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Metabolic Imaging Using Proton Magnetic Spectroscopy as a Predictor of Outcome Following Surgery for Cervical Spondylotic Myelopathy

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Abstract

Study Design—A single center magnetic resonance spectroscopy (MRS) imaging and surgical outcome study involving sixteen patients with cervical spondylotic myelopathy (CSM).

Objective—In the present study, we assess the utility of MRS to quantify metabolic changes within the spinal cord and predict surgical outcome in CSM patients.

Summary of Background Data—MRS is an advanced spinal imaging modality that can provide pertinent metabolic and biochemical information regarding spinal cord function. Previous studies have demonstrated significant abnormalities in specific cellular metabolite concentrations in CSM patients.

Methods—Sixteen patients with CSM were evaluated. Single voxel MRS was performed in the cervical cord. NAA and choline metabolite concentration ratios with respect to creatine were quantified, as well as the presence or absence of a lactate peak. The mJOA scale was used as the functional assessment measure. Correlation of MRS metabolites with change in mJOA score was performed.

Results—The mean follow-up time was 19 months. There was a statistically significant improvement between mean preoperative and postoperative mJOA score following surgery ($P < 0.0001$). The NAA/Cr ratio demonstrated a significant relationship to the change in mJOA score after surgery ($P = .0479$; $R^2 = .2513$). The Cho/NAA ratio demonstrated an even stronger correlation with the change in mJOA score following surgery ($P = .0065$; $R^2 = .4219$). Neither the Cho/Cr ratio, nor the presence of a lactate peak or T2 weighted signal change was significantly correlated with change in mJOA score after surgery.

Conclusion—MRS is a novel, noninvasive imaging modality that provides pertinent information regarding spinal cord cellular and metabolic function. In a cohort of operatively treated CSM

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patients, the NAA/Cr and Cho/NAA ratios were predictive of neurological outcome, as both were significantly associated with change in mJOA score after surgery.

Keywords

cervical; magnetic; spectroscopy; myelopathy; outcome; predictor; spine

Introduction

CSM is a potentially devastating neurological condition that can lead to a loss of neurological function and significant impairment in activities of daily living. The determination of the optimal treatment strategy for these patients can be challenging, and is frequently debated. Although decompression surgery is frequently advocated for this condition, the neurological recovery and clinical response to operative intervention can be quite variable among individuals.

Consequently, there has been an increasing interest in determining radiographical features that may predict clinical outcome following surgery for CSM.¹ The vast majority of these studies have been primarily limited to the neuroanatomical characteristics of the spinal cord such as spinal cord diameter^{2,3,4}, presence of spinal cord signal change⁵⁻¹¹, and degree of spinal cord compression^{12,13}. However, the fact that some patients do not notice improvement of neurological function following surgery, despite macroscopic imaging showing alleviation of the compression and re-expansion of the spinal cord, suggests there may be cellular mechanisms affecting function that are not clearly revealed using standard MRI.

We previously described the use of MR Spectroscopy to evaluate spinal cord injury in CSM.^{14,15} MRS offers metabolic information regarding cellular biochemistry and function of the neural structures within the cervical spine. Although a variety of biomarkers can be assayed with this technique, N-acetyl-aspartate (NAA) is of particular importance, as it is commonly recognized as a reliable marker of neuronal and axonal injury within neural tissue.¹⁶ This study was designed to determine the feasibility of using neurochemical alterations in spinal cord biochemistry to predict the clinical outcomes following surgery in CSM patients.

Materials and Methods

Patient Population

The study cohort consisted of sixteen patients that underwent decompression surgery for symptomatic CSM. All surgeries were performed by the senior author (LTH). There were ten women and six men, and the mean age was 63 years (range 40-80). Conventional cervical spine MRI manifested evidence of cervical stenosis and/or chronic spinal cord injury related to CSM in each case. After the patients agreed to participate in the study and were properly consented, cervical spine MRS was 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

C2 level or cervicomedullary junction, 4) cardiac pacemaker or other non-MRI compatible implant, 5) severe claustrophobia. Baseline neurological examinations were performed on each patient, and the modified Japanese Orthopaedic Association (mJOA) scale was used as the functional assessment measure.^{17,18} The Office for the Protection of Research Subjects at our Institution approved the protocol for this study. We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during the course of this research.

Presenting Symptoms

The most common presenting symptom was gait dysfunction, and was encountered in eleven patients. The duration of the gait deterioration ranged from three weeks to four years prior to their clinic evaluation. Three patients required a cane for ambulation, 2 needed walkers, and 1 was wheelchair-bound. Ten patients presented with deterioration of hand function. This was principally manifested by significant changes in their ability to perform certain activities of daily living such as using utensils, sewing, writing, and buttoning buttons. Seven patients complained of numbness or paresthesias in the hands, and five patients described these symptoms in the lower extremities. Two patients presented with recent changes in bladder or bowel function.

Physical Examination

Nine patients were noted to have weakness in the upper extremities on examination, and six had weakness in the lower extremities. Eight patients had decreased sensation in the upper extremities, and six had sensory changes in the lower extremities. Hyperreflexia was the most common upper motor neuron sign, and was found in ten patients. Hoffman's sign was the second most common, and was observed in seven patients. Six patients had a positive Babinski reflex, and three had clonus in the lower extremities.

Radiographical Imaging

Standard MRI was obtained in all patients, and revealed spinal cord compression in each case. Circumferential spinal cord compression was encountered in eleven 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 five patients, predominantly ventral spinal cord compression was caused by herniated disc and/or osteophytic vertebral body endplates. Nine patients had T2-weighted signal abnormalities located within the spinal cord parenchyma and seven were without signal changes. Nine patients had a lordotic spinal alignment, four had straight cervical spines, and three patients had kyphotic cervical spines.

Surgical Management

The specific surgical approach was determined by the location of the compressive pathology, preoperative spinal alignment, and assessment of spinal stability. Ten of the patients were treated with a posterior approach. Nine underwent laminectomy and fusion (Figure 1a, 1b), two underwent laminectomy without fusion, and one underwent laminoplasty. Anterior

cervical discectomy and fusion was performed in the remaining four patients. None of the patients required a combination anterior-posterior surgery.

MRS Technique

The cervical spine MRI was performed with a neck coil in place on a Siemens Sonata 1.5 Tesla scanner VA25 (Siemens Medical Systems, South Iselin, NJ) utilizing the following sequences: sagittal T1 weighted (TR/TE 450/12ms, matrix, 320x256, slice thickness 4mm) and sagittal T2 weighted (TR/TE 3000/106 ms, matrix, 512x408, slice thickness 4 mm) axial T2 weighted (TR/TE 4970/109 ms, matrix, 512x512, slice thickness 4 mm) images. Pulse oximeter triggering was employed in the MR Spectroscopy (MRS) sequences to reduce artifact from the movement of the spinal cord and cerebrospinal fluid pulsation. A single voxel of $1 \times 1 \times 1.5$ to 2 cm (AP $\times$ TR $\times$ CC) was placed at the C2 spinal cord level. A short-echo point-resolved spectroscopy (PRESS) sequence⁷ (TE=30ms, TR = 1500/3000, 256 averages, acquisition time 3.40 minutes) was used. An MR physicist was on site at the time of the scan to manually shim the magnetic field (18-28 Hz) to minimize inhomogeneity and assure the area of interest is in resonance. Automated shimming is not as precise, and ranges between 68-80 Hz, which causes the MRS metabolic peaks to become irregular. The MRS exam took approximately 8-10 minutes to perform (3 to 5 minutes for shimming and 4 minutes for scan time). The patients were also asked not to swallow during the study to minimize swallowing artifact.

MR spectroscopy values were calculated using automated Siemens post processing program. The height of NAA (2.0 ppm), Creatine (3.03ppm), Choline (3.25 ppm) and Lactate (1.32 ppm) peaks were measured on the screen. The NAA/Cr, Choline/Cr and Cho/NAA ratio were calculated.

Statistical Analysis

The linear correlation between preoperative metabolic measurements within the spinal cord and change in mJOA score was evaluated using Pearson's correlation coefficient. A significant linear correlation was determined by testing whether the slope of the linear trend line was significantly different from zero using an *F*-test. Differences in mJOA before and after surgery were compared using a paired *t*-test. The change in mJOA after surgery was compared between patients exhibiting T2 hyperintensity within the cord and those with no signal change using an unpaired *t*-test. Similarly, the change in mJOA after surgery was compared between patients exhibiting a lactate peak in their MR spectra and patients without a lactate peak using an unpaired *t*-test. The level of significance was set to $\alpha = 0.05$ and a P-value less than 0.05 was considered statistically significant.

Results

The mean follow-up time was 19 months, with a range from 12-40 months. The mean preoperative mJOA score was 12.1, with a range from 9 to 17. The mean postoperative mJOA score was 14.6 with a range from 11-17. There was a statistically significant improvement between mean preoperative (12.1) and postoperative (14.6) mJOA score following surgery ($P < 0.0001$).

The mean Cho/NAA ratio was 0.75, with a range from 0.34 to 1.45. The mean Cho/NAA ratio was significantly correlated with the change in mJOA score following surgery ($P=.0065$; $R^2=.4219$) (Figure 2). The mean NAA/Cr ratio was 1.44, with a range between 0.86 and 2.24. The NAA/Cr ratio demonstrated a significant relationship to the change in mJOA score after surgery ($P=.0479$; $R=.2513$) (Figure 3). The mean Cho/Cr ratio was 0.98, with a range from 0.57 to 1.45. There was no significant relationship between Cho/Cr ratio and change in mJOA score after surgery ($P=.2616$; $R^2=.0981$). There was no statistical relationship between the presence of a lactate peak and change in mJOA score after surgery.

There was no significant association between the presence of T2 weighted signal change and change in mJOA score following surgery, ($P=0.3135$)

Discussion

Rationale

CSM is associated with significant alterations in neurological function that can be quite debilitating and markedly impair activities of daily living. As this condition is associated with age-related degeneration of the spine, and patients are living longer and desiring to maintain an active lifestyle in their older years, it is likely that this condition will be treated with increasing frequency in the future.¹⁹ Thus, the development of a method to predict neurological response to surgery for CSM is of high importance.^{1, 20}

The surgical treatment of CSM can involve relatively complex decompression and instrumentation procedures that can carry significant perioperative risks, particularly in the elderly population. The challenge remains in determining the patients that are most likely to obtain clinical benefit following surgical intervention, and avoid exposing those that are unlikely to improve with surgery to its associated risks. Based on data from the latest National Inpatient Sample of CSM patients undergoing surgery from 1993 to 2002, the postoperative complication rate was 13.4%.²¹ A single postoperative complication led to a four day increase in mean length of hospital stay, increased the mortality rate 2-fold, and added more than \$10,000 to hospital charges. Patients aged 65 to 84 years had 8- and 14-fold increases in complications and mortality respectively compared to patients less than 44 years of age.

Consequently, due to the potentially poor natural history of CSM, inherent risks of surgery, and individual/societal cost associated with this disorder, there is a distinct need to develop noninvasive methods to predict neurological recovery following operative intervention so that the optimal management strategy can be initiated. Additionally, studies have shown that some CSM patients may improve or stabilize clinically with nonoperative management, thereby providing a reasonable treatment option in a subset of patients unlikely to improve after surgery.^{22,23} A number of potential radiographical predictors have been studied, yet a definitive prognostic indicator remains elusive. Although commonly quoted as potential predictors of outcome following surgery, multi-segmental T2 weighted signal change, combined T1/T2 weighted, and spinal cord atrophy only reach Class III levels of evidence.¹

Advanced Imaging Techniques and CSM

Identification of CSM patients with reversible spinal cord injury is a difficult proposition, as standard MRI can only macroscopically demonstrate signal abnormalities of unclear significance. As such, there has been recent interest in the utility of advanced imaging techniques that can analyze the spinal cord microstructure. MRS has become widely performed as a non-invasive method to provide information regarding cellular biochemistry in the central nervous system, and has recently been adapted for use within the spinal cord.^{14, 15, 24-26} This advanced MRI technique takes advantage of the strong and unique MR signal associated with NAA, a derivative of aspartic acid, which is almost exclusively found within axons and neurons. A reduction in the levels of NAA are considered to be indicative of axonal or neuronal injury. Choline is a major component of plasma membranes, and fluctuations of this marker are considered to be an indicator of cellular turnover related to both membrane synthesis and degradation.²⁷ Creatine is a measure of global cellular metabolic activity and its peak remains stable under many pathological conditions; therefore it is commonly utilized as an internal control to which the signals of the other major metabolites can be compared. Our laboratory previously evaluated MR Spectroscopy to assess baseline spinal cord axonal injury in a cohort of operatively and nonoperatively treated CSM patients, and determined that the spinal cord NAA/Cr ratio was significantly lower in CSM patients than age matched controls.¹⁴ A separate study determined that both NAA and choline alterations are considered to be late biochemical changes in the pathogenesis of CSM.¹⁵

The goal of the present study was to investigate the utility of several different cellular metabolites to predict neurological outcome following decompression surgery in CSM patients. We postulated that levels of NAA and choline could be used to assay the degree of spinal cord injury and viability, as well as to prognosticate recovery following surgery. Our results demonstrated that there was a statistically significant relationship between preoperative NAA/Cr and Cho/NAA and change in mJOA scores following surgery. A higher preoperative spinal cord NAA/Cr ratio was associated with a better neurological recovery than a lower NAA/Cr ratio. One potential explanation is that the higher NAA/Cr ratio reflects an increased population of functioning and reversibly injured axons, and therefore predictive of a more favorable neurological recovery. The Cho/NAA ratio appeared to have an even stronger, yet inverse, statistical relationship with improvement in mJOA score than the NAA/Cr ratio: a lower preoperative Cho/NAA was associated with a greater improvement in mJOA score after surgery. The stronger relationship is likely due to the fact that the Cho/NAA ratio assays both the integrity of axons and neurons as well as the amount of cellular injury and turnover. Thus patients with either elevated choline (increased cellular injury and turnover), and decreased NAA (axonal or neuronal injury), had a poorer prognosis following surgery. The Cho/Cr ratio was not statistically related to change in mJOA score after surgery, and suggests that cellular injury and turnover may not be as predictive of outcome as damage to axons and neurons.

The application of these neurochemical biomarkers as predictors of outcome is analogous to the rationale behind the use of neuroanatomical characteristics such as the presence of spinal cord signal change to predict clinical outcome in postoperative CSM patients. Investigators

have suggested that the intensity of the signal change brightness, shape of the signal change, or presence/absence of sharp borders may have an impact on outcome.¹ In truth, these radiographical characteristics allow us only to infer that there is spinal cord microstructural injury, but the exact meaning and degree of recuperative potential is not known. Moreover, the magnitude of the cellular injury cannot be assessed using the aforementioned neuroanatomical markers, in direct contrast to neurochemical imaging techniques such as MRS. Therefore, it is not unreasonable to postulate that novel spinal cord imaging techniques such as MRS, although still in its relative infancy, could potentially offer an accurate method of predicting outcome in this patient population. Further investigation will be required in order to validate this application of MRS to the management of CSM patients.

Conclusions

MRS is a novel, noninvasive imaging modality that provides pertinent information regarding spinal cord cellular and metabolic function. In a cohort of operatively treated CSM patients, the NAA/Cr and Cho/NAA ratios were predictive of neurological outcome, as both were significantly associated with change in mJOA score after surgery.

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Figure 1.

(a): ¹H-MR spectrum and voxel localization images in a 68 year old male with CSM. MRS revealed Cho/Cr = 0.86, Cho/NAA = 0.57, NAA/Cr = 1.51, and slightly elevated levels of lactate, suggestive of moderate but reversible damage to the spinal cord. The patient underwent cervical laminectomy and fusion and showed an improvement in mJOA from an 11 (pre-op) to 13 (post-op). (b) Postoperative MRI demonstrating satisfactory decompression of the spinal cord following surgery.

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Figure 2. Graph demonstrating a statistically significant relationship between preoperative Cho/NAA level and change in mJOA score after surgery ($P=.0065$; $R^2=.4219$).

Figure 3.
Graph demonstrating a statistically significant relationship between NAA/Cr ratio and change in mJOA score after surgery ($P = .0479$; $R = .2513$).