Predictors of neuropsychiatric damage in systemic lupus erythematosus: data from the Maryland lupus cohort

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Objective. To identify factors predictive of significant neuropsychiatric (NP) damage in systemic lupus erythematosus (SLE).

Methods. One hundred and thirty patients with SLE were followed at the University of Maryland Lupus Clinic from 1992 until 2003. NP manifestations were defined according to the revised American College of Rheumatology (ACR) nomenclature and case definitions for NP–SLE syndromes. Disease activity was measured using the SLE Disease Activity Index (SLEDAI), organ damage using the Systemic Lupus International Collaborating Clinics Damage Index SLICC/ACR (SDI); NP damage (NPDI) was measured with the corresponding domain of the SDI. At end of study period, 64 patients exhibited no NP damage (NPDI = 0) and 66 patients developed significant NP damage (defined as NPDI ≥1). The baseline features for these two patient groups were compared, and variables found to be significantly different were examined by multivariable analyses to determine their contribution to NP damage.

Results. Significant NP damage is common in SLE; mortality is infrequent and the cause of death is unrelated to NP damage. Independent predictors of significant NP damage were disease activity, Caucasian ethnicity and the presence of antiphospholipid antibodies and anti-Ro/SSA antibody. Certain clinical features at baseline predicted specific NP damage. For example, higher disease activity at baseline was predictive of psychosis and cognitive impairment, anti-dsDNA was predictive of polyneuropathy, and antiphospholipid antibodies were predictive of seizures and cerebrovascular accidents.

Conclusions. In this longitudinal SLE cohort, significant cumulative NP damage occurred. Early aggressive therapy targeted towards NP manifestations may prevent the occurrence of NP damage.

KEY WORDS: Systemic lupus erythematosus, Neuropsychiatric damage, Risk factors.
time the analyses to be presented were done (range 1–10 yr). Data on demographic variables, clinical and laboratory manifestations, including age at disease onset, symptom duration at disease onset, duration and types of NP events and therapies received for these events, are collected, as are all comorbidities, and recorded on standard forms.

Disease onset was defined as the time at which a patient met four ACR criteria for the classification of SLE; patients were then enrolled into the study. SLE patients with NP manifestations prior to enrolment were excluded from the analyses. NP manifestations were clinically ascertainned and classified into distinct syndromes as per the ACR nomenclature. Cognitive function was assessed, if indicated, using the ACR-recommended battery for neuropsychological testing plus the Mini-Mental State Examination [23]. Disease activity was measured with the SDI activity index or SLEDAI [24]. Imaging studies were performed if clinically indicated.

Antinuclear antibodies (ANA) were measured with an immuno-fluorescent test using rat liver as the substrate and following the World Health Organization (WHO) recommendations [25]. AntidS DNA antibodies were examined with the Crithidia luciliae assay [26]; anti-Ro/SSA and anti-La/SSB antibodies were tested using the traditional Ouchterlony double immunodiffusion method [27]. Anti-Smith (Sm) and anti-iRNP antibodies were detected using a commercial enzyme-linked immunosorbent assay (ELISA), and if these antibodies fluctuated over time on repeated testing an immunoprecipitation test was done to confirm these antibodies [28]. The lupus anticoagulant (LAC) was ascertained using the guidelines established by the 1991 Scientific Subcommitte criteria, later simplified by Exner [29]; anti-IgM and IgG anticardiolipin (aCL) antibodies were measured using a commercial ELISA [30]. Anti-ribosomal P antibodies were determined in selected patients using a commercial ELISA method.

SDI and definition of damage (overall and NP)

The SDI measures cumulative damage accrued since disease onset. The SDI includes 41 non-reversible items encompassing nine organ systems: diabetes, malignancies and infertility are the three additional domains of SDI. Each item must be present for at least 6 months to be scored. For a repeated event to be scored (e.g. a new stroke) it has to occur at least 6 months apart from the first; the same item cannot be scored twice. The SDI was scored according to the definitions outlined in the corresponding glossary and it was obtained in all patients 6 months after disease onset and biannually thereafter. Patients with an SDI score ≥1 are said to have accrued overall damage. The NP damage index (NPDI) was ascertained 6 months after the occurrence of an acute NP event (Appendix 1, available as supplementary data at Rheumatology Online). An NPDI score ≥1 was felt to be clinically significant; thus an increment of ≥1 was considered as NP damage worsening.

Mortality and causes of death

The causes of death in this SLE cohort were categorized as follows in accordance with previously published work [31]: (i) SLE-related causes, including active disease (particularly nephritis, vasculitis leading to NP-SLE syndromes, and end-organ failure (renal, cardiac or pulmonary)), infections, and others (particularly vascular events); (ii) unrelated to SLE (particularly malignancies, suicide); and (iii) unknown.

Statistical methods

First, the baseline features of those patients accruing and those not accruing any NP damage were examined. Comparisons were done using the χ² test and analysis of variance (ANOVA) for categorical and continuous variables respectively. Subsequently, patients were divided into three groups as follows: (i) no NP damage, NPDI = 0; (ii) mild damage, NPDI = 1 or 2; and (iii) severe damage, NPDI ≥ 3. Baseline features were compared among these three groups. Given that damage tends to accrue over time, disease duration was included in these analyses as a covariate.

Demographic features, such as ethnicity, gender, age at onset, socioeconomic status, including the type of health-care delivery system that is available, clinical manifestations frequently occurring in SLE, including arthritis, skin rashes, fever, pleurisy, pericarditis, nephritis (defined as mesangial, focal proliferative, diffuse proliferative or membranous glomerulonephritis according to the WHO classification on histopathology, or persistent proteinuria of >0.5 g/day, or proteinuria of >3.5 g/day, or cellular casts of any kind according to the ACR criteria), alopecia, vasculitis, Raynaud’s phenomenon, adenopathy, splenomegaly, myositis, myocarditis, anaemia, leucopenia, thrombocytopenia and immunological abnormalities, including anti-dsDNA, antiphospholipid, anti-Ro/SSA, anti-La/SSB and anti-Smith antibodies, as well as disease activity, were examined in relation to NP manifestations according to the ACR nomenclature. The possible relationship between NP damage and mortality was also examined.

Multivariable analyses were performed using logistic regression with NP damage as the dependent variable in one of them. In other regression analyses, the dependent variable was mild or severe damage. Finally, an attempt was made to examine the variables associated with the occurrence of specific NPDI items. In a separate regression, the factors associated with mortality were examined. In all regressions, P < 0.05 was considered significant.

All analyses were done with SPSS for Windows, version 11.0 (SPSS, Chicago, IL, USA). Informed consent was obtained from all patients prior to enrolment into the study. This clinical research followed the code of ethics approved by the Institutional Review Board at the University of Maryland.

Results

Patient population, NP manifestations and NP damage

The U of M lupus cohort consists of 130 SLE patients; 121 (93%) are women and 83 (64%) are African-Americans. The average age at disease onset in these patients was 37 yr. NP-SLE manifestations occurred at any time during the course of SLE along with other features of SLE or as isolated events as part of the NP-SLE syndromes. Seventy-four of the 130 patients with SLE had NP manifestations, including psychosis, seizures, polyneuropathy, cerebrovascular accidents (CVA), myocarditis and headache.

Seven years from enrolment into the cohort, on the average, nearly half the patients have yet to accrue any damage, NP included. Some SLE manifestations, particularly headaches related to SLE, have been common but they have not been followed by NP damage. Nonetheless, individual NP damage items accrued with variable frequency, cognitive impairment being the most common (27.3%); other NP damage items were as follows: CVA, 25.7%; polyneuropathy, 18.2%; psychosis, 15.1%; seizures, 7.6%; and transverse myelitis, 6.1%. Some patients have accrued more than one NP damage item.

Neuropsychiatric damage

Baseline demographic and clinical features of patients with and without NP damage are shown in Table 1. The two patient groups had comparable disease durations and numbers of ACR criteria for the classification of SLE. Likewise, other socioeconomic features, including education, health insurance and access to...
Predictors of neuropsychiatric damage in SLE

The occurrence of NP damage (any) was more frequent among patients of non-African–American ethnicity and of older age at diagnosis. Renal (but not cardiovascular) involvement was more frequent in patients with NP damage than in those without it. Cutaneous vasculitis, arthritis and, not surprisingly, NP manifestations were more frequent in patients who later developed NP damage than in those without it. Autoantibodies were present with comparable frequency in the two groups, with the exception of antiphospholipid antibodies, particularly LAC and IgG aCL, which were more frequent in the NP damage group. Abnormal magnetic resonance imaging (MRI) of the brain [including focal lesions in white matter, white matter hyperintensity, increased intensity in grey matter, fluid-attenuated inversion recovery (FLAIR) lesions, areas of infarction, intracerebral bleed, demyelination and cortical atrophy] was more frequent in patients who later developed NP damage. Of importance, patients in the NP damage group were also more likely to have active disease and be treated more aggressively, as evidenced by a higher dose of corticosteroids and the more frequent use of immunosuppressive therapy.

**Severity of NP damage**

Baseline demographic and clinical manifestations as a function of the severity of NP damage are presented in Table 2. Features associated with more severe damage included disease duration, non-African-American ethnicity, older age at diagnosis, male gender, disease activity, cutaneous vasculitis and the use of antiphospholipid antibodies. Cognitive impairment was associated with greater disease activity and the presence of antiphospholipid antibodies, particularly LAC and IgG aCL. Polynuropathy was associated with the presence of serum anti-dsDNA antibodies. Psychosis was associated with greater disease activity and the presence of the anti-dsDNA antibodies. CVA was associated with the presence of antiphospholipid antibodies. Cognitive impairment was associated with greater disease activity and older age at SLE diagnosis.

**Discussion**

During the past two decades, a great deal has been written about the frequency and clinical presentations of NP features in SLE. However, the relationship of various clinical variables with NP damage has not been adequately examined. Thus, we have reviewed our experience with NP damage in SLE, paying particular attention to the socioeconomic, demographic and clinical predictors of NP damage.

**Table 1. Baseline sociodemographic and clinical features of SLE patients as a function of the later occurrence of NP damage**

<table>
<thead>
<tr>
<th>NPDI = 0 (n = 64)</th>
<th>NPDI ≥ 1 (n = 66)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at SLE diagnosis (yr)</td>
<td>Mean: 35.6</td>
<td>39.7</td>
</tr>
<tr>
<td></td>
<td>Range: 21.9–55.1</td>
<td>26.0–60.4</td>
</tr>
<tr>
<td>Ethnicity African–American, (%)</td>
<td>73.4</td>
<td>54.5</td>
</tr>
<tr>
<td>Gender: women (%)</td>
<td>96.8</td>
<td>90.9</td>
</tr>
<tr>
<td>Duration of SLE (yr)</td>
<td>Mean: 7.2</td>
<td>8.5</td>
</tr>
<tr>
<td></td>
<td>Range: 2.6–11.8</td>
<td>3.4–13.6</td>
</tr>
<tr>
<td>NP-SLE manifestations (%)</td>
<td>Confusional state</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Psychosis</td>
<td>3.1</td>
</tr>
<tr>
<td></td>
<td>Seizures</td>
<td>3.1</td>
</tr>
<tr>
<td></td>
<td>Cerebrovascular accident</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Polynuropathy</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Denyelinating disease</td>
<td>0.0</td>
</tr>
<tr>
<td>Other SLE manifestations (%)</td>
<td>Glomerulonephritis</td>
<td>17.2</td>
</tr>
<tr>
<td>Autoantibodies (%)</td>
<td>Anti-cardiolipin IgG</td>
<td>15.6</td>
</tr>
<tr>
<td></td>
<td>Lupus anticoagulant</td>
<td>1.6</td>
</tr>
<tr>
<td>Abnormal brain MRI (%)</td>
<td>3.0</td>
<td>45.0</td>
</tr>
<tr>
<td>Therapy used</td>
<td>Cyclophosphamide (%)</td>
<td>6.3</td>
</tr>
<tr>
<td></td>
<td>Prednisone (mg/day): mean</td>
<td>4.5</td>
</tr>
<tr>
<td>SLEDAI</td>
<td>Mean: 4.8</td>
<td>15.4</td>
</tr>
<tr>
<td></td>
<td>Range: 2–8</td>
<td>9–21</td>
</tr>
<tr>
<td>SDI</td>
<td>Mean: 1.0</td>
<td>3.8</td>
</tr>
<tr>
<td></td>
<td>Range: 0–3</td>
<td>2–5</td>
</tr>
</tbody>
</table>

NPDI = 0, NP manifestations not fulfilling damage glossary definitions. P value <0.05.

Disease duration was a covariate in these analyses. MRI = magnetic resonance imaging.

Damage in the other domains of the SDI and NP damage

Although renal and pulmonary manifestations occurred with increased frequency in the NP damage group, the overall SDI or damage in these particular organs did not associat with NP damage accrual. Likewise, none of the other damage items associated with NP damage but osteoporosis, alopecia, cataracts and vascular damage were more frequent among patients in the NP damage group than in the group with no NP damage, but the differences were not statistically significant (data not shown).

Mortality and NP damage

At the time these analyses were conducted, eight deaths had occurred; all eight patients had developed NP damage, death occurring 5 yr after NP damage ensued. The cause of death in these patients was unrelated to NP damage and NP damage was not retained in a logistic regression model in which mortality was the dependent variable (data not shown).

Neuropsychiatric damage: multivariable analyses

**NP damage.** Variables independently associated with the occurrence of NP damage (any) were disease activity, non-African–American ethnicity, age at disease onset and the presence of antiphospholipid antibodies, particularly LAC and IgG aCL. After adjusting for age at onset in the multivariate analysis, the variables retained in the model were the same. These data are shown in Table 3.

**Severe damage.** Male gender, vasculitis and anti-Ro/SSA antibodies were independently associated with severe NP damage. These data are also shown in Table 3.

**Specific NP damage.** The variables independently associated with specific NP damage items are shown in Table 4. Seizures were associated with CVA and the presence of antiphospholipid antibodies, particularly LAC and IgG aCL. Polynuropathy was associated with the presence of serum anti-dsDNA antibodies. Psychosis was associated with greater disease activity and the presence of the anti-dsDNA antibodies. CVA was associated with the presence of antiphospholipid antibodies. Cognitive impairment was associated with greater disease activity and older age at SLE diagnosis.
In this longitudinal cohort, significant NP damage was present in 51% of SLE patients with mean disease duration of 7 yr; the most frequent NP damage was cognitive impairment. The strongest risk factors for the development of significant NP damage was the presence of greater disease activity at the NP–SLE event. Significant NP damage (any) was particularly noted among Caucasian patients, patients who were older at SLE onset, and having antiphospholipid antibodies, particularly LAC and IgG aCL. Severe NP damage was greater among male patients having vasculitis and anti-Ro/SSA antibodies.

Prior studies [19, 20, 32, 33] have shown that significant overall damage, NP included, is more common in patients with evidence of clinical activity, particularly vasculitis [33], diffuse glomerulonephritis [14] and multiple autoantibodies [34, 35], including anti-dsDNA, anti-Smith antibodies and antiphospholipid antibodies. Similarly, we showed that NP damage was associated with greater disease activity particularly NP manifestations, but also manifestations in other organ systems. Of importance in this regard, most patients with mild disease activity at time of NP events developed only mild NP damage. Furthermore, subsequent NP damage occurred more frequently in patients with greater or persistent disease activity.

The clinical relevance of autoantibodies in SLE is well recognized for the diagnosis, and in some cases, the prediction of
disease activity [36–40]; however, the relation with damage has not been established. In this cohort, anti-Ro/SSA was associated with severe NP damage, whereas no association with anti-La/SSB was noted. However, whether these antibodies are implicated in NP damage cannot be determined from the data obtained in this study. Nevertheless, knowing of this association may be important. Our study also supports the importance of antiphospholipid antibodies, particularly aCL antibodies and LAC, as independent risk factors associated with different NP manifestations, such as seizures, CVA and cognitive impairment, but also, more importantly, significant NP damage, as has been shown by others [41–43]. The association of cognitive impairment with aCL antibodies and LAC at baseline was examined. Patients with persistent elevated aCL antibodies and LAC were found to have more thrombotic events with CVA, and this may contribute to cognitive decline.

Ethnic differences in survival have often been reported for SLE patients, with poorer long-term outcomes/damage noted among minority or underprivileged patient groups [5]. This is attributed primarily to differences in exposure to environmental or other socioeconomic factors rather than to differences in genetic predisposition [3, 44–45]. In this cohort, NP damage accrued rapidly in all ethnic groups; however, a greater proportion of Caucasian patients exhibited more NP damage accrual. These findings may be attributed to the presence of advanced disease at the time of NP events or comorbid conditions. The lack of contribution of socioeconomic factors to the occurrence of NP damage was evident in the regression analyses.

The influence of gender (similar to ethnicity) upon SLE is profound. Many differences have been described, including the greatly increased frequency of SLE in women, but also the differences in clinical features, serology and genetics. While there have been conflicting results in the literature, males have generally been reported to have more NP symptoms. Our study supports the overall conclusion that men are more likely to develop NP symptoms more rapidly, and consequently to have severe NP damage. It remains to be determined whether gender modifies NP severity among patients with a particular autoantibody specificity.

The limitations of our study deserve some discussion. First, the high prevalence of NP damage in our cohort has been observed in other studies [4, 5, 7], but may represent an oversaturation bias, given that our patients were specifically asked about their NP symptoms and were systematically ascertained for the presence of cognitive impairment. Secondly, the limited number of manifestations of active disease used in the analyses may have precluded the identification of an important clinical variable. Perhaps the addition of tests that assess functional damage, including electroencephalography, electromyography, evoked potential diagnostics, functional MR/glucose metabolism neuroimaging [14] or markers of neuronal damage [46], will complement clinical findings to define damage more accurately and at earlier stages. Thirdly, the SLICC/ACR SDI and the NPDI are valid and reliable standard assessments of damage, but they are not meant to distinguish the underlying cause of any of the damage items.

In summary, significant NP damage is common in SLE. Independent predictors of significant NP damage were disease activity, Caucasian ethnicity, older age at SLE onset, and the presence of anti-Ro/SSA and antiphospholipid antibodies, particularly LAC and IgG aCL. Controlling disease activity in this subset of SLE patients may improve long-term outcome and reduce NP damage. Further studies are needed, including randomized clinical trials to address whether the use of immunosuppressive therapy or thrombophylaxis will reduce NP damage.

Acknowledgement

We gratefully acknowledge Dr Gaciela S. Alarcón for her invaluable critical review and comments.

The authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at Rheumatology Online.

References


Table 4. Multivariable analysis of baseline clinical and sociodemographic predictors of specific NP damage items according to the NPDI

<table>
<thead>
<tr>
<th>NP damage</th>
<th>Predictor</th>
<th>Odds ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizures</td>
<td>Anticardiolipin antibody</td>
<td>4.3 (1.2–15.3)</td>
<td>0.02</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>Cerebrovascular antibody</td>
<td>5.6 (2.1–14.3)</td>
<td>0.05</td>
</tr>
<tr>
<td>Polyneuropathy</td>
<td>Anti-dsDNA antibody</td>
<td>2.3 (1.0–5.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Psychosis</td>
<td>Disease activity</td>
<td>22.2 (2.8–177.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Cerebrovascular accidents</td>
<td>Disease activity</td>
<td>9.7 (3.5–26.3)</td>
<td>0.02</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>Disease activity</td>
<td>16.0 (3.8–66.3)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Older age at SLE diagnosis</td>
<td>13.4 (4.0–36.6)</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.8 (1.2–6.2)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Disease duration was a covariate in all analyses. Only significant variables are shown.