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MINIREVIEWS

# Application of magnetic resonance imaging in cervical spondylotic myelopathy

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## Abstract

Cervical spondylotic myelopathy (CSM) is the most common cause of spinal cord dysfunction and is caused by static or dynamic repeated compression of the spinal cord resulting from degenerative arthritis of the cervical spine and some biological injuries to the cervical spine. The T2 signal change on conventional magnetic resonance imaging (MRI) is most commonly associated with neurological deficits. Diffusion tensor imaging and MR spectroscopy show altered microstructure and biochemistry that reflect patient-specific pathogenesis and can be used to predict neurological outcome and response to intervention. Functional MRI can help to assess the neurological functional recovery after decompression surgery for CSM.



**Key words:** Cervical spondylotic myelopathy; Magnetic resonance imaging; Diffusion tensor imaging; Magnetic resonance spectroscopy; Functional magnetic resonance imaging

**Core tip:** This article attempts to investigate the application of magnetic resonance (MR) technology to the management of cervical spondylotic myelopathy (CSM) patients and discusses recent and future advances in both conventional and novel MR techniques. The novel MR techniques, including diffusion tensor imaging, MR spectroscopy and functional MR imaging, have all played an essential role in the management of patients with CSM.

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## INTRODUCTION

Magnetic resonance imaging (MRI) plays an essential role in the management of patients with cervical spondylotic myelopathy (CSM). There have been many advances in MR technology over the past few years and the resolution and image quality have improved greatly. With these improvements, the application of MRI in CSM has progressed in parallel. The novel MR techniques not only offer a diagnostic modality, but also can be used to predict neurological outcome and response to intervention.

In addition to conventional MRI, recent application of novel techniques in CSM, such as diffusion tensor imaging (DTI)[1], MR spectroscopy (MRS)[2] and functional MR imaging (fMRI)[3], further highlights the potential influence of MR technology on the disease process. By providing pertinent information about the spinal cord microstructure and metabolism, and assessing the neurological function after surgery, these novel techniques

provide increased sensitivity to diagnosis of spinal cord injury, especially the cellular injury that ubiquitously occurs during CSM pathogenesis[4,5].

This article attempts to investigate the application of MR technology to the management of CSM patients and discusses recent and future advances in both conventional and novel MR techniques.

## PATHOPHYSIOLOGY OF CSM

In order to be fully aware of the importance of MRI in the management of CSM, an advance in understanding of the complex CSM pathophysiology is necessary. CSM is the most common cause of spinal cord dysfunction[6-8]. CSM is caused by static or dynamic repeated compression of the spinal cord resulting from degenerative arthritis of the cervical spine and some biological injury to the cervical spine cord. The preceding mechanism is mechanical injury, including compression, distraction and shear[9], and direct spinal cord compression is the most frequently encountered mechanism. The biological injury in CSM is likely related to a variety of mechanisms, such as free radical-mediated cell injury, cation-mediated cell injury, glutamergic toxicity and apoptosis[10]. Ischemia of the cervical spinal cord is considered to be a significant contributor to the pathophysiology of CSM, which includes compression of larger vessels and impaired microcirculation[11].

## CONVENTIONAL MRI

Before MR technology was well developed, computed tomography with or without myelography was commonly used for spinal structural diagnosis in CSM patients. These modalities could offer some useful anatomical information in patients with CSM, but there were some patients without myelopathy despite compression of the spinal cord and only limited information could be directly ascertained about the condition of the spinal cord. Therefore, there were some limitations in the assessment of spinal cord injury.

Through providing high-resolution imaging of soft tissue anatomy, MRI provides excellent anatomical information about the spinal cord macrostructure and gives insight into structural histopathological changes in CSM patients. In order to investigate myelomalacia, edema, gliosis and ischemic white matter changes of the spinal cord, a large number of clinical studies have examined changes in TI- and T2-weighted signals. Some authors considered that these observations were caused by irreversible spinal cord injury[12], but others felt that these regions represented a wide spectrum of recuperative potential[13]. Recently, several grading systems have been proposed to classify the spinal cord signaling change subtypes[14], but the specific grading remains one of the most controversial topics in the field of degenerative spinal disease.

Assessment of the utility of MRI to predict neurological outcome following decompression surgery for CSM has attracted much attention. In 2009, the Guidelines for the Surgical Management of Cervical Degenerative Disease were published by an expert group that represents the Joint Section on Disorders of the Spine and Peripheral Nerves of the American Association of Neurological Surgeons and Congress of Neurological Surgeons[15]. They established the relationship between spinal cord signal changes and clinical outcome in CSM patients. According to their extensive literature review, they concluded that multilevel T2 hyperintensity, T1 focal hypointensity combined with T2 focal hyperintensity, and spinal cord atrophy each indicate poor prognosis following surgical intervention. This has been confirmed by other authors. For example, Uchida *et al*[16] reported that a T1/T2 low signal/high signal imaging pattern was associated with poor neurological recovery. On the contrary, a study has shown that the regression of high signal changes on T2 postoperatively correlates with better functional outcomes[17]. Furthermore, some studies have suggested that if surgeons use MRI signal intensity to estimate the risk of poor outcome after surgery, they should use high signal changes in T2 in combination with other signal intensity parameters and not in isolation[18]. Therefore, more robust and objective modalities for assessment of the condition of the spinal cord need to be developed.

## DTI

### *Principles and parameters of DTI*

DTI is a noninvasive MRI technique that measures the random motion of water molecules and provides information about the cellular integrity and pathology of anisotropic tissues[19,20]. DTI can provide unique quantitative information on the microstructural features of white matter in the central nervous system[21]. Diffusion properties can be evaluated using quantitative indices such as the apparent diffusion coefficient (ADC), mean diffusivity (MD) and fractional anisotropy (FA). The ADC reflects the average diffusivity of water molecules in all directions. The stronger water molecules diffuse within a tissue, the larger the ADC. In contrast, the weaker water molecules diffuse within a tissue, the lower the ADC. Therefore, tissues with high water mobility and few boundaries to water motion have high ADC values, such as cerebrospinal fluid and vasogenic edema, whereas tissues with a high degree of complexity and boundaries to diffusion have a relatively lower ADC, such as white matter fiber bundles and tumors[22]. MD represents the degree of diffusional motion of water molecules (regardless of direction) and is measured in $mm^2/s$. FA represents a rotationally invariant parameter, where 0 represents completely isotropic diffusion and 1 represents extremely limited diffusion in only one direction[19].

### *Main features of DTI*

An increasing number of studies has indicated the significance of ADC and FA and has defined the character-

istics of the two measurements within CSM patients. At the site of compression in the cervical spinal cord, FA is significantly lower and ADC significantly higher[23]. These two measurements of DTI are more sensitive and specific than conventional MRI and can detect damage of the white matter tracts before a high signal lesion appears on T2 imaging[23]. This theory has been demonstrated by Lee *et al*[24]. In that study, four patients who had no abnormal signal changes on MRI also had lower FA and higher ADC. In addition, there was another view about the effects of DTI. Some researchers consider that it may have the potential to distinguish between a symptomatic and asymptomatic group of patients. This view has also been proposed in a study by Kerkovsky *et al*[23] in which FA was significantly lower and ADC significantly higher in a symptomatic group than in an asymptomatic spondylotic cervical cord encroachment subgroup.

### Role of ADC and FA in identification of acute and chronic compression

In addition to the above-mentioned effects, the two measurements were also commonly used in the identification of acute and chronic compression in CSM. Some studies have suggested that acute compression of spinal cord tissue may result in a focal decrease in ADC as well as a focal increase in FA. Through the establishment of diffusion MR simulations, Ford *et al*[25] have suggested that compression of axon fibers results in a decrease in ADC, which may lead to a slight increase in FA. Nilsson *et al*[26] have clearly demonstrated decreased ADC with increasing compression of spinal cord white matter. Facon *et al*[27] explored acute spinal cord compression in two patients and noted a slightly elevated FA at the level of compression compared to normal controls (0.80-0.83 *vs* 0.75 in healthy volunteers). Compared with the diffusion characteristics of acute compression of the spinal cord, clinical studies have clearly documented a significant increase in ADC and decrease in FA in the late stages of chronic compression of the spinal cord[28]. Through the establishment of an animal model of chronic compression, Cheung *et al*[29] illustrated a characteristic increase in ADC and decrease in FA as late as 9 mo after the start of compression. Specifically, the changes in diffusion characteristics may result from chronic, repeated ischemic insults to the spinal cord, leading to downstream histopathological changes, including gliosis, loss of motor neuron function, vasogenic edema and ultimately necrosis and cavitation[30]. All the pathological changes lead to elevation of ADC due to the increase in extracellular water and suppression of FA due to lack of directional organization within the spinal cord.

### Significance of MD

Some studies have indicated that an increase in MD and decrease in FA have diagnostic utility in myelopathy and the sensitivity and specificity for prediction are higher with MD than with FA. After using the following parameters: TE: 80 ms; image matrix of 256 × 195 pixels; nominal voxel size of 0.9 mm × 1.17 mm, three sections 5-mm thick and a gap of 1 mm, Demir *et al*[5] suggested approximately 80% sensitivity and 53% specificity for detecting myelopathy in patients with spinal cord compression. Furthermore, when using a single-shot fast spin-echo-based sequence with the following parameters: TE/TR, 80/6000 ms; number of excitations, 1; field of view, 240 $mm^2$; matrix size, 160; voxel size, 1.5 $mm^2$ × 1.5 $mm^2$ in-plane; slice thickness, 3 mm; gradient directions, 15; and b values, 0 and 1000 s/$mm^2$, and from the results of receiver operating characteristic (ROC) curve analysis, when using the optimal cutoff point (an MD $z$ score of 1.40 at the most compressed spinal level), Uda *et al*[19] indicated that myelopathy could be predicted with a sensitivity of 100% and specificity of 75%. In conclusion, MD should receive more attention in the management of CSM patients.

## MRS

### Background to application of MRS

Although chronic spinal cord has been accepted as a major feature of CSM, the time course and evolution of cellular and microstructural damage are yet to be understood clearly. This is largely because conventional MRI, despite providing excellent macroscopic anatomical detail, provides constrained information about spinal cord cellular function and microarchitecture. Some authors postulate that there is a spectrum of cellular and microstructural changes that occur within the spinal cord as patients with cervical spondylosis progress from being asymptomatic to manifesting neurological impairment[31]. Surgical intervention of the spinal cord in its reversible state (*i.e.*, before the onset of irreversible injury) confers better neurological outcomes. Therefore, understanding of progressive cellular alteration of the spinal cord as the patient advances to a symptomatic state would be a compelling achievement in the treatment of cervical spondylosis.

### Principles and characteristics of MRS

Compared with DTI, the application of MRS to CSM has more advantages. MRS can provide metabolic information about the cellular biochemistry and function of the neural structures within the cervical spinal cord[32]. MRS also can be used to assay a series of pertinent biochemical markers, such as *N*-acetyl aspartate (NAA), lactate, choline (Cho), myo-inositol (Myo-I), glutamine-glutamate complex (Glx) and creatinine (Cr), with particular sensitivity to NAA and lactate[2]. Some studies have indicated that NAA is only found in axons and neurons and is considered an indicator of axonal integrity[33]. Although little is known of the specific mechanism, lactate is considered to play a central role in metabolic dysfunction after central nervous system injury and may be related to ischemia and mitochondrial dysfunction.

### MRS features of CSM

In recent years, spinal cord MRS has been most frequent-

ly used to investigate multiple sclerosis lesions[33]. Many studies have demonstrated suppressed levels of NAA in multiple sclerosis patients when compared to normal volunteers and some correlation between NAA levels and clinical status[34]. Although less studied, cervical spine MRS has recently been used in CSM. In a cohort of 21 CSM patients, Holly *et al*[2] indicated that the NAA/Cr ratio was significantly lower in CSM patients than in normal volunteers, which suggested increased neuronal and axonal injury. Nearly one-third of CSM patients appeared to have an abnormal lactate signal and the control subjects did not, which further supports the importance of ischemia in the pathogenesis of CSM.

### Early and late changes in MRS metabolites

In a study of 21 patients with cervical spondylosis and 11 healthy controls, Salamon *et al*[31] discussed the early and late changes in MRS metabolites. In the early changes, the observation of a cervical stenosis patient without spinal cord signal changes showing slightly higher Myo-I and Glx compared to that of the control group suggested Myo-I as a potential early marker for spinal cord inflammation and early stage demyelination in cervical stenosis before neurological impairment. In the late changes, while the patient with spinal cord signal changes had a significantly higher Cho/Cr ratio than the control, the patient without spinal cord signal changes had no significant difference compared to the control. These results show that increased Cho levels appear later than the aforementioned cellular metabolic changes as cervical spondylosis progresses to a symptomatic state. In addition, they also found that higher Cho/NAA ratio was significantly associated with poorer neurological function and Cho/NAA had a significant correlation with the Modified Japanese Orthopedic Association score (mJOA), providing a potential clinically useful radiographic biomarker in the management of cervical spondylosis.

## fMRI

### Principle and features of fMRI

fMRI is a functional neuroimaging procedure using MRI technology that measures brain activity by detecting associated changes in blood flow[35]. This technique relies on the coupling of cerebral blood flow and activation of neurons. When an area of the brain is active, the flow of blood in the region also increases[36]. Discovered in 1990 by Ogawa *et al*[37], fMRI uses blood oxygenation level dependent (BOLD) contrast. BOLD fMRI is a noninvasive and repeatable imaging modality capable of detecting changes in brain function over time. In recent years, spinal cord injury and CSM have been shown to induce changes in cortical activation during sensorimotor tasks. Although these changes have not been precisely determined, they can reflect part of the relationship between the recovery of limb motor function and the volume of cortical activation area after injury[38]. CSM is always combined with limb motor dysfunction and pain, particularly in the upper limbs. fMRI is being developed to assess neurological function after surgery.

### Applications of fMRI to CSM

Compared with the clinical application of the aforementioned MR techniques, the current clinical application of fMRI is relatively small. Some researchers consider that spinal fMRI can reveal spinal cord function below the site of injury and may provide objective information that can be used for assessing retained function, designing rehabilitation programs, predicting the potential for recovery of function in spinal cord injury, and for assessing new experimental treatment strategies[39]. In addition, several studies have assessed neurological function by fMRI after decompression surgery. Tam *et al*[38] concluded that fMRI detected increased cortical activation in the primary motor cortex during finger tapping after decompression surgery in a CSM patient. These changes become more significant with the recovery of motor function. Upper and lower extremity motor subscores of the Japanese Orthopedic Association scale demonstrated a 40% and 43% improvement, respectively. According to their observation, they suggested that cortical reorganization or recruitment may be associated with the recovery of neurological function after spinal cord injury.

## LIMITATIONS OF MR TECHNIQUES

In spite of these advanced imaging techniques offering novel insights into CSM, there are some limitations. The spinal cord is relatively small and has differences in magnetic susceptibility from the adjacent tissues; thus, there will be some artifacts. In the commonly used types of MRS, the minimum voxel size is only slightly smaller than the cross-sectional area of the spinal cord and a significant decrease in signal-to-noise ratio can be caused by a suboptimally placed voxel[40]. Both MRS and DTI are sensitive in patients with CSM and the structural movement during scan acquisition. The physiological rostral-caudal movement of the spinal cord in response to cardiac pulsations and the respiratory cycle is significant and even more marked than in the brain[38]. Furthermore, spinal fMRI encounters major technical challenges with cardiac noise being considered a major source of noise[41]. Therefore, cardiac gating, specialized radiofrequency coils and MR signal suppression bands are more frequently used to improve the quality of MRS, DTI and fMRI in the spinal cord. In addition to the physiological noise with fMRI, there are some other limitations; the most common are the repeatability of examination and the veracity of spatial orientation[42].

## FUTURE DIRECTIONS

An increasing number of studies has suggested that DTI and MRS play a significant role in the management of CSM patients, not only to predict outcome following surgical intervention, but they also have several other po-

tential future applications. Some studies have suggested that some patients with mild CSM can be successfully treated nonoperatively. Advanced MRI techniques such as DTI or MRS have the potential to serve as noninvasive methods to monitor asymptomatic or mildly affected patients treated nonoperatively for impending neurological deterioration. However, providing an early warning is difficult because, despite the progression of cellular spinal cord injury and subsequent neurological symptoms, they present with a stable radiographic appearance in a serial standard MRI. In summary, DTI and MRS as advanced methods to assess the progression of subclinical disease are necessary.

In addition, a recently introduced extension of the DTI technique called diffusional kurtosis imaging (DKI) shows greater promise than DTI in evaluating the microstructure and pathological condition of neuronal tissue, especially gray matter[43,44]. Hori *et al*[45] studied 13 consecutive patients with cervical myelopathy and concluded that the mean diffusional kurtosis (MK) in the spinal cord may reflect microstructural changes and damage of the spinal cord gray matter. Although further studies of the imaging-pathology relationship are needed, MK has the potential to provide new information beyond that provided by conventional diffusion metrics such as ADC and FA, which are based on the monoexponential model[45].

Recently, investigation of novel molecular and biochemical therapies to treat the biological injury in cells that occurs during CSM pathogenesis has attracted more attention. These include inhibition of apoptosis with a Fas ligand-blocking antibody[46,47], administration of neurotropins either through genetically altered fibroblasts[48] or adenovirus-mediated retrograde spinal cord delivery[49], and diet therapy to repair injured plasma membranes and cellular oxidative damage[50]. Once translated to clinical use, all the therapy methods need a noninvasive modality to ascertain cellular response to intervention. DTI, MRS and DKI could potentially serve as such a modality, which can identify subtle changes in spinal cord microarchitecture and biochemistry.

In addition, fMRI plays an important role in assessing neurological functional recovery after decompressive surgery for CSM. According to the trend of MR techniques development and the requirement to quantify neuronal function, fMRI will more frequently be used to detect functional impairment and localize regions of injury in CSM patients in the future[4]. Furthermore, fMRI combined with DTI can establish a functional connectivity network diagram of active location. Perhaps this will be used frequently to explain the relationship between neurological structure and function in the future.

## CONCLUSION

MR techniques play an indispensable role in the management of CSM patients and have evolved primarily from a diagnostic modality to a method that can potentially predict patient outcome following surgical intervention. DTI and MRS have further enhanced our knowledge about the pathogenic mechanism in CSM by providing detailed information regarding the spinal cord microstructure and biochemistry. In addition, fMRI can help to assess the neurological functional recovery after decompression surgery in CSM. Generally speaking, these MR techniques and others may play an expanded role in the management of CSM patients in the future.

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