Neuropsychiatric Events in Systemic Lupus Erythematosus

Predictors of occurrence and resolution in a longitudinal analysis of an international inception cohort

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Abstract

Objectives: To determine predictors for change in neuropsychiatric (NP) event status in a large, prospective, international, inception cohort of SLE patients

Methods: Upon enrollment and annually thereafter, NP events attributed to SLE and non-SLE causes and physician determined resolution were documented. Factors potentially associated with onset and resolution of NP events were determined by time-to-event analysis using a multistate modelling structure.

Results: NP events occurred in 955/1,827 (52.3%) patients and 592/1910 (31.0%) unique events were attributed to SLE. For SLE NP events multivariate analysis revealed positive associations with male sex, concurrent non-SLE NP events excluding headache, active SLE and corticosteroids. There was a negative association with Asian race/ethnicity, post-secondary education, and immunosuppressive or anti-malarial drugs. For non-SLE NP events, excluding headache, there was a positive association with concurrent SLE NP events and negative associations with African and Asian race/ethnicity. NP events attributed to SLE had a higher resolution rate than non-SLE NP events, with the exception of headache that had comparable resolution rates. For SLE NP events, multivariate analysis revealed resolution was more common with Asian race/ethnicity and for central/focal NP events. For non-SLE NP events resolution was more common with African race/ethnicity and less common with older age at SLE diagnosis.

Conclusions: In a large and long-term study of the occurrence and resolution of NP events in SLE we identified subgroups with better and worse prognosis. The course of NP events differs greatly depending on their nature and attribution.

Neurologic and psychiatric clinical events resulting from abnormalities of the central, peripheral and autonomic nervous systems occur in patients with systemic lupus erythematosus (SLE)(1, 2). Recent studies suggest that approximately 30 – 50% of all NP events in SLE patients are attributable to SLE(3, 4) although the exact proportion varies depending on the type of NP event. Prospective, observational cohort studies of SLE patients have reported differences in the outcome of NP events depending, in part, on their attribution to SLE and non-SLE causes.

In a recent study(5), using multistate modeling at the patient level, we reported the occurrence, attribution and outcome of all NP events in SLE patients. Regardless of attribution, NP events occurred most frequently around the diagnosis of SLE and had a significant negative impact on health-related quality of life (HRQoL). Although the majority of NP events resolved over time, patients with NP events attributed to SLE had a higher mortality rate.

To further advance understanding of nervous system disease in SLE patients, we wished to identify the clinical and laboratory variables associated with the development and resolution of NP events over time. The current study in a large, prospective, international, inception cohort of SLE patients was performed to determine predictors for change in a patient's NP event status, based on a multistate modelling approach and attribution rules previously described(5).

Patients and Methods

Research study network: The study was conducted by the Systemic Lupus International Collaborating Clinics (SLICC)(6), a network that currently consists of 52 investigators at 43 academic centres in 16 countries. At the initiation of the current study, recently diagnosed SLE patients were recruited from the then 31 SLICC sites in Europe, Asia, and North America. Data were collected per protocol at enrollment and annually ensuring data quality, management and security. The Nova Scotia Health Authority central zone Research Ethics Board and each of the participating centres' research ethics review boards approved the study.

Patients: Enrollment was permitted up to 15 months following diagnosis of SLE, taken as when the revised ACR classification criteria(7) were first recognized. Lupus-related variables included the SLE Disease Activity Index 2000 (SLEDAI-2K)(8) and SLICC/ACR Damage Index (SDI)(9).

Neuropsychiatric events: NP events were first characterized within an enrollment window (6 months prior to the diagnosis of SLE up to the enrollment date) using ACR case definitions for 19 NP syndromes(10). Patients were reassessed annually within a 6-month window using a detailed protocol to record information on the same 19 NP syndromes(10), presence of pre-specified non-SLE causes, results of appropriate investigations, medications and outcomes. New NP events since the last study assessment and status of previous NP events were determined at each assessment. For recurring events within an assessment period, the date of the first episode was taken as the onset of the event.

NP events were also classified into the following mutually exclusive categories: Central/Diffuse NP events included aseptic meningitis, demyelinating syndrome, headache, acute confusional state, anxiety disorder, cognitive dysfunction, mood disorder and psychosis; Central/Focal NP Events included cerebrovascular disease, movement disorder, myelopathy and seizure disorders; Peripheral NP events included autonomic neuropathy, mononeuropathy, myasthenia gravis, Guillain-Barre syndrome, cranial neuropathy, plexopathy and polyneuropathy.

Attribution of NP events: Factors considered in the attribution decision rules included: (i) temporal onset of NP event(s) in relation to the diagnosis of SLE; (ii) concurrent non-SLE factor(s), such as potential causes ("exclusions") or contributing factors ("associations") for each NP syndrome listed in the glossary for the ACR case definitions of NP events(10); and (iii) "common" NP events that are frequent in normal population controls as described by Ainiala et al(11). These include isolated headaches, anxiety, mild depression (mood disorders failing to meet criteria for "major depressive-like episodes"), mild cognitive impairment (deficits in less than three of the eight specified cognitive domains) and polyneuropathy without electrophysiological confirmation. Two attribution decision rules of different stringency (models A and B) were designed(12, 13). ***Attribution Model A (more stringent):*** NP events attributed to SLE (i) had their onset within the enrollment window or subsequently and (ii) had no "exclusions" or "associations" and (iii) were not one of the NP events identified by Ainiala(11).

Attribution Model B (less stringent): NP events attributed to SLE (i) had their onset within 10 years prior to the diagnosis of SLE and were still present within the enrollment

window, or occurred subsequently, and (ii) had no “exclusions” and (iii) were not one of the NP events identified by Ainiala(11).

All NP events attributed to SLE using model A were included in the NP events using model B. All other events were classified as a non-SLE NP event.

Outcome of NP events: Physician-generated 7-point Likert scale score at each follow-up assessment compared the change in NP events between onset and follow-up (1=patient demise, 2=much worse, 3=worse, 4=no change, 5=improved, 6=much improved, 7=resolved)(14). A precise date was recorded for outcomes 1 and 7.

Factors potentially associated with NP events: Variables of interest included sex, race/ethnicity/location, age at SLE diagnosis, education, concurrent NP events with a different attribution and updated at each assessment, SLEDAI-2K and SDI scores (excluding NP variables) as well as medication. Central/Diffuse, Central/Focal and Peripheral events were also considered in the analyses as were lupus anticoagulant (LAC), IgG anticardiolipin, anti-β_2 glycoprotein-I, anti-ribosomal P (anti-P) and anti-NR2 glutamate receptor antibodies.The LAC assay was performed using screen-and-confirm reagents (RainbowScientific, Windsor, CT) and the other autoantibodies were measured by enzyme-linked immunosorbent assay (ELISA) at the Oklahoma Medical Research Foundation, USA (15-18). Autoantibodies were measured once at enrollment.

Statistical analysis: As we previously described(5), multistate patient level models, characterized by transition rates between states, were examined, one for NP events attributed to SLE(model B) and the other for non-SLE events (Figure 1). In the current study, an additional multistate model for non-SLE events excluding headache was

examined due to the predominance of headache in the non-SLE NP events. Models for SLE NP events restricted by Central/Diffuse, Central/Focal and Peripheral events were also examined. Events other than the type being modelled were excluded when fitting each model. The four states in the multistate models were:

1. No NP event ever.
2. No current NP event but ≥1 in the past. State entry was the time of resolution of the last active NP event after entry into State 3.
3. New/Ongoing NP event(s) with state entry at the onset of any NP event when previously in States1 or 2.
4. Death

Modelling assumed transitions could occur between and not just at assessments and each site investigator provided the approximate dates for onset and resolution of NP events and precise dates for death.

The time origin was 6 months before SLE diagnosis. Patients could move back and forth between States 2 (resolution of NP event) and 3 (new/ongoing NP event). The model incorporates deaths occurring from any of States 1 to 3.

For the purposes of this analysis, the transition rates were estimated using Cox's semi-parametric relative risk regression model. This allows explanatory (predictor) variables to influence transition rates through a regression model on the logarithm of the transition rates while the baseline transition rate is allowed to be an arbitrary function of time since entering the state. The primary focus is on hazard rate (HR) estimates, and confidence intervals which are provided based on univariate (single factor) analyses and from

multivariate models. Effects are assumed to be the same on the transitions to the NP event state from both the no NP event and the resolved state. Model estimation was implemented using the R(19) package 'survival'(20) .

Kaplan-Meier like estimates of the probability of onset and probability of resolution over time were also calculated for both transitions within the multi-state models and for some NP event level analyses.

Results

Patients: 1,827 patients were recruited from October 1999 through December 2011, from the United States [n=540 (29.5%)], Europe [n=477 (26.1%)], Canada [n=418 (22.9%)], Mexico [n=223 (12.2%)] and Asia [n=169 (9.3%)]. At enrollment, the mean (SD) age was 35.1 (13.3) years, 88.8% of patients were female, with variable race/ethnicity (Caucasian 48.8%, African 16.8%, Hispanic 15.4%, Asian 15.1% and other 3.9%) and the mean (SD) disease duration was 5.6 (4.2) months. The mean (SD) SLEDAI-2K was 5.3 (5.4) and SDI was 0.32 (0.74). Medications at enrollment included corticosteroids (70.3%), antimalarials (67.4%), immunosuppressants (40.1%), warfarin (5.4%), low dose aspirin (14.3%), antidepressants (10.1%), anticonvulsants (4.4%) and antipsychotic drugs (0.7%). The mean follow-up was 7.6±4.6 years, with 1 to 19 assessments and ended in September 2017. One hundred patients (5.6%) died during the study. The number of patients dying while in States 1, 2 and 3 were 61, 18 and 21 respectively for the SLE NP event modelling and 66, 13 and 21 for the non-SLE event model.

Neuropsychiatric manifestations: NP events occurred in 955/1,827 (52.3%) patients and 493/1,827 (27.0%) had ≥2 events. There were 1,910 unique NP events, encompassing all 19 NP syndromes(10), of which 1,749 (91.6%) involved the CNS and 161 (8.4%) the peripheral nervous system (PNS)(10). Further classification of the NP events revealed that 1479/1,910 (77.4%) were central/diffuse, 270/1,910 (14.1%) were central/focal and 161/1,910 (8.4%) were peripheral. The NP events attributed to SLE varied from 17.9% (attribution model A) to 31.0% (attribution model B) and occurred in 13.5% (model A) to 21.2% (model B) of patients. Of the 593 events attributed to SLE by model B, 231(31.0%), 244(41.1%) and 118(19.9%) were central/diffuse, central/focal and peripheral respectively. For the 1317 non-SLE events, the comparable numbers were 1248(94.8%), 26(2.0%) and 43(3.2%).

Factors associated with onset of SLE NP events: For SLE NP events, univariate analyses of transitions to the NP event state revealed a positive association [HR (CI)] with male sex [1.39 (1.07,1.81); P=0.014], SLEDAI-2K without NP variables [1.13 (1.01,1.27)]; P=0.030], SDI without NP variables [1.12 (1.01,1.24); P=0.029], corticosteroid use [1.50 (1.13,2.01); P=0.006], and concurrent non-SLE NP events [1.58 (1.25,2.01); P=0.002]. There was a negative association with Asian race/ethnicity [0.57 (0.41,0.79); P<0.001], post-secondary education [0.71 (0.59,0.86); P<0.001] and anti-malarial drug use [0.72 (0.55,0.94); P=0.014]. There was no association with aCL [1.05 (0.75,1.47); P=0.766], anti-β_2 glycoprotein-I [0.93 (0.67,1.30); P=0.69], lupus anticoagulant [1.10 (0.84,1.45); P=0.478], anti-ribosomal P [0.95 (0.64. 1.40); P=0.781] or anti-NR2 [0.78 (0.52,1.16); P=0.216] antibodies.

The results of multivariate analyses for SLE NP events in the multistate models are summarized in Table 1. For transitions to the NP event state from either State 1 or State 2, two models, with associated estimated HRs and CIs and p-values, are presented. The first model only includes time invariant variables or those defined at all time points and is estimated on all 492 observed transitions into State 3. (New events occurring while other events are ongoing do not represent a transition). The second model is restricted to the 192 transitions for which there is information on all the variables in the first model and additional time variable explanatory variables, the latter only being available for events occurring after the initial patient assessment. Results discussed are based on the first model when possible and on the second model otherwise.

For SLE NP events there was a positive association with male sex [1.35 (1.03,1.78)]; P=0.028], concurrent non-SLE NP events excluding headache [1.83 (1.31,2.55); P<0.001], SLEDAI-2K without NP variables [1.19 (1.04,1.36) P=0.012] and corticosteroid use [1.59 (1.12,2.34) P=0.008]. There was a negative association with Asian race/ethnicity [0.59 (0.42,0.82); P=0.002] post-secondary education [0.72 (0.59,0.88); P=0.001] and immunosuppressive drug use [0.67(0.50,0.94); P=0.019]. The negative association with anti-malarial drug use approached statistical significance [0.74 (0.54,1.01); P=0.056.

Factors associated with onset of non-SLE NP events: For non-SLE NP events, univariate analyses revealed a positive association [HR (CI)] with Caucasian race/ethnicity at US sites [1.37 (1.14,1.65); P<0.001], corticosteroid use [1.30 (1.09,1.55); P=0.004) and concurrent SLE NP events [1.61 (1.29,2.02); P<0.001]. There was a negative association with male sex [0.56 (0.44,0.71); P<0.001], Hispanic race/ethnicity

[0.70 (0.57,0.86); P=<0.001], age at SLE diagnosis [0.99 (0.98,0.99); P<0.001], and immunosuppressive drug use [0.78 (0.66,0.93); P=0.005].

As headache was a very frequent non-SLE NP event, occurring in 670(36.7%%) of patients and accounting for 916(69.5%) of non-SLE NP events, the univariate analysis for non-SLE NP events was repeated excluding headache. This revealed a lower number of significant associations, albeit with substantially fewer transitions, that included a positive association with concurrent SLE NP events [2.37 (1.72,3.29); P<0.001] and negative associations with African race/ethnicity at non-US sites [0.54 (0.32,0.89); P=0.015], Asian race/ethnicity [0.38 (0.28,0.58); P<0.001] and immunosuppressive drug use [0.67 (0.49,0.92); P<0.001]. Complete univariate analyses for SLE NP events, non-SLE NP events, non-SLE NP events without headache and headache only revealed additionally that Asian race/ethnicity has a positive association with headaches so that the negative association with other non-SLE events led to no demonstrable association when all non-SLE events were examined. A comprehensive analysis of predictors for headaches is provided in a previous publication(21).

The results of multivariate analyses for non-SLE events excluding headache in the multistate models are summarized in Table 1. For non-SLE events, variables included in the model are defined at all time points and therefore only one model is presented. Excluding headache, there was a positive association with concurrent SLE NP events [2.31 (1.66,3.21) P<0.001] and negative associations with African race/ethnicity at non-US sites [0.52 (0.32,0.86); P=0.012] and Asian race/ethnicity [[0.40 (0.26,0.62); P<0.001].

Onset of new SLE NP events categorized in into Central/Diffuse, Central/Focal and Peripheral groups: Estimated probability of onset curves and the number of patients at

risk for new and recurrent SLE NP events, representing entries into multi-state model state 3, are provided in Figure 2 and Table 2 respectively. The NP events are clustered into Central/Diffuse, Central/Focal and Peripheral groups with curves based on multi-state models for each group. As can be seen the rates for new and recurrent NP events in each of these clusters are similar with the exception of the higher rate of recurrence in the Central/Focal group.

An initial investigation of the potential differential effects for predictors for Central/Diffuse, Central/Focal and Peripheral SLE NP events revealed no marked variation. An approximate global test for differential effects, used to make allowance for multiple comparisons, for the factors in the model in column 2 of Table 1 generated a chi-squared statistic of 21.8 on 20 degrees of freedom(df) [P=0.34]. The only estimated quantitative difference of note was for the effect of Hispanic ethnicity which had a common estimated non-significant effect [0.93 (0.71,1.21); P=0.57] but had somewhat different estimated effects in the Central/Diffuse, Central/Focal and Peripheral groups of [0.50 (0.31,0.83); P=0.007] [1.34 (0.90,1.99); P=0.15] and [1.13 (0.65,1.99); P=0.66] respectively. For the additional variables in the second SLE NP events model in Table 1, a global test of differential effects generated a chi-squared statistic of 18.66 on 10df, P=0.04. There was some evidence that the corticosteroid effect was more marked in the Central/Focal group [2.42 (1.40,4.17); P=0.002] than in the Central/Diffuse [1.40 (0.84,2.33); P=0.20] and Peripheral [1.30 (0.69,1.46); P=0.42] groups. There was also some evidence that the effect of anti-malarial drugs was more evident in the Central/Focal [0.69 (0.45,1.07); P=0.09] and Central/Diffuse [0.60 (0.37,0.95); P=0.03] groups than in the Peripheral group [0.93 (0.50,1.74; P=0.83]. Multiplicity considerations suggest that these findings

should be treated cautiously. Sample size was insufficient to address differential effects for non-SLE NP events.

We looked for an association between Central/Focal NPSLE with antiphospholipid antibodies and between Central/Diffuse NPSLE with generalized SLE disease activity, as reflected in SLEDAI-2K scores. Neither association was identified in our analysis. Specifically, although the presence of lupus anticoagulant had a slightly higher HR for Central/Focal events it was not significant in the univariate analysis and there was no evidence for differential effects by event type (P=0.33). The same pattern emerged if lupus anticoagulant was added to the multivariate model with the test for differential effects having P=0.22. With respect to SLEDAI-2K, there was no clear evidence for differential effects by event type. A formal test generates P=0.10 and when we looked at individual effects the largest effect was for Central/Focal events, not Central/Diffuse.

Resolution of NP events:

Central/Diffuse, Central/Focal and Peripheral Events: To provide background to the development of regression models for transitions to the resolved state, probability of resolution curves at the event level, i.e. each event provides one observation, are presented in Figure 3 and Table 2. Due to the predominance of headache in the non-SLE NP event group, headache is separated from the other non-SLE NP events in this analysis. As a group, NP events attributed to SLE have a higher rate of resolution than non-SLE NP events, with the exception of headache that has a comparable rate of resolution to SLE NP events (Figure 3A). Within the SLE NP events, the rate of resolution was highest for Central/Focal NP events compared to Central/Diffuse and Peripheral NP events (Figure 3B). For the non-SLE NP events a similar pattern of resolution was seen

(Figure 3C) which was more apparent when the rate of resolution for headache was separated from the other Central/Diffuse NP events (Figure 3D).

Factors associated with resolution of NP events: As predictors for resolution of headaches has been presented elsewhere(21), in this analysis, predictors for the transition to the resolved state, 2, from the new/ongoing NP event state, 3, were examined for SLE NP events and non-SLE events excluding headaches. For these multistate models, explanatory variables were defined as binary indicators of any peripheral event in the active state and of any Central/Focal event in the active state because multiple types of events may be present for patients in the NP event state. The reference category for the effects associated with these indicators was all active events being Central/Diffuse because these events were the most frequent.

For SLE NP events, univariate analyses of transitions to the resolved NP state revealed a positive association with Asian race/ethnicity [1.77 (1.19,2.63); P=0.004] and any Central/Focal NP event [1.66 (1.29,2.15); P<0.001]. For non-SLE NP events there was a positive association with Hispanic race/ethnicity [1.69 (1.14,2.48); P=0.008] and with African race/ethnicity at non-US sites [1.99(1.10,3.61); P=0.022].

The results of multivariate analysis are summarized in Table 3. For SLE NP events there was a positive association with Asian race/ethnicity [1.72 (1.17,2.54); P=0.006] and with any Central/Focal NP event [1.74 (1.33,2.27); P<0.001]. For non-SLE NP events there was a positive association with African race/ethnicity at non-US sites [2.06 (1.14,3.73); P=0.017] and a negative association with age at diagnosis of SLE [0.98(0.96,0.99); P<0.001].

Discussion

Long-term observation of a large international SLE disease inception cohort was used to identify predictors for both the occurrence and resolution of NP events with current standard of care. The inclusion of all NP events, regardless of attribution, provided insight into differences between NP events attributed to SLE and to non-SLE causes. The predominance of headache within the non-SLE NP group prompted a separate analysis of this individual event. The results of our study indicate heterogeneity in the occurrence, resolution and recurrence of different NP events and in predictors for same over time. As multiple NP events due to different causes may present concurrently in individual patients, the findings emphasize the importance of recognizing attribution of NP events as a determinant of clinical outcome.

The SLICC SLE disease inception cohort is well suited for the current study. Over the course of 21 years since enrollment began, this large, prospective, international cohort has provided the basis for examining several SLE manifestations and complications including atherosclerosis(22), lupus nephritis(23), cumulative organ damage(24), frailty(25) and NP disease(4). The study of NP disease has been facilitated by standardized data collection, use of predetermined rules to identify attribution of NP events to SLE and non-SLE causes and recruitment of patients close to the time of diagnosis of SLE. Previous studies of NP disease in the SLICC cohort have focused upon individual NP manifestations(4, 21, 26-29) made possible by the large size of the cohort and prolonged followup. In the current study, using a multi-state modelling approach, we have examined the long-term course of all NP events in the SLICC cohort, with a particular emphasis on the factors associated with clinically meaningful change in NP

status over time. NP events occur frequently in SLE patients(30, 31). In the current study over half of the patients had at least a single event during the study and over a quarter had two or more events. There was also a wide spectrum of manifestations and all 19 of the individual ACR case definitions for NP disease in SLE were represented. Over three-quarters of the NP events were in the Central/Diffuse category and only 31% of all events were attributed to SLE.

There is limited information on predictors of NP events in SLE. This is partly due to study limitations including small cohort size, failure to determine attribution of NP events in a standardized way and short observation period(32-34). In the current study, multivariate analysis of predictors for the onset of SLE NP events indicated a higher risk in men than in women and a reduced risk in individuals of Asian race/ethnicity. Of interest, the risk was also reduced in patients with post-secondary education, in keeping with a study of 1,121 Korean SLE patients(30). Likewise, Asian race/ethnicity was also associated with a lower risk for non-SLE NP events as was African race/ethnicity at non-US sites. For both types of NP events there was a significant association with concurrent NP events of the alternate attribution, indicating that NP events due to SLE and non-SLE causes present concurrently in many patients. As the etiology of NP events due to SLE and non-SLE causes is different, their co-occurrence emphasizes the importance of determining the correct attribution which will direct therapy. In support of this point and in keeping with the findings of other studies(30, 35), the current study found that the onset of NP events attributed to SLE was associated with SLE disease activity and corticosteroid use. None of the lupus autoantibodies measured at enrollment predicted the onset of NP events. This is not surprising given that previous autoantibody associations with SLE NP events

have been restricted to specific NP manifestations such as cerebrovascular events (26) and psychosis (27).

Previous studies have sought predictors of clinical outcome in patients with NPSLE. In a study of 32 hospitalized SLE patients(36), 14 of whom had antiphospholipid syndrome (APS), NP status improved in 69% of cases over 2 years of followup. In the same study, prior NP events and APS were associated with adverse outcomes. An increased mortality risk in SLE patients with NP disease has been reported in previous studies(5, 30), especially in patients with Central/Focal NP events(30). In the current study there were group differences in the rate of resolution of NP events. Overall, SLE NP events were more likely to resolve compared to non-SLE NP events with the exception of headache. Resolution of SLE events was more likely in patients with Asian race/ethnicity and those with Central/Focal nervous system disease. For non-SLE NP events, African race/ethnicity at non-US sites and younger age was associated with a better outcome. There was no association between resolution of NP events and lupus autoantibodies measured at enrollment.

The higher rate of recurrence for Central/Focal SLE NP events (Figure 2) likely explains the overall higher rate for SLE versus non-SLE events attributed to SLE previously described(5). Central/Focal disease also had the highest rate of resolution of SLE NP events (Figure 3B). This group of NP events includes transient ischemic attacks (TIAs) which, by definition, resolve within 24 hours and thus could have influenced both recurrence and resolution rates. However, this is very unlikely as TIAs were few in number (n=29) and the curves for both recurrence and resolution were not appreciably different when TIAs were removed from the analysis (data not shown). Overall the Central/Focal

SLE NP group were not associated with lupus autoantibodies, although we have previously reported an association between stroke and TIAs with antiphospholipid antibodies in the SLICC cohort (26). Likewise, in the current study we found an association overall between SLE NP events and global SLE disease activity, excluding neurological variables, but no such association was found with Central/Diffuse SLE NP events per se.

How can the findings of this study inform our approach to patient management? First, although nervous system events occur frequently in SLE patients the majority are not a direct effect of a targeted autoimmune lupus response. The management of these non-SLE NP events rests primarily on the treatment of comorbid conditions and symptomatic therapies. Second, as is the case with other lupus manifestations such as nephritis(23), SLE NP events occur most frequently early in the disease course (5). Third, the presentation of SLE NP events is often associated with generalized SLE disease activity and has a more favourable outcome than NP events attributed to non-SLE causes. Finally, the associations with race/ethnicity, sex and education and the lack of association with lupus autoantibodies emphasizes the importance of not overlooking etiological factors beyond the more traditional autoimmune disease paradigms for NPSLE. For example, the negative association between the onset of SLE NP events with education may be due to differences in adherence to prescribed medications(37).

There are limitations to the current study. First, the predominance of Caucasian race/ethnicity in the cohort may have limited the ability to find additional associations for NPSLE in racial/ethnic minorities. Second, the clustering of NP events into a limited number of categories reduced the likelihood of finding specific clinical-serological

associations such as cerebrovascular disease with antiphospholipid antibodies(26). Third, assessment of the outcome of NP events was restricted to physician determinations and did not include patient-centered perceptions as has been done in previous reports of individual NP manifestations in the SLICC inception cohort(4, 21, 26-29). Finally, although the study was well suited to evaluate NP events early in the disease course when events are frequently due SLE disease activity, the mean follow up of 7.6 years is likely insufficient for the study of later NP events such as cerebrovascular disease attributed to accelerated atherosclerosis. Despite these limitations the current study provides valuable data on the presentation, outcome and predictors of NP disease in SLE patients enrolled in a long-term, international, disease inception cohort.

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Table 1: Multivariate analysis of predictors for transitions to the NP event state for events attributed to SLE (SLE NP events) and non-SLE NP events excluding headaches.

SLE NP events	Model 1 (n = 426 transitions)		Model 2 (n = 192 transitions)	
Variable	**HR (CI)**	**p-value**	**HR (CI)**	**p-value**
Male sex	1.35 (1.03,1.78)	0.028	1.55 (1.05,2.29)	0.026
Asian race/ethnicity*	0.59 (0.42,0.82)	0.002	0.60 (0.37,0.98)	0.04
Post-secondary education	0.72 (0.59,0.88)	0.001	0.73 (0.55,0.98)	0.040
Past non-SLE NP events (without headache)	1.21 (0.74,1.98)	0.434	1.16 (0.68,1.99)	0.59
Concurrent non-SLE NP events (without headache)	1.83 (1.31, 2.55)	<0.001	1.79 (1.17,2.75)	0.007
SLEDAI-2K (without NP variables)			1.19 (1.04,1.36)	0.012
SLICC (without NP variables)			1.05 (0.94,1.18)	0.35
Corticosteroids			1.59 (1.12,2.34)	0.008
Anti-malarial drugs			0.74 (0.54,1.01)	0.056
Immunosuppressive drugs			0.67 (0.50,0.94)	0.019

Non-SLE NP events excluding headaches	Model 1 (n = 337 transitions)		Model 2 (not applicable)
Variable	**HR (CI)**	**p-value**	
Non-US African race/ethnicity*	0.52 (0.32,0.86)	0.012	
Asian race/ethnicity*	0.40 (0.26,0.62)	<0.001	
Past SLE NP events	1.29 (0.84,2.00)	0.24	
Concurrent SLE NP events	2.31 (1.66,3.21)	<0.001	

Model 1 includes time invariant variables or those defined at all time points. Model 2 is restricted to transitions for which there is information as in model 1 and additional time variable explanatory variables available only for events occurring after the initial patient assessment.
*: Other race/ethnicities were included in the analysis, but the results were not significant.

Table 2: The number of patients at risk for probability of onset or recurrence of NP events attributed to SLE in Figure 2 and for the probability of resolution of NP events attributed to SLE and non-SLE causes in Figure 3.

Numbers of patients at risk in figure 2

	Entry	5 yrs	10 yrs	15 yrs
Initial Peripheral	1827	1340	695	175
Recurrent Peripheral	59	31	14	1
Initial Central/Focal	1827	1295	666	174
Recurrent Central/Focal	144	64	22	1
Initial Central/Diffuse	1827	1271	654	175
Recurrent Central/Diffuse	102	65	20	4

Number of patients at risk in figure 3A

	Entry	5 yrs	10 yrs	15 yrs
Non-SLE Events	401	109	31	6
SLE NP Events	593	120	41	12
Headache	916	198	57	11

Number of patients at risk in figure 3B

	Entry	5 yrs	10 yrs	15 yrs
Peripheral	118	34	10	5
Central/Focal	244	31	12	2
Central/Diffuse	231	55	19	5

Numbers of patients at risk in figure 3C

	Entry	5 yrs	10 yrs	15 yrs
Peripheral	43	15	3	1
Central/Focal	26	4	3	0
Central/Diffuse	1248	288	82	16

Number of patients at risk in figure 3D

	Entry	5 yrs	10 yrs	15 yrs
Peripheral	43	15	3	1
Central/Focal	26	4	3	0
Central/Diffuse	332	90	25	5
Headache	916	198	57	11

Table 3: Multivariate analysis of predictors for transitions to the resolved NP State for events attributed to SLE (SLE NP events) and non-SLE excluding headaches.

SLE NP events

	(n = 270 transitions)	
Variable	**HR (CI)**	**p-value**
Asian race/ethnicity*	1.72 (1.17,2.54)	0.006
Any Peripheral	0.89 (0.65,1.24)	0.500
Any Central-Focal	1.74 (1.33,2.27)	<0.001
All Central-Diffuse	1.00	
Past non-SLE NP events (without headache)	0.93 (0.59,1.47)	0.76
Concurrent non-SLE NP events (without headache)	0.63 (0.44,0.91)	0.12
Previous headache	0.98 (0.67,1.43)	0.93
Current headache	0.80 (0.58,1.09)	0.15

Non-SLE NP events excluding headaches

	(n = 176 transitions)	
Variable	**HR (CI)**	**p-value**
Hispanic race/ethnicity*	1.43 (0.96,2.13)	0.082
Non-US African race/ethnicity*	2.06 (1.14,3.73)	0.017
Age at SLE diagnosis	0.98 (0.96,0.99)	<0.001
Any Peripheral	0.76 (0.44,1.29)	0.306
Any Central-Focal	1.38 (0.72,2.64)	0.328
All Central-Diffuse	1.00	

* Other race/ethnicities were included in the analysis but the results were not significant

Legends for figures

Figure 1: Multistate model for observed transitions in neuropsychiatric (NP) status in patients with SLE.

Figure 2: Curves for the probability of onset or recurrence of NP events attributed to SLE using attribution model B.

Figure 3: Curves for the probability of resolution of NP events attributed to SLE and non-SLE causes using attribution model B.