

Autoantibodies as Biomarkers for the Prediction of Neuropsychiatric Events in Systemic Lupus Erythematosus

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Abstract

Objective—Neuropsychiatric (NP) events occur unpredictably in systemic lupus erythematosus (SLE) and most biomarker associations remain to be prospectively validated. We examined a disease inception cohort of 1047 SLE patients to determine which autoantibodies at enrollment predicted subsequent NP events.

Methods—Patients with recent SLE diagnosis were assessed prospectively for up to 10 years for NP events using ACR case definitions. Decision rules of graded stringency determined whether NP events were attributable to SLE. Associations between the first NP event and baseline autoantibodies (lupus anticoagulant, anticardiolipin, anti- β_2 glycoprotein-I, anti-ribosomal P and anti-NR2 glutamate receptor) were tested by Cox proportional hazards regression.

Results—Disease duration at enrollment was 5.4 \pm 4.2 months, followup was 3.6 \pm 2.6 years. Patients were 89.1% female with mean (\pm SD) age 35.2 \pm 13.7 years. 495/1047 (47.3%) developed 1 NP event (total 917 events). NP events attributed to SLE were 15.4% (model A) and 28.2% (model B). At enrollment 21.9% of patients had lupus anticoagulant, 13.4% anticardiolipin, 15.1% anti- β_2 glycoprotein-I, 9.2% anti-ribosomal P and 13.7% anti-NR2 antibodies. Lupus anticoagulant at baseline was associated with subsequent intracranial thrombosis (total n=22) attributed to SLE (model B) (Hazard ratio, HR 2.54 (95% CI: 1.08–5.94). Anti-ribosomal P antibody was associated with subsequent psychosis (total n=14) attributed to SLE (model B) (HR: 3.92 (95% CI:1.23–12.5); p=0.02). Other autoantibodies did not predict NP events.

Conclusion—In a prospective study of 1047 recently diagnosed SLE patients, lupus anticoagulant and anti-ribosomal P antibodies are associated with an increased future risk for intracranial thrombosis and lupus psychosis respectively

Keywords

Systemic lupus erythematosus; Neuropsychiatric; Inception cohort; Autoantibodies; Biomarkers

Nervous system involvement in systemic lupus erythematosus (SLE) encompasses a variety of neurological (N) and psychiatric (P) features. Using the American College of Rheumatology (ACR) case definitions (1), the prevalence of neuropsychiatric (NP) disease in SLE varies from 21–95%, but only 19–38% of events are attributable to lupus (2–6). NP

events present or reoccur at any time in the disease course, although the majority occurs around the time of diagnosis of SLE, particularly those attributable to SLE (7–11). The identification of biomarkers at the time of diagnosis to quantify the subsequent risk of NP events attributable to SLE (NPSLE) would be helpful.

NPSLE is likely mediated by autoantibodies, microvasculopathy, and the intracranial production of inflammatory mediators (12–15), often in combination. Lupus related autoantibodies most frequently associated with NPSLE include antiphospholipid antibodies, anti-ribosomal P antibodies and autoantibodies which bind to neuronal antigens such as the N-methyl-D-aspartate (NMDA) glutamate receptor (anti-NR2) (16). Although there is biological plausibility and experimental data (16–20) to implicate these autoantibodies in the causality of nervous system disease, studies of human SLE have provided inconsistent findings (21–25). Limitations of previous studies include their cross-sectional design, inclusion of patients with variable disease duration, and lack of standardization in both the classification of NP events and the methodology used for autoantibody detection. We have assembled an international, inception cohort of SLE patients to examine the association between a panel of autoantibodies measured within a mean of 6 months of the time of diagnosis and subsequent nervous system events over a mean followup of 3.6 years. Attribution models of different stringency were used to distinguish NP events attributed to SLE and non-SLE causes.

Patients and Methods

Research study network

The study was conducted by members of the Systemic Lupus International Collaborating Clinics (SLICC) (26) a network of 37 investigators in 30 international academic medical centres in 11 countries. Twenty-one centres participated in the study. Data were collected prospectively on patients presenting with a new diagnosis of SLE. All information was submitted to the coordinating centre in Halifax, Nova Scotia, Canada and entered into a centralized Access database. Appropriate procedures ensured data quality, management and security. The study was approved by the Capital Health Research Ethics Board, Halifax, Nova Scotia, Canada and by each of the participating centre's own institutional research ethics review boards.

Patients

Patients fulfilled the ACR classification criteria for SLE (27) provided written informed consent. The date of diagnosis was when these cumulative criteria were first recognized. Enrollment was permitted up to 15 months following the diagnosis. Variables collected included age, gender, ethnicity, education and medication history. Lupus-related variables included the ACR classification criteria for SLE (27), the SLE Disease Activity Index (SLEDAI) (28) and the SLICC/ACR damage index (SDI) (29). Laboratory variables were hematology, serum and urine chemistry and immunologic variables (including anti-DNA antibodies) required for the generation of SLEDAI and SDI scores.

Neuropsychiatric (NP) events

An enrollment window within which all NP events were captured extended from 6 months prior to the diagnosis of SLE up to the enrollment date. NP events were characterized using the ACR nomenclature and case definitions for 19 NP syndromes (1). These were diagnosed by clinical evaluation and investigations were performed if clinically warranted.

Patients were reviewed annually with a 6-month window around the anticipated assessment date. New NP events since the previous study visit and their attribution were determined.

Supplementary information was recorded as per the ACR glossary for NP syndromes (1) to identify other potential causes (“exclusions”) or contributing factors (“associations”) for each of the NP events. These “non-SLE factors” were used in part to determine the attribution of NP events. Patients could have more than one type of NP event and repeated episodes of the same event within the enrollment window or within a follow-up assessment period were recorded once. The date of the first episode was taken as the onset of the NP event within the particular time frame.

Attribution of NP events

Decision rules were used to determine the attribution of all NP events. Factors considered in the decision rules included: (i) onset of NP event(s) prior to the diagnosis of SLE; (ii) concurrent non-SLE factor(s) identified from the ACR glossary for each NP syndrome and (iii); “common” NP events which are frequent in normal population controls as described by Ainiala et al (30). These include all headaches, anxiety, mild depression (mood disorders failing to meet criteria for “major depressive-like episodes”), mild cognitive impairment (deficits in less than 3 of the 8 specified cognitive domains) and polyneuropathy without electrophysiological confirmation.

Attribution of NP events was determined by the central application of decision rules of different stringency (models A and B) as described in detail elsewhere (31, 32). NP events which fulfilled the criteria for model A (the most stringent) or for model B (the least stringent) were attributed to SLE. By definition, all NP events attributed to SLE using model A were included in the group of NP events attributed to SLE using model B. Those events which did not fulfill these criteria were attributed to non-SLE causes

Determination of autoantibodies

Autoantibodies were measured in Dr. Joan Merrill’s laboratory at the Oklahoma Medical Research Foundation, USA. Autoantibody determinations were made without knowledge of the occurrence of NP events or their attribution in individual patients.

ELISA for anti-NR2 antibodies—NR2 human peptide sequence, (Asp Trp Glu Tyr Ser Val Trp Leu Ser Asn)₈ Lys 4 Lys₂ Lys-β Ala, was synthesized using f-moc chemistry, purified by HPLC and confirmed by Edman degradation at the Molecular Biology Proteomics Facility of the University of Oklahoma Health Sciences Centre, Oklahoma City, OK. High binding, Nunc 96-well polystyrene plates were coated with 5 ug/mL of NR2 peptide in borate buffered saline and blocked with borate buffered saline, bovine serum

albumin (Fraction V, Sigma) and 1.2% Tween 80. Patient sera, positive and negative controls were added, diluted 1/100 in the same blocking buffer. Plates were washed with borate buffered saline between each step with vigorous pounding to eliminate non-specific binding. Secondary antibody was an alkaline phosphatase conjugated goat anti-human IgG (Sigma) with the addition of goat serum to block non-specific binding (donor herd, Sigma). Plates were developed using p-NPP substrate buffer (Sigma). Optical density of the enzyme-linked immune assay were read at 405 (primary wavelength) and 450 (secondary wavelength). Serial dilutions of a high binding positive control were used as a calibrator.

Antiphospholipid, anti- β_2 glycoprotein-I, and anti-ribosomal P antibodies—

Lupus anticoagulant (LA) and ELISAs for anticardiolipin, anti- β_2 glycoprotein-I and anti-ribosomal P protein were performed as previously described (33–35). The LA assay was performed using screen and confirm reagents from Rainbow Scientific, 83 Maple Ave., Windsor, CT. Each reagent was standardized against 20 plasma samples (collected in citrate) from healthy donors. A normal reference range was derived from calculating two standard deviations above the mean of healthy controls on the screen and confirm (phospholipid quenched) tests and calculating the ratio of screen value/confirm value. Patient's clotting time for LA Screen was divided by the LA Confirm's clotting time. If this number was above the normal reference range, the patient was considered positive for LA. β_2 glycoprotein-I, purified from human plasma, was the gift of Drs. Naomi and Charles Esmon, and ribosomal P protein was provided by Dr. Morris Reichlin, Oklahoma Medical Research Foundation. Each ELISA was validated against a curve, constructed using serial dilutions of a high binding serum. In the case of anticardiolipin and anti-ribosomal P protein, these calibrators were previously established in Dr. Reichlin's laboratory. In the case of anti- β_2 glycoprotein-I the calibrator was established by the Registry for the Antiphospholipid Syndrome at Oklahoma. The cutoff for positive was defined as 2 SD above the mean of 60 healthy controls and/or position on the flat part of the calibrator curve, whichever was associated with the higher O.D. 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 a valid assay.

Statistical analysis

Chi-square tests were used to examine the association of autoantibody prevalence at enrollment with geographical regions or ethnic/racial groups. The associations of autoantibodies at enrollment with the time to the first occurrence of NP events overall, or events attributed to SLE (model A or model B) as well as the time to the first occurrence of individual events (cerebrovascular disease and psychosis) were examined using Coxproportional hazards regression.

Results

Patients

A total of 1047 patients were recruited between October 1999 and April 2010. The median (range) number of patients enrolled in each of the 21 centres was 31 (6–161). The patients

were predominantly women, with a mean (\pm SD) age of 35.2 ± 13.7 years and a wide ethnic distribution although predominantly Caucasian (Table 1).

At enrollment the mean disease duration was only 5.4 ± 4.2 months despite the opportunity to recruit patients up to 15 months following the diagnosis of SLE. The prevalence of individual ACR classification criteria at enrollment reflected an unselected patient population. The mean SLEDAI and SDI scores revealed moderate global disease activity and minimal cumulative organ damage respectively. Therapy at enrollment reflected the typical range of lupus medications. The number of assessments in individual patients varied from 1 to 10 over a mean followup 3.6 ± 2.6 years.

Neuropsychiatric (NP) manifestations

495/1047(47.2%) patients had 1 NP event and 226/1047(21.5%) had 2 events. The events and their attribution are summarized in Table 2.

There were 917 NP events, encompassing 17 of the 19 NP syndromes: headache (52.0%), mood disorders (14.4%), seizure disorder (5.8%), anxiety disorder (5.7%), cerebrovascular disease (5.1%), cognitive dysfunction (4.5%), polyneuropathy (2.5%), acute confusional state (2.3%), mononeuropathy (1.7%), psychosis (1.7%), cranial neuropathy (1.2%), movement disorder (0.9%), myelopathy (0.9%), aseptic meningitis (0.7%), demyelinating syndrome (0.4%), autonomic neuropathy (0.1%) and plexopathy (0.1%). The proportion of NP events attributed to SLE varied from 15.4% – 28.2% using alternate attribution models and occurred in 9.7% [model A] – 16.5% [model B] of patients. There were no patients with Guillain-Barré syndrome or myasthenia gravis. Of the 917 NP events 865 (94.3%) affected the central nervous system and 52 (5.7%) involved the peripheral nervous system. The classification of events into diffuse and focal was 749 (81.7%) and 168 (18.3%), respectively.

Autoantibodies and Racial/Ethnic Group

The prevalence of autoantibodies is illustrated in Figure 1. This varied from 9.2% (91/991) for anti-ribosomal P antibodies, 13.4% (133/995) for anticardiolipin, 13.7% (126/923) for anti-NR2, 15.1% (150/994) for anti- β_2 glycoprotein-I and 21.9% (228/1042) for LA. The number of patients with 1, 2 or 3 positive antibody tests were 312, 107 and 61, respectively. The frequency of autoantibodies varied by geographical region. Specifically the frequency of LA was lower in Canadian centres (15.2%) compared to centres in the USA (26.0%), Europe (23.1%), Asia (22.6%) and Mexico (30.8%) ($p=0.015$), and the frequency of anti-ribosomal P antibodies was higher in Mexico (29.0%) compared to Canada (7.3%), USA (7.5%), Europe (8.0%) and Asia (13.7%) ($p<0.001$). In large part these findings were due to the association of racial/ethnic group with autoantibody frequencies (Table 3).

Autoantibodies and overall NP events

There was no significant positive association between autoantibodies and first occurrence of NP events overall, or events attributed to SLE (model A or model B). Clustering of NP events into diffuse/focal and central/peripheral manifestations did not change the outcome of this analysis. In keeping with our previous findings (36) the presence of anti-DNA

antibodies measured at individual SLICC sites did not positively predict the occurrence of NP events (data not shown).

Autoantibodies and individual NP events

Analyses were also performed to examine specific a priori clinical-serologic associations. The association between antiphospholipid antibodies and cerebrovascular disease and between anti-ribosomal P antibodies and psychosis were of particular interest (Table 4 and Figure 2).

Cerebrovascular disease includes stroke, transient ischemic attack, chronic multifocal disease, subarachnoid or intracranial hemorrhage and sinus thrombosis. There was no strong relationship demonstrated between cerebrovascular disease, so defined, and the presence of any one of either anti- β_2 glycoprotein-I, anticardiolipin antibody or LA (Hazard ratio, HR 1.26 (95% CI 0.69–2.30)). However, LA at baseline and the occurrence of cerebrovascular disease approached statistical significance (HR 1.84 (95% CI) 0.92–3.68) and the association with stroke/sinus thrombosis (total n=22) attributed to SLE (model B) was statistically significant (HR 2.54 (95% CI 1.08–5.94)). The median (range) between the detection of LA and first stroke/sinus thrombosis was 5.02 (0–7.36) years. In addition, anti-ribosomal P antibody at baseline was associated with psychosis (total n=14) attributed to SLE (model B) (HR 3.92 (95% CI 1.23–12.5)). Seven of the patients with psychosis were African, 5 Caucasian and 1 each Hispanic and Asian. Given the higher rate of psychosis in Africans ($p < 0.01$), adjustment for racial/ethnic group (African/others) was undertaken. This led to a reduction in the hazard ratio for anti-ribosomal P antibody and subsequent psychosis to 3.1 with a corresponding shift in the confidence interval (0.95–9.99). The median (range) between the detection of anti-ribosomal P antibody and first episode of psychosis was 5.69 (0–9.16) years.

Discussion

We have evaluated the usefulness of measuring selected autoantibodies for predicting the occurrence of NPSLE in a large, international, inception cohort of SLE patients over the first 10 years of disease. Our findings provide some evidence that LA and anti-ribosomal P antibodies are significantly associated with specific manifestations of NP disease attributed to SLE, namely intracranial thrombosis and psychosis respectively. Variability in the frequency of some autoantibodies with racial/ethnic group supports previous observations of this kind (36, 37) and likely alters the risk profile for the occurrence of NP events in some groups of patients.

There several strengths to our study. In contrast to previous retrospective and cross-sectional clinical studies of NPSLE, ours was prospective to identify the characteristics and attribution of all NP events using a predefined annual data collection protocol. The multi-centre, international, longitudinal study design provides a basis for extrapolating our findings to the broader community of SLE patients. Although nervous system involvement by SLE has long been recognized, the lack of specificity of multiple individual manifestations and difficulty in identifying the correct attribution of the clinical NP events has been challenging. The ACR case definitions of 19 NP syndromes (1) which were developed over a decade ago have

provided a much needed and now widely used platform for the classification of NP events in SLE cohorts. We have also used the accompanying ACR glossary with other information to derive decision rules for determining attribution of NP events to SLE or non-SLE causes (32). In previous studies the application of these decision rules has demonstrated significant correlations with clinical outcomes and selected autoantibodies (31, 32, 38, 39). The use of these rules in the current study provides an excellent platform for the prospective evaluation of potential biomarkers of NPSLE.

The search for biomarkers of NPSLE is based upon what is already known of the pathogenesis of the disease. There is robust evidence from several sources to implicate a pathogenic role for autoantibodies, microvasculopathy, and the intracranial production of inflammatory mediators. These studies have provided a menu of biomarker candidates, including autoantibodies, cytokines and other inflammatory molecules (40) as well as soluble markers of neuronal and glial degradation (41). Detailed discussion is not possible here but a few general observations are worthy of comment. First, given the multitude of clinical manifestations it is very unlikely that a single biomarker will reliably predict all NP events. Second, the anatomical location of biomarkers is important in some cases. For example the association of diffuse NP events with autoantibodies is significantly stronger if these are measured in cerebrospinal fluid (CSF), whereas autoantibodies associated with focal NP events are best studied in peripheral blood. An alternative to accessing CSF, is to find a biomarker of increased permeability of the blood-brain-barrier, a critical factor if some autoantibodies are to reach their target antigen and cause clinical disease. Finally, it is possible that combinations of biomarkers reflecting different components of the pathogenic model of NPSLE will best predict clinical events. To our knowledge, there are no previous studies which have set out to evaluate biomarkers of NPSLE in a large multi-ethnic cohort of patients specifically recruited as close to the diagnosis of SLE as possible and followed over an extended period. Some but not all previous cross-sectional studies with smaller sample sizes have found an association between lupus anticoagulant and intracranial thrombosis (42) and between anti-ribosomal P antibodies and lupus psychosis (24, 43–47). However, in these studies the autoantibodies were measured in close temporal proximity to the clinical event. In contrast, our study is the first to demonstrate the risk of a single autoantibody determination around the time of diagnosis of SLE for a subsequent and often remote NP event.

There are several limitations to the current study. First, the number of autoantibodies studied was limited and CSF samples were not available. The selection of autoantibodies was based upon the evidence of their pathogenic role. Access to CSF samples in our study was infrequent and was restricted to situations when a lumbar puncture was clinically indicated. Also, the small number of specific NP events allowed little power for adjusted analyses. Second, as the study involved antibody determination at a single point in time, no information is yet available on the predictive value of sustained circulating levels of autoantibodies. Third, the classification of NP status was determined primarily by clinical assessment and using appropriate investigations only when clinically indicated. Specialized and sensitive investigations such as MRI neuroimaging studies and formal neuropsychological assessment of cognitive function were not routinely done on all patients. Their use would very likely have resulted in the recognition of additional structural and

function abnormalities of the nervous system. However, many of the abnormalities would be of dubious clinical significance and the routine use of such investigations, although justified in the context of a clinical study, would not mirror what is most commonly done in clinical practice. Finally, the duration of followup in the current study does not reflect the lifetime experience with NP events experienced by the majority of SLE patients. We and others have previously reported that NP events, especially those attributed to SLE, occur most frequently within the first 2 years of the diagnosis of SLE (7–11), thus emphasizing the importance of this period of observation. Nevertheless further followup is required to identify the longer term association between autoantibodies detected either at baseline or over the duration of a patients' illness and clinical expression of NPSLE. The long-term objective of our prospective study is to follow all patients for 10 years which will provide an excellent platform to find new and stronger associations with circulating serological biomarkers.

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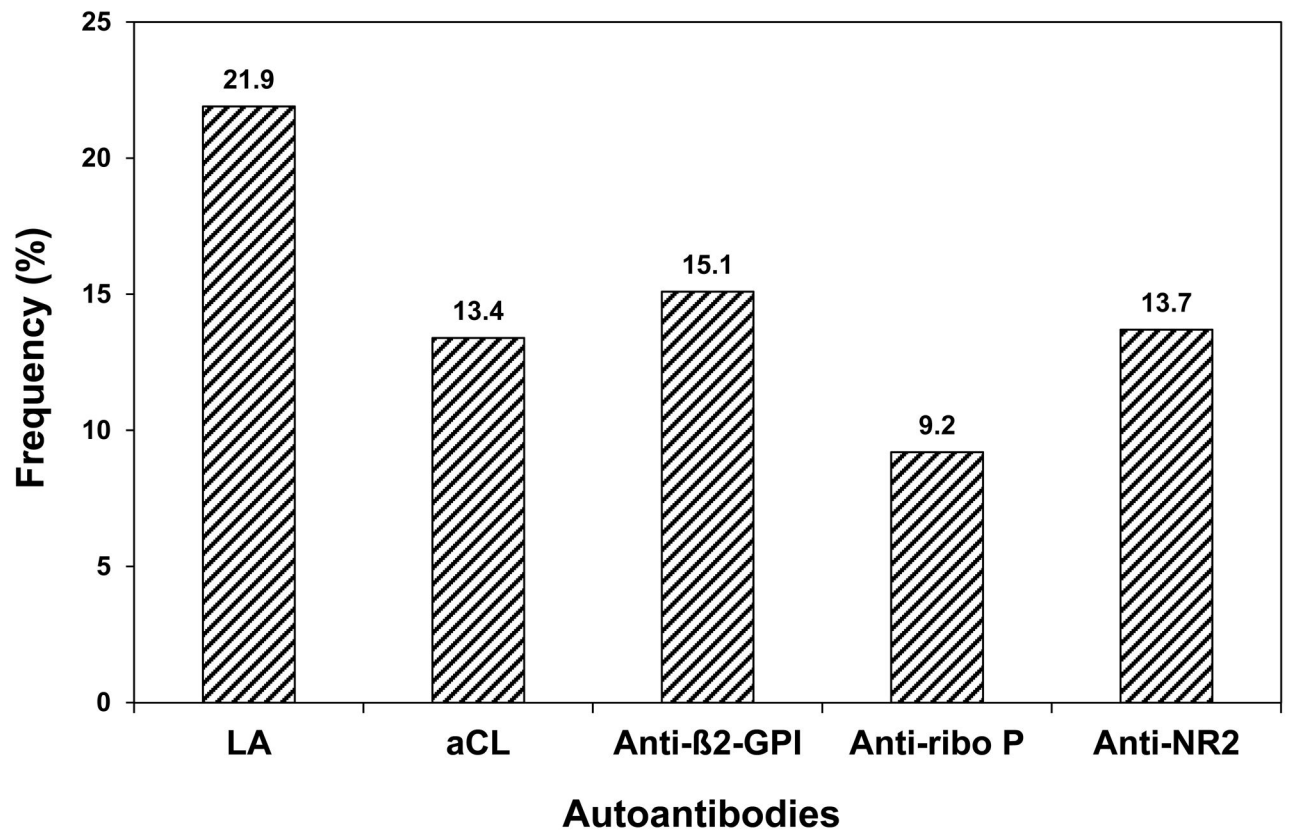


Figure 1.

Frequency of autoantibodies at enrollment. (LA=lupus anticoagulant; aCL=IgG anticardiolipin antibody; Anti-β₂-GPI=IgG anti-β₂ glycoprotein I antibody; Anti -ribo P=IgG anti-ribosomal P antibody; Anti-NR2=IgG anti-NR2 glutamate receptor antibody)

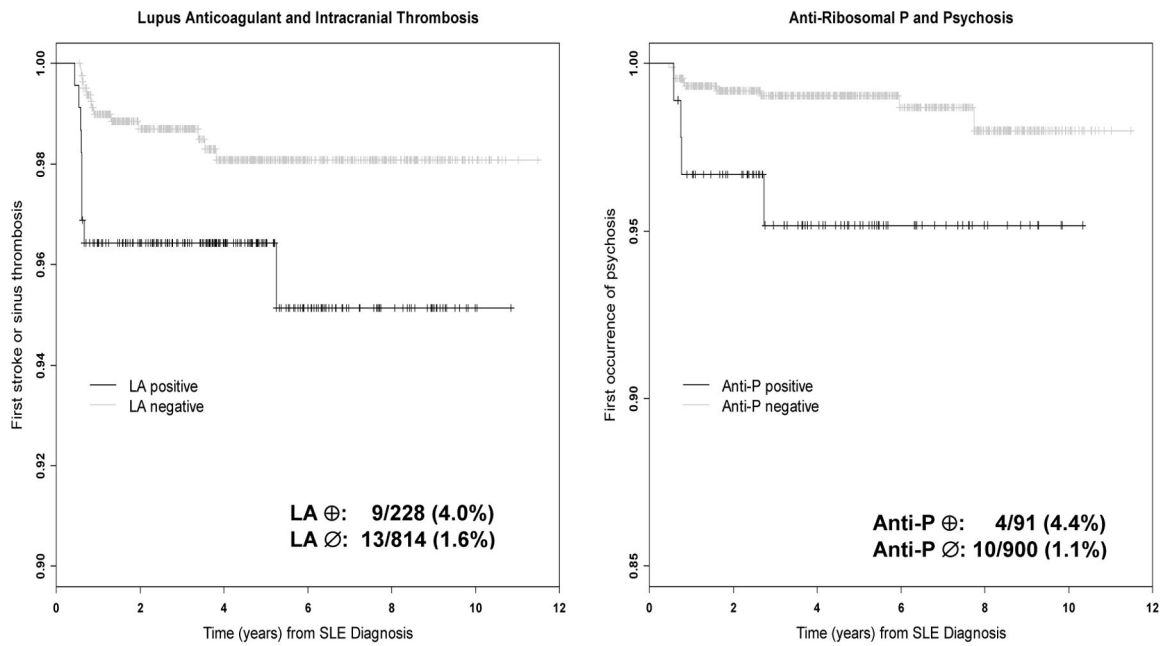


Figure 2. Kaplan-Meier time-to-event curves for intracranial thrombosis in patients with and without lupus anticoagulant (LA) (left panel) and for psychosis in patients with and without anti-ribosomal P antibodies (Anti-P) (right panel).

Table 1

Demographic and clinical manifestations of SLE patients at enrollment

Number of Patients	1047
Gender	
Female	933 (89.1%)
Male	114 (10.9%)
Age (years) (mean \pm SD)	35.2 \pm 13.7
Race/Ethnicity:	
Caucasian	545 (52.1%)
Asian	225 (21.5%)
African	160 (15.3%)
Hispanic	73 (7.0%)
Other	44 (4.2%)
Single/Married/Other	481 (45.9%)/435 (41.6%)/131(12.5%)
Post secondary education	672 (66.9%) (range 36.4–100%)
Disease duration (months) (mean \pm SD)	5.4 \pm 4.2
Number of ACR criteria (mean \pm SD)	4.9 \pm 1.0
Cumulative ACR manifestations	
Malar rash	364 (34.8%)
Discoid rash	118 (11.3%)
Photosensitivity	368 (35.1 %)
Oral/nasopharyngeal ulcers	391 (37.3%)
Serositis	280 (26.7%)
Arthritis	759 (72.5%)
Renal disorder	278 (26.6%)
Neurological disorder	57 (5.4%)
Hematologic disorder	639 (61.0%)
Immunologic disorder	807 (77.1%)
Antinuclear antibody	1017 (97.1%)
SLEDAI score (mean \pm SD)	5.5 \pm 5.4
SLICC/ACR damage index score (mean \pm SD)	0.24 \pm 0.67
Medications	
Corticosteroids	718 (68.6%)
Antimalarials	690 (65.9%)
Immunosuppressants	402 (38.4%)
ASA	144 (13.8%)
Antidepressants	104 (9.9%)
Warfarin	58 (5.5%)
Anticonvulsants	37 (3.5%)
Antipsychotics	6 (0.6%)

Table 2

Characteristics of cumulative neuropsychiatric syndromes over the study period in SLE patients with 1 autoantibody measurement at enrollment (n=1047). The number of NP events and their attribution are indicated using attribution models A and B

	NP events (%) regardless of attribution	NP events due to SLE (model A)	NP events due to SLE (Model B)	NP events due to non-SLE causes
Headache	477 (52.0)	0	0	477
Mood disorders	132 (14.4)	23	54	78
Seizure disorder	53 (5.8)	32	44	9
Anxiety disorder	52 (5.7)	0	0	52
Cerebrovascular disease	47 (5.1)	22	46	1
Cognitive dysfunction	41 (4.5)	10	28	13
Polyneuropathy	23 (2.5)	7	11	12
Acute confusional state	21 (2.3)	10	15	6
Mononeuropathy	16 (1.7)	6	16	0
Psychosis	16 (1.7)	9	16	0
Cranial neuropathy	11 (1.2)	8	8	3
Movement disorder	8 (0.9)	1	5	3
Myelopathy	8 (0.9)	4	7	1
Aseptic meningitis	6 (0.7)	4	4	2
Demyelinating syndrome	4 (0.4)	1	4	0
Autonomic disorder	1 (0.1)	1	1	0
Plexopathy	1 (0.1)	0	0	1
Guillain-Barre syndrome	0	0	0	0
Myasthenia gravis	0	0	0	0
Total	917	141	259	658
% among 917 NP events		15.4	28.2	71.8

*The attribution of neuropsychiatric (NP) events to SLE was determined using two attribution models:

Attribution Model A: NP events which had their onset within the enrollment window and had no “exclusions” or “associations” and were not one of the NP events identified by Ainiala (30) were attributed to SLE.

Attribution Model B: NP events which had their onset within 10 years of the diagnosis of SLE and were still present within the enrollment window and had no “exclusions” and were not one of the NP events identified by Ainiala (30) were attributed to SLE.

Table 3

The association between autoantibody frequency and racial/ethnic group

	Caucasian	Asian	African	Hispanic	Other	P value
Lupus anticoagulant (%)	22.5	22.4	16.3	30.1	18.2	0.17
Anticardiolipin (%)	13.6	12.8	14.0	11.3	14.0	0.98
Anti- β_2 -GPI (%)	17.1	12.8	11.5	7.3	25.6	0.02
Anti-ribosomal P (%)	4.9	13.8	15.3	18.3	4.9	<0.001
Anti-NR2 (%)	14.3	16.6	12.2	5.8	7.9	0.25

Table 4

The association between autoantibodies and the time to specific NP manifestations as indicated by hazard ratio (95% CI)

	LA	aCL	Anti- β_2 -GPI	Anti- β_2 -GPI or aCL or LA
Any cerebrovascular Event (model B)	1.84 (0.92–3.68)	1.25 (0.52–3.02)	1.14 (0.48–2.76)	1.26 (0.69–2.30)
Stroke or sinus thrombosis (model B)	2.54 (1.08–5.94)	0.65 (0.15–2.78)	0.27 (0.04–2.04)	1.25 (0.58–2.72)
	Anti-ribosomal P			
Psychosis (model B)	3.92 (1.23–12.50)			