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Antibodies Against N-Methyl-D-Aspartate Receptors in Patients with Systemic Lupus Erythematosus without Major Neuropsychiatric Syndromes

Elizabeth Kozora, Ph.D.[1,2], **Sterling G. West, M.D.**[2], **Steven F. Maier, Ph.D.**[3], **Christopher M. Filley, M.D.**[2,4], **David B. Arciniegas, M.D.**[2], **Mark Brown, Ph.D.**[2], **David Miller, Ph.D.**[2], **Alex Grimm, M.D.**[2], and **Lening Zhang, M.D., Ph.D.**[1,2]

[1]National Jewish Health, Denver, CO

[2]University of Colorado Hospital, Aurora, CO

[3]University of Colorado, Boulder, CO

[4]Denver Veterans Affairs Medical Center, Denver, CO

Abstract

Purpose—Approximately 14-54% of patients with systemic lupus erythematosus without a history of major neuropsychiatric syndromes (nonNPSLE) have cognitive deficits. Elevated N-methyl-D-aspartate (NMDA) receptor antibodies (anti-NR2) have been reported in 35% of patients with SLE, but few studies have utilized controls or a composite memory index. We hypothesized that serum anti-NR2 would be elevated in nonNPSLE compared to healthy controls, and that elevated anti-NR2 would be associated with memory dysfunction and depression.

Methods—Subjects included 43 nonNPSLE patients with a mean age of 36.5 (SD=9.0) and mean education level of 14.7 years (SD=2.5). Twenty-seven healthy control subjects with similar demographic characteristics were also enrolled in this study. A global cognitive impairment index (CII) and a memory impairment index (MII) were calculated using impaired test scores from the ACR-SLE neuropsychological battery. Serum samples were analyzed using a standard ELISA for anti-NR2.

Results—Elevations of serum anti-NR2 were found in 14.0% of the nonNPSLE and 7.4% of the controls (p=0.47). There was no relationship between elevated anti-NR2 status and higher CII or performance on the MII. No relationship between levels of depressive symptoms and anti-NR2 was found.

Conclusions—The frequency of elevated anti-NR2 was low (14.0%) in this sample of SLE patients and not significantly different from controls. A relationship was not found between the presence of anti-NR2 in serum and global cognitive or memory indices, or with depression. Results suggest that serum anti-NR2 is not likely related to mild cognitive dysfunction in SLE patients without a prior history of NPSLE.

Correspondence to: Elizabeth Kozora, Ph.D., ABPP/CN, National Jewish Health, 1400 Jackson Street, B106, Denver, Colorado 80206, Phone: (303) 398-1071, Fax: (303) 270-2143, Kozorae@njhealth.org.

Keywords

SLE; neuropsychology; autoantibodies; NMDA

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by multi-system involvement and diverse manifestations (1). Over 50% of patients with SLE demonstrate neuropsychiatric disorders indicating central nervous system (CNS) involvement at some time during their disease course, which may include major manifestations (i.e. stroke syndromes and seizures) or less severe abnormalities including headaches, minor mood disorders and cognitive impairment (2). SLE patients with a history of major neurological or psychiatric syndromes (NPSLE) have demonstrated more severe deficits than those patients without major NP syndromes (nonNPSLE). However, cognitive dysfunction, particularly in the areas of attention, learning and memory has been identified in up to 50% of nonNPSLE patients (3-15).

The etiology of cognitive dysfunction in SLE remains unclear, and disease duration, disease activity, prednisone use and psychological distress have not been identified as primary factors (4,7,10-12,16-22). A variety of autoimmune processes have been explored in relation to cognitive dysfunction in SLE, including antibodies to the N-methyl-D-aspartate (NMDA) receptor (23). Antibodies to NMDA were discovered as a subset of anti-double stranded DNA antibodies (anti-dsDNA) with cross-reactivity against a consensus peptide sequence of the extracellular, ligand-binding domain of the NMDA receptors, NR2a and NR2b (anti-NR2) (24). Subsequently, non cross-reacting anti-NMDA antibodies with specificity only against NR2 epitopes have been demonstrated. The NR2 receptors are expressed on neurons in the hippocampus and cortex and bind the excitatory amino acid neurotransmitter glutamate. These receptors have been postulated to be important in mechanisms underlying learning and memory.

Anti-NR2 antibodies have been demonstrated in the serum and cerebrospinal fluid (CSF) of SLE patients. In mouse models, these antibodies can gain access to the CSF through a compromised blood-brain barrier. They can bind to hippocampal neurons, altering their metabolism or causing excitotoxic neuronal death by excessive entry of calcium into cells, and thus produce impaired learning and memory (25). In three studies, 25-35% of SLE patients had circulating serum anti-NR2 that showed no association with cognitive dysfunction (26-28). Visual memory and fine motor functions were associated with elevated anti-NR2 in SLE patients in one study, and two studies reported a relationship between depression and elevated anti-NR2 (27,29). No studies to date have studied CSF anti-NR2 and cognition in SLE.

Few of the recent studies of anti-NR2 antibodies and cognition in SLE have utilized control groups to confirm the unique presence of this autoantibody in SLE. In addition, despite the animal data suggesting memory deficits, few SLE studies have attempted to maximize their learning and memory data and explore the relationship with anti-NR2. This study aimed to first examine the frequency of elevations of anti-NR2 antibodies in nonNPSLE patients compared to controls. Second, we aimed to explore both global cognitive impairment, and more specifically, learning and memory dysfunction in SLE subjects with anti-NR2. Finally, we set out to examine anti-NR2 in relation to depressive symptoms.

Methods

Procedures

All subjects for this study were enrolled in a large prospective study of cognitive and immune function in SLE that commenced in August of 2005. Subjects signed an approved consent form authorized by the Colorado Multiple Institutional Review Board. The SLE subjects were obtained from a pool of SLE patients seen at National Jewish Health, the University of Colorado Hospital and local rheumatology clinics. All SLE subjects fulfilled the revised criteria as defined by the American College of Rheumatology (ACR) (30,31). The SLE patients' rheumatologist completed checklists containing SLE-related syndromes to confirm the diagnosis of SLE and to ensure that patients had no past or current major neuropsychiatric disorders other than suspected cognitive dysfunction. SLE disease activity was measured with the Systemic Lupus Disease Activity Index (SLEDAI) (32) by the patient's rheumatologist. Information regarding current medication and date of the SLE clinical diagnosis was also collected. Our rheumatology consultant reviewed all information prior to enrollment and if necessary, assured accuracy through contact with the physicians.

Patients with SLE were also screened for additional inclusion and exclusion criteria over the telephone using a 10-15 minute interview (8). Specifically excluded were other autoimmune disorders, genetic diseases, developmental delay, learning disability, demyelinative diseases, traumatic brain injury, infectious diseases, stroke, neurodegenerative diseases, neoplasms, metabolic disorders, toxic exposure, substance abuse, schizophrenia, and major mood disorders. Additional descriptors of SLE that were obtained included duration of SLE (from time of clinical diagnosis) and current medications. Control subjects were also screened and excluded for the presence of neuropsychiatric or medical histories prior to enrollment in the study, and all subjects with major depression were excluded (33).

Measures

Neuropsychological Measures—The Wechsler Test of Adult Reading Full Scale IQ (34) was obtained to evaluate overall intelligence between groups. A test battery proposed by the ACR-SLE (30) was administered by a trained psychometrician. Reliability and validity of the battery and details of the tests were published previously (12). The following tests and test scores utilized included: *WAIS-R Digit Symbol subtest-total score* (35), *Trail Making Test-Part B* (36), *Stroop Color and Word Test*-Color-Word total score (37), the learning trial and short delayed free recall scores from the *California Verbal Learning Test-Form II* (CVLT-II) (38), the immediate and 30-minute delayed recall scores the *Rey-Osterrieth Complex Figure Test* (Rey-O) (39), *WAIS-III Letter Number Sequencing-total score* (40), *Controlled Oral Word Association Test-total score and Animal Naming Test-total score* (41) and the Finger Tapping Test (36). *The Beck Depression Inventory-Second Edition* (BDI-II) (42) was administered as a self-report measure of depressive symptoms in the two weeks prior to completion.

A previously established Cognitive Impairment Index (CII) was calculated utilizing demographically-corrected T-scores for 12 tests identified in the ACR-SLE battery (12). T-scores below 40 were considered impaired. The CII has a range of 0 to 12, with a higher number representing greater cognitive impairment. A Memory Impairment Index (MII) was derived from the four learning and memory scores: learning trials and long-delayed recall from the CVLT-II (38), and immediate and delayed recall scores from the Rey-O (39). The four scores were converted to T-scores (M=50, SD=10) using available normative data for the tests. Each test score below a T-score of 40 was considered impaired. The range of the MII was from 0 (none) to 4 (most impaired).

Anti-NR2 Antibody Analysis—Serum samples were obtained from all subjects at the time of the cognitive testing via venipuncture and were stored at minus 70 degrees Celsius. Quantification of anti-NR2 antibodies was performed in an outside laboratory (Columbia University, New York) with an enzyme linked immunosorbent assay (ELISA) using a peptide sequence previously described (24). Anti-NR2 antibodies were classified as elevated if the value was two or more standard deviations above the mean optical density for controls. Results are presented as elevated or non-elevated anti-NR2.

Statistical Analyses

All statistical analyses were conducted with the SAS statistical analysis package (version 9.1; SAS Institute Inc., Cary, NC). Data are presented as means ± standard deviations for continuous variables and percent of subjects for categorical variables. For evaluation of group differences between nonNPSLE and controls, Student's t-test was used for continuous data that were normally distributed, and a non-parametric Wilcoxon's Rank Sums test was used on non-normally distributed continuous variables. Fisher's exact test was utilized for comparison of categorical variables. For all analyses, two-tailed tests were used and p-values less than 0.05 were designated to be statistically significant.

Results

There were 40 female and 3 male nonNPSLE participants, and 26 female and one male healthy control participants. The groups did not significantly differ in age, education level, gender distribution, and race/ethnicity (see Table 1). Seventy-five percent of the nonNPSLE and 100% of controls were employed (or students), and no significant difference was found on yearly salary (p=0.35). The mean estimated IQ was 101 (SD=7.7) for nonNPSLE and 106 (SD=6.9) for controls (p=0.01). The nonNPSLE group had a mean SLEDAI score of 5.3 (SD=5.6), a mean disease duration of 87.8 (SD=69.5) months, and 51% had elevated anti-DNA antibodies. Clinical manifestations for nonNPSLE patients and medications for nonNPSLE and controls at the time of enrollment into the study can be found in Tables 2 and 3.

Anti-NR2 antibodies were categorized as elevated or non-elevated. Six of 44 (14%) of the nonNPSLE subjects and 2 of 27 (7.4 %) controls showed elevation of anti-NR2 antibodies. There was no significant difference between the proportions (p=0.47). No significant differences in elevations of anti-NR2 associated with age, education, gender or ethnicity were found. No relationships between elevations of anti-NR2 and length of diagnosis, steroid dose or SLEDAI were reported in the nonNPSLE group.

Compared to controls, verbal recall was significantly lower for nonNPSLE subjects compared to controls (Table 4). Trends were noted for nonNPSLE patients to perform below controls on working memory and verbal learning. No significant differences were noted between the CII and MII when nonNPSLE subjects and controls were compared; 25.6% of the SLE subjects and 14.8% of the controls were impaired on the CII, and 33% of the nonNPSLE subjects and 18.5% of the control group were impaired on the MII.

There was a significant difference between the nonNPSLE and control groups on the total BDI-II score (p<0.001). The median (and inter-quartile range) was 9 (10) for nonNPSLE subjects and 2 (4) for controls; 96.3% of the controls showed minimal depressive symptoms compared to 76.7% of the nonNPSLE subjects.

As demonstrated in Table 5, there were no significant associations between elevations of anti-NR2 in the nonNPSLE sample and CII, MII and BDI-II levels. Only impairment on the Stroop Color Word Test was associated with the presence of anti-NR2 (see Table 6).

Discussion

Despite evidence of anti-NR2 antibodies inducing neuronal injury in animal models of SLE (24,25), our results are similar to those reported in three of four prior studies that did not find a relationship between cognitive impairment and the presence or elevation of anti-NR2 antibodies in patients with SLE. The overall frequency of elevated anti-NR2 was 14.0% in our sample of nonNPSLE patients, a relatively low figure compared to prior studies reporting frequencies ranging from 19% to 35% in SLE patients (26-29). Mild SLE disease activity, low levels of anti-dsDNA antibodies, and strict exclusion of patients with major neurological or psychiatric features may have contributed to these lower levels of anti-NR2 in our nonNPSLE sample.

The presence of anti-NR2 in 7.4% of controls in our study was somewhat surprising, although prior studies have reported a 4% to 5% incidence in healthy controls (29,43). Results indicated a higher level of cognitive impairment in our control subjects in this current study (14.8%) compared to a prior study using exactly the same procedures (12). Concerns about the suitability of this particular control group (13), and the presence of anti-NR2 in many subjects bring up the possibility that subclinical autoimmune disease activity occurred in some of the control sample. In our nonNPSLE group, the presence of anti-NR2 was not associated with demographics or disease characteristics such as disease activity or duration, similar to a prior study with SLE patients (29).

The current study shows no relationship between global cognitive function and the presence of anti-NR2 in nonNPSLE patients. The nonNPSLE patients in this study had no history or presence of major neurological or psychiatric syndromes. These patients were selected on this basis, and due to this extensive screening and the sample size of 43 patients was small compared to the sample sizes of prior studies (ranging from 57-93). Lack of statistical significance on hypothesis testing could be due to the small sample sizes and/or large variability of the data. Our results are not surprising given that prior studies including NPSLE patients with higher cognitive impairment (23-50%) showed no associations with elevations in anti-NR2 (26-28). None of these studies used the same approach to defining global cognitive impairment, nor did they include healthy controls, making additional comparisons difficult. In the current study, only one test of complex attention was more impaired in the subjects with elevated anti-NR2. Because only six nonNPSLE patients had elevated anti-NR2, the statistical significance may represent a small sample size problem.

Given the interest in hippocampal function in relation to anti-NR2 antibodies, our study was uniquely designed to investigate whether impairment on a memory index might be associated with anti-NR2. The MII utilized a very high cut-off whereby at least 3 of 4 verbal and nonverbal learning and memory tests from the ACR-SLE battery were required to be in the impaired range. Although 33% of the nonNPSLE patients showed memory impairment using this approach, there was no association between a high score on the MII (or on specific measures of verbal and nonverbal learning and memory) and presence of anti-NR2. One prior study did report a relationship between a specific test of immediate visual memory and anti-NR2, but not with delayed visual recall or immediate and delayed verbal recall (29). None of the other studies reported a correlation with individual tests of learning and memory (26-28). The relevance of this one prior finding is therefore limited.

This study also found no relationship between elevated anti-NR2 and levels of depression using a self-report measure. Notably, all SLE and control subjects with overt NP activity were screened out and a structured clinical interview was administered to exclude any patients with major depression. The nonNPSLE patients had higher levels of depressive symptoms compared to controls, with approximately 23% in the mild to moderate range.

The lack of association between anti-NR2 and depression is consistent with two prior studies (26,28). In contrast, two other studies did find an association: one group reported that anti-NR2 levels were associated with total BDI-II score (but specific BDI-II scores for the SLE group were not reported and no controls were available; 29), and another found that 11/60 (18%) of their SLE patients had at least mild depression levels that were associated with serum levels of anti-NR2 (27). As patients in our sample were not excluded for other NP manifestations, there may be some differences in sample selection. Continued studies with a range of SLE patients may be necessary to better understand the conflicting results.

Lack of a relationship between elevated anti-NR2 and cognitive or memory dysfunction suggests that measurement of serum NMDA antibody activity may not be a fruitful approach to understanding mechanisms of mild cognitive dysfunction in SLE. Mild cognitive dysfunction has been associated with white matter abnormalities in nonNPSLE, suggesting that white matter changes precede or occur independently of severe cognitive dysfunction that may be associated with more specific neuronal damage (44). Recent studies suggest that elevated anti-NR2 in the CSF was associated with severe neuropsychiatric dysfunction in SLE (45-47). In earlier animal models, breakdown of the blood-brain barrier is necessary for NMDA autoantibodies to cause neuronal death, alter hippocampal metabolism, and result in cognitive dysfunction (25). Furthermore, in SLE patients with severe and progressive cognitive dysfunction, anti-NMDA receptor antibodies have been eluted from brain tissue obtained postmortem (48). These observations indicate that anti-NMDA receptor antibodies in the CSF may be an important pathogenic mechanism in SLE patients with more severe cognitive decline than our patient population. A rough correlation exists between serum and CSF measures of anti-NR2, and thus continued studies of anti-NR2 in the CSF of SLE patients with more severe NP syndromes such as severe cognitive dysfunction may be useful. It is not likely that CSF analysis of nonNPSLE patients with mild cognitive problems will yield any associations since anti-NR-2 antibodies were not demonstrated in the serum of these patients.

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Table 1

Demographics for nonNPSLE and Controls

	nonNPSLE (n=43)			Controls (n=27)			p-value
	Mean	SD	Range	Mean	SD	Range	
Age (years)	36.5	9.0	18-51	33.9	8.8	19-49	0.23
Education (years)	14.7	2.5	10-20	15.3	2.1	12-20	0.25
Gender (% male)	7.0			3.7			1.00
Ethnicity (% A/AA/C/H)	4.7/25.6/55.8/14.0			7.4/7.4/70.4/14.8			0.29
Handedness (% right)	95.5			89.7			0.36

Table 2
Clinical Manifestations of nonNPSLE Subjects

Malar rash	44.2
Discoid rash	18.6
Photosensitivity	55.8
Oral ulcers	41.9
Renal disorder	18.6
Seizures or psychosis	0.0
Non-erosive arthritis	81.4
Hematologic disorder	34.9
Immunologic disorder	67.4
Positive antinuclear antibody	95.3
Positive anti-double stranded DNA antibody	51.0
Pleuritis or pericarditis	25.6

Table 3
Medication Use for nonNPSLE and Control Subjects

Variable	nonNPSLE (%)	Controls (%)	p-value
MEDICATIONS			
Non-steroidal anti-inflammatory drugs	23.3	0.0	0.005
Steroidal anti-inflammatory drugs; Prednisone	55.8	0.0	<.0001
Non-steroidal immunosuppressant	83.3	0.0	<.0001
Opioids	7.0	0.0	0.292
Anti-depressant	25.6	0.0	0.005
Anti-hypertensive drugs	30.2	0.0	0.001
Thyroid medications	25.6	8.0	0.111
Estrogen	2.3	0.0	1.000
GI drugs	25.6	4.0	0.044

Table 4

Comparison of Mean and SD for individual ACR tests, Cognitive Impairment Index and Memory Impairment Index Across groups

T-scores for Individual ACR Tests (see legend below)	nonNPSLE N=43		Controls N=27		p-value from Student t-test
	Mean	Std Dev	Mean	Std Dev	
Digit Symbol	48.44	10.65	52.33	7.88	0.106
Letter-Number Sequencing	51.47	10.59	56.15	9.62	0.067
Stroop Color-Word	50.33	8.67	53.07	9.22	0.212
Trail Making Part B	52.07	10.41	51.85	9.71	0.930
Letter fluency	46.21	10.34	44.44	10.99	0.500
Category fluency	49.95	9.79	49.22	7.74	0.743
Verbal learning	48.49	11.26	53.33	12.51	0.098
Verbal recall	45.35	11.41	51.67	10.74	*0.022
Nonverbal recall	36.42	12.33	41.19	11.31	0.109
Nonverbal learning	38.67	11.70	42.93	12.03	0.148
Tapping-dominant hand	50.98	11.78	50.56	9.51	*0.709
Tapping-non-dominant hand	49.21	9.29	51.67	10.03	0.300
Impairment Indices					
Cognitive Impairment Index (range 0-12)	2.63	2.21	2.04	1.63	0.236
Memory Impairment Index (range 0-4)	1.56	1.35	1.15	1.26	0.209

*p-value for Verbal recall and Tapping-dominant hand from Wilcoxon Rank Sums test for non-normally distributed data. For Verbal recall, the median (inter-quartile range) for nonNPSLE was 45 (15) and 55 (15) for controls. For Tapping-dominant hand, the median (interquartile range) for SLE was 50 (19) for SLE and 50 (7) for controls.

Digit Symbol=Wechsler Adult Intelligence Scale-Revised Digit Symbol Test, total score; Letter-Number Sequencing=Wechsler Adult Intelligence Scale-III Letter Number Sequencing Test, total score; Stroop Color Word=Stroop Color-Word Test, color-word score; Trail Making Part B=Trail Making Test-Part B, total completion time; Letter fluency=Controlled Oral Word Association Test, letters F, A, and S; Category fluency=Animal Naming Test, total score; Verbal recall=California Verbal Learning Test-II, short-delayed recall; Verbal learning=California Verbal Learning Test-II, learning trials 1-5; Nonverbal recall=Rey-Osterrieth delayed recall; Nonverbal learning= Rey-Osterrieth immediate recall; Tapping-dominant hand=Finger Tapping Test-dominant hand; Tapping-non-dominant hand =Finger Tapping Test-non-dominant hand

Table 5

Associations between Elevated anti-NR2 and CII, MII and BDI-II in nonNPSLE Only (N=43)

Variable	Level	Elevated anti-NR2 N (%)		p-value from Fisher's Exact Test
		No	Yes	
CII	No (< 4)	28 (75.7)	4 (66.7)	0.637
	Yes (≥ 4)	9 (24.3)	2 (33.3)	
MII	No (0-2)	28 (75.7)	5 (83.3)	1.000
	Yes (3-4)	9 (24.3)	1 (16.7)	
BDI	Minimal (0-13)	28 (75.7)	5 (83.3)	1.000
	Mild (14-19)	5 (13.5)	1 (16.7)	
	Moderate (20-28)	4 (10.8)	0 (0)	

CII=Cognitive Impairment Index (4 or more of 12 scores impaired)

MII= Memory Impairment Index (3 or 4 of 4 scores impaired)

BDI-II=Beck Depression Inventory-Form II (minimal score 0-13; mild score 14- 19; moderate score 20-28; severe score 29-63)

Table 6

Association between Elevated Anti-NR2 and Impairment on Individual ACR Tests in nonNPSLE

Impaired ACR Test	Elevated Anti-NR2				p-value from Fisher's Exact Test
	No		Yes*		
	N	%	N	%	
Digit Symbol	6	16.2	0	0.0	0.571
Letter-Number Sequencing	5	13.5	0	0.0	1.000
Stroop Color-Word	2	5.4	3	50.0	0.014
Trail Making Part B	4	10.8	1	16.7	0.547
Letter fluency	8	21.6	3	50.0	0.164
Category fluency	4	10.8	0	0.0	1.000
Verbal learning	8	21.6	0	0.0	0.574
Verbal recall	11	29.7	1	16.7	0.659
Nonverbal learning	20	54.1	2	33.3	0.412
Nonverbal recall	21	56.8	4	66.7	1.000
Tapping-dominant hand	6	16.2	1	16.7	1.000
Tapping-non-dominant hand	5	13.5	1	16.7	1.000

* Six SLE patients with elevated anti-NR2; 37 without anti-NR2