Systemic Autoimmune Features and Multiple Sclerosis
A 5-Year Follow-up Study

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Objectives: To evaluate in patients with multiple sclerosis (MS) the occurrence of clinical systemic signs and biological autoimmune abnormalities, including positive titers of antinuclear antibodies and antiphospholipid antibodies, suggestive of autoimmune diseases that may affect the central nervous system. Also, to compare the clinical and magnetic resonance imaging features and evolution of MS in patients with and without autoimmune abnormalities.

Design and Patients: Prospective study of 161 patients fulfilling the criteria of having probable or definite MS hospitalized in our institution between November 1990 and June 1992.

Results: Among the 161 patients, 84 (52.1%) had at least 1 clinical and/or biological general sign suggestive of an autoimmune disease; 64 were followed up for 4 to 5 years. The diagnosis of MS was confirmed in 50 patients and is still pending in 14 of them. No significant difference was found between patients with MS who were free of autoimmune features and those with autoimmune abnormalities (MS plus) concerning the age of disease onset, the presenting symptoms and signs, symptoms found on neurologic examination, and the course of the disease. For all patients with confirmed MS, general signs were found in 13.3%, positive titers of antinuclear antibodies in 26%, and positive titers of antiphospholipid antibodies in 6.2%.

Conclusions: Patients with MS with autoimmune features, including those with titers of antinuclear antibodies of 1:100 or less and/or antiphospholipid antibodies, are not different than others with MS, and therefore should not be excluded from clinical trials.

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Multiple sclerosis (MS), the most frequent demyelinating disease in adults, is thought to be an autoimmune disease. Symptoms and signs observed in MS reflect lesions present mainly in the white matter of the central nervous system (CNS). The diagnosis remains difficult, at least concerning presenting symptoms, because of their low specificity and the absence of specific paraclinical markers of the disease. Diagnosis criteria are usually based on dissemination of clinical signs in time and space, evoked potentials, findings of magnetic resonance imaging (MRI), results of cerebrospinal fluid (CSF) examination, and the exclusion of other diagnoses possibly explaining the clinical signs. However, no clinical or paraclinical investigation can distinguish with certainty MS from other autoimmune or inflammatory diseases predominantly affecting the CNS. These other disorders include sarcoidosis, vasculitides, systemic lupus erythematosus (SLE), and Behçet and Lyme diseases.

Previous reports have shown the presence of antinuclear antibodies (ANAs) and antiphospholipid antibodies (aPLs) in patients with MS. Whether the clinical and paraclinical characteristics of these patients differ from those in patients with MS free of these abnormalities is not known. The aim of this study, conducted in patients with suspected or definite MS, was to evaluate the occurrence of abnormalities suggestive of autoimmune diseases that may affect the CNS. We then compared the clinical and MRI features and evolution of MS among patients with and without autoimmune abnormalities.

RESULTS

Among the 161 patients there were 104 women (65%) and 57 men. The mean age of onset of neurologic symptoms and/or signs was 31 years (range, 15-64 years). In 77 patients (48%), no systemic clinical and/or biological abnormalities could be found. These patients are referred to as group 1. The other 84 patients (52%) had
PATIENTS AND METHODS

Between November 1990 and June 1992, 161 consecutive patients were examined in the Fédération de Neurologie at the Hôpital de la Salpêtrière, Paris, France, for having probable or confirmed MS fulfilling the criteria of Poser et al.3 These patients were included in this prospective study. Aside from the performance of a detailed neurologic examination, attention was focused on general symptoms and signs suggestive of a systemic disease, such as buccal or genital aphthosis, photosensitivity, Raynaud syndrome, erythema chronicum migrans, facial erythema, livedo reticularis, pseudofolliculitis, dermal sarcoidosis, articular or ocular signs, and peripheral nervous system involvement. Obstetrical data were collected.

Laboratory investigations included standard biochemistry workup, red and white blood cell counts, clotting tests, erythrocyte sedimentation rate, and tests for cholesterolemia, triglyceridemia, glycemia, and uricemia. The following levels were also determined: total IgG, IgM, and IgA; rheumatoid factor; total hemolytic complement and complement components C3 and C4; cryoglobulins; and circulating immune complexes. A biological false-positive serologic test for syphilis was defined as positive results of a VDRL test and negative results of a Treponema pallidum hemagglutination or fluorescent treponemal antibody absorption test. The presence of lupus anticoagulant was determined by kaolin clotting and activated partial thromboplastin time. The abnormal test result was not corrected by a volume-to-volume mixture of patient and control plasma before and after incubation for 1 hour at 37°C. In contrast, adjunction of phospholipids corrected clotting test results. Titers of anticardiolipin antibodies (aCLs) were measured using a solid-phase immunoassay and results were considered positive when the titer was higher than 3 SDs above the mean of the controls (normal, <15 U of G-type phospholipids and/or <10 U of M-type phospholipids) on 2 or more occasions. Antinuclear antibodies were detected by immunofluorescence on rat liver and were considered positive when the titer was 1:50 or greater. Patients with drug-induced ANAs and/or aCLs were excluded from the study. Antinuclear antibody and aCL titers in patients with MS were compared with those observed in 160 healthy subjects (100 women and 60 men), aged 20 to 50 years, who were examined in the same manner. Levels of anti-double-stranded DNA antibodies were measured using an enzyme-linked immunosorbent assay and immunofluorescence performed on Crithidia luciliae. The presence of the following antibodies was also determined whenever ANA titers were positive: anti–Ro-SSA, anti–La-SSB, anti–ENA, and anti–Sm. Anti–Borrelia burgdorferi antibodies were detected in serum and CSF using an indirect immunofluorescence technique. Serum and CSF levels of angiotensin-converting enzyme were also determined (normal values, <135 U/min per liter in serum and <0.4 U/L in CSF).

Magnetic resonance imaging examinations were performed using a superconductive 1.5-T magnet (Signa, General Electric, Milwaukee, Wis.). Hypersignals on T2-weighted sequences for MS were considered according to the criteria of Lee et al.12

Analysis of CSF included red and white blood cell count, measurement of protein concentration, globulin electrophoresis, IgG intrathecal synthesis, and oligoclonal band determination.13

at least 1 abnormality that is not typical for MS (“MS plus”): 42 had isolated positive titers of ANA, 9 had isolated positive titers of aCL, 14 had titers positive for both ANA and aCL, 3 had isolated cryoglobulinemia, 6 had increased levels of circulating immune complexes, 5 had decreased levels of C3 and/or C4, 1 had an isolated positive titer for neuroborreliosis in the serum and CSF, 1 had increased levels of angiotensin-converting enzyme in the serum, and the 3 remaining patients had isolated clinical abnormalities. Presenting symptoms and signs are listed in Table 1. In control subjects, titers of ANA were positive in 18 women at 1:50 (age range, 36-48 years) and negative in all men. Titers of aCL were negative in all control subjects.

Among the 84 patients in the MS plus group, 64 were followed up clinically and biologically in our institution and their files were reviewed in January 1997. Their clinical and biological features were compared with those of the 20 patients who were not followed up; no significant differences were found between these 2 groups. Positive ANA titers were found in 45 of 64 patients with the following titers: 1:50 in 14 patients, 1:100 in 17, 1:200 in 9, and 1:500 in 5 patients. Among these 64 patients followed up in our institution, no diagnosis other than MS could be established in 50 patients (Table 2); they are referred to as group 2. Thirty-three of these 50 patients had positive ANA titers: 14 patients had titers of

Table 1. Comparative Symptoms and Signs at Onset in Patients With Multiple Sclerosis (MS)

<table>
<thead>
<tr>
<th>Clinical Findings</th>
<th>MS Only (n=77)</th>
<th>MS Plus (n=84)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at onset, y (range)</td>
<td>29.94 (15-64)</td>
<td>32.29 (18-56)</td>
</tr>
<tr>
<td>Women/men (ratio)</td>
<td>46/31 (1.48)</td>
<td>58/26 (2.23)</td>
</tr>
<tr>
<td>Optic neuritis</td>
<td>24</td>
<td>26</td>
</tr>
<tr>
<td>Deep or superficial sensitivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>symptoms or signs</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>Motor disturbance</td>
<td>24</td>
<td>19</td>
</tr>
<tr>
<td>Balance disturbance</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Diplopia</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Facial palsy</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Seizures</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Urinary dysfunction</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Lateral homonymous hemianopia</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Vertigo</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

*MS plus patients were those with at least 1 clinical and/or biological sign suggestive of an autoimmune disease. All data are presented as number of patients with the exception of mean age and the sex ratio.

1:50, 15 had titers of 1:100, and 4 had titers of 1:200. No patient had an ANA titer of 1:500. Positive ANA titers were found in 8 patients 40 years and older (5 women and 3 men), and in 25 patients younger than 39 years...
Association criteria were not satisfied, 2 for a neurologic disease associated with aPL antibodies, and 1 for Sjo¨gren syndrome. Among these 50 patients in group 2, 8 patients (16%) had positive anticardiolipin antibody titers with or without positive ANA titers. 

Table 3. Positive ANA Titer Distribution in Patients With Multiple Sclerosis According to Their Age and Sex*

<table>
<thead>
<tr>
<th>Age Range, y</th>
<th>1:50</th>
<th>1:100</th>
<th>1:200</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F</td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>18-29</td>
<td>4</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>30-39</td>
<td>4</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>40-49</td>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>5</td>
<td>13</td>
</tr>
</tbody>
</table>

* ANA indicates antinuclear antibody; F, female; and M, male.

(19 women and 6 men) (Table 3). No significant difference was found in the clinical course of the disease between patients with positive ANA titers and those without (P > .05). Even if more patients with positive ANA titers had a secondary progressive course, this difference was not statistically significant (P > .05) (Table 4). Among these 50 patients in group 2, 8 patients (16%) had positive titers for aCL with or without positive ANA titers, 5 had a decrease in levels of C3 or C4, 5 had an increase of circulating immune complexes, 3 had isolated cryoglobulinemia, 5 had an increase of angiotensin-converting enzyme, 1 had positive titers for Lyme disease (IgG), and 1 had an increase in levels of angiotensin-converting enzyme. Two patients presented with clinical particularities only (arthralgia and livedo). A diagnosis other than MS was still suspected in 64 patients; 11 for SLE even if American Rheumatism Association criteria were not satisfied, 2 for a neurologic disease associated with aPL antibodies, and 1 for Sjogren syndrome.

Neurologic presenting symptoms were comparable in both groups of patients with an initial (group 1) and final (group 2) diagnosis of MS except for diplopia, more frequently encountered in patients of group 2 (P = .04). In all patients with the final established diagnosis of MS after a 4- to 5-year follow-up (n = 127), ANAs were found in 33 (26%), aPLs in 8 (6.2%), and general clinical signs were encountered in 17 (13.3%) (Table 5).

Magnetic resonance imaging findings of 75 of the 84 patients in the MS plus group were reviewed and classified according to the criteria of Lee et al. Four patients had more than 4 lesions on T2-weighted images, but these were punctiform, with a diameter of less than 3 mm. Five patients had fewer than 3 lesions, no patients had periventricular lesions, 6 patients had only infratentorial lesions, 2 patients had large and diffuse areas of mild hypersignal (also involving the spinal cord in 1), 6 patients had normal findings of cerebral MRI, and cervical MRI showed hypersignal in 5 patients. Thus, according to the criteria of Lee et al., cerebral lesions demonstrated by MRI were suggestive of MS in 33 patients (69.3%). However, if patients with infratentorial and cervical spinal cord lesions were added, MRI findings may be considered suggestive of MS in 64 patients (85.3%). In 9 of 84 patients, MRI was not available.

OTHER BIOLOGICAL FINDINGS

Levels of IgM were elevated in the serum of 27 patients (35%) belonging to group 1 (mean, 2.6 g/L; range, 1.5-4.2 g/L), and in 50 (59.5%) of the 84 MS plus patients (mean, 2.7 g/L; range, 1.7-7.9 g/L). Levels of IgG were elevated in 6 patients (mean, 18.2 g/L; range, 16.3-22.8 g/L) in group 1 and in 4 of the MS plus patients, while they were decreased in 6 patients. Levels of IgA were el-
We report a prospective study of patients presenting with symptoms and signs of MS who were assessed for clinical and paraclinical features suggestive of an autoimmune disease to consider a diagnosis other than MS, and to estimate the frequency of these abnormalities in patients with the final diagnosis of MS. Patients were divided in 2 groups according to the presence of these abnormalities. At least 1 clinical and/or biological sign that is not usually associated with MS was found in 84 (52.2%) of 161 patients. No significant difference was found between those with only MS and MS plus patients regarding age of disease onset, presenting symptoms and signs, and clinical evolution. Oligoclonal bands and/or IgG synthesis on CSF analysis were found with comparable frequency in both groups.

In MS plus patients, the diagnosis of MS was established in 50 (78.1%) of 64 patients after 5 years of disease evolution. In the 14 remaining patients, we found a combination of clinical, biological, and MRI abnormalities: an ANA titer of 1:200 or 1:500 (12 patients) in combination with aPLs in 6 patients; the presence of anti-DNA antibodies in 4 patients; myositis in 1 patient; Sjogren syndrome in 1 patient; and particular findings on MRI in 7 patients (normal [n=1], punctiform hypersignals [n=2] on T2-weighted images, diffuse light hypersignals [n=4], and exclusive involvement of the pons [n=1]).

The diagnosis of MS is based on temporal and spatial dissemination of lesions involving the white matter of the CNS and the exclusion of another diagnosis. Magnetic resonance imaging has been useful in identifying local lesions possibly mimicking MS in clinical presentation, but seems less sensitive to differentiate MS from other autoimmune diseases. Although differences in lesion topography have been reported between MS and Behçet disease. Similarly, the presence of IgG synthesis and/or oligoclonal bands cannot differentiate MS from other inflammatory disorders.

The significance of autoimmune abnormalities in patients with MS is still unknown. The presence of these abnormalities at the onset of this disease may be suggestive of systemic disease primarily or predominantly affecting the CNS. A large number of these systemic disorders may affect the CNS, more often in the progressive course of the disease. In these cases, CNS involvement is an important factor for prognosis. In some cases, the presenting symptoms and signs involve the CNS and may occur in a relapsing-remitting fashion. Numerous cases of SLE with MS-like clinical presentation have been reported. Neuropathologically, necrotic lesions predominate, but demyelination has been reported. Recent cases of transverse myelitis and/or optic neuritis, which can follow a relapsing course, associated with SLE and/or aPLs have been reported. Some patients may fulfill criteria for both SLE and MS; this association is called lupoid sclerosis. In these cases, MRI shows high signals compatible with MS and additional nonspecific white matter lesions suggesting small vessel occlusion. In some of these cases, the presence of aPLs and antimeylin antibodies has been reported. Magnetic resonance imaging of the spinal cord shows signal abnormalities that seem to correlate with clinical episodes.

A differential diagnosis of Behçet disease may be difficult when neurologic involvement precedes aphthosis, when signs and symptoms follow a relapsing-remitting course, and/or when the optic nerve is involved. The primary involvement of the CNS in Sjogren syndrome is still a matter of debate. Multiple sclerosis and primary Sjogren syndrome may coexist, but this is still controversial.

In some patients in this study, the presence of ANAs and/or aPLs might have suggested a systemic connective tissue disease, particularly SLE. In most patients (93.5%) with an ANA titer of 1:100, the final diagnosis was MS. The frequency of ANAs in MS and their significance remains a matter of debate. Our study is in agreement with the findings of others but our frequency of positive ANA titers is higher than that described in other series using a different technique for detection and with lower titers of ANA. However, in our study both the frequency and titers of ANA are significantly increased in patients with MS compared with controls (10% with a titer of 1:50). In addition, ANAs were found in young patients. Usually, aPLs are associated with SLE but are also described in association with neurologic conditions, including MS. In the study by Fukazawa et al, the frequency of these antibodies was estimated at 5.3% in Japanese patients with clinically definite MS. Isolated cases of aPL-associated disease mimicking MS have been reported. These antibodies have been found in the serum and CSF in individuals with numerous neurologic conditions, including MS and SLE. In control subjects, aCL titers were negative in all cases. Finally, clinical and/or biological systemic signs in patients presenting with the criteria for MS of Poser et al may reveal the existence of a systemic disorder confined to the CNS. On the other hand, these signs may reflect the systemic immune dysregulation and/or the possible association with another systemic disease. Another possibility, which remains to be established, is the association of these antibodies with some HLA subtypes that are more frequently present in patients with MS. However, the final diagnosis may remain difficult to confirm when a combination of these abnormalities is present in a single patient. This is the case in 14 patients in this study. The prognosis of patients with such associations is unknown. However, 6 of 14 patients had a steady disease condition after 5 years of progression.
In conclusion, it seems that the differential diagnosis between MS and other autoimmune diseases is not always easy to establish. It could be important to add to the criteria of Poser et al for MS diagnosis the systematic and at least twice-repeated screening for ANAs and aPLs. It is still unknown if patients with such abnormalities should be excluded from clinical trials of MS. However, according to this study, patients with MS with autoimmune features, including low titers (<1:100) of ANA and/or biologically isolated aPLs, are not different from other patients with MS and should not be excluded from clinical trials.

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