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High-resolution magnetization transfer MRI in Patients with Cervical Spondylotic Myelopathy

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Abstract

Magnetization transfer (MT) contrast has been established as a marker of myelin integrity, and cervical spondylotic myelopathy is known to cause demyelination. Ten patients with clinical and magnetic resonance imaging (MRI) manifestations of cervical spondylotic myelopathy (CSM) were compared to the MRIs of seven historic healthy controls, using the magnetization transfer ratio (MTR) and Nurick scores as the primary metrics. Transverse slices through the intervertebral discs of the cervical spine were acquired using a gradient echo sequence (MEDIC) with and without an MT saturation pulse on a 3 Tesla Siemens Prisma scanner (TR=300 ms, TE_{eff}=17 ms, flip angle=30°, in-plane resolution=0.47×0.47 mm²). The CSM patients tended to have a lower mean MTR (30.4 ± 6.5) than the controls (34.8 ± 3.8), but the difference was not significant (independent samples t-test, $p = 0.110$, Cohen's $d = 0.80$). The mean MTR across all intervertebral disc levels was not significantly correlated to the Nurick score (Spearman's $\rho = -0.489$, $p = 0.151$). The intervertebral level with the lowest MTR in each cohort was not significantly different between groups (equal variances not assumed, $t = 1.965$, $\text{dof} = 14.8$, $p = 0.068$, Cohen's $d = 0.88$), but the CSM patients tended to have a lower MTR. The mean MTR at this level was negatively correlated to the Nurick score among CSM patients (Spearman's $\rho = -0.725$, $p = 0.018$). CSM patients tended to have decreased MTR indicating myelin degradation compared to our healthy subjects, and MTR was negatively correlated with the severity of CSM.

Keywords

Magnetization Transfer Contrast Imaging; cervical spondylosis; myelopathy; diagnostic imaging

Introduction

Cervical spondylotic myelopathy (CSM) is a chronic progressive degenerative disease of the spine that has significant clinical morbidity[1] and a highly variable presentation[2]. Patients with cervical myelopathy may complain of loss of upper extremity dexterity, gait imbalance, and/or nonspecific weakness. Bowel and bladder symptoms are less commonly the primary complaint[2]. Signs and symptoms of myelopathy often develop insidiously and are varied

in the population[3]. In addition to a clinical examination, surgeons rely on imaging modalities to confirm the diagnosis.

Early surgical intervention in CSM is recommended as soon as the diagnosis is made[4], which has been shown to effectively disrupt disease progression and improve neurological prognosis[5]. Yet, despite the goal of early decompression immediately after diagnosis, neurologic recovery is rarely full and often difficult to predict. Thus, surgeons have sought other diagnostic tools to detect CSM earlier, better characterize prognostic indicators, and assist with selecting appropriate treatment strategies.

Advanced imaging with magnetic resonance imaging (MRI) has largely been accepted as a tool to evaluate CSM[6]. MRI has the ability to evaluate the degree of spinal cord compromise, presence of intramedullary lesions, and severity of degenerative changes[7]. It is theorized that myelopathic symptoms are present in patients following a 30% reduction in the size of the spinal cord as visualized on an MRI[8]. However, there are limitations to the predictability of clinical deterioration based on MRI. As such, MRI primarily serves to confirm the diagnosis and assist with predicting clinical response to surgical intervention[7].

Many parameters have been investigated as potential detectors of CSM, including: high T2-weighted signal intensity (especially in conjunction with low T1-weighted signal intensity), decreases in cross sectional spinal cord area, and the anteroposterior compression ratio (AP diameter/transverse diameter of the spinal cord). Conventional MRI is estimated to have a sensitivity ranging from 15 to 65% for the detection of the spondylotic alterations responsible for CSM[9]. One systematic review identified three important negative predictors of neurologic recovery after surgical intervention: 1) high signal intensity (SI) on T2-weighted images (T2WI) in combination with low SI changes on T1-weighted images (T1WI), 2) a high ratio of T2SI between compressed and non-compressed segments, and 3) a greater number of high SI segments on T2WI[7].

Diffusion tensor imaging (DTI) is an alternative advanced magnetic resonance technique in which conventional MR images provide functional information regarding water molecule diffusion directionality, which detects disturbances on a cellular level[9]. The sensitivity of detecting myelopathy is substantially higher than conventional MR; however, the level of sensitivity may be so high that the clinical relevance of DTI metrics must be questioned[9]. Elderly individuals without clinical myelopathy also demonstrate abnormal metrics merely due to the presence of spondylosis[10].

Magnetization transfer (MT) is a technique employed by MR technology based on the application of off-resonance radio-frequency pulses and observing their effects on the MR signal[11]. MT offers a unique window for characterizing tissues and can improve tissue contrast. The technique is sensitive to the exchange of magnetization between immobile protons bound in macromolecular matrix and free-water protons. The pulsed application of radiofrequency preferentially saturates the macromolecular protons. This saturation is subsequently transferred to the liquid proton pool by cross-relaxation, chemical exchange, and other processes[12]. The size of this effect can be measured quantitatively by the MTR, which is a comparison of the signal intensity with and without the radio-frequency

pulses[13]. Advantages of MT imaging over diffusion based methods is higher signal to noise and higher spatial resolution which reduces partial volumes effects of CSF.

MT contrast has been established as a marker of myelin integrity via its ability to measure the exchange of freely moving protons to large macromolecules[13]. As such, the MTR has been previously established as a useful tool for accurately assessing disease burden among patients with multiple sclerosis[14]. In a cross-sectional analysis, Oh et al. concluded that microstructural changes that were not detectable by conventional MRI were better evaluated by quantitative MR indices such as MTR[14]. Decreased MTR has also been shown to correlate with histopathological loss of myelin[15]. Additionally, volumetric measures of MTR within the brain have correlated with the severity of neuropsychological disability in patients with MS[16]. Histologic evaluation of cadaveric spinal cords with a diagnosis of CSM has demonstrated gliosis and demyelination[17], two features common to multiple sclerosis as well.

Theory

Given that MT allows for better structural evaluation of white matter tracts than conventional T1 and T2 imaging[18], we sought to compare the magnetization transfer ratio (MTR) in healthy subjects to CSM patients. We predicted that, similar to MS, a decreased MTR would be identified in regions with critical levels of spinal canal stenosis.

Materials and Methods

The research protocol was approved by our Institutional Review Board prior to initiation of the study. All participants provided written informed consent and were screened for contraindications to MRI prior to scanning.

Participants

Ten patients (6 male and 4 female; mean age = 67.2 ± 11.4 years, Figure 1) with clinical and imaging manifestations of cervical spondylotic myelopathy were identified by three board-certified spine surgeons and recruited to participate in the study. The ten patients were recruited consecutively from outpatient encounters. Imaging manifestations used to make the diagnosis included but were not limited to: cord signal changes, effacement of the spinal cord, and diminished cerebrospinal fluid presence at stenotic levels. The severity of CSM was assessed via the Nurick score, which is a six-grade system based on difficulty in walking (with anchors of 0 being signs or symptoms of root involvement but without evidence of spinal cord disease and 5 being chair-bound or bedridden)[3,19]. For comparison to the CSM patients, seven historic MRIs of healthy volunteers (6 male and 1 female; mean age = 34.1 ± 7.5 years) were used as controls. The healthy controls reported no significant pain or neuromusculoskeletal diseases.

Imaging Protocol

Both the CSM and control cohorts had the same imaging protocols performed. Imaging was performed on a 3 T Siemens MAGNETOM Prisma scanner (Siemens Medical Solutions

USA, Inc., 2016, Malvern, PA) equipped with a 64-channel head/neck coil. For imaging, subjects were placed supine on the scanner bed, and transverse slices across the intervertebral discs of the cervical spine were acquired using a gradient-echo sequence called multiple-echo data imaging combination (MEDIC) that combines multiple echoes to increase the signal to noise. Data were collected with (MT) and without (noMT) an MT saturation pulse (TR = 300 ms, TE_{eff} = 17 ms (combined echoes of 7.86, 13.75, 19.83, 26.12), flip angle = 30°, IPAT=2, slice thickness of 3mm, in-plane resolution = 0.47×0.47 mm²). For registration purposes, a T₂-weighted anatomical image of the cervical spine was acquired using a spin-echo sequence with sagittal orientation (TR = 3000 ms, TE = 104 ms, flip angle 120°, slice thickness = 2 mm, in-plane resolution = 1.1×1.1 mm²).

Image Analysis

Image processing was performed using the Spinal Cord Toolbox and the MNI-Poly-AMU T₂-weighted spinal cord template (resolution = $0.5 \times 0.5 \times 0.5$ mm³)[20,21]. To generate the MT ratio (MTR) images, the MT images at each intervertebral disc level were first registered to the corresponding noMT images using a non-linear deformation constrained to the axial plane. From the coregistered MT and noMT images, the MTR images were then calculated using the following formula: (noMT – MT) / noMT * 100. For spatial normalization to the spinal cord template, the T₂-weighted structural image of the cervical spine was cropped to include the C2 to T1 vertebrae. The C2 and T1 vertebrae were manually identified, and a vertebral landmark mask was generated. The structural image was then straightened along the spinal cord using a binary mask of the spinal cord, and then non-rigid registration to the MNI-Poly-AMU T₂-weighted spinal cord template was performed using the vertebral landmarks mask (structural to standard registration). The noMT images were then registered to the T₂-weighted structural image using a non-linear deformation constrained to the axial plane (MT to structural). The deformation fields were then concatenated allowing for the forward transformation of the MTR images to standard space and the inverse transformation of the spinal cord mask in standard space to native space. Using the transformed masks, the mean MTR was calculated at each intervertebral disc level. For quality control, the transformed images at each step were visually inspected (Figure 1).

Statistical analysis

To test for a difference in MTR between the CSM patients and the controls, the mean MTR was calculated across all of the intervertebral discs and compared using an independent samples two-tailed t-test. To assess for a relationship between MTR and the severity symptoms in the CSM patients, two-tailed Spearman's correlations were performed between the MTR and the Nurick score. For statistical tests, IBM SPSS Statistics for Windows Version 22.0 (IBM Corp., Armonk, NY) was used, and an $\alpha < 0.05$ was used as the threshold for statistical significance.

Results

The mean MTR across all intervertebral disc levels was 30.4 ± 6.5 for the CSM patients and 34.8 ± 3.8 for the controls. The CSM patients tended to have a lower mean MTR than the controls, but the difference was not significant (equal variances not assumed, $t = 1.782$, $\text{dof} = 14.8$, $p = 0.095$, Cohen's $d = 0.80$). The mean MTR across all intervertebral disc levels was not significantly correlated to the Nurick score (Spearman's $\rho = -0.489$, $p = 0.151$). When focusing only at the intervertebral disc level with the lowest MTR for each subject, the mean MTR was 24.8 ± 7.4 for CSM patients and 30.3 ± 4.3 for the controls. While the difference was not significant between groups (equal variances not assumed, $t = 1.965$, $\text{dof} = 14.8$, $p = 0.068$, Cohen's $d = 0.88$), the CSM patients tended to have a lower MTR and the mean MTR at this level was negatively correlated to the Nurick score (Spearman's $\rho = -0.725$, $p = 0.018$) (Figure 2).

Discussion

While patient questionnaires such as the Japanese Orthopaedic Association (JOA) have been established as reliable measures of CSM severity[22,23], the reliance upon subjective self-assessment of dysfunction is more likely to be confounded by a patient's comorbidities. Despite advances in traditional MRI, there remains a need for objective measures of CSM severity based on imaging studies so that prognosis can be better predicted and response to treatment more reliably assessed[24]. CSM is currently a clinical diagnosis that clinicians corroborate with available diagnostic studies. Advanced imaging is obtained to identify stenosis of the cervical spinal canal, and traditional MRI has been well-established for this purpose[6]. To our knowledge, MTRs have never been analyzed in relation to establishing a diagnosis of CSM. Given the ability of MTR to evaluate the structural integrity of white matter tracts, we hypothesized that a correlation would exist between the measured MTR and the severity of CSM. We aimed to identify whether MTR has any correlation to the severity of CSM as measured by the Nurick classification.

In this study, as hypothesized, we have identified that among patients with a clinical diagnosis of CSM, the lowest MTR at the level of an intervertebral disc has a negative correlation with Nurick score. That is, the lower the MTR, the lower the myelin, the greater the Nurick classification severity. The difference in MTR was not statistically different from controls when comparing the mean MTR across all cervical disc levels, which is fitting with the notion that microstructural changes in CSM occur at the sites of greatest compression, not globally. When comparing each patient's level with the lowest MTR, the CSM cohort trended towards a lower mean value; although, this was not statistically significant. Post-hoc power analysis was performed and identified that this statistical test was underpowered (23 patients would be required in each cohort to achieve 80% power) to fully assess this comparison. These results derived from our pilot study can be utilized to plan future clinical investigations.

The negative correlation between the level with the lowest MTR and the Nurick classification may prove as a useful guide to surgeons for determining the level that should be targeted during surgical decompression. A threshold MTR, below which surgical

decompression is recommended, would be a potential application that may come of this discovery as future studies regarding the MTR in CSM are conducted.

This study has several limitations, including a small sample size. Additionally, our control patients were much younger than those with cervical myelopathy. Serbruyns et al. recently identified that aging was associated with decreased MTR on brain imaging[25]. Additionally, these decreases correlated with poorer task-switching performance, suggesting that demyelination is related to decreased functionality with aging. Our analysis identified that the Nurick score negatively correlated to the MTR, suggesting that, despite this potential confounding factor, the cervical level with the lowest MTR can still be relied upon as a predictor of functional deficits. As such, we caution that the MTR should be interpreted strictly as a quantifiable tool to identify demyelination of any cause, not only CSM. Future analyses will need to further delineate how much of the observed MTR decrease can be attributed to CSM as opposed to normal aging.

Regardless, this study identifies several topics that need to be evaluated with future research. Firstly, how closely does the MTR correlate to metrics with more gradations such as the modified JOA myelopathy questionnaire? Secondly, does the MTR change in response to surgical management? Additionally, would routine assessment of the MTR allow for earlier diagnosis of CSM, and if so, would this allow for better prevention of neurologic decline in the general population? Lastly, is there a threshold of MTR, below which surgical decompression may or may not be effective?

Conclusions

CSM patients tended to have decreased MTR indicating myelin degradation compared to our healthy subjects, and MTR was negatively correlated with the severity of CSM. MT MRI may have the potential to better detect structural changes in white matter than conventional T1 and T2 imaging techniques.

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Figure 1: Example Images

A) Registration of magnetization transfer (MT) images to standard spinal cord template. B) Example transverse MT, no MT, and computed MT ratio images of the cervical spinal cord at the C2-C3 intervertebral disc level.

Figure 2: Results

A) The mean magnetization transfer ratio (MTR) across the cervical spinal cord for the controls and cervical spondylotic myelopathy (CSM) patients is shown. B) The correlation between Nurick's score and the mean MTR across all intervertebral disc levels is shown. C) The mean MTR at the intervertebral disc level with the lowest MTR for the controls and CSM patients is shown. D) The correlation between Nurick's score and the intervertebral disc level with the lowest MTR for each patient is shown.

Table 1:

Patient Demographics

Patient #	Sex	Age (years)	Level(s)
1	M	62	Left C5
2	F	73	Bilateral C4-C6
3	F	70	Bilateral C4-C6
4	M	78	Bilateral C4-C7
5	F	62	Bilateral C4-C6
6	M	45	Bilateral C4-C6
7	M	82	Bilateral C3-C6
8	F	58	Bilateral C3-C7
9	M	63	Bilateral C4-C6
10	M	79	Bilateral C3-C5