Anti-GM1 and anti-sulfatide antibodies in patients with systemic lupus erythematosus, Sjögren’s syndrome, mixed cryoglobulinemia and idiopathic systemic vasculitis


Abstract

Objectives
Over the last two decades, increasing interest has been focused on the association between autoimmune polyneuropathies and anti-neuronal autoantibodies in immune-mediated polyneuropathy. The possible appearance of these autoantibodies in systemic diseases that are not limited to the nervous system has not been fully addressed yet.

Methods
We evaluated 32 patients with systemic lupus erythematosus, 34 patients with hepatitis C virus-associated mixed IgM-k/IgG cryoglobulinemia, 19 with small vessel ANCA-associated vasculitis, and 20 patients with Sjögren’s syndrome by means of an immunoenzyme method of anti-neuronal autoantibody detection.

Results
As compared to normals, a significant increase (p < 0.001) in plasma titers of both IgM and IgG anti-GM1 ganglioside and IgM and IgG anti-sulfatide was observed in patients with systemic lupus erythematosus, mixed cryoglobulinemia and Sjögren’s syndrome. Idiopathic systemic vasculitis patients were found to have significantly increased levels of anti-sulfatide IgG autoantibodies (p < 0.001). Clinical and electrophysiologic studies revealed that abnormal titers of anti-neuronal antibodies were associated with evidence of neuropathy in patients with systemic lupus erythematosus and ANCA-related vasculitis (p < 0.05) as well as in patients with mixed cryoglobulinemia and Sjögren’s syndrome (p < 0.001).

Conclusion
Anti-GM1 and anti-sulfatide antibodies are frequently found in patients with small vessel ANCA-associated vasculitis and other multi-organ immune-mediated diseases. Upon detection of these antibodies, accurate neurologic examination should be carried out due to the significant association that can be found between these serologic abnormalities and the involvement of the peripheral nervous system as also detected by electrophysiologic studies. This study supports the unexpected possibility that anti-neuronal reactivity may be a direct trigger of neurologic injury in these systemic disorders.

Key words
Anti-neuronal antibodies, systemic lupus erythematosus, mixed cryoglobulinemia, ANCA-associated vasculitis, Sjögren’s syndrome.
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Please address correspondence to: Dario Roccatello, Centro Multidisciplinare di Ricerche di Immunopatologia e Documentazione su Malattie Rare (CMID), Ospedale G. Bosco, Piazza del Donatore di Sangue 3, 10154 Torino, Italy. E-mail: dario.roccatello@unito.it

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Introduction
Over the last two decades, increasing interest has been focused on the association between autoimmune polyneuropathies and high titers of anti-neuronal antibodies, i.e., antibodies anti-GM1 ganglioside and anti-sulfatide (1-5). The mechanism by which these antibodies might cause nerve injury remains unclear (6-8). Low to moderate titers of both anti-ganglioside and anti-sulfatide autoantibodies can be found in non-immune-mediated polyneuropathies, and low affinity anti-neuronal antibodies are part of the normal human immunological repertoire (5, 9, 10). Polyneuropathies are frequently observed in systemic idiopathic vasculitis (VAS), such as ANCA-associated angiitis, or in others multi-organ immune-mediated diseases such as systemic lupus erythematosus (SLE), mixed cryoglobulinemia (MC), and Sjögren’s syndrome (SS), which are characterized by a broad spectrum of clinical manifestations and several immunologic abnormalities. Nevertheless, peripheral nervous system involvement has not been extensively investigated by an electrophysiologic approach, thus the reported prevalence of peripheral neuropathy in these conditions varies among studies, and reflects the different criteria that are used to clinically define polyneuropathies (11-14). The occurrence of autoimmune diseases (i.e., SLE) associated with a priori idiopathic polyneuropathy has previously been reported (15). Furthermore, serum anti-neuronal antibodies have been detected in SLE (16-19) and primary Sjögren’s syndrome (20-22).

In the present study, anti-ganglioside GM1 and anti-sulfatide antibodies were detected in several patients with idiopathic systemic vasculitis and hepatitis C virus (HCV)-associated MC, as well as SLE and SS. The results were related to some serologic parameters of disease activity and electrophysiologic indices of peripheral neuropathy.

Methods
Patients
Serum samples were obtained from 32 patients with systemic lupus erythematosus, 34 patients with HCV-associated mixed (IgM-k/IgG) cryoglobulinemia, 19 patients with small vessel ANCA-associated idiopathic vasculitis, and 20 patients with Sjögren’s syndrome. Both patients symptomatic for peripheral neuropathy and asymptomatic patients were considered eligible for the study. Each patient gave informed consent.

Diagnosis of SLE was established according to the 1982 American Rheumatism Association revised criteria (23). Demographic data are shown in Table I. Clinical activity was established by assessing SLEDAI score system. Diagnosis of hepatitis C virus-associated MC and SS were based on previously established criteria (24, 25), while diagnosis of small vessel ANCA-associated vasculitis was made according to Jennette et al. (26). Sixteen patients with SLE, 10 with MC, 10 with ANCA-associated idiopathic vasculitis and 5 with SS were in mild activity or in clinical and serologic remission at the time of study. Sera of 34 healthy blood donors and reference sera from antibody positive patients with Guillain Barré syndrome were used as negative and positive controls, respectively (27). The diagnosis of neuropathy was made in the presence of at least one of the following criteria: weakness, decrease or loss of tendon reflexes, sensory symptoms such as paresthesia or dysesthesia. Neuropathy was assumed to be secondary to SLE, SS, MC or idiopathic systemic vasculitis if all of the following features were absent: history or laboratory findings suggestive of diabetes mellitus, hypothyroidism, uremia, vitamin B1, B12 or E deficiency, alcohol abuse, HIV-infection or Lyme’s disease, trauma, paraneoplastic syndromes, hereditary neuropathies. Based on clinical examination, patients were grouped into three categories: sensory neuropathy, motor neuropathy and mixed sensory-motor neuropathy (28).

Antibody assay
Sera from all patients and controls were tested by an enzyme-linked immunosorbent assay (ELISA) for the presence of IgM-IgG antibodies to GM1 gangliosides and sulfatides. The ELISA test was carried out by adding 500 ng of either purified GM1 (Sigma,
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**Table 1. Demographic characteristics of the patients under study.**

<table>
<thead>
<tr>
<th></th>
<th>SLE</th>
<th>MC</th>
<th>VAS</th>
<th>SS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean ± SD)</td>
<td>42 ± 17</td>
<td>61 ± 12</td>
<td>61 ± 15</td>
<td>64 ± 10</td>
</tr>
<tr>
<td>Male</td>
<td>28 (87%)</td>
<td>19 (56%)</td>
<td>7 (37%)</td>
<td>18 (90%)</td>
</tr>
<tr>
<td>Female</td>
<td>4 (13%)</td>
<td>15 (44%)</td>
<td>12 (63%)</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Disease duration: years (range)</td>
<td>9 (4-14)</td>
<td>8 (3-13)</td>
<td>9 (4-14)</td>
<td>5 (2-8)</td>
</tr>
<tr>
<td>Pts treated with Steroids and/or Immunosuppressive drugs</td>
<td>23</td>
<td>20</td>
<td>17</td>
<td>6</td>
</tr>
</tbody>
</table>

SLE: systemic lupus erythematosus; MC: mixed cryoglobulinemia; VAS: idiopathic systemic vasculitis; SS: Sjögren’s syndrome.

St. Louis, MO, USA) or sulfatide (Sigma, St. Louis, MO, USA) in 100 μl of methanol to each well of a microtiter plate (Pharmacia & Upjohn, Michigan, USA). After methanol evaporation, wells were blocked by incubation with 200 μl 1% bovine serum albumin (BSA) in phosphate-buffered saline (PBS) and incubated overnight at 4°C. Wells were then washed three times with 250 μl 1% BSA in PBS, and 100 μl aliquots of the patient’s serum were serially diluted in washing buffer (starting with a dilution of 1:200 for anti-GM1 antibody and 1:800 for anti-sulfatide antibody) and then added in duplicate and incubated overnight at 4°C. After washing twice, 100 μl aliquots of peroxidase-conjugated rabbit anti-human IgM or IgG (Dako, Ontario, Canada) diluted at 1:1000 in buffer were added and incubated overnight at 4°C. After washing again, 100 μl of a developing solution containing 0.1% o-phenylenediamine (Sigma, St. Louis, MO, USA) in 0.1 M citric acid buffer and 0.04 % H₂O₂ were added, and the reaction was stopped by adding 100 μl 1 N sulphuric acid 20 minutes later. Lastly, the plates were incubated at room temperature for 30 min before measuring the absorbance at 490 nm with an ELISA counter. Antibody titers were calculated as previously described by Pestronk et al. (4). Reference sera from patients with Guillain-Barré syndrome with high titers of IgM anti-GM1, or IgM anti-sulfatide antibodies were used to determine inter- and intra-assay variability. Accuracy data, as determined by Receiver Operator Characteristic analysis of anti-neuronal antibody levels applied in polyneuropathies, including Guillain Barré syndrome, have been described elsewhere (29).

**Other laboratory parameters**

Antinuclear antibodies (ANA) and anti-tissue DNA were detected by immunofluorescence (IF) on HEp2 cells (Diastorin s.p.a., Vercelli, Italy) and immunofluorescent Chritidia test (Daltec Instrument s.r.l., Milan, Italy), respectively. ANA was also detected by I.F. (Bouty s.p.a., Milan, Italy) and Rheumatoid factor was determined by immunoturbidimetric assay (Roche, Monza, Italy). Antineutrophil cytoplasmic antibodies were detected by I.F. (Daltec Instrument s.r.l., Milan, Italy) and by EIA (Bouty s.p.a., Milan, Italy) and Rheumatoid factor was determined by immunoturbidimetric assay (Roche, Monza, Italy). Antineutrophil cytoplasmic antibodies were detected by I.F. (Daltec Instrument s.r.l., Milan, Italy) and by EIA (Bouty s.p.a., Milan, Italy). Anti-Ro/SSA and anti-La/SSB antibodies were detected by ELISA (Bouty s.p.a., Milan, Italy) in 16 out of 20 SS patients. Cryoglobulins were determined as follows. After isolation and washing, the cryoprecipitate was quantified and expressed as a percentage of precipitate/serum volume (i.e., cryocrit). Components of the cryoprecipitate were characterized by using immunofixation electrophoresis (CRYOKIT, Helena Labs, Milan, Italy).

**Electrophysiologic studies**

A careful neurological examination could be done in 30 of 32 patients with SLE, 33 of 34 patients with cryoglobulinemia, 18 out of 20 patients with Sjögren’s syndrome and all 19 with idiopathic systemic vasculitis at the time of blood sampling. Each neuropathy established on a clinical ground was electrophysiologically examined. The following electrophysiologic investigations were done on both legs in 12 out of 30 SLE, 22 out of 33 cryoglobulinemic patients, 8 out of 19 patients with ANCA-positive systemic vasculitis and 11 out of 18 patients with Sjögren’s syndrome. Motor conduction velocities were determined on deep peroneal nerves. Interval between stimulating and recording electrodes was 8 cm at ankle. M wave amplitude, distal latency, and maximal conduction velocity were considered. Antidromic sensory velocities were done on sural nerve at external malleolus-surae tract. Sensory potential amplitude and maximal conduction velocity were measured. Neuropathies were classified as demyelinating when the neurophysiologic criteria for the demyelination, as defined by the “ad Hoc Subcommittee” (i.e., critical reduction of conduction velocity with normal M wave amplitude and increased distal latency), were fulfilled (30). In the presence of a decrease in M wave amplitude and temporal dispersion with < 30% reduction of conduction velocity, the neuropathy was classified as axonal. When criteria for both demyelinating and axonal neuropathy were fulfilled, a mixed form was diagnosed. Values for nerve conduction velocity and nerve action potentials were compared with control values obtained in 34 healthy, age-matched subjects. Patients’ variables were considered abnormal if outside the standard deviation range.

**Statistical analysis**

Titers of anti-GM1, anti-sulfatide antibodies and electrophysiologic data among the groups were compared by Student’s t-test (associated to Bonferroni’s correction when necessary). The χ² and Fisher’s Exact Test were used to determine the relationship between the presence of neuropathy and type of nerve damage (axonal, demyelinating, or axonal and demyelinating) and the detection of anti-GM1 and/or anti-sulfatide antibodies. The same analysis was used to determine the correlation between SLEDAI score and anti-neuronal antibodies. Pearson’s correlation coefficients were used to determine possible associations between titers of anti-neuronal antibodies and antineutrophil cytoplasmic antibodies (ANCA), anti-dsDNA, ANA, anti-Ro/
SSA, anti-La/SSB, presence of rheumatoid factor (RF) and cryocrit. \( p \) values < 0.05 were considered statistically significant.

Results
A significant increase in plasma IgM and IgG anti-GM1 titers was found in the SLE patients (1:618 ± 1:514; 1:465 ± 1:308) as compared to normal controls (1:176 ± 1:205 and 1:204 ± 1:103; \( p < 0.001 \)). IgM and IgG anti-sulfatide titers (1:2941 ± 1:2734; 1:1580 ± 1:1166) were also found to be higher than in control subjects (1:1042 ± 1:840 and 1:621 ± 1:243; \( p < 0.001 \)). Mean plasma IgM and IgG anti-GM1 antibody titers of cryoglobulinemic patients were 1:524 ± 1:384 and 1:488 ± 1:389, respectively, which again were significantly higher than normal controls (\( p < 0.0001 \)). Plasma IgM and IgG anti-sulfatide titers in this group (1:1841 ± 1:1101 and 1:1200 ± 1:829) were also significantly higher than in normal subjects (\( p < 0.001 \)). A significant increase in anti-sulfatide IgG class levels (1:1400 ± 1:708) was observed in the vasculitis subjects as compared to controls (\( p < 0.001 \)). Mean plasma IgM and IgG anti-GM1 titers of patients with Sjögren’s syndrome were respectively, 1:811 ± 1:334 and 1:538 ± 1:247, again higher than in controls (\( p < 0.001 \)). Mean plasma IgM and IgG anti-sulfatide titers in this group were 1:2079 ± 1:948 and 1:1890 ± 1:483 (\( p < 0.001 \) as compared to normal controls). These results are summarized in Figures 1 and 2.

Clinical neurological examination was found to be abnormal in 12 out of 30 SLE patients (40%), in 22 of the 33 cryoglobulinemic patients we studied (67%), in 8 of the 19 ANCA-related vasculitis patients (42%), and in 11 out of the 18 patients with Sjögren’s syndrome who were tested (61%). Table II summarises the clinical and electrophysiological findings. In 13 patients (5 with SLE, 5 with cryoglobulinemia, 2 with Sjögren’s syndrome and 1 with ANCA-positive systemic vasculitis patients) a predominantly sensory neuropathy was found. In 31 patients (4 with SLE, 16 with cryoglobulinemia, 6 with Sjögren’s syndrome and 5 with ANCA-positive systemic vasculitis) a mixed sensory and motor neuropathy was detected. The remnant patients (3 with SLE, 1 with cryoglobulinemia, 3 with Sjögren’s syndrome and 2 with ANCA-positive systemic vasculitis patients) had prevalent signs of motor neuropathy.

Examination of the neurophysiological parameters showed some prevalence of mixed features of axonal and demyelinating neuropathy in MC and VAS neuropathic patients (15 out of 22 and 7 out of 8, respectively). Mixed and axonal forms of neuropathy were equally observed in SLE and SS patients.

A significant difference was found between patients with or without clinical signs of neuropathy as regard to anti-neuronal antibodies (Table III).

With regards to sensitivity of antibody detection in patients with electrophysiologic abnormalities, 11 of the 12 (91%) SLE patients with abnormal electrophysiologic data were found to have anti-neuronal (anti-GM1 and/or anti-sulfatide) antibodies. Abnormal titers of anti-neuronal antibodies were found to be associated with electrophysiologic abnormalities in 19 out of 22 (86%) cryoglobulinemic patients, 5 out of 8 (62%) ANCA-related vasculitis patients, and in 10 out of 11 patients (91%) with Sjögren’s syndrome. Specificity for neuronal involvement of antibody detection was 61% (11 antibody-negative patients out of 18 patients without electrophysiologic abnormalities) in SLE, 82% (9 out of 11 patients) in MC, 100% (11 out of 11 patients) in idiopathic systemic vasculitis.
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Table II. Summary of abnormal neurological findings in patients who had undergone a complete clinical evaluation (upper pannel), including electrophysiologic data in patients with abnormal neurologic examination. Six MC patients, 1 VAS patient and 3 SS patients had nonmeasurable amplitude values (assumed to be equal to zero).

<table>
<thead>
<tr>
<th></th>
<th>SLE (*30)</th>
<th>MC (*33)</th>
<th>VAS (*19)</th>
<th>SS (*18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory, n (%)</td>
<td>5 (17%)</td>
<td>5 (15%)</td>
<td>1 (5%)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Motor, n (%)</td>
<td>3 (10%)</td>
<td>1 (3%)</td>
<td>2 (11%)</td>
<td>3 (17%)</td>
</tr>
<tr>
<td>Sensory/motor, n (%)</td>
<td>4 (13%)</td>
<td>16 (49%)</td>
<td>5 (26%)</td>
<td>6 (33%)</td>
</tr>
<tr>
<td>Total, n (%)</td>
<td>12 (40%)</td>
<td>22 (67%)</td>
<td>8 (42%)</td>
<td>11 (61%)</td>
</tr>
</tbody>
</table>

Axonal Neuropathy
Low MAP and/or SAP, n (%)

<table>
<thead>
<tr>
<th></th>
<th>SLE (*12)</th>
<th>MC (*22)</th>
<th>VAS (*8)</th>
<th>SS (*11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow MCV and/or SAP, n (%)</td>
<td>7 (23%)</td>
<td>2 (6%)</td>
<td>1 (5%)</td>
<td>7 (39%)</td>
</tr>
</tbody>
</table>

Demyelinating Neuropathy

<table>
<thead>
<tr>
<th></th>
<th>HS (*34)</th>
<th>SLE (*12)</th>
<th>MC (*22)</th>
<th>VAS (*8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow MCV and/or SAP, n (%)</td>
<td>0</td>
<td>5 (15%)</td>
<td>7 (37%)</td>
<td>4 (22%)</td>
</tr>
<tr>
<td>Mixed form, n (%) Sural</td>
<td>5 (17%)</td>
<td>15 (46%)</td>
<td>4.4 (0.9)</td>
<td>4.8 (1.8)**</td>
</tr>
<tr>
<td>Peroneal DL (sec)</td>
<td>3.8 (0.6)</td>
<td>3.7 (0.7)</td>
<td>4.8 (1.6)'</td>
<td>4.4 (0.9)</td>
</tr>
<tr>
<td>Peroneal MCV (m SEC)</td>
<td>49.1 (4.4)</td>
<td>46.5 (5.4)</td>
<td>37.2 (15.1)'</td>
<td>40.1 (9.6)**</td>
</tr>
<tr>
<td>Peroneal AMP (mV)</td>
<td>6.3 (2.4)</td>
<td>5.7 (2.7)</td>
<td>2.2 (1.6)'</td>
<td>4.1 (3.7)</td>
</tr>
<tr>
<td>Sural AMP (mV)</td>
<td>15.5 (6.7)</td>
<td>7.2 (3.4)'</td>
<td>3.9 (4.6)'</td>
<td>5.5 (3.4)'</td>
</tr>
<tr>
<td>Sural SCV (m SEC)</td>
<td>48.0 (3.0)</td>
<td>46.0 (6.3)</td>
<td>23.0 (21.0)'</td>
<td>34.1 (21.0)&quot;</td>
</tr>
</tbody>
</table>

No statistical correlation was found between anti-neuronal antibodies and some serologic markers of disease activity, including ANA in SLE, ANCA titers in idiopathic systemic vasculitis, RF or cryocrit in MC, anti-Ro/SSA and anti-La/SSB in SS (Table IV), nor with clinical and histologic extent of renal involvement. A weak correlation was observed between IgG anti-sulfatide and anti-DNA antibodies ($p = 0.05$).

SLEDAI score was $> 15$ in 5 SLE patients, $> 10$ and $< 15$ in 6, $> 5$ and $< 10$ in 13, $< 5$ in the remaining 8. Some relationship ($p < 0.05$) was found between SLEDAI score and IgG anti-sulfatide antibodies by dividing patients in 2 subsets with $> 10$ or $\leq 10$ SLEDAI score.

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Discussion
The reported prevalence of neuropathy in primary systemic vasculitis, SLE, mixed cryoglobulinemia and SS is possibly underestimated (31-33). The present study showed that approximately 60% of the patients with SLE (20 out of 32) or mixed cryoglobulinemia (21 of 34), 55% of the patients with Sjögren’s syndrome (11 out of 20) and 26% of patients with small vessel ANCA-associated idiopathic systemic vasculitis (5 out of 19) had increased levels of anti-ganglioside and/or anti-sulfatide antibodies. These patients were often found to have electrophysiologic abnormalities of the peripheral nervous system and, conversely, most of the patients with electrophysiologic abnormalities also had increased levels of anti-neuronal antibodies. Peripheral neuropathy is generally thought to be caused by small vessel inflammatory vasculopathy of the vasa nervorum. As recently emphasized, the blood-nerve barrier is not as efficient as the blood-brain barrier at limiting the inflammatory cell infiltration into the vasa nervorum and epineural arteries, and is susceptible to ischemic injuries and prone to develop blood-nerve barrier breaches due to release of reactive oxygen species, cytokines and metalloproteinases (34).
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Table IV. Serologic markers of disease activity (expressed in mean ± SD) and anti-GM1 and anti-sulfatide antibodies in SLE patients, patients with mixed cryoglobulinaemia (MC), patients with ANCA-associated vasculitis (VAS) and in SS patients. Pearson’s correlation coefficients are shown.

<table>
<thead>
<tr>
<th>Serum markers</th>
<th>IgM anti-GM1</th>
<th>IgG anti-GM1</th>
<th>IgM anti-sulfatide</th>
<th>IgG anti-sulfatide</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA in SLE pts (≥32)</td>
<td>R²: -0.03</td>
<td>R²: -0.03</td>
<td>R²: 0.03</td>
<td>R²: -0.031</td>
</tr>
<tr>
<td>1.7 ± 1 AU (n.v. &lt; 0.7)</td>
<td>ρ: 0.82</td>
<td>ρ: 0.70</td>
<td>ρ: 0.16</td>
<td>ρ: 0.81</td>
</tr>
<tr>
<td>anti-dsDNA in SLE pts (≥32)</td>
<td>R²: 0.033</td>
<td>R²: -0.03</td>
<td>R²: 0.08</td>
<td>R²: 0.1</td>
</tr>
<tr>
<td>99 ± 131 IU/ml (n.v. &lt; 30)</td>
<td>ρ: 0.15</td>
<td>ρ: 0.76</td>
<td>ρ: 0.06</td>
<td>ρ: 0.05</td>
</tr>
<tr>
<td>RF in MC pts (≥54)</td>
<td>R²: -0.01</td>
<td>R²: -0.01</td>
<td>R²: 0.0015</td>
<td>R²: 0.011</td>
</tr>
<tr>
<td>525 ± 1880 IU/ml (n.v. &lt; 14)</td>
<td>ρ: 0.44</td>
<td>ρ: 0.42</td>
<td>ρ: 0.29</td>
<td>ρ: 0.25</td>
</tr>
<tr>
<td>ANCA in VAS pts (≥19)</td>
<td>R²: 0.10</td>
<td>R²: -0.05</td>
<td>R²: 0.138</td>
<td>R²: -0.05</td>
</tr>
<tr>
<td>1.5 ± 1.3 IU/ml (n.v. &lt; 2)</td>
<td>ρ: 0.09</td>
<td>ρ: 0.84</td>
<td>ρ: 0.06</td>
<td>ρ: 0.8</td>
</tr>
<tr>
<td>anti-Ro/SSA; anti-La/SSB in SS pts (≥16)</td>
<td>R²: 0.013</td>
<td>R²: -0.06</td>
<td>R²: 0.10</td>
<td>R²: -0.040</td>
</tr>
<tr>
<td>39 ± 31 IU/ml (n.v. &lt; 10 IU/ml)</td>
<td>ρ: 0.29</td>
<td>ρ: 0.74</td>
<td>ρ: 0.11</td>
<td>ρ: 0.5</td>
</tr>
<tr>
<td>RF in SS pts (≥20)</td>
<td>R²: -0.05</td>
<td>R²: -0.022</td>
<td>R²: -0.05</td>
<td>R²: -0.03</td>
</tr>
<tr>
<td>29 ± 20 IU/ml (n.v. &lt; 0.93)</td>
<td>ρ: 0.51</td>
<td>ρ: 0.45</td>
<td>ρ: 0.86</td>
<td>ρ: 0.51</td>
</tr>
</tbody>
</table>

Fig. 3. Percentage of patients with (ab+) or without (ab-) antineuronal antibodies related to the presence (NP+) or absence (NP-) of neuropathy. *p < 0.001 and †p < 0.05 by the χ² test.

Anti-ganglioside and anti-sulfatide antibodies might be the result of a phlogistic and ischemic damage which exposes normally segregated neuronal epitopes. Their presence in serum might reflect a secondary immune reaction to neural damage. Alternatively, the appearance of these autoantibodies may be the sequela of a co-infection with bacteria or viruses that bear cross-reactive lipopolysaccharides, as demonstrated in the Guillain-Barré syndrome (35-37). Finally, anti-neuronal immune response might represent an independent pathway of the autoimmune repertoire of these multiorgan disorders, i.e., the expression of the polyclonal activation of B lymphocytes, a common feature of autoimmune diseases.

The levels of anti-GM1 and anti-sulfatide antibodies did not correlate with the values of ANA in SLE, or with ANCA titers in idiopathic systemic vasculitis, or with RF or cryocrit in cryoglobulinemia. A weak correlation was found between IgG anti-sulfatide and anti-DNA antibodies (ρ = 0.05). No data are presently available to determine whether IgM or IgG isotypes have different clinical impact as in other biological setting, such as anti-dsDNA or anticaldilipin antibodies. IgG might be more promising. For instance, IgM anti-sulfatide titers did not reach statistical levels of significance in the VAS group while IgG isotype did and IgG anti-sulfatide was found to be related to both anti-dsDNA levels and SLEDAI score. While the present findings should be interpreted with caution due to the lack of significant correlations with other indices of disease activity, detecting anti-neuronal antibodies might provide additional diagnostic and prognostic insight into systemic immune-mediated disorders. Data on sensitivity and specificity showed patients with anti-neuronal antibodies to have definite damage of peripheral nervous system. These antibodies might play a role in the pathogenesis of the neurological manifestations that are observed in ANCA-associated systemic vasculitis and in other multi-organ immune-mediated disease, such as Systemic Lupus Erythematosus, HCV-related mixed cryoglobulinemia and Sjögren’s syndrome.

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References

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