Proton magnetic resonance spectroscopy to evaluate spinal cord axonal injury in cervical spondylotic myelopathy

Laboratory investigation

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Object. Magnetic resonance spectroscopy is commonly used to provide cellular and metabolic information in the management of a variety of pathological processes that affect the brain, and its application recently has been expanded to the cervical spine. The majority of radiographic investigations into the pathophysiology of cervical spondylotic myelopathy (CSM) have been focused on the spinal cord macrostructure. The authors sought to determine the feasibility of using MR spectroscopy to analyze spinal cord biochemical function in patients with CSM.

Methods. Twenty-one patients with clinical and radiographic evidence of CSM were prospectively enrolled in this study. The patients underwent preoperative neurological examination, functional assessment, and cervical spine MR spectroscopy. Voxels were placed at the C-2 level, and the MR spectroscopy spectra peaks for N-acetylaspartate (NAA), choline, lactate (Lac), and creatine (Cr) were measured. Thirteen age-matched healthy volunteers served as controls.

Results. The NAA/Cr ratio was significantly lower in patients with CSM than in controls (1.27 vs 1.83, respectively, p < 0.0001). The choline/Cr ratio was not significantly different between the 2 groups. Seven of the patients with CSM had a Lac peak, whereas no peaks were noted in the control group (p < 0.05). There was no correlation between the severity of myelopathy and the NAA/Cr ratio in the CSM cohort.

Conclusions. Data in this study demonstrated the feasibility of using MR spectroscopy to evaluate the cellular biochemistry of the spinal cord in patients with CSM. Patients with CSM had a significantly lower NAA/Cr ratio than healthy controls, likely because of axonal and neuronal loss. The presence of Lac peaks in one-third of the patients in the CSM cohort further supports the role of ischemia in the pathophysiology of CSM.

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Key Words • cervical location • myelopathy • spectroscopy • spine

Since its advent, MR imaging has become an invaluable tool in the diagnosis and management of CSM. Numerous investigations into the radiographic characteristics, pathophysiology, and prognosis of CSM have been performed using this imaging modality. The majority of these studies have been focused on the spinal cord macrostructure, with an emphasis on clearly visible factors such as spinal cord signal abnormalities, spinal alignment, and degree of spinal cord compression. In contrast, the spinal cord microstructure and biochemical function have been relatively understudied in patients with CSM.

Magnetic resonance spectroscopy is an advanced imaging technique that provides metabolic information regarding cellular function and has been extensively used in the brain. A number of pertinent biochemical markers can be assayed with MR spectroscopy including NAA, Lac, Cho, and Cr. Of particular interest is NAA, which is found almost exclusively in axons and neurons and is an indicator of axonal integrity. Decreases in NAA are considered a sign of axonal loss or dysfunction.

The use of MR spectroscopy in the cervical spine has been reported only recently. Several investigations have revealed that the NAA concentration within the cervical spinal cord in patients with MS is reduced compared with that in healthy controls. Furthermore, there appears to be a potential correlation between the NAA/Cr ratio and the degree of neurological disability in this patient population. To our best knowledge, the use of MR spectroscopy in the evaluation of patients with CSM has not been described. We sought to determine the feasibility of using MR spectroscopy to investigate biochemical function in the spinal cord in patients with CSM.

Abbreviations used in this paper: Cho = choline; Cr = creatine; CSM = cervical spondylotic myelopathy; Lac = lactate; mJOA = modified Japanese Orthopaedic Association; MS = multiple sclerosis; NAA = N-acetylaspartate.
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Methods

Patient Population

The study cohort consisted of 21 patients with signs and symptoms of CSM. There were 11 women and 10 men, and the mean age was 60 years (range 41–80 years). Standard MR imaging of the cervical spine demonstrated evidence of cervical stenosis and/or spinal cord injury related to CSM in each case. Once the diagnosis of CSM was confirmed clinically and radiographically, MR spectroscopy studies of the cervical spine were performed in each patient. Exclusion criteria included: 1) previous cervical spine surgery, 2) acute change in neurological function related to central cord syndrome or other traumatic event, 3) spinal cord compression at the C-2 level or cervicomedullary junction, 4) cardiac pacemaker or other implant incompatible with MR imaging, and 5) severe claustrophobia. Baseline physical examinations were performed on each patient, and the mJOA scale1 was used as the neurological assessment measure. Thirteen age-matched healthy volunteers without evidence of neurological symptomatology underwent the same cervical spine MR spectroscopy protocol and served as the control group. The Office for Protection of Research Subjects at our institution approved the study protocol.

Presenting Symptoms

The most common presenting symptom was gait dysfunction, which was encountered in 16 patients. The duration of the gait deterioration ranged from 3 weeks to 4 years prior to the clinical evaluation. Five patients required a cane for ambulation, 2 needed walkers, and 1 was wheelchair bound. Fifteen patients presented with deterioration in hand function, principally manifested by significant changes in their ability to perform certain activities of daily living such as manipulating utensils, sewing, writing, and buttoning buttons. Ten patients reported numbness or paresthesias in the hands, and 6 described these symptoms in the lower extremities. Two patients presented with recent changes in bladder or bowel function.

Physical Examination

On examination, 11 patients had weakness in the upper extremities, and 6 in the lower extremities. Eight patients had decreased sensation in the upper extremities, and 6 had sensory changes in the lower extremities. Hyperreflexia was the most common upper motor neuron sign and was found in 13 patients. A positive Hoffmann sign was the second most common sign and was observed in 9 patients. Seven patients had a positive Babinski reflex, and 4 had clonus in the lower extremities.

Radiographic Imaging

Standard MR imaging was performed in all patients and revealed spinal cord compression in each case. Circumferential spinal cord compression was encountered in 13 patients. In these cases the spinal canal narrowing was related to advanced cervical spondylosis manifested by a combination of facet arthropathy, ligamentum flavum hypertrophy, and varying degrees of ventral disc-osteophyte compression. In the remaining 7 patients, predominantly ventral spinal cord compression was caused by a herniated disc and/or osteophytic vertebral body endplates. Thirteen patients had T2-weighted MR imaging signal abnormalities within the spinal cord parenchyma and 8 were without signal changes. Eleven patients had a lordotic spinal alignment, 6 had straight cervical spines, and 4 had kyphotic cervical spines.

Magnetic Resonance Spectroscopy Technique

Cervical spine MR imaging was performed with a neck coil in place on a 1.5-T Sonata VA25 unit (Siemens Medical Systems) by utilizing the following sequences: sagittal T1-weighted images (TR 450 msec, TE 12 msec, matrix 320 × 256, and slice thickness 4 mm), sagittal T2-weighted images (TR 3000 msec, TE 106 msec, matrix 512 × 408, slice thickness 4 mm), and axial T2-weighted images (TR 4970 msec, TE 109 msec, matrix 512 × 512, and slice thickness 4 mm). Pulse oximeter triggering was used in the MR spectroscopy sequences to reduce any artifact from movement of the spinal cord and CSF pulsation. A single voxel measuring 1 × 1 × 1.5–2 cm (anteroposterior × transverse × craniocaudal) was placed at the C-2 spinal cord level for MR spectroscopy. A short echo time point-resolved spectroscopy sequence2 (TE 30 msec, TR = 1500 or 3000 msec, average 256, and acquisition time 3.40 minutes) was obtained. An MR physicist was on site at the time of imaging to manually shim the magnetic field (18–28 Hz) to minimize inhomogeneity and assure that the area of interest was in resonance. Automated shimming is not as precise, as it ranges between 68–80 Hz and is associated with irregular MR spectroscopy metabolic peaks. The MR spectroscopy examination takes ~8–10 minutes to perform, including the manual shimming step (3–5 minutes for shimming and 4 minutes for imaging). Patients were asked not to swallow during the study to minimize the swallowing artifact.

Magnetic resonance spectroscopy values were calculated using an automated Siemens postprocessing program. The heights of NAA (2.0 ppm), Cr (3.03 ppm), Cho (3.25 ppm), and Lac (1.32 ppm) peaks were measured on the screen. The NAA/Cr and Cho/Cr ratios were calculated.

Statistical Analysis

Statistical analyses of the data included: analyses of variance; the conventional t-test and its robust equivalent—the Yuen-Welch test;18,19 the Tukey post hoc comparison; and the Fisher exact test for categorical data. All data management and analysis were conducted using R, version 2.7.0 (R Development Core Team).

Results

Patients With CSM Compared With Controls

Magnetic resonance spectra were successfully ac-
quired in all patients and controls (Figs. 1 and 2). The patient group showed significantly lower NAA/Cr ratios (mean ± SD 1.27 ± 0.52) than the control group (1.83 ± 0.18, p < 0.0001; Fig. 3). However, the 2 groups did not differ significantly in the Cho/Cr ratios (patients 0.96 ± 0.24, controls 0.93 ± 0.18). Seven of the 21 patients had demonstrable Lac peaks on the MR spectra, whereas such peaks were not found in any of the controls (p < 0.05; Fig. 4). There were statistically significant differences in the NAA/Cr ratio in CSM patients with (1.05) or without

Fig. 1. Left: Sagittal cervical spine MR spectroscopic image obtained in a 41-year-old man with CSM who had presented with severe gait dysfunction and decreased hand dexterity, showing evidence of significant spinal cord compression in the midcervical spine. White rectangular box is the voxel that has been placed at the C-2 level. Right: Magnetic resonance spectra showing a large Lac peak and small NAA/Cr ratio.

Fig. 2. Left: Sagittal cervical spine MR spectroscopic image obtained in a healthy 35-year-old man, demonstrating no evidence of spinal cord compression or injury. Right: Magnetic resonance spectra revealing a normal NAA/Cr ratio and no Lac peak.
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(1.39) Lac peaks compared with the control group (1.86, p = 0.003 and p < 0.05, respectively; Fig. 5).

Comparisons Within the CSM Cohort

The mean mJOA score in the patient group was 12.3 ± 2.2, with a range from 9 to 17. There was no significant difference in the NAA/Cr ratio in patients with CSM whose mJOA scores were < 12 as opposed to ≥ 12. Although the NAA/Cr ratio was lower in CSM patients with a positive Lac signal than in those without, the difference did not reach statistical significance (1.05 vs 1.39, respectively, p = 0.24). The T2-weighted MR signal abnormalities were encountered in 13 patients, of whom 6 (46%) had evidence of a Lac peak. Only 1 (13%) of the 8 patients without a T2-weighted signal abnormality had a Lac peak. The relationship between having a T2 signal abnormality and a Lac peak was not significant (p = 0.17). Additionally, there was no statistical relationship between the presence of a T2-weighted signal change and the mJOA score or NAA/Cr ratio.

Discussion

Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy has become widely accepted as a noninvasive method of providing information about cellular biochemistry in the CNS and is commonly used as an adjunct to standard MR imaging in the evaluation of neoplastic, inflammatory, and infectious disorders affecting the brain. A variety of specific biochemical markers can be assayed using this technique including Lac, NAA, Cr, and Cho. Interestingly, NAA is found almost exclusively in neurons and axons, and a reduction in this metabolite is associated with the neuronal damage commonly seen in intracranial tumors, MS, and head injury. The presence of a Lac peak generally indicates significant anaerobic metabolism and an alteration in the normal cellular biochemical oxidative process. This abnormality may be related to inflammation, local ischemia, and/or neuronal mitochondrial dysfunction with the resultant production of excess Lac. Choline is a common component of many phospholipids, and fluctuations in the concentration of this marker are considered an indicator of cellular turnover related to both membrane synthesis and degradation. Creatine is a measure of global cellular metabolic activity, and its peak remains stable under many pathological conditions affecting the CNS. Thus, it frequently serves as an internal control to which the signals of the other major metabolites can be compared.

In contrast to its use in the brain, MR spectroscopy in the cervical spine has received relatively little attention, and its application has been reported only recently. Gomez-Anson et al. first described the feasibility of cer-
The present study is the largest reported investigation of cervical spine MR spectroscopy and the first in which is described the use of MR spectroscopy in the evaluation of patients with CSM. There was a highly significant correlation between a decreased NAA/Cr ratio in the CSM cohort compared with healthy controls. This finding is likely reflective of the axonal and neuronal damage that are the histopathological hallmarks of this disease process and indicates that the injury can also occur in regions that appear radiographically normal. There was no significant difference in the Cho/Cr ratio between patients with CSM and controls, suggesting that the membrane cell turnover simultaneously performed in the brain, the selected cerebral voxel may not sample areas involved in the spinal cord pathways. Thus, the variable contribution of cerebral pathology to decreased levels of NAA in the cervical spinal cord is difficult to quantify. In contrast, patients with CSM commonly suffer from focal neuronal damage limited to the cervical spine, and thus appear to be a more homogeneous and predictable population for this imaging modality. Moreover, the unique pathophysiology of CSM makes this disease process well suited for clinical and experimental applications of MR spectroscopy. Cervical spondylotic myelopathy is caused by progressive abnormalities of the vertebral column that lead to spinal cord damage due to both primary mechanical and secondary biological injury. The histopathological features of CSM demonstrate a consistent pattern of deleterious changes including cystic cavitation, focal necrosis of central gray and white matter, and anterior horn dropout.

Standard MR imaging provides excellent macroscopic anatomical detail but limited specific information regarding the cellular function of the spinal cord microarchitecture. Presumed spinal cord damage in CSM is commonly manifested by T2- and/or T1-weighted signal changes, but the exact degree of injury and the significance of these changes are often debated. These abnormalities have been described in the medical literature as gliosis, myelomalacia, edema, and ischemic white matter changes. Some authors have considered these changed areas as irreversible spinal cord injury, whereas others believe that these regions represent a wide spectrum of recuperative potential. Attempts to classify these areas have been further limited because of subjectivity, ambiguity, and a lack of standardization in the nomenclature. For instance, Mehalic et al. have described a grading scale for increased signal on T2-weighted images from 0 (none) to 4 (very intense), Yukawa et al. have reported a similar scale with 3 categories: Grade 0, none; Grade 1, light (obscure); and Grade 2, intense (bright).

Many other authors have evaluated the relationship between spinal cord signal changes, and neurological status and surgical outcome in patients with CSM. Not surprisingly, there has been a lack of consensus regarding the relationship between these signal abnormalities, and neurological status and prognosis. Magnetic resonance spectroscopy has the potential to provide microcellular biochemical information and novel characterization of these areas, as well as advance our current understanding of radiographically normal and abnormal regions of the spinal cord in patients with CSM.

Cervical Spondylotic Myelopathy

In addition to axonal loss related to spinal disease, decreased levels of NAA in the cervical spinal cord in patients with MS can also be caused by axonal injury occurring within the brain. Differentiating between these 2 potential origins of NAA loss in the cervical spine is likely quite difficult. Even when MR spectroscopy is simultaneously performed in the brain, the selected cerebral voxel may not sample areas involved in the spinal cord pathways. Thus, the variable contribution of cerebral pathology to decreased levels of NAA in the cervical spinal cord is difficult to quantify. In contrast, patients with CSM commonly suffer from focal neuronal damage limited to the cervical spine, and thus appear to be a more homogeneous and predictable population for this imaging modality. Moreover, the unique pathophysiology of CSM makes this disease process well suited for clinical and experimental applications of MR spectroscopy. Cervical spondylotic myelopathy is caused by progressive abnormalities of the vertebral column that lead to spinal cord damage due to both primary mechanical and secondary biological injury. The histopathological features of CSM demonstrate a consistent pattern of deleterious changes including cystic cavitation, focal necrosis of central gray and white matter, and anterior horn dropout.

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![Boxplot demonstrating that the NAA/Cr ratio was significantly lower in CSM patients with or without a Lac peak than in the control group (p = 0.003 and p < 0.05, respectively). The NAA/Cr ratio was lower in the CSM patients with a Lac peak than in those without, but the difference did not reach statistical significance.](image-url)
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was similar between the 2 groups. Although the NAA/Cr ratio was markedly different, this finding is not surprising because an increase in Cho levels in neuronal tissue has been more closely associated with glial cell and inflammatory proliferation than myelin damage. Moreover, this increase may represent areas in which myelin was preserved despite the loss of axons. The statistically significant presence of a Lac signal in one-third of the study patients further accords with the postulation that cellular ischemia plays a role in the pathogenesis of CSM. There was no statistical relationship between the NAA/Cr ratio and the presence of a Lac peak, and neurological status within the CSM group. The association between these parameters will require continued investigation with a larger cohort.

Limitations of Cervical Spine MR Spectroscopy

Currently, there are several limitations in cervical spine MR spectroscopy that make this imaging modality technically challenging. The physiological rostral-caudal movement of the spinal cord in response to cardiac pulsations is fairly significant and even more marked than in the brain. Additionally, the respiratory cycle causes alterations in CSF flow at the cervico-medullary junction that can result in spinal cord movement. Cardiac gating is often used to enhance the quantitative spectroscopy and minimize artifact. Moreover, the spinal cord itself is quite small, and accurate voxel placement is mandatory. The cross-sectional area of the spinal cord is only slightly larger than the voxel size, and a suboptimally placed voxel can cause a significant decrease in the signal-to-noise ratio. In cases of a patent spinal canal, extending the voxel further than the cord boundaries can result in lipid contamination from the surrounding spinal fluid and epidural soft tissue.

In patients with CSM, the spinal cord can be compressed to a cross-sectional area smaller than the presently available voxel size, leading to a low signal-to-noise ratio and significant artifacts from compressive soft tissue and osseous elements. To address this limitation, voxels were placed at the C-2 level. We believed that this strategy would be sufficient to identify spinal cord abnormalities in patients with CSM, as it is known that severe Wallerian degeneration can occur in the posterior columns and lateral corticospinal tracts cephalad and caudal to the level of compression in this population. Furthermore, diffusion tensor imaging has demonstrated evidence of abnormalities in the spinal cord microstructure proximal to the area of compression, in regions that appeared normal on standard MR images obtained in patients with CSM. It is difficult to estimate how long the compression must exist for Wallerian degeneration to occur. The fact that chronic spinal cord injury frequently occurs before the onset of symptomatology also makes this determination quite challenging. However, most patients in the present study had noted clinical symptoms of CSM for at least 1 year.

Future study will likely involve smaller voxel sizes and improved resolution to better evaluate the spinal cord microstructure and cellular function at the level of compression and obvious injury. In addition to providing further clinical information in surgical patients with moderate and severe forms of CSM, this technique can be used in the management of mild or nearly asymptomatic forms of this disease. Magnetic resonance spectroscopy can be used to serially evaluate these patients for progressive spinal cord injury that might precede the manifestation of symptoms. Moreover, chronic spinal cord injury can also develop in patients with CSM prior to the obvious radiographic signs such as myelomalacia or gliosis. Magnetic resonance spectroscopy could potentially detect these pathological changes earlier than conventional MR imaging and thus lead to changes in the treatment strategy.

Conclusions

Magnetic resonance spectroscopy provides a non-invasive method of investigating the spinal cord microstructure and cellular function in patients with CSM. These patients demonstrate a significant decrease in the spinal cord NAA/Cr ratio compared with that in healthy controls, and this reduction is likely caused by neuronal and axonal injury. The presence of a Lac signal in one-third of our patient group further implicates ischemia as a clinical factor in the pathogenesis of CSM. The neural injury associated with CSM appears to involve not only areas of obvious damage, but also those that look normal radiographically.

Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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References

invisible brain stem damage” and predict “vegetative states”. J Neurotrauma 23:674–685, 2006

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