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Spinal Cord Syndromes in Patients with Systemic Lupus Erythematosus: Differentiating Lupus Myelitis, Neuromyelitis Optica, and Multiple Sclerosis

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Abstract

Objective—Non-infectious myelitis in SLE may be due to SLE myelitis, comorbid multiple sclerosis (MS), or neuromyelitis optica (NMO). We compared characteristics of these three conditions in SLE patients at a large academic institution.

Methods—We searched for neurologic diagnoses of SLE myelitis, NMO myelitis, and MS myelitis among 2,297 patients with at least four 1997 ACR revised criteria for SLE between 2000 and 2015. Each subject was reviewed by a neurologist to confirm the underlying neurologic diagnosis. Demographic, clinical, laboratory, and radiographic data were extracted and compared using Fisher's exact test, analysis of variance, and Wilcoxon rank-sum test.

Results—Fifteen of the 2,297 subjects with SLE (0.7%) met criteria for a spinal cord syndrome: seven had SLE myelitis, three had AQP4 seropositive NMO, and five had MS. The median SLEDAI-2K score at time of neurologic syndrome presentation was higher in SLE myelitis subjects (8, IQR 7–16) compared to subjects with NMO (6, IQR 0–14) or MS (2, IQR 0–4), p=0.02. Subjects with SLE myelitis were also more likely to have elevated anti-dsDNA antibodies at presentation (86%) compared to subjects with NMO (33%) or MS (0%), p=0.03.

Conclusion—Myelitis occurs rarely among patients with SLE. Compared to subjects with SLE + NMO and subjects with SLE + MS, subjects with SLE myelitis had higher SLE disease activity at presentation.

Keywords

Systemic Lupus Erythematosus; Neuropsychiatric Lupus; Anti-DNA antibodies

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DECLARATION OF CONFLICTING INTERESTS

The Author(s) declare(s) that there is no conflict of interest.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic disease characterized by autoreactivity of the innate and adaptive immune systems, leading to autoantibody production and immune complex deposition within tissues.[1] It is estimated to affect approximately 161,000 to 322,000 adults within the United States (US), and typically involves multiple organ systems.[2] Neurologic manifestations of SLE include, among others, seizures, psychosis, acute confusional state, neuropathy, stroke, and myelitis.[3] Myelitis, or inflammation of the spinal cord, occurs in 1–2% of patients with SLE and may present with motor, sensory, or autonomic deficits below the level of spinal inflammation, leading to significant morbidity.[4] Several case series and small case-control studies have examined patients with SLE myelitis and have found that the clinical presentation, laboratory evaluation, and radiographic features of this disease are often heterogeneous.[5–20] In addition, several other autoimmune conditions may affect the spinal cord. Among them, multiple sclerosis and anti-aquaporin-4 antibody (AQP4) mediated neuromyelitis optica (NMO) may be difficult to distinguish clinically from SLE myelitis.[21,22] Differentiating between these three conditions is important because they require different treatment approaches.[23, 24, 25] Thus, we sought to compare the demographic, clinical, laboratory, and radiographic characteristics of these three conditions within an SLE registry from a large academic hospital in Boston, Massachusetts (MA).

PATIENTS AND METHODS

Subjects were identified by searching the Brigham and Women's Hospital Lupus Center Registry comprised of 2,297 patients with at least four 1997 American College of Rheumatology (ACR) revised criteria for SLE.[26] All included subject records were reviewed by an attending rheumatologist to confirm the diagnosis of SLE. Neurologic diagnoses within this population were identified by text string searches within electronic medical records for the terms "myelitis", "NMO", "neuromyelitis optica", and "multiple sclerosis" between January 1, 2000 and December 31, 2015. Each subject's record was then reviewed by an attending neurologist (SB) to confirm the diagnosis of SLE myelitis, AQP4 seropositive NMO, or MS. Subjects with positive AQP4 antibodies were, by definition, classified as NMO (as all patients had myelitis and would thus meet the International Panel for NMO Diagnosis (IPND) diagnostic criteria).[27] MS was classified based on the 2010 McDonald Criteria.[28] Patients were excluded if they did not have clinical, laboratory, and imaging data at the time of spinal cord syndrome presentation.

Data were extracted regarding demographics (age at time of presentation, sex, race), clinical factors (years since onset of SLE symptoms, presence of concurrent SLE flare, sensory loss, weakness, bowel/bladder dysfunction, concurrent optic neuritis, treatment, follow-up course), laboratory features (cerebrospinal fluid (CSF) profile, inflammatory markers, complement levels, autoantibody profiles), and radiographic features (lesion number, pattern, contrast enhancement, and follow-up resolution). Bowel/bladder dysfunction included urinary urgency, urinary hesitancy, or fecal incontinence; constipation was not included. Inflammatory markers included erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Complement levels included C3, C4, and/or CH50. Specific

autoantibodies included anti-double stranded DNA antibody (anti-dsDNA), lupus anticoagulant (LAC), anticardiolipin (aCL) IgM and IgG antibodies, and anti-beta-2 glycoprotein-I (anti-β2GPI) IgM and IgG antibodies. In addition, the SLE Disease Activity Index 2000 score (SLEDAI-2K)[29] at the time of presentation was determined for each patient. Neurologic impairment at the time of presentation and at 1-year follow-up was measured using the American Spinal Injury Association Impairment Scale (AIS), with categories including complete motor and sensory loss (A), complete motor loss with preserved sensation (B), incomplete motor loss with muscle strength <3/5 (C), incomplete motor loss with muscle strength ≥3/5 (D), and normal function (E).[30]

Although the expanded disability status scale (EDSS) is commonly used to measure disability caused by MS or NMO, this study utilized the AIS because the EDSS also includes other aspects of neurologic dysfunction not related to the spinal cord. Characteristics of these three groups were compared using Fisher's exact test for categorical variables and analysis of variance for continuous variables. Wilcoxon rank-sum test was used for SLEDAI-2K score, ESR, and CRP level as these values were not normally distributed. Data were analyzed using SAS 9.4 (Cary, North Carolina, US). This study was approved by the Institutional Review Board (IRB) of Brigham and Women's Hospital (2016P002848). The IRB granted a waiver for the requirement of informed consent by study subjects given the retrospective nature of the study design. The primary data from this study can be obtained by contacting the first author listed above.

RESULTS

Fifteen of the 2,297 subjects with SLE (0.7%) met criteria for a spinal cord syndrome: seven had SLE myelitis, three had AQP4+ NMO, and five had MS. Demographic, clinical, laboratory, and magnetic resonance imaging (MRI) characteristics of the study population are displayed in Table 1. There were no significant demographic differences between these three groups, with mean age at presentation in the 5th decade for all three groups. The majority of subjects in all three groups were white females.

As far as clinical characteristics, the median SLEDAI-2K score at time of neurologic syndrome presentation was higher in SLE myelitis subjects (8, interquartile range (IQR) 7–16) compared to subjects with NMO (6, IQR 0–14) or MS (2, IQR 0–4), p=0.02. None of the subjects in the NMO or MS group were having a concurrent SLE flare at the time of neurologic syndrome presentation, whereas 43% of the SLE myelitis subjects were having a flare at presentation. For those with concurrent SLE flare, the other involved organ systems included the skin and joints. Optic neuritis was present in both the SLE myelitis group (n=2) and the NMO group (n=2). Importantly, all subjects presented with clinical evidence of myelitis including weakness, sensory loss, and/or bowel or bladder dysfunction. Diagnosis of spinal cord syndrome occurred within 21 days of symptom onset for 6 out of 7 subjects with SLE myelitis, 2 out of 3 subjects with NMO, and 3 out of 5 patients with MS.

As described by Birnbaum et al, we did categorize our 15 subjects as either white matter myelitis (characterized by spasticity and/or hyperreflexia) or gray matter myelitis (characterized by flaccidity and/or hyporeflexia).[10] Of our 15 subjects, only 2 had evidence

of gray matter myelitis (1 was in the SLE + NMO group and 1 was in the SLE + MS group). Unlike Birnbaum et al, we did not find that those with gray matter myelitis had irreversible paraplegia, CSF profile consistent with bacterial meningitis, or evidence of high SLE disease activity at presentation. Only one of the subjects with gray matter myelitis had urinary symptoms, and 100% had a monophasic course (as compared to 82% of those with white matter myelitis). There was no statistical difference between those with SLE myelitis, SLE + NMO, or SLE + MS in regard to white matter vs gray matter myelitis (p=0.6).

A greater proportion of subjects in the SLE myelitis group had elevated anti-dsDNA antibodies at presentation (86%) compared to subjects with NMO (33%) or MS (0%), p=0.03. There were otherwise no statistically significant differences in laboratory characteristics between these three groups, although there was increased antiphospholipid antibody positivity in the SLE myelitis group as compared to the NMO and MS groups (71% vs. 0% vs. 20%, p=0.15) and higher CRP in the SLE myelitis and NMO groups compared to the MS group (p=0.07). On cerebrospinal fluid (CSF) analysis, oligoclonal bands were seen in the SLE myelitis and MS groups, but not in the NMO group. The majority of subjects did not have inflammatory CSF features such as pleocytosis, elevated protein, or low glucose. Additionally, there was no difference in the presence of inflammatory CSF features between the 3 groups. Spinal MRI characteristics did not differ between the groups (Figure 1). The radiographic pattern of longitudinally extensive myelitis involving at least three vertebral segments was seen in all three groups. In all three groups, 100% of subjects who had a repeat MRI of the spine ≥6 months after spinal disease onset had persistent lesions.

All subjects in the SLE myelitis and NMO groups received steroids at presentation; 3/5 subjects in the MS group did. In the SLE myelitis group, two subjects received cyclophosphamide (29%) and one subject received plasma exchange (14%). In the NMO group, one subject received plasma exchange + mycophenolate mofetil (33%) and one subject received rituximab (33%). In the MS group, one subject received mycophenolate mofetil (20%) and one subject received azathioprine (20%). Outcomes did not differ significantly between these three groups (Table 2). Most subjects had a single episode of myelitis, remained on immunosuppression through last follow-up, and were able to ambulate independently at last follow-up. One year after spinal disease onset, all subjects were either in AIS category D (incomplete motor loss, ≥4/5 strength) or category E (normal function).

DISCUSSION

Myelitis is a rare complication of SLE which may lead to significant morbidity, and thus it is important to identify this condition and differentiate it from similarly presenting conditions which may occur in patients with SLE (such as NMO and MS) so that it may be promptly and appropriately treated. This study of 15 patients with SLE and spinal cord syndromes seen at a large academic hospital in Boston, MA sought to compare the demographics, clinical presentation, laboratory and radiographic features, and treatment outcomes of SLE myelitis, SLE + NMO, and SLE + MS from 2000–2015.

The functional deficits associated with these three conditions are particularly concerning given that they tend to affect young and middle-aged adults, with a mean age at onset in the 5th decade of life in our study. Other studies have similarly reported a mean age at SLE myelitis onset of 25–42 years[10, 13–14], NMO median age at onset in the late 4th decade,[31] and MS mean age at onset of 28–31 years.[32] Interestingly, our small study population was more likely to be white (93%) than the general SLE population of the hospital which participated in the study (66% white). Although our study population was small, this suggests that white patients with SLE may be more likely to develop spinal cord syndromes or there may be disparities in the diagnosis which favor white patients. Other studies of SLE myelitis have reported study populations that are 36–46% white[10], in comparison to the SLE adult population within the US, which is approximately 55% white.[2] The majority of patients with NMO are non-white[31, 33–35], in contrast to MS, which is most common amongst patients of northern European ancestry.[32]

Optic neuritis is a cardinal feature of NMO, but we also found that approximately 30% of subjects in the SLE myelitis group had optic neuritis, in line with the previously noted association between SLE myelitis and optic neuritis.[13] We found that subjects in the SLE myelitis group had higher disease activity at presentation as measured by median SLEDAI-2K scores and proportion of subjects with elevated anti-dsDNA antibodies. This may provide clinicians with a diagnostic clue favoring SLE myelitis over SLE + NMO or SLE + MS in practice. The majority of our SLE myelitis group had antiphospholipid antibodies (71%), which has been noted in other studies.[9, 13–14, 20] This is in contrast to the general SLE population in which 30–40% have antiphospholipid antibodies.[36] The majority of subjects in the NMO and MS groups did not have antiphospholipid antibodies, but these differences did not reach statistical significance. It has been proposed that hypercoagulability associated with antiphospholipid antibodies may play a role in the pathophysiology of SLE myelitis by leading to spinal cord ischemia, however a previous study of 70 patients found no evidence that anticoagulation improves outcomes in these patients.[37]

A study by Birnbaum et al published in 2009 categorized patients with SLE myelitis into white matter myelitis (characterized by spasticity and hyperreflexia) and gray matter myelitis (characterized by flaccidity and hyporeflexia).[10] They found that white matter myelitis was associated with NMO and presence of antiphospholipid antibodies, whereas gray matter myelitis was associated with irreversible paraplegia, monophasic course, higher SLEDAI scores, urinary retention, and CSF analysis resembling bacterial meningitis. However, when we classified our 15 subjects into white matter myelitis (N=13) and gray matter myelitis (N=2), we did not find any of these associations reported by Birnbaum et al. Longitudinally extensive myelitis (LEM) is classically associated with NMO (though short-segment lesions can occur) [38, 39], and we did see LEM in a greater proportion of our NMO group as compared to the MS and SLE myelitis groups (although not statistically significant). This pattern may also occur in SLE myelitis as noted in several studies.[7–8, 11,14] Additionally, we found that radiographic improvement may temporally lag clinical improvement, as all subjects with follow-up imaging had persistent radiographic lesions at 6 months or later. Thus, it appears that following a patient's exam and symptoms may be more likely to assist with prognostication than subsequent imaging.

The outcomes of subjects were relatively favorable; 87% of subjects were treated with steroids at myelitis onset and 87% had a single episode of myelitis. All subjects had either minor impairment in motor function (strength ≥4/5) or normal function at 1-year follow-up. Previous studies have suggested that the addition of cyclophosphamide to steroids in SLE myelitis is associated with improved outcomes.[12,13, 25] In support of this previous finding, the only subject in our study who had a full response to acute treatment in the SLE myelitis group received both cyclophosphamide and steroids. Azathioprine is also a first-line agent for SLE myelitis, with plasma exchange used in refractory cases.[25] In contrast, steroids in combination with rituximab or azathioprine has often been among first-line management options for NMO, with plasma exchange reserved for refractory cases.[23] Lastly, MS flares are typically managed with steroids followed by plasma exchange in refractory cases.[24] The long-term treatment approaches for these three conditions differ, highlighting the need for accurate identification in the clinical setting.

Strengths of our study include extensive follow-up time for our study population (mean 5.7 years, range 6 months-13 years) and comprehensive clinical, laboratory, and MRI data. Limitations include our small study population and retrospective study design. Furthermore, the neurologic outcomes of our study population were favorable at 1 year, which may have been due to milder disease at presentation and/or earlier diagnosis (the majority of our study population was diagnosed with a spinal cord syndrome within 21 days of symptom onset). The neurologic outcomes of subjects in our study was overall similar to the findings of a 2015 study by Saison et al[12], which showed that after a median of 5.9 years of follow-up, only 3 of 18 patients with SLE myelitis required aid with ambulation. In summary, in these rare instances of myelitis among the SLE registry population, we found that compared to subjects with SLE + NMO and subjects with SLE + MS, subjects with SLE myelitis had significantly higher SLE disease activity at myelitis onset as indicated by SLEDAI-2K scores and elevated anti-dsDNA antibody levels. Further studies with larger patient populations are needed in order to determine how best to differentiate these 3 conditions in clinical practice.

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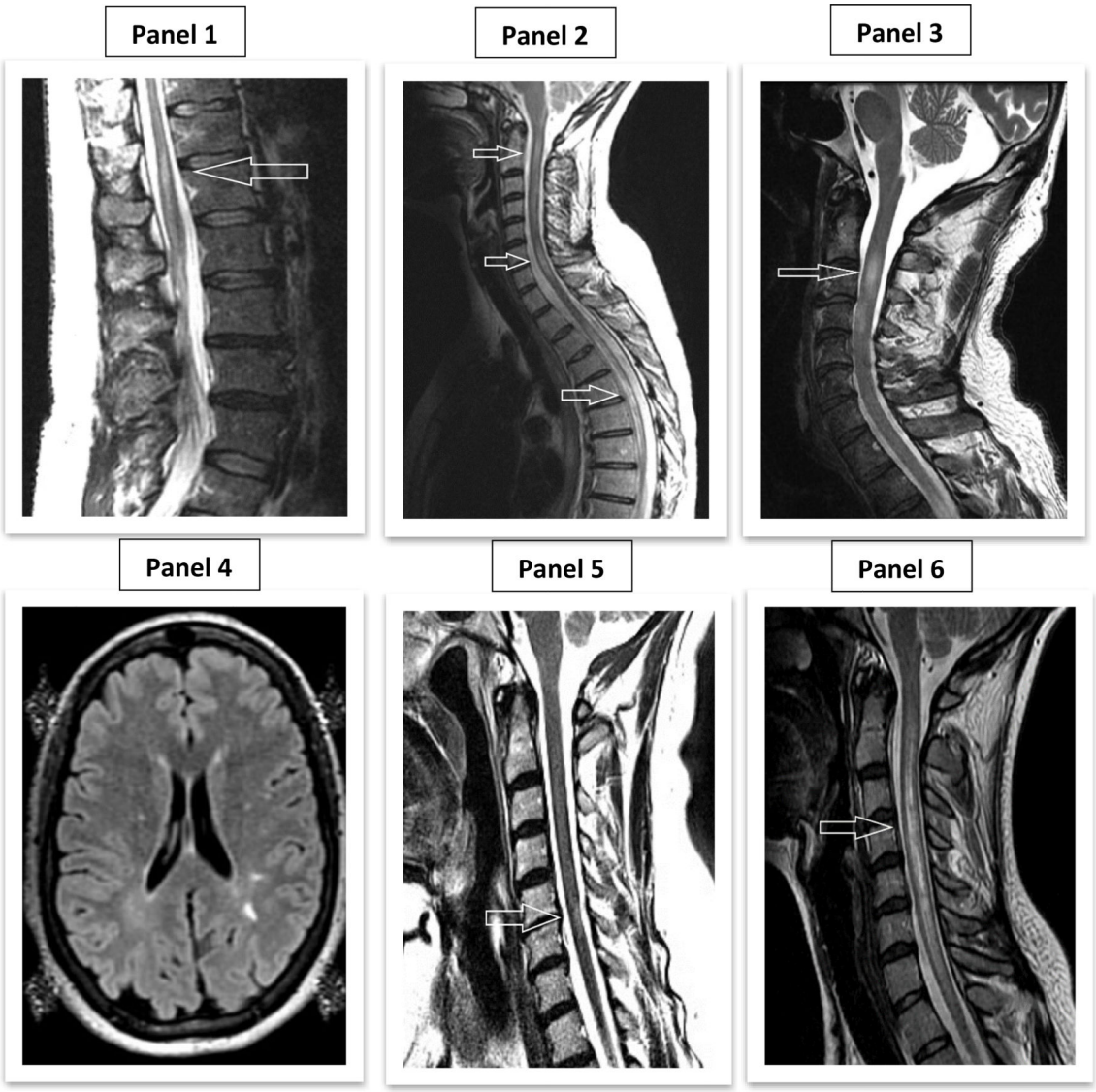

Figure 1.

Examples of Spinal MRI Findings in SLE Myelitis (Panels 1-3), Brain and Spinal MRI Findings in SLE + MS (Panels 4-5), and Spinal MRI Findings in SLE + NMO (Panel 6)

Table 1.

Characteristics of subjects with SLE myelitis, SLE + NMO, and SLE + MS at neurologic event presentation

	SLE myelitis (n=7)	SLE + NMO (n=3)	SLE + MS (n=5)	p-value
Demographic Characteristics				
Age, mean ± SD years	41 ± 10	46 ± 14	40 ± 13	0.80
Sex				0.67
Female	5 (71)	3 (100)	5 (100)	
Male	2 (29)	0 (0)	0 (0)	
Race[a]				1.00
White	6 (86)	3 (100)	5 (100)	
Black	1 (14)	0 (0)	0 (0)	
Years since SLE onset, mean ± SD	10 ± 11	22 ± 15	16 ± 3	0.23
Clinical Characteristics				
SLE flare	3 (43)	0 (0)	0 (0)	0.25
Median SLEDAI-2K score (IQR)	8 (7–16)	6 (0–14)	2 (0–4)	**0.02**
Sensory loss	6 (86)	1 (33)	3 (60)	0.39
Weakness	4 (57)	2 (67)	1 (20)	0.41
Bowel or bladder symptoms	3 (60)	1 (33)	1 (20)	0.77
Optic neuritis	2 (29)	2 (67)	0 (0)	0.13
Laboratory Characteristics				
Elevated anti-dsDNA antibody	6 (86)	1 (33)	0 (0)	**0.03**
Hypocomplementemia	4 (57)	1 (33)	1 (33)	1.00
Antiphospholipid antibody positive	5 (71)	0 (0)	1 (20)	0.15
Median ESR in mm/hr (IQR)[b]	19 (12–45)	22 (13–34)	11 (5–20)	0.24
Median CRP in mg/L (IQR)[b]	7 (2–13)	5 (2–8)	0.6 (0.6–2)	0.07
Oligoclonal bands in CSF	2(67)	0 (0)	2 (100)	0.23
MRI Characteristics				
Single spinal lesion	5 (71)	1 (50)	1 (25)	0.39
Contrast-enhancing lesion(s)	4 (67)	1 (50)	1 (25)	0.48
Longitudinally extensive myelitis[c]	2 (29)	1 (50)	1 (25)	1.00

SLE=systemic lupus erythematosus; NMO=neuromyelitis optica; MS=multiple sclerosis; SD=standard deviation; SLEDAI-2K= SLE Disease Activity Index 2000; IQR=interquartile range; dsDNA=double-stranded deoxyribonucleic acid; ESR=erythrocyte sedimentation rate; mm/hr=millimeters per hour; CRP=C-reactive protein; mg/L=milligrams per liter; CSF=cerebrospinal fluid; MRI=magnetic resonance imaging.

[a] All patients were non-Hispanic.

[b] Reference range for ESR is 0–20 mm/hr. Reference range for CRP is 0–8.0 mg/L.

[c] Longitudinal extension: involving ≥3 vertebral segments.

Table 2.

Comparison of outcomes among subjects with SLE myelitis, SLE + NMO, and SLE + MS

	SLE myelitis (n=7)	SLE + NMO (n=3)	SLE + MS (n=5)	p-value
Mean follow-up time ± SD years	7 ± 5	3 ± 3	6 ± 3	0.33
Full response to acute treatment	1 (14)	0 (0)	1 (20)	1.00
Recurrence of disease	1 (14)	1 (33)	0 (0)	0.67
AIS Category E (normal) at 1 year	3 (43)	1 (50)	3 (60)	1.00
Immunosuppression at last visit	6 (86)	3 (100)	5 (100)	1.00
Independent ambulation at last visit	6 (86)	2 (67)	4 (80)	1.00
MRI lesion(s) after ≥6 months	6 (100)	1 (100)	4 (100)	N/A

SLE=systemic lupus erythematosus; NMO=neuromyelitis optica; MS=multiple sclerosis; SD=standard deviation; AIS=American Spinal Injury Association Impairment Scale; MRI=magnetic resonance imaging; N/A=not applicable.