

## Original Article

# Prevalence of Cognitive Disorders in Patients with Systemic Lupus Erythromatosus; a Cross-sectional Study in Rasoul-e-Akram Hospital, Tehran, Iran

Aliyeh Mahdavi Adeli MD<sup>1</sup>, Anousheh Haghighi MD<sup>\*2</sup>, Seyed Kazem Malakouti MD MBA<sup>3</sup>

## Abstract

**Background:** Neuropsychological manifestations are present in 60% of patients with Systemic Lupus Erythematosis (SLE) among which cognitive dysfunction is the most common. This study aims to determine the prevalence of cognitive disorders in SLE patients, and the relationship between cognitive disorder domains and depression and anxiety.

**Methods:** In this cross-sectional study, 54 patients with SLE and 48 healthy subjects were included. Mini-Mental State Examination (MMSE), Clock Drawing Test (CDT) and Trail Making Test part A (TMT-A) were used to screen for cognitive impairments. All subjects were evaluated with the Beck Depression Inventory (BDI) and the Beck Anxiety Inventory (BAI) to determine depression and anxiety as probable confounding variables.

**Results:** The mean MMSE scores in SLE and control group patients ( $26.12 \pm 3.58$  and  $28.01 \pm 1.99$ , respectively) were significantly different ( $P = 0.001$ ). The sub-scores in all areas assessed with MMSE were lower in SLE patients; however, it was only significant in the areas of orientation, recall and language ( $P < 0.05$ ). SLE patients showed a significantly poorer performance in TMT compared to healthy controls ( $P = 0.01$ ). The CDT according to the Watson scoring system showed significant difference between the two groups ( $P = 0.03$ ). The Sunderland scoring system also indicated poorer performance in the SLE group, but the difference was not significant.

**Conclusion:** Our study showed that cognitive disorders are more than 3-fold higher in SLE patients compared to normal subjects. The most impaired domains include orientation, Memory (recall), Language, Executive function, and psychomotor speed. Anxiety and depression are mostly correlated with domains included in the MMSE test.

**Keywords:** Anxiety, cognition disorders, cognitive tests, depression, systemic lupus erythematosis

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## Introduction

Systemic Lupus Erythromatosus (SLE) is an idiopathic autoimmune disease, mostly occurring in young and middle-aged women. Studies have demonstrated that the prevalence and incidence of SLE are approximately 10 and 2 per 100,000 individuals, respectively. However, these numbers are increasing with time.<sup>1,2</sup> SLE can manifest in any organ, but generally, neuropsychological symptoms are seen in more than 60% of patients.<sup>2</sup> It has been stated that genetic and environmental factors (e.g., microorganisms, exposure to ultraviolet radiation) as well as hormonal changes can trigger SLE.<sup>1-4</sup>

As an autoimmune disease, both cellular and humoral defense can target the Central Nervous System resulting in encephalopathy, meningitis, intracranial pressure rise, and indirect changes in psychological and mental state. Researchers have demonstrated two main pathophysiologies for these changes: 1) hemorrhage, ischemia and other microvascular-related complications, and 2) direct autoantibody damages in neurons. However, not all dam-

ages are irreversible; neuropsychological symptoms represent transient or chronic changes in the CNS.<sup>3,4</sup>

In 1999, the American College of Rheumatology (ACR) demonstrated a type of focal/diffuse SLE under the name of Neuropsychiatric SLE (NP-SLE), which can be present with any Central or Peripheral nervous symptoms such as meningitis, headache, seizures, anxiety disorders, cognitive dysfunction, mood disorders and psychosis, as well as neuropathies and autonomous disorders.<sup>5</sup> Furthermore, different studies demonstrated that 21% to 80% of patients without any gross neuropsychological symptom suffer from mild to moderate disorders in one or more psychological domains.<sup>3,6</sup> For example, an American research demonstrated a 50% cognitive disorder in CNS healthy-looking SLE patients, mostly in psychomotor, verbal speed/fluency and verbal memory domains.<sup>7</sup>

Scientists have demonstrated that the diagnostic criteria used by most physicians are limited to psychosis and seizure, and other domains are not well-evaluated.<sup>8</sup> This issue can lead to diagnosis delay, which can be very costly. Cognitive disorders, especially chronic diseases such as SLE, can negatively influence self-image and daily communications in suffering patients, and also negatively affect intelligence, learning and memorizing processes in children (and even in aged individuals).<sup>9</sup> Nevertheless, prompt diagnosis and considering neuropsychological symptoms in the primitive state help with early treatment and lead to higher quality of life in SLE patients.<sup>10</sup>

According to similar results in Iran, Borhani & Haghighi have

**Authors' affiliations:** <sup>1</sup> School of Medicine, Iran University of Medical Sciences (IUMS), Tehran, Iran. <sup>2</sup>Rassoul Akram Hospital, Associate Professor of Iran University of Medical Sciences (IUMS), Tehran, Iran. <sup>3</sup>Professor of Psychiatry, School of Behavioral Sciences and Mental Health, Mental Health Research Centre, Iran University of Medical Sciences (IUMS), Tehran, Iran. MD, MBA. WHO Collaborating Center in mental health, Director.

•**Corresponding author and reprints:** Anousheh Haghighi MD, Rassoul Akram Hospital, Associate professor of Iran University of Medical Sciences (IUMS), Tehran, Iran. Tel: 00982166515001-9; E-mail: Haghighi533@yahoo.com  
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demonstrated 2.1% neuropsychological symptoms, whereas another study found 55.5% neuropsychological symptoms, as some of the most prevalent symptoms. It must be noted that these two studies used different ways to gather information.<sup>11,12</sup> These controversial results on neuropsychological symptoms in Iranian SLE patients, and the insufficient attention of physicians to psychological signs, call for more attention by health policy makers. This study was designed to demonstrate the prevalence of cognitive and other psychological disorders in this group of patients.

## Materials and Methods

### Subjects

This cross-sectional study was carried out in Rasoul-e-Akram tertiary Hospital, affiliated with Iran University of Medical Sciences (Tehran, Iran) during 2012 and 2013. All SLE patients aged between 15 and 70 years from the rheumatology day care clinic were included. The diagnosis of SLE was established according to ACR criteria and patients meeting 4 or more ACR criteria were enrolled. The other normal group consisted of non-SLE individuals who were selected from the patients' next of kin, group-matched for age and sex. Fifty subjects were included in each group, calculated using  $\alpha = 0.05$ , power = 80%, and 50% for prevalence of cognitive disorder in SLE and 20% in Non-SLE patients.<sup>13</sup> Illiterate patients and subjects with other rheumatologic, known neuropsychological and chronic disorders, as well as pregnant patients were excluded from our study.

All patients knew that they are participating in our study. We kept all information confidential and only presented the results as anonymous. The ethical board of Iran University of Medical Sciences approved the study and the research deputy provided the grant for the study without any third party support (Code: 697, 2011).

### Data collection

Demographic information was collected with a pre-prepared checklist consisting of age, sex, education level, disease duration, corticosteroid dosages and SLE disease activity index (SLEDAI), using laboratory data, history, signs and symptoms, completed by a rheumatologist. Furthermore, Mini Mental State Examination (MMSE), Clock Drawing Test (CDT) and Trail Making test (TMT)-Part I were used to evaluate cognitive disorders; the validity and reliability of all these tests have been previously assessed in the Iranian population.<sup>14-16</sup> The tests are described below:

- MMSE: A brief 30-point questionnaire test that is used to screen for cognitive impairment, consisting of 7 aspects of cognition i.e. Time orientation (5 points), Place orientation (5 points), Registration (3 points), Attention and calculation (5 points), Recall (3 points), Language (2 points) and Repetition (1 point) and Complex commands (6 points). We used the Persian style of MMSE, ( $\alpha = 0.81$ , sensitivity = 90% and specificity = 93% with cut-off point at 22).<sup>14</sup>

- CDT: The Clock drawing test (CDT) is a brief cognitive task that can be used by physicians who suspect neurological dysfunction based on history and physical examination. In this test, the examinee is asked to draw a circle and place the numbers according to a clock. Two scoring systems were used to evaluate the CDT.

- o The scoring method described by Watson and colleagues is objective and based on dividing the clock into quadrants. The

score is determined from the number of digits in each quadrant; 0 to 3 represents a normal score and 4 to 7 an abnormal score. This method takes into account the digit positioning only and not the positioning of the hands of the clock.

- o The Sunderland method takes into account hand positioning, and the score is determined using a 10-point scale (10 = perfect and 0 = very poor); scores of 6 or more are considered normal.

- TMT- Part A: The Trail Making Test is a neuropsychological test of visual attention and task switching. The subject is instructed to connect a set of 25 numbers as fast as possible. Normal people can do this in less than 25 seconds; performing this task in more than 78 seconds is considered as impaired cognition.

In this study, we evaluated Beck's Depression and Anxiety Inventory, since there is a significant amount of information in medical literature indicating the relation between cognitive disorders and depression and anxiety. These two questionnaires (BDI and BAI) consist of 21 questions, scored on a 0–3 Likert scale. Interpretations of these questionnaires are as follows:

- BDI <10: least depression, 10–18: minor depression, 19–29: moderate depression, and >30 major depression disorder (used the Iranian form with  $\alpha$ : 0.89).<sup>17</sup>

- BAI <7: least anxiety, 8–15: mild anxiety, 16–25: moderate anxiety, and >26: severe anxiety (used the Iranian form with  $\alpha$ : 0.92).<sup>18</sup>

### Statistical analysis

Data were expressed as means and standard deviations for quantitative variables, and frequency (percentage) for categorical variables. Data was analyzed with SPSS (v. 16) using *t*-test for evaluating the cognitive test scores and also depression and anxiety levels between the two groups. Chi-square was used to determine the prevalence of cognitive disorders according to the tests' cut-off points in both groups. Pearson correlation test was performed to evaluate the association of quantitative variables. We used ANOVA to evaluate these tests between educational levels, with the *post-hoc* Scheffé test. For all analyses, two-tailed *P*-values less than 0.05 were considered significant.

## Results

### Demographic data

At the end of the evaluation, 102 individuals were included consisting of 54 SLE and 48 non-SLE subjects. The mean age was  $34.38 \pm 11.37$  years with a 13/89 male to female ratio. SLEDAI was  $3.5 \pm 4.4$  in patients with  $98.66 \pm 99.95$  months history of diagnosed SLE. No significant difference was found between our groups in demographic data, referring to Table 1.

### Psychological tests

Table 2 and Table 3 demonstrate scores of all tests performed in this study. The results show that in all cognition tests, including MMSE (Place Orientation, Recall and Language aspects), CDT (Watson method) and TMT, the SLE patients obtained significantly lower scores ( $P < 0.05$ ). However, there was not any significant difference between the two groups in BAI ( $P = 0.178$ ) and BDI ( $P = 0.705$ ). Using these tests' cut-off points, we observed that 18 cases (33.3%) in SLE and 5 cases (10.4%) in non-SLE groups had cognitive disorders, which is significant ( $P = 0.006$ ), referring to Table 4.

For further analysis, the correlations of SLEDAI with cognition

**Table 1.** Demographic and health variables. Values are Numbers (percentages) unless stated otherwise.

	SLE patients N = 54	Non-SLE patients N = 48
Mean(SD) Age(years)	35.14(11.41)	33.52(11.38)
Male	7(13)	6(12.5)
Female	47(87)	42(87.5)
Educational level		
Elementary & middle school	27(50)	14(29.2)
Diploma	19(35.2)	18(37.5)
Associate & bachelor	6(11.1)	12(25)
Master & above	2(3.7)	4(8.3)
Mean (SD) SLE duration(months)	98.66(91.95)	—
Mean (SD) SLEDAI	3.5(4.45)	—
SLEDAI = systemic lupus erythromatosus disease activity index		

**Table 2.** The results of cognitive tests and sub-tests in both groups.

	SLE patients	Non-SLE patients	P-value
MMSE	26.12(±3.58)	28.01(±1.99)	0.001
Orientation	9.31(±1.17)	9.89(±0.30)	0.001
Recall	2.03(±1)	2.47(±0.74)	0.013
Registration	3	3	0.999
Attention and calculation	3.22(±1.71)	3.75(±1.45)	0.098
Language	7.73(±0.56)	7.97(±0.14)	0.004
Visuospatial skill	0.77(±0.26)	0.83(±0.20)	0.235
CDT-S	8.77(±1.7)	9.27(±0.84)	0.067
CDT-W	2.16(±2.5)	0.93(±1.42)	0.003
TMT	62.74(±47.99)	37.89(±18.54)	0.001
MMSE = mini-mental state examination, CDT-S = clock drawing test (Sunderland Method), CDT-W = clock drawing test (Watson Method), TMT = trail Making Test; P-value from student's <i>t</i> -test.			

**Table 3.** The results of cognitive tests and sub-tests in both groups.

	SLE patients	Non-SLE patients	P-value*
Beck anxiety inventory	16.43(±10.93)	19.40(±10.91)	0.178
Beck depression inventory	12.14(±10.59)	12.98(±11.34)	0.705
*from student's <i>t</i> -test			

**Table 4.** Number (percentage) of patients with cognitive disorders (values lower than the cut-off points) in our two groups.

	SLE patients	Non-SLE patients	P-value
MMSE	11(20.4)	0	0.001
CDT.S	6(11.1)	0	0.028
CDT.W	15(27.8)	3(6.3)	0.004
TMT	10(18.5)	3(6.3)	0.064
MMSE = mini-mental state examination, CDT-S = clock drawing test (Sunderland Method), CDT-W = clock drawing test (Watson Method), TMT = trail making test; P-value from Pearson Chi-square.			

tests were evaluated. SLE had significant correlation with TMT test ( $P < 0.001$ ,  $r = 0.486$ ). We did not find any significant correlation of SLEDAI with MMSE and CDT ( $P = 0.125$ , and  $P = 0.073$ , respectively), and the Beck's depression and anxiety inventory ( $P = 0.610$ , and  $P = 0.672$ , respectively).

All cognitive tests had significant correlation with each other ( $P < 0.001$ ,  $R > 0.65$ ). MMSE had significant negative correlation with Age ( $P = 0.012$ ,  $r = -0.24$ ), BAI ( $P = 0.011$ ,  $r = -0.25$ ) and BDI ( $P = 0.009$ ,  $r = 0.026$ ). TMT had significant negative correlation with Age ( $P = 0.001$ ,  $r = -0.33$ ) and was the only test

correlated with corticosteroid dosages ( $P = 0.020$ ,  $r = 0.34$ ). Other correlations were not significant ( $P > 0.05$ ).

We used ANOVA to evaluate these tests between educational levels, with the *post-hoc* Scheffe test. We found significant difference in lower educational levels ( $P < 0.05$ ), but not in other educational levels, referring to Table 5. No other difference was found.

## Discussion

Cognitive disorders are not well evaluated in SLE patients. Phy-

**Table 5.** Analysis of variances (ANOVA) results, evaluation of our mean test scores among different educational levels.

	F	Significant
MMSE	13.525	.000
M. orientation	4.663	.004
M. registration	-	_*
M. recall	6.945	.000
M. attention. calculation	10.126	.000
M. language	5.071	.003
M. visuospatial skill	7.407	.000
CDT.S	6.456	.000
CDT.W	6.013	.001
TMT	8.567	.000

\* In "M. orientation" almost all individuals get the 3 points score.

sicians generally limit their focus to psychosis and seizures as neuropsychological disorders in SLE, two of the ACR criteria for diagnosis. However, the prevalence of neuropsychological disorders in the initial stages of SLE is too high to be neglected. Therefore, rapid diagnosis can help both patients and health services. The aim of this study was to evaluate this issue.<sup>1-4</sup>

In line with our findings, other studies have also shown that SLE patients are prone to cognitive disorders. Cavaco *et al.* in 2012 demonstrated that NP-SLE patients have moderate to severe cognitive disorders in memory, verbal and psychomotor domains.<sup>19</sup> Also, Kozora *et al.* demonstrated that SLE patients have disorders in visuomotor speed and visual complex attention domains.<sup>20</sup> These two studies used complex computer-based neuropsychological tests. Our study showed that SLE patients are poorer in Orientation, Recall and Language, calculated by MMSE. Differences seen in the domains may be due to different types of evaluation.

Vogel *et al.* from Denmark and Glanz *et al.* from the USA demonstrated that cognitive disorders are significantly higher in SLE patients, ranging from 35% to 50% of all patients.<sup>21,7</sup> Our study found 33.3% prevalence. However, the domains are different in these three studies. The difference may originate from the differences in used tests and cut-off points. Benedict *et al.* demonstrated that memory and visual/place orientation are the most prevalently affected domains and Petri *et al.* found attention, memory and visual perception as the most prevalently subsided domains.<sup>3,4</sup> Altogether, "visual place orientation" and "memory" should be considered as the most common cognitive disorders in SLE patients. But taking into account that results vary in different studies, dominization may not be a good conception for SLE-Related cognitive disorders. For example, some studies (e.g., Hanly *et al.*) have found a 21% cognitive disorder among SLE patients using MMSE but have used only one test for SLE evaluation, which can explain this low percentage.<sup>22</sup>

It is noteworthy that all MMSE, CDT and TMT scores had significant correlation with each other; however, depression and anxiety indices did not fully correlate with cognitive scores. Our results demonstrate that BDI and BAI have the highest correlation with factors evaluated by MMSE; therefore, it seems that psychomotor speed and executive functions are not highly in relation with depression and anxiety. Furthermore, these factors were dependent on age and educational levels. There are studies demonstrating the relation of cognitive disorders and SLE, but most of them lack analysis of anxiety and depression.<sup>23,24</sup> MMSE and CDT, unlike TMT, did not have any significant correlation with

SLEDAI. We conclude that SLE severity can only be related to psychomotor speed domain in cognitive disorders.

The demographic characteristics of SLE patients such as age, sex, disease duration, etc. varied in our study. There are not many studies considering these factors in evaluating the effect of SLE on cognition disorders. Maneeton *et al.* showed that there are no significant changes in cognitive scores at different ages and disease durations,<sup>24</sup> whereas our study found significant difference in age, but not in disease duration, as in some other studies.<sup>25,26</sup> These dissimilarities may originate from different sampling and sample sizes between these studies. Significant relation with educational levels can be due to independent relation of cognition and education, regardless of SLE.

The main intent of this study was to demonstrate the neglected psychological aspects of SLE patients. Psychological impairments such as cognitive disorders are important in managing SLE cases. Utilizing psychological evaluations and treatments will result in better management and prognosis. Our study demonstrated that cognition tests are more or less impaired. However, lack of a systematic test that contains all domains of cognition disorders can hamper general evaluation. We included the most important cognition tests in our study to demonstrate the most comprehensive evaluation in SLE patients. More original studies are needed to generate a review process regarding this issue.

In conclusion, this study showed that cognitive disorders are more than 3-fold higher in SLE patients compared to normal subjects, independent of demographic factors, anxiety and depression. The most impaired domains include Orientation, Memory (recall), Language, Executive function and Psychomotor speed. Anxiety and depression are mostly correlated with domains included in the MMSE test. SLE severity, calculated by SLEDAI, has significant correlation with psychomotor speed. Systematic tests containing all domains of cognition disorders may be needed for better evaluation.

### Conflict of Interest

The authors declare that they have no conflict of interest

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