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Brain Magnetic Resonance Imaging in Newly Diagnosed Systemic Lupus Erythematosus

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Abstract

Objective—We wished to determine the prevalence of cerebral atrophy and focal lesions in a cohort of patients with newly diagnosed systemic lupus erythematosus (SLE) and the association of these brain abnormalities with clinical characteristics.

Methods—A total of 97 patients with SLE, within 9 months of diagnosis, with 4 or more American College of Rheumatology classification criteria, were enrolled. Brain magnetic resonance imaging was performed.

Results—The patients were 97% female, mean age 38.1 (SD 12.2) years, education 15.1 (2.8) years; 59 Caucasian, 11 African American, 19 Hispanic, 5 Asian, and 3 other ethnicity. Cerebral atrophy was prevalent in 18% (95% CI 11%–27%): mild in 12%, moderate in 5%. Focal lesions were prevalent in 8% (95% CI 4%–16%): mild in 2%, moderate in 5%, severe in 1%. Patients with cerebral atrophy were more likely to have anxiety disorder ($p = 0.04$). Patients with focal lesions were more likely to be African American ($p = 0.045$) and had higher Safety of Estrogens in Lupus Erythematosus National Assessment SLEDAI scores ($p = 0.02$) and anti-dsDNA ($p = 0.05$).

Conclusion—In this population with newly diagnosed SLE, brain abnormalities were prevalent in 25% of patients. These findings suggest that the brain may be affected extremely early in the course of SLE, even before the clinical diagnosis of SLE is made. Followup of these patients is planned, to determine the reversibility or progression of these abnormalities and their association with and potential predictive value for subsequent neuropsychiatric SLE manifestations.

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Key Indexing Terms

SYSTEMIC LUPUS ERYTHEMATOSUS; MAGNETIC RESONANCE IMAGING; CEREBRAL ATROPHY

Brain imaging is a powerful tool to noninvasively identify and differentiate the pathophysiological mechanisms responsible for neuropsychiatric systemic lupus erythematosus (NPSLE) syndromes. Anatomic magnetic resonance imaging (MRI) is a widely used brain imaging technique to study NPSLE syndromes.

Research using structural MRI in SLE patients with longstanding disease has found that small focal lesions concentrated in the periventricular and subcortical white matter are common in patients with NPSLE[1–4]. Multiple discrete white-matter lesions in the periventricular, cortical/subcortical junction, and frontal lobe regions are more common in patients with past NPSLE manifestations than in SLE patients without a history of NPSLE[1]. Multiple small periventricular and subcortical white-matter lesions seen by MRI also contribute to severe impairment in tests of strategic cognitive flexibility in patients with current and past NPSLE[5].

Cerebral atrophy has also been reported in SLE patients with longstanding disease duration, but the reported frequency of this abnormality is more variable[6–10]. Several groups have shown an association between cerebral atrophy and disease duration, antiphospholipid antibodies, and cognitive impairment[8,9]. The relationship between cerebral atrophy and other immunological markers, acute disease activity, corticosteroid use, and other chronic diseases such as hypertension is inconsistent[6,7,8,11].

To our knowledge, no study has evaluated brain MRI changes in a group of patients with newly diagnosed SLE. We investigated the relationship between baseline brain MRI findings and clinical and laboratory abnormalities in a multicenter inception SLE cohort.

MATERIALS AND METHODS

Patients

SLE patients meeting 4 or more American College of Rheumatology (ACR) revised classification criteria[12,13] who had been diagnosed within the previous 9 months were enrolled between March 2003 and December 2004. Patients were recruited from 3 sites: Johns Hopkins University School of Medicine in Baltimore, University of Texas Health Science Center in San Antonio, and Cedars-Sinai Hospital in Los Angeles. Institutional review board approval was obtained at each site. Informed consent was obtained from all patients.

Clinical data

Demographic information including age, sex, ethnicity, and education level was recorded. The ACR NPSLE case definitions were recorded[14]. Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), an internationally-derived instrument to measure disease activity, consisting of 24 descriptors (with preassigned severity weights) was utilized. The range of

possible scores is 0 (no disease activity) to 105 (maximum)[15]. We used the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) SLEDAI revision of the SLEDAI[16].

The Systemic Lupus International Collaborating Clinics (SLICC) Damage Index was completed. The Damage Index records irreversible changes in organ function that have been present for at least 6 months[17]. The presence of diabetes mellitus was recorded as part of this index.

All medications were recorded, including prednisone, hydroxychloroquine, and immunosuppressant doses. Taking hypertensive medications was used as a surrogate measure for hypertension.

The laboratory tests needed to complete the SELENA SLEDAI were performed at baseline, including the complete blood count, serum creatinine, urine protein, urine red blood cells, urine white blood cells, anti-dsDNA, and complement (C3, C4). Antiphospholipid assays, including anticardiolipin IgG and IgM, and the lupus anticoagulant (by modified Russell viper venom time) were performed.

Depression was assessed using the Calgary Depression Scale (CDS). The CDS was developed primarily to assess depression in individuals who might be concurrently experiencing psychotic symptoms[18]. It is a 9-item scale, each item scored 0–3. The scale was derived from the Hamilton Depression Rating Scale and the Present State Examination. It assesses the symptoms of depression at any stage of disease.

Fibromyalgia was assessed at baseline using a simple fibromyalgia screening tool. Uniform thumb pressure of about 4 kg was applied over predefined tender point sites (bilateral occiput, low cervical, trapezius, second ribs, supraspinatous, lateral epicondyles, gluteal, greater trochanters, and medial fat pad of the knees)[19]. If the patient stated that the palpation was painful, a tender point was considered present.

Fatigue was assessed by the Krupp Fatigue Severity Score. The 9 items on the questionnaire are scored from 1 (“strongly disagree”) to 7 (“strongly agree”), and the overall score is calculated by taking the mean of the 9 items. A higher score indicates greater fatigue[20].

Cognitive data

Patients underwent cognitive function testing using 9 subtests of the Automated Neuropsychological Assessment Metrics (ANAM), a repeatable, computerized cognitive battery[21]. The subtests were 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 (sustained attention/working memory), Mathematical Processing (simple mental arithmetic), and Matching to Sample Test (visuospatial perception and working memory).

Brain MRI

Anatomic brain MRI scans were obtained at the baseline visit from each subject and at each site, using the same parameters for all sites. These scans included T1-weighted, T2-weighted, and a proton density-weighted acquisition. The parameters for the T1-weighted image were TR 500 ms, TE 20 ms, and tip angle 90°. A dual-echo pulse sequence with TR 3400 ms, TE 20/80 ms, and tip angle 90° was used for acquiring the T2-weighted and proton density-weighted images.

All MRI scans were read by 3 experienced readers (RLB, PTF, and SN) at the University of Texas Health Science Center at San Antonio, blinded to patient age, study site, and disease status. Each reading session included roughly 10 scans of individuals of similar age who were enrolled in an epilepsy study. Readings for each scan were arrived at by consensus. Ten percent of all scans were re-read, for quality assurance purposes, with excellent agreement. The markers for cerebral atrophy were cerebrospinal fluid space (CSF) volume and relative intracranial CSF space volume. The validated method described by Kipps and colleagues was utilized with minor modification[22].

The ratings for brain MRI abnormalities were 0 to 3. For brain atrophy, grade 0 was normal, grade 1 mild, grade 2 moderate, and grade 3 severe. For focal T2 lesions, grade 0 was normal, grade 1 included < 5 white-matter lesions, grade 2 included ≥ 5 white-matter lesions or any cortical lesion involving one lobe, grade 3 included ≥ 5 white-matter lesions and more than 1 focal cortical lesion.

Normal scans were defined by their similarity to anatomic brain MRI findings in a previous study by our group measuring age-related morphology trends of cortical sulci[23]. That study evaluated 20 normal, healthy individuals in each of 4 decades: 20–29, 30–39, 40–49, and 50–60 years. Small, periventricular T2 high signal-intensity changes in the area of the centrum semiovale not visible on T1-weighted images were not considered to be abnormal.

Statistical considerations

Brain MRI results were dichotomized as absence (grade 0) or presence of atrophy (grade 1–3) and also as absence (grade 0) or presence of focal lesions (grade 1–3). Continuous measures were summarized as means and standard deviations and group comparisons were made using 2-sample t-tests. Categorical data were summarized with frequencies and percentages and group comparisons were made using Fisher’s exact test. Logistic regression analyses to permit adjustment for factors such as age, ethnicity, and hypertension were performed. Confidence intervals were calculated using standard methods. Analyses were performed using SAS version 9.1.3 (SAS Institute, Cary, NC, USA) and Stata version IC10 (Stata, College Station, TX, USA). All reported p values are 2-sided and the significance level was set at 0.05.

RESULTS

Ninety-seven patients with recently-diagnosed SLE had a brain MRI at baseline. Demographic and clinical characteristics for these patients are reported in Table 1. Cerebral atrophy was found in 18% (95% CI 11%–27%) of the patients: mild atrophy was present in

12%, moderate atrophy in 5%, and no patient had severe atrophy. Focal lesions were found in 8% (95% CI 4%–16%) of the patients: mild focal lesions were present in 2%, moderate in 5%, and severe in 1%.

Demographic and clinical characteristics of the patients (Table 2) and throughput performance on the ANAM subtests (Table 3) were compared by the presence or absence of cerebral atrophy and focal lesions. Patients with atrophy tended to be older than those without (43.0 vs 37.1 years; p = 0.07). Adjusting for age, patients with anxiety disorder were more likely to have atrophy (OR 6.3, 95% CI 1.1–35.8). Patients with cerebral atrophy performed more poorly on the Coding Immediate (p = 0.04) and Delayed (p = 0.007) Memory subtests of the ANAM. However, the relationship was no longer significant after adjusting for age, sex, education, and race/ethnicity. No association was seen for sex, education, ethnicity, depression, or other clinical characteristics and atrophy.

African Americans were more likely to have focal lesions than non-African Americans (p = 0.04) and Caucasians were less likely than non-Caucasians (p = 0.05). The association of African American race with focal lesions was independent of age and hypertension medication status (results not shown). Adjusting for African American race, the SELENA SLEDAI score was higher in those with focal lesions (p = 0.02). The SLICC Damage Index was higher (p < 0.05) and there was a trend (p = 0.07) for higher prednisone use in those with focal lesions (75%) compared to those without focal lesions (39%). However, these associations were attenuated after adjustment for race. Patients taking prednisone had significantly higher SLICC damage (results not shown). Patients with focal lesions were more likely to have abnormal anti-dsDNA (p = 0.05). No association was seen for age, sex, education, depression, and any of the ANAM throughput measures with focal lesions.

DISCUSSION

This study demonstrates, for the first time, that brain imaging abnormalities are present in 25% (95% CI 17%–35%) of patients with newly diagnosed SLE. This is surprising, as most studies have found an association between brain MRI abnormalities in SLE patients and longer disease duration, higher cumulative damage, and higher total lifetime corticosteroid dose[7,8,10]. Thus, previous studies suggested that structural brain abnormalities were a function of SLE-related or iatrogenic damage over time. All these previous studies described SLE patients with variable disease duration, generally many years. Our study differs in that patients with newly diagnosed SLE were studied. The presence of brain abnormalities at or around the diagnosis of SLE may indicate that the clinical diagnosis of SLE is preceded by the presence of lupus autoantibodies for many years[24] and that the brain is particularly vulnerable early in the disease course.

The frequency of cerebral atrophy in SLE patients, the most common abnormality seen in this study, has been inconsistently reported, from 8.7% to 32% in past studies6,7,9–11. Chinn and colleagues found cerebral atrophy in 32% of 47 SLE patients, confirmed by an increase in the CSF to intracranial volume ratio[9]. Ainiala and colleagues, in a sample of 43 SLE patients, found that the mean relative intracranial CSF volume was significantly higher in SLE than in healthy controls, but the frequency of brain abnormalities was not reported[7].

SLE patients with cognitive impairment and longer duration of disease had more cerebral atrophy. Appenzeller and colleagues, in a sample of 115 SLE patients, showed that a reduction in cerebral and corpus callosum volumes was associated with the duration of SLE, history of central nervous system involvement, and cognitive impairment[6]. The MRI findings included 10 patients (8.7%) with cerebral atrophy and 25 (21.7%) with corpus callosum atrophy. Csépány, *et al* studied 81 SLE patients and found abnormal MRI results in 40 (49%), including 15 (18.5%) patients with brain atrophy and 25 (30.8%) with focal parenchymal lesions[11]. Zhang and colleagues recently reported on diffusion and anatomic brain MRI changes in 34 SLE patients compared with 29 age-matched controls[10]. Twenty SLE patients (58.8%) had abnormal findings: atrophy in 3 (9%), focal white-matter disease in 15 (45%), and both in 2 patients (6%). Quantitative diffusion-tensor imaging analysis indicated that increased brain diffusion and decreased white-matter anisotropy were more common than anatomic abnormalities and could be present in anatomically normal-appearing brain regions.

Another recent study by Appenzeller, *et al* reported a longitudinal analysis of gray and white-matter loss over a 12 to 24-month period in 75 SLE patients[8]. A significant reduction in gray and white-matter volume was seen in SLE patients as compared to controls at study entry, associated with disease duration and positive antiphospholipid antibody (aPL) values. Patients with severe cognitive impairment had a more pronounced white and gray-matter reduction than patients with moderate or no cognitive impairment. Total corticosteroid dose was associated with gray but not white-matter reduction. A significant reduction in both gray and white-matter loss was seen in SLE patients on the followup brain MRI.

The relationship between atrophy and clinical disease progression has been best studied in multiple sclerosis (MS). Atrophy is found in both the brain and spinal cord in primary and secondary progressive MS[25]. MRI data led to the hypothesis that progression of MS, up to an irreversible stage, is dependent on the cumulative effect of axonal damage[26]. This may result in cerebral atrophy, detectable by MRI[25]. In a study evaluating cerebral atrophy among patients with relapsing-remitting disease, Gasperini, *et al* showed that the extent of inflammation over a relatively short period of time contributes to atrophy that develops later and over a longer period of time[27]. Studies in MS have suggested a link between increasing atrophy and disability[28,29]. The longitudinal study by Appenzeller, *et al* suggests that brain atrophy in patients with SLE is similarly progressive and associated with worsening neurological manifestations[8]. If confirmed, brain imaging studies may prove to be important for following disease progression or response to therapy in SLE as they are in patients with MS. The marked increased sensitivity of newer brain imaging techniques such as diffusion-tensor imaging in patients with SLE[10] holds even greater promise than anatomic MRI measures of atrophy.

Studies in SLE have suggested that cerebral atrophy in established lupus might be the result of corticosteroids[30,31], although other studies found no association[32–35], and some suggested that both disease activity and use of corticosteroids were responsible[31,35]. In one study, cerebral atrophy was associated with a neuropsychiatric manifestation (seizures)[30]. Because corticosteroids are used to treat active lupus, it is impossible to completely separate primary versus secondary associations. However, it is well known that corticosteroids adversely

affect memory centers in the brain in humans[36] and in animals[37,38]. The ability of the hippocampus to filter out irrelevant information is harmed by glucocorticoids[39,40]. In our study, there was a trend for higher prednisone use in patients with focal lesions, but not cerebral atrophy.

We found that anxiety disorder was more common in those with cerebral atrophy. Anxiety disorder has been found frequently in SLE patients[41,42], but was felt to be a nonspecific finding in SLE patients that did not differ from controls[7]. Our study suggests that there may be a relationship between brain volume loss and anxiety.

Antiphospholipid antibodies, through microvascular and macrovascular thrombi, can be associated with cerebral atrophy[43–46]. Interestingly, Appenzeller, *et al* found no association between total cerebral or corpus callosum volume and the presence of aPL or presence of microinfarcts in MRI in a cross-sectional study[6], but did find an association between cerebral atrophy and aPL in a longitudinal analysis[8]. This appears to be consistent with findings in several longitudinal (but not cross-sectional) studies of an association between aPL and cognitive dysfunction in patients with SLE[47–50]. One of these studies also included brain imaging, and found that IgG anticardiolipin was also associated with abnormal brain MRI, including general atrophy and diffuse white-matter changes, rather than focal damage[48]. We found no association of IgG anticardiolipin with cerebral atrophy or focal lesions. As our report describes the baseline evaluation of a longitudinal study, it is possible that we will see an association over time.

There are several limitations of our study. First, we did not have a matched control group scanned in an identical manner to the patient group to use as a direct comparison to define normal. Our group has experience, however, in assessing age-related brain morphology in age groups by decade ranging from 20 to 80 years of age[23]. For the qualitative visual analysis of this study, this experience gave us a solid base from which to gauge a normal anatomic MRI brain study. In addition, a large study has shown that age-related changes in both men and women are small prior to age 50 years[51]. The average age of our patients was 38 ± 12 years. Another recent MRI-based study of volume and variance with age and sex also showed only a mild reduction in cerebral volumes with age, nearly all attributable to males, with female brain volumes remaining stable over a span of 15 to 69 years of age[52]. Thus, we believe it is unlikely that lack of a direct comparison, age-matched control group created biased results. The second limitation is that fluid-attenuated inversion recovery (FLAIR) images were not obtained on all subjects. While we realize that T2 images are not as sensitive as FLAIR, the 2 methods are closely correlated ($r = 0.97$, $p < 0.0001$)[53]. Therefore, it is unlikely that a significant number of focal lesions were overlooked.

We found that 25% of patients with newly diagnosed SLE had anatomic brain abnormalities on MRI. These abnormalities were more likely to consist of cerebral atrophy than focal lesions. In this cross-sectional study, cerebral atrophy was associated with 2 subtests of the ANAM, but not when adjustment for age and other factors was made. Focal lesions were associated with African American ethnicity, anti-dsDNA, and higher SELENA SLEDAI results. These findings indicate that the brain may be affected extremely early in the disease course, even before the clinical diagnosis of SLE is made. Other studies have suggested that

abnormalities noted on brain imaging may be progressive, implying that continuing damage to brain structures also occurs. Given the high frequency of NPSLE manifestations and structural brain abnormalities, more research is urgently needed to determine the underlying pathophysiology of these changes, in order to develop rational treatment options.

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Table 1

Demographic and clinical characteristics of the 97 patients with recently diagnosed SLE.

Characteristic	Mean (SD) or N (%)
Age, yrs	38.1 (12.2)
Sex, female	94 (97)
Ethnicity:	
Asian	5 (5)
African American	11 (11)
Hispanic	19 (20)
Caucasian	59 (61)
Other	3 (3)
Education, yrs	15.1 (2.8)
Diabetes	2 (2)
Hypertension	14 (14)
Hypercholesterolemia	8 (8)
SELENA SLEDAI	4.1 (4.6)
SLICC Damage Index	0.7 (1.2)
Krupp Fatigue Severity	4.8 (1.7)
Calgary Depression	4.9 (4.6)
Prednisone use	41 (42)
Hydroxychloroquine use	67 (69)
Fibromyalgia tender points	2.5 (4.6)
ACR neuropsychiatric definitions	
Cerebrovascular disease	4 (4)
Headache	9 (9)
Seizures	5 (5)
Anxiety disorder	6 (6)
Cognitive dysfunction	6 (6)
Mood disorder	8 (8)
Low C3	12 (14)
Low C4	15 (17)
IgG anticardiolipin-positive	2 (2)
IgM anticardiolipin-positive	27 (35)
Anti-ds DNA, abnormal	36 (44)
Lupus anticoagulant (RVVT)	11 (15)

SELENA: Safety of Estrogens in Lupus Erythematosus National Assessment, SLEDAI: SLE Disease Activity Index, SLICC: Systemic Lupus International Collaborating Clinics, ACR: American College of Rheumatology, RVVT: Russell viper venom time.

Table 2

Demographic and clinical characteristics by presence or absence of cerebral atrophy and focal lesions on MRI. Data are mean (SD) or N (%).

Characteristic	Cerebral Atrophy				Focal Lesions			
	Absent, n = 80	Present, n = 17	p	Adjusted p*	Absent, n = 89	Present, n = 8	p	Adjusted p**
Age, yrs	37.1 (11.8)	43.0 (13.5)	0.07	—	38.3 (12.2)	36.3 (12.8)	0.66	0.80
Sex, female	78 (98)	16 (94)	0.44	0.59	86 (97)	8 (100)	1.0	0.98
Ethnicity								
Asian	4 (5)	1 (6)	1.0	0.93	5 (6)	0 (0)	1.0	—
African American	9 (11)	2 (12)	1.0	0.83	8 (9)	3 (38)	0.045	—
Hispanic	15 (19)	4 (24)	0.74	0.67	16 (18)	3 (38)	0.19	—
Caucasian	50 (63)	9 (53)	0.59	0.46	57 (64)	2 (25)	0.054	—
Other	2 (3)	1 (6)	0.44	0.38	3 (3)	0 (0)	1.0	—
Education, yrs	15.0 (2.8)	15.5 (2.6)	0.50	0.53	15.2 (2.7)	14.1 (3.1)	0.30	0.44
Diabetes	1 (1)	1 (6)	0.31	0.31	2 (2)	0 (0)	1.0	0.99
Hypertension	11 (14)	3 (18)	0.71	0.83	13 (15)	1 (13)	1.0	0.80
Hypercholesterolemia	6 (8)	2 (12)	0.63	0.95	8 (9)	0 (0)	1.0	0.97
SELENA SLEDAI	4.0 (4.7)	4.9 (4.1)	0.47	0.40	3.8 (3.8)	8.6 (9.6)	0.23	0.02
SLICC Damage Index	0.7 (1.2)	0.8 (1.3)	0.84	0.94	0.6 (1.1)	1.5 (1.7)	0.048	0.11
Krupp Fatigue Severity	4.7 (1.7)	5.0 (1.7)	0.65	0.93	4.8 (1.7)	4.8 (1.8)	0.99	0.94
Calgary Depression	4.7 (4.6)	5.9 (4.4)	0.34	0.28	4.8 (4.5)	6.1 (5.1)	0.42	0.63
Prednisone use	31 (39)	10 (59)	0.18	0.13	35 (39)	6 (75)	0.07	0.15
Hydroxychloroquine use	57 (71)	10 (59)	0.39	0.32	62 (70)	5 (63)	0.70	0.75
Fibromyalgia tender points	2.3 (4.2)	3.4 (6.3)	0.52	0.82	2.5 (4.7)	2.3 (4.1)	0.87	0.60
Cerebrovascular disease	2 (3)	2 (12)	0.14	0.09	3 (3)	1 (13)	0.30	0.36
Headache	6 (8)	3 (18)	0.19	0.16	8 (9)	1 (13)	0.56	0.48
Seizures	4 (5)	1 (6)	1.0	0.83	4 (4)	1 (13)	0.36	0.44
Anxiety disorder	3 (4)	3 (18)	0.06	0.04	6 (7)	0 (0)	1.0	0.98
Cognitive dysfunction	4 (5)	2 (12)	0.28	0.28	6 (7)	0 (0)	1.0	0.98
Mood disorder	7 (9)	1 (6)	1.0	0.57	7 (8)	1 (13)	0.51	0.66
Low C3	10 (14)	2 (14)	1.0	0.63	11 (14)	1 (17)	1.0	0.94
Low C4	12 (17)	3 (21)	0.70	0.61	14 (18)	1 (17)	1.0	0.57

Characteristic	Cerebral Atrophy				Focal Lesions			
	Absent, n = 80	Present, n = 17	p	Adjusted p*	Absent, n = 89	Present, n = 8	p	Adjusted p**
IgG anticardiolipin-positive	2 (3)	0 (0)	1.0	0.99	1 (1)	1 (14)	0.16	0.16
IgM anticardiolipin-positive	23 (35)	4 (33)	1.0	0.83	24 (34)	3 (43)	0.69	0.59
Anti-dsDNA, abnormal	30 (44)	6 (43)	1.0	0.81	31 (41)	5 (83)	0.08	0.05
Lupus anticoagulant (RVVT)	10 (16)	1 (9)	1.0	0.94	11 (17)	0 (0)	0.58	0.97

Definitions as in Table 1. Unadjusted p values are from 2-sample t-test for continuous measures and Fisher's exact test for dichotomous measures. Adjusted p values are from the Wald chi-square test.

*Adjusted for age;

**adjusted for African American race.

Table 3

Performance on Automated Neuropsychological Assessment Metrics[21], by presence or absence of cerebral atrophy and focal lesions on MRI.

Characteristic	Cerebral Atrophy				Focal Lesions			
	Absent, n = 80	Present, n = 17	p	Adjusted p*	Absent, n = 89	Present, n = 8	p	Adjusted p*
Coding delayed memory	33.7 (13.9)	26.4 (8.4)	0.007	0.11	32.6 (13.2)	30.1 (15.7)	0.61	0.99
Coding immediate memory	33.1 (14.4)	27.7 (8.2)	0.04	0.30	32.6 (13.7)	27.1 (12.6)	0.28	0.41
Code substitution	42.3 (11.2)	38.7 (8.9)	0.21	0.56	42.2 (10.6)	36.7 (12.7)	0.17	0.41
Continuous performance	79.8 (17.6)	75.3 (15.3)	0.33	0.92	79.7 (16.2)	71.1 (25.9)	0.38	0.41
Matching to sample	24.6 (8.9)	22.4 (7.1)	0.34	0.47	24.7 (8.0)	19.1 (13.2)	0.28	0.22
Mathematical processing	17.8 (8.5)	19.5 (6.8)	0.46	0.32	18.6 (7.9)	13.1 (10.4)	0.07	0.42
Spatial processing	18.5 (5.7)	19.0 (5.4)	0.76	0.56	18.9 (5.4)	15.8 (6.9)	0.13	0.48
Simple reaction time	191 (47)	182 (40)	0.42	0.43	191 (45)	171 (53)	0.23	0.57
Sternberg	65.4 (16.0)	58.4 (14.7)	0.10	0.23	64.7 (15.9)	58.4 (16.4)	0.29	0.32

*Adjusted for age, sex, education, and race/ethnicity.