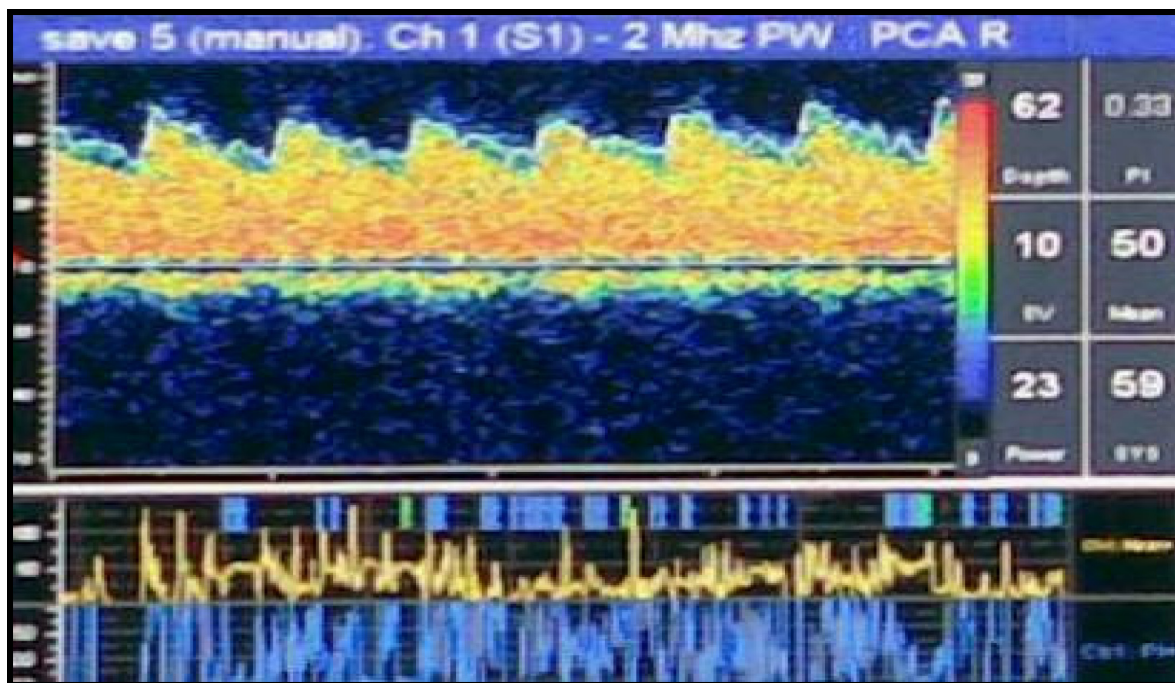
**Abbreviations:** MCA, middle cerebral artery; ACA, anterior cerebral artery; BA, basilar artery; PCA, posterior cerebral artery; PI, pulsatility index; MV, mean velocity; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; NS, nonsignificant.

**Table 6** Correlation between TCD findings of different intracranial vessels and neurological findings depression, anxiety and cognitive functions of all patients group

Item	MV		PI	
	r	P value	r	P value
ACA correlated with hamilton anxiety scale	-0.413	0.036*	-	-
VA correlated with hamilton depression score	0.420	0.033*	-	-
BA correlated with fluency	-	-	0.485	0.012*

**Notes:** Significant data only are expressed. \*Correlation is significant at the 0.05 level (2-tailed); \*\*Correlation is significant at the 0.01 level (2-tailed).

**Abbreviations:** ACA, anterior cerebral artery; VA, vertebral artery; BA, basilar artery; PI, pulsatility index; MV, mean velocity.

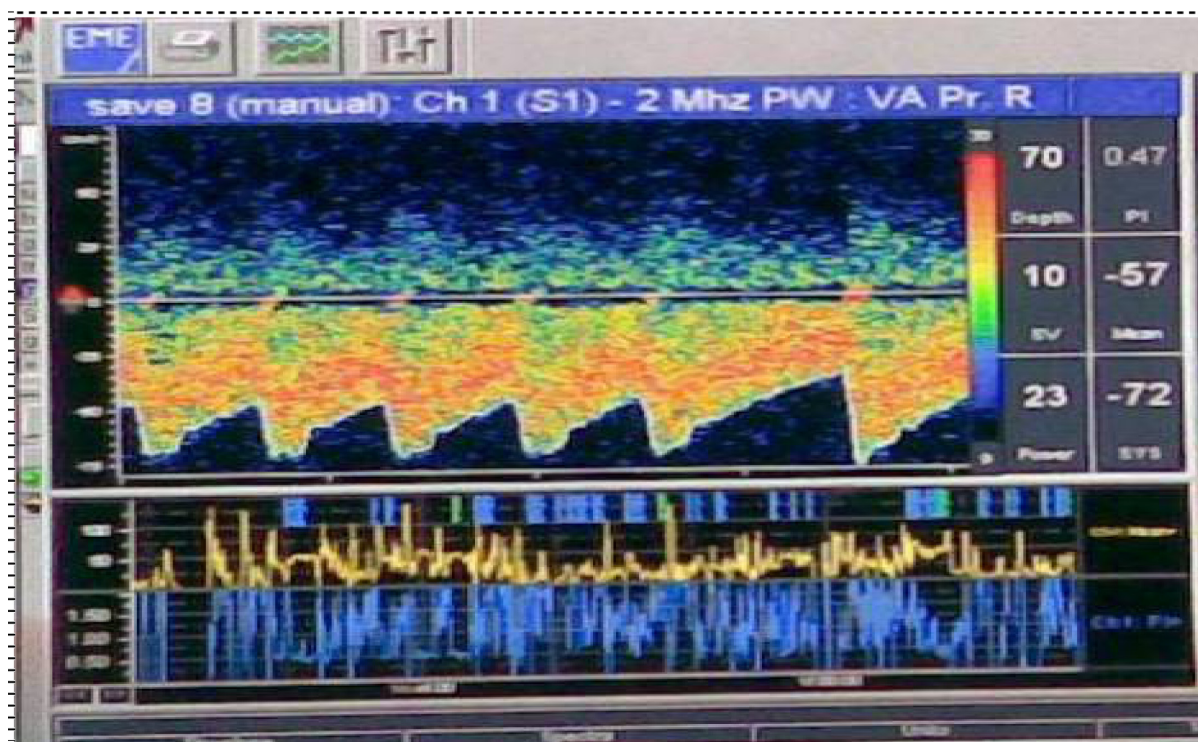


**Figure 1** The view showing transcranial duplex study of right posterior cerebral artery with abnormally high mean velocity (50 cm/sec) and abnormally low pulsatility index (0.33).

SLE patients due to the skin and facial disfigurements that can result from the disease or treatment.

Colombo and colleagues<sup>3</sup> reported that the leading cause of morbidity and mortality in SLE patients is represented

by an increased occurrence of cerebrovascular diseases secondary to accelerated atherosclerosis. Moreover, TCD has a sensitivity of 70%–80% and a specificity of 90%–99% to image intracranial segment of the vertebral arteries and the



**Figure 2** The view showing transcranial duplex study of right vertebral artery with abnormally high mean velocity (57 cm/sec) and abnormally low pulsatility index (0.47).

basilar artery, and the MCA stem is relatively easy to study, so ultrasound has a sensitivity and specificity of 90%–99% for finding a stenosis or an occlusion.<sup>36</sup> The second aim in the present study is early detection of cerebrovascular affection using TCD even when the MRI brain scan in all cases was normal.

There are significant increases in mean velocities and decreases in pulsatility index of most studied intracranial vessels in SLE patients compared with control. These increases and decreases can be explained by the narrowing, constriction, stenosis or occlusion of the vessel in most pathologic conditions affecting the large intracranial arteries, which results in increased mean flow velocity and decreased pulsatility index.<sup>28,37</sup> These results were matched with a study on 167 SLE patients evaluated by the TCD technique. Results could not be obtained in 14 patients due to technical difficulties. In the remaining 153 patients, results of 138 TCD techniques were normal, and 15 patients (9%) had one or more abnormalities.<sup>38</sup>

In our study, there was significant correlation with clinical disease activity as measured by SLE-DAI with MCA and PCA pulsatility indexes ( $P = 0.035, 0.021$ , respectively) and these results agree with the study by Kron and colleagues.<sup>38</sup> In addition, significant correlation was found between ACA mean velocity correlated with Hamilton Anxiety Scale. VA mean velocity correlated with Hamilton Depression Score and BA pulsatility index correlated with fluency. These abnormal findings in transcranial duplex in this study can be attributed to vascular abnormalities in SLE, (noninflammatory vasculopathy, vasculitis, and thrombosis), autoantibodies (antineuronal antibodies, antiribosomal P antibodies, antiphospholipids antibodies) and inflammatory mediators (IL-2, -6, -8, and -10, INF- $\beta$ , TNF- $\beta$ , MMP-9).<sup>31</sup> In addition, accelerated atherosclerosis in SLE plays an important role in cerebrovascular changes in SLE. The cause of atherosclerosis in SLE remains unclear, as it has been demonstrated that traditional risk factors alone cannot explain the increased prevalence of atherosclerosis.<sup>39</sup> Therefore, additional, so-called nontraditional factors, such as systemic chronic inflammation, presence of autoantibodies, enhanced endothelial cell activation, and use of immunosuppressive drugs have been suggested to contribute to SLE. Systemic chronic inflammation might enhance atherosclerosis in this disease. Steroid treatment is often believed to be atherogenic, because its adverse effects, including hypertension, diabetes mellitus and dyslipidemia, are all risk factors for cerebrovascular changes.<sup>40</sup> Transcranial duplex may turn out to be a valuable noninvasive tool in detection of subclinical vascular changes at an early stage among patients

with SLE to identify patients who are at risk from stroke and so preventable management should be started early.

## Conclusion

In summary, our findings show that SLE patients with or without overt neurological involvement are more likely to have subclinical cerebrovascular impairment, cognitive function impairment, depression, anxiety and neurological involvement compared with healthy controls. SLE-DAI are positively correlated with cerebrovascular impairment, cognition, depression and anxiety. Our data strongly recommend the use of standardized cognitive and mood scales along with TCD for assessment of intracranial vessels. Detailed neurological and psychiatric evaluation in detecting subclinical central nervous system involvement in SLE is highly recommended.

## Disclosures

The authors report no conflicts of interest in this work.

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