

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 anticoagulante lúpico. La resonancia magnética confirmó el diagnóstico en 5 de los 6 casos; 3 de los 5 pacientes con anticuerpos antifosfolipídicos fueron anticoagulados o antiagregados, con buena evolución neurológica; 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 antifosfolipídicos 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 antifosfolipídicos.

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

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antiphospholipid antibodies has been described in patients with SLE and ATM than in the general population of patients with SLE,¹⁻³ 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 \pm 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 $27 \pm 27,821$ 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 antiplatelet 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 antiplatelet of anticoagulant therapy, with a favorable evolution of the neurological clinical signs and symptoms; 2 of them remained without sequelae.

Relevant Data of Patients With Systemic Lupus Erythematosus and Transverse Myelitis*

Patient	Age	Sex	Time Since Onset of SLE, Months	Cummulative Clinical Aspects of SLE	Analytical Aspects SLE	SLE Clinical Data	Neurological Clinical Data	MR	Antiplatelet/n Anticoagulation	Evolution
1. SLE	47	Woman	48	Skin affection joint, affection lung, pleuritis, cytopenia, anemia hemolytic autoimmune	ANA+, SP, DF, SP, aCL+ (GPL 19; MPL 27)	Acute onset, hemisection spinal: paresia right LL, hypoesthesia, sensory D3, hypoesthesia LL, level	Axonal neuropathy	Widening and hyperintensity D3-D4 on T2	Antiplatelet	Asymptomatic. Death by liver failure (history of infection chronic HCV)
2. SLE	46	Male	6	Skin affection-joint, affection lung, pericarditis, cytopenia	ANA+, CY, DF, anti-DNA, anti-Sm, aCL+ (GPL 43; MPL 1)	Subacute onset, hypoesthesia LL, flaccid paraparesia, sphincter affection, sensory level L1	Neuropathy sensory-motor demyelinating	Normal		Paraparesia
3. SLE	27	Woman	12	Skin affection-joint, cytopenia	ANA+, SP, CY, NC, anti-DNA	Acute onset, anesthesia LL, paraparesia flaccid, affection sphincter, level sensitive D11	Neuropathy sensory demyelinating	Widening D10-L1, hyperintensity D11-12 on T2		Paraplegia
4. SLE	31	Woman	0	Skin affection-joint, cytopenia	ANA+, SP, NC, aCL+, LA+ (GPL 23; MPL 1)	Subacute onset, spinal hemisection, paraparesia predominantly D, hypoesthesia predominantly I, sensitive level D4	Myelopathy	Hyperintensity D2 on T2		Asymptomatic
5. SLE	47	Women	72	Skin affection-joint	ANA+, SP, NC, cytoplasmic, aCL+ (GPL 9; MPL 14)	Acute onset, tetraparesia, sphincter affection, relapse at 8 months		Widening and hiperintensity at spinal level cervical in T2	Anticoagulation (suspended due to bladder subdural on first episode, reintroduced in second episode with good response)	Hipoesthesia LL neurogenous hematoma
6. SLE, APS	26	Male	24	Skin affection-joint, affection lung, cytopenia, DVT	ANA+, SP, anti-DNA, anti-Sm, aCL+ (GPL 24; MPL 45), ACL+	Subacute onset, dysesthesia UL and LL, optic neuritis retrobulbar	Moderate neuropathy LL	Hyperintensity lateral columns protuberance, anterolateral cervical spinal in T2	Anticoagulation	Asymptomatic

*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 varied⁴ 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.⁵

One of our patients developed optic neuromyelitis, described by Devic in 1894 and related to the presence of antiphospholipid antibodies.⁶

Through MR, considered the best imaging technique for ATM,⁷ 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 al⁸ observed MR alterations in 56%, Kovacs et al² in 70%, and D'Cruz et al¹ 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 al² 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 al¹⁰ in patients with SLE and neurological manifestations, cyclophosphamide is more efficacious than the use of methylprednisolone, used in a dose of 0.75 g/m² body surface monthly during 1 year and every 3 months for another year. Mok et al⁸ 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,^{1-3,9} 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

Figure. Magnetic resonance indicating a widening and increase in intensity of signal in the cervical spinal cord on T2.

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.

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