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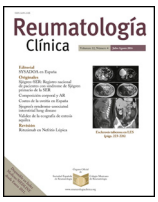

Review Article

Myelitis and Lupus: Clinical Manifestations, Diagnosis and Treatment. Review☆

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ABSTRACT

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that affects multiple systems. Myelopathy is one of 19 neuropsychiatric syndromes related to SLE defined by the American College of Rheumatology. Although infrequent, it is a severe manifestation, leading to motor and sensory deficits, and sphincter dysfunction. The pathogenesis is not clearly known, but may be related to arterial thrombosis and vasculitis. Diagnosis is based on clinical findings, laboratory tests and the use of gadolinium-enhanced magnetic resonance imaging. The standard therapy is the combination of intravenous cyclophosphamide and glucocorticoids. In refractory disease, other treatments such as plasmapheresis or rituximab have been used.

Mielitis y lupus: clínica, diagnóstico y tratamiento. Revisión

Palabras clave:
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RESUMEN

El lupus eritematoso sistémico (LES)es una enfermedad autoinmune crónica que afecta múltiples sistemas. La mielopatía es uno de los 19 síndromes neuropsiquiátricos relacionados al LES, definidos por el Colegio Estadounidense de Reumatología. Aunque infrecuente, es una manifestación grave que cursa con déficit motor y sensitivo, y disfunción de los esfínteres. La fisiopatogenia no se conoce claramente, pero podría estar relacionada con trombosis arterial y/o vasculitis. El diagnóstico se basa en los hallazgos clínicos, los exámenes de laboratorio y el uso de la resonancia magnética con gadolinio. El tratamiento estándar es la combinación de ciclofosfamida y glucocorticoides por vía intravenosa. En casos refractarios se han utilizado otros tratamientos, como plasmaféresis o rituximab.

Introduction

Acute myelitis (AM) involves inflammation of the spinal cord and is characterized by neuronal and axonal damage, which provokes paralysis or paresis, sensory deficit and autonomic dysfunction. The incidence in the general population is 1–4 cases per 1 million population per year.[1] Of the multiple causes of AM, systemic autoimmune diseases play a major role and, among them, systemic lupus erythematosus (SLE) is one of those most frequently related.[2]

Myelopathy due to SLE is one of the 19 associated neuropsychiatric syndromes defined by the American College of Rheumatology (ACR)[3] (Table 1). Taking into account the common neurological manifestations, such as headache, mood disorder and cognitive dysfunction, myelopathy is one of the least common neuropsychiatric syndromes (between 1% and 2% of the patients).[4] In the majority of the cases it occurs within the first 5 years after the onset

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Table 1
Diagnostic Criteria for Myelitis in Systemic Lupus Erythematosus.

Diagnostic criteria for myelopathy in SLE proposed in 1999 by the ACR[3]
Sudden onset (days or hours) of the following signs/symptoms
Bilateral weakness of lower limbs that may or may not include upper limbs (paraplegia or tetraplegia). It can be asymptomatic
Change in sensory sensitivity corresponding to a motor impairment, with or without intestinal-bladder dysfunction
Exclusion criteria
Compressive spinal cord lesion (e.g., disk prolapse)
Cauda equina syndrome

ACR, American College of Rheumatology; SLE, systemic lupus erythematosus.

of SLE[4] and, in nearly half of the cases, is the initial manifestation,[4,5] with a recurrence rate of between 18% and 50%.[4–6]

Pathophysiology

The pathophysiology is not yet fully known. Based on pathological and serological findings, it has been proposed that small vessel vasculitis and thrombosis would be the 2 major mechanisms most directly responsible for the neuronal and axonal damage.[4,7–9] Depending on the type of spinal cord compromise (extensive or limited), one of the mechanisms will better explain the manifestations than the other. In the case of transverse myelitis, the frequent involvement at the thoracic level[4,8] (a region with vessels of a smaller caliber than the spinal cord vasculature and, thus, more vulnerable to thrombosis) and the presence in serum of antiphospholipid antibodies (aPL),[4,8] are features that indicate that thrombosis will have a preponderant pathogenic role.[4,8–10] However, this mechanism would not explain longitudinal myelitis with continuous compromise.[6]

A number of reports indicate an important association between aPL and myelopathy in lupus,[4,8,9] although the prevalence of positive serology is not much greater than that of patients with no spinal cord involvement.[4,9,10] The most probable mechanism of action is thrombosis. It has also been proposed that aPL could have a direct cytotoxic effect, which would correlate with the presence of oligoclonal bands in aPL-positive patients.[6,9,10] Another mechanism could involve the so-called "cooperation between antibodies"[9]: ischemia would induce the synthesis of aquaporin-4 with the subsequent development of lupus myelitis associated with the neuromyelitis optica (NMO) spectrum mediated by anti-aquaporin-4 immunoglobulin (Ig) G (AQP4-IgG) or another type of antibody.[9,10]

Despite the above, the role of aPL is debatable.[9,10] A systematic review[9] compared aPL-positive and aPL-negative patients in terms of the rate of relapses and overall clinical course. Paradoxically, thoracic involvement was observed more frequently among patients who were negative for aPL. Another fact to be considered is that according to a large number of published reports,[4–6,8,9] only anticardiolipin (aCL) antibodies and/or lupus anticoagulant were determined, but their exact values were not expressed or were provided using nonstandard units and in the absence of information on cutoff values (in accordance with the classification criteria for antiphospholipid syndrome, the value is 40 IU measured by enzyme-linked immunosorbent assay [ELISA][11]). Moreover, there is no information on the isotypes studied: for example, in a nonspecific manner, IgM aCL antibody positivity can be found in a number of processes. Another oversight of the articles is that, in general, the patients being studied have only undergone aPL determination once, and the possibility of its being a transient phenomenon has not been ruled out.[11]

Although no specific pathogenic role has been attributed to anti-Ro/SSA antibody, its association with recurrent myelitis is well known.[12] This antibody has been identified in patients with MNO and in transverse myelitis even in the absence of a diagnosis of Sjögren's syndrome.[13] Curiously, in one of the largest series of lupus myelitis[9] it was observed that patients with recurrent disease were more frequently anti-Ro/SSA-positive than those with monophasic disease (single episode).

Another pathophysiological mechanism proposed is the change in the blood–brain barrier due to autoantibodies,[12] especially in cases of overlapping with NMO, although there are no consistent findings to validate this hypothesis.[12]

The lack of gadolinium uptake in magnetic resonance imaging (MRI) in certain cases of myelitis suggests a hemodynamic pathophysiological mechanism: spinal cord inflammation, when produced in a rigid anatomic space, would generate progressive venous hypertension (due to compression of the dorsal venous plexus) with the consequent reduction of the perfusion gradient between the radicular arteries of the spinal cord and the venous plexus of the pia mater, generating spinal cord ischemia.[9] This mechanism, not yet confirmed, would not explain the initial inflammatory process.

Clinical Manifestations

Along general lines, the onset is acute and progresses over hours or days, although in many cases, the nadir occurs within the first 24 h.[9,14] It can be preceded by general symptoms like fever, headache and vomiting,[6,9] and, later by a short period that begins with paresthesia and paresis of the lower limbs. This is generally severe, and can lead to paraplegia or, less frequently, to tetraplegia, sensory deficit and sphincter dysfunction, which is expressed as urinary and fecal incontinence.[4–6,8,9]

Motor involvement is almost always bilateral, although not necessarily symmetrical, and the severity is variable, and can range from mild paresis to tetraplegia.[4–6,8,14] The most common motor deficit is spastic paraparesis.[4,8]

The sensory loss, like the motor dysfunction, is bilateral—with signs of differing severity—ranging from anesthesia (below the level of the spinal cord lesion) to the achievement of exclusive dissociation of thermal analgesia.[4,6,8,15] The thoracic segment is the region most frequently affected (from T5 to T8, especially T7)[4–6,8] and is usually well defined.

The autonomic nervous system is often compromised, including urinary retention and intestinal paralysis, which leads to bladder and fecal incontinence.[4,11] There can be reduced vasomotor function, resulting in pallor and a cold sensation in the limbs.

Acute myelitis can be accompanied by other neurological manifestations. Optic neuritis (ON) is associated with relative frequency[4,5,9] (20%–50%). Others less widespread are depression, memory impairment, seizures, psychosis and ophthalmoplegia.[4,6]

Longitudinal Myelitis

For years it was thought that SLE-related longitudinal myelitis was an uncommon mode of presentation of this neurological disorder.[15,16] However, a systematic review found that it was the form most frequently encountered.[16] This is probably because of improvements in the quality of MRI, which would enable a better visualization of spinal cord lesions.[14] In the majority of the cases, more than 4 segments were affected,[10,14] and the lesions viewed with MRI were continuous or patchy.[15] Cervical and mid-thoracic segments (T5–T8) were found to be those most widely affected.[6] Although it normally develops in cases of SLE in which there are high indices of activity, up to one third occur with low or no activity.[15]

From the clinical point of view, the most common manifestations (80%–90%) are sensory and motor deficits and urinary sphincter dysfunction. The level of impairment is variable: it can