Quantitative magnetization transfer MRI measurements of the anterior spinal cord region are associated with clinical outcomes in cervical spondylotic myelopathy

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**Study Design:** case-control

**Objective:** To understand the role of magnetization transfer ratio in identifying patients with clinically significant myelopathy and disability.

**Summary of Background Data:** Magnetization transfer ratio (MTR) is a quantitative measure that correlates with myelin loss and neural tissue destruction in a variety of neurological diseases. However, the usefulness of MTR in patients with cervical spondylotic myelopathy (CSM) has not been examined.

**Methods:** We prospectively enrolled seven CSM patients and seven age-matched controls to undergo MRI imaging of the cervical spine. Nurick, Neck Disability Index (NDI), and modified Japanese Orthopedic Association (mJOA) scores were collected for all patients. Clinical hyperreflexia was tested at the MCP joint, using a 6-axis load cell. Reflex was simulated by quickly moving the joint from maximum flexion to maximum extension (300 °/sec). Anterior, lateral, and posterior cord MTR measurements were compared to clinical outcomes.

**Results:** Compared to controls, CSM patients had lower anterior cord MTR (38.29 v. 29.97, Δ = -8.314, p=0.0022), and equivalent posterior cord (p=0.2896) and lateral cord (p=0.3062) MTR. Higher Nurick scores were associated with lower anterior cord MTR (p=0.0205), but not lateral cord (p=0.5446) or posterior cord MTR (p=0.1222). Lower mJOA was associated with lower anterior cord MTR (p=0.0090), but not lateral cord (p=0.4864) or posterior cord MTR (p=0.4819). There was no association between NDI and MTR of the anterior (p=0.4351), lateral (p=0.7557), or posterior cord (p=0.9171). There was a linear relationship between hyperreflexia and anterior cord MTR (slope = -117.3, R = 0.6598, p = 0.0379), but not lateral cord (p=0.1906, R=0.4511) or posterior cord (p=0.2577, R=0.3957) MTR.
**Conclusion:** Anterior cord MTR correlates with clinical outcomes as measured by mJOA index, Nurick score, and quantitative hyperreflexia, and could play a role in the preoperative assessment of CSM.

**Keywords:** Cervical spondylotic myelopathy; CSM; myelopathy; hyperreflexia; spasticity; spine; magnetization transfer ratio; MTR; spine; cervical spine; spinal cord, magnetic resonance imaging; MRI

**Level of Evidence:** 2
Introduction:

Cervical spondylotic myelopathy (CSM) is a common spinal condition characterized by narrowing of the cervical spinal canal that leads to progressive pain and neurological impairment. CSM is one of the most common spinal cord disorders of the elderly. Surgeries to decompress the spine in CSM patients are rising, presumably with an ever-increasing ageing population across the globe. Although surgical techniques continue to advance and improve care, nearly 40% of CSM patients undergoing surgery achieve less than a 50% recovery using common clinical outcome metrics. These key metrics include scales for myelopathy as well as scores for pain and disability associated with this condition. Therefore, there is an urgent need to better understand the pathophysiological mechanisms contributing to clinical signs and symptoms associated with CSM, which in turn could improve assessment and management.

Magnetization transfer ratio (MTR) is a quantitative magnetic resonance imaging (MRI) measure that correlates with myelin loss and neural tissue destruction, and correlates with clinical manifestations of a variety of neurological diseases. For example, in patients with multiple sclerosis (MS), MTR of white matter lesions may predict clinical disability. However, the study of MTR in patients with CSM has not been undertaken. We hypothesized that the MTR would be significantly lower among patients with CSM who have not undergone surgical decompression than among age-matched controls.

As CSM is common in neurosurgical practice, a more detailed understanding of factors contributing to CSM outcomes, on a patient-by-patient basis, is warranted. This may allow for more thoughtful and effective surgical candidate selection and also inform our understanding of prognosis. The purpose of this preliminary study is to examine whether patients with CSM demonstrate lower MTR within the cervical spine when compared to age-matched controls without spinal cord compression.
Material and Methods:

We prospectively enrolled a cohort of seven CSM patients and six aged-matched controls to undergo MRI imaging of the cervical spine for analysis of MTR. All CSM patients included were diagnosed at Northwestern Memorial Hospital (Chicago, IL) based on both clinical and radiographic findings. Inclusion criteria for entry included the following in all patients diagnosed with CSM (Table 1): classic CSM symptoms; exam findings of weakness, hyperreflexia, or change in coordination; radiographic signs of spinal compression; Nurick grade I-IV\textsuperscript{11}; and modified Japanese Orthopedic Association (mJOA) score 8-18\textsuperscript{12}. Exclusion criteria included the following: age < 21 or > 80, comorbid neural disease (e.g., multiple sclerosis), pregnant or nursing, active systemic rheumatological disease, active peripheral or vascular neuropathy, urgent need for surgery. The study was conducted with the approval of Northwestern’s Institutional Review Board (IRB).

MRI Measures and Analysis. All imaging data were collected with a 3.0 Tesla Siemens Prisma magnetic resonance scanner (Siemens, Erlangen, Germany) equipped with a 64-channel head/neck coil. Participants were placed supine on the scanner bed, and a localizer scan was obtained to identify the location of the intervertebral discs of the cervical spine (C2-3, C3-4, C4-5, C5-6, C6-7, and C7-T1). Six transverse slices were prescribed within the plane of each cervical intervertebral disc, and imaging was performed using a multi-echo gradient-echo sequence (multi-echo data image combination: MEDIC) with (MTC\textsubscript{1}) and without (MTC\textsubscript{0}) a magnetization transfer pulse (TR = 300 ms, TE = 17 ms, Flip angle = 30°, FOV = 180 × 180, Matrix size = 384 × 384, In-plane resolution = 0.47 × 0.47 mm\textsuperscript{2}, Slice Thickness = 4 mm, number of averages = 2). Image processing was performed using the Spinal Cord Toolbox\textsuperscript{13}. For each slice, the MTC\textsubscript{1} image was registered to the corresponding MTC\textsubscript{0} image using a non-linear deformation constrained to the axial plane. MTR images were then generated using the co-registered images based on the following formula: $\text{MTR} = 100\times\left(\frac{\text{MTC}_0 - \text{MTC}_1}{\text{MTC}_0}\right)$. MTR metrics were extracted from the MTR images using hand-drawn region of interest masks that
were defined on the mean image of the co-registered MTC₀ and MTC₁ images. The regions of interest included the entire cord and the anterior, lateral (left + right), and posterior regions (Figure 1AB). Borders in areas of distortion were analyzed and agreed upon by both investigators and an independent radiologist.

Hyperreflexia measurements. Subjects were tested for hyperreflexia in the hand using a custom motorized device. The device determines hyperreflexia with the use of a motorized shaft with torque sensors and surface electromyographic (EMG) sensors to determine the amount of muscle response a subject has at reflex (hyperreflexia). Subject’s forearms are placed in a cast to maintain neutral wrist posture and their fingers placed in a stationary position to isolate the metacarpophalangeal (MCP) joint. Reflex is simulated by quickly moving the MCP joint from maximum flexion to maximum extension (300°/sec). To compensate for natural stiffness or tone in the MCP joint, the fingers were rotated slowly (5°/sec) and the passive stiffness was subtracted from the reflex response. Hyperreflexia is quantified in the motor system by amount of torque at the MCP joint, normalized to maximum strength, and muscle activity response of extensor digitorum communis (EDC), normalized to maximum muscle activations. To compensate for differences in age and gender the spastic torque responses were normalized to each subject’s maximum MCP joint strength.

Statistical Analysis. Statistical analysis was performed using and Stata 12.0 (StataCorp, College Station, TX, USA) and Prism 6.0b (GraphPad Software, Inc., La Jolla, CA, USA). Mean MTR was compared between CSM patients and controls. For each CSM patient, MTR was also compared above and below the level of injury. Mean MTR, baseline demographic and clinical characteristics, and clinical outcome metrics were compared using unpaired t-tests, Kolmogorov-Smirnov tests, Fisher’s exact tests, and chi-square tests, as appropriate. Linear regression analysis was performed to examine the relationship between MTR and hyperreflexia.
Results:

There was no difference between patients with CSM and controls with respect to age (59.7 ± 13.3 v. 46.2 ± 13.0, p = 0.1375), gender (57.1% male v. 50% male, OR 1.333 [0.149, 11.936], p=1.000), height (67.1 ± 3.3 inches v. 68.7 ± 3.9 inches, p=0.811), weight (161.4 ± 17.5 pounds v. 166.3 ± 23.6 pounds, p=0.979), smoking status (28.6% ever smokers v. 16.7% ever smokers, OR 2.000 [0.134, 29.828], p=1.000), or race (85.7% Caucasian v. 100% Caucasian, OR 0.333 [0.0113, 9.801], p=1.000) (Table 2). There was a trend toward significance with respect to employment status (42.9% working v. 100% working, OR 0.0598 [0.00244, 1.466], p=0.0699) and level of education (p=0.0643). Compared to controls, CSM patients had lower anterior cord MTR (38.29 v. 29.97, Δ = -8.314, p=0.0022, Figure 2), and equivalent posterior cord (p=0.2896) and lateral cord (p=0.3062) MTR.

Among the seven CSM patients, five patients had C3 as their most cranial level of stenosis, and two patients had C4 as their most cranial level of stenosis. The mean anterior MTR above the level of stenosis was 36.77 ± 4.66, and 37.89 ± 4.56 below the level of stenosis. There was no difference in anterior MTR above and below the level of stenosis (36.77 [31.88, 41.65] v. 37.89 [33.11, 42.68], p=0.5965).

Higher Nurick scores were associated with lower anterior cord MTR (p=0.0205, Figure 3), but not lateral cord (p=0.5446) or posterior cord MTR (p=0.1222). The mean Nurick score among CSM patients was 1.714 [1.263, 2.166] ± 0.488. Lower mJOA was associated with lower anterior cord MTR (p=0.0090, Figure 4), but not lateral cord (p=0.4864) or posterior cord MTR (p=0.4819). The mean mJOA score among CSM patients was 14.29 [12.46, 16.11] ± 1.976. There was no association between NDI and MTR of the anterior (p=0.4351), lateral (p=0.7557), or posterior cord (p=0.9171). There was a linear relationship between hyperreflexia and anterior cord MTR (slope = -117.3, R = 0.6598, p =
0.0379, Figure 5), but not lateral cord (p=0.1906, R=0.4511) or posterior cord (p=0.2577, R=0.3957) MTR.

Discussion:

Cervical spondylotic myelopathy is a common cause of progressive pain and neurological impairment and many patients experience suboptimal improvement after surgery despite advances in surgical techniques. Decreased MTR has been found to be associated with a variety of neurological pathologies, including demyelinating disease, spinal cord injury, dementing illnesses, Huntington’s Disease, and Parkinson’s Disease. Here, we compared MTR in patients with CSM to age-matched controls, and found that lower MTR in the cervical spinal cord is associated with the clinical manifestations of CSM, including worse Nurick Scores and mJOA scores, as well as increased hyperreflexia of the upper extremity.

As the incidence of asymptomatic radiographic degenerative changes is significant, particularly with increasing age, the clinical exam remains the gold standard for diagnosis of CSM. For patients with radiographic abnormalities and only mild or minimal clinical symptoms, MTR imaging may be an important diagnostic support tool for early identification of patients at risk for true clinical CSM, and to expand the use of early care. Some recent series have identified findings other than degenerative musculoskeletal changes that can distinguish CSM and non-CSM patients, namely spinal cord volume. However, the interpretation of this data on the individual patient level is difficult, and spinal cord volume data does not clarify the integrity of the neural tissue, though MTR is believed to.

Indeed, the quantitative data within MTR may allow its usefulness to may extended beyond cases of mild CSM. As opposed to patients with only mild clinic symptoms, some patients have spinal injury out of proportion to compression on standard imaging. In such cases, the data provided by
MTR imaging may provide further insight into the patients' pathology. Such cases are not explored in the current series, but could be examined in future studies on MTR imaging of the spinal cord.

Our finding that MTR correlated with clinical manifestations of CSM is consistent with the existing literature on MTR from other neurological pathologies. Magnetization transfer contrast is based on the interaction between hydrogen protons bounded to macromolecules like the lipids that compose the myelin sheaths of axons, allowing MTR to serve as a proxy measurement for myelin content. MT has therefore been extensively studied for primary demyelinating disorders such as multiple sclerosis, including the effects of MS on the spinal cord. Patients with multiple sclerosis have lower MTR metrics than controls, and has been shown to correlate with disease burden. Moreover, MTR provides additional insight not given by traditional MRI, as MTR is decreased in patients with diagnoses of MS who have negative conventional MRI imaging. To our knowledge, MTR has been underutilized in the study of spinal cord pathologies.

Additionally, our finding that lower MTR in patients with CSM is localized to the anterior cord is consistent with current understanding of the disease. Symptoms such as hand weakness and hyperreflexia are hallmarks of CSM, due to compromise of the descending anterior corticospinal tracts. Furthermore, the anterior cord compromise among our CSM patients observed in the MTR data is consistent with our finding that MTR was linearly correlated with neuromechanical testing for hyperreflexia. High-resolution MTR has been previously demonstrated to be capable of assessing demyelination of specific spinal pathways, allowing it to provide tract-specific data. Our own results show that unique MTR metrics can be obtained from separate regions of the spinal cord. The regional findings observed here consistently indicate that anterior cord dysfunction may be a leading contributor to the clinical disability observed among our patients with CSM. This is consistent with the symptomsthat are typically observed.
Our finding that CSM patients have lower anterior cord MTR is consistent with existing literature on MTR for other spinal pathologies as well. Histopathological studies have shown that low MTR is specific for demyelination and degeneration\textsuperscript{14,15}, so tract disruption that leads to anterograde Wallerian demyelination or retrograde degeneration should be detectable using MTR. Indeed, Cohen-Adad \textit{et al.} (2011) found MTR correlates with ASIA score in patients with spinal cord injury\textsuperscript{8}. For both primary demyelinating disorders of the spine, such as MS, as well as other insults that later manifest as demyelination and degeneration, MTR correlates with clinical outcome metrics.

In our study, NDI was not associated with MTR, though existing literature suggests that NDI scores are associated with CSM outcomes. Along with the mJOA and Nurick score, the NDI has been used to assess postoperative improvement in myelopathic signs and symptoms in a large, prospective, multi-center study on surgical outcomes for CSM\textsuperscript{32}. However, one recent systemic review examining the validity, reliability, and responsiveness of existing clinical metrics found that NDI is not commonly used among CSM patients, while the mJOA and Nurick scores were among the most widely used metrics\textsuperscript{33}. Moreover, studies comparing clinical scores among CSM patients have shown consistency between mJOA and Nurick scores with respect to their ability to measure postoperative recovery\textsuperscript{34,35}. Notably, our study was small (n=13), which may have limited our ability to detect statistical differences. While we did not find that NDI was significantly associated with MTR, future investigations with a larger sample size may find such a relationship.

Our study has a number of important limitations. The sample size was small, including a total of only 13 participants. While all measurements were taken while blinded, true blinding cannot be achieved when viewing radiographic studies. Measurement errors and variability in methods complicate comparing our methodology to other reported studies. Partial volume averaging at the edge of the parenchyma of the spinal cord on axial cuts limits the precision of our data. This technical hurdle may be improved upon in the future with smaller voxel sizes, and it may in fact be of benefit not to
include the very periphery of cord in MTR analysis. Many radiographic studies have reported the use of DTI for imaging the spinal cord for a variety of pathologies. While we attempted to obtain DTI on all patients we enrolled, the quality of the images obtained was insufficient for formal analysis for many patients, so comparisons to DTI imaging could not be made. Lastly, white-matter tract imaging metrics, including both DTI and MTR, have been found to vary with age\textsuperscript{36}, but age-based reference ranges for MTR have not been developed. To our knowledge, the current study is the first to report direct comparisons of MTR between CSM patients and age-matched controls.

As 3T MTR of the cervical cord has been shown to be highly reproducible\textsuperscript{37}, MTR measurement could prove to be a robust modality for the evaluation of patients with CSM. Here, we have shown that MTR of the anterior spinal cord is significantly lower among patients with CSM than controls. Furthermore, we found that MTR correlates with clinical disability among CSM patients, as measured by the mJOA and Nurick scores. Lastly, there was a linear relationship between MTR and hyperreflexia, as measured by a novel, quantitative method of measuring hyperreflexia.

Conclusions:

Anterior cord MTR correlates with clinical outcomes as measured by mJOA index, Nurick score, and quantitative hyperreflexia. Anterior cord MTR is associated with clinically relevant hyperreflexia, and could play a role in the preoperative assessment of CSM. Further understanding this radiological metric may refine surgical decision-making.
References


Tables & Figures

Table 1. Inclusion and exclusion criteria for entry into the current study. The criteria included the following in all patients diagnosed with CSM: classic CSM symptoms; exam findings of weakness, hyperreflexia, or change in coordination; radiographic signs of spinal compression; Nurick grade I-IV; and modified Japanese Orthopedic Association (mJOA) score 8-18. Exclusion criteria included the following: age < 21 or > 80, comorbid neural disease, pregnant or nursing, active systemic rheumatological disease, active peripheral or vascular neuropathy, urgent need for surgery.

Table 1: Entrance Criteria

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<th>Inclusion</th>
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<td>Classic CSM symptoms.</td>
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<td>Exam findings of weakness, hyperreflexia, or change in coordination</td>
<td>Diagnosis neural disease (ex: MS)</td>
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<td>Radiographic signs of spinal compression</td>
<td>Pregnant or nursing</td>
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<td>Nurick grade I-IV and mJOA 8-18</td>
<td>Active systemic rheumatological disease</td>
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<td>Active peripheral or vascular neuropathy</td>
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**Table 2:** Baseline Demographic and Clinical Data

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<td>Women</td>
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<td>3 (50%)</td>
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<td><strong>Height</strong></td>
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<td>68.7 ± 3.9</td>
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<td><strong>Weight</strong></td>
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<td>Currently Employed</td>
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<td>6 (100.0%)</td>
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Figure 1. A) Example images with \((MTC_1)\) and without \((MTC_0)\) a magnetization transfer (MT) pulse and the corresponding MT ratio (MTR) image are shown. B) MTR metrics were extracted from the entire spinal cord (Blue) and from the anterior (Yellow), lateral (Orange), and posterior (Red) spinal cord regions. Images shown are from a healthy participant at the C5-6 intervertebral disc level.
Figure 2. Anterior cord MTR for CSM patients versus controls. Compared to controls, CSM patients had lower anterior cord MTR (38.29 v. 29.97, Δ = -8.314, p=0.0022).
Figure 3. The relationship between anterior cord MTR and Nurick scores. The mean Nurick score among CSM patients was 1.714 [1.263, 2.166] ± 0.488. Higher Nurick scores were associated with lower anterior cord MTR (p=0.0205).
**Figure 4.** The relationship between anterior cord MTR and mJOA scores. The mean mJOA score among CSM patients was 14.29 [12.46, 16.11] ± 1.976. Lower mJOA was associated with lower anterior cord MTR ($p=0.0090$).
**Figure 5.** Linear regression analysis comparing anterior cord MTR and quantitative hyperreflexia measurements. There is a linear relationship between hyperreflexia and anterior cord MTR (slope = -117.3, R = 0.6598, p = 0.0379).