COGNITIVE FUNCTIONS IN SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS

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KEY WORDS: COGNITIVE FUNCTIONS, SLE.

ABSTRACT

Objective: to assess cognitive function in patients with SLE and to determine its correlation to demographics, quality of life, and disease-related variables.

Methodology: Twenty patients with systemic lupus erythematosus (SLE) who fulfilled the revised criteria for classification of SLE of the American College of Rheumatology and twenty healthy control subjects apparently free from any relevant disease were included in this study. All patients were subjected to full history taking, thorough clinical examination, assessment of disease activity using SLAM index and assessment of quality of life using Beck Questionnaire as well as detection of IgG anticardiolipin antibodies using ELISA.

Cognitive function tests were performed by Stanford-Binet IV scale which measure verbal ability, visual/abstract ability, short-term memory, and general intelligence quotient (IQ).

Results: the mean scores of all cognitive function tests (verbal ability, visual ability, short term memory and (I.Q.)) in SLE patients showed a statistically significant decrease (p<0.05) as compared to controls. Cognitive functions of SLE patients correlated positively with quality of life and correlated negatively with disease activity, antiphospholipid antibodies, and CNS manifestations of SLE patients.

Conclusion: Cognitive functions of SLE patients showed a significant impairment compared with normal people. Disease
activity, antiphospholipid antibodies, quality of life and CNS manifestations of SLE patients were associated with impairment in cognitive functions. Evaluation of cognitive function, improving of disease activity and quality of life should be given greater emphasis in SLE patients especially in the presence of antiphospholipid antibodies and CNS manifestations.

**INTRODUCTION**

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with multiorgan involvement characterized by an immune response against nuclear components (Nuttal et al., 2003). SLE patients experience a waxing and waning disease course and a wide variety of clinical manifestations, reflecting the systemic nature of the disease. The skin, kidneys, joints and central nervous system may become the target of SLE-included inflammation at its onset or during the course of the disease (Blanco et al., 2005).

Cognition is the sum of intellectual functions that result in thoughts. The functions include perception of external stimuli, information processing, learning and expression. Cognitive functioning can be conceptualized as consisting of domains or categories, each of which involves a variety of cognitive processes (Chin & Latov, 2005).

Some reports claim that an association between cognitive impairment and antineuronal or antiphospholipid antibodies can be found but other studies found no correlation with these or other antibodies (Harrison et al., 2006).

The variability of prevalence of cognitive dysfunction in SLE may be due to diversity of demographic and SLE disease characteristics, the variety of neuropsychological test employed and the diversity of outcome definitions of cognitive impairment, all of which contribute to the complexity of developing clear understanding of this condition (Harrison & Ravidin, 2002).

**Aim of the work:**

The aim of this work was to assess cognitive function in patients with SLE and to determine its correlation to demographics, quality of life, and disease-related variables.
SUBJECTS AND METHODS

This study was carried out on twenty patients with systemic lupus erythematosus (SLE) attending the outpatient clinic or were admitted to the inpatient unit of the Rheumatology and Rehabilitation Department of Benha University Hospitals. All Patients fulfilled the revised criteria for classification of SLE of the American College of Rheumatology (Tan et al., 1982). Their mean age was 27.15 ± 9.4 years, male to female ratio was 1:19 and the mean duration of illness was 5.45 ± 4.1 years. Also, 20 healthy control subjects apparently free from any relevant disease were included in the study.

All subjects were subjected to the following:

- Full history taking
- Full clinical examination
- Clinical assessment of disease activity was done for SLE patients by using SLAM index (Liang et al., 1989).
- Laboratory investigations
  - ESR and complete blood picture
  - Liver and kidney functions.
  - Antinuclear antibody using latex test
  - Anti double stranded DNA using ELISA
  - IgG anticardiolipin antibodies using ELISA. The test samples were reported positive when their values exceeded that of the mean plus three standard deviations of ten normal control sera.

Beck Questionnaire for quality of life (Beck, 1993):

It measures 6 aspects for quality of life (physical, cognitive, affective, social, economic and ego aspects). Each aspect is composed of 5 questions; with each question answer is graded from 0 to 5 reflecting the severity level of the item asked about. The quality of life is calculated by a percentage. So 100% is the best quality of life, 50% represents average quality of life while 0% is the poorest quality of life.

Cognitive function tests:

Stanford-Binet IV scale (Thorndike et al., 1986).

The total scale consists of four main mental (cognitive) abilities and six subscales. The main abilities are Verbal ability, Visual/Abstract ability, Short-term memory and General intelligence quotient (IQ).
The six subscales are:

1. **Vocabulary test:** Forty six Items: 1-14 were picture vocabulary; 15-46 were verbal vocabulary (words) of increasing difficulty and the patient was asked to tell the meaning of each word.

2. **Comprehension test:** 42 items representing direct questions of increasing difficulties. The patient was asked to answer these questions in an orderly way, and see if the patient can understand and answer them correctly.

3. **Pattern analysis:** Forty two items:
   - One-six items were wooden board with dug geometric shape and separate wooden pieces of the same shape.
   - Seven- forty two items were wooden blocks (2x2 cm) and printed cards contain different shapes. The patient was asked to constitute the same shape. In seven-twenty four items, the patient was asked to design blocks in shapes the same as displayed by the examiner. In twenty five-forty two items, the patient was asked to design blocks the same as in shapes shown in cards.

4. **Matrices:** Twenty six progressive matrices printed in cards each one consisted of a number of blocks all of them were filled with a related shaped with a missing block. The patient had to detect the logic arrangement and chose the correct shape from a list below and put it in the missing block site to complete the matrices.

5. **Memory for digits test:** Composed of two subtests: The 1st composed of 14 series of numbers of increasing difficulty and the patient was asked to repeat the series in the same direction in a spoken way. The 2nd composed of 12 series of numbers of increasing difficulty in which the patient was asked to repeat them in the opposite direction in a spoken way.

6. **Bead memory:** It composed of plastic beads of different shapes and colors and iron rod fixed on a metal base. Printed cards contained different designs of the beads were displayed to patient who asked to memorize and design the same shape shown in cards.

**The scoring system:**

The standardized age score of each mental ability is calculated as the following (*Thorndike et al., 1986*):
A. The standardized age score for verbal ability is calculated by adding the standardized age score for the vocabulary and that of the comprehension.

B. The standardized age score for visual/abstract ability is calculated by adding the standardized age score for pattern analysis and matrices.

C. The standardized age score for short term memory is calculated by adding the standardized age score for bead memory and memory for digits.

D. The standardized age score for verbal, visual and short term memory are converted to general intelligence quotient (IQ).

Statistical Analysis:

Statistical analysis was done by using SPSS statistical package for social science. The data were parametric by using Kolmogrov-Smirrov test. The qualitative data presented in the form of number and percentage. The qualitative data presented in the form of mean, standard deviation and range. Students- t- test was used to compare two groups. Pearson correlation coefficient was done to study the relation between variables. Values of p<0.05 were considered significant, but insignificancy was considered when p-value> 0.05.

RESULTS

Table (1) shows demographic data and disease variables in SLE patients.

Table (2) shows cognitive function scores in SLE patients and healthy controls.

The mean scores of all cognitive function tests {verbal ability, visual ability, short term memory and (I.Q.)} in SLE patients showed a statistically significant decrease (p<0.05) as compared to controls.

Table (3) shows correlation coefficients (r) between cognitive functions and different variables in SLE patients.

Cognitive functions of SLE patients correlated positively with quality of life and correlated negatively with disease activity, antiphospholipid antibodies and CNS manifestations of SLE patients.
Table (1): Demographic data and disease variables in SLE patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>27.15 ± 9.4271</td>
</tr>
<tr>
<td>Sex (%♀)</td>
<td>95%</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>5.45 ± 4.1355</td>
</tr>
<tr>
<td>Years of education (years)</td>
<td>10 ± 5.3213</td>
</tr>
<tr>
<td>Marital state (%)</td>
<td>70%</td>
</tr>
<tr>
<td>Quality of life (%)</td>
<td>52%</td>
</tr>
<tr>
<td>ESR (mm/hr)</td>
<td>42.6 ± 36.5404</td>
</tr>
<tr>
<td>HB (gm %)</td>
<td>10.58 ± 1.3485</td>
</tr>
<tr>
<td>WBCS( cells/mm3)</td>
<td>5.7825 ± 1.2337</td>
</tr>
<tr>
<td>SLAM index</td>
<td>14.35 ± 1.14</td>
</tr>
<tr>
<td>Anti ds-DNA (%)</td>
<td>75%</td>
</tr>
<tr>
<td>Anticardiolipin G (%)</td>
<td>25%</td>
</tr>
<tr>
<td>Renal affection (%)</td>
<td>45%</td>
</tr>
<tr>
<td>Cardiopulmonary affection (%)</td>
<td>30%</td>
</tr>
<tr>
<td>CNS affection (%)</td>
<td>35%</td>
</tr>
</tbody>
</table>

Table (2): Cognitive function scores in SLE patients and healthy controls.

<table>
<thead>
<tr>
<th></th>
<th>SLE (mean ± SD)</th>
<th>Controls (mean ± SD)</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal ability</td>
<td>79.4 ( ± 17.02)</td>
<td>90.2 ( ± 13.85 )</td>
<td>9.15</td>
<td>0.04*</td>
</tr>
<tr>
<td>Visual/Abstract ability</td>
<td>79.2 ( ± 16.87 )</td>
<td>88.35 ( ± 13.15 )</td>
<td>10.85</td>
<td>0.019*</td>
</tr>
<tr>
<td>Short term memory</td>
<td>76.25 ( ± 16.28 )</td>
<td>89.3 ( ± 12.72 )</td>
<td>13.05</td>
<td>0.009*</td>
</tr>
<tr>
<td>I.Q.</td>
<td>77.3 ( ± 17.44 )</td>
<td>89.4 ( ± 13.08 )</td>
<td>12.1</td>
<td>0.012*</td>
</tr>
</tbody>
</table>

*Significant (p<0.05).
Table (3): Correlation coefficients (r) between cognitive functions and different variables in SLE patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Verbal ability (r)</th>
<th>Visual/abstract ability (r)</th>
<th>Short term memory (r)</th>
<th>I.Q. (r)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.217</td>
<td>-0.210</td>
<td>-0.315</td>
<td>-0.241</td>
</tr>
<tr>
<td>Disease duration</td>
<td>-0.178</td>
<td>-0.243</td>
<td>-0.329</td>
<td>-0.261</td>
</tr>
<tr>
<td>Years of education</td>
<td>0.357</td>
<td>0.342</td>
<td>0.317</td>
<td>0.378</td>
</tr>
<tr>
<td>Marital state</td>
<td>0.266</td>
<td>0.280</td>
<td>0.270</td>
<td>0.230</td>
</tr>
<tr>
<td>Quality of life</td>
<td>0.425*</td>
<td>0.627*</td>
<td>0.823**</td>
<td>0.724**</td>
</tr>
<tr>
<td>ESR</td>
<td>-0.353</td>
<td>-0.359</td>
<td>-0.418</td>
<td>-0.418</td>
</tr>
<tr>
<td>HB%</td>
<td>0.424</td>
<td>0.443</td>
<td>0.447*</td>
<td>0.447*</td>
</tr>
<tr>
<td>WBCs</td>
<td>-0.185</td>
<td>-0.172</td>
<td>-0.136</td>
<td>-0.163</td>
</tr>
<tr>
<td>Anti ds-DNA</td>
<td>-0.223</td>
<td>-0.232</td>
<td>-0.338</td>
<td>-0.338</td>
</tr>
<tr>
<td>Anticardiolipin G</td>
<td>-0.612*</td>
<td>-0.639*</td>
<td>-0.739**</td>
<td>-0.729**</td>
</tr>
<tr>
<td>SLAM index</td>
<td>-0.488*</td>
<td>-0.510*</td>
<td>-0.549*</td>
<td>-0.449*</td>
</tr>
<tr>
<td>Renal affection</td>
<td>-0.191</td>
<td>-0.206</td>
<td>-0.250</td>
<td>-0.250</td>
</tr>
<tr>
<td>Cardiopulmonary affection</td>
<td>-0.393</td>
<td>-0.219</td>
<td>-0.204</td>
<td>-0.204</td>
</tr>
<tr>
<td>CNS affection</td>
<td>-0.521*</td>
<td>-0.555*</td>
<td>-0.519*</td>
<td>-0.619*</td>
</tr>
</tbody>
</table>

*Significant (p<0.05).
**Highly significant (p<0.001).

DISCUSSION

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease of unknown etiology predominantly affecting women in their reproductive years (Mymok et al., 2000).

Nervous system dysfunction occurs in a variable proportion of SLE patients depending on the sampling procedures and diagnostic criteria used. Despite its frequency and severity, nervous system involvement is underdiagnosed and poorly understood. SLE related nervous system involvement includes wide spectrum of overt neurological and psychiatric features ranging from strokes, seizures, peripheral neuropathy, chorea, dementia, psychosis, anxiety and depression to more subtle cognitive abnormalities such as attention, memory and visuospatial abnormalities (Harel et al., 2006).

Cognitive problems have frequently been found in patients with SLE. The pathogenesis of the impairments is uncertain and although the role
of autoantibodies has been examined, results have been conflicting (Hanly et al., 2006).

The aim of this work was to assess cognitive function in patients with SLE and to determine its correlation to demographics, quality of life, and disease-related variables.

In our study the mean scores of all cognitive function tests {verbal ability, visual ability, short term memory and (I.Q.)} in SLE patients showed a statistically significant decrease (p<0.05) as compared to controls. Our findings were coincided with those of Glanz et al. (2005) who reported that SLE patients performed worse than the control group in all cognitive function tests.

Brey et al. (2002) examined the prevalence of neuropsychiatric syndromes in SLE and found cognitive impairment to occur in 79% of SLE patients, 43% had mild impairment, 30% had moderate impairment and 6% had severe impairment. Sanna et al. (2003) examined neuropsychiatric manifestation is 323 SLE patients and found cognitive impairment to occur in 35 (10.8%) patients and Cheng & Xiaoxia, (2006) found cognitive impairment to occur in 24% of SLE patients.

As regard demographic variable, we did not find any significant correlations (p>0.05) between all cognitive functions and age, level of education, marital status and disease duration. These results were in accordance with those of Waterloo et al. (2002). On the other hand, Harrison & Ravidin (2002) found that these demographic variables contributed significantly to the explanation of cognitive dysfunction in SLE.

In our study, we found a positive significant correlation between cognitive functions and quality of life in patients with SLE. Similar results were previously reported by Sweet et al. (2004) who found a significant correlation between quality of life and cognitive impairment in patients with SLE.

As regards disease related aspects, we found significant negative correlations between cognitive dysfunctions and disease activity in SLE. These negative significant correlations between cognitive dysfunctions and disease activity in SLE demonstrated in our study were in agreement with many studies. Leritz et al. (2000) identified disease activity as a primary factor for cognitive dysfunction in SLE. Also Gladman et al. (2000) stated that higher activity scores at initial presentation (SLEDAI>10) were predictive of cognitive impairment in patients with SLE. Lastly, Kozora et al. (2001) hypothesized a role for IL-6 (an inflammatory mediator) and
various hormones known to be abnormal in SLE in the development of cognitive dysfunction.

On the other hand, our significant correlations between disease activity and cognitive dysfunction in SLE were contrasted by other studies. Carlomagno et al. (2000) did not detect any significant correlation between disease activity and cognitive functions in SLE. Also Waterloo et al. (2002) stated that neither demographic variables nor disease activity parameters were associated with cognitive dysfunction in patients with SLE.

Our results showed negative significant correlations between anticardiolipin IgG antibody and overall cognitive dysfunction. This finding agreed to many works.

Grisanti et al. (2001) reported that cognitive dysfunction was two or three times more prevalent in SLE patients who were positive for antiphospholipid antibodies than in those were negative for these antibodies.

Menon et al. (1999) determined the relationship between persistently elevated anticardiolipin antibodies levels and neuropsychological performance in 45 SLE patients. They found that IgG anticardiolipin antibodies that were persistently elevated over a 2-3 years were associated with significantly poorer performance in cognitive functions.

Also Hanly et al. (1999) analyzed prospectively the association between changes in cognitive function and anticardiolipin antibodies over a period of 5 years in SLE patients. Their results showed that patients with a persistent IgG anticardiolipin positivity had a reduction in psychomotor speed and patients with persistent IgA anticardiolipin antibodies had a reduction in conceptual reasoning and executive ability suggesting that IgG and IgA anticardiolipin antibodies may be responsible for long term subtle deterioration in cognitive functions in SLE patients.

On the other hand, Emori et al. (2005) stated that presence of antiphospholipid antibodies was not associated with a significant difference in cognitive function test results. Also, Cappa et al. (2003) stated that the prevalence of cognitive impairment was similar in SLE patients with and without antiphospholipid antibodies.

Our results showed negative significant correlations between CNS manifestations of SLE patients and overall cognitive dysfunction. Our results were matched with the study made by Hanly et al. (2006) who reported that cognitive dysfunctions were more common in SLE patients with CNS affections compared to those without CNS affection. Hay, (1994) examined neuropsychiatric symptoms and cognitive dysfunction in 49 SLE
patients and found correlations between changes in severity of cognitive dysfunction and the neuropsychiatric symptoms. On the other hand, Sweet et al. (2004) reviewed that SLE even inactive or without manifestation of neuropsychiatric involvement commonly involve neurocognitive functions.

**Conclusion:**

Cognitive function of SLE patients showed a significant impairment compared with normal people. Disease activity, antiphospholipid antibodies, quality of life and CNS manifestations of SLE patients were associated with impairment in cognitive functions. Evaluation of cognitive function, improving of disease activity and quality of life should be given greater emphasis in SLE patients especially in the presence of antiphospholipid antibodies and CNS manifestations.

**REFERENCES**


دراسة الوظائف المعترفة لدى مرضى الذنبة الحمراء

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الهدف من البحث: هو دراسة الوظائف المعترفة لدى مرضى الذنبة الحمراء وكذلك تحري العلاقة بالסיכرومات المرخصة مع وجود مضادات الكاردوبيتين في الدم ونوعية الحياة.

الطريقة: وقد أُجري هذا البحث على 20 مريض مصاب بالذنبة الحمراء و20 من الأصحاء كمجموعة ضابطة وقد تم أخذ التاريخ المرضي وكذلك الفحص الخلقي والعملي لجميع المرضى وقياس درجة نشاط المرض وتقدير نوعية الحياة وقياس مضادات الكاردوبيتين في الدم مع عمل اختبار "ستانفورد بينية" للذكاء النسخة الرابعة لقياس الوظائف المعترفة الآلية.

النتائج: وقد أظهرت نتائج هذا البحث انخفاض ذا إحصائيات في جميع الوظائف المعترفة لدى مرضى الذنبة الحمراء مقارنة بالجموعة الضابطة كما وجدت علاقة سلبية ذات دلالة إحصائية بين الوظائف المعترفة ودرجة نشاط المرض مع وجود مضادات الكاردوبيتين في الدم مع وجود أعراض تؤثر في الجهاز العصبي المركزي كما وجدت علاقة إيجابية ذات دلالة إحصائية بين الوظائف المعترفة ونوعية الحياة لدى مرضى الذنبة الحمراء.

الاستنتاج: أن مرضى الذنبة الحمراء له تأثير سلبي على الوظائف المعترفة وهذا التأثير السلبي يزيد مع زيادة نشاط المرض وسوء نوعية الحياة مما نتصح بالآلي لتجنب الأضطرابات المعترفة لدى مرضى الذنبة الحمراء:

1. السيطرة على نشاط المرض
2. تحسين نوعية الحياة للمرضي

خاصة في المرضى الذين لديهم أعراض تؤثر في الجهاز العصبي المركزي مع وجود مضادات الكاردوبيتين في الدم.