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ORIGINAL ARTICLE

Cervical spinal degenerative disease in multiple sclerosis

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Abstract

Background and purpose: Root and cord irritation from cervical spinal degenerative disease (SDD) may share clinical features with progressive multiple sclerosis (MS), so diagnostic overshadowing may occur. We hypothesized that cervical stenotic SDD is commoner in people with progressive MS, compared to controls.

Methods: A retrospective case–control study of 111 cases (56 with progressive MS and 55 age- and sex-matched controls) was conducted. Five types of cervical SDD (disc degeneration, posterior disc protrusion, endplate changes, canal stenosis and foraminal stenosis) were assessed objectively on magnetic resonance imaging using published scales. Multivariable regression analysis was performed.

Results: Moderate-to-severe cervical spinal degeneration occurred more frequently in progressive MS, compared to controls. In multivariable regression, foraminal stenosis was three times more likely in progressive MS (odds ratio 3.20, 95% confidence interval 1.27, 8.09; $p = 0.014$), and was more severe ($p = 0.009$). This finding was confirmed on retrospective evaluation of clinical radiology reports in the same population. Foraminal stenosis was twice as likely in progressive MS, compared to relapsing-remitting MS.

Conclusions: People with progressive MS are susceptible to foraminal stenosis. A higher index of suspicion for cervical SDD is required when appropriate neurological symptoms occur in the setting of progressive MS, to guide appropriate treatment or monitoring.

KEYWORDS
disc disease, foraminal stenosis, multiple sclerosis, radiculopathy, spinal degenerative disease

INTRODUCTION

Cervical spinal degenerative disease (SDD) and multiple sclerosis (MS) share clinical features, and misdiagnosis may occur. While cervical radicular pain in people with MS (PwMS) [1] should prompt a search for a compressive cause, it may uncommonly be a presenting symptom of MS in the absence of radicular compression [2–4], mostly due to root entry zone lesions. Painless cervical nerve root compression may occur in PwMS [5], where it is possible that pain pathways have been disrupted. Myelopathic symptoms could result from spinal cord demyelination or compressive canal stenosis; in particular, lower cervical or thoracic disc protrusions are easily missed [6] in people with progressive MS because a gradually worsening spastic paraparesis with bladder disturbance is one of the main clinical features in progressive MS and the cord may not be routinely imaged during follow-up. Multilevel disc herniations and compressive

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myelopathy may mimic the multifocal nature of MS [7]. Lhermitte's sign can occur in cervical myelopathy [8] or milder forms of cervical SDD [9]. In both conditions, symptoms can come on sub-acutely and subsequently demonstrate a progressive course. In summary, there is a real risk of "diagnostic overshadowing", the erroneous attribution of new symptoms to an underlying health condition, especially in individuals with progressive neurological disability [10].

A study in 2017 examined the prevalence of disc dehydration and protrusion in 42 PwMS versus 42 age- and sex-matched controls, and found these abnormalities to be more common in MS [11]. Another study showed a high incidence of disc herniation (19.4%) in 330 PwMS, although no control population was included [12]. It remains unclear whether foraminal and canal stenosis occurs more commonly in MS. A predisposition of PwMS to stenotic SDD has clinical implications, since decompressive surgery may relieve symptoms, and should lead to heightened awareness of SDD when PwMS present with new or progressive neurological symptoms. Hence we undertook a retrospective case–control study to compare the incidence of these and other types of SDD in progressive MS versus age- and sex-matched control subjects.

METHODS

Study setting

The study was conducted after national and institutional ethical approvals (Health Research Authority 18/LO/0938, University of Southampton ERGO 44539) at the University Hospital Southampton NHS Foundation Trust (Southampton, UK), which provides a tertiary neurological service. During the study period, magnetic resonance (MR) image acquisition in the hospital was almost exclusively performed on either a 3-T Skyra or a 1.5-T Aera scanner (Siemens Healthineers). The MR protocol for cervical spine imaging always included T1- and T2-weighted imaging.

Inclusion and exclusion criteria

For PwMS, inclusion criteria were: (1) McDonald criteria-confirmed MS [13] and (2) cervical spine MR imaging carried out between 2013 and 2018 at the study centre. MS subtypes were defined according to the 2013 Lublin recommendations [14]. For control cases, inclusion criteria were: (1) cervical spine MR imaging during the same timeframe at the study centre and (2) no clinical, radiological or laboratory evidence or suspicion of MS or other spinal inflammatory disease. An inclusion criterion common to both groups was age 18 years or above. In order to avoid selection biases, exclusion criteria for both groups comprised: (1) symptoms suggestive of cervical SDD at the time of imaging, since this study was conducted in a hospital population; (2) history of spinal trauma [15] or surgery [16] due to risk of subsequent SDD; and (3) known SDD in another spinal region, since this is associated with cervical SDD [17].

Study design

This was a retrospective case–control study consisting of two substudies.

In the main study, previously acquired cervical spine images from consecutive people with progressive MS and control subjects were manually reassessed for the presence and severity of five types of cervical SDD (disc degeneration, posterior disc protrusion, end plate changes, canal stenosis, foraminal stenosis) by a double board-certified neurologist and neuroradiologist, using the published grading systems detailed in Table 1. The worst affected cervical spinal level was graded. The assessor was not informed of the clinical details and was blinded to the radiology reports, but it was not possible to ensure complete blinding in MS cases with cord lesions (41% of cases). To assess intra-rater variability, the reader was asked to re-read 20 randomly selected images, renamed for blinding purposes, more than a year later; there was 93% agreement within one score between the two assessments.

To validate these findings with different image readers, a second pragmatic study was conducted using already available radiology reports to identify the presence and severity of stenotic cervical SDD (foraminal and canal stenosis) amongst PwMS, compared to controls. The reader from the first study was not involved with the second study.

Statistics

Data were prepared in Excel 2016 and analysis was performed using IBM SPSS Statistics version 27. Mann–Whitney and independent

TABLE 1 Grading systems used to determine the severity of cervical spinal degenerative disease in this study

Type of cervical spinal degenerative disease	Grading system	Grades
Disc degeneration	Modified Pfirmann Grading System for Lumbar Intervertebral Disc Degeneration (2007)	1–8
Posterior disc protrusion	Matsumoto et al. (1998)	0–2
Endplate changes	Rajasekaran et al. (2008)	1–6
Canal stenosis	Kang et al. (2011)	0–3
Foraminal stenosis	Park et al. (2013)	0–3

samples t-tests were used for nonparametric and parametric data, respectively. Logistic regression was used to determine the association between presence of each type of cervical SDD (as the dependent variable), and diagnosis of MS versus controls. Ordinal regression was used to determine the associations of the severity of cervical SDD. The logit link function was used, and the proportionality odds assumption was fulfilled, unless otherwise indicated. All the regression models were adjusted for age [18] and gender [19] unless otherwise indicated since these are the strongest risk factors known to predispose to SDD. Other risk factors tested in sensitivity analyses included smoking [20], body mass index (BMI) [18] and number of comorbidities as a marker for poor health [21]. A p value <0.05 was taken to indicate statistical significance.

RESULTS

Main study: objective assessment

In this study, the cervical spine images of 56 progressive MS and 55 control subjects were retrospectively re-examined and graded objectively for presence and severity of SDD types using established grading systems (Table 1). The clinical and demographic characteristics of the progressive MS and control groups are laid out in Table 2. None of the individuals with progressive MS had spinal cord relapses or received steroids. Although age and sex were not significantly different between MS and control groups, there was a higher ratio of males in the control group. The occurrence of various types of SDD in the MS and control groups is shown in Table 3.

Age and sex are the strongest predictors of SDD in the general population [18,19]. Logistic regression modelling adjusting for these two covariates demonstrated that people with MS were over three times more likely to develop foraminal stenosis compared to controls (odds ratio [OR] 3.2, 95% confidence interval [CI] 1.27–8.09; p = 0.014 [Table 4]). They were also significantly more likely to have higher grades of foraminal stenosis at the time of imaging (OR 3.4, 95% CI 1.3–8.5; p = 0.009 [Table 4]). There was no difference in other types of SDD between the MS and the control groups. Sensitivity analysis to explore the robustness of these findings while controlling for additional risk factors (smoking, BMI and number of comorbidities) yielded similar results (Appendix S1).

Within the MS group (n = 56), the univariate association of the severity of SDD types with various potential susceptibility factors (age, gender, smoking, BMI and number of comorbidities) was examined; age, but not the other risk factors, was associated with severity of various types of SDD (Table 5).

In order to examine whether proximity to a cervical MS plaque was associated with the severity of foraminal stenosis, the MS cases were divided into two groups: in 16 individuals the MS plaque and foraminal stenosis occurred at the same intervertebral level, or within one level's difference, while in 40 individuals the MS plaque was more distant or not present. Cases with severe canal stenosis (>3) with signal change in the cord at the same level were excluded from this analysis (n = 4). There was no difference in the severity of foraminal stenosis between these two groups (Mann–Whitney U-test, Z = −0.282, p = 0.778).

TABLE 2 Demographic data for participants (n = 111) in the primary analysis

Characteristic	MS	Controls	p
Number	56	55	
Age, years	54 ± 8.3	53 ± 8.6	0.464[a]
Sex			
Male	25	34	0.565[b]
Female	31	21	
Smoking status			
Never smoked	11	16	0.883[b]
Ex-smoker	8	10	
Current smoker	5	9	
Data not recorded	32	20	
BMI,			
<18.5 kg/m^2	0	0	0.297[b]
18.5–24.9 kg/m^2	15	8	
25.0–29.9 kg/m^2	15	10	
> 30.0 kg/m^2	14	17	
Data not recorded	12	20	
Number of comorbidities	1.6 ± 1.7	2.7 ± 2.1	**0.004**[c]
Progressive MS type			
Primary	32		
Secondary	24		
MS duration, years	12.2 ± 8.6		
EDSS at time of study	5.7 ± 1.30		

Note: Data are shown as mean ± standard deviation where applicable. Bold font indicates p < 0.05.

For p values: [a]independent samples t-test; [b]chi-squared test; [c]Mann–Whitney U-test.

TABLE 3 Frequency of moderate-severe and severe cervical spinal degenerative disease in multiple sclerosis and control groups

		Frequency	
Cervical SDD	Grades defining severe SDD	MS (n = 56)	Control (n = 55)
Disc degeneration	6–8	46.4%	36.4%
Posterior disc protrusion	1–2	69.6%	61.8%
Endplate changes	5–6	16.1%	5.5%
Canal stenosis	3	7.1%	0%
Foraminal stenosis	2–3	8.9%	0%

Abbreviations: MS, multiple sclerosis; SDD, spinal degenerative disease.

TABLE 4 Prevalence of cervical spinal degenerative disease (presence or absence, of any severity) and severity in the multiple sclerosis group (n = 56) compared with the control group (n = 55), adjusting for age and sex

	Prevalence		Severity	
Cervical SDD	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Disc degeneration	Some degree present in all		1.1 (0.6, 2.1)	0.764
Posterior disc protrusion	1.40 (0.61, 3.18)	0.427	1.0 (0.5, 2.1)	0.917
Endplate changes	0.91 (0.05, 15.50)	0.946	1.5 (0.8, 3)	0.234
Canal stenosis	1.45 (0.61, 3.46)	0.397	1.0 (0.5, 2.1)	0.929*
Foraminal stenosis	3.20 (1.27, 8.09)	**0.014**	3.4 (1.3, 8.5)	**0.009**

In the ordinal regression with severity as dependent variable, the proportionality odds assumption was not met where an asterisk is present. Bold font indicates $p < 0.05$.

Abbreviations: CI, confidence interval; OR, odds ratio; SDD, spinal degenerative disease.

TABLE 5 The effect of age (by decade) on the severity of cervical spinal degenerative disease within the multiple sclerosis group (n = 56)

	Association of age with SDD severity	
Cervical SDD	**OR (95% CI)**	***p***
Disc degeneration	2.5 (1.4, 4.6)	**0.003**
Posterior disc protrusion	1.6 (0.9, 2.9)	0.135
Endplate changes	3.0 (1.5, 5.8)	**0.001**
Canal stenosis	2.1 (1.1, 4)	**0.023**
Foraminal stenosis	2.2 (1, 4.5)	**0.04**

Bold font indicates $p < 0.05$.

Abbreviations: CI, confidence interval; OR, odds ratio; SDD, spinal degenerative disease.

Pragmatic study: radiology reports

In order to confirm reproducibility by different image assessors and to determine whether the same finding could be recapitulated using routine radiology reports as generated in clinical practice, without time-consuming objective grading systems, the radiology reports of the same 56 progressive MS and 55 control consecutive cases were retrieved. The presence or absence of canal and foraminal stenosis, and a subjective descriptor of their severity (mild, mild-moderate, moderate, moderate-severe or severe), could be consistently extracted from the radiology reports. In this dataset, people with progressive MS were more likely to develop foraminal stenosis, compared with controls [OR (95% CI = 2.4 (1.09–5.14), p = 0.03], adjusting for age and sex (Table 6). There was more severe foraminal stenosis in the MS group, compared to controls (Table 6).

Encouraged by the fact that subjective reporting was sufficient to detect a difference in foraminal stenosis between MS and controls, the presence of stenotic SDD deduced from radiology reports was compared between relapsing-remitting (n = 153) and progressive (n = 78) forms of all eligible MS cases. Individuals with progressive MS were over twice as likely to develop foraminal stenosis compared with the RRMS group [OR (95% CI) = 2.17 (1.12–4.18), p = 0.021], adjusting for age and sex.

DISCUSSION

In 1949, Bucy noted "the simulation of multiple sclerosis and other degenerative diseases of spinal cord by herniation of cervical intervertebral discs" [22,23]. Subsequently in 1957, Brain and Wilkinson [24] reported 17 cases with coexistent cervical spondylosis and MS. Correct diagnosis influences management, either with high-dose steroids or disease-modifying immunotherapies in MS, or nerve root injections or surgical decompression in SDD. Delay in correct diagnosis and institution of the appropriate management strategy may result in irreversible disability.

This study provides evidence for a susceptibility to stenotic cervical SDD in people with MS. The predisposition of PwMS to develop SDD may be due to various factors. Reduced exercise tolerance, high BMI [25] and reduced core muscle strength [26] may lead to abnormal posture and loss of the normal spinal curvature

TABLE 6 Prevalence of stenotic cervical spinal degenerative disease (of any severity) and severity in the multiple sclerosis group (n = 56) compared with the control group (n = 55), adjusting for age and sex, using subjective data from clinical radiology reports

	Prevalence		Severity	
Cervical SDD	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Canal stenosis	0.94 (0.25, 3.49)	0.921	0.9 (0.2, 3.4)	0.893
Foraminal stenosis	2.40 (1.09, 5.15)	**0.030**	2.5 (1.2, 5.6)	**0.021**

Note: Subjective reports of severity (mild, mild-moderate, moderate, moderate-severe or severe) was converted to a five point scale. The ordinal regression with severity as dependent variable controlled for age, but not sex (to fulfil proportionality odds assumption). Bold font indicates $p < 0.05$.

Abbreviations: CI, confidence interval; OR, odds ratio; SDD, spinal degenerative disease.

[11], placing excessive or non-physiological mechanical stresses on the spinal column. PwMS are usually low in vitamin D [27], which is essential for musculoskeletal health, and SDD is associated with low levels of this vitamin [28]. Bone health is suboptimal in MS (via a number of mechanisms including reduced physical activity, smoking, alcohol and substance misuse, corticosteroid and anticonvulsant use) [29]. The cervical cord is disproportionately affected by MS [30] and this inflammation may trigger or accelerate degenerative change in the adjoining spinal structures via a bystander mechanism.

The contribution of MS and SDD to symptoms may be hard to disentangle. Imaging may help by providing evidence of compression or MS lesion at the neuroanatomically relevant site. On MR images, white matter lesions in the cord are different in MS versus cord compression. In MS, plaques appear as characteristically asymmetric and wedge-shaped lesions [31], peripherally located in the dorsal and lateral columns. In cord compression, they are usually bilateral, symmetric and central [32]. Contrast enhancement can occur with spondylotic myelopathies; it may be distinguished from demyelination by persistent enhancement lasting several months and location well within the boundaries of the associated T2 hyperintensity [33]. A scoring system has been devised, to help differentiate white matter lesions due to compressive myelopathy and MS [34], which awaits validation. It becomes difficult when typical MS lesions and SDD are both present together at the same clinically relevant location. Further clinical and radiological evaluation with time may help to pinpoint which of the two processes is changing in phase with symptoms.

Although Brain and Wilkinson [24] recommended against decompressive surgery in 1957, a lot has improved since then, including diagnostic tests, neurointerventional and surgical techniques, and our understanding of both conditions, so that carefully selected individuals will now benefit from decompressive surgery [35]. A recent review included all studies examining outcomes of decompressive surgery in PwMS with SDD [35]. It was concluded that decompressive surgery may be indicated for relief of neck pain and radicular symptoms, and that myelopathic symptoms will either reach stability if compressive in origin, or progress if due to MS. It was further concluded that the collective evidence suggests that decompressive surgery does not result in exacerbations of MS. Overall, these conclusions represent a marked improvement since the 1940s when Brain commented that "patients with disseminated sclerosis in general stand surgery badly".

This study has a number of strengths and limitations. Strengths include the case–control design and the employment of objective grading systems for each type of SDD. Age was significantly associated with cervical SDD, which validates the dataset, since this would be expected. The finding that PwMS are predisposed to foraminal stenosis was robust to sensitivity analyses and was reproduced using two approaches: objective grading by a semi-blinded assessor and analysis of hospital radiology reports. Limitations include the fact that imaging was not performed on the same scanner using the same protocol. However, the usage of different scanners was balanced across the MS and control groups. This was a retrospective study, and future prospective studies would be able to collect more phenotypic data in both MS and controls (including, for instance, physical activity, alcohol and substance misuse, corticosteroid and anticonvulsant use, vitamin D), with a homogenous imaging protocol to provide quantitative estimates of MS lesion number and volume, and evoked potential studies to assess cord function. Finally, the study was conducted in a hospital population, and therefore, one cannot assume that findings are generalizable at an epidemiological level.

It is possible that coexisting MS and cervical SDD interact, resulting in exacerbation or worsening of both. At autopsy, Brain and Wilkinson [24] had noted that cord demyelination was most extensive at compression sites. Lesions typical of MS were more likely to occur at levels of existing cervical spondylosis, versus levels without, in PwMS [36]. The pathophysiological basis for such an interaction could include bystander activation of local inflammatory responses in either cord parenchyma or surrounding musculoskeletal structures, as well as compressive ischaemia of the cord. Degenerated discs are known to contain high levels of matrix metalloproteinases and proinflammatory mediators such as interleukin (IL)-1β, tumour necrosis factor-α, IL-6 and IL-8 [37]. MS-type pathology is aggravated in the presence of bystander inflammation via matrix metalloproteinases [38] and hypoxia [39], and inflammation may contribute to SDD [37]. Further autopsy and imaging studies are needed to study these possible interactions.

DATA AVAILABILITY STATEMENT

Data are available from the corresponding author, upon reasonable request, subject to institutional agreements and ethical approvals.

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REFERENCES

1. Mullen AE, Wilmarth MA, Lowe S. Cervical disk pathology in patients with multiple sclerosis: two case reports. *Phys Ther*. 2012;92(8):1055-1064.
2. Ramirez-Lassepas M, Tulloch JW, Quinones MR, Snyder BD. Acute radicular pain as a presenting symptom in multiple sclerosis. *Arch Neurol*. 1992;49(3):255-258.
3. Tosi L, Righetti CA, Zanette G, Beltramello A. A single focus of multiple sclerosis in the cervical spinal cord mimicking a radiculopathy. *J Neurol Neurosurg Psychiatry*. 1998;64(2):277.
4. Uldry PA, Regli F. Pseudoradicular syndrome in multiple sclerosis. 4 cases diagnosed by magnetic resonance imaging. *Rev Neurol (Paris)*. 1992;148(11):692-695.
5. Burgerman R, Rigamonti D, Randle JM, Fishman P, Panitch HS, Johnson KP. The association of cervical spondylosis and multiple sclerosis. *Surg Neurol*. 1992;38(4):265-270.
6. Bohlman HH, Zdeblick TA. Anterior excision of herniated thoracic discs. *J Bone Joint Surg Am*. 1988;70(7):1038-1047.
7. Korovessis P, Maraziotis T, Stamatakis M, Baikousis A. Simultaneous three-level disc herniation in a patient with multiple sclerosis. *Eur Spine J*. 1996;5(4):278-280.
8. Signorini GC, Beltramello A, Pinna G, Dalle OG. The significance of preoperative neurological disorders in predicting outcome of cervical spondylotic myelopathy after surgery. *J Neurosurg Sci*. 1984;28(2):89-92.

9. Chen JJ, Kung KL, Chen CJ, Yeh YS, Chen DL, Tang YM. Reverse Lhermitte's phenomenon provoked by cervical cord compression. *Acta Neurol Taiwan*. 2012;21(1):35-38.
10. Iezzoni LI. Dangers of diagnostic overshadowing. *N Engl J Med*. 2019;380(22):2092-2093.
11. Xydis VG, Zikou AK, Kostadima V, Astrakas LG, Kosta P, Argyropoulou MI. The association between multiple sclerosis and spondylosis: when and why. *Eur J Radiol*. 2017;91:47-51.
12. Drenska KV, Kaprelyan AG, Tzoukeva AJ, Georgiev R, Todorov IT. Simultaneous disc herniation in patients with multiple sclerosis. *J Int Med Assoc Bulgaria*. 2013;19(1):399-401.
13. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. 2018;17(2):162-173.
14. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014;83(3):278-286.
15. Alkhatib B, Rosenzweig DH, Krock E, et al. Acute mechanical injury of the human intervertebral disc: link to degeneration and pain. *Eur Cell Mater*. 2014;28:98-111; discussion 110-111.
16. Matsumoto M, Okada E, Ichihara D, et al. Anterior cervical decompression and fusion accelerates adjacent segment degeneration: comparison with asymptomatic volunteers in a ten-year magnetic resonance imaging follow-up study. *Spine (Phila Pa 1976)*. 2010;35(1):36-43.
17. Okada E, Matsumoto M, Fujiwara H, Toyama Y. Disc degeneration of cervical spine on MRI in patients with lumbar disc herniation: comparison study with asymptomatic volunteers. *Eur Spine J*. 2011;20(4):585-591.
18. Teraguchi M, Yoshimura N, Hashizume H, et al. Prevalence and distribution of intervertebral disc degeneration over the entire spine in a population-based cohort: the Wakayama Spine Study. *Osteoarthritis and Cartilage*. 2014;22(1):104-110.
19. Matsumoto M, Fujimura Y, Suzuki N, et al. MRI of cervical intervertebral discs in asymptomatic subjects. *J Bone Joint Surg Br Vol*. 1998;80-B(1):19-24.
20. Battie MC, Videman T, Gill K, et al. Smoking and lumbar intervertebral disc degeneration: an MRI study of identical twins. *Spine (Phila Pa 1976)*. 1991;16(9):1015-1021.
21. Croft PR, Lewis M, Papageorgiou AC, et al. Risk factors for neck pain: a longitudinal study in the general population. *Pain*. 2001;93(3):317-325.
22. Bucy PC. Simulation of multiple sclerosis and other degenerative diseases of spinal cord by herniation of cervical intervertebral discs. *Miss Valley Med J*. 1949;71(3):85-87.
23. Bucy PC. The simulation of multiple sclerosis and other degenerative diseases of the spinal cord by herniation of cervical intervertebral discs. *Cinci J Med*. 1949;30(1):16-18.
24. Brain R, Wilkinson M. The association of cervical spondylosis and disseminated sclerosis. *Brain*. 1957;80(4):456-478.
25. Munger KL, Chitnis T, Ascherio A. Body size and risk of MS in two cohorts of US women. *Neurology*. 2009;73(19):1543-1550.
26. Yoosefinejad AK, Motealleh A, Khademi S, Hosseini SF. Lower endurance and strength of core muscles in patients with multiple sclerosis. *Int J MS Care*. 2017;19(2):100-104.
27. Murphy O, Zandi MS, Lindenberg N, Murphy E, Chataway J. Bone health in patients with multiple sclerosis relapses. *Mult Scler Relat Disord*. 2016;6:75-80.
28. Zolfaghari F, Faridmoayer A, Soleymani B, Taji M, Mahabadi M. A Survey of vitamin D status in patients with degenerative diseases of the Spine. *Asian Spine J*. 2016;10(5):834-842.
29. Dobson R, Yarnall A, Noyce AJ, Giovannoni G. Bone health in chronic neurological diseases: a focus on multiple sclerosis and parkinsonian syndromes. *Pract Neurol*. 2013;13(2):70-79.
30. Bot JC, Barkhof F, Polman CH, et al. Spinal cord abnormalities in recently diagnosed MS patients: added value of spinal MRI examination. *Neurology*. 2004;62(2):226-233.
31. Moccia M, Ruggieri S, Ianniello A, Toosy A, Pozzilli C, Ciccarelli O. Advances in spinal cord imaging in multiple sclerosis. *Ther Adv Neurol Disord*. 2019;12:1756286419840593.
32. You JY, Lee JW, Lee E, Lee GY, Yeom JS, Kang HS. MR classification system based on axial images for cervical compressive myelopathy. *Radiology*. 2015;276(2):553-561.
33. Wang Y, Newsome SD. Cervical spondylotic myelopathy mimicking transverse myelitis. *Mult Scler Relat Disord*. 2019;31:131-133.
34. Givon U, Hoffman C, Friedlander A, Achiron A. Cervical MRI rating scale: innovative approach to differentiate between demyelinating and disc lesions. *Clin Neuroradiol*. 2019;29(4):639-644.
35. Purvis TE, Lubelski D, Mroz TE. Is decompressive surgery for cervical spondylotic myelopathy effective in patients suffering from concomitant multiple sclerosis or Parkinson's disease? *Brain Sci*. 2017;7(4):39.
36. Gratch D, Do D, Khankhanian P, Schindler M, Schmitt JE, Berger JR. Impact of cervical stenosis on multiple sclerosis lesion distribution in the spinal cord. *Mult Scler Relat Disord*. 2020;45:102415.
37. Rider SM, Mizuno S, Kang JD. Molecular mechanisms of intervertebral disc degeneration. *Spine Surgery and Related Research*. 2019;3(1):1-11.
38. Newman TA, Woolley ST, Hughes PM, Sibson NR, Anthony DC, Perry VH. T-cell- and macrophage-mediated axon damage in the absence of a CNS-specific immune response: involvement of metalloproteinases. *Brain*. 2001;124(11):2203-2214.
39. Desai RA, Smith KJ. Experimental autoimmune encephalomyelitis from a tissue energy perspective. *F1000Res*. 2017;6:1973.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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