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Autoantibodies and Neuropsychiatric Events at the Time of Systemic Lupus Erythematosus Diagnosis

Results From an International Inception Cohort Study

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Objective. **To examine, in an inception cohort of systemic lupus erythematosus (SLE) patients, the association between neuropsychiatric (NP) events and anti–ribosomal P (anti-P), antiphospholipid (lupus anticoagulant [LAC], anticardiolipin), anti–β2-glycoprotein I, and anti–NR2 glutamate receptor antibodies.**

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Methods. **NP events were identified using the American College of Rheumatology case definitions and clustered into central/peripheral and diffuse/focal events. Attribution of NP events to SLE was determined using decision rules of differing stringency. Autoantibodies were measured without knowledge of NP events or their attribution.**

Results. **Four hundred twelve patients were studied (87.4% female; mean ± SD age 34.9 ± 13.5 years, mean ± SD disease duration 5.0 ± 4.2 months). There were 214 NP events in 133 patients (32.3%). The proportion of NP events attributed to SLE varied from 15% to 36%. There was no association between autoantibodies and NP events overall. However, the frequency of anti-P antibodies in patients with central NP events attributed to SLE was 4 of 20 (20%), versus 3 of 107 (2.8%) in patients with other NP events and 24 of 279 (8.6%) in those with no NP events ($P = 0.04$). Among patients with diffuse NP events, 3 of 11 had anti-P antibodies (27%), compared with 4 of 111 patients with other NP events (3.6%) and 24 of 279 of those with no NP events (8.6%) ($P = 0.02$). Specific clinical–serologic associations were found between anti-P and psychosis attributed to SLE ($P = 0.02$) and between LAC and cerebrovascular disease attributed to SLE ($P = 0.038$). There was no significant association between other autoantibodies and NP events.**

Conclusion. **Clinically distinct NP events attributed to SLE and occurring around the time of diagnosis were found to be associated with anti-P antibodies and LAC. This suggests that there are different autoimmune pathogenetic mechanisms, although low sensitivity limits the clinical application of testing for these antibodies.**

Neurologic and psychiatric events are well described in patients with systemic lupus erythematosus (SLE). The reported frequency of neuropsychiatric (NP) disease among patients with SLE, classified using the American College of Rheumatology (ACR) case definitions (1), varies from 37% to 95% (2–6). The clinical significance of NP events is highlighted by their negative impact on health-related quality of life (4,7) and increased mortality among patients with NPSLE (8). Determining the correct attribution of NP events is a significant challenge when managing nervous system disease in individual SLE patients and is a critical factor in selecting the correct treatment and determining prognosis. To date there are no reliable biomarkers that can be used to make these decisions.

Lupus-specific mechanisms underlying NP disease include vasculopathy of intracranial vessels, local or systemic production of inflammatory mediators, and generation of specific autoantibodies (9–12). The latter include antiphospholipid antibodies (aPL), anti–ribosomal P antibodies (anti-P), and autoantibodies that bind to neuronal antigens such as the recently described antibodies to the NR2 glutamate receptor (13). Although there is biologic plausibility and data from in vitro studies and animal studies to implicate these autoantibodies in the causality of nervous system disease (13–17), studies of humans with SLE have yielded inconsistent findings (18–22). Previous investigations have been limited by their cross-sectional study design, heterogeneity of study patients in terms of disease duration, and lack of standardization in both the classification of NP events and the methodology used for autoantibody detection. Therefore, in the current study, we assembled an international inception cohort of SLE patients to examine the association between a panel of autoantibodies and nervous system events at the time of diagnosis of SLE.

PATIENTS AND METHODS

Research study network. The study was conducted by members of the Systemic Lupus International Collaborating Clinics (SLICC) (23), which consists of 30 investigators at 27 international academic medical centers. Data were collected prospectively on patients presenting with a new diagnosis of SLE as previously described (7). The study protocol was approved by the Capital Health Research Ethics Board (Halifax, Nova Scotia, Canada) and by each participating center's own institutional research ethics review board.

Patients. All patients fulfilled the ACR classification criteria for SLE (24) and provided written informed consent. The date of diagnosis was taken as the time when these cumulative criteria were first recognized as being met. Enrollment was permitted for up to 15 months from the time of diagnosis. Variables recorded included age, sex, ethnicity, education level, and medication history. Lupus-related variables included the ACR criteria for SLE, the SLE Disease Activity Index (SLEDAI) (25), and the SLICC/ACR damage index (SDI) (26) in patients whose disease duration was ≥6 months. Routine laboratory data recorded included results of hematologic testing, serum and urine chemistry analyses, and testing for immunologic variables required for the generation of the SLEDAI and SDI scores.

Identification of neuropsychiatric events. An enrollment window was defined, within which all NP events were captured. To ensure inclusion of NP events that may have been a component of the presentation of lupus, the enrollment window extended from 6 months prior to the date of diagnosis of SLE up to the enrollment date. Because the latter could occur up to 15 months following the diagnosis of SLE, the maximum duration of the enrollment window was 21 months.

The specific NP events identified within this time frame were based on the ACR nomenclature and case definitions for 19 NP syndromes described in SLE (1). Screening for all NP syndromes was done primarily by clinical evaluation, and subsequent investigations were performed only if clinically warranted. In order to further improve the consistency of data collection, a checklist of NP symptoms was distributed to each of the participating sites for use during patient encounters. In the majority of cases, the diagnosis of cognitive impairment was made on the basis of clinical assessment using a standard definition of cognitive impairment from the SDI rather than formal neuropsychological testing, which was not available at all sites. When neuropsychological testing was available and was completed because of clinical suspicion of cognitive impairment, the 8 cognitive domains assessed were simple attention, complex attention, memory, visual-spatial processing, language, reasoning/problem-solving, psychomotor speed, and executive functions. When the site investigator believed there were sufficient grounds to make a clinical diagnosis of cognitive impairment, he or she identified deficits in the domains affected using the definitions provided with the ACR case definitions (1).

All NP events occurring within the enrollment window were identified, and additional information was recorded; the specific information depended on the type of NP event and was guided by the ACR glossary for the 19 NP syndromes (1). This included a list of potential etiologic factors other than SLE that were identified for exclusion or recognized as an "association," acknowledging that in some situations it is not possible to be definitive about attribution. Collectively, these "exclusions" and "associations" were referred to as "non-SLE factors" and were used in part to determine the eventual attribution of NP events. Patients could have more than one type of NP event, but repeated episodes of the same NP event occurring within the enrollment window were recorded only once. In the latter case the time of the first episode was taken as the date of onset of the NP event.

Attribution of neuropsychiatric events. Staff at participating centers were asked to report all NP events regardless of etiology, and decision rules were derived to determine the attribution of NP events. Factors that were considered included 1) onset of NP event(s) prior to the enrollment window, 2) presence of concurrent non-SLE factor(s) that were identified as part of the ACR definitions for each NP syndrome and considered to be a likely cause or significant contributor to the event, and 3) occurrence of "minor" NP events as defined by Ainiala et al, who have previously reported the occurrence of such events in a high proportion of normal population controls (2). These latter NP manifestations include all headaches, anxiety, mild depression (i.e., all mood disorders that fail to meet criteria for major depression–like episodes), mild cognitive impairment (deficits in <3 of 8 specified cognitive domains), and polyneuropathy without electrophysiologic confirmation.

The attribution of NP events to SLE and non-SLE causes was determined using 2 sets of decision rules of differing stringency (7), as follows. In attribution model A, NP events that occurred within the enrollment window but had their onset prior to the enrollment window *or* had at least one "exclusion" or "association" *or* were one of the NP events identified by Ainiala et al (2) were attributed to a non-SLE etiology. In attribution model B, NP events that occurred within the enrollment window but had their onset at least 10 years prior to the diagnosis of SLE *or* had at least one "exclusion" *or* were one of the NP events identified by Ainiala et al were attributed to a non-SLE etiology.

Determination of autoantibodies. The median interval between collection of serum and plasma samples and assessment at enrollment was 0 days (range 0–96). The interval between the onset of all NP events within the enrollment window and assessment was 131 days (range 0–533) and was comparable across the subsets of NP events (for SLE-attributed NP events by model A, median 139 days [range 44–332]; for SLE-attributed NP events by model B, median 146 days [range 0–533]; for non-SLE NP events, median 120 days [range 0–500]). However, for the 81% of all NP events that were still ongoing at the time of assessment, the interval between antibody testing and active NP manifestations was negligible. For the 41 NP events (19%) that were not ongoing, the median interval between resolution of the event and assessment was 58 days (range 0–380). Autoantibodies, with the exception of anti–double-stranded DNA (anti-dsDNA), were measured at the laboratory of one of the authors (JTM). Autoantibody determinations were made without knowledge of the occurrence of NP events or their attribution in individual patients.

Enzyme-linked immunosorbent assay (ELISA) for anti-NR2 antibodies. NR2 human peptide sequence, (Asp Trp Glu Tyr Ser Val Trp Leu Ser Asn)$_8$ Lys4 Lys2 Lys-β Ala, was synthesized using f-moc chemistry, purified by high-performance liquid chromatography, and confirmed by Edman degradation, at the Molecular Biology Proteomics Facility of the University of Oklahoma Health Sciences Center, Oklahoma City. High-binding 96-well polystyrene plates (Nunc, Roskilde, Denmark) were coated with 5 μg/ml of NR2 peptide in borate buffered saline and blocked with borate buffered saline, bovine serum albumin (Fraction V; Sigma, St. Louis, MO), and 1.2% Tween 80. Patient sera and positive and negative controls were added (diluted 1:100 in the same blocking buffer). Plates were washed with borate buffered saline between all steps, with vigorous pounding to eliminate nonspecific binding. Secondary antibody was alkaline phosphatase–conjugated goat anti-human IgG (Sigma), with the addition of goat serum to block nonspecific binding (donor herd; Sigma). Plates were developed using *p*-nitrophenyl phosphate buffer (Sigma). Optical density (OD) in the ELISA was read at 405 nm (primary wavelength) and 450 nm (secondary wavelength). Serial dilutions of a high-binding positive control were used as a calibrator.

Antiphospholipid, anti–β_2-glycoprotein-I (anti-β_2GPI), and anti-P antibodies. Lupus anticoagulant (LAC) testing and ELISAs for anticardiolipin (aCL), anti-β_2GPI, and anti-P were performed as previously described (27–29). The LAC assay was performed using screen-and-confirm reagents (Rainbow Scientific, Windsor, CT). Each reagent is standardized against 20 plasma samples (collected in citrate) from healthy donors. A normal reference range is derived by calculating 2 standard deviations above the mean in healthy controls on the screen-and-confirm tests (with phospholipid quenching) and then calculating the ratio of the screen value to the confirm value. Patient clotting time in the LAC screen is divided by the

clotting time in the LAC confirm. If this number is above the normal reference range, the patient is considered to be positive for LAC. Ribosomal P protein was provided from the laboratory of Dr. Morris Reichlin (Oklahoma Medical Research Foundation), and β_2GPI, purified from human plasma, was the gift of Drs. Naomi and Charles Esmon (Oklahoma Medical Research Foundation, Oklahoma City, OK). Each ELISA was validated against a curve, constructed using serial dilutions of a high-binding serum. In the case of aCL and anti-P, these calibrators were previously established in Dr. Reichlin's laboratory. In the case of anti-β_2GPI, the calibrator was established by the Registry for the Antiphospholipid Syndrome at Oklahoma Medical Research Foundation. The cutoff for positivity was defined as 2 standard deviations above the mean in 60 healthy controls and/or position on the flat part of the calibrator curve, whichever was associated with the higher OD. On each ELISA plate, positive and negative control sera (established previously from the laboratory collection and frozen at −80°C in assay-specific aliquots) were run to ensure validity of the assay.

Anti-dsDNA antibodies. Anti-dsDNA antibodies were measured at each of the participating SLICC centers and reported as positive or negative according to the center's specific normal range. The laboratory methods available at the centers were the *Crithidia luciliae* assay (67% of centers), ELISA (43% of centers), and Farr assay (33% of centers).

Statistical analysis. Individual NP manifestations were categorized by attribution to SLE (model A or model B) or non-SLE causes. The distribution of patients within this hierarchy plus a no-NP-event class was examined for associations with different autoantibodies. In addition, the NP manifestations were clustered into subgroups for additional analyses of clinical–serologic associations. Thus, the 19 NP syndromes were grouped into central and peripheral nervous system manifestations as previously described (1). In addition, diffuse NP syndromes were identified as aseptic meningitis, demyelinating syndrome, headache, acute confusional state, anxiety disorder, cognitive dysfunction, mood disorder, and psychosis. Focal NP syndromes were cerebrovascular disease, Guillain-Barré syndrome, movement disorder, myelopathy, seizure disorders, autonomic neuropathy, mononeuropathy, myasthenia gravis, cranial neuropathy, plexopathy, and polyneuropathy. In view of previously reported clinical–serologic correlations, the following associations were also specifically examined: 1) LAC, aCL, and anti-β_2GPI with cerebrovascular disease, seizure disorders, demyelinating syndrome, and movement disorder; and 2) anti-P and anti-NR2 antibodies with mood disorder, cognitive impairment, and psychosis. Since individual NP events were not examined in the primary analyses and the antibodies examined were each of established interest, the analyses were considered to relate to separate scientific questions of interest (30), and no formal multiplicity adjustments were made. When positive associations were evident, further analyses, such as those in subgroups of the data, were undertaken to examine, to the extent possible, the internal consistency of any finding. Reported significance levels were determined by chi-square test or Fisher's exact test, as appropriate. No general need for multivariate regression analyses emerged, although ordinal regression analysis was used to examine the rates of antibody positivity at different clinical centers.

Table 1. Demographic and clinical characteristics of the 412 SLE patients*

Sex	
Female	360 (87.4)
Male	52 (12.6)
Age, mean ± SD years	34.9 ± 13.5
Ethnicity	
White	256 (62.1)
Hispanic	12 (2.9)
Asian	70 (17.0)
Black	58 (14.1)
Other	16 (3.9)
Marital status	
Single	178 (43.2)
Married	170 (41.3)
Other	64 (15.5)
Post-secondary education	274 (66.5)
Disease duration, mean ± SD months	5.0 ± 4.2
No. of ACR SLE criteria met, mean ± SD	4.9 ± 1.0
Individual ACR criteria	
Malar rash	140 (34.0)
Discoid rash	46 (11.2)
Photosensitivity	163 (39.6)
Oral/nasopharyngeal ulcers	152 (36.9)
Serositis	114 (27.7)
Arthritis	311 (75.5)
Renal disorder	112 (27.2)
Neurologic disorder	26 (6.3)
Hematologic disorder	256 (62.1)
Immunologic disorder	320 (77.7)
Antinuclear antibody	408 (99.0)
SLEDAI score, mean ± SD	6.1 ± 5.9
SDI score, mean ± SD	0.32 ± 0.72
Treatment	
Corticosteroids	268 (65.0)
Antimalarials	256 (62.1)
Immunosuppressants	150 (36.4)
Aspirin	62 (15.0)
Antidepressants	41 (10.0)
Anticonvulsants	18 (4.4)
Warfarin	18 (4.4)
Antipsychotics	3 (0.7)

* Except where indicated otherwise, values are the number (%). SLE = systemic lupus erythematosus; ACR = American College of Rheumatology; SLEDAI = SLE Disease Activity Index; SDI = Sytemic Lupus International Collaborating Clinics/ACR Damage Index.

RESULTS

Patient characteristics. A total of 412 patients were recruited at 18 centers between October 1999 and April 2005. The median number of patients enrolled at each center was 13 (range 3–56). The majority of the patients were women, with a mean ± SD age of 34.9 ± 13.5 years and a wide ethnic distribution, although most were white (Table 1). At the time of enrollment

Table 2. Frequency of occurrence of NP events in SLE patients and their attribution using models A and B*

NP event	No. (%) of events regardless of attribution	No. of events due to SLE by model A	No. of events due to SLE by model B but not model A	No. of events due to SLE by model B	No. of events due to non-SLE causes
Headache	86 (40.2)	0	0	0	86
Mood disorders	32 (15.0)	3	12	15	17
Anxiety disorder	17 (7.9)	0	0	0	17
Cerebrovascular disease	14 (6.5)	6	8	14	0
Cognitive dysfunction	14 (6.5)	1	8	9	5
Seizure disorder	11 (5.1)	4	5	9	2
Acute confusional state	11 (5.1)	5	3	8	3
Polyneuropathy	8 (3.7)	1	3	4	4
Psychosis	7 (3.3)	3	4	7	0
Mononeuropathy	6 (2.8)	4	2	6	0
Cranial neuropathy	4 (1.9)	2	0	2	2
Aseptic meningitis	2 (0.9)	2	0	2	0
Myelopathy	1 (0.5)	1	0	1	0
Movement disorder	1 (0.5)	0	0	0	1
Autonomic disorder	0	0	0	0	0
Guillain-Barré syndrome	0	0	0	0	0
Demyelinating syndrome	0	0	0	0	0
Myasthenia gravis	0	0	0	0	0
Plexopathy	0	0	0	0	0
Total	214	32	45	77	137

* The attribution of neuropsychiatric (NP) events to systemic lupus erythematosus (SLE) was determined using 2 attribution models. In model A, onset of the NP event any time prior to the enrollment window, identification of any non-SLE factor that contributed to or was responsible for the NP event ("association" or "exclusion" factors), or classification as a "minor" NP event as defined by Ainiala et al (2) indicated that the NP event was not attributed to SLE. In model B, onset of the NP event >10 years prior to the diagnosis of SLE, identification of any non-SLE factor that was responsible for the NP event ("exclusion" factors only), or classification as a "minor" NP event as defined by Ainiala et al (2) indicated that the NP event was not attributed to SLE.

the mean ± SD disease duration was only 5.0 ± 4.2 months. The prevalence of individual ACR classification criteria that were met reflected an unselected SLE patient population. The mean SLEDAI and SDI scores revealed moderate global disease activity and minimal cumulative organ damage. Therapy at the time of enrollment reflected the typical range of lupus medications.

Neuropsychiatric manifestations. Within the enrollment window described in Patients and Methods, 133 of the 412 patients (32.3%) had at least 1 NP event and 47 (11.4%) had 2 or more events. Of the 7 patients with ≥2 NP events, 5 had 4 NP events, 1 had 5 events, and 1 had 7 events. The NP events (n = 214), which encompassed 14 of the 19 NP syndromes (1), and their attribution are summarized in Table 2. The proportion of NP events attributed to SLE varied from 15% (32 of 214) to 36% (77 of 214) depending on the attribution model used; events attributed to SLE based on model A occurred in 5.8% of the patients, and events attributed to SLE based on model B occurred in 12.9% of the patients. Of the 214 NP events, 196 (91.6%) affected the central nervous system and 18 (8.4%) involved the peripheral nervous system. One hundred sixty-nine of the events (79.0%) were classified as diffuse and 45 (21.0%) as focal.

Associations between autoantibody positivity and overall occurrence of neuropsychiatric events. The prevalence of the different autoantibodies varied from 8% for anti-P antibodies to 45% for anti-dsDNA antibodies (Figure 1). The number of patients who were positive for 1, 2, or ≥3 antibodies was 134, 41, and 32, respectively. Ordinal regression analysis revealed no evidence that the pattern of positive results differed among the 18 SLICC centers ($P = 0.51$). There was no significant association between the frequency of autoantibodies in patients with and those without NP events regardless of attribution to SLE or non-SLE causes (Figure 1).

The NP events were then classified by attribution to determine if this would reveal a stronger correlation with specific autoantibodies. Four mutually exclusive groups were examined: patients with NP events attributed to SLE who qualified under model A, patients with

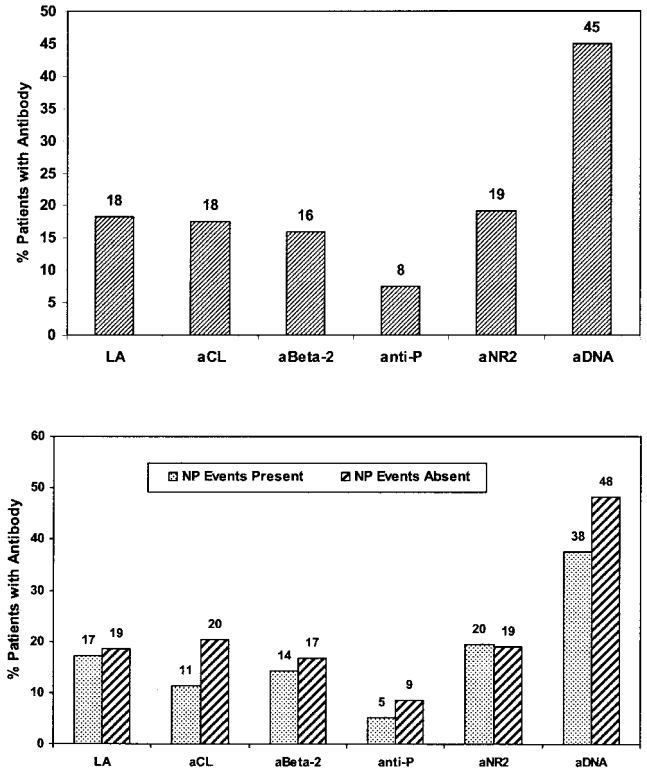

Figure 1. Frequency of autoantibodies in the systemic lupus erythematosus (SLE) inception cohort. **Top,** Frequency of each autoantibody in the SLE patient group overall. **Bottom,** Frequency of each autoantibody in the patients with and those without neuropsychiatric (NP) events. LA = lupus anticoagulant; aCL = IgG anticardiolipin antibody; aBeta-2 = anti–β_2-glycoprotein I; anti-P = anti–ribosomal P antibody; aNR2 = anti–NR2 glutamate receptor antibody; aDNA = anti–double-stranded DNA antibody.

NP events attributed to SLE who qualified under model B but not model A, patients with NP events attributed to non-SLE causes, and patients with no NP events (Figure 2). In this analysis the only clinical–serologic association that approached significance was between NP events attributed to SLE and anti-P antibodies (P = 0.07). The frequency of anti-P antibodies in patients with NP events due to SLE as determined using the more stringent of the 2 attribution models (model A) was 4 of 24 (16.7%), compared with 3 of 109 (2.8%) among patients with all other NP events and 24 of 279 (8.6%) among patients with no NP events. The specific events in the 4 patients with anti-P antibodies and NP events attributed to SLE based on model A were psychosis only (1 patient), psychosis and cognitive dysfunction (1 patient), acute confusional state, myelopathy, and mononeuropathy (1 patient), and cerebrovascular disease (1 patient).

Stronger associations between anti-P antibodies and NP events attributed to SLE based on model A were observed for central NP events (P = 0.04) and diffuse NP events (P = 0.02) (Figure 3). For central NP events, the frequency of anti-P antibodies in patients with NP events attributed to SLE (according to model A) was 4 of 20 (20%), compared with 3 of 107 (2.8%) among patients with all other central NP events and 24 of 279 (8.6%) among patients with no NP events. For diffuse NP events, the anti-P antibody frequencies in these groups were 3 of 11 (27%), 4 of 111 (3.6%), and 24 of 279 (8.6%), respectively. Significant differential effects between central/peripheral and diffuse/focal classifications could not be detected with the small number of cases available.

Associations between autoantibody positivity and individual neuropsychiatric events. Analyses were also performed to examine specific clinical–serologic associations. The power of these analyses was limited due to small numbers of cases. Of the 14 patients with cerebrovascular disease, 11 had a thrombotic stroke, 2 had a transient ischemic attack (1 of whom also had a stroke), 2 had chronic multifocal disease (1 of whom also had a stroke), and 1 had a sinus thrombosis. No patient had a subarachnoid or intracranial hemorrhage. All of these NP events occurred within the enrollment window and were attributed to SLE based on either attribution model A (6 patients) or attribution model B (8 patients). Six of the 14 patients (43%) (1 in model A and 5 in model B) had LAC only (4 patients with stroke only, 1 with a stroke and transient ischemic attack, and 1 with sinus thrombosis), compared with 52 of 279 patients (19%) without NP events (P = 0.038). One patient with chronic multifocal disease who was negative for LAC had aCL and anti-β_2GPI antibodies. Thus 7 of 14 patients with cerebrovascular disease (50%) were positive for at least 1 type of aPL, but this was not significantly different from the frequency of positivity for any aPL among the patients without NP events (114 of 279 [41%]). No associations of LAC, aCL, or anti-β_2GPI antibodies with seizure disorders, demyelinating syndrome, or movement disorder could be demonstrated.

There was no demonstrable association between anti-NR2 antibodies and cognitive dysfunction or mood disorder. In 9 of the 14 patients with cognitive impairment, it was attributed to SLE using either attribution model A (1 patient) or model B (8 patients). Only 1 of the 9 (11%) had anti-NR2 antibodies, which was a lower

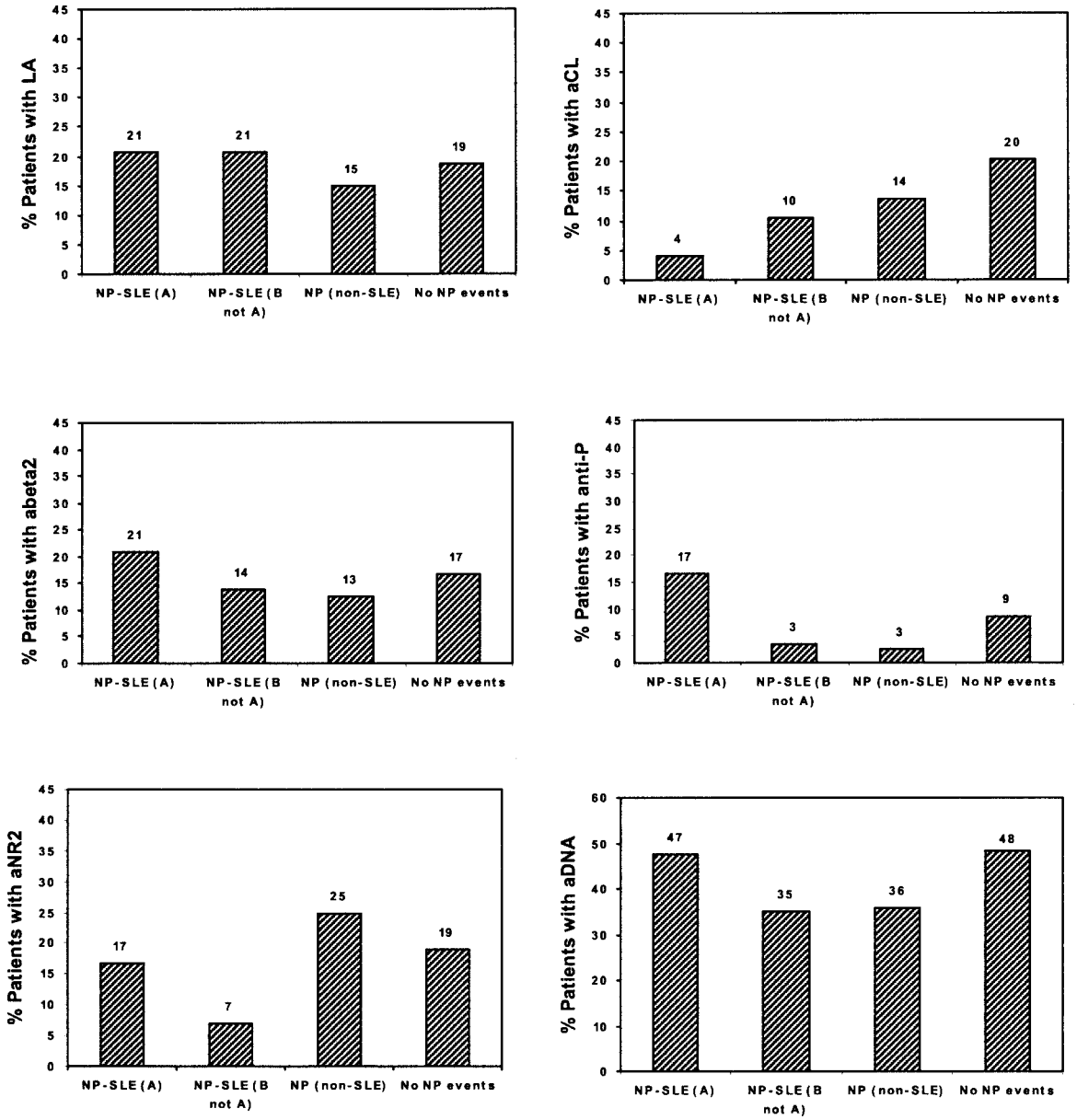

Figure 2. Frequency of autoantibodies in SLE patients with and those without NP events. Four mutually exclusive groups were examined: patients with NP events attributed to SLE according to model A, patients with NP events attributed to SLE according to model B but not model A, patients with NP events attributed to non-SLE causes, and patients with no NP events. See Patients and Methods for explanation of model A and model B; see Figure 1 for definitions.

frequency than that in patients without NP events (53 of 279 [19%]). In 15 of the 32 patients with a mood disorder, this was attributed to SLE based on either model A (3 patients) or model B (12 patients). Only 2 of the 15 patients (13%) had anti-NR2 antibodies, compared with 53 of the patients without NP events (19%).

Seven patients had psychosis that was attributed to SLE. Two of the 3 patients whose psychosis was attributed to SLE by model A and 1 of the 4 in whom psychosis was attributed to SLE by model B had anti-P antibodies. The latter patient was not included under model A because corticosteroids were identified as a potential contributing factor to the psychosis and thus recognized as an "association" according to the ACR

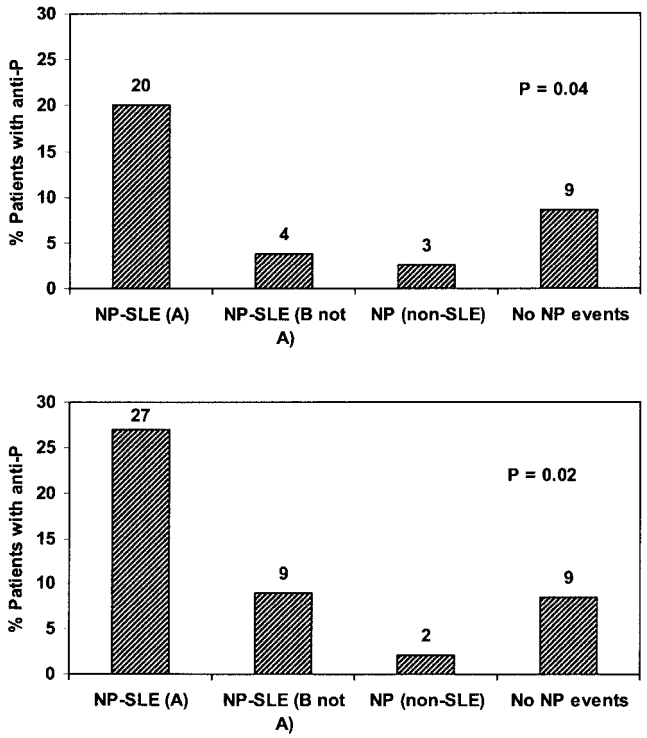

Figure 3. Frequency of anti-P antibodies in SLE patients with and those without central NP events (**top**) and in SLE patients with and those without diffuse NP events (**bottom**). Central NP manifestations were those described in ref. 1. Diffuse NP syndromes were identified as aseptic meningitis, demyelinating syndrome, headache, acute confusional state, anxiety disorder, cognitive dysfunction, mood disorder, and psychosis. Four mutually exclusive groups were examined: patients with NP events attributed to SLE according to model A, patients with NP events attributed to SLE according to model B but not model A, patients with NP events attributed to non-SLE causes, and patients with no NP events. See Patients and Methods for explanation of model A and model B; see Figure 1 for definitions.

case definition for psychosis (1). While the frequency of anti-P antibodies among patients with SLE-attributed psychosis based on model A compared with the frequency among patients with no NP events achieved statistical significance ($P = 0.02$), the significance would have been even stronger if this latter patient had been included ($P = 0.003$). Although some caution must be exercised in interpreting this finding, it indicates the importance of psychosis in explaining the observed association between anti-P antibodies and neuropsychiatric events attributed to SLE.

DISCUSSION

Several autoimmune and inflammatory mechanisms likely play a role in the pathogenesis of NPSLE (9–12). Given the wide variety of clinical manifestations, it is unlikely that a single pathogenic mechanism is responsible for all of them. In addition to autoantibodies, there is evidence to support the notion that proinflammatory cytokines (31,32) and chemokines (33), which have been identified in cerebrospinal fluid (CSF) from SLE patients with NP disease (31–33), have a pathogenic role. With regard to autoantibodies, the current data suggest that aPL cause focal NP disease (e.g., stroke, seizures) by promoting intravascular thrombosis (5). In contrast, anti-P antibodies (21,22), and possibly anti-NR2 antibodies (13,15), cause diffuse NP events (e.g., psychosis, depression, cognitive impairment) through a direct effect on neuronal cells; a critical factor in this is the ability of these antibodies to directly access neuronal cells either through intrathecal production or via passage from the circulation across a permeabilized blood–brain barrier.

The most direct evidence supporting the hypothesis of autoantibody involvement in NPSLE is derived from studies of animal models (13–17), whereas evidence from human studies is frequently conflicting or inconclusive (18–22). This may be due in part to methodologic difficulties involving, for example, selection of patients for study, lack of rigor in the characterization of NP events, and differences between laboratories in assay techniques. We therefore assembled an international disease inception cohort of SLE patients utilizing a standardized approach for characterizing NP events and determining their attribution. Our primary objective was to examine the association between a panel of specific autoantibodies and NPSLE events occurring around the time of diagnosis of SLE. We found that only LAC and anti-P antibodies showed evidence of an association with NP events attributed to SLE.

Testing of serum for autoantibodies of interest in NPSLE was performed at a single center in order to avoid variability in laboratory methodology. In general, the prevalence of autoantibodies was lower than that reported in other lupus cohorts (20,21,34,35). However, this was the first study to measure this complete panel of autoantibodies in a disease inception cohort, which, in combination with our efforts to minimize nonspecific antibody binding, is probably the explanation for the lower prevalence rates. With further followup, the frequency of all autoantibodies in this cohort will very likely increase, in accordance with findings in previous longitudinal studies of SLE patients (36).

In the present study, anti–ribosomal P antibodies demonstrated an association with NP events attributed to SLE. The decision on attribution was made indepen-

dently of the centralized testing of antibodies for the study. The highest frequency of anti-P autoantibodies occurred in patients with NP events attributed to SLE as defined using the more stringent of the attribution rules. This finding provides support for the notion that anti-P antibodies have a role in NPSLE and, in particular, in psychosis. However, as was also shown in a recent meta-analysis (22), anti-P has low sensitivity for NPSLE, which limits the clinical utility of testing for this autoantibody. Thus, it cannot be recommended as a reliable biomarker, particularly if used in isolation, to determine the attribution of NP events or to distinguish between various NP disease phenotypes.

Antiphospholipid antibodies (LAC, aCL) and anti–β_2-GPI antibodies have been associated with a number of neuropsychiatric manifestations in SLE (34,37–39), in particular, focal events such as stroke (39,40). In the present study, although there was no association with overall NPSLE as defined by attribution model A or B, LAC was associated with cerebrovascular disease, particularly nonischemic stroke. There are a number of potential explanations for this observation. First, as has been found in extracranial venous thrombosis (41), LAC may be a better predictor of thrombotic events than are other antiphospholipid antibodies. Second, the majority of previous studies supporting associations with aPL have included patients with well-established lupus of several years' duration, with considerably longer autoantibody exposure than in patients enrolled in a disease inception cohort such as ours. Thus, as has been demonstrated in studies of cognitive function in SLE, it is the persistence of elevated aCL levels over several years which confers the greatest risk for cognitive decline (42,43). This may also be true for other NP manifestations including stroke. Further followup of our inception cohort will be necessary in order to address these possibilities.

We did not find an association between NP events and anti–NR2 glutamate receptor antibodies. Previous studies in humans with lupus have yielded conflicting results. Omdal et al (19) reported an association between anti-NR2 antibodies and depressed mood as well as decreased short-term memory and learning. However, although there has been 1 additional report of an association with depression (44), 4 cross-sectional studies (20,44–46) did not confirm these findings. In animal models, enhanced permeability of the blood–brain barrier was a critical factor for anti-NR2 antibodies to enter the intrathecal space and gain access to neuronal cells (15). The blood–brain barrier may be permeabilized by factors attributed to SLE (e.g., immune complex deposition and cytokines) or independent of SLE (e.g., smoking and hypertension). Therefore, demonstration of a stronger link with NP events might be expected from measurement of anti-NR2 antibodies within the CSF. Yoshio et al (47) studied both serum and CSF samples from 80 SLE patients (53 with NPSLE and 27 without NPSLE) and found NP events to be more strongly associated with CSF autoantibodies than with circulating autoantibodies. Thus, although animal studies illustrate an interesting model of autoantibody-mediated neuronal injury, studies of humans with SLE have not elucidated the precise role of anti-NR2 antibodies in NPSLE pathogenesis and diagnosis.

There are a number of limitations to our study. First, due to the lack of specificity of most of the NP events, composite arbitrary decision rules for attribution had to be developed, as previously described (7). Second, although our disease inception cohort was of reasonable size, many of the individual NP events attributed to SLE were infrequent, which limited the statistical power of the analysis. Third, the study protocol did not require formal confirmation of NP events by relevant subspecialists such as neurologists, psychiatrists, and neuropsychologists. However, all of these disciplines were represented in the derivation of the ACR case definitions for NP events (1), which were rigorously applied in the current study, and many patients with NP events were assessed by specialists from these disciplines as part of their routine clinical care. Fourth, because autoantibodies were measured at a single time point, it is possible that some patients with an evanescent pattern of autoantibody production could have been overlooked. Finally, because CSF was not sampled and no circulating biomarker of blood–brain barrier permeability was used, the question of whether autoantibodies were present within the intrathecal space was not addressed.

Despite these limitations, this study provides novel information on the prevalence of specific autoantibodies in an international SLE inception cohort. We found that clinically distinct subsets of NPSLE were associated with lupus anticoagulant and anti–ribosomal P antibodies. By design, we focused exclusively on NP events occurring around the time of diagnosis of SLE rather than on the cumulative burden of NP disease that accrues over time. Future studies will be conducted to determine the reproducibility of these findings in an expanded disease inception cohort and to examine whether any of these autoantibodies predict the subsequent development or course of NP events over time.

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AUTHOR CONTRIBUTIONS

Dr. Hanly had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Hanly, Urowitz, Farewell, Gordon, Bae, Isenberg, Dooley, Clarke, Fortin, Manzi, Steinsson, Aranow, Wallace, Ramsey-Goldman, Sanchez-Guerrero, Khamashta, Merrill.

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Analysis and interpretation of data. Hanly, Siannis, Farewell, Gordon, Clarke, Bernatsky, Aranow, Wallace, Sturfelt, Nived, Alarcón, Zoma, Thompson, Merrill.

Manuscript preparation. Hanly, Siannis, Farewell, Gordon, Isenberg, Clarke, Bernatsky, Gladman, Fortin, Manzi, Bruce, Ginzler, Aranow, Wallace, Ramsey-Goldman, van Vollenhoven, Alarcón, Khamashta, Merrill.

Statistical analysis. Hanly, Siannis, Farewell, Clarke, Thompson.

Database development. Douglas, Qi.

Measurement of autoantibodies. Merrill.

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