Risk factors for central nervous system involvement in systemic lupus erythematosus

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Summary

We investigated risk factors for central nervous system (CNS) involvement in systemic lupus erythematosus (SLE), in 32 such patients individually matched 1:3 to 96 control SLE patients without CNS events. Univariate analysis showed that CNS involvement was significantly associated with the antiphospholipid syndrome (APS) as well as its features: arterial thrombosis, recurrent fetal loss, livedo reticularis and IgG anticardiolipin (aCL) antibodies in high titres. Other potential associations included cutaneous vasculitic lesions, thrombocytopenia, positive ANA, anti-SS-B/La and low serum levels of C₃ and C₄ complement components, while articular manifestations and discoid rash were significantly less common in patients with neuropsychiatric (NP) disease. In multivariate modeling, CNS involvement was strongly associated with cutaneous vasculitic lesions OR 33, 95% CI 1.5–720) and arterial thromboses (OR 13, 95%CI 0.82–220), and negatively related to the presence of articular manifestations (OR 0.015, 95%CI 0.00–0.17) and discoid rash (OR 0.004, 95%CI 0.00–0.35). Associations with APS-related arterial thromboses and vasculitis point to the importance of arterial vascular pathophysiology in the pathogenesis of NP disease in SLE. Patients with articular manifestations and discoid rash are at very low risk of NP events. Patients with an adverse SLE disease profile may require closer observation and may be the target group for studying pre-emptive interventions.

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by multisystemic involvement and diverse manifestations. A large percentage of patients demonstrate severe psychiatric and/or neurological symptoms indicating central nervous system (CNS) involvement.¹ ² Such involvement constitutes a leading cause of morbidity in SLE, because patients with neuropsychiatric (NP) manifestations—especially those with focal symptoms—often do not reverse their deficits during therapy.² Neuropsychiatric systemic lupus erythematosus (NPSLE) also adversely affects survival in such patients: 7% to 13% of deaths in SLE have been attributed to CNS involvement.³ ⁶

NPSLE may be seen in the context of antiphospholipid (aPL) antibodies⁷ ⁹ and/or in the presence of overarching antiphospholipid syndrome (APS). The syndrome encompasses a variety of clinical manifestations. These include recurrent pregnancy loss and vascular thrombosis, which are considered to be the key manifestations in the recently developed preliminary classification criteria for APS;¹⁰ and others such as haemolytic anemia, thrombocytopenia, livedo reticularis, and NP manifestations, the
The exact relationship of which with APS still needs further investigation.\textsuperscript{10–12} There is limited knowledge about which of these manifestations associate most strongly with NPSLE. It is also unknown whether additional laboratory and clinical manifestations of SLE are associated with the development of CNS involvement. Early reports emphasized relationships with thrombocytopenia, vasculitis and livedo reticularis.\textsuperscript{13,14} The independent associations of such manifestations with NPSLE have been difficult to study, since it has been difficult to conduct studies with an adequate sample size.

Given the significant morbidity of NPSLE, it is important to determine risk factors for CNS involvement in SLE. Our study was designed to determine the independence of potential risk factors for CNS involvement in SLE, using an individually-matched nested case-control approach in patients from a large cohort of SLE patients.

**Methods**

**Patient selection and classification**

SLE patients seen at the Department of the Pathophysiology were enrolled into this nested case-control study. All patients fulfilled four or more of the revised criteria for SLE.\textsuperscript{15} The medical records of 324 consecutive SLE patients were reviewed, with particular attention to history of CNS manifestations and/or thrombotic events objectively documented with imaging or Doppler studies. Five patients with transient cognitive disorders not causing functional impairment (\(n = 2\)), mild psychiatric manifestations (\(n = 1\)) and anxiety disorders (\(n = 2\)) were excluded from this study. From the remaining cohort, we found 32 patients who were hospitalized between August 1994 and July 1996 for definitive, severe NP events not attributed to any cause other than SLE. Their manifestations were classified according to the American College of Rheumatology (ACR) case definitions for NP lupus syndromes.\textsuperscript{16} Patients without NP symptoms served as the source population for selecting the control group. NPSLE patients were individually matched 1:3 for sex, age (±5 years) and disease duration (±5 years) to controls.

Patients were also categorized according to whether at the time of evaluation they met at least one clinical and at least one laboratory criterion of the recently adopted classification criteria for APS.\textsuperscript{10} The relevant exclusions for vascular thromboses, for those who had such events,\textsuperscript{17} were also taken into account in this categorization.

**Detection of autoantibodies**

**Serological studies**

Sera were tested for the presence of antinuclear antibodies (ANA) by immunofluorescence (human epithelial cells [Hep-2] as substrate, positive titre ≥ 1/80, Innova), C_3 and C_4 components of complement by nephelometry (Beckman), autoantibodies to cellular antigens (SS-A/Ro, SS-B/La, U_1 RNP and Sm) by counterimmunoelectrophoresis and antibodies to dsDNA by ELISA (as previously described).\textsuperscript{18}

**Lupus anticoagulant**

Each patient with a prolonged partial thromboplastin time (PTT) underwent further studies to determine if a lupus anticoagulant (LA) was present. A LA was documented if the PTT was >5 s over the laboratory’s normal upper limit, there was incomplete correction on 50:50 mixing with normal plasma and there was no other cause for the coagulopathy. The platelet neutralization test and/or dilute Russell’s viper venom test were used for further confirmation.\textsuperscript{19}

**Anticardiolipin assay**

Sera from all patients were tested for anticardiolipin (aCL) antibodies by an ELISA method, as previously described.\textsuperscript{20} Negative aCL titre was defined when it had a value of <4 SD above the mean of 100 healthy subjects, low/moderate positive when levels were between ≥4 SD and <7 SD of mean normal values and high positive when ≥7 SD of reference values.\textsuperscript{20}

**Statistical analysis**

The NPSLE group (cases) were compared with SLE patients without CNS involvement (controls) for several selected characteristics. To compare the two groups, univariate and multivariate conditional logistic regression models were applied based on maximization of conditional likelihood. Statistical analyses used the SPSS statistical package. All \(p\)-values are two-tailed.

**Results**

The study population consisted of 112 women and 16 men. Patients’ mean age (SD) at SLE onset (evaluated from the first, well-described sign or symptom compatible with the disease) was 25.9 (11.6) years (range 5–60 years) and was similar in cases and controls: 26 (12) years vs. 26 (11) years, respectively (\(p = 0.9\)). The mean (SD) time from SLE onset was 9.5 (8.4) years, and was also similar in cases and controls: 9.8 (9.1) years vs. 9.4 (8.2) years, respectively (\(p = 0.85\)).

The most frequent NPSLE syndrome was cerebrovascular disease, affecting nine patients (28%). Seizures were seen in eight patients (25%) while acute confusional states occurred in six (19%) and psychosis in three (9%). Three more patients (9%)...
Table 1  Selected clinical and laboratory characteristics of 32 NPSLE patients and 96 SLE patients without CNS involvement

<table>
<thead>
<tr>
<th>Variables</th>
<th>NPSLE patients (n = 32)</th>
<th>SLE patients (n = 96)</th>
<th>p</th>
<th>Odds ratio*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical characteristics</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Antiphospholipid antibody syndrome</td>
<td>14 (44%)</td>
<td>13 (14%)</td>
<td>&lt;0.001</td>
<td>5.1</td>
<td>2.32–11.6</td>
</tr>
<tr>
<td>Arthralgias/arthritis</td>
<td>4 (13%)</td>
<td>79 (82%)</td>
<td>&lt;0.001</td>
<td>0.03</td>
<td>0.01–0.12</td>
</tr>
<tr>
<td>Discoid rash</td>
<td>1 (3%)</td>
<td>28 (29%)</td>
<td>&lt;0.001</td>
<td>0.07</td>
<td>0.02–0.3</td>
</tr>
<tr>
<td>Cutaneous vasculitic lesions</td>
<td>14 (44%)</td>
<td>12 (13%)</td>
<td>&lt;0.001</td>
<td>8.5</td>
<td>3.0–24</td>
</tr>
<tr>
<td>Livedo reticularis</td>
<td>13 (41%)</td>
<td>13 (14%)</td>
<td>0.002</td>
<td>4.3</td>
<td>2.0–9.2</td>
</tr>
<tr>
<td>Serositis</td>
<td>5 (16%)</td>
<td>28 (29%)</td>
<td>0.13</td>
<td>0.4</td>
<td>0.1–1.3</td>
</tr>
<tr>
<td>Arterial thrombosis</td>
<td>10 (31%)</td>
<td>5 (5%)</td>
<td>&lt;0.001</td>
<td>9.3</td>
<td>2.8–31</td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td>4 (13%)</td>
<td>14 (15%)</td>
<td>0.67</td>
<td>0.8</td>
<td>0.4–1.9</td>
</tr>
<tr>
<td>Pregnancy loss**</td>
<td>7 (22%)</td>
<td>6 (6%)</td>
<td>0.004</td>
<td>6.0</td>
<td>1.8–20</td>
</tr>
<tr>
<td>Renal disease</td>
<td>14 (44%)</td>
<td>51 (53%)</td>
<td>0.20</td>
<td>0.7</td>
<td>0.4–1.2</td>
</tr>
<tr>
<td><strong>Laboratory data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemolytic anaemia</td>
<td>4 (13%)</td>
<td>6 (6%)</td>
<td>0.12</td>
<td>2.5</td>
<td>0.8–8.0</td>
</tr>
<tr>
<td>Leukopenia (&lt;3500/mm³)</td>
<td>10 (31%)</td>
<td>16 (17%)</td>
<td>0.08</td>
<td>2.4</td>
<td>0.9–6.2</td>
</tr>
<tr>
<td>Thrombocytopenia (&lt;100,000/mm³)</td>
<td>7 (22%)</td>
<td>0</td>
<td>&lt;0.001</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Positive ANA</td>
<td>32 (100%)</td>
<td>81 (84%)</td>
<td>0.02</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Positive anti-dsDNA</td>
<td>16 (50%)</td>
<td>57 (59%)</td>
<td>0.35</td>
<td>0.7</td>
<td>0.3–1.5</td>
</tr>
<tr>
<td>Positive anti-Sm</td>
<td>1 (3%)</td>
<td>10 (10%)</td>
<td>0.20</td>
<td>0.3</td>
<td>0.03–2.3</td>
</tr>
<tr>
<td>Positive anti-SS-A/Ro</td>
<td>12 (38%)</td>
<td>34 (35%)</td>
<td>0.83</td>
<td>1.1</td>
<td>0.5–2.7</td>
</tr>
<tr>
<td>Positive anti-SS-B/La</td>
<td>7 (22%)</td>
<td>8 (8%)</td>
<td>0.01</td>
<td>4.3</td>
<td>1.4–13</td>
</tr>
<tr>
<td>Positive anti-nRNP</td>
<td>2 (6%)</td>
<td>11 (11%)</td>
<td>0.40</td>
<td>0.5</td>
<td>0.11–2.5</td>
</tr>
<tr>
<td>Positive aCL IgM in high titre</td>
<td>5 (16%)</td>
<td>12 (13%)</td>
<td>0.56</td>
<td>1.3</td>
<td>0.6–2.7</td>
</tr>
<tr>
<td>Positive aCL IgG in high titre</td>
<td>12 (38%)</td>
<td>15 (16%)</td>
<td>0.001</td>
<td>4.5</td>
<td>1.9–10.9</td>
</tr>
<tr>
<td>Positive LA</td>
<td>6 (19%)</td>
<td>6 (6%)</td>
<td>0.29</td>
<td>1.8</td>
<td>0.6–5.4</td>
</tr>
<tr>
<td>C₃ &lt; 53 mg%</td>
<td>8 (25%)</td>
<td>7 (7%)</td>
<td>0.003</td>
<td>3.8</td>
<td>1.6–9.4</td>
</tr>
<tr>
<td>C₄ &lt; 20 mg%</td>
<td>16 (50%)</td>
<td>21 (22%)</td>
<td>&lt;0.001</td>
<td>3.5</td>
<td>1.8–6.8</td>
</tr>
</tbody>
</table>

Data are numbers (percentages). * Derived from conditional logistic regression analysis. ** Results were similar regardless whether the analysis included all women (main analysis) or only women with a history of pregnancies. ACL, antcardiolipin; ANA, antinuclear antibodies; CI, confidence interval; CNS, central nervous system; LA, lupus anticoagulant; NPSLE, neuropsychiatric systemic lupus erythematosus; SLE, systemic lupus erythematosus.

met the diagnostic criteria for demyelinating syndrome, and three patients (9%) had cranial neuropathies. All three patients who developed isolated but significant deficits in cognitive functions had sAPS. Other NP manifestations (including myelopathy, chorea, major depressive episode, and Guillain-Barre syndrome) were less common. Twelve patients (38%) presented with a combination of two or more symptoms concurrently.

Table 1 shows the potential associations of CNS involvement with various clinical and laboratory characteristics in univariate relationships. APS was more common among patients who developed NP events. A history of arterial thrombosis and recurrent fetal loss, as well as the occurrence of IgG isotype aCL antibodies in high titres, were strongly associated with the risk of CNS involvement. Similarly livedo reticularis, another clinical feature often associated with APS, was a significant predictor of NPSLE. Cutaneous vasculitic lesions also correlated with CNS involvement whereas discoid rash, as well as musculoskeletal manifestations of arthralgias and arthritis, was significantly less common in patients with NP disorders. All NPSLE patients were positive for ANA, with titres above 1/160. None of the SLE control group had thrombocytopenia. There was also some evidence that anti-SS-B/La antibodies, as well as low serum levels of C₃ and C₄ complement components, were related to CNS involvement.

Factors associated with NP manifestations in the univariate analysis were entered stepwise into a multiple conditional logistic regression model. As shown in Table 2, articular manifestations and
discoid rash remained as independent protective factors, while cutaneous vasculitic lesions and arterial thromboses were independent predictors of NPSLE. Articular manifestations reached the highest level of statistical significance, but the absolute magnitude of the associations for all these four predictors was very large. When APS was considered as a candidate predictor, instead of its individual laboratory and clinical components, it was selected as an independent predictor of CNS involvement in the multivariate model, and in addition, low C₄ complement level was an independent risk factor, while arthralgias/ arthritis and discoid rash were independent protective factors with odds ratios of similar magnitude (not shown).

Discussion

Central nervous system involvement remains a major cause of morbidity and mortality in SLE. Nevertheless, the overall prevalence of major NP disorders varies among series. This is mainly due to the difficulty in defining psychiatric abnormalities and cognitive dysfunction in this disease. In some cases it is difficult to determine whether occasional NP manifestations reflect organic damage caused by SLE, or are simply psychological reactions to the stress of having a major chronic systemic illness. In an effort to provide more accurate results, we chose to exclude poorly-defined cognitive dysfunction, anxiety disorders and subtle psychiatric manifestations from our study for the purposes of defining CNS disease as rigorously as possible.

Early observations suggested that vasculitis and thrombocytopenia are significantly and strikingly correlated with NP involvement in SLE patients. Our study confirms these observations. The presence of cutaneous vasculitic lesions was significantly associated with NPSLE in our best-fit multivariate model, and thrombocytopenia also was a significant risk factor for such involvement, at least in univariate analysis.

The most common neuropathological finding in autopsy studies of NPSLE is a small-vessel non-inflamatory proliferative vasculopathy characterized by hyalinization, occasionally associated with occlusion, pericapillary microglia, microinfarcts and microhemorrhages. These findings differ from those seen in chronic cutaneous lupus erythematosus, such as discoid lesions, where a perivascular mononuclear inflammatory infiltrate from activated T cells predominates. Different tissue pathology may reflect different pathophysiological mechanisms, and this could explain the strong negative correlation between NPSLE manifestations and the presence of discoid lesions. Furthermore, this association may also indicate that SLE patients with discoid lesions have a more benign disease course overall.

Although articular manifestations are frequent in SLE patients, in our study those patients with NP manifestations had significantly less arthralgia or acute symmetric arthritis than patients without CNS involvement. Recall bias stemming from the retrospective design of the study could possibly affect the strength of this association. Nevertheless, this negative correlation agrees with the results of another study in Greek SLE patients, in which articular manifestations tended to accompany rashes or constitutional symptoms, but not CNS involvement, during flares of the disease. Toubi et al. reported no significant difference in the prevalence of skin manifestations and arthritis between NPSLE and SLE control patients. This study was conducted in a different continent, and Black patients represented 20% of the total NPSLE group. Moreover, no exact figures were provided, so it is unknown whether any tendency for a difference might have been present.

On the other hand, West et al. showed a trend toward a smaller prevalence of articular manifestations in NPSLE group compared with that of SLE control patients. Thus, small sample sizes, patient selection, racial and genetic heterogeneity or differences in environmental factors which may influence disease expression, could explain discrepancies between studies in this field.

Previous studies have tried to determine diagnostic laboratory markers to define or detect active NPSLE, but these have yielded conflicting data, and have generally failed to establish clearly defined pathogenic factors. Elevated antibody titres to dsDNA have been proposed as helpful in identifying NPSLE patients, but CNS involvement can occur in the presence of normal values of anti-dsDNA antibodies. Controversy also exists regarding the association of anti-Sm antibody with NPSLE manifestations. Increased antibody titres to dsDNA, as well as anti-Sm antibody, were not correlated with NP manifestations in our study. On the contrary, low serum levels of C₃, and particularly of C₄ complement components, were seemingly strongly associated with NPSLE. This association probably implies an underlying relation to common pathogenic mechanisms, such as local deposition of immune complexes in blood vessel walls with subsequent complement activation, resulting in vasculitis. Vasculitis of the brain vessels has been documented in 7–15% of NPSLE autopsy cases.

Clinical and experimental evidence indicates that aPL antibodies are significantly associated with, and may have a causative role in, vascular thromboses and pregnancy losses. These antibodies have also been implicated as a risk factor for CNS involvement in SLE, especially for manifestations...
of vascular origin. Touli et al. reported that 55% of their CNS/SLE patients had aPL antibodies, compared with 20% in the SLE control group. In that report, SLE patients with thromboembolic manifestations were excluded from the control group. Therefore, certain patients who might have had aPL antibodies were rejected from that study. In our study, we also found that the likelihood of developing CNS events is enhanced in SLE patients by the presence of APS, and that the occurrence of IgG isotype aCL antibodies in high titres is strongly associated with NPSLE. Patients with a history of thromboses in several anatomical sites of arterial circulation, affecting mostly large or medium arteries but also occasionally small vessels, were more likely to have NPSLE. This finding supports previous studies which have shown that recurrent events in patients with aCL antibodies cluster to either the arterial or the venous circulation, and patients tend to have recurrent events of the same type. Factors influencing arterial and venous thrombosis may differ. We also noted that women with a history of two or more spontaneous abortions were six times more likely to have CNS events than those without any recurrent abortions and that livedo reticularis, a minor feature of APS, was a significant predictor for NP disease in a univariate analysis.

The pathogenetic mechanism underlying the association with aPL antibodies is still uncertain. Some studies suggest that it involves interactions between antibodies to anionic phospholipid-protein complexes and antigen targets on platelets, endothelial cells or components of the coagulation cascade. The possibility that aPL may react with complex brain lipids such as cephalin or sphingomyelin has also been suggested. A genetic component, at least partially mediated through HLA associations, may also explain diversity in studies of different populations.

In summary, CNS involvement in SLE was most strongly associated with the presence of APS features, in particular with arterial thrombosis, and with cutaneous vasculitic lesions. It was negatively related to the presence of articular manifestations and discoid rash. The definition of a group of SLE patients with adverse predictors for NP disease may be important for therapeutic or preventive purposes. Although pulsed cyclophosphamide treatment can achieve favourable responses during NP events, other therapeutic options for NPSLE patients are currently limited. Therefore, pre-emptive interventions may need to be studied in high-risk patients defined by the presence of adverse predictors.

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