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Original article

Impact of cervical stenosis on multiple sclerosis lesion distribution in the spinal cord

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ABSTRACT

Objective: To determine whether demyelinating lesions attributable to multiple sclerosis (MS) occur more commonly in regions of pre-existing cervical stenosis (CS).

Design/Methods: One hundred comorbid MS/CS patients and 100 MS-only controls were identified via ICD codes and radiology reports from a retrospective chart review of the records of the University of Pennsylvania Hospital System (UPHS) from January 1st, 2009 to December 31st, 2018. For each patient, axial and sagittal T2 sequences of cervical MRI scans were examined. The cervical cord was split into 7 equal segments comprising the disc space and half of each adjacent vertebral body. Each segment was assessed for the presence of MS lesions and grade 2 CS or higher by previously published criteria. Lesions which were concerning for spondylotic-related signal change based on imaging characteristics were excluded (n = 6, 3.2%). Clinical data was extracted from the electronic medical record.

Results: Average age at the time of MRI was 57.0 +/- 10.5 years and average time with MS diagnosis was 15.3 +/- 9.2 years. The majority of patients had a diagnosis of relapse-remitting MS (81.0%) and the F:M ratio was 3.5. Eighty-five percent of patients were on treatment at the time of MRI, most often glatiramer acetate (35.0%). Spinal segments with at least grade 2 stenosis were significantly associated with the presence of an MS lesion in the same segment (χ^2 = 19.0, p < 0.001, OR = 2.6, 95% CI 1.8-3.7).

Conclusions: Our data suggest there is a significant association between segments of spinal cord with at least moderate CS and segments with MS lesions. Further analysis is required to assess if cervical stenosis is a causative or aggravating factor in multiple sclerosis.

1. Introduction

Multiple sclerosis (MS) is an autoimmune disease that targets myelin in the central nervous system resulting in the destruction of tissue in the brain and/or spinal cord. Its prevalence can range from 2/100,000-100/100,000 depending on location (Poser, 1994). Cervical stenosis (CS) is a much more common condition that is most often the result of age-related arthritic changes in the spinal canal known as spondylosis (Ronthal, 2006). When severe, CS can lead to compression of the spinal cord and cause an associated myelopathy. Presenting symptoms of severe CS and spinal cord MS overlap significantly and can include gait dysfunction, ataxia, extremity weakness, sensory disturbances, and bowel and bladder dysfunction. Because of these similarities, determining the contribution of each disorder to the clinical features of cervical myelopathy can prove to be quite challenging (Young et al., 1999; Bashir et al., 2000; Bashir et al., 2001; Tan et al., 2014; Lubelski et al., 2014; Lubelski et al., 2014; Lubelski et al., 2015; Xydis et al., 2017).

The seminal paper on the relationship between MS and CS was published in 1957 by Brain and Wilkinson (Brain and Wilkinson, 1957). In this small case series of seventeen patients, the authors questioned "whether the clinical picture of [MS] is actually modified in its character or distribution by the supervention of compression of the cervical cord by disc protrusions," but concluded, "this is a question that can only be answered by a larger experience." Interestingly, regarding the two patients in the series who went to autopsy, the authors note that the distribution of MS lesions within the spinal cord "may have been a chance finding, but it is more likely that the site of demyelination was

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associated with the presence of spondylotic bars. These bars may have caused interferences with the blood supply of the cord or actual compression of the cord. It is quite likely that both these factors play a part."

Twenty years later, Oppenheimer, a neuropathologist, examined the spinal cords of 18 deceased multiple sclerosis patients and noted that their lesions tended to be fan-shaped and located in the lateral columns, hypothesizing that these findings suggest that "mechanical stresses" play a role in plaque formation (Oppenheimer, 1978). However, he disagreed with Brain and Wilkinson, as he found no correlation between the lesions and the points of compression by spondylotic "bars". Notably, only 3 of the 18 patients were observed to have severe spondylosis. He did concede that spondylosis could be involved in plaque formation but posited a different mechanism, namely, "tethering" on the dura by fibrous adhesions rather than by direct cord compression.

To date, no large cohort study or randomized trial has been performed to further characterize the relationship between MS and CS. However, many authors have addressed whether cervical decompression surgery is beneficial for patients with both co-morbidities (Young et al., 1999; Bashir et al., 2000; Bashir et al., 2001; Tan et al., 2014; Lubelski et al., 2014; Lubelski et al., 2014; Lubelski et al., 2015; Purvis et al., 2017; Vedantam and Rajshekhar, 2013). Only retrospective data exist to answer this question, and their findings are mixed. Most authors concur that carefully selected MS patients could benefit from decompressive surgery, however, the marginal improvement in symptoms appears to be less than in the population with cervical spondylosis without MS (Purvis et al., 2017).

The objective of this study is to use qualitative imaging analysis to determine if patients with MS have an increased likelihood of exhibiting lesions at levels of existing CS compared to levels without CS. To the best of our knowledge, no studies have been conducted to examine this. If an association proves true, it can shed further light on the pathogenesis and dissemination of MS lesions in the spinal cord, which remain largely unknown.

2. Methods

2.1. Study design

A retrospective cohort study was conducted by examining the medical records of MS patients who were seen at the University of Pennsylvania Health System (UPHS). This study was approved by the UPHS Institutional Review Board. Because data were collected retrospectively and analyzed anonymously, individual patient consents were not required.

Study data were collected and managed using REDCap electronic data capture tools hosted at UPHS (Harris et al., 2009). REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

2.2. Population

A retrospective study of 100 co-morbid MS/CS patients and 100 MS-only control patients was conducted. The study population was selected from a database of MS patients identified via ICD codes who sought care in the University of Pennsylvania Hospital System (UPHS) from January 1st, 2009 to December 31st, 2018. Patients with concurrent CS were identified by querying a database of radiology reports and were included if they had at least two MRIs of the cervical spinal cord available for review that showed at least grade 2 CS as determined by established neuroradiological criteria (Table 1) (Muhle et al., 1998). Matched MS-only controls were obtained by selecting patients with radiology reports that did not include reference to moderate or severe stenosis, and images were reviewed to confirm the absence of at least grade 2 CS. Patients were excluded from the study if they had previous spinal cord surgery, other confounding spinal canal pathology (e.g. congenital cervical spinal fusions or deformities, cervical spinal cord tumors, a history of cervical fracture or trauma), or poor imaging quality.

Table 1
Cervical stenosis grading scheme

Grade	Definition
0	Normal width of the spinal canal, no signs of anterior and posterior subarachnoid space narrowing
1	Partial obliteration of anterior or posterior subarachnoid space or both
2	Complete obliteration of anterior or posterior subarachnoid space or both
3	Anterior or posterior cord impingement or both (pincer effect)

2.3. Data collection

Sagittal and axial T2 images for each patient were reviewed. The cervical cord was split into seven equal "segments" consisting of the cord at the levels of the intervertebral disc space and half of each adjacent vertebral body (Fig. 1). For each of these segments, the presence of stenosis was assessed and graded according to criteria previously mentioned. In addition, the presence of at least one MS lesion was also determined. Lesions were defined as a focal T2 signal hyperintensity seen on at least two planes of view and persisting over time in more than one MRI scan in order to minimize the contribution of artifacts. Lesions were excluded if they showed axial patterns highly associated with compressive myelopathy, namely, if they were very bright, diffuse, or symmetrically bilateral (Fig. 2) (You et al., 2015). However, these radiographic features do not entirely exclude the possibility that such lesions were the consequence of demyelinating disease.

For each patient, clinical parameters were gathered from the electronic medical record, including age, sex, MS subtype, years with diagnosis at the time of MRI, and disease modifying therapy within 6 months of the MRI.

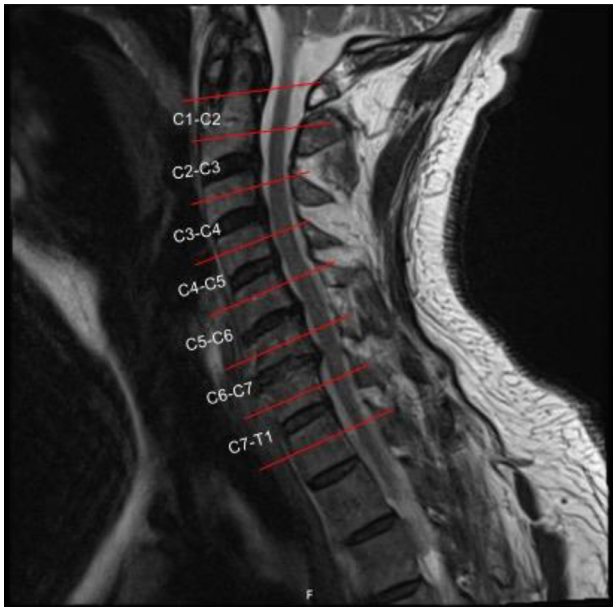

Fig. 1. Segmentation scheme used to analyze images. For each patient, seven segments of equal area were generated containing the cord at the level of intervertebral disc space as well the cord at half of each adjacent vertebra. Lesions and stenosis were counted for each segment individually. Note, the grade 2 stenosis at C5-C6 and grade 3 stenosis at C6-C7.

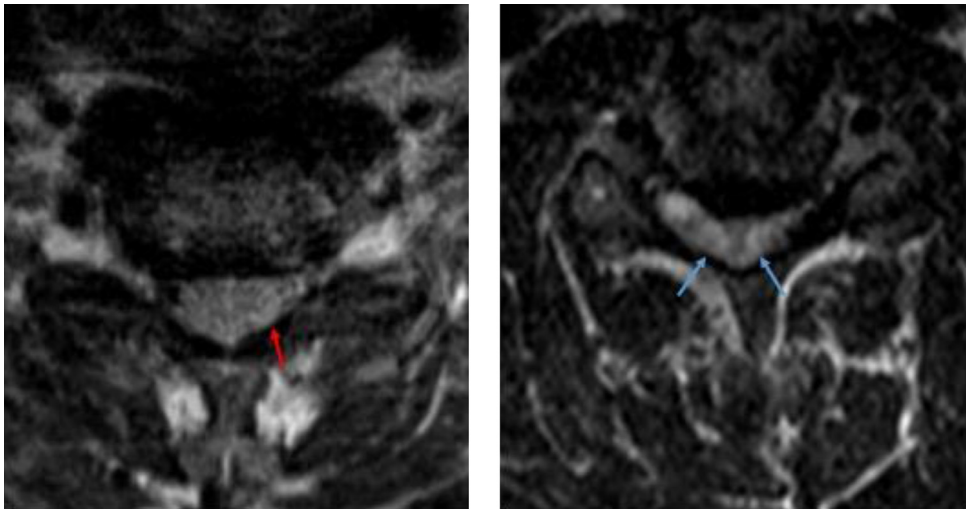

Fig. 2. Representative lesion that was included in the study (single arrow, left) compared to a lesion that was excluded from the study in this case due to bilaterality (double arrows, right) from two different patients.

2.4. Statistical analysis

Baseline and demographic characteristics were summarized using descriptive statistics. Student's T-tests were performed to evaluate the statistical significance of differences in demographic data and lesion distribution between groups. A chi-squared test was done to further asses the relationship between variables. Expected values for the frequency of MS lesions at each cervical segment were determined using the MS-only control population and were compared to the observed frequencies seen in the experimental MS/CS group. Odds ratios were calculated to estimate effect sizes.

Two-tailed values of $p < 0.05$ were regarded as statistically significant. Statistical analysis was conducted through Microsoft Excel (Microsoft, Redmond, WA, USA).

3. Results

A summary of the baseline and demographic characteristics of our patients and controls is found in Table 2. For comorbid patients, average age at the time of MRI was 57.0 +/- 10.5 years, and average length of MS diagnosis was 15.3 +/- 9.2 years. The majority of patients had a diagnosis of relapsing-remitting MS (81.0%) and the female-to-male ratio was 3.5. Eighty-five percent of patients were on treatment at the time of MRI. The most common disease modifying therapy (DMT) was glatiramer acetate (35.0% of all patients). Of those treated, 58.0% were on an injectable drug, 16.0% were on an oral drug, and 11% were on an infusion-based DMT. Comparable characteristics were seen in the MS-only control population.

Six lesions in the MS/CS group (3.2% of lesions observed) were excluded from the study based on meeting radiographic criteria for hyperintensities more likely associated with severe spondylotic myelopathy (Table 3). No significant differences were seen with regard to overall lesion burden, number of patients with lesions in every segment, and number of patients with no lesions seen. None of the lesions were gadolinium enhancing. In MS/CS patients, more lesions occurred in the lower cervical cord with 39 lesions seen in the C5-C6 segment (Fig. 3). C5-C6 was also the segment most often affected by cervical stenosis comprising 39.2% of all grade 2 or worse stenosis seen (data not shown). In MS-only patients, most lesions occurred in the upper cervical cord with 33 and 42 lesions seen in the C2-C3 and C3-C4 segments, respectively. When comparing the overall distributions, however, there was no significant difference seen assuming lesion frequency as a continuous variable with normal distribution ($p = 0.8103$).

For co-morbid patients, spinal segments with at least grade 2 stenosis were found to be significantly associated with the presence of an MS lesion in the same segment ($\chi^2 = 19.0$, $p < 0.001$, OR = 2.6, 95% CI 1.8-3.7) (Table 4). The same was true for segments with grade 3 stenosis ($\chi^2 = 8.2$; $p = 0.004$; OR = 2.8, 95% CI 1.6-4.8), and for segments with grade 2 stenosis alone, i.e. excluding grade 3 stenosis *and* no stenosis ($\chi^2 = 8.48$, $p = 0.004$, OR = 1.93, 95% CI 1.33 – 2.81) (data not shown).

Table 2
Clinical and demographic characteristics

Characteristics	MS/CS (n = 100)	MS-Only (n = 100)	p-value
Segments analyzed, n	700	700	
Females, n	78	78	1.00
Age, mean (SD), range	57.0 (10.5), 31.0-78.2	56.3 (10.5), 31.5-75.6	0.61
MS disease length in years, mean (SD)	15.3 (9.2)	16.6 (9.4)	0.35
MS subtype			
RRMS, n	81	79	0.61
PPMS, n	11	10	0.75
SPMS, n	6	9	0.21
PRMS, n	2	2	1.0
Treatment type			
None, n	15	14	0.78
Injectable, n	58	55	0.54
Oral, n	16	17	0.79
Infusion, n	11	14	0.34
Race			
White, n	63	61	0.68
Black, n	28	28	1.0
Other, n	9	11	0.49
Insurance status			
Public, n	41	36	0.16
Private, n	57	64	0.31
Other, n	2	2	0.15

4. Discussion

Cervical spondylosis is known to affect predominantly the lower cervical spine, with C5-C6 the most commonly affected level, followed by C6-C7 and C4-C5 (Morishita et al., 2011). Our data are consistent with this finding even in the MS population. On the other hand, MS is known principally to affect the upper cervical cord, most likely due to the increased amount of white matter tracts found cranially (Oppenheimer, 1978; Eden et al., 2019; Valsasina et al., 2018).

Table 3
Lesion characteristics

	MS/CS (n = 100)	MS-Only (n = 100)	p-value
Total lesions seen	187	186	0.95
Lesions excluded for more likely CS-associated (%)	6 (3.2)	0 (0)	0.014*
Lesions with gadolinium enhancement	0	0	1.0
Patients with at least one lesion in every segment	6	6	1.0
Patients with no lesions at any segment	17	22	0.37

However, as shown in Fig. 3, the segment with the most MS lesions in our co-morbid population was C5-C6. Compared to the general MS population, our comorbid population have more lesions than expected in the lower cervical cord near areas affected most by cervical stenosis.

As previous authors have shown, MS patients have a higher incidence of spondylosis than controls and develop spondylosis at younger ages (Xydis et al., 2017). Xydis et al hypothesized that spasticity caused by MS increases muscle tone, stresses the axial skeleton, and ultimately leads to worsening degenerative disease. However, as Brain and Wilkinson first suggested, we postulate that there may also be a causal relationship in the reverse direction, namely that spondylotic changes in the spinal canal could play a role in the exacerbation of MS. With the advent of gadolinium-enhanced MRI, we now know that the breakdown of the blood-CNS barrier plays a vital role in MS lesion development (Grossman et al., 1988; Miller et al., 1988; Willoughby et al., 1989; Kermode et al., 1990; Ortiz et al., 2014; Spencer et al., 2018). One can easily envision that in patients with significant CS, repetitive trauma at the site of stenosis leads to the breakdown of the blood-spinal cord barrier, invasion by immune-competent cells to the CNS, and subsequent plaque formation.

The idea that trauma to the central nervous system could cause or worsen MS has been proposed since the era of Charcot (Charcot, 1879). However, despite the biological feasibility of this idea, it remains quite controversial due to a lack of definitive epidemiological evidence and the inherent challenges of proving such a broad connection. An official position paper published by the AAN in 1999 concluded that "…despite the long history of this idea, the proposed causal link between [trauma] and MS has yet to be established or refuted conclusively." (Goodin et al., 1999) In their analysis, they show that although many studies have been conducted over the past century, they have been flawed either due to small cohorts, small effect sizes, recall bias, unclear definitions of trauma, ambiguous timelines, and/or other similar methodological issues (Goodin et al., 1999).

While our data are retrospective and merely suggest a correlation rather true causation, they provide a novel approach to test the trauma hypothesis with a geographic association rather than a temporal one. By highlighting that a correlation does exist, our data suggest repetitive mechanical stress placed on the cord and surrounding blood supply by adjacent areas of spondylosis could play a role in MS pathogenesis. Of course, CS cannot possibly be the only factor in determining when and where a lesion will develop given that lesions develop throughout the CNS, including in areas presumably free of any trauma.

Table 4
Relationship between MS lesions and segments affected by cervical stenosis

n observed (n expected)			
	MS Lesion +	*MS Lesion -*	*Total*
At least Grade 2 CS	87 (64.7)	137 (159.3)	224
Less than Grade 2 CS or no stenosis	94 (121.3)	382 (354.7)	476
Total	181	519	700
Df = 1; χ^2 = 19.0; p = <0.001; OR = 2.6 (95% CI 1.8-3.7)			
Grade 3 CS	27 (18)	31 (40)	58
Less than Grade 3 CS or no stenosis	154 (168)	488 (474)	642
Total	181	519	700
Df = 1; χ^2 = 8.2; p = 0.004; OR = 2.8 (95% CI 1.6-4.8)			

A clear limitation of this study is lack of blinding, which is unavoidable given the methodology we proposed. We have attempted to increase the reproducibility of this study by including strict criteria for stenosis and MS lesions as described above. Another limitation of this study is that severe CS and cord compression is known in itself to cause T2 signal changes in spinal cord MRI images (Vedantam and Rajshekhar, 2013; You et al., 2015; Takahashi et al., 1987; Chen et al., 2001). We have attempted to account for this by excluding lesions that appear more consistent with cord compression than MS based on established radiologic criteria. Moreover, while any level of stenosis can be associated with compressive myelopathy, one should expect the confounding effect to primarily bias the most severe cases in which there is visible cord compression, i.e., grade 3 stenosis. However, when our analysis is repeated for grade 2 stenosis *alone*, a significant association was still present.

Another limitation of this study is the data for C1-C2 in our trial are not easily comparable to other studies due to the exclusion of the uppermost C1 level of cord. We chose not to count lesions in this segment because of the lack of associated disc space that could cause stenosis there. We have controlled for the potential bias from this exclusion by

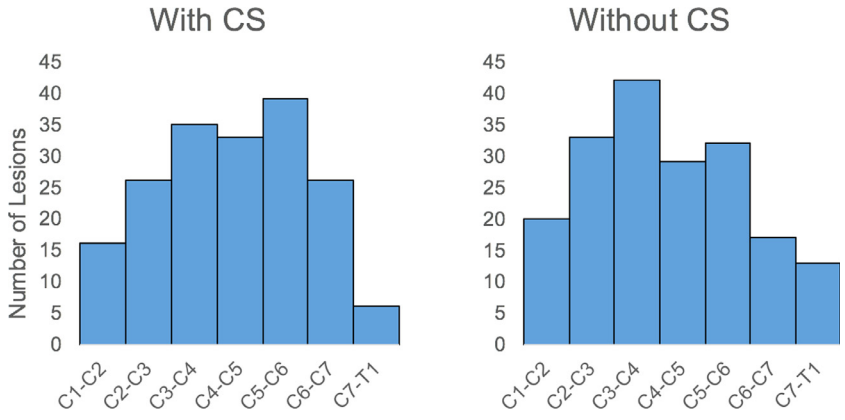

Fig. 3. MS lesion distribution across the seven different segments of cervical cord in patients with and without cervical stenosis. The difference in overall distribution was not significantly different assuming lesion frequency as a continuous variable with normal distribution (p = 0.8103)

using expected values generated from an MS-only cohort, and using the same segmentation schema across the two populations.

Finally, while this study has no direct bearing on the question of whether decompressive surgery can be beneficial for MS/CS co-morbid patients, it has some potentially interesting consequences. By showing a larger proportion of demyelinating-appearing lesions exists at sites of cervical stenosis than expected, our data are consistent with the observation that many co-morbid patients fail to sustain clinical improvement after decompressive surgery (Lubelski et al., 2014; Lubelski et al., 2014). Therefore, we agree that providers must be very careful before recommending their MS patients proceed with decompressive surgery as they may have limited relief of their myelopathy.

5. Conclusion

The results of this study show that there is a statistical association between the presence of cervical spinal cord parenchymal lesions and the existence of at least moderate cervical stenosis in patients with MS. Further studies would be necessary to tease out the temporality of this relationship and whether CS can truly be considered a causal or aggravating factor in the pathogenesis of spinal cord MS. Possible future directions include examining patterns of gadolinium enhancement in these co-morbid patients, as previous authors have demonstrated characteristic findings in cervical myelopathy, but never specifically in patients with concurrent MS (Flanagan et al., 2014).

Table 1. Cervical stenosis grading scheme adapted from Muhle et al.

Table 2. Summarizes the clinical and demographic characteristics of our cohort. SD = standard deviation, RRMS = relapsing-remitting MS, PPMS = primary progressive MS, SPMS = secondary progressive MS, PRMS = progressive relapsing MS. Two tailed p-values were estimated from Student's T-tests or z-tests where applicable with asterisks (*) denoting significance.

Table 3. Summarizes relevant data regarding lesion distribution and characteristics across the two groups. Two tailed p-values were estimated from Student's T-tests or z-tests where applicable with asterisks (*) denoting significance.

Table 4. Chi-squared test for association between segments with at least grade 2 CS and segments with an MS lesion; as well as, test for association between segments with grade 3 CS and segments with an MS lesion. OR = odds ratio, CI = 95% confidence interval.

Declaration of Competing Interest

Drs. Gratch, Do, Khankhanian, Schindler, and Schmitt have no conflicts of interest to disclose.

Dr. Berger has received grants from Biogen and Genentech/Roche. He is on the Scientific Advisory Board for Novartis and Inhibikase. He serves as the Chair of the Data and Safety Monitoring Board for MAPI. He has received consultant fees from Biogen, Genentech/Roche, Celgene, Millennium/Takeda, Excision Bio, Amgen, Shire, Dr. Reddy, Serono, Morphic, Encycle, Merck, and MAPI. He is the Infection Section Editor of Multiple Sclerosis and Associated Disorders.

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