Cognitive Function in a Systemic Lupus Erythematosus Inception Cohort

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ABSTRACT. ***Objective.*** Measurable cognitive impairment occurs in 30–75% of patients with systemic lupus erythematosus (SLE). We compared cognitive functioning in recently-diagnosed SLE patients and normal controls.

Methods. The Automated Neuropsychological Assessment Metrics (ANAM), a repeatable computerized cognitive battery assessing cognitive processing speed and efficiency, was administered to 111 recently diagnosed SLE patients and 79 normal controls. Throughput scores on ANAM subtests were compared using linear regression.

Results. After adjusting for age, gender, ethnicity, and education, SLE patients scored significantly lower than controls on throughput measures of 4 ANAM subtests: code substitution immediate recall ($p = 0.02$), continuous performance ($p = 0.02$), matching to sample ($p = 0.02$), and Sternberg subtest ($p = 0.0002$).

Conclusions. Recently diagnosed SLE patients performed significantly worse than normal controls on 4 of 9 ANAM subtests. ANAM subtests of cognitive efficiency requiring sustained attention/vigilance, visuospatial span of attention/working memory, and simple reaction time showed the greatest impairment. These cognitive deficits were particularly striking, because the SLE patients in this sample were not selected for the presence of neuropsychiatric manifestations, had mild SLE-related disease/damage, and were recently diagnosed with SLE. This suggests that deficits in cognitive efficiency and sustained attention are present early in the course of SLE and in the absence of other significant neuropsychiatric manifestations. (First Release July 15 2008; J Rheumatol 2008;35:1776–81)

Key Indexing Terms:
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Patients with systemic lupus erythematosus (SLE) frequently report cognitive and memory problems[1]. Important cognitive deficits can be assessed with traditional neuropsychological test batteries[2-5]. Cognitive deficits in SLE have been reported in the areas of attention, cognitive flexibility, free recall memory, and speed of information processing. This pattern of impairment suggests the presence of a subcortical cognitive syndrome[2-6], sometimes reaching the severity range of dementia[5,7-11]. However, many traditional neuropsychological tests are unsuitable for repeated measures over short intervals because of expected improvement due to test-retest or practice effects. This is especially true for traditional tests of memory, motor speed, and novel problem solving[8]. These effects may reduce the sensitivity of the traditional tests to detect changes over time.

To address this challenge, the Brain CONECTIONS (Brain Imaging and Cognitive Function in SLE) study, a US National Institutes of Health funded observational study of cognitive functioning and brain imaging in newly diagnosed patients with SLE, has employed the Automated Neuropsychological Assessment Metrics (ANAM), a repeatable, computerized cognitive battery. ANAM was developed by the US military to assess the effects of chemical agents, extreme environments, and fatigue on cognitive functioning, especially complex attention, cognitive processing speed, and cognitive efficiency[10,11].

Bleiberg and colleagues found significant correlations

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between ANAM and analogous traditional neuropsychological tests in young normal subjects[12]. In SLE, the San Antonio Lupus Study of Neuropsychiatric Disease (SALUD) found that ANAM is strongly correlated with cognitive impairment as assessed by traditional neuropsychological tests, with ANAM accounting for over 60% of the variance in traditional neuropsychological tests[13]. ANAM was found to be less subject to ethnic differences than traditional neuropsychological tests. ANAM also added precise measures of cognitive efficiency and processing speed, which are not well assessed by traditional neuropsychological tests.

The Brain CONECTIONS study was conducted to assess cognitive function in recently-diagnosed SLE patients, and to determine whether cognitive performance was associated with clinical status. In our report, we detail the findings at the baseline visit of the study. We also report the comparison of recently-diagnosed SLE patients and controls.

MATERIALS AND METHODS

Patients with SLE meeting 4 or more American College of Rheumatology (ACR) revised criteria[14,15] and diagnosed within 9 months of enrollment were eligible for Brain CONECTIONS. Both male and female adults were enrolled. Pregnancy at the time of enrollment was an exclusion criterion. Patients were recruited from 3 major sites: Johns Hopkins University School of Medicine in Baltimore, University of Texas Health Science Center at San Antonio (UTHSC), and Cedars-Sinai in Los Angeles. Institutional review board approval was obtained at each site, and informed consent was obtained from all patients.

Seventy-nine controls, selected for the absence of psychiatric, neurologic, or rheumatic diseases were enrolled at the UTHSC. The normal control subjects were a convenience sample of friends and relatives of the SALUD patients and other community members selected for the absence of any active psychiatric, neurologic, or rheumatologic illness. Demographics of the SLE patients and the controls are summarized in Table 1.

The cohort of recently diagnosed SLE patients and the control subjects underwent baseline cognitive function testing using 9 subtests of the ANAM: Simple Reaction Time, Continuous Performance (vigilance/sustained attention), Code Substitution (visual scanning and learning) with Immediate and Delayed Memory (non-verbal memory), Simultaneous Spatial Processing (visual perception and mental rotation), Sternberg subtest (sustained attention/working memory), Mathematical Processing (simple mental arithmetic), and Matching to Sample Test (visuospatial perception and working memory).

Table 1. Demographic characteristics of patients and controls summarized as frequency (%) or mean ± standard deviation.

Characteristic	SLE patients, n = 111	Controls, n = 79	p*
Gender, male	3 (3)	26 (33)	< 0.0001
Age, yrs	38.0 ± 12.1	40.6 ± 15.4	0.23
Education, yrs	15.1 ± 2.7	14.6 ± 2.5	0.23
Ethnicity			
Caucasian	61 (55)	34 (43)	0.11
African American	17 (15)	2 (3)	0.004
Hispanic	23 (21)	43 (54)	< 0.0001
Asian	6 (5)	0 (0)	0.04
Other	4 (4)	0 (0)	0.14

* p value from chi-square test for categorical data and 2-sample t-test for continuous data.

Practice items preceded each ANAM subtest to ensure understanding of instructions and to stabilize scores. All ANAM tests used the 2 standard mouse buttons for responding, decreasing reaction time artifact from unfamiliarity with the computer keyboard or problems with joint mobility. The test battery was administered at a single session, in a fixed order, and took about 20–30 minutes to complete.

Each ANAM test was computer scored for 5 measures: "Lapses" for failure to answer during the allotted response window, "Median Reaction Time" for correct responses, "Accuracy" as the percentage of correct responses, "Standard Deviation of Reaction Time", and "Throughput" as the number of correct responses per minute. Since throughput combines lapses, reaction time, accuracy, and consistency, it was used as the primary measure of cognitive processing efficiency in the analyses. Typically, the other ANAM measures were used only to better understand throughput scores: such as whether low efficiency was caused by slowed reaction time without many errors, versus very quick reaction times but with many errors. ANAM test scores were examined individually by subtest.

Clinical characteristics of the SLE patients were assessed at the baseline visit. Disease activity was assessed using the physician's global assessment and the SELENA Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)[16]. The Calgary depression scale, fibromyalgia tender points, Krupp fatigue severity scale, Medical Outcome Study Short Form, Brief Symptom Inventory, and ACR Neuropsychiatric Systemic Lupus Erythematosus (ACR NP-SLE) case definitions[9] were completed. Pain was not recorded; however, only 2 patients were taking narcotic pain medications. The Systemic Lupus Erythematosus International Collaborating Clinics (SLICC) Damage Index was also completed at baseline[17]. All medications were recorded. Laboratory testing included anticardiolipin antibody and the lupus anticoagulant.

Statistical considerations. Patient demographic and clinical characteristics were summarized using appropriate descriptive statistics. Categorical data were summarized with frequencies and percentages, and patients were compared to controls using the chi-square test of proportions. Continuous data were tested for normality, and normally distributed data were summarized with means and standard deviations (SD), and groups were compared using the 2-sample t-test. Data that were not normally distributed were summarized with medians and ranges. Group differences on the ANAM throughput measures were assessed after adjusting for factors known to be associated with cognitive performance (i.e., age, gender, education, and ethnicity). Clinical characteristics as predictors for performance on ANAM measures were assessed in a similar manner.

Analyses were performed using SAS Version 9.1.3 (SAS Institute, Cary, NC, USA). All tests were 2-sided, and significance was set at $p < 0.05$, except for the tests of association of clinical characteristics with ANAM performance for the SLE patients, where a more stringent significance level of $p < 0.01$ was set because of the large number of comparisons.

RESULTS

Between March 2003 and December 2004, 111 SLE patients (60 at Johns Hopkins, 20 at UTHSC, and 31 at Cedars-Sinai) were enrolled. Seventy-nine controls were enrolled at the UTHSC. Demographic characteristics of the 2 groups are compared in Table 1. A greater proportion of the SLE group was female ($p < 0.0001$), African-American ($p = 0.004$), and Asian ($p = 0.04$) versus the control group, and a smaller proportion were Hispanic ($p < 0.0001$).

Clinical characteristics of the SLE patients are summarized in Table 2, and results of laboratory assays, in Table 3. The SLE patients exhibited mild to moderate disease activity on the SELENA SLEDAI. The mean SLICC damage

Table 2. Clinical characteristics of the SLE patients at baseline.

Characteristic	n (%) or Mean ± SD (range)
SELENA SLEDAI	3.9 ± 4.4 (0–28)
SLICC damage score	0.6 ± 1.1 (0–4)
Krupp total score	4.7 ± 1.7 (1–7)
Calgary depression score	4.9 ± 4.5 (0–18)
ACR criteria	
Malar rash	43 (38.7)
Discoid rash	19 (17.1)
Photosensitivity	65 (59.1)
Oral ulcers	55 (49.6)
Arthritis	75 (67.6)
Serositis	25 (22.5)
Renal disorder	14 (12.6)
Neurological disorder	7 (6.3)
Hematological disorder	37 (33.6)
Immunologic disorder	68 (61.8)
ANA abnormal	107 (96.4)
SLE treatments:	
Prednisone	47 (42.3)
Methylprednisolone	2 (1.8)
Hydroxychloroquine	72 (64.9)
Nonsteroidal antiinflammatory drugs	19 (17.1)
Aspirin	13 (11.7)
Methotrexate	8 (7.2)
Azathioprine	10 (9.0)
Mycophenolate mofetil	6 (5.4)
Cyclophosphamide	4 (3.6)
IV methylprednisolone pulse	3 (2.7)

Table 3. Laboratory assays for the SLE patients at baseline.

Characteristic	n (%)
Elevated serum creatinine	5 (4.7)
Proteinuria	24 (24.0)
Low C3	13 (13.0)
Low C4	17 (17.2)
Positive anti-dsDNA	41 (43.2)
Lupus anticoagulant	5 (10.6)
Positive Anticardiolipin IgG	2 (2.2)
Positive Anticardiolipin IgM	33 (36.3)

score was low at 0.6 ± 1.1 (range: 0–4). Forty-two percent were taking prednisone. Ten percent of the patients had the lupus anticoagulant.

The frequency and percentage of patients with an NP-SLE syndrome as defined by the ACR case definitions are presented in Table 4. Most of the ACR NP-SLE events were headache, anxiety, and mood disorder, and were not attributed to SLE. Only 4 ACR NP-SLE events (2 polyneuropathy, 1 seizure, 1 headache) were attributed to SLE.

Baseline ANAM throughput scores for SLE patients were compared to controls (Table 5). After adjusting for age, gender, ethnicity, and education, SLE patients scored significantly lower than controls on 4 ANAM subtests: code substitution immediate recall (p = 0.02), continuous performance (p = 0.02), matching to sample (p = 0.02), and Sternberg subtest (p = 0.0002).

Table 4. Frequency and percentage of SLE patients with each American College of Rheumatology neuropsychiatric systemic lupus erythematosus (ACR NP-SLE) syndrome[9].

NP-SLE Syndrome	n (%) positive
1. Guillain-Barré syndrome	1 (0.9)
2. Aseptic meningitis	1 (0.9)
3. Autonomic disorder	1 (0.9)
4. Cerebrovascular disease	4 (3.6)
5. Demyelinating syndrome	1 (0.9)
6. Headache	10 (9.0)
7. Mononeuropathy	2 (1.8)
8. Movement disorder	1 (0.9)
9. Myasthenia gravis	1 (0.9)
10. Myelopathy	1 (0.9)
11. Neuropathy, cranial	2 (1.8)
12. Plexopathy	1 (0.9)
13. Polyneuropathy	2 (1.8)
14. Seizures and seizure disorder	5 (4.5)
15. Acute confusional state	1 (0.9)
16. Anxiety disorder	7 (6.3)
17. Cognitive dysfunction	6 (5.4)
18. Mood disorder	6 (5.4)
19. Psychosis	3 (2.7)

Table 5. Mean (standard deviation) of Automated Neuropsychological Assessment Metrics (ANAM) throughput measures for SLE patients at the baseline visit, and for normal controls.

ANAM Measure	SLE n = 111	Controls n = 79	p*
Coding delayed memory	32.2 (12.9)	33.6 (16.2)	0.17
Coding immediate memory	31.7 (12.9)	35.5 (16.6)	0.02
Code substitution	41.4 (10.6)	41.1 (10.7)	0.33
Continuous performance	78.4 (17.0)	84.0 (19.4)	0.02
Matching to sample	23.8 (8.7)	26.1 (9.4)	0.02
Mathematical processing	17.7 (8.0)	18.3 (5.9)	0.64
Simultaneous spatial processing	18.8 (8.0)	20.1 (6.2)	0.15
Simple reaction time	187.6 (46.8)	202.0 (39.7)	0.09
Sternberg subtest	64.0 (16.6)	71.0 (18.1)	0.0002

* p value adjusted for age, gender, ethnicity, and education.

The number of SLE patients that scored at least 2 SD below the controls on each ANAM measure ranged from 0 (0%) on the code substitution tests to 12 (10.8%) on simple reaction time (Table 6). Forty-three (38.7%) of the SLE patients did not score at least one SD and 90 (81.1%) did not score at least 2 SD below the controls on any of the 9 ANAM subtests.

To assess whether there were site differences for the ANAM throughput measures, the SLE patients were compared across sites, after adjusting for age, education, and ethnicity. Eight of the 9 throughput measures did not significantly differ by site. Only the simple reaction time subtest

Table 6. Frequency (percentage) of all SLE patients in the study (n = 111) that performed more poorly than the normal control population on each of the Automated Neuropsychological Assessment Metrics (ANAM) throughput measures at baseline. Forty-three (38.7%) patients did not score ≥ 1 SD below the controls and 90 (81.1%) did not score ≥ 2 SD below the controls on any ANAM measure.

ANAM Measure	≥ 1 SD below control mean	≥ 2 SD below control mean
Code substitution, delayed memory	11 (9.9)	0 (0)
Code substitution, immediate memory	18 (16.2)	0 (0)
Code substitution	18 (16.2)	0 (0)
Continuous performance test	20 (18.0)	4 (3.6)
Matching to sample	22 (19.8)	2 (1.8)
Mathematical processing	26 (23.4)	5 (4.5)
Simultaneous spatial processing	25 (22.5)	4 (3.6)
Simple reaction time	29 (26.3)	12 (10.8)
Sternberg subtest	26 (23.4)	3 (2.7)

differed across sites. This difference in performance was attributed to the Cedars-Sinai patients performing significantly better than the other 2 sites ($p = 0.02$). There was no difference ($p = 0.74$) in performance on the subtest between the Texas patients and the Johns Hopkins patients.

In a subset analysis, SLE patients from the UTHSC site (n = 20) were compared to the controls (all from the UTHSC site) on age, education, ethnicity, gender, and ANAM throughput scores. For the demographic characteristics, only gender differed between the groups (33% of controls were male vs 0% of SLE patients, Fisher's exact test: $p = 0.001$). Although gender was not significant in multiple regression analysis of any of the ANAM throughput scores, we left it in the model along with age, education, and ethnicity. Power was limited for this subset analysis because there were only 20 SLE patients from the UTHSC site. The UTHSC SLE patients performed more poorly than controls on all throughput measures except for spatial processing, although only simple reaction time was significant ($p = 0.01$).

The patient sample was then analyzed to look for associations of clinical characteristics and cognitive performance. Patients with higher scores on the SLICC damage scale and the Calgary depression scale exhibited poorer performance on the spatial recognition test. Higher scores on the SLICC damage scale were associated with poorer performance on the continuous performance test. A higher erythrocyte sedimentation rate was associated with poorer performance on matching to sample. All of these associations were significant at $p < 0.01$ and adjusted for age, ethnicity, gender, and education. No significant associations with cognitive performance were found for any SLE medications, or other laboratory measures, including anti-dsDNA, low complement, and antiphospholipid antibodies.

DISCUSSION

Brain CONECTIONS is the first multicenter study of cognitive function in recently diagnosed SLE patients. The comparison between the newly diagnosed SLE patients at baseline and the controls demonstrates that recently diagnosed SLE patients performed significantly worse on throughput measures from 4 of the 9 ANAM subtests. These cognitive deficits are particularly striking, because the SLE patients in this sample were not selected for the presence of neuropsychiatric manifestations, had mild SLE-related disease/damage, and were recently diagnosed with SLE. This suggests that deficits in cognitive efficiency and sustained attention are present early in the course of SLE and in the absence of other significant neuropsychiatric manifestations. Before our study, reports of cognitive impairment in SLE were limited to patients with established disease or those selected for neuropsychiatric involvement[7,13,18-23].

Previous studies of cognitive impairment in SLE have suggested that persistence of antiphospholipid antibodies was associated with cognitive impairment[3,24,25,26]. For example, cognitive dysfunction was 2 to 3 times more prevalent in SLE patients positive for antiphospholipid antibodies versus those who were negative[3]. It is possible that other processes may be important in the development of early cognitive impairment, whereas persistently positive antiphospholipid antibodies play a greater role later in the disease course.

The newly-diagnosed SLE patients scored significantly lower than the controls for 4 ANAM subtests: code substitution immediate recall subtest (measuring non-verbal memory), continuous performance subtest (measuring vigilance/sustained attention), matching to sample subtest (measuring visuospatial perception and working memory), and Sternberg subtest (measuring sustained attention and working memory). Previous studies in SLE patients suggested that verbal memory and psychomotor speed explained the neuropsychiatric symptoms seen in SLE patients, whereas frontal lobe function remained intact[27]. In some studies[3,28], decreased verbal memory and decreased psychomotor speed were associated with cognitive dysfunction. Work done using magnetoencephalography to assess the role of brain oscillations in the frontal lobe in memory tasks suggests that the Sternberg subtest used in our study is an important measure of memory retention[29]. This suggests a physiological basis for our finding of an association between both sustained attention and working memory with frontal lobe involvement[29].

Cognitive impairment was not associated with corticosteroid use. This finding was consistent with previous studies that showed prednisone use was not associated with cognitive dysfunction in established SLE[2,7,30-32]. On the other hand, a non-lupus clinical study found that preterm infants exposed to corticosteroids suffered cognitive impairment in childhood[33]. In animal models, corticosteroids were observed to damage memory centers, such as the hippocampus. In the hippocampus of rats, corticosteroid hormones were shown to reduce the length of dendrites and the num-

ber of branch points[34,35]. Corticosteroids cause dendritic atrophy of pyramidal neurons in the hippocampus of adult male Sprague-Dawley rats[36]. CA3 and CA4 hippocampal neurons were lost as a result[37]. That our study suggests that cognitive impairment early in patients with SLE is not related to medication is perhaps due to the lower cumulative corticosteroid exposures.

There are a few limitations to our study, mostly attributed to the ANAM control data. The ANAM test was developed and validated by the US Department of Defense, and therefore most of the published normative data are for young men. Our study was not funded to enroll controls, so we used the control data from the SALUD study[13]. Because the control participants were all enrolled at the UTHSC site, we were unable to adjust for site effects in the primary analyses comparing SLE patients to controls. To address this, we compared the SLE patients across sites and compared the UTHSC SLE patients to the controls. Only one ANAM subtest differed by site. We have no explanation as to why the Cedars-Sinai patients performed significantly better on simple reaction time, but if there was a true site difference, then the comparison to controls from UTHSC would be more conservative than if controls from Cedars-Sinai were also included. Because the patients' performance on ANAM throughput measures was similar across sites, the comparison of the UTHSC SLE patients to controls resulted in similar differences in throughput scores, although there was reduced power to observe significance. Additionally, our analyses were adjusted for age, education, ethnicity, and gender.

In conclusion, patients with SLE at or near the time of diagnosis differed from controls in cognitive functioning in multiple areas. No clinical, laboratory, or treatment variable assessed accounts for this early cognitive impairment. Recently-diagnosed SLE patients with mild SLE-related disease/damage had cognitive impairment even before significant neuropsychiatric manifestations. Followup of the Brain CONECTIONS cohort will allow further understanding of predictors of progression or improvement in cognitive functioning over time.

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