Anti-NR2 Glutamate Receptor Antibodies and Cognitive Function in Systemic Lupus Erythematosus

JOHN G. HANLY, JODY ROBICHAUD, and JOHN D. FISK

ABSTRACT. ***Objective.*** To determine the prevalence of circulating anti-NR2 antibodies and their association with neuropsychiatric systemic lupus erythematosus (NP-SLE), particularly cognitive function, in women with SLE.

Methods. Cognitive function was assessed in 65 consecutive women with SLE from a single referral center using standardized neuropsychological tests. These were selected subtests of the Wechsler Adult Intelligence Scale-Revised, the Wechsler Memory Scale-Revised, and the California Verbal Learning Test, which provided information on 8 areas of cognitive function. After a mean followup of 64 (range 52–71) months, cognitive assessments were repeated. Global and domain-specific cognitive impairment was examined using predetermined decision rules, and the change in individual tests of cognitive performance over time was also examined. Overt NP-SLE was identified by clinical assessment and classified using the American College of Rheumatology nomenclature. Circulating IgG anti-NR2 and anti-dsDNA antibodies were determined by ELISA on up to 4 occasions over the study period. A positive result was defined as at least 3 standard deviations above the mean of healthy controls.

Results. At enrollment, 15/65 (23%) patients had cognitive impairment. This fell to 7/54 (13%) at followup. In addition 15/65 (23%) patients had a history of clinically overt NP-SLE. Twenty-three of 65 (35%) patients had anti-NR2 antibodies and 48/65 (74%) had anti-dsDNA antibodies. Anti-NR2 antibodies were present in 18/48 (38%) patients with anti-DNA antibodies, and 18/23 patients (78%) with anti-NR2 antibodies also had anti-dsDNA antibodies. There was no association between global cognitive impairment, domain-specific cognitive impairment, or a history of clinically overt NP-SLE and either the presence or amount of anti-NR2 or anti-dsDNA antibodies ($p > 0.05$). When change in cognitive performance or the occurrence of new NP-SLE events over the 5-year followup period was examined, there was no significant association with persistent elevation of either antibody ($p > 0.05$). Similarly there was no association between a rise in autoantibodies over time and the development of overt NP events or cognitive decline ($p > 0.05$).

Conclusion. These results indicate that anti-NR2 antibodies occur in 35% of women with SLE and are infrequent in the absence of detectable anti-dsDNA antibodies. Their presence in the circulation is not associated with cognitive dysfunction at a single timepoint, and an increase in or persistently elevated antibody levels are not associated with a change in cognitive performance over time. There was no association with clinically overt NP-SLE. However, as our study did not examine cerebrospinal fluid samples, these results do not exclude a potential pathogenic role in selected patients for this group of autoantibodies should they penetrate the blood-brain barrier and thereby gain direct access to neuronal tissues. (J Rheumatol 2006;33:1553–8)

Key Indexing Terms:
GLUTAMATE RECEPTOR ANTIBODIES COGNITIVE IMPAIRMENT LUPUS

Neuropsychiatric (NP) disease is well described in patients with systemic lupus erythematosus (SLE) and clinical manifestations vary from the commonplace, such as headache, to the rare, such as psychosis[1]. Cognitive impairment, demonstrated by formal neuropsychological testing, is one of the most common manifestations and has been reported in 12–87% of patients[2-7]. Although the etiology is likely multifactorial, some studies have reported an association with antiphospholipid antibodies (aPL), particularly if there is persistent elevation in circulating autoantibodies over many years[8,9].

Studies in animal models of SLE have shown that a subset of anti-double-stranded (ds) DNA antibodies crossreact with the extracellular, ligand-binding domain of NR2 receptors[10]. The N-methyl-D-aspartate (NMDA) receptors NR2a and NR2b are present on neurons throughout the forebrain and are known to play a role in learning and memory[11] and in the pathogenesis of psychosis[12]. *In vivo* and *in vitro* studies in ani-

From the Division of Rheumatology, Department of Medicine, and the Department of Psychiatry, Dalhousie University, Halifax, Nova Scotia, Canada.

Supported by a grant from the Canadian Institutes of Health Research.

J.G. Hanly, MD, MRCPI, FRCPC, Professor of Medicine; J. Robichaud, BSc, Research Technologist, Division of Rheumatology, Department of Medicine; J.D. Fisk, PhD, Associate Professor of Psychiatry, Department of Psychiatry, Dalhousie University.

Address reprint requests to Dr. J.G. Hanly, Division of Rheumatology, Nova Scotia Rehabilitation Center, 2nd Floor, 1341 Summer Street, Halifax, Nova Scotia B3H 4K4, Canada.
E-mail: john.hanly@cdha.nshealth.ca

Accepted for publication March 2, 2006.

mal models have found a specific, immune mediated, cytotoxic effect on neuronal cells[10,13], thereby providing a plausible biological role for these autoantibodies in the pathogenesis of NP-SLE. To date, however, most of the information on anti-NR2 receptor antibodies in SLE has been derived from murine models of the disease. Our objective was to determine the prevalence of circulating anti-NR2 antibodies in a group of women with SLE and to examine their possible association with NP disease, in particular cognitive impairment.

MATERIALS AND METHODS

Patients. Sixty-five women who fulfilled the American College of Rheumatology (ACR) criteria for SLE[14] attending a Lupus Clinic at an academic medical center were recruited for the study. Most were part of a cohort of 70 patients with SLE who underwent a prospective analysis of cognitive function over 5 years[8,15]. Seven of the original 70 patients were not included, as they had inadequate stored serum samples available for antibody testing and 2 new patients were recruited to the original cohort. For inclusion in this study all patients were required to have undergone neuropsychological assessment at study entry and to have stored serum available from blood collected on at least 2 and up to 4 occasions over the ensuing 5 years. The mean number of samples available from each patient was 3.5. The interval between the first and second collections was 12 months, between the second and third 24 months, and between the third and final assessment 24 months. Fifty-four (83%) of the 65 patients had repeat neuropsychological testing performed after a mean of 64 (range 52–71) months following the initial assessment. Serum samples were also collected from 50 patients with rheumatoid arthritis (RA) and 68 patients with multiple sclerosis (MS) to be used as controls in the evaluation of anti-NR2 and anti-dsDNA antibodies.

Demographic information and clinical neuropsychiatric events. Disease duration was defined as the interval between the date of diagnosis of SLE and the time of study enrollment. Occurrence of overt NP-SLE was classified according to ACR nomenclature and definitions[16]. These were neurologic or psychiatric events that occurred since the diagnosis of SLE and for which there was no other satisfactory explanation. Other possible etiologies such as infection, hypertension, renal failure, concurrent medication(s), or illness were considered and excluded.

Neuropsychological assessment. Evaluation of cognitive performance was based on 3 standardized tests: the California Verbal Learning Test (CVLT), subsets of the Wechsler Adult Intelligence Scale-Revised (WAIS-R), and subsets of the Wechsler Memory Scale-Revised (WMS-R). An estimate of verbal intelligence quotient (IQ) was provided by the National Adult Reading Test-Revised (NART). This 90-minute test battery permitted evaluation in 8 areas of cognitive function, namely global memory, immediate recall, delayed recall and delayed recognition memory, attention-concentration, verbal abstraction, visual construction, and psychomotor speed. Test procedures and decision rules for overall cognitive impairment and impairment in individual areas of cognitive function have been described[4,8,15,17]. Changes in cognitive function over time in patients grouped according to antibody status were assessed by change in raw scores of individual neuropsychological tests.

Measurement of anti-NR2 glutamate receptor antibodies. IgG anti-NR2 glutamate receptor antibodies were quantified by ELISA[10]. Flat-bottom 96-well microtiter ELISA plates (Grenier-MB 96F; Bellco Glass, Vineland, NJ, USA) were coated with 50 μl/well of 10 g/ml L-DWEYS peptide (AnaSpec, San Jose, CA, USA) overnight at 37°C. Wells were blocked with heat inactivated 3% fetal bovine serum (FBS; Gemini Bio Products, Woodland, CA, USA) (100 μl/well) at room temperature (RT) for 1 h and washed with phosphate buffered saline (PBS)–Tween (0.05%). Samples diluted (1:50) in 3% FBS were added in triplicate to plates and incubated for 1 h at RT. Plates were then washed with PBS-Tween, and further incubated with goat anti-human IgG linked to alkaline phosphatase (Southern Biotech, Birmingham, AL, USA) for 1 h at RT. Plates were washed again with PBS-Tween and developed with alkaline phosphatase substrate tablets (p-nitrophenyl phosphate; Sigma, St. Louis, MO, USA), and absorbance at 405 nm was measured using a Titertek Multiscan Plus ELISA reader. Seven sera from a pool of 30 healthy individuals were included on each plate. The level of autoantibodies was expressed as a Z score using the following formula, as described[8]: [mean optical density (OD) of sample – mean OD of controls]/standard deviation (SD) of controls. Determination of Z scores provides a quantitative measure of autoantibody and permits comparison of results from different ELISA plates.

At study enrollment, a positive result was defined as at least 3 standard deviations (Z score $\geq$ 3) above the mean of healthy controls. Decision rules were defined *a priori* to determine antibody status for each patient throughout the study period. Thus, patients who had at least 2 antibody levels of 3 (Z score) or more were assigned to group 3a+, and patients whose mean anti-NR2 antibody level over the period of study was 3 (Z score) or more were assigned to group 3b+. Patients who had at least 2 antibody levels $\geq$ 5 (Z score) were assigned to group 5a+ and those whose mean anti-NR2 antibody level over the study was $\geq$ 5 (Z score) were assigned to group 5b+.

Measurement of anti-dsDNA antibodies. IgG anti-dsDNA binding activity was tested by ELISA[10]. Flat-bottom 96-well microtiter ELISA plates were coated with 25 μl/well of 100 μg/ml PBS of calf thymus DNA, which had been sonicated and filtered to remove single-stranded DNA. The plates were incubated overnight at 37°C until dry, washed with distilled water, and blocked with 1% bovine serum albumen (BSA; 50 μl/well) in PBS for 1 h at 37°C. After washing with PBS-Tween, samples diluted (1:250) in 0.2% BSA-PBS were added in triplicate and incubated at 37°C for 1 h. Plates were washed with PBS-Tween and further incubated with goat anti-human IgG linked to alkaline phosphatase for 1 h at 37°C. Plates were again washed with PBS-Tween and developed with alkaline phosphatase substrate tablets (p-nitrophenyl phosphate; Sigma) and absorbance at 405 nm was measured using a Titertek Multiscan Plus ELISA reader. Levels of anti-DNA antibodies were expressed as Z scores and a positive result at study enrollment was defined as at least 3 standard deviations above the mean of healthy controls. The decision rules used to determine anti-DNA antibody status throughout the study period (3a+, 3b+; 5a+, 5b+) were identical to those used for anti-NR2 antibodies.

Statistical analysis. Differences between proportions of patients assigned to groups were determined by Fisher's exact test. Differences between mean scores of performance on individual neuropsychological tests were examined by paired t test. Due to the exploratory design of the study no adjustments were made for multiple comparisons.

RESULTS

Patient demographics. Clinical features of the 65 patients with SLE are summarized in Table 1. The study population consisted predominantly of middle-aged, Caucasian women with a mean disease duration of 5.5 years.

Anti-NR2 glutamate receptor antibodies. A total of 23/65 (35%) patients had elevated anti-NR2 antibodies (i.e., Z score $\geq$ 3) at study entry, all but 5 of whom also had elevated anti-dsDNA antibodies. For the total group at study entry there was also a significant correlation between the levels of anti-NR2 and anti-dsDNA antibodies ($r = 0.37$; $p < 0.01$). Three of 50 (6%) patients with RA and 6/68 (8.8%) patients with MS were also positive for anti-NR2 antibodies. With the exception of one patient with MS, all of these patients also had elevated anti-dsDNA antibodies. The proportion of SLE patients who fulfilled the decision rules for persistent anti-NR2 glutamate receptor antibody positivity is summarized in Table 2. Forty-four percent and 39% of patients fulfilled the decision rules for groups 3a+ and 3b+. A lower proportion of patients, 17%

Table 1. Clinical and demographic features of women with SLE (n = 65) at study enrollment.

Age, yrs	38.8 ± 11.1
Caucasian: African American: Native American	61:3:1
Disease duration, yrs	5.5 ± 6.4
Medications (%)	
NSAID	28 (43)
Antimalarials	30 (46)
Prednisone	23 (35)
Immunosuppressives	9 (14)

NSAID: nonsteroidal antiinflammatory drugs.

Table 2. Proportion of patients with persistently elevated IgG anti-NR2 glutamate receptor antibodies and anti-dsDNA antibodies. Groups 3a+ and 5a+ represent patients with a minimum of 2 anti-NR2 or anti-dsDNA antibody levels ≥ 3 and 5 Z scores, respectively. Groups 3b+ and 5b+ indicate patients with a mean anti-NR2 or anti-dsDNA antibody level of at least 3 and 5 Z scores, respectively, over the period of study.

Group	Anti-NR2 Antibodies n = 54 (%)	Anti-dsDNA Antibodies n = 54 (%)
3a+	24 (44)	40 (74)
3b+	21 (39)	43 (80)
5a+	9 (17)	35 (65)
5b+	7 (13)	39 (72)

and 13%, fulfilled the more demanding decision rules for groups 5a+ and 5b+. These decision rules identified 2 groups of patients with persistent separation in their anti-NR2 antibody levels over the 5-year study period, as illustrated in Figure 1. Identification and study of such distinct serologic populations was of interest in view of the documented correlation between persistent anticardiolipin antibody (aCL) production and cognitive decline in patients with SLE[8,9].

Anti-dsDNA antibodies. Forty-eight of 65 patients (74%) had elevated anti-dsDNA antibodies (i.e., Z score ≥ 3) at study entry, compared to 8/50 (16%) patients with RA and 16/68 (23.5%) patients with MS. Regarding persistence of anti-dsDNA antibodies, 74% and 80% of patients with SLE fulfilled the decision rules for 3a+ and 3b+, respectively, while 65% and 72% of patients met the decision rules for 5a+ and 5b+, respectively (Table 2, Figure 1).

Clinical-serologic associations. At the initial assessment 15/65 (23%) patients fulfilled criteria for overall cognitive impairment compared to 7/54 (13%) at followup 52–71 months later. This is comparable to our findings in a larger study population[15]. At study enrollment there was no association between the presence of cognitive impairment, as reflected by overall impairment or impairment in any of the 8 areas of cognitive function, and the presence or amount of either anti-NR2 or anti-dsDNA antibodies ($p > 0.05$; Table 3). Further, when the association between elevated autoantibodies and change in individual cognitive test scores over the 5-year period of study was examined, there was no association

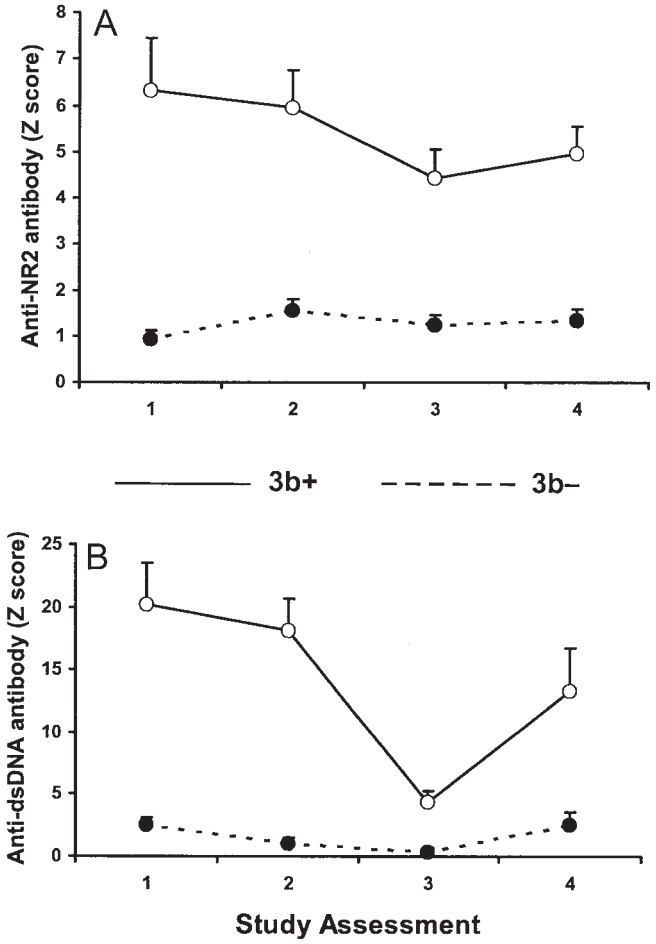

Figure 1. Mean (± SEM) IgG anti-NR2 glutamate receptor antibody levels (A) and anti-dsDNA antibody levels (B) for groups of SLE patients identified by decision rule 3b. Two serologically distinct populations of SLE patients are identified over the 5-year period of study. The interval between the first and second assessments was 12 months, between the second and third 24 months, and between the third and final assessment 24 months.

between the persistence of either antibody and change in cognitive performance over time ($p > 0.05$; Figure 2). We also examined whether a rise in autoantibodies over time, defined as an increase in Z score of 2 or more between study enrollment and any of the subsequent assessments, was associated with a change in scores of individual cognitive tests. No such association was found ($p > 0.05$; data not shown).

The cumulative NP-SLE manifestations in the study sample included seizures, stroke, transient cerebral ischemia, transverse myelitis, cranial neuropathy, peripheral neuropathy, acute confusional state, psychosis, and depression requiring medical intervention. A total of 15 (23%) patients had at least one clinically overt manifestation of NP-SLE (Table 4). However, there was no association between the occurrence of any of these manifestations, individually or collectively, with either anti-NR2 or anti-dsDNA antibodies ($p > 0.05$). Similarly, the development of new NP-SLE events over time was not associated with either persistently elevated anti-NR2

Table 3. Association between elevated IgG anti-NR2 glutamate receptor antibodies, anti-dsDNA antibodies, and cognitive impairment in 65 patients with SLE at study enrollment. Elevated IgG anti-NR2 glutamate receptor antibodies and anti-dsDNA antibodies were defined as 3 or more standard deviations above the mean of controls. Results are expressed as number (percentage).

Cognitive Domain	Total Impaired	Impaired		Impaired	
		Anti-NR2 Positive, n = 23	Anti-NR2 Negative, n = 42	Anti-dsDNA Positive, n = 48	Anti-dsDNA Negative, n = 17
Attention/concentration	9 (14)	3 (13)	6 (14)	6 (13)	3 (18)
Verbal abstraction	2 (3)	1 (4)	1 (2)	1 (2)	1 (6)
Visual construction	24 (37)	8 (35)	16 (38)	15 (31)	9 (53)
Psychomotor speed	12 (19)	5 (22)	7 (17)	8 (17)	4 (24)
Recent memory	9 (14)	2 (9)	6 (17)	6 (13)	3 (18)
Delayed memory	5 (8)	2 (9)	3 (7)	3 (6)	2 (12)
Retrieval memory	25 (39)	9 (39)	16 (38)	20 (42)	5 (29)
Global memory	5 (8)	3 (13)	2 (5)	4 (8)	1 (6)
Overall cognitive impairment	15 (23)	6 (26)	9 (21)	10 (21)	5 (29)

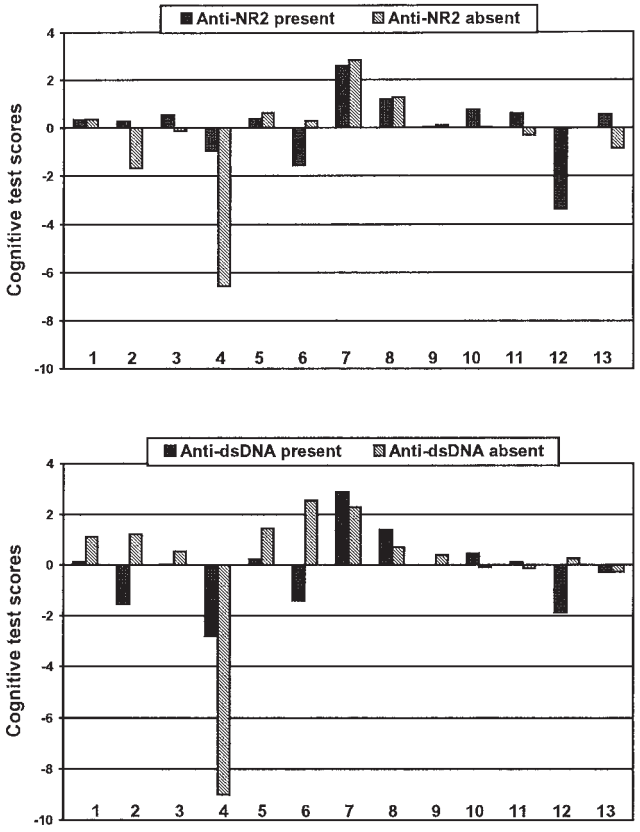

Figure 2. Mean change in raw scores of individual neuropsychological tests over the 5-year period of study. A positive change indicates improvement, negative change indicates decline in test performance. None of the changes reached statistical significance ($p > 0.05$). Individual tests included: 1: CVLT trial 1 recall; 2: trials 1–5 total recall; 3: 20 minute delayed recall; 4: recognition discriminability; 5: WAIS-R Information; 6: Similarities; 7: Block Design; 8: Digit Symbol; and 9: Picture Completion; 10: WMS-R Digit Span Backwards; 11: Digit Span Forwards; 12: Visual Span Backwards; and 13: Visual Span Forwards.

or anti-dsDNA autoantibodies ($p > 0.05$), and there was no association between a rise in autoantibodies and the development of new NP-SLE events ($p > 0.05$; data not shown).

DISCUSSION

Nervous system manifestations of SLE include a range of neurologic and psychiatric features[1]. Although the etiology of NP-SLE is multifactorial, it is likely that some subsets of NP disease are attributable to pathogenic autoantibodies[1,18]. Previous targets of autoantibody reactivity have included both nervous system-specific (e.g., neuronal) and nonspecific (e.g., ribosomes, serum phospholipid-binding proteins) antigens. A recent and novel target for autoantibody reactivity in SLE patients with NP disease is the family of surface neuronal NR2 glutamate receptors[10,13]. Studies in inbred strains of lupus mice have shown the presence of anti-NR2 antibodies that have the ability to induce neuronal injury[10,13]. We found anti-NR2 autoantibodies in 35% of unselected patients with SLE. However, in our study population, there was no demonstrable association with clinically overt NP disease, and in particular, there was no association with cognitive impairment.

Of the many clinical manifestations of NP-SLE, abnormalities in cognitive function have been the most thoroughly studied. Using various standardized neuropsychological tests, the majority of cross-sectional studies have shown an increased prevalence of cognitive impairment in patients with SLE compared to appropriately matched healthy subjects[3,4,6] and patients with disease that does not primarily affect central nervous system functioning[4,19,20]. Most of the SLE patients have mild impairment and a limited number of longitudinal studies have indicated relatively little overall progression over 5 years[15,17,21-23]. However, subsets of SLE patients do show a significant decline in selected areas of cognitive performance over time, and both clinical and laboratory variables have

Table 4. Association between elevated IgG anti-NR2 glutamate receptor antibodies, anti-dsDNA antibodies, and clinically overt NP-SLE in 65 patients at study enrollment. Elevated IgG anti-NR2 glutamate receptor antibodies and anti-dsDNA antibodies were defined as 3 or more standard deviations above the mean of controls. Results are expressed as number (percentage).

NP-SLE Feature	Total NP-SLE	NP-SLE		NP-SLE	
		Anti-NR2 Positive, n = 23	Anti-NR2 Negative, n = 42	Anti-dsDNA Positive, n = 48	Anti-dsDNA Negative, n = 17
Seizures	4 (6)	1 (4)	3 (7)	2 (4)	2 (12)
Stroke	1 (2)	1 (4)	0 (0)	1 (2)	0 (0)
Transient cerebral ischemia	2 (3)	1 (4)	1 (2)	2 (4)	0 (0)
Transverse myelitis	1 (2)	0 (0)	1 (2)	1 (2)	0 (0)
Cranial neuropathy	4 (6)	0 (0)	4 (10)	3 (6)	1 (6)
Peripheral neuropathy	3 (5)	0 (0)	3 (7)	1 (2)	2 (12)
Acute confusional state	5 (8)	1 (4)	4 (10)	4 (8)	1 (6)
Psychosis	1 (2)	1 (4)	0 (0)	1 (2)	0 (0)
Depression	3 (5)	2 (9)	1 (2)	3 (6)	0 (0)
Any NP-SLE event	15 (23)	5 (22)	10 (24)	11 (23)	4 (24)

been examined as potential predictors of such changes. Autoantibodies studied in this regard include antineuronal[24–26], antiribosomal[26], lymphocytotoxic[26-28], and antiphospholipid antibodies[8,9,26,29]. Only antiphospholipid antibodies, whether determined by immunoassays (aCL) or functional coagulation tests (lupus anticoagulant), have shown an association with cognitive impairment[8,9,26,29]. In particular, 2 prospective studies have reported an association between persistent IgG or IgA aCL reactivity and decline in selected areas of cognitive function over 2–5 years[8,9].

NMDA receptors NR2a and NR2b, which are present on neurons throughout the forebrain, play a role in cognitive functioning, such as learning and memory[11]. They display altered expression in patients with major psychosis[12] and if engaged by receptor antagonists cause hallucinations and paranoia[30]. Studies in lupus-prone mice found that a subset of anti-dsDNA antibodies crossreact with a pentapeptide consensus sequence that is present in the extracellular, ligand-binding domain of NR2 receptors[10]. The antibodies were also isolated from the serum of 4 SLE patients and from the cerebrospinal fluid (CSF) of one SLE patient with progressive cognitive decline[10]. Of critical importance is the observation that these antibodies induced apoptotic cell death of neurons *in vitro* and *in vivo*[10]. Thus, in contrast to the previously described antineuronal antibodies in SLE, the anti-NR2 glutamate receptor antibodies appear to have a functional consequence leading to neuronal injury in a manner similar to that seen in excitatory amino acid toxicity[31]. This effect is mediated via the antigen-binding portion of the molecule and is specifically inhibited by memantine, an NMDA receptor antagonist[13]. Morever, enhanced permeability of the blood-brain barrier is critical for circulating autoantibodies to enter the CSF and gain access to neuronal cells[13].

We found that IgG anti-NR2 antibodies occur in 35% of SLE patients and in 38% of patients with anti-dsDNA antibodies. The detection of anti-DNA antibodies, albeit in a low frequency, in patients with RA and MS is in keeping with previous studies[32-34]. However, the frequency of anti-NR2 antibodies was low in both populations. Although levels of circulating anti-NR2 antibodies in patients with SLE may fluctuate over time, some patients had persistently elevated levels. In cross-sectional analyses, we were unable to find an association between the anti-NR2 antibodies and with either impairment in overall cognitive function or with any of the individual domains of cognition. Further, there was no association between a rise in or persistently elevated autoantibody levels and change in cognitive function over 5 years. Similarly, there was no association with clinically overt manifestations of NP-SLE. To our knowledge this is the first study to prospectively evaluate the association between circulating anti-NR2 antibodies and nervous system disease in SLE.

Despite many novel aspects to our study there were a number of shortcomings that should be considered in future work. The major clinical focus of NP-SLE in our study was cognitive function. This was appropriate, given the high relative frequency of cognitive impairment in SLE and preliminary data from murine and human lupus studies reporting an association with anti-NR2 antibodies[10]. Other NP manifestations were infrequent and a larger study will be required to examine the potential pathogenic role of anti-NR2 antibodies in these manifestations. Finally, as our study did not include analysis of the CSF, we do not know if anti-NR2 antibodies penetrated the blood-brain barrier, which is critical for interaction with neuronal antigens. As this is essential for these autoantibodies to exert their pathogenic effect, future studies will need to incorporate some measurement of blood-brain barrier integrity by means of neuroimaging or direct sampling of CSF.

ACKNOWLEDGMENT

We are grateful to the attending staff rheumatologists and the Multiple Sclerosis Research Unit at Dalhousie University for allowing us to study their patients, and to Dr. Betty Diamond, Columbia University, New York, New York, USA, for measuring anti-NR2 and anti-dsDNA antibodies.

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