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Original article

Myelopathy in systemic lupus erythematosus: clinical, laboratory, radiological and progression findings in a cohort of 1,193 patients

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ABSTRACT

Objective: To describe clinical, laboratory, radiological and progression characteristics of myelopathy in systemic lupus erythematosus (SLE).

Patients and methods: A retrospective analysis was performed on a cohort of 1193 patients with SLE (ACR criteria) in order to identify patients with myelopathy (neuropsychiatric ACR). Disease activity was assessed by the SLE activity index (SLEDAI) on the date of the event and functional capacity was assessed by the Expanded Disability Status Scale (EDSS) at the last visit.

Results: We identified 14 (1.2%) patients with myelopathy. All were women with a mean age of 30 ± 11.5 years. Myelopathy occurred at the diagnosis of SLE in four (28%) patients; and nine (64%) patients had another type of neuropsychiatric manifestation associated. Neurological recurrence was observed in one (7%) patient. Disease activity was observed in 2 (14%) patients. Cerebrospinal fluid presented pleocytosis on 7 (53%) patients; antiphospholipid antibodies were positive in 5 (45%). Magnetic resonance imaging (MRI) showed T2 hyperintensity with a predominance of longitudinal involvement in 6 (86%) patients. Most were treated with intravenous corticosteroids and cyclophosphamide. No patient had full recovery and four (36%) had high EDSS scores. Three (21%) patients died from sepsis early in the course of their myelopathy, during or after immunosuppressive therapy.

Conclusions: Myelopathy occurred in 14 (1.2%) of the patients in our cohort and this may be the first manifestation of the disease occurring independently of systemic disease activity. Although rare, myelopathy shows great morbidity and mortality, can be recurrent and MRI is critical for diagnosis.

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Mielopatia no lúpus eritematoso sistêmico: achados clínicos, laboratoriais, radiológicos e evolutivos em uma coorte de 1.193 pacientes

Palavras-chave:
Lúpus eritematoso sistêmico
Mielopatia
Mielite transversa
Ressonância magnética

RESUMO

Objetivo: Descrever características clínicas, laboratoriais, radiológicas e evolutivas de mielopatia no lúpus eritematoso sistêmico (LES).

Pacientes e métodos: Foi realizada análise retrospectiva de uma coorte de 1193 pacientes com LES (critérios ACR), para identificar os pacientes com mielopatia (ACR neuropsiquiátrico). A atividade de doença foi analisada pelo Índice de Atividade do LES (SLEDAI) na data do evento e a capacidade funcional pela Escala Expandida do Estado de Incapacidade (EDSS) na última consulta.

Resultados: Foram identificados 14 (1,2%) pacientes com mielopatia. Todas eram mulheres com média de idade de 30 anos (DP ± 11,5 anos). A mielopatia ocorreu no diagnóstico do LES em quatro (28%) e em nove (64%) havia outro tipo de manifestação neuropsiquiátrica associada. Recorrência do quadro neurológico foi observado em uma (7%) paciente. Atividade de doença foi observada em 2 (14%) pacientes. O líquido cefalorraquidiano apresentava pleocitose em 7 (53%) pacientes anticorpos antifosfolípides eram positivos em 5 (45%). A ressonância magnética (RM) demonstrou hipersinal em T2 com predomínio do comprometimento longitudinal em 6 (86%) pacientes. A maioria foi tratada com corticosteroides e ciclofosfamida endovenosos. Nenhuma paciente teve completa recuperação e quatro (36%) tinham escores altos da EDSS. Óbito foi observado em 3 (21%) durante episódio de mielopatia, por septicemia durante ou após terapia imunossupressora.

Conclusões: A mielopatia ocorreu em 14 (1,2%) dos pacientes da nossa coorte e pode ser a primeira manifestação da doença ocorrendo independentemente de atividade sistêmica da doença. Embora rara, é de grande morbimortalidade, pode ser recorrente e a RM é fundamental para o diagnóstico.

Introduction

Neuropsychiatric manifestations in systemic lupus erythematosus (SLE) have an important impact on the prognosis of the disease by their frequency and severity.[1] Myelopathy is a manifestation of the central nervous system (CNS) that occurs only rarely in SLE, affecting about 1–2% of patients.[1–3]

In 1999, the American College of Rheumatology (ACR) established the criteria of neuropsychiatric manifestations in SLE, including myelopathy. This possibility should be considered if the patient shows a rapid progression (hours or days) of one or more of the following signs/symptoms: bilateral muscle weakness in lower limbs, with or without involvement upper limbs; a sensory disorder with similar level of motor impairment, with or without bowel or bladder involvement. Expansive injury causing spinal cord compression and *cauda equina* injury should be ruled out.[4]

In 2002, the Transverse Myelitis Consortium Working Group proposed diagnostic criteria for idiopathic transverse myelitis, defined with the clinical manifestations described above, associated with inflammation within the spinal cord demonstrated by cerebrospinal (CSF) pleocytosis or increased IgG index or gadolinium enhancement in magnetic resonance imaging (MRI).[5]

Myelopathy may present as a transverse myelopathy with sectional involvement of one level of the spinal cord, or as a longitudinal myelopathy in which more than three segments are affected, continuously or not.[6]

The term myelitis is still used by many authors; however, myelopathy is more suitable to characterize spinal cord changes associated with inflammatory diseases such as SLE, this being the nomenclature recommended by ACR.[4]

The cause of myelopathy in SLE is not well understood and the participation of both thrombosis and vasculitis have been implicated in this process.[3] Some authors suggest that there is a relationship between antiphospholipid antibodies and myelopathy, which would augment the possibility of thrombosis; but other studies do not confirm this association.[7–10]

Although rare, thanks to its importance this condition was recently included in the new classification criteria of the disease.[11] The literature only presents case reports, with the publication of case series only by a few authors.[8,10,12–19]

The aim of this study is to describe cases of myelopathy in SLE, from a cohort of a single university hospital, describing their clinical picture, laboratory results, imaging findings on MRI of the spinal cord, treatment and outcome.

Patients and methods

Medical records of a cohort of 1193 patients with SLE,[20] followed at the Rheumatology outpatient clinic of the Hospital das Clínicas, Universidade Estadual de Campinas (UNICAMP) were analyzed retrospectively.

Patients with myelopathy were identified by the presence of acute clinical manifestations suggestive of spinal cord

injury, and of sensory and motor changes, sphincter dysfunction, or a combination of these, and changes consistent at the neurological examination.[4,5] Patients with other causes of myelopathy such as compression, trauma, malignancies and infections were excluded. Information on demographics, clinical data of SLE disease duration of the myelopathy episode, adjuvant tests, including imaging studies, auto-antibodies and cerebrospinal fluid screening were collected. Disease activity was analyzed by the Systemic Lupus Erythematosus Disease Activity Index – SLEDAI[21] on the day of the event, when data for application were available, considering disease activity if SLEDAI ≥6, discrete activity when SLEDAI <6, and inactivity when SLEDAI = zero.

Information about prescribed treatment and progression of these patients were also collected. To evaluate the functional capacity after myelopathy, the Expanded Disability Status Scale (EDSS) of Kurtzke, applied in the last follow-up visit, was used.[22] This is a method used to quantify disability occurring during progression and over time.

Ethical aspects

Authorization of the Research Ethics Committee – FCM UNICAMP was obtained for use of data from patients' medical records (Opinion of the Ethics Committee of FCM-UNICAMP: NO 920/2007).

Results

Fourteen of 1193 (1.2%) SLE patients with myelopathy, all females and Caucasian, with a mean age at the onset of myelopathy of 30 ± 11.5 years and mean disease duration at the time of myelopathy of 4 ± 5.2 years (Table 1) were identified.

Table 1 shows the cumulative clinical manifestations of SLE until the time of the study. In four of 14 (28%) patients, myelopathy was the initial manifestation. In one (7%) patient, the diagnosis of SLE was confirmed only two years and 3 months after the spinal cord manifestation.

The initial symptoms of these 14 patients included urinary retention in 10 (71%), paraplegia in 7 (50%), fever in 6 (42%), paraparesis in 3 (21%) and paresthesia in 2 (14%). Nine (64%) patients had already had other neuropsychiatric symptoms before the myelopathy, three (21%) patients with a clinical picture of psychosis, two (14%) with seizure, one (7%) with headache, and one (7%) with cerebrovascular disease (stroke). Two (14%) patients also had optic neuritis (ON). One (7%) of these patients had severe bilateral optic neuritis many years after her clinical picture of myelopathy, which was confirmed by visual evoked potential changes, without evidence of demyelinating disease on brain MRI, with a negative result for anti-aquaporin 4 antibody. The other patient had recurrent neuromyelitis optica (NMO) and was positive for anti-aquaporin 4 antibody; and SLE was confirmed 3 years and two months later, when nephritis, lymphopenia, and positivity for antinuclear antibody and anti-DNA were noticed. In these patients we could not perform other autoantibodies such as anti-MOG and anti-aquaporin I, but demyelinating causes were ruled out, and the clinical picture of both of them was attributed to SLE.

Only two (14%) patients had nephritis, one of them concurrently with myelopathy. Six patients had some type of hematological abnormality during the course of SLE.

Two (14%) patients had disease activity during the episode of myelopathy, that is, SLEDAI ≥6; in one (7%) patient SLEDAI was not applied on this occasion, since the diagnosis of SLE had not been confirmed; in three (21%) patients there was no data available for the calculation of SLEDAI. In another 8 (57%) patients SLEDAI was <6, thus with mild disease activity. Only one (7%) patient had no active disease (Table 1). In these 10 patients in whom it was possible to apply the activity index, a SLEDAI score was obtained because of fever in 3 (30%), low complement levels in 9 (90%), anti-DNA positivity in 5 (50%), psychosis in 1 (10%), nephritis in 1 (10%), thrombocytopenia in 1 (10%) and leukopenia in 1 (10%).

Table 2 shows the additional tests performed during the episode of myelopathy. All patients had positive tests for antinuclear antibodies (ANA). Anti-DNA and anti-Sm antibodies were positive in 6 of 13 (46%) patients who were thus examined, and antiphospholipid antibodies were positive in 5 of 11 (45%) patients submitted to this test. Ten in eleven (90%) patients who were examined at the time of the myelopathy had decreased complement levels.

A cerebrospinal fluid (CSF) test was performed in all (100%) patients with normal results in seven (53%). In six (46%) patients, pleocytosis with lymphocyte predominance was noted. The cultures were negative in all 14 (100%) patients. Full details of CSF of one patient were not available, although this test had been conducted.

Seven (50%) patients were examined by MRI. The other 7 patients did not perform the test, and in four (28.5%) MRI was not conducted due to lack of this resource in our Unit at the time of myelopathy. In these latter patients, myelography was performed in order to rule out other causes, with normal results in all these women. The other three (21.5%) patients died without having been able to perform MRI, because there was no clinical stability for performing this test.

Upon the clinical episode, all patients underwent spinal cord MRI in a closed-field device. In 6 (86%) cases, patients had longitudinal lesions with hyperintensity in T2 fast spin-echo sequences, with extension to 4 or more vertebral levels (Fig. 1) and in only one (14%) of these patients the examination was performed at 3 levels (Table 2). There was predominantly thoracic involvement in 6 (85%) of these cases, in 4 (57%) of them with high thoracic levels. A spinal cord swelling effect was noted in 2 (28%) cases, and one (14%) of these patients also showed contrast enhancement. As for contrast uptake, only 2 (28%) patients showed enhancement at the same level of signal exchange in pre-contrast sequences (Fig. 2). In our cases, it was not possible to differentiate between white *versus* gray matter involvement.

With regard to treatment, eight (57%) patients were treated with a combination of pulse therapy with methylprednisolone (MP) followed by intravenous (IV) cyclophosphamide; four (28%) patients used only MP pulse therapy; and two (14%) received oral corticosteroids at high doses, together with azathioprine. All patients were treated within the first hours, or until 4 weeks after the onset of symptoms.

Table 1 – SLE: demographic, clinical, and disease activity data of 14 patients with myelopathy.

Patients ($n = 14$)	Race	Age (years)	Symptoms	SLE duration (years)	Previous NPSLE	Cumulative clinical manifestations[a]	SLEDAI
1	Br	31	Urinary retention/paraparesis	8	Absent	Arthritis/photo/leukopenia/APS	4
2	Bl	40	Urinary retention/paraplegia	2	Absent	Arthritis/leukopenia/thrombocytopenia	0
3	W	29	Difficulty in walking/tactile hypoesthesia	3	Psychosis	Arthritis/malar rash/photo	2
4	W	42	Urinary retention/flaccid tetraparesis	0	Seizure	Malar rash/photo/oral ulcers	2
5	Br	42	Fever/urinary retention/paraplegia	2	Psychosis	Arthritis/malar rash/photo/leucopenia	NA
6	W	19	Urinary retention/paresthesia	6	Stroke	Arthritis/malar rash/photo/thrombocytopenia	3
7	Br	20	Fever/urinary retention/paraplegia	9	Absent	Arthritis/malar rash/photo/nephritis	17
8	W	18	Paraparesis	1	Absent	Arthritis/malar rash/photo/serositis/lymphopenia	3
9	NA	16	Paresthesia/difficulty in walking	NAp	Optic neuritis	Nephritis/lymphopenia	[b]
10	W	9	Fever/urinary retention/paraplegia	1	Optic neuritis	Arthritis/malar rash/photo/pericarditis	3
11	Br	45	Fever/urinary retention/paraplegia	0	Psychosis, stroke	Arthritis/discoid/photo/leucopenia	13
12	W	31	Fever/urinary retention/paraplegia	0	Headache	Arthritis/alopecia	NA
13	Br	41	Paraparesis	16	Seizure and plexopathy	Arthritis	4
14	W	30	Fever/urinary retention/paraplegia	13	Absent	Malar rash/photo/hemolytic anemia	NA

SLE, systemic lupus erythematosus; NPSLE, neuropsychiatric systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; APS, antiphospholipid syndrome; Br, brown; W, white; Bl, black; photo, photosensitivity; NA, not available; NAp, not applicable.

[a] Cumulative until the date of the study.

[b] No diagnosis of SLE available at the time of myelopathy.

Table 2 – Laboratory tests and imaging findings on MRI of 14 SLE patients with myelopathy.

Patients ($n = 14$)	Anti-DNA	Complement	Anti-phospholipid (LA, aCL, β2)	Other antibodies	Imaging findings on spinal cord MRI (T2 FSE)	CSF
1	+	↓	aCL + LA+	–	NA	Normal
2	–	Normal	–	Anti-Sm +	Longitudinal hyperintensity from C7 to T9, poorly defined, predominantly in GM, mild swelling, without contrast enhancement	Pleocytosis (lymphocytes)
3	–	↓	–	–	Longitudinal hyperintensity from T1 to T6, causing tapering without contrast enhancement	Normal
4	–	↓	LA+	Anti-Sm, anti-Ro and anti-LA +	Longitudinal hyperintensity from C7 to T1, focal contrast enhancement in C7	Normal
5	–	NA	ND	–	NA	Normal
6	+	↓	LA+	–	NA	Pleocytosis (lymphocytes)
7	+	↓	–	Anti-Sm +	Longitudinal hyperintensity from C5 to T2, centromedular region, without contrast enhancement	Pleocytosis (lymphocytes)
8	–	↓	β2 +	–	Longitudinal hyperintensity from T1 to T12 and lumbar area, centromedular region without contrast enhancement	Pleocytosis (lymphocytes)
9	NA	↓	aCL+ LA+	Anti-AQP4 IgG+	Hyperintensity in the bulb, cerebellar peduncle and spinal cord through C5, affects WM and GM, w/o swelling, w/o contrast enhancement	NA
10	–	↓	–	Anti-Sm+	NA	Pleocytosis
11	+	↓	ND	Anti-Sm+	NA	Pleocytosis (lymphocytes)
12	–	NA	ND	–	NA	Pleocytosis (lymphocytes)
13	+	↓	–	Anti-Sm+ and anti Ro +	Longitudinal hyperintensity from T11 to L1 with discrete swelling effect, with focal contrast enhancement	Normal
14	+	NA	–	–	NA	Normal
[a]	6/13 (45%)	10/11 (90%)	5/11 (45%)	Anti-Sm 6/13 (46%)	7/7 (100%)	7/13(53%)

SLE, systemic lupus erythematosus; CSF, cerebrospinal fluid; NA, not available; ND, not done; aCL, anticardiolipin antibody; LA lupus anticoagulant; β2, anti-beta 2 glycoprotein I antibody, anti-AQP4 IgG, anti-aquaporin 4; WM, white matter; GM, gray matter; MRI, magnetic resonance imaging, T2 FSE, T2 fast spin-echo sequence

[a] Ratio between number of changes and tests performed.

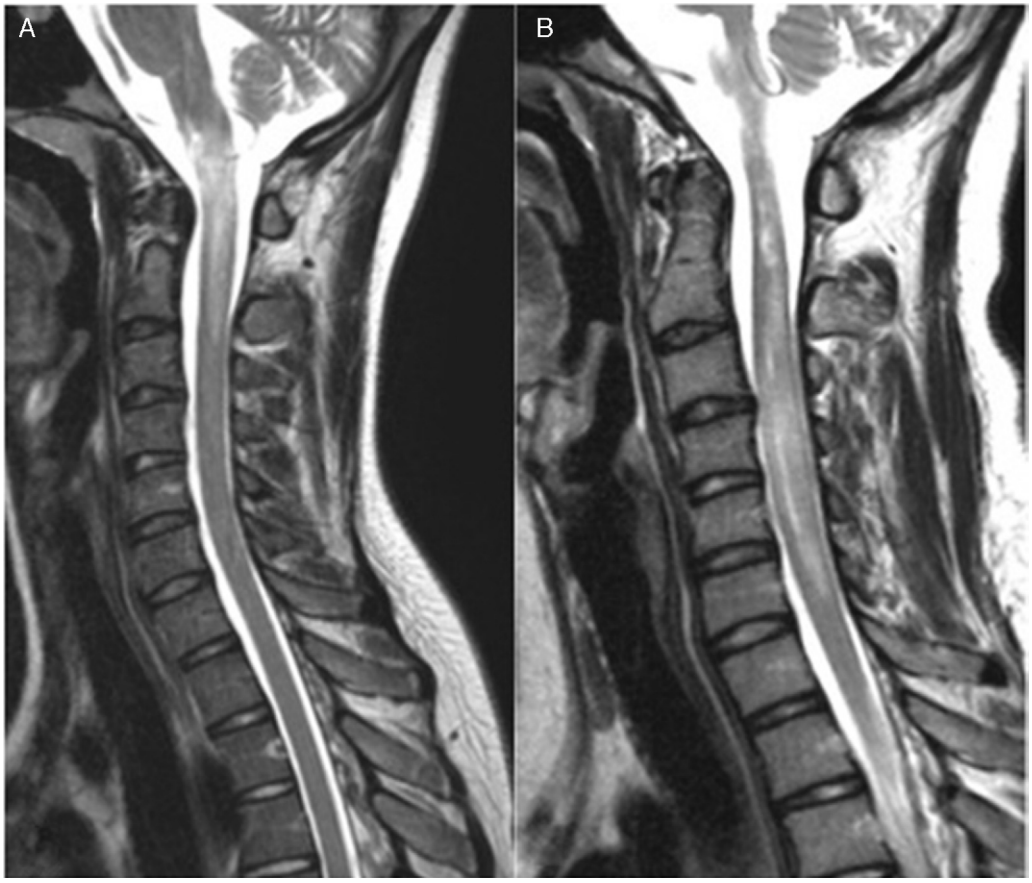

Fig. 1 – Sagittal T2-weighted images showing hyperintensity in spinal cord, extending from the bulb to C3 in the first episode (A) and hyperintensity and increased spinal cord volume extending to C5 in the second episode, seven months after the first one (B).

Upon the application of EDSS after a mean follow-up of 11.5 ± 10.4 years, it was observed that all 11 (78%) patients in which it was possible to apply this scale had some degree of disability, whose score ranged from 3 to 8, *i.e.* from patients able to walk but with some degree of disability, to patients with neurogenic bladder requiring wheelchair use. No patient obtained a full recovery.

Three (21%) deaths occurred during the myelopathy manifestation, caused by a widespread infection that occurred during or shortly after the immunosuppressive therapy prescribed for treatment of myelopathy in all three cases.

Table 3 lists treatment, monitoring and progression data.

Table 4 shows the relevant series of cases of myelopathy in SLE which have been published in English language, including the present series, with information on MRI findings. Twelve case series are presented, with results showing 4–22 patients and their demographic, respective clinical and laboratory characteristics and MRI, treatment and outcome data. Disease activity, recurrence of episodes and the presence of other neuropsychiatric symptoms, in addition to the occurrence of myelopathy as the first manifestation of the disease, are also highlighted in this table, whenever mentioned by their authors.

Table 3 – Treatment, monitoring and progression of 14 patients with SLE and myelopathy.

Patients	Treatment	Follow-up	EDSS
1	IV MP and IV CYC	6 years	5.5
2	IV MP and IV CYC	14 years	3
3	CS and AZA	15 years	6
4	IV MP and IV CYC	22 years	7.5
5	IV MP	3 years	6
6	IV MP and IV CYC	2 months	Death
7	IV MP E IV CYC	4 months	3.5
8	IV MP and IV CYC	12 months	6
9	IV MP, IV CYC, IVIG and MMF	3 years	3
10	IV MP	24 years	8
11	IV MP	2 months	Death
12	CS and AZA	1 year	8
13	IV MP and IV CYC	2 years	8
14	IV MP	8 years	Death

SLE, systemic lupus erythematosus; EDSS, Expanded Disability Status Scale; IV MP, intravenous methylprednisolone; IV CYC, intravenous cyclophosphamide; AZA, azathioprine; IVIG, intravenous immunoglobulin; CS, oral corticosteroids; MMF, mycophenolate mofetil.

Table 4 – Case series of myelopathy in SLE.

Case series	*n*	Age at diagnosis of myelopathy (years)	Gender	Race	SLE duration	Myelopathy as the first manifestation (*n*)	Active SLE	Previous NPSLE
Salmaggi et al.[12]	5	18–46	F (5)	NA	2–5 years[a]	2	0	Absent
Provenzale et al.[13]	4	33–47	F (4)	NA	NA	1	NA	Absent
Harisdangkul et al.[14]	7	16–52	F (7)	NA	3 months to 4 years	4	2	Absent
Kovacs[10]	14	23–77	F (12) M (2)	NA	0–21 years	6	NA	D(2)/ON(3)/OS(1)
Telles-Zenteno[15]	6	23–37	F (6)	NA	7 months-16 years	0	3	NA
D'Cruz[8]	15	21–68	F (15)	NA	0 years[a]	15	15	Absent
Lu[23]	14	15–45	F (12) M (2)	A(14)	2 months to 20 years	1	14	ON(3)/ICH(1) E(1)/OS(1)/HL(1)
Birnbaun[16]	22	15.5–48.1 (GM) and 16.6–70.5 (WM)	F (20) M (2)	AA(8)/W(9)/other (5)	5.4–6.5 years	6	11 (GM) and 6 (WM)	ON(6)
Espinosa[17]	22	12–53	F (17) M (5)	NA	0–17 years	5	NA	CHO(3)/CE(1)/AM(1)
Schultz[18]	15	22–78	F (14) M (1)	AA(8)/W(7)	NA	15	NA	ON (2)
Saison[19]	20	22.9–67.3	F (17) M (3)	W (12)/AA(2)/A(3)/NA(3)	0–36 years[a]	8	20	ON(4)/SE(1)
Costallat et al. (2015)	14	9–42	F (14)	W(7)/AA(2)/Br(5)	0–16 years[a]	4	8	ON(2)/SE(2)/OS (3)[c]/CVA (1)/HE(1)/PLE (1)[b]

Complement↓ (%)	APL+ (%)	CSF findings	Spinal cord MRI (T2 FSE)	Treatment	Recurrence (%)	Progression
40	20	Oligoclonal bands (1)	Longitudinal hypersignal (2)/N (3)	IV MP (4)/1 CS(1)	60	CR(3)/PR(2)
NA	NA	NA	Hypersignal (4)	IV MP(4)/IV CYC (2)	75	NA
NA	NA	NA	Longitudinal hypersig-nal(3)/ND(4)	IV MP(4)/CS(3)	43	CR(2)/ND(2)/DEATH(4)
50	54	NA (8)/N (2)/↑protein (4)	Changed (9)/N (5)	IV CYC (9)/P(4)	NA	CR (3)/PR(2)/UR(9)
50	66	↑protein (2)	Longitudinal hypersignal(6)	IV MP(6)/IV CYC (5)	50	5 w/oR (5)/PR(1)

Table 4 – (*Continued*)

Complement↓ (%)	APL+ (%)	CSF findings	Spinal cord MRI (T2 FSE)	Treatment	Recurrence (%)	Progression
NA	73	Pleocytosis (2)/N (13)	Changed (11)/N (2)/ND(1)	IV MP(7)/CS (6)/AZA (6)	6	CR(6)/PR(9)
28	11	Pleocytosis (6)	Longitudinal hypersignal(6) focal(5)/N(1)/ND(2)	CS(14)/IV CYC (2)/P(1)	7	R(4)
NA	54	Pleocytosis (GM)	Longitudinal hypersignal 92% (GM) and 74% (WM)	GM group, more aggressive therapy	9 (GM) and 73(WM)	GM group, more disability (mean of EDSS > in GM group)
74	50	Predominance of pleocytosis	Longitudinal hypersignal (22)	IV MP(22)/IV CYC (13)/IV IG(4)/P(4)/RTX (2)	18	CR(3)/PR(13)/w/oR(6)
87	11	↑protein	Predominance of focal lesion	IV MP(14)/IV CYC (2)/P(1)	NA	NA
87	45	Pleocytosis (5)	Longitudinal hypersignal(9)/N (3)	IV MP (18)/IV CYC (11)/IV IG(2)/P(3)/RTX(3)	50	CR(5)/PR(12)/w/oR(1)/O(1)
90	45	Pleocytosis (7)/N (6)	Longitudinal hypersignal(7)	IV MP(12)/CS (2)/IV CYC (10)/AZA(1)	7	CR(0)/PR(7)/w/oR(4)/DEATH(3)

SLE, systemic lupus erythematosus; NPSLE, neuropsychiatric systemic lupus erythematosus; APL, antiphospholipid antibody; CSF, cerebrospinal fluid; FSE T2, T2 fast spin-echo sequence; F, female; M, male; AA, African American; Br, brown,; A, Asian; W, white; NA, not available; ND, not done; N, Normal; GM, gray matter; WM, white matter; CHO, chorea; CE, cerebritis; HE, headache; SE, seizure; AM, aseptic meningitis; ICH, intracranial hemorrhage; HL, hearing loss; PS psychosis; PLE, plexopathy; E, epilepsy; ON, optic neuritis; D, depression; CVA, stroke; IV MP, intravenous methylprednisolone; IV CYC, intravenous cyclophosphamide; AZA, azathioprine; IVIG, intravenous immunoglobulin; CS, corticosteroids; P, plasmapheresis; RTX, Rituximab; CR, complete remission; PR, partial remission; R, remission; w/oR without remission.

[a] With cases of myelopathy preceding SLE.
[b] With seizure.
[c] With stroke.

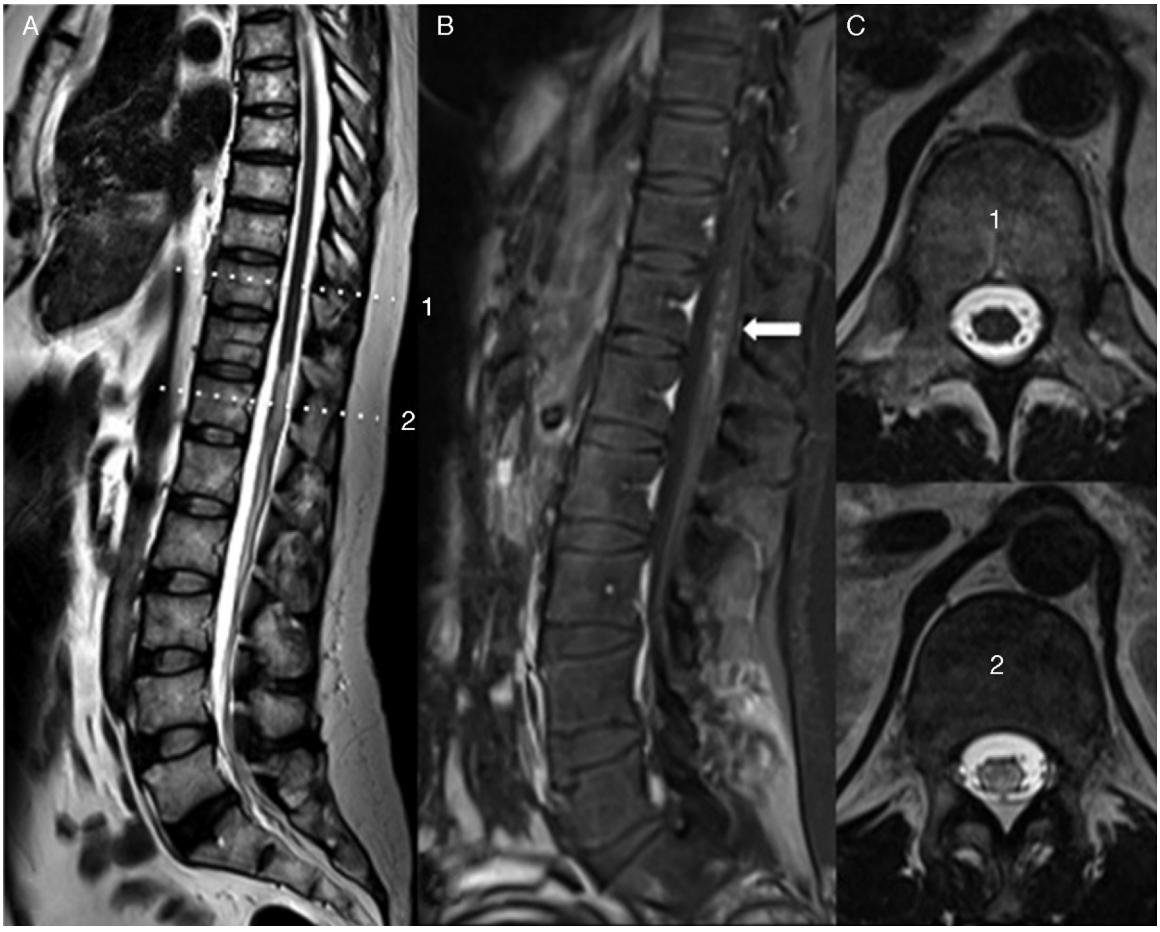

Fig. 2 – Sagittal T2-weighted image, showing hyperintensity and mild enlargement of spinal cord volume, extending from T11 to the medullary cone. B, T1-weighted sagittal image after contrast injection, with foci of medullary enhancement (arrow) extending from T11 to L1. C, Axial T2-weighted images demonstrating the spinal cord with a normal signal obtained at the T10 level (1) and spinal cord with hyperintensity obtained at the level of T12 (2).

Discussion

Myelopathy is one of the most rare neuropsychiatric manifestations in SLE, affecting about 1–2% of patients, but this condition is very relevant, thanks to its high morbidity and mortality and has been included in the new SLE criteria.[11]

Our 14 patients represented 1.2% of the cohort of 1193 patients with SLE, a percentage similar to that observed in previous studies.[1,2]

All patients were female, as noted by all authors and in line with the gender profile of this disease.[8,10,12–19,23] Myelopathy can affect individuals of all ages; our patients had a mean age of 30 years – a lower mean than that observed by other authors,[8,10,12,13,15,17–19,23] and similar to those described in two series.[14,15] As for the race, there is no reference to a higher prevalence of this manifestation in any ethnic group, and many authors have not highlighted this demographic characteristic. However, Schutz et al., in a comparison of myelopathy in SLE *versus* idiopathic myelopathy, comment the highest frequency of African–American women with SLE, but this fact can be attributed to the prevalence of the disease itself in that area.[18]

Initial symptoms are nonspecific and may include a short viral prodrome: fever, photophobia, nausea, vomiting, dizziness and nuchal pain. Subsequently, sensory and motor changes and sphincter dysfunction can occur, and its onset can take hours, days or even weeks. Our myelopathy patients presented with urinary retention and fever, which was initially confused, in some cases, with urinary tract infection. The spinal cord injury clues were paresthesia, walking difficulties, paraplegia and sphincter dysfunction, with sudden onset within hours or days.

In a systematic review of 22 cases reported in the literature by Espinosa et al., the authors observed in 23% of cases a prodromal picture of fever, cough, flu and constitutional symptoms a few days before the onset of myelopathy,[17] which was observed also by Harisdangkul et al.[11] The presence of fever and urinary retention was associated with an irreversible paraplegia, according to Birnbaum et al.[16]

Myelopathy may be the initial manifestation of SLE, as happened with four of our patients; and this fact was noted by all authors listed in Table 4, with the exception of Tellez-Zenteno

et al.[15] Some authors consider that when myelopathy occur in SLE, this can be an initial manifestation in up to 39% of patients within the first five years.[10] By analyzing the series of reported cases (Table 4), and taking into account the time point where the myelopathy may arise during the progression of SLE, we can observe the occurrence of a variable percentage for the duration of SLE, and there are cases in which the patient already had SLE for 36 years before the onset of myelopathy.[19] It is also possible that myelopathy arises before SLE; this happened in one case in our series, in which the patient presented with spinal cord manifestations 2 years and 3 months before her diagnosis of SLE. All 15 cases described by D'Cruz et al.[8] were affected by myelopathy as the initial manifestation of SLE, and only 4 (26%) met ACR criteria for SLE at the onset of myelopathy. Of the five cases of Salmaggi et al.,[12] in two patients myelopathy preceded SLE, and the same occurred with 4 (20%) of 20 cases of a French multicenter study. In this French study, two cases had myelopathy for more than 10 years before the establishment of a diagnosis of SLE.[19] Salmaggi et al.[12] concluded that in women with myelopathy of unknown etiology, exhaustive clinical and laboratory assessments are critical to try to define SLE.

Although myelopathy in SLE can be recurrent,[6,10] in our series 13 (93%) patients had a single episode of this condition; and only one (7%) patient experienced recurrence. Recurrence was observed in many case series, in some of them with high frequency (50–75%) as emphasized in Table 4.[8,10,12–19,23] This significant possibility of recurrence imposes the need for the implementation of a maintenance immunosuppressive treatment for these patients, in an attempt to prevent further crises.

Other neuropsychiatric manifestations have been correlated to the presence of myelopathy in SLE[10]; in our series such events occurred in nine (64%) patients. In most cases, neuropsychiatric involvement was an integral part of the clinical history of the disease, but without a simultaneous occurrence, with the exception of one of the patients who had major manifestation of psychosis concomitantly with spinal cord symptoms, and this patient died after immunosuppressive therapy. Two (14%) patients had optic neuritis. Optic neuritis is a neuropsychiatric manifestation often associated with myelopathy, also known as Devic disease or neuromyelitis optica (NMO), and this condition was reported in some of the series of cases presented in Table 4. For some authors, the association with optic neuritis may be present in 21–48% of cases of myelitis in SLE.[10,16,23] Neuromyelitis optica recurrence has been described in patients positive for anti-aquaporin-4 antibody (anti-AQP4 IgG).[24] One of our patients showed NMO associated with positivity for anti-aquaporin 4 antibody, being the only case with a recurrent picture of myelopathy. Another patient with NMO developed bilateral optic neuritis many years after myelitis, which was confirmed by visual evoked potential test, although anti aquaporin-4 antibody was negative, which can occur in NMO cases. In both cases, the possibility of demyelinating disease was ruled out, and these manifestations have been attributed to SLE.

The occurrence of myelopathy may be associated with disease activity. In our series, two patients had active disease (one with nephritis and the other with psychosis) and one patient showed inactive disease; the remaining cases exhibited mild disease activity. Some patients had no clinical and laboratory data to allow calculation of this index; and SLEDAI was not applied in one patient because at the time of emergence of myelopathy the diagnosis of SLE had not yet been confirmed. Some authors highlight the fact that in one third of cases myelopathy can occur in a scenario of inactive disease.[25] That is important, because in the face of a relevant clinical picture, one should always consider myelopathy, regardless of SLE activity. As for the other authors of the case series presented in Table 4, not everyone recorded data on disease activity.

With respect to other tests, complement was reduced in 10 (90%) patients of our cases, in some cases accompanied by other laboratory changes, and in three cases this was the only punctuation on SLEDAI score.

Antiphospholipid antibodies have been associated with myelopathy in SLE[7,10]; in our series, we found these antibodies in 5 (45%) of cases, just as observed by Saison et al.[17] But only one (7%) of our patients fulfilled the antiphospholipid syndrome (APS) criteria. Other authors have found variable percentages, between 11% and 73% of cases, as shown in Table 4. According to Birnbaum et al.,[16] antiphospholipid antibodies can be important in the pathogenesis of neuromyelitis optica. In an extensive systematic review by Katsiari et al. on the occurrence of these antibodies in cases of transverse myelitis and the use of anticoagulation in the presence of myelopathy, these authors concluded that, while antiphospholipid antibodies may have a role in the pathogenesis of myelopathy, the mere presence of these antibodies is not sufficient to indicate the anticoagulation therapy.[26]

The findings of the cerebrospinal fluid analysis are nonspecific. Some authors found increased cellularity and also proteinorrhachia,[18,23] but often the CSF is normal in patients with myelopathy.[7,10,27] In our series, CSF was collected in all (100%) patients, and the most frequent change was pleocytosis (53%), with lymphocyte predominance.

Magnetic resonance imaging is the most sensitive imaging tool in the evaluation of spinal cord injuries, including in myelopathy associated with SLE. The examination protocol for MRI images should cover the level corresponding to neurological damage observed on clinical examination, but it is strongly recommended to study the entire cord. The imaging findings may vary, with an emphasis on the T2 hyperintense signal on spinal cord, the effect of swelling in cases of spinal cord edema, and also the contrast uptake. Among these findings, the most common is the signal change, as was also observed in our study. We must bear in mind that in some cases, MRI may be normal, especially in the early stages.[8,10,12] In cases where the MRI imaging with contrast is normal, it is recommended that the test be repeated 2–7 days after the initial manifestation.[5]

It is important to note that CT should not be used for diagnosis of myelopathy because of its low sensitivity. This technology should be used in cases where the MRI is unavailable, and only to exclude compressive causes of the spinal cord.[5]

The thoracic region is the most frequently affected part, which also occurred in our patients.[10,23] This may be attributed to the type of blood supply that nourishes the region, with emphasis for the branches of the longitudinal arteries that are less large in the thoracic region when compared to the cervical or lumbar region; this implies limitation

in the vascular supply, as concluded by Kovacs et al.[10] In recent years, with the improvement in the quality of images and equipment, an increase in the identification of longitudinal spinal cord injuries was noted in cases of myelopathy in SLE examined by MRI – a fact also observed in most of our patients.[15,18]

Birnbaum et al. compared patients with lesions in spinal cord white matter (spasticity and hyperreflexia) *versus* patients with lesions in the gray matter (flaccidity and hyporeflexia). These authors concluded that the lesions in the gray matter are associated with irreversible paraplegia and greater disease activity.[16] We could not make this distinction in our patients.

While being very important for the diagnosis of these patients, MRI does not seem to have much use for their follow-up, because there is no clinical correlation after treatment in the initial stages.[18] As for the prognosis, there seems to be a worse prognosis in patients with changes in MRI in the beginning of the process, when compared to patients with normal MRI,[10] especially in those cases with presence of extensive lesions.[15]

The treatment of myelopathy should be instituted immediately after the diagnosis, as this manifestation has a poor prognosis, with high morbidity in up to 50% of cases[10,23] and with high mortality. Delayed institution of an appropriate treatment was the unfavorable outcome factor noted by all authors selected. The combination of intravenous pulses of methylprednisolone and cyclophosphamide is considered the treatment of choice for such patients.[6,27] According to Saison et al.,[19] the use of hydroxychloroquine decreased the neurological flares in cases of myelopathy in SLE, although this finding was not statistically significant. In some cases it is necessary to use intravenous immunoglobulin, plasmapheresis and rituximab,[28] especially in unresponsive or recurrent cases; but the response vary. Twelve (85%) of our patients received pulse MP and 10 (71%) received IV cyclophosphamide within one month of the onset of symptoms. Our unique case of recurrence was treated, along the disease progression, with IV immunoglobulin and mycophenolate mofetil (MMF). None of our patients achieved full recovery. The evaluation of these patients by EDSS resulted in scores of 7.5–8 in four of them, that is, patients with walking difficulties and requiring the use of a wheelchair, besides a neurogenic bladder. All four (28%) patients used MP pulse at high doses, and two (14%) of them were also medicated with IV cyclophosphamide; but even then the outcome was not favorable, perhaps because not all of them have used both medications within two weeks after the onset of the manifestation. In our group, three (21%) deaths occurred, all caused by an infection during or shortly after immunosuppressive therapy for treatment of myelopathy. This reinforces the seriousness of this manifestation.

The prognostic factors of myelopathy are not fully known, but sphincter dysfunction,[16,23] MRI changes,[10,16] involvement of gray matter (flaccidity and hyporeflexia),[16] and initial severity with paraplegia[19] are cited as poor prognostic factors. Muscle strength ≥grade 3 at the time of hospitalization and an aggressive therapy instituted no later than two weeks after the episode of myelopathy are better prognostic factors.[23] In summary, myelopathy in SLE is very rare, but also very serious. It occurred in 14 (1.2%) of our patients. Myelopathy may be the first manifestation of the disease, can occur after many years of an installed SLE, or may even precede the disease. Although rare, myelopathy has high morbidity and mortality and may be present, regardless of disease activity. Moreover, it can be recurrent and therefore it is recommended a maintenance immunosuppressive therapy so that new episodes are prevented. MRI is essential for diagnosis, but this examination may be normal in very early stages.

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Conflicts of interest

The authors declare no conflicts of interest.

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