Depression and Cognitive Impairment in Newly Diagnosed Systemic Lupus Erythematosus

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ABSTRACT. Objective. Cognitive impairment is present in 80% of patients with systemic lupus erythematosus (SLE) 10 years after diagnosis. The natural history of cognitive dysfunction in newly diagnosed SLE is unknown. We examined the association of depression and cognitive performance in newly diagnosed SLE.

Methods. A multicenter cohort of 111 patients newly diagnosed (within 9 months) with SLE underwent cognitive function testing using an automated battery [Automated Neuropsychological Assessment Metrics (ANAM)] with 9 subtests. Depression was measured using the Calgary Depression Scale (CDS).

Results. The patient cohort was 97.3% female, 55.9% white, 15.3% African American, 20.7% Hispanic, mean age 37.8 years, mean education 15.2 years. CDS score ranged from 0 to 18 (mean 5.0 ± 4.6). CDS score did not differ by age, sex, ethnicity, or prednisone dose. Higher Krupp Fatigue Severity Scale scores and presence of fibromyalgia were significantly associated with higher CDS score (p < 0.001; p = 0.006, respectively). Depressed patients, defined by a CDS score > 6, had significantly poorer performance on 5 ANAM throughput measures: code substitution (p = 0.03), continuous performance (p = 0.02), matching-to-sample (p = 0.04), simple reaction time (p = 0.02), and the Sternberg memory test (p = 0.04). Adjusting for age, sex, ethnicity, education, and prednisone dose, a higher CDS score remained significantly associated with poorer performance on 3 measures, but the association was slightly attenuated for code substitution and matching-to-sample. Depression was not associated with mathematical or spatial processing.

Conclusion. Depression, a modifiable risk factor, is associated with significantly poorer function in several cognitive domains in patients newly diagnosed with SLE. Treatment of depression when the CDS score is greater than 6 may improve cognitive functioning and should be further studied.

Key Indexing Terms: SYSTEMIC LUPUS ERYTHEMATOUS AUTOMATED NEUROPSYCHOLOGICAL ASSESSMENT METRICS DEPRESSION

Depression is the most frequent psychiatric manifestation in patients with systemic lupus erythematosus (SLE)1,2,3,4,5,6. Depression in patients with SLE could be due to an immune-mediated brain dysfunction, a reaction to having a chronic disease, or both. Regardless of the cause, depression has been associated with cognitive dysfunction in SLE7,8,9,10,11,12 and in normal, otherwise healthy populations13. Because cognitive dysfunction is an important and common neuropsychiatric manifestation of SLE4,11,14, defining the role of depression is important in understanding the pathophysiology of SLE-related cognitive dysfunction and for developing treatment strategies.

The magnitude of the contribution of depression to poorer cognitive functioning in SLE varies among studies performed to date. Monastero and colleagues found that patients with SLE who have neuropsychiatric (NP) SLE manifestations were significantly more anxious and depressed than patients who did not have NP manifestations7. In multivariate analyses, depression was the only clinical variable associated with cognitive dysfunction. Our group has previously shown that age, education, and depression were all strong predictors of cognitive dysfunction in patients with established SLE11. Kozora and colleagues
found that, while depression was a common finding in patients with SLE, the magnitude and pattern of cognitive dysfunction could not be explained by depression alone. Further, depressed patients with SLE had significantly worse cognitive functioning than a matched, otherwise healthy control group with depression. Only patients with SLE who had longstanding disease duration have been studied to date. Therefore little is known about the prevalence of depression, or its association with cognitive function in patients newly diagnosed with SLE.

Brain CONECTIONS (Brain Imaging and Cognitive Function in SLE) is a multicenter study funded by the US National Institutes of Health to evaluate changes in cognitive function and brain imaging (structural magnetic resonance imaging and fluorodeoxyglucose positron emission tomography) over time in an SLE inception cohort. The Brain CONECTIONS study used Automated Neuropsychological Assessment Metrics (ANAM)15, a repeatable, computerized cognitive battery, at the study visit. The Calgary Depression Scale (CDS) was used to assess depression. The CDS has been shown to be particularly useful for populations with chronic medical diseases because many somatic symptoms that may overlap with depression have been removed. We report on the association of depression, measured by CDS, with cognitive performance in patients newly diagnosed with SLE, at the baseline visit.

MATERIALS AND METHODS

Patients. Patients with SLE, meeting 4 or more American College of Rheumatology (ACR) revised classification criteria, who had been diagnosed within the previous 9 months, were enrolled in the Brain CONECTIONS study. The Johns Hopkins University School of Medicine in Baltimore, MD, the University of Texas Health Science Center in San Antonio, TX, and Cedars-Sinai Medical Center in Los Angeles, CA, were the 3 patient recruiting sites. Institutional Review Board approval was obtained at each site. Informed consent was obtained from all patients.

Controls. Forty-nine controls, selected for the absence of psychiatric, neurologic, or rheumatic diseases, were enrolled. Exclusion criteria for the controls included prior experience with the ANAM test, history of head trauma leading to loss of consciousness, current illicit drug or alcohol abuse, known structural brain lesions, inability to complete study followup or inability to give informed consent. In addition, controls were excluded if they had clinical or laboratory abnormalities that could be consistent with the diagnosis of SLE.

Automated Neuropsychological Assessment Metrics. ANAM is a set of computer-administered neuropsychological tests selected from a larger battery of performance tests developed by the US Department of Defense15 and designed specifically for repeated measures applications so that scores stabilize after a few practice administrations. ANAM tests selected for this study included simple reaction time, continuous performance (vigilance/sustained attention), code substitution (visual scanning and learning) with immediate and delayed memory (nonverbal memory), simultaneous spatial processing (visual perception and mental rotation), Sternberg memory (sustained attention/working memory), mathematical processing (simple mental arithmetic), and matching to sample (visuospatial perception and working memory) tests. Practice items preceded each test to ensure understanding of instructions and to stabilize scores. All ANAM tests used the standard mouse buttons for responding, decreasing reaction time artifact from unfamiliarity with the computer keyboard or problems with joint mobility.

The battery was administered in a single session, in a fixed order, and took about 20–30 min. ANAM was administered on standard PC or laptop computers using the Windows 2000 operating system.

Five measures were computer-scored for each ANAM test: lapses for failure to answer during the allotted response window, median reaction time for correct responses, accuracy as the percentage of correct responses, SD of reaction time, and throughput as the number of correct responses per minute. Because throughput is the combination of lapses, reaction time, accuracy, and consistency, it was used as the primary measure of cognitive processing efficiency in the analyses. The remaining ANAM measures help to understand the throughput scores; e.g., whether low efficiency is caused by slowed reaction time without many errors versus very quick reaction times, but with many errors.

Calgary Depression Scale. The CDS was developed primarily to assess depression in individuals who may be concurrently experiencing psychotic symptoms. This was the first scale specifically designed and validated for the evaluation of depressive symptoms in patients with schizophrenia16. It is a semistructured interview based on self-report and examiner observations. The CDS was derived from the Hamilton Depression Rating Scale15 and Present State Examination using factor analytic techniques to arrive at a scale focusing on the cognitive aspects of depression. CDS was found to be monodimensional, indicated by exploratory factor analysis17. Compared to the Hamilton Depression Scale, CDS has fewer factors and less overlap with positive and negative symptoms22–24. The extraction of the somatic items makes this scale an excellent tool for assessing depression in a chronically ill population. It assesses the symptoms of depression at any stage of disease. Further reliability and validity were established using confirmatory factor and discriminatory analysis. Convergent validity was demonstrated in comparison to the Beck Depression Scale, a widely used self-report measure of depression16.

The CDS is a 9-item scale that rates the symptoms of depression, hopelessness, self-depreciation, guilty ideas of reference, pathological guilt, morning depression, early awakening, suicide, and observed depression. Each item is scored by a trained interviewer on a 0–3 scale: absent (0), mild (1), moderate (2), and severe (3). Each is anchored with behavioral descriptions of the symptom in question. The total score is obtained by adding each of the item scores. A CDS score above 6 has 82% specificity and 85% sensitivity for predicting the presence of a major depressive episode.

Clinical data. The SELENA (Safety of Estrogens in Lupus Erythematosus: National Assessment) revision of the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) was used to assess SLE disease activity25. It is an internationally developed instrument to measure disease activity and consists of 24 descriptors with preassigned severity weights. The range of possible scores is 0 (no disease activity) to 105. The Systemic Lupus International Collaborating Clinics (SLICC) Damage Index26 quantified irreversible changes in organ function that had been present for at least 6 months. All medications were recorded, including prednisone, hydroxychloroquine, and immunosuppressant doses.

Fibromyalgia (FM) was assessed by the presence of FM tender points and chronic pain. Tender points were assessed over predefined tender point sites (bilateral occiput, low cervical, trapezius, second ribs, supraspinatus, lateral epicondyles, gluteal, greater trochanters, and medial fat pad of the knees), with the application of 4 kg uniform thumb pressure27. Painful palpation was the indicator to consider a tender point.

Fatigue was assessed using the Krupp Fatigue Severity Score, a 9-item questionnaire in which each item was scored from 1 (“strongly disagree”) to 7 (“strongly agree”). The final score was calculated by taking the mean of the 9 items. A higher score indicates greater fatigue28.

The ACR nomenclature for 19 NPSLE syndromes was completed by a study physician.

Laboratory tests performed at baseline included complete blood count, creatinine, urine protein, urine red blood cells, urine white blood cells, anti-dsDNA, and complement (C3, C4). Antiphospholipid assays were
done, including antcardiolipin (IgG, IgM, and IgA) and the lupus anticoagulant (by modified Russell’s viper venom test). Anti-NR2 (N-methyl-D-aspartate receptor) glutamate receptor assays were also performed, by Dr. Betty Diamond at Columbia University31.

Statistical considerations. Demographic and clinical characteristics were summarized using appropriate descriptive statistics. Categorical data were summarized with frequencies and percentages and continuous data with means and SD. Depression was analyzed as a continuous variable and dichotomized into “not depressed” and “depressed” based on the cutoff point of greater than 6 on the CDS. Demographic and clinical characteristics as well as ANAM throughput scores were compared across depression groups using Fisher’s exact tests or 2-sample t-tests. Multiple linear regression analysis was used to examine the association of CDS score on ANAM throughput scores, while adjusting for other factors (age, sex, ethnicity, education, and prednisone use) that may be related to cognitive performance. Analysis was performed using SAS version 9.1.3 (SAS Institute Inc., Cary, NC, USA). All reported p values are 2-sided, and p < 0.05 was considered significant.

RESULTS

Between March 2003 and December 2004, 111 patients with SLE were enrolled. The demographic and clinical characteristics for all patients are reported in Table 1. Only 24.3% of patients had 1 or more ACR neuropsychiatric case definitions, which included headache (8.1%), mood disorder (8.1%), anxiety disorder (5.4%), cognitive dysfunction (5.4%), seizures and seizure disorder (3.6%), cerebrovascular disease (2.7%), psychosis (2.7%), polyneuropathy (1.8%), and mononeuropathy and cranial neuropathy (0.9% each). No patients had Guillain-Barré syndrome, aseptic meningitis, autonomic disorder, demyelinating syndrome, movement disorder, myasthenia gravis, myelopathy, plexopathy, or acute confusional state.

The CDS total score ranged from 0 to 18 (mean 5.0 ± 4.6), with a higher score indicative of greater depression. The prevalences of the individual depressive symptoms from the CDS are presented in Table 2. Depressed mood and early morning awakening were the most prevalent symptoms, occurring in more than half of the patients. Of the 111 patients, 35 (31.5%) had CDS scores > 6 and were classified as depressed.

The association of depression with other patient characteristics is reported in Table 3. Depressed patients had a higher Krupp Fatigue Severity Score (p < 0.001) and were more likely to have FM (p = 0.006) and mood disorder (p = 0.03). The depressed patients did not significantly differ from the patients without depression on demographic characteristics of sex, ethnicity, and age, or on clinical characteristics of prednisone use, SELENA SLEDAI, or SLICC damage index. There was no association of depression with anti-NR2 titer abnormality. Anti-NR2 titer was abnormal in 23% of depressed patients and 18% of nondepressed patients.

The ANAM throughput scores by depression group are reported in Table 4. The depressed groups exhibited statistically significant lower throughput scores on 5 of the ANAM subtests: code substitution, continuous performance, matching-to-sample, simple reaction time, and the Sternberg memory test. After adjustment for factors that may be associated with cognitive performance (age, sex, ethnicity, education, and prednisone dose), a higher CDS score (more depression) was significantly associated with poorer performance on 3 of these ANAM throughput measures: continuous performance, simple reaction time, and the Sternberg memory test. The association was attenuated for the other 2 ANAM measures. Depression was not associated with poorer performance on tests of mathematical processing and spatial processing. After adjustment for FM, the association remained for matching to sample (p = 0.04) and simple reaction time (p = 0.003), and was borderline for code substitution (p = 0.062), continuous performance (p = 0.074), and Sternberg memory (p = 0.076).

The controls were 59% women and 41% men, mean ± SD age 42.7 ± 15.1 years, and education 14.9 ± 3.0 years. They were 47% white, 39% African American, 12% Hispanic, and 2% other ethnicities. Of the 49 controls, 6 (12%) had CDS scores > 6 and were classified as depressed. The comparison between 35 depressed patients with SLE and 6 depressed controls is presented in Table 5. We did not find any significant differences between the 2 groups.

DISCUSSION

Depression was present in 31% of our cohort of patients newly diagnosed with SLE. This prevalence is similar to that found in SLE cohorts of longer disease duration32. We found a significant association of depression with vigilance and sustained attention, visual scanning and learning, simple reaction time, and working memory in our newly diagnosed cohort, similar to findings in patients with established

Table 1. Demographic and clinical characteristics of the 111 patients with SLE.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. Patients (%)</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>37.8 ± 12.2</td>
<td></td>
</tr>
<tr>
<td>Sex (men)</td>
<td>3 (2.7)</td>
<td></td>
</tr>
<tr>
<td>Education, yrs</td>
<td>15.2 ± 2.8</td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White non-Hispanic</td>
<td>62 (55.9)</td>
<td></td>
</tr>
<tr>
<td>African American non-Hispanic</td>
<td>17 (15.3)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>23 (20.7)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>5 (4.5)</td>
<td></td>
</tr>
<tr>
<td>Native American</td>
<td>2 (1.8)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2 (1.8)</td>
<td></td>
</tr>
<tr>
<td>SELENA SLEDAI</td>
<td>3.9 ± 4.6</td>
<td></td>
</tr>
<tr>
<td>SLICC damage index</td>
<td>0.7 ± 1.2</td>
<td></td>
</tr>
<tr>
<td>Calgary Depression Scale</td>
<td>5.0 ± 4.6</td>
<td></td>
</tr>
<tr>
<td>Krupp Fatigue Severity Scale</td>
<td>4.7 ± 1.7</td>
<td></td>
</tr>
<tr>
<td>Taking prednisone</td>
<td>46 (41.4)</td>
<td></td>
</tr>
<tr>
<td>Prednisone dose (mg), if taking</td>
<td>22.0 ± 15.7</td>
<td></td>
</tr>
<tr>
<td>NR2 titer abnormal</td>
<td>18 (20.0)</td>
<td></td>
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Intervention trials of antidepressants for a CDS > 6 are clearly indicated in depressed patients with SLE who have cognitive impairment. No study of depression in SLE has targeted patients newly diagnosed with SLE. Our past study of 349 patients, for example, found depression to be associated with...
seizures, psychosis, aseptic meningitis, and encephalopathy. Our current study of patients newly diagnosed with SLE, in contrast, included only 24% with 1 or more ACR neuropsychiatric case definitions.

The cause of cognitive dysfunction in patients with SLE is not clear. However, the effects of disease mechanisms on the central nervous system and indirect effects through fatigue or psychiatric disturbances are suspected. Our study demonstrates that depression is associated with significantly poorer cognitive function in several cognitive domains in newly diagnosed patients with SLE. Depression has been associated with structural brain damage in areas related to mood regulation, including the hippocampus, amygdala, basal ganglia, and frontal cortex. Neuronal damage caused by SLE disease activity might lead to depression. In a case-control study of 62 unselected patients with SLE and 62 age-matched and sex-matched healthy participants, Harboe and colleagues found an association between increased cerebral white matter hyperintensities and increased fatigue, a commonly reported symptom in depressed patients.

Depression is an important confounder in studies of cognitive dysfunction. However, it is possible that depression and cognitive impairment are actually linked by the same underlying pathophysiological process. For example, cognitive dysfunction may persist after depression is successfully treated, suggesting that the same process that leads to depression could have adverse and persistent effects in brain regions subserving cognition. A genetic vulnerability to depression, cognitive dysfunction, and vascular disease has been identified and is associated with genes involved in inflammation and the serotonin system, supporting a pathophysiological relationship among these clinical manifestations.

<table>
<thead>
<tr>
<th>ANAM Measure</th>
<th>Not Depressed, n = 76</th>
<th>Depressed, n = 35</th>
<th>p*</th>
<th>CDS Coefficient**</th>
<th>p***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coding delayed recall</td>
<td>33.7 ± 13.6</td>
<td>29.4 ± 11.2</td>
<td>0.11</td>
<td>-0.34</td>
<td>0.20</td>
</tr>
<tr>
<td>Coding immediate recall</td>
<td>33.1 ± 12.8</td>
<td>28.4 ± 12.7</td>
<td>0.08</td>
<td>-0.33</td>
<td>0.22</td>
</tr>
<tr>
<td>Code substitution</td>
<td>42.7 ± 10.6</td>
<td>38.1 ± 9.8</td>
<td>0.03</td>
<td>-0.37</td>
<td>0.07</td>
</tr>
<tr>
<td>Continuous performance</td>
<td>80.6 ± 15.2</td>
<td>73.0 ± 18.8</td>
<td>0.02</td>
<td>-0.61</td>
<td>0.05</td>
</tr>
<tr>
<td>Matching to sample</td>
<td>24.4 ± 8.3</td>
<td>21.1 ± 7.6</td>
<td>0.04</td>
<td>-0.28</td>
<td>0.10</td>
</tr>
<tr>
<td>Mathematical processing</td>
<td>17.3 ± 6.8</td>
<td>18.0 ± 9.9</td>
<td>0.72</td>
<td>0.11</td>
<td>0.47</td>
</tr>
<tr>
<td>Simultaneous spatial processing</td>
<td>18.4 ± 5.3</td>
<td>18.6 ± 11.6</td>
<td>0.93</td>
<td>0.08</td>
<td>0.64</td>
</tr>
<tr>
<td>Simple reaction time</td>
<td>194.7 ± 40.2</td>
<td>169.3 ± 53.9</td>
<td>0.02</td>
<td>-2.87</td>
<td>0.003</td>
</tr>
<tr>
<td>Sternberg memory test</td>
<td>65.6 ± 15.9</td>
<td>58.8 ± 16.2</td>
<td>0.04</td>
<td>-0.67</td>
<td>0.04</td>
</tr>
</tbody>
</table>

* From 2-sample t-tests comparing depression groups. ** The coefficient is the amount of change on the ANAM measure that is predicted by a 1-point increase on the CDS score. A negative estimate indicates that higher depression score is associated with poorer performance on the ANAM measure. *** Test of whether CDS coefficient from adjusted model is significantly different from zero (no association). ANAM: Automated Neuropsychological Assessment Metrics.

<table>
<thead>
<tr>
<th>ANAM Measure</th>
<th>Depressed SLE, n = 35</th>
<th>Depressed Controls, n = 6</th>
<th>p*</th>
<th>Mean Difference**</th>
<th>p***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coding delayed recall</td>
<td>29.4 ± 11.2</td>
<td>43.2 ± 26.5</td>
<td>0.26</td>
<td>-5.07</td>
<td>0.47</td>
</tr>
<tr>
<td>Coding immediate recall</td>
<td>28.4 ± 12.7</td>
<td>39.6 ± 21.1</td>
<td>0.08</td>
<td>-6.67</td>
<td>0.42</td>
</tr>
<tr>
<td>Code substitution</td>
<td>38.1 ± 9.8</td>
<td>41.7 ± 15.3</td>
<td>0.46</td>
<td>-3.71</td>
<td>0.55</td>
</tr>
<tr>
<td>Continuous performance</td>
<td>73.0 ± 18.8</td>
<td>81.1 ± 26.7</td>
<td>0.36</td>
<td>-10.17</td>
<td>0.39</td>
</tr>
<tr>
<td>Matching to sample</td>
<td>21.1 ± 7.6</td>
<td>19.2 ± 10.0</td>
<td>0.60</td>
<td>-1.14</td>
<td>0.83</td>
</tr>
<tr>
<td>Simultaneous spatial processing</td>
<td>18.6 ± 11.6</td>
<td>18.3 ± 9.2</td>
<td>0.95</td>
<td>1.73</td>
<td>0.81</td>
</tr>
<tr>
<td>Simple reaction time</td>
<td>169.3 ± 53.9</td>
<td>189.9 ± 26.7</td>
<td>0.37</td>
<td>-21.74</td>
<td>0.55</td>
</tr>
<tr>
<td>Sternberg memory test</td>
<td>58.8 ± 16.2</td>
<td>52.1 ± 11.3</td>
<td>0.34</td>
<td>7.97</td>
<td>0.47</td>
</tr>
</tbody>
</table>

* From 2-sample t-tests comparing depressed patients with SLE to depressed controls. ** The least-squares mean difference on the ANAM measure for the depressed patient with SLE compared to the depressed controls. A negative estimate indicates the patients with SLE performed more poorly than controls. *** From t-test of the least-squares mean estimate from adjusted model comparing depressed patients with SLE to depressed controls. ANAM: Automated Neuropsychological Assessment Metrics.
Some studies have suggested that depression in SLE might be related to disease activity. Our study, however, found no association with disease activity measured by SELENA SLEDAI. In a cross-sectional study of 60 patients with SLE who had inactive disease, Lapteva and colleagues found an association of depression with anti-NR2, but not with cognitive dysfunction. Depression was evaluated with the Beck Depression Inventory II and psychiatric interview. In contrast, we did not find any association between anti-NR2 and depression or cognitive dysfunction. Harrison and colleagues also did not find any significant association between NR2a antibody positivity and cognitive dysfunction.

Depression, fatigue, and cognitive impairment have been associated in several SLE studies. Kozora and colleagues, in a case-control study, reported higher levels of cognitive problems, depression, pain, and fatigue among patients with SLE than in controls. Hanly and colleagues, in an age-matched and sex-matched case-control study of 53 patients with SLE who had neuropsychiatric syndromes and 53 patients with rheumatoid arthritis who had neuropsychiatric syndromes, found more symptoms of depression and cognitive dysfunction among patients with SLE who had neuropsychiatric syndromes. Omdal and colleagues indicated fatigue to be a part of a complex response to chronic disease among 57 white patients with SLE. In our study, the Krupp Fatigue Inventory score and FM were significantly associated with higher depression score.

The cause of cognitive dysfunction in patients with SLE is not clear. However, the effects of disease mechanisms on the central nervous system and indirect effects through fatigue or psychiatric disturbances are suspected. This study demonstrates that depression is associated with significantly poorer cognitive function in several cognitive domains in newly diagnosed patients with SLE, as has also been shown in cohorts of longer disease duration.

Depression is common and is associated with significantly poorer cognitive function in patients newly diagnosed with SLE. Further studies should be directed toward investigating whether treatment of depression improves cognitive impairment, and exploring the neurologic mechanisms that explain the connection of depression and cognition in SLE.

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REFERENCES
23. Addington D, Addington J, Atkinson M. A psychometric