Transverse Myelitis in Systemic Lupus Erythematosus

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Objective: Transverse myelitis (TM) is a rare complication in patients with systemic lupus erythematosus (SLE). We reviewed a series of our SLE patients to determine the prevalence of TM, and evaluate the clinical characteristics, medical tests, evolution, and response to the treatment.

Patients and method: Six patients with TM were identified and underwent a neurological evaluation, MRI, electrophysiologic study, and were all subjected to the same treatment. A descriptive statistical study was conducted.

Results: We observed a prevalence of 0.92% in our patients with SLE. Eighty-three point three per cent had antiphospholipid antibodies and/or lupus anticoagulant. The MRI confirmed the diagnosis in 5 cases. Of the 5 patients with antiphospholipid antibodies, 3 were anticoagulated or took aspirin with a good neurological outcome, leaving 2 of them without posterior complications.

Conclusions: We found a prevalence similar to that observed in other series, around 1%. The high prevalence of antiphospholipid antibodies in these patients, with good outcome in those anticoagulated or treated with antiplatelet agents suggests an important pathogenic role in the development of TM, and emphasized the possibility of adding to the standard treatment, antiplatelet agents, or anticoagulation.

Key words: Transverse myelitis. Systemic erythematosus lupus. Antiphospholipid antibodies.

Mielitis transversa en lupus eritematoso sistémico

Objetivo: La mielitis transversa aguda (MTA) es una rara complicación en los pacientes con lupus eritematoso sistémico (LES). Revisamos nuestra serie de pacientes con LES para determinar la prevalencia de MTA y analizar las características clínicas, las pruebas complementarias, la evolución y la respuesta al tratamiento.

Pacientes y método: Se identificó a 6 pacientes con MTA que se sometieron a valoración clínico-neurológica, resonancia magnética y estudio electrofisiológico, y recibieron el mismo tratamiento. Realizamos un estudio estadístico descriptivo.

Resultados: Observamos una prevalencia de MTA del 0,92% de nuestros pacientes con LES. El 83,3% presentaba anticuerpos antifosfolipídicos y/o lupus anticoagulante. La resonancia magnética confirmó el diagnóstico en 5 casos. De los 5 pacientes con antifosfolípidos, 3 fueron anticoagulados o tomaron aspirina con buen resultado neurológico; 2 de ellos han quedado sin secuelas.

Conclusiones: Encontramos una prevalencia similar a la observada en otras series, en torno al 1%. La alta prevalencia de anticuerpos antifosfolípidicos en los pacientes, con buen resultado en los antiagregados o anticoagulados, indica un importante papel patogénico en el desarrollo de la MTA, y nos hace plantearnos la importancia de añadir al tratamiento estándar terapia antiagregante o anticoagulante.

Palabras clave: Mielitis transversa. Lupus eritematoso sistémico. Anticuerpos antifosfolípidicos.

Introduction

Neuropsychiatric manifestations are present in up to 60% of patients with systemic lupus erythematosus (SLE). Acute transverse myelitis (ATM), a very uncommon neurological manifestation, occurs in 1%-2%. The physiopathologic mechanism of ATM in SLE is unknown, though inflammatory and arterial thrombotic phenomena have been proposed. A greater prevalence of
antiphospholipid antibodies has been described in patients with SLE and ATM than in the general population of patients with SLE: something that could have important implications to decide whether if these patients are suitable for anticoagulant treatment or not.

Different authors have proposed different treatment regimens for this entity, based on high-dose steroids, combined or not with immunosuppressants and/or plasmapheresis.

The main objective of the present study is to determine the prevalence of ATM in our series of patients with SLE and to describe their clinical characteristics as well as the findings of complementary testing as well as the evolution and the response to treatment.

**Patients and Methods**

From a total population of 650 patients with SLE, classified according to the ACR criteria and attended at the Unit of Collagenosis of the Hospital Virgen del Rocio in Sevilla, 6 patients with ATM were identified in the last 10 years.

The diagnosis of ATM was done according to the clinical characteristics that reflected spinal cord lesion, such as sensory and/or motor sphincter dysfunction, documented with the magnetic resonance imaging (MR) findings, and other tests.

Patients were studied through a clinical and neurological evaluation, MR and an electrophysiologic study. ELISA (enzyme-linked immunosorbent assay) was employed for the determination of anticardiolipin antibodies and normal values were 0 to 20 and 0 to 10 units GPL and MPL for IgG and IgM isotypes, respectively. All patients were treated using the same therapeutic scheme.

A descriptive statistical analysis was carried out, taking into account numerical and qualitative variables, expressed as means ± standard deviations and expressed through Tables and percentages.

The most relevant patient data reviewed is presented in Table 1.

**Results**

In our series of patients with SLE, ATM was seen with a frequency of 0.92%; 66.6% of patients were women; mean age at the onset of ATM was 37.33±10.367 years.

The clinical characteristics related to lupus were varied.

All patients had skin and joint affection; 50% had lung involvement; 33.3% had presented serositis in some moment of their evolution; 83.3% had some type of cytopenia and 16.7% had presented autoimmune hemolytic anemia.

We proved the presence of antinuclear antibodies (ANA) in all patients, with diverse immunofluorescence patterns: speckled (present in 83.3%), diffuse (66.7%), cytoplasmic (50%), nucleolar (50%), anti-Sm antibodies (33.3%), and nuclear (16.7%). Anti-DNA antibodies were positive in 50%.

As for the presence of antiphospholipid antibodies, 83.3% (5 of 6 patients) had positive results for anticardiolipin antibodies and/or lupus anticoagulant: IgG anticardiolipin antibodies in 60% and IgM in 40% and lupus anticoagulant (elongated partial thromboplastin time without correction after the addition of normal plasma) in 33.3%. Only 1 patient had presented a previous thrombotic event, namely a deep venous thrombosis.

The time since onset of SLE, when ATM appeared, was 27±27,821 months; it was the first manifestation of SLE in 1 of the 6 patients.

The start of the manifestation was acute in 50% of cases and subacute in the rest. In 33.3%, ATM was manifested as a Brown-Sequard syndrome. In the majority of patients (5 out of 6) a sensitive level was present: 4 in the dorsal spine and 1 in the lumbar spine. Sphincter dysfunction was present in 50% and 1 patient had a case of optic neuritis; 33.3% of cases were associated to fever.

RM confirmed the diagnosis in 83.3% of cases, showing widening and an increase in signal of the spinal cord tissue, on T2 (Figure 1). An electrophysiologic study was carried out in 5 of 6 patients; they all showed alterations compatible with sensorymotor demyelinating axonal neuropathy.

As mentioned, the same therapeutic scheme was employed in all patients, consisting in 3 bolus doses of 1 g methylprednisolone on 3 consecutive days when starting with the manifestations and 6 bolus doses of cyclophosphamide at 15 mg/kg, monthly during the first 6 months and 6 trimestral doses during the following 18 months. After the pulse therapy, patients received oral steroids at a dose of 0.5–1 mg/kg/day of prednisone or the equivalent, in a descending pattern until a maintenance dose of 10–15 mg/day was reached; 16.7% of the patients received antipatelet therapy and 33.3% received anticoagulation. One of the latter presented a subdural hematoma that forced the suspension of oral anticoagulants.

The evolution of the hematoma was favorable, but a new bout of ATM developed (the only patient that presented recurrence) 8 months later; anticoagulation was restored, with a good response. Response to treatment was favorable in 83.3% of cases, with a very heterogeneous time of recuperation; 50% of patients remained asymptomatic and without sequelae. The mean follow-up time of these patients up until currently was 8 years. A patient with chronic hepatitis C infection died as a consequence of the progressive deterioration of liver function. Apart from standard therapy, 3 of the 5 patients positive for antiphospholipid antibodies received antipatelet of anticoagulant therapy, with a favorable evolution of the neurological clinical signs and symptoms; 2 of them remained without sequelae.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Time Since Onset of SLE (Months)</th>
<th>Cumulative Clinical Aspects of SLE</th>
<th>Analytical Aspects SLE</th>
<th>SLE Clinical Data</th>
<th>Neurological Clinical Data</th>
<th>MR</th>
<th>Antiplatelet/In Anticoagulation</th>
<th>Evolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. SLE</td>
<td>47</td>
<td>Woman</td>
<td>48</td>
<td>Skin affection joint, febrile, pleuritis, cytopenia, anemia hemolytic autoimmune</td>
<td>ANA+, SP, DF, SP, aCL+ (GPL 19; MPL 27)</td>
<td>Acute onset, hemisection spinal: paresia right LL, hypoesthesia, sensory D3, hypoesthesia LL, level</td>
<td>Axonal neuropathy</td>
<td>Widening and hyperintensity D3-D4 on T2</td>
<td>Antiplatelet</td>
<td>Asymptomatic. Death by liver failure (history of infection chronic HCV)</td>
</tr>
<tr>
<td>2. SLE</td>
<td>46</td>
<td>Male</td>
<td>6</td>
<td>Skin affection-joint, febrile, pericarditis, cytopenia</td>
<td>ANA+, CY, DF, anti-DNA, anti-Sm, aCL+ (GPL 43; MPL 1)</td>
<td>Subacute onset, hypoesthesia LL, flaccid paraparesia, sphincter affection, sensory level L1</td>
<td>Neuropathy sensory-motor demyelinating</td>
<td>Normal</td>
<td>Paraparesia</td>
<td></td>
</tr>
<tr>
<td>3. SLE</td>
<td>27</td>
<td>Woman</td>
<td>12</td>
<td>Skin affection-joint, cytopenia</td>
<td>ANA+, SP, CY, NC, anti-DNA</td>
<td>Acute onset, anesthesia LL, paraparesia flaccid, affection sphincter, level sensitive D11</td>
<td>Neuropathy sensory demyelinating</td>
<td>Widening D10-L1, hyperintensity D11-D12 on T2</td>
<td>Paraplegy</td>
<td></td>
</tr>
<tr>
<td>4. SLE</td>
<td>31</td>
<td>Woman</td>
<td>0</td>
<td>Skin affection-joint, cytopenia</td>
<td>ANA+, SP, NC, aCL+, LA+ (GPL 23; MPL 1)</td>
<td>Subacute onset, spinal hemisection, paraparesia predominantly D, hypoesthesia predominantly I, sensitive level D4</td>
<td>Myelopathy</td>
<td>Hyperintensity D2 on T2</td>
<td>Asymptomatic</td>
<td></td>
</tr>
<tr>
<td>5. SLE</td>
<td>47</td>
<td>Woman</td>
<td>72</td>
<td>Skin affection-joint</td>
<td>ANA+, SP, NC, cytoplasmic, aCL+ (GPL 9; MPL 14)</td>
<td>Acute onset, tetraparesia, sphyncter affection, relapse at 8 months</td>
<td>Widening and hyperintensity at spinal level cervical in T2</td>
<td>Anticoagulation (suspended due to bladder subdural on first episode, reintroduced in second episode with good response)</td>
<td>Hipoesthesia LL neurogenous hematoma</td>
<td></td>
</tr>
<tr>
<td>6. SLE, APS</td>
<td>26</td>
<td>Male</td>
<td>24</td>
<td>Skin affection-joint, febrile, cytopenia, DVT</td>
<td>ANA+, SP, anti-DNA, anti-Sm, aCL + (GPL 24; MPL 45), ACL+</td>
<td>Subacute onset, dysesthesia UL and LL, optic neuritis retrobulbar</td>
<td>Moderate neuropathy LL</td>
<td>Hyperintensity lateral columns proutberase, anterolateral cervical spinal in T2</td>
<td>Anticoagulation</td>
<td>Asymptomatic</td>
</tr>
</tbody>
</table>

*aCL indicates anticardiolipin; LA, lupus anticoagulant; ANA, antinuclear antibodies; DF, diffuse; EEP, electrophysiologic study; SLE, systemic lupus erythematosus; LL, lower limbs; UL, upper limbs; CY, cytoplasmic; SP, speckled; NUC, nuclear; NC, nucleolar; MR, magnetic resonance; APS, antiphospholipid syndrome; DVT, deep venous thrombosis.
Discussion

ATM is a rare but serious complication in patients with SLE. Its low prevalence is estimated approximately 1%-2% of this patient population, and this is confirmed once more in our series of patients, which was around 1%.

Our patients developed it in the first 6 years since disease diagnosis, coinciding with the start of the disease in one of them, circumstance that has been mentioned in some studies in which it is communicated in up to 39% of cases in which ATM was the initial manifestation of SLE.\(^1,2\)

The clinical spectrum of the disease is varied and we found no trace of the underlying disease associated in a characteristic manner to ATM.

The case of the patient with chronic hepatitis C infection, who died due to liver dysfunction, a special mention is deserved because it is the first communicated case in the medical literature of interferon-alpha induced SLE in patients with hepatitis C.\(^3\)

One of our patients developed optic neuritis, described by Devic in 1894 and related to the presence of antiphospholipid antibodies.\(^4\)

Through MR, considered the best imaging technique for ATM,\(^5\) the diagnosis was confirmed in 5 of 6 patients. Nonetheless, in close to 40% of ATM there are no demonstrable alterations through MR: Mok et al\(^6\) observed MR alterations in 56%, Kovacs et al\(^7\) in 70%, and D’Cruz et al\(^8\) in 93%.

There is no consensus for the treatment of this manifestation of SLE, probably due to its scarce incidence, though the majority of the authors coincide in the importance of its early installation.\(^9\) The use of steroids at a high dose is recommended, associated to the use of immunosuppressants. Kovacs et al\(^10\) observed that the clinical manifestations of ATM improve with the administration of intravenous methylprednisolone, but the results are better if pulse cyclophosphamide is added. In a clinical trial published by Barile et al\(^11\) in patients with SLE and neurological manifestations, cyclophosphamide is more efficacious than the use of methylprednisolone, used in a dose of 0.75 g/m\(^2\) body surface monthly during 1 year and every 3 months for another year. Mok et al\(^11\) pointed out that cyclophosphamide seems to be more effective than azathioprine regarding the remaining functional situation.

Several authors have shown that the strong association between ATM and the presence of antiphospholipid antibodies,\(^1,3,8\) larger than in the general population of SLE patients (estimated in 30%-50%). It seems very probable that they have an important role in the pathogenesis of this disease, through their interaction with the spinal phospholipids.\(^11\) Thrombosis of the spine blood vessel would explain a larger dorsal affection because the vessels are smaller but, in the few autopsy studies published, necrosis of the spine has been shown, but no thrombosis of the spinal vessels. In any case, it is difficult to precise if it is a thrombotic phenomenon or an inflammatory one, or a combination of both.

The role of anticoagulation is a controversial topic, still not having been resolved in the ATM associated to SLE. It seems reasonable to install it in patients with antiphospholipid antibodies due to their prothrombotic power. The high prevalence of antiphospholipid antibodies in our patients (83.3%), with a good outcome in those that underwent anticoagulant or antiplatelet therapy, indicating the important role these antibodies play in the pathogenesis and development of ATM and forces us to consider adding anticoagulant or antiplatelet therapy to the standard therapy with steroids and immunosuppressants.

Controlled studies are needed to approach the development of therapeutic strategies, attending specially the need for anticoagulation and antiplatelet therapy.

References