

Neurocognitive Impairment in Corticosteroid-naïve Patients with Active Systemic Lupus Erythematosus: A Prospective Study

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ABSTRACT. Objective. Neurocognitive impairment (NCI) has been intensively studied in patients with systemic lupus erythematosus (SLE). However, those studies have mostly included patients who were treated with corticosteroids, which may itself induce NCI. We investigated NCI in corticosteroid-naïve people with SLE who did not exhibit any overt neuropsychiatric manifestations.

Methods. Forty-three inpatients with SLE who had no current or past neuropsychiatric history participated in the study. Patients and 30 healthy control subjects with similar demographic characteristics were given a 1-h battery of neuropsychological tests. NCI was defined as scores at least 2 SD below the mean of the healthy control group on at least 2 of the 7 neurocognitive domains. Results of clinical, laboratory, and neurologic tests were compared regarding the presence of NCI.

Results. NCI was identified in 12 patients (27.9%) with SLE and in 2 control subjects (6.7%). Patients with SLE showed a significant impairment compared with controls on tasks assessing immediate recall, complex attention/executive function, and psychomotor speed. We identified psychomotor speed (Digit Symbol Substitution Test) as the factor that best differentiated the 2 groups. Further, we identified the score of the SLE Disease Activity Index 2000 as an independent risk factor for NCI in patients with SLE.

Conclusion. We conclude that reduced psychomotor speed is an SLE-specific pattern of NCI. Verbal-memory deficits that have been reported in patients with SLE were not evident among patients who were corticosteroid-naïve. Our results indicate that impaired psychomotor speed may be added to the symptoms of early SLE. (First Release Jan 15 2015; J Rheumatol 2015;42:441–8; doi:10.3899/jrheum.140659)

Key Indexing Terms:

SYSTEMIC LUPUS ERYTHEMATOSUS

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Systemic lupus erythematosus (SLE) is a chronic autoimmune disease involving multiple systems that has primary and secondary effects on the central nervous system (CNS) and psychosocial well-being. Neuropsychiatric (NP) manifestations are common in patients with SLE. Among the 19 different NPSLE syndromes identified by the American College of Rheumatology (ACR)¹, neurocog-

nitive impairment (NCI) is the most frequent and is accompanied by a decreased quality of life. However, despite its prevalence, the etiology, nature, course, and treatment of SLE-associated NCI remains elusive.

NCI has been reported in patients with SLE who have^{2,3,4} and do not have^{4,5,6} overt NP symptoms. These studies suggest that NCI may be residual in patients with previous CNS impairments or may serve as an early marker of CNS impairment in patients who have not shown NP symptoms. However, to date, the nature of SLE-associated NCI has been studied mainly in longterm patients. One study, which targeted patients with newly diagnosed SLE, concluded that depression was associated with worse function in several cognitive domains⁷. Because SLE is typically a disease that takes some time to diagnose, NCI as well as other physical symptoms may occur before its diagnosis.

The mechanisms underlying SLE-associated NCI remain unknown. Antiphospholipid antibodies (aPL) have been reported to be associated with NCI, and neuroimaging studies have demonstrated that damage to white matter tracts may be a factor related to NPSLE, including NCI⁸. SLE-associated NCI might result directly from SLE or have

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the same origin as NCI in the non-SLE population (e.g., psychological or psychiatric disturbances, pain, fatigue, sleep disturbance, or medication such as corticosteroids), and perhaps is exacerbated by SLE⁸.

Specifically, corticosteroids are commonly used to treat SLE and are associated with NCI, whether patients have medical conditions⁹ or are otherwise healthy¹⁰. The most extensively reported cognitive changes resulting from corticosteroid treatment involve declarative (verbal) memory, and occur during both short-term (high-dose)⁹ and long-term (relatively low-dose)¹¹ therapies, reflecting a hippocampus-dependent process¹². Further, even severe cognitive disorders such as dementia and delirium have been reported¹³. Corticosteroid-induced cognitive deficits have been thought to be related to dysfunctional hippocampal and frontal cortical neuroanatomic circuits¹⁴. Thus, corticosteroid therapy may affect the incidence and profile of NCI in patients with SLE. At the same time, although hippocampal atrophy in SLE has been demonstrated in 1 study, the use of corticosteroids could not be excluded as a factor that contributed to the memory deficits¹⁵. The 16/6 idiotype antibody of the human anti-DNA antibody has been reported to impair visual and spatial memory by causing hippocampal injury in mice¹⁶. Similarly, a recent study has indicated that anti-NMDA receptor subunit 2 (NR2) antibodies can cause neuronal death observed as hippocampal atrophy in patients with SLE¹⁷, as previously demonstrated in mice with autoimmune disease¹⁸.

In patients with SLE, however, the relationship between NCI and the use or dose of corticosteroids is controversial with negative^{3,5,6,19,20} and positive^{2,21} findings. McLaurin, *et al* reported that prednisone is associated with decreased cognitive functioning independent of SLE-associated disease activity²¹. In our present study we investigated whether SLE-associated NCI is related to corticosteroid treatment. We compared cognitive functioning between corticosteroid-naïve patients with SLE and healthy control subjects, and studied psychological/health characteristics as well as neurological/immunological markers in SLE patients with or without NCI.

MATERIALS AND METHODS

Subjects. Subjects were Japanese patients who were admitted to the Institute of Rheumatology, Tokyo Women's Medical University Aoyama Hospital between 2000 and 2006 and who met all of the following criteria: (1) diagnosed with SLE based on the classification criteria of the ACR²²; (2) no history of corticosteroid or other immunosuppressive therapy; (3) no physical condition such as high fever or general fatigue that would make them unable to participate in a psychiatric interview or complete the neuropsychological tests and questionnaires; (4) no history of major psychiatric disorders including substance abuse, except for adjustment disorder; and (5) no history of neurologic illness (e.g., persistent headache, strokes, seizures or movement disorders, head injury resulting in loss of consciousness, or any problems at birth). All patients were screened for current and previous major psychiatric conditions using the Structured Clinical Interview from the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, Axis I Disorders, Non-patient Edition (with

psychotic screening), Version 2.0 (SCID-I-NP)^{23,24}. The study was approved by the ethics committee of Tokyo Women's Medical University and all participants gave informed written consent.

Of the 54 corticosteroid-naïve patients with SLE who were admitted during the study period, 1 declined the invitation to participate, 2 were excluded based on the initial interview using SCID-I-NP (criterion 4), and 8 could not complete the neuropsychological tests (criterion 3). As a result, data from 43 patients were available for analysis. Demographic, clinical, and psychological characteristics for SLE and control groups can be seen in Table 1.

Controls. Thirty healthy controls were recruited from hospital staff and their relatives for neuropsychological testing. All controls were Japanese women with no history of major psychiatric disorder or neurologic illnesses as determined by the SCID-I-NP and neurologic history-related questions. This control group was similar in age and education to the SLE group (Table 1).

Neuropsychological assessment and data analysis. First, patients and controls completed the Mini-Mental State Examination (MMSE) to assess global cognitive functioning. Then a 1-h battery of neuropsychological tests was administered to both participant groups by a clinical psychometrist who was not aware of the clinical status and current medication of any patient. The neuropsychological tests included the Digit Span Test, Forward and Backward Test, Digit Symbol Substitution Test, Block Design Test, Similarities subsets of the Wechsler Adult Intelligence Scale-Revised (WAIS-R)²⁵; Word Fluency Test (Animal Naming Test)²⁶; Trail Making Test, Part A and B^{26,27}; Rey Auditory-Verbal Learning Test (RAVLT)²⁶; Wisconsin Card Sorting Test, Keio version (KWCST), and the Japanese version of the WCST^{26,28}. In the Japanese version of the Trail Making Test, Part B, kana (Japanese phonograms) were used instead of Roman alphabet letters because performance has been shown to be similar²⁷. These tests evaluated the following 7 cognitive domains: simple attention, complex attention/executive function, memory, visuospatial processing, language, reasoning/problem solving, and psychomotor speed. Table 2 shows the specific tests included in each domain and a short description of each test. These tests are consistent with the neuropsychological test battery recommended by the ad hoc committee of the ACR¹.

Because published normative data for the psychological tests used in this study lacked Japanese representation (except for the above-mentioned subsets of the WAIS-R), we used data from the healthy control group to estimate the population data. Scores on the Word Fluency Test and Trail Making Test Parts A and B were significantly different from those found in international normative data²⁹ (likely owing to linguistic differences or different formats), while scores on the RAVLT and KWCST were not different (data not shown). However, the scaled scores from an age-matched reference group (ages 25–34 yrs) were comparable to those of our healthy control group on several subsets of the Japanese WAIS-R (each of the 4 common subsets in the reference group: 10 ± 3; our controls: 9–12, with Digit Span = 9, Digit Symbol Substitution = 12, Block Design = 11, and Similarities = 11). This shows that our healthy controls had normal neurocognitive function.

Raw scores on the neuropsychological tests were converted to Z scores. Based on the criteria recommended by the Ad Hoc Committee on Lupus Response Criteria³⁰, performance on a single neuropsychological test was classified as impaired if the Z scores were at least 2 SD below the mean of the normal controls (rather than the recommended published normative data). If scores were impaired in at least 2 of the 7 neurocognitive domains, individuals were designated as cognitively impaired. When a domain comprised more than 1 test (e.g., complex attention/executive function), the domain was classified as impaired if at least 1 test showed significant impairment.

Psychological/health assessment. Following the neuropsychological session, both patients and controls were evaluated by the Profile of Mood States (POMS)³¹. POMS provides scores on 6 separate scales reflecting tension-anxiety, depression-dejection, anger-hostility, vigor, fatigue, and

Table 1. Demographic, clinical, and psychological characteristics of corticosteroid-naïve patients with SLE versus healthy controls. Data are no./no. assessed (%) or median (interquartile range).

Characteristics	Patients with SLE, n = 43	Controls, n = 30	p
Demographics			
Age, yrs	28 (21–35)	25.5 (23.8–31.3)	0.822
Female	41/42 (97.6)	30/30 (100)	
Education, yrs	14 (12–15)	12 (12–15)	0.963
Clinical characteristics			
Disease duration, mos ^a	13 (5–36)	NA	
Time since SLE diagnosis, mos	0 (0–0)	NA	
Performance status ^b	0 (0–1)	NA	
Pain, VAS, mm	28 (8–57)	NA	
Fatigue, VAS, mm	26 (9–55)	NA	
SLEDAI-2K ^c	10 (8–16)	NA	
Profile of Mood State			
Tension-Anxiety	14 (8–20)	8.5 (7–15)	0.043 ^d
Depression-Dejection	13 (6–22)	7 (4–17)	0.045 ^d
Anger-Hostility	5 (3–14)	6 (4–8.3)	0.915
Vigor	8 (4–13)	10.5 (5.8–15.5)	0.098
Fatigue	10 (6–16)	8.5 (6–15)	0.590
Confusion	9 (6–13)	9 (6–12)	0.682
Total Mood Disturbance	44 (22–69)	30.5 (12–45)	0.074
Global cognitive functioning			
MMSE	30 (29–30)	30 (30–30)	0.017 ^d

P values were determined by Fisher's exact test or Mann-Whitney U test. ^a Defined as the time between the SLE-attributable symptom onset and assessment. ^b Defined by Eastern Cooperative Oncology Group criteria. ^c Items included low complement in 37 patients (86.0%), increased DNA binding in 36 (83.7%), arthritis in 26 (60.5%), new rash in 20 (46.5%), leukopenia in 15 (34.9%), fever in 11 (23.2%), proteinuria in 9 (20.9%), hematuria in 8 (18.6%), urinary casts in 8 (18.6%), alopecia in 7 (16.3%), pleurisy in 5 (11.6%), pyuria in 5 (11.6%), thrombocytopenia in 4 (9.3%), mucosal ulcers in 3 (7.0%), pericarditis in 2 (4.7%), vasculitis in 1 (2.3%), myositis in 1 (2.3%), and visual disturbance in 1 (2.3%). The other SLEDAI-2K items (seizure, psychosis, organic brain syndrome, cranial nerve disorder, lupus headache, and cerebrovascular accident) were not found in any patient. ^d Significant variables. SLE: systemic lupus erythematosus; NA: not applicable; VAS: visual analog scale; SLEDAI-2K: SLE Disease Activity Index 2000; MMSE: Mini-Mental State Examination.

Table 2. Short description of neuropsychological test battery and examined cognitive domains.

Domain	Test	Short Description of Test
Simple attention	Digit Span, Forward*	Repeating random number sequences forward.
Complex attention/ executive function	Trail Making Test, Part B	Drawing lines to connect circles, alternating between numbered and lettered circles consecutively as quickly as possible.
	Digit Span, Backward*	Repeating random number sequences backward.
	Wisconsin Card Sorting Test, Keio version (KWCST)	Placing cards one by one under 4 stimulus cards, according to a principle that the subject must deduce from the pattern of the examiner's responses to the subject's placement of the card. Two sessions, each of which is composed of 48 trials.
Memory	Rey Auditory-Verbal Learning Test	Immediate recall trials after each of 5 repeated oral presentations of a 15-word list. Delayed recall trial after 20 min, followed by recognition of the 15 items among 15 distractor words.
Visual-spatial processing	Block Design*	Using 4 or 9 blocks (each block has 2 red, 2 white, and 2 red-white sides) to construct replicas of designs printed in a smaller scale.
Language	Animal Naming Test	Naming as many different animals as possible in 1 min.
Reasoning/problem solving	Similarities*	Describing how similar 2 words that represent common objects or concepts are.
Psychomotor speed	Trail Making Test, Part A	Drawing lines to connect consecutively numbered circles as quickly as possible.
	Digit Symbol Substitution*	Filling in blanks with symbols that are paired to numbers as quickly as possible for 90 s.

*Subsets of the Wechsler Adult Intelligence Scale-Revised.

confusion. The POMS Total Mood Disturbance score was derived by summing the scores on all the scales except vigor, which was subtracted out. The severity of depressive and anxious symptoms in patients was

objectively evaluated by 1 of 2 psychiatrists (KN and MO) using the 17-item Hamilton Depression Rating Scale (HAM-D-17) and the Hamilton Anxiety Rating Scale (HAMA). Sleep disturbance levels were derived by

summing the scores of 3 HAMD subscales for insomnia (initial, middle, and delayed insomnia, each value: 0–2). Daily-living activity was evaluated using Performance Status according to the Eastern Cooperative Oncology Group. Patients also completed a questionnaire regarding pain and fatigue using visual analog scales (VAS) for pain and fatigue (0–100 mm, 100 mm being most severe).

Assessment of disease activity and neurological/immunological markers. Patient records were reviewed by an experienced rheumatologist (MH). Disease duration was defined as the time between onset of SLE-attributable symptoms and assessment. Global SLE disease activity was evaluated using the SLE Disease Activity Index 2000 (SLEDAI-2K)³² at the same time as the neurocognitive assessment or within the preceding 10 days. Anti-dsDNA antibodies and serum complement CH50 were measured as markers of disease activity. Based on published reports regarding NPSLE including NCI⁸, the following potentially relevant laboratory and neurologic variables were selected: aPL, cerebrospinal fluid (CSF) tests [immunoglobulin G index, interleukin 6 (IL-6), IL-8, and interferon- α], magnetic resonance imaging (MRI) of the brain, and electroencephalography (EEG). Of the 43 patients, CSF tests were performed in 37, brain MRI in 41, and EEG in 41. These neuropsychological, laboratory, and neurological tests were completed within 1 week after admission and before corticosteroid or other immunosuppressive therapies were administered. Control participants completed the neuropsychological tests, but did not have MRI of the brain, EEG, or CSF tests.

Statistical analyses. For the univariate analyses, a non-parametric Mann-Whitney U test was used to identify differences between groups for continuous variables, and Fisher's exact test was used for categorical variables. To identify (1) neuropsychological variables that best discriminated between the patients with SLE and the healthy controls; and (2) independent risk factors for NCI in patients with SLE, multiple logistic regression analysis was performed, with forward stepwise variable selection. Variables from the univariate analyses with $p < 0.25$ were entered into a forward logistic regression model. Regression coefficients were used to calculate the OR and 95% CI of the OR. In all statistical analyses, p values < 0.05 were considered statistically significant. We performed all analyses using the SPSS Statistics 17.0 (SPSS Inc.).

RESULTS

Prevalence and profile of NCI. Although MMSE scores were significantly lower in the SLE group than in the control group ($p = 0.017$), both groups had a median score of 30 (ranges, 26–30 and 26–30; interquartile range, 29–30 and 30–30, respectively; Table 1). However, while 40% (17/42) of the patients scored below 30 on the MMSE, only 17% (5/30) of healthy controls did.

NCI was identified in significantly more patients with SLE (12, 27.9%) than normal controls (2, 6.7%; $p = 0.033$). Univariate analysis of the group comparison using the Mann-Whitney U test indicated that patients with SLE showed significantly worse scores for the following tests than control subjects: RAVLT Trials 1 to 5 ($p = 0.022$), reflecting immediate recall; Trail Making Test, Part B ($p = 0.001$), reflecting complex attention/executive function; Trail Making Test, Part A ($p = 0.001$); and Digit Symbol Substitution ($p < 0.001$), both reflecting psychomotor speed (Table 3).

The multiple logistic regression analysis showed that Digit Symbol Substitution was the only variable that could be used to differentiate patients with SLE from controls. The OR for Digit Symbol Substitution was 0.924 (95% CI, 0.881–0.969, $p = 0.001$).

Risk factors for NCI in patients with SLE. Patients were divided into 2 groups according to the presence or absence of NCI, and demographic, psychological/health characteristics, and neurological/immunological markers were compared between the 2 groups (Table 4). Among these items, only SLEDAI-2K score was significantly higher in patients with NCI than in those without ($p = 0.022$). No significant differences between the 2 groups were found in age, sex, education, disease duration, time since SLE diagnosis, performance status, VAS pain/fatigue, mood state (HAMD-17, HAMA, POMS scores), or sleep disturbance. Neither were significant differences between the 2 groups found in any of the neurological/immunological markers.

The multiple logistic regression analysis showed that SLEDAI-2K was the only independent risk factor for NCI in SLE patients. The OR for SLEDAI-2K was 1.141 (95% CI, 1.001–1.300, $p = 0.048$).

DISCUSSION

Although results from our present study did not directly establish whether SLE-associated NCI was related to corticosteroid treatment, there were 3 major findings. First, the prevalence of NCI in corticosteroid-naïve patients with SLE without overt NP symptoms was much higher than that of healthy control subjects. Second, the NCI was associated with general SLE disease activity as assessed by the SLEDAI-2K but not with other relevant laboratory and neurologic variables. Third, multivariate analysis showed that the dominant pattern of NCI in this population was a decrease in psychomotor speed.

The prevalence rate of NCI observed here (28%) was lower than that of studies^{33,34,35,36,37} using similar neuropsychological test batteries¹. We speculate that this reflects nonuse of corticosteroids and shorter disease durations, which were characteristic of the patients in our study. Regular treatment with prednisone has been reported to be associated with decreased cognitive functioning in patients with SLE²¹. Although a metaanalysis using a random-effects model demonstrated that the prevalence rate for NCI was estimated to be 19.7% (95% CI 10.7%–36%), NCI prevalence was interpreted as underestimated because the analysis included studies that did not involve formal neuropsychological testing³⁸. When proper neuropsychological testing was conducted in patients with SLE, the prevalence of cognitive dysfunction was much higher (23–60% in most series)^{33,34,35,36,37}.

Here, NCI was associated with general SLE disease activity as assessed by the SLEDAI-2K. Past studies regarding the association between disease activity and NCI in patients with SLE have drawn conflicting conclusions. While some studies^{6,39,40} are consistent with our results and show that higher disease activity is an independent predictor of NCI in patients with SLE, other studies^{5,19,41} have not. Unlike other studies, most patients here had overall disease

Table 3. Neuropsychological performances of corticosteroid-naïve patients with SLE versus healthy controls: univariate analysis. Data are median (interquartile range).

Neurocognitive Tests	Patients with SLE, n = 43	Controls, n = 30	p
Digit Span, Forward ^a	8 (7–9)	8 (6.8–9.3)	0.814
Trail Making Test, Part B ^b	75 (65–95)	60.5 (54.8–78.3)	0.001 ^c
Digit Span, Backward ^a	7 (6–8)	7 (6–8.3)	0.977
KWCST			
Categories achieved	5 (1–6)	5 (3.8–6)	0.148
Total errors ^b	13 (9.8–20.3)	11 (10–13.3)	0.126
Perseverative errors ^b	0 (0–2)	0 (0–1)	0.190
Difficulty of maintaining set ^b	1 (0–3)	0 (0–2)	0.144
RAVLT			
Trial I to V, immediate recall	55 (48–61)	60 (53.8–64)	0.022 ^c
Trial VII, delayed recall	13 (11–14)	13 (12–14)	0.256
Recognition	14 (13–15)	14 (14–15)	0.722
Block Design ^a	45 (42–49)	47 (42.8–51.5)	0.090
Word Fluency Test (Animal Naming)	17 (16–20)	18.5 (17–22.3)	0.099
Similarities ^a	18 (16–21)	20 (17.5–22.3)	0.066
Trail Making Test, Part A ^b	65 (54–78)	51.5 (43.8–59.8)	0.001 ^c
Digit Symbol Substitution ^a	65 (61–73)	79 (68.8–85.3)	< 0.001 ^c

P values were determined by Mann-Whitney U test. ^a Subsets of the Wechsler Adult Intelligence Scale-Revised.

^b Higher score signifies worse function. ^c Significant variables. KWCST: Wisconsin Card Sorting Test, Keio version; RAVLT: Rey Auditory-Verbal Learning Test.

activity (SLEDAI-2K ≥ 6 in 88.4%) that was moderate or high and free from the potential influence of medication. Thus we assert that a positive association between NCI and disease activity was clearly shown.

Additionally, because the disease duration of our patients was not long and because they had no history of corticosteroid therapy, most patients did not have disease-related or treatment-related damage, which have been reported to be the main factors affecting severity of cognitive impairment in SLE³⁷. Although uncomfortable disease-related physical and emotional symptoms derived from high disease activity might have affected cognitive performance, we found no association between NCI and pain, fatigue, mood state, or sleep disturbance.

In patients with SLE, notable deficits appear in attention, information processing, learning and memory, and executive function⁸. Here, although univariate analysis demonstrated deficits in verbal memory, complex attention/executive function, and psychomotor speed in the corticosteroid-naïve patients, multivariate analysis demonstrated a deficit only in psychomotor speed as assessed by the Digit Symbol Substitution Test. A lower score on this test has been reported in patients with SLE^{4,20,35,42} and NPSLE^{4,35} and is currently considered to reflect difficulty in visually guided active and speedy psychomotor coordination. Impairment seen here in Trail Making Tests A and B may reflect similar problems with speedy visuomotor ability, despite not being statistically significant. In fact, Glanz, *et al*⁴² and Kozora, *et al*³⁵ found that patients with SLE performed worse than controls on the Digit Symbol

Substitution Test and on Trail Making Tests A and B. Lower psychomotor speed may result from reduction in corpus callosum volume or other white matter abnormalities⁴³. Indeed, injury to white matter myelin may underlie the earliest cognitive dysfunction observed in SLE⁸.

Regarding memory, the analysis demonstrated that patients with SLE were impaired in serial verbal learning, but were comparable to control subjects in their delayed recall and recognition. Accordingly, we speculate that their ability to memorize or learn new facts *per se* would be well preserved. Impaired serial learning may reflect problems with time constraints and high-load cognitive activities similar to the Trail Making Tests and Digit Symbol Substitution Test. These findings are consistent with those in the literature suggesting deficits in declarative (verbal) memory after acute (high-dose) and chronic (relatively low-dose) corticosteroid use¹². Therefore, similar memory deficits that have been reported in patients with SLE might also have their roots in corticosteroid therapy.

Results from our present study suggest the need to consider the presence of NCI in early SLE when determining treatment. Because autoantibodies appear long before clinical symptoms and have been associated with inflammation in SLE⁴⁴, they may also play a relevant role in the development of NCI in patients with early SLE. Although persistent elevation of aPL has been consistently reported as a significant risk factor for SLE-associated NCI^{21,39,45,46,47}, we found no association between NCI and aPL. Other relevant autoantibodies associated with NPSLE such as anti-NR2 or antiribosomal P protein were not

Table 4. Health/psychological and clinical characteristics of patients with SLE who have neurocognitive impairment versus those who do not. Data are no./no. assessed (%) or median (interquartile range).

Variables	Impaired, n = 12	Not Impaired, n = 31	p
Demographics			
Age, years	34.5 (28–38.8)	26 (21–33)	0.086
Sex, female/male	12/0	30/1	> 0.999
Education, years	12 (11.3–15.5)	14 (12–15)	0.328
Health/psychological characteristics			
Disease duration, mos	9 (5–38)	14 (5–35)	0.841
Time since SLE diagnosis, mos	0 (0–0)	0 (0–0)	0.542
SLEDAI-2K	15.5 (9.5–21.3)	9.0 (8.0–14.0)	0.022 ^a
Performance Status ^b	1 (0–1)	0 (0–1)	0.063
Pain, VAS, mm	51.5 (7.5–66.0)	23.0 (9.0–40.0)	0.174
Fatigue, VAS, mm	39.0 (2.0–65.0)	25.0 (13.0–57.0)	0.841
HAMD-17, total	5.0 (1.3–9.5)	2.0 (1.0–5.0)	0.126
HAMA, total	3.5 (2.3–10.0)	3.0 (1.0–5.0)	0.246
POMS			
Tension-Anxiety	15.0 (6.0–21.8)	14.0 (9.0–19.0)	0.989
Depression-Dejection	12.0 (5.3–22.3)	13.0 (6.0–22.0)	0.924
Anger-Hostility	5.0 (1.0–13.3)	5.0 (3.0–15.0)	0.495
Vigor	5.5 (0.3–14.5)	9.0 (5.0–11.0)	0.212
Fatigue	12.0 (7.0–20.5)	10.0 (6.0–14.0)	0.260
Confusion	9.5 (6.5–12.5)	8.0 (6.0–14.0)	0.871
Total mood disturbance	47.5 (19.0–75.8)	44.0 (22.0–68.0)	0.862
Sleep disturbance ^c	0 (0–2)	0 (0–1)	0.655
Clinical characteristics			
Anti-DNA antibody, IU/ml	36 (13–196)	39 (9–97.3)	0.691
CH50, U/ml	12.6 (10.0–33.1)	16.2 (10.0–31.4)	0.964
Antiphospholipid antibody, positive ^d	1/12 (8.3)	13/31 (41.9)	0.067
Cerebrospinal fluid tests			
IgG index, positive (normal < 0.70)	0/10 (0)	6/27 (22.2)	0.162
Interleukin 6, pg/ml	2.9 (1.2–9.7)	3.3 (1.4–7.1)	0.973
Interleukin 8, pg/ml	62.1 (27.5–133.8)	42.0 (22.4–125.6)	0.638
Interferon- α , IU/l	0 (0–5.7)	0 (0–14.8)	0.349
Brain MRI, abnormal	2/12 (16.7)	4/29 (13.8)	> 0.999
Electroencephalogram, abnormal	5/12 (41.7)	13/29 (44.8)	> 0.999

P values were determined by Fisher's exact test or Mann-Whitney U test. ^a Significant variable. ^b Defined by Eastern Cooperative Oncology Group criteria. ^c Total scores of sleep-related 3 items in HAMD-17. ^d Antiphospholipid antibodies include anticardiolipin- β_2 -glycoprotein-I complex and SLE anticoagulant. SLE: systemic lupus erythematosus; SLEDAI-2K: SLE Disease Activity Index 2000; VAS: visual analog scale; HAMD-17: Hamilton Depression Rating Scale-17 item; HAMA: Hamilton Anxiety Rating Scale; POMS: Profile of Mood States; MRI: magnetic resonance imaging; aPL: antiphospholipid antibodies.

evaluated in our present study. There have been both negative^{36,48} and positive⁴⁹ findings for the association between anti-NR2 and NCI, while no association has been reported between antiribosomal P protein antibodies and NCI^{8,50}. Thus, we think that monitoring levels of these autoantibodies may be crucial for clarifying the pathogenesis of NCI in early SLE. Further studies are certainly needed.

The strengths of our study are the early-stage, corticosteroid-naïve SLE population, an appropriate neuropsychological test battery, and the use of multivariate methods to identify specific patterns and predictive factors for NCI in patients with SLE. However, our study has several limitations. First, because the published normative data for the psychological tests were limited in Japanese representation,

we used our data from control subjects as a reference for the normal population. The number of control subjects was relatively small, and may not be the best estimate of population data. Second, because this study used a cross-sectional design, it lacked longitudinal analysis that could have been helpful for defining predictors of neurocognitive deficits. Third, the power in this study was relatively low for identifying the specific patterns and detecting predicting factors for NCI in patients with SLE. Fourth, because the study subjects were limited to Japanese people who spoke Japanese, our findings may not be applicable to other ethnicities and languages. Fifth, because results from our study were limited to relatively young patients with SLE, the findings may not be applicable for all patients with SLE, in particular those with longer disease duration.

The dominant NCI in a corticosteroid-naïve SLE population was decreased psychomotor speed that was associated with higher general SLE disease activity. Verbal-memory deficits that have been reported in patients with SLE were not evident. Results from our study suggest that impaired psychomotor speed may be added to the symptoms of early SLE. Further followup studies using larger sample sizes are needed.

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