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Clinical biomarkers differentiate myelitis from vascular and other causes of myelopathy

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Abstract

Objective

To assess the predictive value of the initial clinical and paraclinical features in the differentiation of inflammatory myelopathies from other causes of myelopathy in patients with initial diagnosis of transverse myelitis (TM).

Methods

We analyzed the clinical presentation, spinal cord MRI, and CSF features in a cohort of 457 patients referred to a specialized myelopathy center with the presumptive diagnosis of TM. After evaluation, the myelopathies were classified as inflammatory, ischemic/stroke, arteriovenous malformations/fistulas, spondylotic, or other. A multivariable logistic regression model was used to determine characteristics associated with the final diagnosis and predictors that would improve classification accuracy.

Results

Out of 457 patients referred as TM, only 247 (54%) were confirmed as inflammatory; the remaining 46% were diagnosed as vascular (20%), spondylotic (8%), or other myelopathy (18%). Our predictive model identified the temporal profile of symptom presentation (hyperacute <6 hours, acute 6–48 hours, subacute 48 hours–21 days, chronic >21 days), initial motor examination, and MRI lesion distribution as characteristics that improve the correct classification rate of myelopathies from 67% to 87% (multinomial area under the curve increased from 0.32 to 0.67), compared to only considering CSF pleocytosis and MRI gadolinium enhancement. Of all predictors, the temporal profile of symptoms contributed the most to the increased discriminatory power.

Conclusions

The temporal profile of symptoms serves as a clinical biomarker in the differential diagnosis of TM. The establishment of a definite diagnosis in TM requires a critical analysis of the MRI and CSF characteristics to rule out non-inflammatory causes of myelopathy.

Classification of evidence

This study provides Class IV evidence that for patients presenting with myelopathy, temporal profile of symptoms, initial motor examination, and MRI lesion distribution distinguish those with inflammatory myelopathies from those with other causes of myelopathy.

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Glossary

AUC = area under the curve; **AVF** = arteriovenous fistulas; **AVM** = arteriovenous malformations; **CCR** = correct classification rate; **CI** = confidence interval; **Gd+** = gadolinium enhancement; **IDI** = integrated discrimination increment; **IM** = inflammatory myelopathy; **LE** = longitudinally extensive; **MS** = multiple sclerosis; **NMOSD** = neuromyelitis optica spectrum disorder; **NRI** = net reclassification improvement; **OCB** = oligoclonal bands; **OM** = other causes of myelopathy; **OR** = odds ratio; **SM** = spondylotic myelopathy; **TM** = transverse myelitis; **VM** = vascular myelopathy.

Transverse myelitis (TM) is an inflammatory disorder affecting the spinal cord. TM is recognized to be a heterogeneous syndrome, which manifests with motor, sensory, and autonomic symptoms attributable to spinal cord dysfunction.[1,2] The term TM has been applied broadly to myelopathic syndromes in the setting of autoimmune, demyelinating, infectious, and post-infectious disorders. The diagnosis of TM presents a challenge to the clinician as the list of possible differential diagnoses is extensive and non-inflammatory myelopathies with neoplastic, vascular, compressive, or metabolic etiologic origin often mimic TM.[3–5] While CSF pleocytosis or lesion enhancement on MRI have been widely used to define inflammatory myelopathies, similar features have been reported in non-inflammatory myelopathies.[3,4,6,7] The overlap of clinical, MRI, and CSF features among the wide spectrum of myelopathies may lead to an erroneous diagnosis of TM, and subsequent unwarranted treatments with potentially harmful immunosuppressive therapies and delays in adequate therapeutic measures.[8,9]

We performed a detailed evaluation of different types of myelopathies and determined the value of the clinical features, the temporal profile, spinal cord MRI, and CSF characteristics for establishing a more accurate diagnosis in a group of over 450 patients presenting with myelopathy.

Methods

Study design and patient population

We retrospectively analyzed the clinical presentation, initial neurologic examination, and characteristics of the initial MRI and CSF profile in 457 out of 575 patients referred to a specialized myelopathy center for a newly established diagnosis of TM from 2010 to 2015. A total of 118 patients were excluded due to lack of complete or verifiable information regarding their initial presentation. Patients referred for reasons other than presumed TM, including those with a previously established etiologic diagnosis (e.g., multiple sclerosis [MS], neuromyelitis optica spectrum disorder [NMOSD], spinal vascular malformations) were not included. We recorded demographic characteristics, medical history, and information on the clinical presentation including the temporal profile, initial symptoms, and the neurologic examination. CSF analysis and MRI features including lesion topography at the initial assessment were analyzed. As clinically indicated, patients underwent additional studies including serologic and imaging studies (e.g., spinal angiogram) (see e-Methods, http://links.lww.com/WNL/A10).

Definitions

The final diagnosis was classified as inflammatory myelopathy (IM), vascular myelopathy (VM), spondylotic myelopathy (SM), or other causes of myelopathy (OM) (table 1). The temporal profile from symptom onset to nadir neurologic dysfunction was classified as hyperacute (<6 hours), acute (6–48 hours), subacute (>48 hours–21 days), or chronic (>21 days). Nadir was defined as the point of worst neurologic function, before improvement or plateau, based on history and neurologic examination. Features of the initial presentation were confirmed during the clinical visit interview.

Statistical analysis

Our analysis had 2 aims: to (1) assess descriptively how specific characteristics are associated with myelopathies of different etiologies and (2) derive a subset of predictors that improve the prediction accuracy of identifying etiologic origin of a given myelopathy. For the first stage, we grouped characteristics into 5 sets of potentially relevant predictors: demographic/medical history (age, sex, ethnicity, smoking status, obesity, hypertension, diabetes, dyslipidemia, autoimmune disease, infection in the last 30 days, vaccination in the last 90 days), clinical presentation (temporal profile, presence of motor, sensory, or bladder/bowel symptoms, new onset back pain, worsening by exercise), neurologic examination (motor examination, sensory abnormality, presence of urinary retention or abnormal rectal tone, reflexes), MRI (sagittal lesion location and extension, gadolinium enhancement [Gd+], multifocality, axial lesion topography), and CSF (pleocytosis, protein, immunoglobulin G index, and oligoclonal bands [OCB]). For each group of predictors, we fit a multinomial regression model where we considered each myelopathy type as an outcome. Models for MRI and CSF features were adjusted for time to MRI or time to lumbar puncture.

Our second objective was to evaluate, after accounting for Gd+ and pleocytosis, whether a subset of predictors would improve accuracy in discriminating the different myelopathy categories. We focused on estimation of the multinomial-generalized integrated discrimination increment (IDI), a measure of separation of the predicted probabilities for each type of event, and the net reclassification improvement (NRI), the proportion of participants correctly vs incorrectly classified between 2 models, as measures that estimate prediction increment of new variables[15] (see e-Methods, http://links.lww.com/WNL/A10). Statistical analyses were

Table 1 Definitions of diagnostic categories[a]

Myelopathy	A clinical syndrome characterized by motor, sensory, or autonomic symptoms attributable anatomically to spinal cord dysfunction
Inflammatory myelopathy	Myelopathy meeting the diagnostic criteria for known specific inflammatory disorders including MS,[10] NMOSD,[11] sarcoidosis,[12] and rheumatologic myelopathies[13] when other alternative etiologies were ruled out; or meeting criteria for idiopathic TM[2]
Vascular myelopathy related to ischemic disease (strokes)	
Definite	• Myelopathy
	• MRI hyperintense lesion in a defined vascular territory or watershed area[b] on T2-weighted images
	• Vascular abnormality demonstrated on spinal angiogram explanatory of the clinical presentation
	• Exclusion of other etiologies
Probable	• Myelopathy
	• MRI-hyperintense lesion in a defined vascular territory or watershed area on T2-weighted images
	• Spinal angiogram negative or not available
	• Positive DWI or known stroke risk factors or mechanism explanatory of the clinical presentation (i.e., severe hypotension, hypercoagulable state)
	• Exclusion of other etiologies
Possible	• Myelopathy
	• MRI hyperintense lesion in a defined vascular territory or watershed area on T2-weighted images
	• Spinal angiogram and DWI negative or not available
	• No identifiable risk factor or mechanism
	• Exclusion of other etiologies
Vascular myelopathy associated with AVM/AVF	
Definite	• Myelopathy
	• MRI hyperintense lesion in the spinal cord on T2-weighted images
	• Angiogram proven AVM or AVF
	• Exclusion of other etiologies
Probable	• Myelopathy
	• MRI hyperintense lesion in the spinal cord on T2-weighted images
	• MRI vasculature abnormality consistent with AVF or AVM (prominent flow voids)
	• Spinal angiogram not available
	• Exclusion of other etiologies
Spondylotic myelopathy	Myelopathy with MRI hyperintense lesion in the spinal cord on T2-weighted images in the region of spine degenerative changes such as disc herniation, spondylolisthesis, cervical stenosis, or osteophyte mass effect, and where other causes were ruled out
Other myelopathies[c]	Non-inflammatory myelopathies not meeting criteria for the above diagnostic categories

Abbreviations: AVF = arteriovenous fistulas; AVM = arteriovenous malformations; DWI = diffusion-weighted imaging; MS = multiple sclerosis; NMOSD = neuromyelitis optica spectrum disorder; TM = transverse myelitis.
[a] For a diagnosis to be made, all the conditions in the definition need to be met.
[b] Arterial territory supplied by sources flowing in opposite directions; includes the upper thoracic region, isolated gray matter, and the posterior lumbosacral watershed area.[14]
[c] Includes myelopathies of metabolic, neoplastic, infectious, and unknown etiology.

implemented with R, version 3.2.2 (https://www.r-project.org/). This study provides Class IV evidence that for patients presenting with myelopathy, temporal profile of symptoms, initial motor examination, and MRI lesion distribution distinguish those with inflammatory myelopathies from those with other causes of myelopathy.

Standard protocol approvals, registrations, and patient consents

The institutional review board at Johns Hopkins Hospital approved the study and waived patient consent (IRB00115274).

Results

Patient population

A total of 457 patients (58% female, median age 46 years, interquartile range 33–56 years) with the presumptive diagnosis of TM were analyzed (table 2 and tables e-1, e-2, and e-3, http://links.lww.com/WNL/A9). After thorough assessment of the clinical, MRI, and CSF features, final diagnoses were reclassified as IM in 247 (55%) patients, VM in 92 (20%) patients (62 ischemic/stroke and 30 arteriovenous malformations [AVM]/arteriovenous fistulas [AVF]), SM in 35 (8%) patients, and OM in 83 (18%) patients. For the VM ischemic/stroke category, the diagnosis was definite in 13, probable in 26, and possible in 23 patients. For 28 patients with AVM/AVF, the diagnosis was definite; 2 patients with prominent flow voids on MRI and a compatible clinical profile declined angiography and were classified as probable VM-AVM/AVF.

Demographics and medical history

The majority of patients were Caucasian in all categories. Relative to the inflammatory group, AVM/AVF and SM were more likely with increasing age (for AVM/AVF odds ratio [OR] per 10 years increment: 1.78; 95% confidence interval [CI] 1.34–2.44; for SM, OR 2.04; 95% CI 1.5–2.88). AVM/AVF and SM were more common in men than in women (for VM-AVM/AVF: OR 5.04; 95% CI 1.81–14.07; for SM: OR 3.09; 95% CI 1.29–7.35). A history of autoimmune disease was less frequent in the VM-ischemic/stroke group compared to IM (OR 0.25; 95% CI 0.07–0.89) and while a history of a preceding infection was more frequent in IM, this was not statistically significant in multivariate analysis (figure 1 and table e-1, http://links.lww.com/WNL/A9).

Temporal profile

IM presented more often with a subacute temporal profile (55%). Relative to IM, VM-ischemic/stroke exhibited more frequently a hyperacute profile (89%; OR 35.19; 95% CI 8.92–138.90) in contrast to VM-AVM/AVF, SM, and OM, which were significantly more likely to exhibit a chronic pattern (83%, 86%, 61%, respectively; all OR > 3).

Initial symptoms

The presence of acute excruciating back pain at onset was associated with the VM-ischemic/stroke group relative to IM (OR 7.30; 95% CI 2.21–24.11); bladder/bowel dysfunction and symptom worsening with exercise were associated with the VM-AVM/AVF relative to IM (for bladder/bowel dysfunction: 4.12; 95% CI 1.37–12.44; for worsening with exercise: 13.99; 95% CI 2.02–97.11).

Neurologic examination

While weakness was present in the majority of patients, a higher frequency was seen in the VM group (98%, table 2). In participants with VM-ischemic/stroke and VM-AVM/AVF, flaccid weakness was substantially more common relative to IM (all OR >10). Hyporeflexia was more frequent in the VM-ischemic/stroke group (63%) relative to other types. Participants with SM or OM were less likely to have compromised sphincters relative to IM (for SM: OR 0.30; 95% CI 0.09–0.99; for OM: 0.37; 95% CI 0.18–9.80). A sensory level was more frequently seen in the VM-ischemic/stroke and VM-AVM/AVF groups (79%, 70%) as compared with the IM, SM, and OM groups (50%, 51%, and 49%, respectively). In all categories the most frequent sensory level was thoracic.

MRI characteristics

Longitudinally extensive myelopathy (LE; 3 or more vertebral levels in length) was observed in all groups but most frequently in the VM group (ischemic/stroke 60%, AVM/AVF 70%). For VM-ischemic/stroke, this was significantly more frequent when compared to IM (OR 3.87; 95% CI 1.15–13.02). Almost half of the IM and SM lesions (44% and 46%, respectively) exhibited LE. The likelihood of multifocal lesions was higher in the IM group relative to any other myelopathy category. All of the reclassified myelopathies were less likely to have Gd+ (all OR <0.50) relative to IM; however, notably, this finding was not specific as 21% of the VM-ischemic/strokes, 60% of the VM-AVM/AVF, and 46% of SM patients category were also enhancing.

The pattern of lesion distribution for each diagnostic category in both axial and sagittal views is shown in figure 2. The IM lesions affected more frequently the posterolateral spinal cord relative to all other myelopathy groups (all OR <1.0), and were located more often in the cervical and upper thoracic spinal cord (C1-T6). Lesions in the VM-ischemic/stroke group were more frequently anterior (67%); these lesions were involving more commonly the cervical cord and the lower thoracic spinal cord. SM lesions tended to locate in the central spinal cord (77%; OR relative to IM 4.59; 95% CI 1.50–14.0) and to be more frequently cervical. Lesions involving the conus medullaris were more common in VM-AVM/AVF than IM (OR 19.23; 95% CI 3.35–110.38); these lesions were less likely to involve the posterior cord relative to IM (OR 0.19; 0.04–0.76) and were more frequently central (77%).

CSF features

The laboratory profile of the initial CSF obtained after the onset of symptoms was available for 390 patients. Pleocytosis was observed more frequently in the IM group (57%); however, it is worth noting that pleocytosis was also present in

Table 2 Clinical features of 457 patients with myelopathy by diagnostic category[a]

Category	Inflammatory (n = 247)	Ischemic/stroke (n = 62)	AVM/AVF (n = 30)	Spondylotic (n = 35)	Other (n = 83)
Demographics/medical history					
Age, y, median (IQR)	42 (31–54)	47 (27–58)	56 (42–68)	53 (46–63)	47 (36–56)
Male	91 (37)	25 (40)	23 (77)	22 (63)	33 (40)
Caucasian	169 (68)	49 (79)	23 (77)	28 (80)	71 (85)
Arterial hypertension	56 (23)	21 (34)	12 (40)	12 (34)	25 (30)
Diabetes mellitus	19 (8)	12 (19)	3 (10)	3 (9)	9 (11)
Current smoker	35 (14)	13 (21)	2 (7)	7 (20)	10 (12)
Autoimmune disease	43 (17)	3 (5)	2 (7)	2 (6)	7 (8)
Infection in last 30 d	50 (20)	8 (13)	4 (13)	0 (0)	14 (17)
Vaccine in last 90 d	17 (7)	2 (3)	1 (3)	1 (3)	8 (10)
Initial symptoms					
Hyperacute (<6 h)	9 (4)	55 (89)	2 (7)	0 (0)	5 (6)
Acute (6–48 h)	35 (14)	6 (10)	2 (7)	3 (9)	13 (16)
Subacute (>48 h–21 d)	136 (55)	0 (0)	1 (1)	2 (6)	14 (17)
Chronic (>21 d)	67 (27)	1 (2)	25 (83)	30 (86)	51 (61)
Motor symptoms	167 (68)	61 (98)	27 (90)	27 (77)	63 (76)
Sensory symptoms	224 (91)	56 (90)	26 (87)	31 (86)	68 (82)
Sphincter symptoms	113 (46)	37 (60)	22 (73)	16 (46)	34 (41)
Back pain	42 (17)	43 (69)	9 (30)	6 (17)	18 (21)
Worsened by exercise	4 (2)	6 (10)	7 (23)	1 (3)	1 (1)
Neurologic examination					
Weakness	160 (65)	61 (98)	28 (93)	26 (74)	58 (70)
Spastic tone	53 (21)	4 (6)	9 (30)	19 (54)	24 (29)
Flaccid tone	16 (6)	33 (53)	6 (20)	1 (3)	6 (7)
Sensory abnormality	199 (81)	56 (90)	25 (83)	30 (86)	64 (77)
Vibration/proprioception	104 (42)	28 (45)	17 (57)	21 (60)	36 (43)
Light touch	107 (43)	39 (63)	18 (60)	17 (49)	34 (41)
Pain/temperature	139 (56)	51 (82)	18 (60)	20 (57)	41 (49)
Sensory level	124 (50)	49 (79)	21 (70)	18 (51)	41 (49)
Sphincter involvement	60 (24)	37 (60)	9 (30)	5 (14)	14 (17)
Hyporeflexia[b]	39 (16)	39 (63)	9 (30)	4 (11)	6 (7)
Hyperreflexia	131 (53)	10 (16)	16 (53)	25 (71)	47 (57)
MRI[c]					
LE	110 (44)	37 (60)	22 (73)	16 (46)	33 (40)
Gd+	168 (68)	13 (21)	18 (60)	16 (46)	22 (26)
Multifocality	88 (36)	3 (5)	2 (7)	3 (1)	14 (17)
Central pattern	107 (43)	25 (40)	23 (77)	23 (66)	28 (34)

Continued

Table 2 Clinical features of 457 patients with myelopathy by diagnostic category[a] *(continued)*

Category	Inflammatory (n = 247)	Ischemic/stroke (n = 62)	AVM/AVF (n = 30)	Spondylotic (n = 35)	Other (n = 83)
Anterior pattern	61 (24)	42 (67)	3 (10)	9 (26)	16 (19)
Posterior pattern	134 (54)	12 (19)	6 (20)	14 (40)	35 (42)
Lateral pattern	118 (48)	10 (16)	3 (10)	13 (37)	33 (40)
Cervical lesion	173 (70)	29 (47)	7 (23)	26 (74)	37 (44)
Upper thoracic (T1–T6)	116 (47)	24 (39)	12 (40)	9 (26)	28 (34)
Lower thoracic (T7–T12)	108 (44)	28 (45)	23 (77)	4 (11)	30 (36)
Conus medullaris	10 (4)	8 (13)	10 (33)	1 (3)	7 (8)
CSF[d]					
Pleocytosis (>5 cells/μL)	128/224 (57)	10/57 (17)	8/23 (35)	2/20 (10)	10/66 (15)
Protein >45 mg/dL	103/224 (46)	21/57 (37)	17/23 (74)	9/20 (45)	19/66 (29)
Oligoclonal bands	85/188 (45)	1/44 (2)	0/17 (0)	1/15 (7)	8/50 (16)
IgG index >0.7	54/166 (32)	3/35 (9)	1/14 (7)	1/18 (5)	2/41 (5)

Abbreviations: AVF = arteriovenous fistulas; AVM = arteriovenous malformations; Gd+ = gadolinium enhancement; IgG = immunoglobulin G; IQR = interquartile range; LE = longitudinally extensive.
Values are n (%).
[a] Percentages include all participants in each category as the denominator.
[b] Information for reflexes available for 444/457 patients.
[c] MRI data were obtained from first MRI available after onset of symptoms: 67 were done in <2 days, 74 were done from 2 to 5 days, 58 from 6 to 10 days, 72 from 11 to 30 days, and 186 were done >30 days after onset of symptoms.
[d] Percentages based on the total of patients tested. CSF data were obtained from first CSF evaluated after onset of symptoms: 53/390 were obtained in <2 days, 62/390 were obtained from 2 to 5 days, 58/390 were obtained from 6 to 10 days, 45/390 were obtained from 11 to 30 days, and 172/390 were obtained >30 days after onset of symptoms.

a substantial proportion of VM-AVM/AVF (35%) and VM-ischemic/stroke (17%). Moreover, 43% of the patients who met the criteria for IM did not exhibit pleocytosis. Elevated protein was more frequently observed in the VM-AVM/AVF and SM group (74% and 45%, respectively). OCB were almost exclusive of the IM group, although they were only present in 45% of patients tested. Participants with VM-ischemic/stroke were less likely to have pleocytosis or OCB relative to IM (all ORs <1).

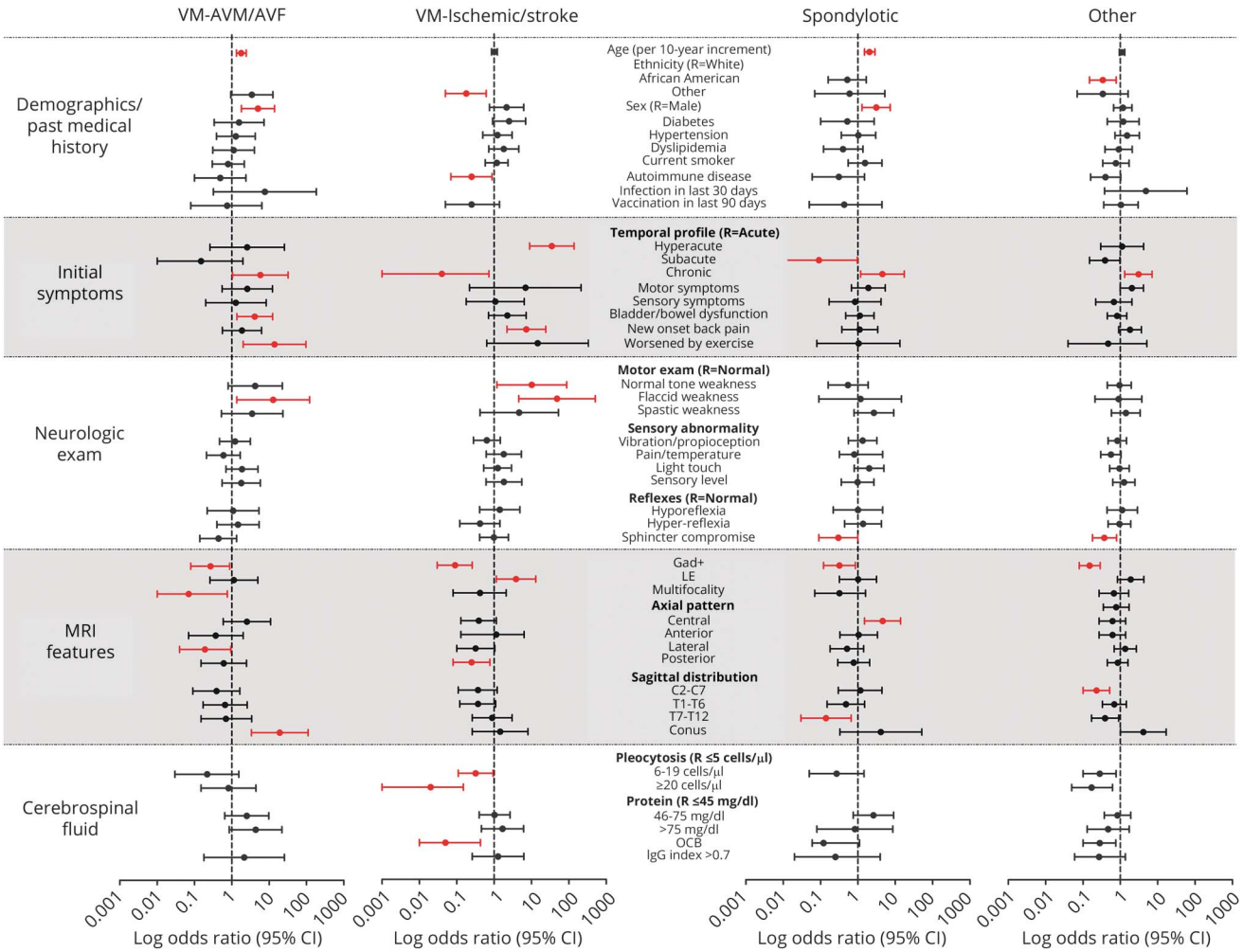
Prediction model for identifying diagnostic category of myelopathies

Our predictive model selected the following predictors as characteristics that improve discriminatory power for identifying the correct diagnostic category of a given myelopathy: temporal profile of symptoms, motor examination findings, conus medullaris involvement, and presence of posterior spinal cord lesions (table 3). By including these 4 additional characteristics, the correct classification rate (CCR) increased from 67% to 87% and the multinomial area under the curve (AUC) increased from 0.32 to 0.67, suggesting marked improvements in the correct classification of a given myelopathy. NRI (34%) and IDI (38%) values associated with this predictor set are also notable as both the CCR and AUC are sensitive to the differences in the prevalence of underlying outcomes. This suggests improved classification and more succinct separation in prediction of diagnostic categories of given myelopathies, relative to only considering Gd+ and pleocytosis (typically used to define IM). Of all the predictors considered, the temporal profile contributed to the largest changes in IDI, NRI, and CCR relative to the traditional model (Gd+ and pleocytosis). By including the temporal profile only (and no other predictor), the CCR is 0.68 and the multinomial AUC is 0.39.[16] Relative to the null model (no predictors), inclusion of the temporal profile results in an improved integrated discrimination index of 15% (12%–19%) and improved net reclassification index of 15% (2%–28%) (table e-4, http://links.lww.com/WNL/A9). Results of our sensitivity analyses (derivation of a prediction model only considering demographics, clinical presentation, and neurologic examination and no additional MRI findings) were consistent. Relative to a model considering Gd+ and pleocytosis, with the inclusion of motor examination findings and the temporal profile of symptoms, the CCR increased from 67% to 81% and the multinomial AUC increased from 0.32 to 0.60. IDI (26%) and potentially NRI (22%) similarly suggested improved discriminatory power associated with the inclusion of the temporal profile and motor examination findings.

Discussion

The broad differential diagnosis of TM makes it necessary to develop strategies that accurately distinguish among the different etiologies of myelopathy. Our study, which is the largest known cohort evaluating patients with presumed TM,

Figure 1 Individual clinical predictors for each diagnostic category



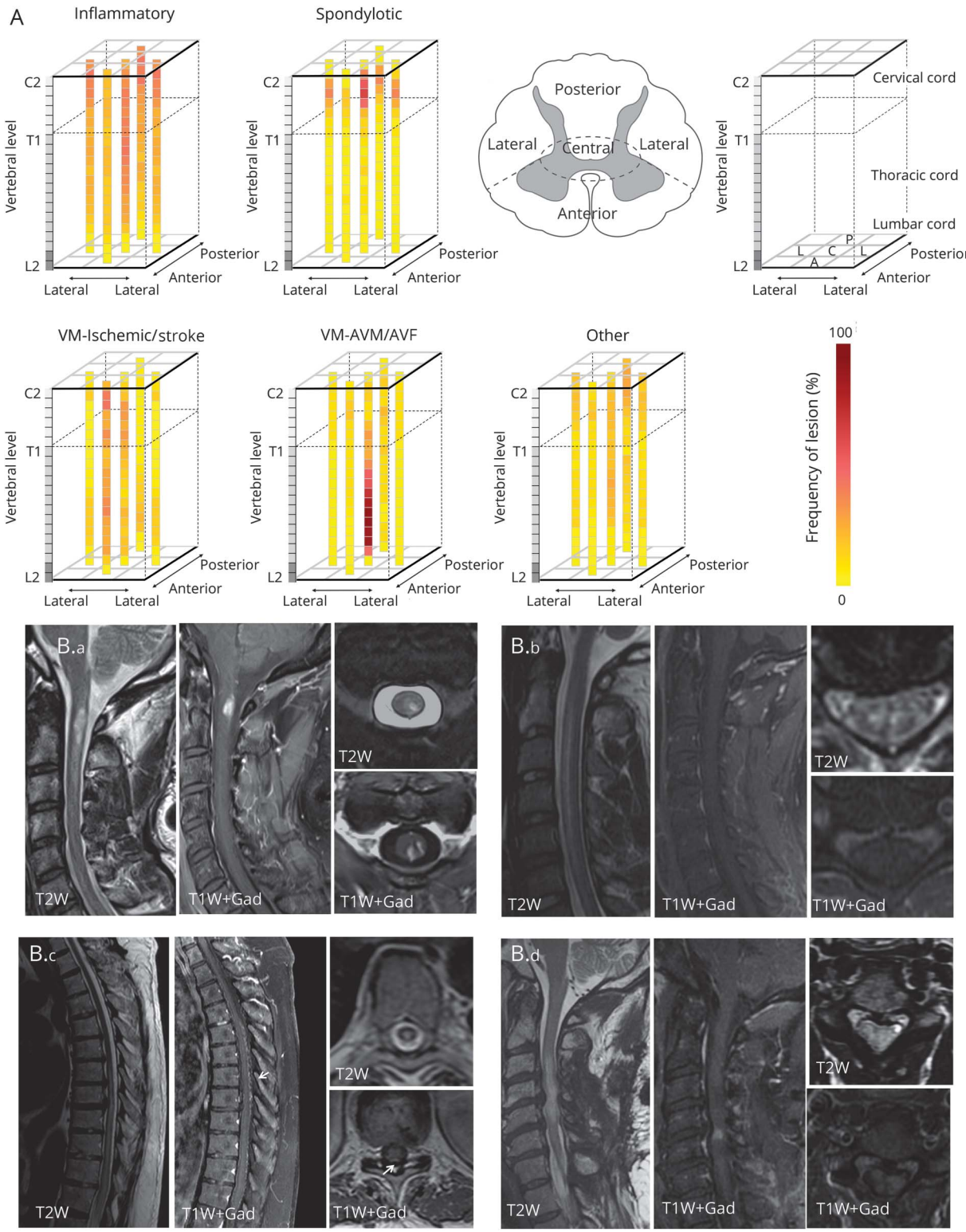
Odds ratio estimates and 95% confidence intervals (CI) are shown for each diagnostic category relative to the inflammatory group; statistically significant associations ($p < 0.05$) are highlighted in red. AVF = arteriovenous fistulas; AVM = arteriovenous malformations; Gad+ = gadolinium-enhanced lesions; IgG = immunoglobulin G; LE = longitudinally extensive lesions; OCB = oligoclonal bands; R = reference group; VM = vascular myelopathy.

demonstrated that only 54% of the patients referred as TM had a confirmed inflammatory etiology. While this may reflect to some degree a referral bias, it also reflects the confusion surrounding the term "transverse myelitis" among clinicians in the community. The use of this term is challenging since inflammatory myelopathies do not always present in agreement with the "classic" definition of the syndrome, as unilateral, asymmetric, and chronic presentations can occur,[17] signs of upper motor neuron disease are often not present acutely, and sensory levels are frequently absent.[1,9] In addition, the term TM is often used by clinicians to describe involvement of the spinal cord in different pathologic conditions even without clear evidence of inflammation, an approach that delays proper diagnosis and treatment. Hence, it is critically important to identify clinical biomarkers that help establish a correct etiologic diagnosis.

In our analysis, the clinical features distinguishing IM from other causes of myelopathies at first presentation included the temporal profile of symptoms (initial onset to nadir dysfunction), the initial motor examination findings, and the pattern of lesion distribution on MRI. Since the temporal profile was the most helpful predictor in improving the diagnostic accuracy, it could be used in the clinical setting to guide the diagnosis of myelopathy. A subacute presentation suggests an inflammatory etiology, as described previously,[2,9] while a hyperacute presentation suggests a spinal cord ischemic stroke. A chronic evolution suggests a vascular lesion, such as VM- AVM/AVF, a chronic SM, or other causes of myelopathy. These findings are in agreement with previous descriptions of spinal cord stroke,[18,19] compressive myelopathies,[4,5] and vascular malformations.[7,20]

Another important factor to consider is the medical history. In our cohort, a history of sudden back pain or worsening by exercise pointed towards a vascular etiology, which is in accordance with previous descriptions.[1] Conversely, a prior diagnosis of systemic inflammatory disorder suggests an inflammatory myelopathy. Several systemic disorders are known to potentially cause

Figure 2 Spinal cord MRI lesion patterns in patients with myelopathies



(A) Heatmap representation of lesion distribution frequency for each diagnostic category. The y axis represents sagittal localization based on using the vertebral levels (C2–L2) and the x–z axes represent the axial distribution of the lesion as affecting the anterior, central, lateral, or posterior regions of the spinal cord. Frequency for each localization ranges from 0% (yellow) to 100% (bright red). (B) MRI examples in the different myelopathy diagnostic categories. (B.a) Cervical spine MRI from a patient with idiopathic inflammatory myelopathy reveals signal intensity abnormality in T2-weighted sequences and enhancement in the postero-lateral region of the cervical cord (T1-weighted + gadolinium [Gad]). (B.b) Cervical spine MRI from a patient with vascular myelopathy (VM)–ischemic/stroke shows an anterior signal intensity abnormality in T2-weighted sequences in both sagittal and axial views, which appears unenhanced in T1-weighted sequences + Gad. (B.c) Thoracic MRI in a patient with a VM–arteriovenous fistula (AVF) seen as a longitudinal extensive myelopathy and diffuse intra-axial enhancement in the central cord; there are enlarged vessels in the dorsal surface of the cord (arrow). (B.d) Cervical spine MRI in a patient with spondylotic myelopathy shows signal intensity abnormality in T2-weighted sequences and patchy enhancement (T1 + Gad) in the central cervical cord. AVM = arteriovenous malformations.

Table 3 Results for top discriminatory model to predict the myelopathy diagnostic category[a]

Variable	Integrated discrimination increment (95% CI)	Net reclassification improvement (95% CI)	Correct classification rate	Multinomial AUC[b]
Lesion enhancement + pleocytosis	—	—	0.67	0.32
+ Temporal profile[c]	0.16 (0.12–0.19)	0.14 (−0.01 to 0.27)	0.77	0.54
+ Motor examination findings	0.10 (0.06–0.14)	0.05 (−0.11 to 0.21)	0.70	0.46
+ Posterior cord lesion	0.03 (0.01–0.04)	0.07 (−0.05 to 0.19)	0.68	0.37
+ Conus medullaris lesion	0.02 (0.00–0.04)	0.08 (−0.05 to 0.20)	0.69	0.37
All of the above[d]	0.38 (0.28–0.47)	0.34 (0.08–0.61)	0.87	0.76

Abbreviations: AUC = area under the curve; CI = confidence interval.
[a] Model was derived in the training set; values displayed are derived from fitting the model with the selected characteristics in the testing set.
[b] In the multinomial extension, a noninformative value is 1/M!, where M is the number of outcome categories. In this case, M = 5 and a non-informative multinomial AUC is 1/5! = 1/125 = 0.008.
[c] Multinomial model includes lesion enhancement, pleocytosis, and individual selected characteristic (e.g., [lesion enhancement, pleocytosis, temporal profile] or [lesion enhancement, pleocytosis, motor examination]).
[d] Multinomial model including lesion enhancement, pleocytosis, temporal profile, motor examination, conus medullaris lesion location, posterior cord lesion.

myelitis, such as Sjögren syndrome, systemic lupus erythematosus, and sarcoidosis,[1,13] making a thorough medical history crucial.

The assessment of lesion distribution on MRI is also extremely important. The axial pattern may provide meaningful information about the underlying pathogenic mechanism. For instance, MS would preferentially affect the myelinated tracts in the posterolateral spinal cord. Similarly, a lesion affecting a discrete vascular distribution or a spinal cord watershed area would be highly suggestive of an ischemic stroke. Venous congestion and venous hypertension in the setting of VM-AVM/AVF or compression of the vasculature in SM would more frequently affect the central cord region. The classification of LE vs non-LE lesions was less helpful; while non-LE was suggestive of IM, the differential diagnosis of LE lesions remained broad, and included inflammatory etiologies (NMOSD, sarcoidosis, rheumatologic and idiopathic myelitis) as well as VM and SM lesions.

Regarding MRI and CSF findings traditionally considered to be associated with IM, such as pleocytosis, elevated CSF protein, and Gd+, our cohort showed that these features were not specific to the IM group. This is highlighted by the low diagnostic accuracy in our model when considering only Gd+ and pleocytosis to differentiate IM from other myelopathies. Moreover, previous studies described Gd+ and CSF pleocytosis occurring in vascular[6] and spondylotic myelopathies.[5] A recent study of 56 patients with spondylotic myelopathy showed CSF pleocytosis in 12.5%, elevated CSF protein in 70%, and Gd+ lesions in up to 80% of patients.[4] The high frequency of these CSF and MRI features in non-inflammatory myelopathies may account for their frequent misdiagnosis as TM. Part of the difficulty in making this distinction arises from the common assumption that all CNS inflammation is due to a primary inflammatory disorder. Any injury to the CNS has the potential to cause a secondary inflammatory response that may manifest with some degree of pleocytosis or disruption of the blood–brain barrier, causing Gd+; in addition, hemodynamic changes in the lesion such as vasodilation and "luxury perfusion" may also result in Gd+.[21] This situation is well-illustrated by Gd+ in ischemic brain strokes within 1 week of onset.[22] Thus, evidence of a Gd+ lesion on MRI or CSF pleocytosis is not definitively diagnostic of a primary inflammatory disease, and immunosuppressive therapy may not be warranted. Instead, these findings should be considered with the temporal profile and clinical presentation of the myelopathy, motor examination findings, and MRI lesion distribution (particularly, the axial pattern). Taking these features into account can increase significantly the correct diagnostic classification of myelopathies.

The term TM should be used with caution as IMs do not always present with a "transverse" sensory level and non-IM may mimic inflammatory disorders. This highlights some of the limitations of the 2002 acute TM criteria,[2] which require a clear sensory level and bilateral findings to diagnose TM and additionally rely on CSF pleocytosis and MRI Gd+ to define inflammation; the criteria could perhaps be improved by not using the word "transverse," not requiring bilateral findings or a sensory level, and emphasizing the importance of the temporal profile and consideration of non-inflammatory myelopathies even in presence of CSF pleocytosis or MRI Gd+. It would be less confusing to describe the myelopathic syndrome as being caused either by a primary inflammatory or non-inflammatory etiology, the latter secondary to a specific pathologic process. Once a diagnostic category is established, a critical analysis of ancillary tests, including brain MRI and spinal angiography, as indicated, is necessary to define the specific etiology before assigning the label of idiopathic TM.

This study is limited by its retrospective nature. By analyzing the inflammatory group as a category, this study may not reflect important differences among specific etiologies within the inflammatory group such as MS vs NMOSD or NMOSD vs sarcoidosis myelopathy as has been shown previously. In addition, as a major referral center, cases that pose a diagnostic challenge

are overrepresented in our cohort; therefore, the percent of IM may not be reflective of what is seen in the community.

Myelopathies may encompass a wide differential diagnosis that requires a thorough diagnostic workup with consideration of inflammatory and non-inflammatory etiologies. The temporal profile of symptoms might serve as a potential clinical biomarker in the differential diagnosis of myelopathies, which should be considered in conjunction with a critical analysis of MRI and CSF characteristics.

Author contributions

Paula Barreras: study design, acquisition of data, analysis and interpretation of the data, study coordination, drafting and revising of the manuscript. Kathryn C. Fitzgerald: statistical analysis, analysis and interpretation of the data, revising the manuscript. Maureen A. Mealy: acquisition and interpretation of the data, revising the manuscript. Jorge A. Jimenez: study design, acquisition of the data, revising the manuscript. Daniel Becker: examination of patients, revising the manuscript. Scott D. Newsome: examination of patients, interpretation of data, revising the manuscript. Michael Levy: examination of patients, interpretation of data, revising the manuscript. Philippe Gailloud: study design, interpretation of the data, revising the manuscript. Carlos A. Pardo: conception and design of the study, obtaining funding, study supervision, examination of patients, analysis and interpretation of the data, drafting and revising the manuscript.

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Clinical biomarkers differentiate myelitis from vascular and other causes of myelopathy

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Study question

Which clinical and paraclinical features of patients diagnosed with transverse myelitis (TM) can differentiate those who have inflammatory myelopathies from those with non-inflammatory myelopathies?

Summary answer

The temporal profile of symptoms is the most powerful biomarker for differentiating inflammatory and non-inflammatory myelopathies.

What is known and what this paper adds

TM is a highly heterogeneous inflammatory syndrome; non-inflammatory myelopathies are often misdiagnosed as TM. Gadolinium enhancement in MRI and CSF pleocytosis have been used to define inflammation in TM. This study shows that these features are nonspecific and that the subacute onset of symptoms, the absence of flaccid weakness, and the presence of multifocal (cervical and thoracic, and posterior lateral) lesions on MRI suggest an inflammatory etiology.

Participants and setting

The study examined 457 of 575 patients who had been diagnosed with TM and referred to a specialized myelopathy center between 2010 and 2015. The other 118 were excluded due to incomplete or unverifiable information.

Design, size, and duration

This study retrospectively analyzed patient records, including demographic characteristics, medical histories, temporal symptom profiles, initial symptoms, and results from neurologic, MRI, and CSF examinations. The final diagnosis was classified as inflammatory, vascular, spondylotic, or other causes of myelopathy. Multinomial regression modeling was applied to determine characteristics associated with each final diagnosis and predictors that would improve classification accuracy.

Variables considered	Correct classification rate	Multinomial area under the curve
MRI lesion enhancement and pleocytosis	0.67	0.32
+ Temporal profile	0.77	0.54
+ Motor exam findings	0.70	0.46
+ Posterior cord lesion	0.68	0.37
+ Conus medullaris lesion	0.69	0.37
All of the above	0.87	0.76

Main results and the role of chance

Of the 457 myelopathies evaluated, 247 (54%) patients had a confirmed inflammatory etiology. Compared to inflammatory cases, vascular myelopathies related to ischemic strokes were more likely hyperacute (odds ratio [OR] 35.19, 95% confidence interval 8.92–138.90), and other non-inflammatory cases were more likely to exhibit chronic patterns (ORs >3). Adding the temporal profile, initial motor examination features and MRI pattern of lesion distribution to the multinomial predictive model provided greater predictive power than only considering CSF pleocytosis and MRI gadolinium enhancement. Of all predictors, the temporal profile contributed the most to the increased discriminatory power.

Bias, confounding, and other reasons for caution

The study is limited by its retrospective nature. The study also grouped all inflammatory myelopathy cases together, not accounting for important distinctions between various types of inflammatory myelopathies.

Generalizability to other populations

This study examined cases at a major referral center, and therefore, diagnostically challenging cases were probably overrepresented in the cohort. The frequency of inflammatory myelopathies may not reflect that found in the general patient population.

A draft of the short-form article was written by M. Dalefied, a writer with Editage, a division of Cactus Communications. The authors of the full-length article and the journal editors edited and approved the final version.

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