Journal of Clinical Neuroscience xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Case study

High-resolution magnetization transfer MRI in patients with cervical spondylotic myelopathy

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ARTICLE INFO

Article history:
Received 25 July 2017
Accepted 24 February 2018
Available online xxxx

Keywords:
Magnetization transfer contrast imaging
Cervical spondylosis
Myelopathy
Diagnostic imaging

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 m m^2). 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 ρ = −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, 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 ρ = −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.

1. 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

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https://doi.org/10.1016/j.jocn.2018.02.023
0967-5868/

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 radiofrequency 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.

2. 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.

3. 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.

3.1. Participants

Ten patients (6 male and 4 female; mean age = 67.2 ± 11.4 yea rs, Table 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 a ge = 34.1 ± 7.5 years) were used as controls. The healthy controls reported no significant pain or neuromusculoskeletal diseases.

3.2. 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 3 mm, in-plane resolution = 0.47 × 0.47 mm^2). For registration purposes, a T_2-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 resolu tion = 1.1 × 1.1 mm^2).

3.3. Image analysis

Image processing was performed using the Spinal Cord Toolbox and the MNI-Poly-AMU T_2-weighted spinal cord template (resolu tion = 0.5 × 0.5 × 0.5 mm^3) [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

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

Please cite this article in press as: Suleiman LI et al. High-resolution magnetization transfer MRI in patients with cervical spondylotic myelopathy. J Clin Neurosci (2018), https://doi.org/10.1016/j.jocn.2018.02.023