Cognitive impairment in non-neuropsychiatric systemic lupus erythematosus

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Abstract Introduction: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease which can cause prominent central nervous system (CNS) involvement. Cognitive dysfunction is one of the major neuropsychiatric syndromes of SLE.

Aim of the work: To evaluate cognitive functions in SLE patients without evident neuropsychiatric manifestations and to find out if it is correlated with disease activity and with treatment.

Patients & methods: Thirty SLE patients without evident neuropsychiatric manifestations were evaluated. The evaluation included full clinical examination, assessment of SLE disease activity index-2k (SLEDAI-2k), routine laboratory investigations, autoantibodies assessment and cognitive function assessment using Montreal cognitive assessment (MoCA) scale and trail making test (TMT) (part A and part B). Twenty apparently healthy individuals were taken as control.

Results: Cognitive dysfunction is present in all SLE patients included in our study. During assessment of cognitive functions, a highly statistically significant difference was observed between patients and control subjects, even with equal levels of education. While patients with higher
1. Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that is characterized by multisystem involvement and diverse manifestations. It can affect almost any organ in the body; the primary areas affected by SLE include the heart, lungs, skin, joints, blood-forming organs, kidneys, and the central nervous system (CNS) [1].

Over 50% of patients with SLE demonstrate major psychiatric and neurologic disorders indicating CNS involvement. Neuropsychiatric (NP) syndromes in SLE may include major manifestations, such as stroke syndromes, seizures, and psychotic episodes. They may also include less severe abnormalities including headaches, minor mood disorders, and cognitive difficulties [2].

In the revised criteria for neuropsychiatric lupus, 19 neuropsychiatric syndromes were defined including 11 CNS disorders and eight peripheral nervous system disorders. In this revised nomenclature, cognitive dysfunction was identified as one of the major neuropsychiatric syndromes and was defined as “significant deficits in any or all of the following cognitive functions: complex attention, executive skills (e.g., planning, organizing, sequencing), memory (e.g., learning, recall), visual-spatial processing, language (e.g., verbal fluency), and psychomotor speed” [3].

Studies to date suggest that cognitive impairment in SLE is in part mediated by autoantibody activity and mechanisms associated with ischemia [4]. Additional mediators of cognitive function in SLE patients include health characteristics (disease activity, disease duration, medication use), immune activity (autoantibodies, proinflammatory cytokines), and behavioral factors such as depression, pain, and fatigue [5].

It has been claimed that a subset of anti-DNA antibodies cross react with a sequence in the extracellular ligand-binding domain of NR2 receptors [6]. These receptors are subtypes of N-methyl-D-aspartate (NMDA) receptors which bind to the excitatory neurotransmitter glutamate. They are present at high density in the hippocampus, which is closely linked to learning and memory [7].

Omdal et al. reported an association between anti-NR2 antibodies and decreased short-term memory and learning [8], and also with depressed mood [9].

Antiphospholipid syndrome is associated with focal manifestations of NPSLE, such as stroke and seizures [10]. Persistently elevated levels of anti-cardiolipin antibodies (ACL) are associated with decline in cognitive dysfunction, possibly due to thrombosis within vessels of minute calibers [11].

A previous study identified a relationship between serum IL-6 production and learning deficits in SLE. It was also demonstrated that elevated levels of C-reactive protein (CRP) are correlated with deficits in information processing [12].

Patients with neuropsychiatric systemic lupus erythematosus (NPSLE), especially those with cognitive impairment were found to have elevated levels of matrix metalloproteinase-9 (MMP-9) in the serum [13] and in the cerebrospinal fluid (CSF) [14].

The aim of this study was to evaluate the state of cognitive functions in SLE patients without evident neuropsychiatric manifestations and to find out if it correlated with disease activity and with treatment or not.

2. Patients and methods

2.1. Patients

Fifty subjects were included in this study. All subjects were recruited from the out-patient clinics and follow-up units of the Rheumatology and Rehabilitation Departments, Faculty of Medicine, Zagazig University Hospitals. They were divided into two groups. The first group (I): included 30 SLE patients suffering from lupus nephritis and treated by corticosteroids with either pulsed cyclophosphamide therapy or oral azathioprine. They were diagnosed according to the revised American College of Rheumatology (ACR) criteria for classification of SLE [15]. The second group (II): included 20 apparently healthy subjects, matched for age, sex, total years of education, and social backgrounds, taken as a control group.

In this study, we excluded patients with major psychiatric disorders, mental retardation or family history of organic mental disorders. SLE patients with known comorbid neurologic conditions (traumatic brain injury; degenerative, vascular, or metabolic disorder; neoplasm, or toxic exposure), major substance abuse, or major psychopathology were excluded from the study. An informed consent was taken from all subjects recruited for the study.

2.2. Clinical and laboratory evaluation

All subjects of our study were subjected to full history taking, thorough physical examination and laboratory investigations such as: complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complete urine analysis, 24-h urinary proteins, C3 level, antinuclear antibody (ANA) by immunofluorescent assay, anti-double stranded DNA (Anti-Ds. DNA) done by latex agglutination test and
anti-cardiolipin (ACL) IgM by enzyme-linked immunosorbent assay (ELISA). Assessment of disease activity was done by using systemic lupus erythematosus disease activity index-2k (SLEDAI-2k) [16].

2.3. Assessment of cognitive functions

Assessment of cognitive functions was done by:

a. Montréal cognitive assessment (MoCA) scale [17]. MoCA scale includes several aspects of cognitive functions. Actually, it is divided into several subcores including visuospatial and executive functions, naming, attention, language, abstraction, delayed recall, and orientation [18].

b. Trail making test (TMT) (part A and part B): The TMT assesses mental shifting and consists of two parts. First, the subject is required to draw lines to connect numbers in ascending order as quickly as possible. This part (TMT A) assesses visual perception rapidity and psychomotor rapidity. The second part (TMT B) assesses mental shifting and the subject’s attention ability since s/he is required to do the same as for TMT A, but alternating between numbers and letters. The subject is asked to perform the task as quickly as possible without lifting his/her pen. If the experimenter sees a mistake, s/he tells the patient. The time in seconds required for the performance of part A and part B was used for the analysis. If the time to complete TMT B is longer than 240 s, then the test is stopped and the number of figures connected in the allotted time as well as the number of errors is noted [19].

3. Results

3.1. Grouping of subjects included in the study

This study was performed on 50 individuals, divided into two groups:

Group I: It included 30 SLE patients. Twenty-one patients were suffering from active lupus nephritis, and are under pulsed cyclophosphamide therapy combined with steroid treatment, and have completed the first 6 monthly doses of treatment course. The remaining nine patients are under Azathioprine and steroid treatment.

Group II: It included 20 healthy subjects (control group), of nearly the same epidemiological characters.

All patients and control subjects were further classified, according to the number of years of education, into two subgroups a and b, less than 12 years and more than 12 years, respectively.

3.2. Comparison between clinical & laboratory variables of the two groups

The statistical analyses did not show significant differences among SLE patients and control subjects as regards age, years of education, CRP levels, ACL levels and TMT A scores, while there were highly statistically significant differences between both groups as regards ESR, C3 levels, ANA and anti-DNA titers. There were highly statistically significant differences between patients and control subjects as regards TMT B and MoCA scales for cognitive assessment (Table 1).

3.3. Effect of SLE on cognitive function

In subjects with less than 12 years of education, there was a highly statistically significant difference in MoCA, TMT A and TMT B scores between subgroups I-a and II-a. While in subjects with more than 12 years of education there was a statistically significant difference in MoCA scores and a highly statistically significant difference in TMT B scores between subgroups I-b and II-b (Table 2).

### Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>I (patients)</th>
<th>II (control)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>34.56 ± 6.01</td>
<td>33.4 ± 5.71</td>
<td>0.495</td>
</tr>
<tr>
<td>Years of Education</td>
<td>8.27 ± 4.51</td>
<td>9.2 ± 4.49</td>
<td>0.476</td>
</tr>
<tr>
<td>Diseases duration (years)</td>
<td>5.4 ± 2.21</td>
<td>5.45 ± 1.76</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>31.3 ± 12.4</td>
<td>4.75 ± 1.48</td>
<td>0.123</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>4.86 ± 2.21</td>
<td>3.12 ± 0.75</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C3 (mg/ml)</td>
<td>65.13 ± 21.07</td>
<td>145.1 ± 21.28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ANA (EU/ml)</td>
<td>31.46 ± 6.004</td>
<td>14.6 ± 3.09</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anti-DNA (IU/ml)</td>
<td>26.57 ± 6.37</td>
<td>14.05 ± 2.89</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anti-cardiolipin (MPL/ml)</td>
<td>5.15 ± 1.51</td>
<td>4.69 ± 1.68</td>
<td>0.108</td>
</tr>
<tr>
<td>MoCA</td>
<td>14.66 ± 4.05</td>
<td>27.95 ± 1.19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TMT A (s)</td>
<td>38.3 ± 10.53</td>
<td>28.75 ± 1.033</td>
<td>0.088</td>
</tr>
<tr>
<td>TMT B (s)</td>
<td>294.1 ± 10.21</td>
<td>275–312</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Significant at $P < 0.05$ and **Highly significant at $P < 0.001$. 

Statistical analysis: The data of the patients were entered on Statistical Package for Social Science (SPSS) [20]. Results are presented as mean and standard deviation. The non-parametric unpaired t-test, Mann Whitney U test, is used to assess differences of cognitive functions between each group. Spearman’s correlation coefficient analyses were performed to identify factors associated with cognitive deficits, such as: MoCA, TMT A, TMT B, total SLEDAI-2k and renal index. The statistically significant cutoff value was set at $p < 0.05$. 

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3.4. Effect of education on cognitive function of patients

When comparing the two subgroups of patients (> and <12 years of education) there was a statistically significant difference in MoCA scores, at the same time there is no statistically significant difference between two subgroups as regards TMT A or B (Table 3).

3.5. Relation between disease parameters and cognitive function

There was a statistically significant positive correlation between disease duration and TMT B scores ($p = 0.049$). While there was a non-significant correlation between disease duration and TMT A or MoCA scores. There was, also, a non-significant correlation between any of cognitive assessment scores and SLEDAI-2k or renal activity index (Table 4).

3.6. Effect of treatment on cognitive function

There was a highly statistically significant negative correlation between SLEDAI-2k and cyclophosphamide dose. While there was a statistically significant negative correlation between SLEDAI-2k and steroid dose and between renal activity index and both cyclophosphamide and steroid dose. None of the cognitive assessment scores was correlated with the doses of any of the drugs used in treatment (Table 5).

4. Discussion

SLE is an autoimmune disease with predominance among women of the child-bearing age. It is characterized by chronic tissue/organ inflammation mediated through autoantibodies, immune complexes, and complement activation that results in multiorgan involvement [21].

Neuropsychiatric SLE (NPSLE) occurs in 14% to over 80% of patients with SLE and is associated with increased morbidity and mortality [4].

Cognition is the sum of intellectual functions that result in thought. It includes reception of external stimuli, information processing, learning, storage, and expression [22]. Cognitive dysfunction has been identified in 14–54% of non-NPSLE patients suggesting the presence of a subtle CNS disorder, but investigations into biologic mechanisms have yet to clearly demonstrate the mechanisms underlying the phenomenon. Thus, continued studies into the pathogenesis of subtle brain involvement in non-NPSLE patients are warranted [23].

In this study we evaluated 30 SLE patients suffering from lupus nephritis and evaluated them for the presence of...
cognitive impairment by using MoCA scale and TMT (part A and part B), and compared them with 20 healthy control subjects. We found that all our patients were suffering from different aspects of cognitive impairment in comparison with the control group. When performing MoCA scale, only one of our patients scored as normal and the other 29 patients showed impairment. While in TMT B, all of the patients showed impairment in the form of exceeding 240 s to perform the test. In fact, none of them was able to complete the test even in longer periods. On the contrary, all patients were able to perform TMT A within the normal time as control subjects.

There was a highly statistically significant difference between patients and controls in MoCA scores and TMT B, while there was no significant difference as regards TMT A.

TMT A assesses visual perception rapidity and psychomotor rapidity, while TMT B assesses, in addition, mental shifting and the subject’s attention ability since s/he is required to alternate between numbers and letters [19]. So, TMT A is much easier than TMT B. Besides, MoCA scale measures several aspects of cognitive functions. This is why our patients showed no significant difference with control subjects as regards TMT A, and showed a highly statistically significant difference with control subjects as regards TMT B and MoCA scores.

Glanz et al. stated that cognitive dysfunctions occur in 50% of their SLE patients [24] and Petri et al. reported measurable cognitive impairment in 75% of SLE patients, using the Automated Neurophysiological Assessment Metrics (ANAM). Their patients scored significantly lower than controls in the ANAM [25]. Another study revealed that cognitive dysfunctions occur frequently in SLE patients [26]. Furthermore, Hanly et al. have confirmed that SLE patients have slower performance on cognitive tasks than that of controls [22].

In another study, SLE patients had significantly lower levels than control subjects in the Mini-Mental State score (MMSE). They showed, also, significantly lower level than control subjects in Clock Drawing Test (CDT) [27]. In addition, Ezzat et al. found statistically significant differences between SLE patients and controls in many subsets of Wechsler Adult Intelligence Scale (WAIS) [28].

By observing these results, we conclude that cognitive dysfunctions are apparent in SLE patients despite using different methods of assessment.

It was confirmed that SLE patients with CNS involvement had a higher degree of cognitive impairment than SLE patients without CNS involvement in the areas of attention/calculation, auditory comprehension, visuospatial ability, and executive function [27].

In our study, the three tests were not correlated with total SLEDAI-2k or with the renal activity index. Neither MoCA scale nor TMT A was correlated with disease duration. Whereas TMT B scores had a statistically significant positive correlation with the disease duration.

Trail-Making Test is considered the most difficult and confusing test in our study. Its correlation with disease duration should pay attention to the occurrence of changes in the brain tissue of SLE patients.

In another study performed by Bhasin et al., the presence of cognitive dysfunction in SLE patients did not significantly correlate with duration of disease [29]. This difference can be explained by the longer disease duration in our patients which ranged from 2 to 9 years, while it was 1 to 2 years in that study.

The same study had similar results to ours that cognitive dysfunction in SLE patients did not significantly correlate with indices of disease activity. On the contrary, the Egyptian study by Ezzat et al. revealed statistically significant correlations between some items of WAIS scale and SLEDAI [28]. At the same time, Maneeton et al. found that cognitive scores were not correlated with disease duration or with disease activity [27].

As regards the treatment received by the patients, none of the three tests was correlated with the dose of Cyclophosphamide, Azathioprine or steroid doses. This is in agreement with the results of Maneeton et al. study, in which the cognitive scores did not correlate with glucocorticoids, Chloroquine, Methotrexate or Cyclophosphamide medications [27]. At the same time we found that total SLEDAI-2k and renal activity index had a highly significant negative correlation with the dose of Cyclophosphamide and a significant negative correlation with the dose of steroids.

In an older study done by McLaurin et al., regular prednisone use was associated with decreased cognitive functioning in middle-aged patients with SLE [30]. While, Bhasin et al. revealed that the presence of cognitive dysfunction in SLE patients did not significantly correlate with glucocorticoids, but they found a significant correlation of cognitive dysfunction with use of azathioprine [29].

We conclude that cognitive dysfunctions in SLE occur by another mechanism rather than that of nephritis. This is why it is correlated neither with total SLEDAI-2k or with the renal activity index nor with doses of any of the medications used for treatment of nephritis.

When we compared patients and control subjects who received less than 12 years of formal education, we found a highly statistically significant difference as regards MoCA and TMT B, and a statistically significant difference as regards TMT A. The difference was, also, highly statistically significant between patients & control subjects with more than 12 years of formal education as regards MoCA and TMT B.

When we compared the two subgroups of patients only (i.e. patients with different levels of education), we found that there was a statistically significant difference between them in the MoCA score, while the difference was insignificant as regards TMT A and B. Those results can be explained by the fact that MoCA scale measures different domains of cognitive functions. We noted that the visuospatial & executive domains were the most difficult ones. This is why they can be affected by the level of education. A non-educated person cannot simply draw a cube with accurate measures and cannot draw a clock with accurate numbers and arms on definite time.

Tomietto et al. observed an independent effect of age on the development of cognitive impairment and a protective effect of a high education level on the number of functions impaired may be due to a greater functional brain reserve that delays the onset of clinical manifestations [31]. In addition, Brey et al. identified an association of age and education with some measures of cognitive impairment [32]. Tomietto et al. also stated that the presence of chronic damage (long disease duration) arose as the main factor affecting the severity of impairment [31]. In another previous study done by McLaurin et al., consistent prednisone use and less education were significantly associated with declining cognitive function especially in the middle age group and could not be totally explained by SLE-associated disease activity [30].
We did not find other studies that compared between cognitive functions of patients and control subjects as regards their level of education. But our results in this point confirm that there is a significant impairment in cognitive functions in SLE patients, despite different levels of formal education.

Study limitations included that patients with low level of education were not able to perform some parts of cognitive assessment tests; besides, lack of compliance of the patients to attend regular psychiatric visits in order to assess the deterioration of the condition.

In conclusion, cognitive dysfunction is a prominent feature in SLE patients without symptoms of CNS involvement. Psychological evaluation should be performed for each patient to detect these cognitive dysfunctions. Besides, psychological intervention is recommended to prevent further deterioration. Also, correlation with disease duration should pay attention to the chronicity of disease. Further studies are needed to compare patients with short & long disease duration.

Conflict of interest

The authors have no conflict of interest to declare.

References


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