Proton magnetic resonance spectroscopy of the motor cortex in cervical myelopathy

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Alterations in motor function in cervical myelopathy secondary to degenerative disease may be due to local effects of spinal compression or distal effects related to cortical reorganization. This prospective study characterizes differences in metabolite levels in the motor cortex, specifically N-acetylaspartate, creatine, choline, myo-inositol and glutamate plus glutamine, due to alterations in cortical function in patients with reversible spinal cord compression compared with healthy controls. We hypothesized that N-acetylaspartate/creatine levels would be decreased in the motor cortex of patients with cervical myelopathy due to reduced neuronal integrity/function and myo-inositol/creatine levels would be increased due to reactive gliosis. Twenty-four patients with cervical myelopathy and 11 healthy controls underwent proton-magnetic resonance spectroscopy on a 3.0 Tesla Siemens Magneton Tim Trio MRI. Areas of activation from functional magnetic resonance imaging scans of a finger-tapping paradigm were used to localize a voxel on the side of greater motor deficit in the myelopathy group (n = 10 on right side and n = 14 on left side of the brain) and on each side of the motor cortex in controls. Neurological function was measured with the Neck Disability Index, modified Japanese Orthopaedic Association and American Spinal Injury Association questionnaires. Metabolite levels were measured relative to total creatine within the voxel of interest. No metabolite differences were detected between the right side and left side of the motor cortex in controls. The myelopathy group had significantly decreased neurological function compared with the control group (Neck Disability Index: P < 0.001 and modified Japanese Orthopaedic Association: P < 0.001). There was a significant decrease in the N-acetylaspartate/creatine metabolite ratio in the motor cortex of the myelopathy group (1.21 ± 0.07) compared with the right (1.37 ± 0.03; P = 0.01) and left (1.38 ± 0.03; P = 0.007) motor cortex in controls suggesting neuronal damage or dysfunction distal to the lesion in the spine. No difference was observed in levels of myo-inositol/creatine. Thus, cortical levels of N-acetylaspartate/creatine may be a meaningful biomarker in cervical myelopathy, indicative of neuronal damage or dysfunction.

Keywords: cervical myelopathy; magnetic resonance spectroscopy; N-acetylaspartate; functional MRI; motor cortex
Introduction

Cervical myelopathy secondary to degenerative disease is the most common type of spinal cord dysfunction in people >55 years of age (Simeone and Rothman, 1982), yet its natural history continues to be poorly understood (Bernhardt et al., 1993). The degenerative cascade is characterized by the narrowing of the spinal canal secondary to disc degeneration and herniation, the development of facet arthropathy and ligamentum flavum hypertrophy (Bernhardt et al., 1993; Matz et al., 2009). The natural history is typically a gradual deterioration in a stepwise pattern with clinical manifestations such as numbness, loss of dexterity, instability and bowel and bladder incontinence (Bernhardt et al., 1993; Emery, 2001). The majority of studies on spinal cord compression focus on the local changes in the spinal column or cord and neglect the intimate interconnection with the cerebral cortex.

Patients with spinal cord injury have shown some degree of functional recovery through cortical reorganization and plasticity (Levy et al., 1990; Topka et al., 1990; Bernhardt et al., 1993; Bruehlmeier et al., 1998; Sabbah et al., 2002; Holly et al., 2007; Jurkiewicz et al., 2007; Duggal et al., 2010). In previous work by our group, we demonstrated that patients with cervical myelopathy had a greater volume of activation in the brain than control volunteers when performing a motor task (Duggal et al., 2010). Following decompression surgery, the volume of activation difference between the patients and controls increased, suggesting cortical reorganization and recruitment of surrounding cortex to perform the motor task (Duggal et al., 2010). Similarly, Jurkiewicz et al. (2007) suggested the extent of movement related activation in the primary motor cortex is strongly associated with the return of movement in the upper limbs following spinal cord injury. Based on these results, our goal was to determine if the initial deficits in neurological function experienced by patients with cervical myelopathy were also associated with measurable alterations in cortical metabolite levels.

Proton-magnetic resonance spectroscopy is a non-invasive method that can repeatedly and directly measure levels of relevant metabolites such as N-acetylaspartate, creatine, choline, myo-inositol and glutamate plus glutamine in the brain. N-acetylaspartate, a marker of neural integrity or viability, is localized to neurons and neuronal processes (DeStefano et al., 1995) and is decreased in several pathological conditions such as Alzheimer’s disease, bipolar disease (Molina et al., 2007), epilepsy (Simister et al., 2007), post-traumatic stress disorder (Ham et al., 2007), amyotrophic lateral sclerosis (Rooney et al., 1998), multiple sclerosis (Arnold et al., 1990; Husted et al., 1994) and stroke (Gideon and Hanriksen, 1992). Although the specific role of N-acetylaspartate is still unknown, it has been linked to the functional status of the mitochondria and is therefore considered a marker of cellular function (Geurts and van Horssen, 2010). As a functional indicator, the N-acetylaspartate/creatinine ratio has been shown to increase in the motor cortex of patients with spinal cord injury who experienced functional recovery (Puri et al., 1998).

Myo-inositol, a sugar primarily found in glial cells, has been associated with gliosis (Ross et al., 1998). Neuronal loss or dysfunction is often accompanied by increased levels of myo-inositol that reflect glial activation or proliferation. Zhu et al. (2006) reported increases of myo-inositol and the myo-inositol/creatine ratio in the grey matter of the parietal lobe in Alzheimer’s disease. Many other studies have detected increased myo-inositol levels in multiple sclerosis (Fernando et al., 2004; Vrenken et al., 2005) and epilepsy (Simister et al., 2007) while decreased levels have been found in major depressive disorders (Coupland et al., 2005) and low-grade hepatic encephalopathy (Haussinger et al., 1994).

The purpose of this study was to determine whether altered metabolite levels are detectable in the brain distal to the site of injury in patients with cervical myelopathy using proton magnetic resonance spectroscopy. We hypothesized that N-acetylaspartate levels would be decreased in patients with cervical myelopathy compared with healthy controls due to reduced neuronal integrity/function and myo-inositol levels would be increased due to reactive gliosis.

Materials and methods

Patient population

Twenty-four patients with cervical myelopathy secondary to cervical spondylosis disease were recruited with no other neurological disorder such as cerebral palsy, or a history of trauma. Fifty per cent of patients (12/24) were treated for multilevel spondylotic disease and 50% (12/24) were treated for focal single-level cervical disc herniations causing myelopathy. Patients with cervical myelopathy had symptoms manifesting no longer than 1 year prior to initial clinic visit. Cervical myelopathy was supported by clinical MRI (Fig. 1) in all patients. Subjects ranged in age from 32 to 71 years (mean ± standard error of the mean; 53 ± 2 years, 16 males, 22 right-handed). The youngest subjects had developmental canal stenosis and were carefully assessed prior to inclusion. Eleven subjects of a similar age (46 ± 4 years, seven males, 11 right-handed) with no previous clinical history of cervical myelopathy or neurological disease were recruited as control subjects. Screening MRI of the brain and cervical spine was evaluated by one of the authors (N.D.) to confirm that there was no existing radiographic evidence of cerebral or spinal cord disease, including spinal cord compression. All participants gave written informed consent according to the Declaration of Helsinki (World Medical Association, 2008). This study was approved by the University of Western Ontario’s Human Subjects Research Ethics Board.

All patients with cervical myelopathy were assessed by the American Spinal Injury Association Impairment Classification scale. The maximum motor score is 100 (50 for upper and 50 for lower) and the maximum sensory light touch and pin prick was adjusted to test only levels between C2–T2 and L2–S2 for a total score of 60 for each parameter. All patients and controls completed validated instruments for assessing disability resulting from myelopathy such as the modified Japanese Orthopaedic Association Score as well as patient derived functional assessments that include the disease-specific Neck Disability Index.

Magnetic resonance image acquisition

All magnetic resonance data were acquired using a 3.0 T Siemens Magnetom Tim Trio MRI, using a 12-channel head coil with a neck and spine array. Each exam included the acquisition of sagittal
Activation paradigm

The motor pathway was activated during functional MRI by instructing the participant to perform finger to thumb opposition (‘duck quack’) with the right hand followed by the left hand using a button box placed on the thumb. Participants were instructed to press the button simultaneously with all four fingers followed by an extension upwards to a box surrounding the button. This paradigm ensured all participants performed the finger extension to the same angle. The movement rate of the repetitive task is known to affect cerebral activation (Blinkenberg et al., 1996; Rao et al., 1996; Schlaug et al., 1996). To control the frequency of the tapping, a block paradigm was designed in which participants received visual cues during alternating 30-s intervals of rest and activity. During the activity a visual cue instructed the participants to tap every 3 s for the 30-s interval. Participants received training prior to the functional MRI session to reinforce the standardization and reduce learning effects during the imaging session.

Magnetic resonance spectroscopy acquisition and analysis

The anatomical and functional images were used to guide the placement of a 20 mm isotropic voxel on the activated region near the ‘knob’ area of the motor cortex (Youstry et al., 1997). Youstry et al. (1997) showed that neural elements involved in motor hand function are located in a characteristic ‘precentral knob’, which is a reliable landmark that identifies the precentral gyrus under normal and pathological conditions. This landmark along with the location of hand activation in each subject was used to ensure consistent voxel placement in each participant. In the cervical myelopathy group, the voxel was placed on the motor cortex contralateral to the side with greater functional deficits (n = 11 on right side and n = 13 on left side of the brain) while control data were acquired from two separate voxels placed on each side of the motor cortex. Water suppressed spectroscopic data were localized using PRESS (point resolved spectroscopy) (repetition time/echo time = 2000/135 ms, 192 averages, voxel size = 8 cm$^3$). Any remaining unsuppressed water was removed from the spectrum using a Hankel singular value decomposition by subtracting resonances between 4.1 and 5.1 parts per million (ppm) (water ~4.7 ppm) as determined by the Hankel singular value decomposition algorithm (Kassem and Bartha, 2003).

Resultant metabolite spectra were fit in the time domain using a Levenberg-Marquardt minimization routine incorporating a template of prior knowledge of metabolic lineshapes. The analysis software (fitMAN) is incorporated into a graphical user interface written in our laboratory in the IDL (Version 5.4 Research Systems Inc.) programming language (Bartha et al., 1999). The acquisition of metabolite prior knowledge data has been previously described in detail (Bartha et al., 1999; Kassem and Bartha, 2003). Briefly, high-resolution in vitro spectra were acquired from solutions (pH adjusted to 7.04) of N-acetylaspartate, creatine, choline, myo-inositol, glutamate and glutamine using the same sequence that was used to acquire all in vivo data. Each metabolite solution contained sodium 3-trimethylsilyl-propionic acid (TSP) as a reference for chemical shift and Lorentzian damping (line width). The high resolution metabolite spectra were fitted to produce metabolite templates that were subsequently used to fit in vivo spectra.

The metabolites N-acetylaspartate, creatine, choline, myo-inositol and glutamate and glutamine were examined based on prior studies that have implicated these metabolites in neurological disorders such as spinal cord injury and cervical myelopathy (Puri et al., 1998; Holly et al., 2009), and since these metabolites could be reliably measured. More specifically, metabolite ratios (N-acetylaspartate/creatine, choline/creatine, myo-inositol/creatine and glutamate and glutamine/creatine) were calculated and compared between groups. Metabolite ratios relative to creatine provide a reproducible and sensitive measurement and are not prone to errors associated with absolute

Figure 1 Sagittal cervical spine MRI obtained from a patient with cervical myelopathy; red arrow indicates the compression.
metabolite level measurements such as those attributed to measurement of tissue partial volume and scaling by tissue relaxation time constants. Tissue partial volume effects that arise from having different amounts of white/grey matter and CSF in selected voxels can be largely avoided (Jensen et al., 2006) with metabolite ratios. Ratios can also be more sensitive in detecting metabolite changes when one metabolite in the ratio (e.g. the numerator) increases while the other metabolite in the ratio (e.g. the denominator) decreases.

Statistics

Metabolite ratios were compared between groups using a two-tailed Student’s t-test with alpha error of 0.05. Post hoc analyses utilized the Tukey’s test. The Pearson Product Moment Correlation Coefficient (r) was used to determine whether there were any correlations between metabolite ratios and clinical scores for each group. All statistical tests were two-sided, with significance set at the 0.05 level. Correlations for multiple comparisons were not performed in this exploratory study. Modified Japanese Orthopaedic Association and Neck Disability Index scores were compared between the cervical myelopathy group and controls using a two-tailed Student’s t-test.

Results

Clinical data

Table 1 lists the demographic and clinical data of the study groups. The groups were not different with respect to age (P = 0.158) or sex (P = 0.522). Patients presented with loss of dexterity in the hands and gait dysfunction. Cervical myelopathy and control groups had significantly different Neck Disability Index, modified Japanese Orthopaedic Association and American Spinal Injury Association Impairment scale scores. Neck Disability Index scores were significantly higher in patients compared with controls (15.8 ± 1.6 and 1.7 ± 0.8, respectively, P < 0.0001). Since a score of ≥5 is required to achieve a classification of mild disability on the Neck Disability Index scale, the control group in the current study was considered to have no disability based on the mean Neck Disability Index score of 1.7. The non-zero Neck Disability Index score of 1.7 in the control group was attributed to minor neck pain. The motor upper and lower, sensory upper and sphincter dysfunction segments as well as the mean overall modified Japanese Orthopaedic Association scores were significantly lower in patients compared with controls (P < 0.001). All controls recorded a perfect score of 18 on the modified Japanese Orthopaedic Association questionnaire. As expected, patients had lower American Spinal Injury Association Impairment scale scores. There was no significant asymmetry between the right and left side in the motor upper or lower scores or in the sensory light touch and pin prickle scores. Healthy controls were considered to have perfect American Spinal Injury Association Impairment scale scores as no disability was described.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Cervical myelopathy group</th>
<th>Controls</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>24</td>
<td>11</td>
<td>n/a</td>
</tr>
<tr>
<td>Age</td>
<td>53 ± 2</td>
<td>46 ± 4</td>
<td>0.158</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>16/8</td>
<td>7/4</td>
<td>0.522</td>
</tr>
<tr>
<td>Handedness (right/left)</td>
<td>22/2</td>
<td>11/0</td>
<td>0.083</td>
</tr>
<tr>
<td>NDI</td>
<td>15.8 ± 1.6</td>
<td>1.7 ± 0.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>mJOA scores</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor upper</td>
<td>3.4 ± 0.3</td>
<td>5 ± 0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Motor lower</td>
<td>5.1 ± 0.2</td>
<td>7 ± 0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sensory upper</td>
<td>1.8 ± 0.2</td>
<td>3 ± 0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sphincter dysfunction</td>
<td>2.6 ± 0.1</td>
<td>3 ± 0</td>
<td>0.0011</td>
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<table>
<thead>
<tr>
<th>ASIA scores</th>
<th>Right</th>
<th>Left</th>
</tr>
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<tbody>
<tr>
<td>Upper motor</td>
<td>23.2 ± 0.3</td>
<td>23.4 ± 0.6</td>
</tr>
<tr>
<td>Lower motor</td>
<td>23.9 ± 0.4</td>
<td>24.1 ± 0.3</td>
</tr>
<tr>
<td>Light touch</td>
<td>26.2 ± 1.2</td>
<td>26.7 ± 1.1</td>
</tr>
<tr>
<td>Pin prickle</td>
<td>25.2 ± 1.2</td>
<td>25.9 ± 1.1</td>
</tr>
</tbody>
</table>

ASIA = American Spinal Injury Association Impairment Classification; n/a = not applicable; mJOA = modified Japanese Orthopaedic Association; NDI = Neck Disability Index.

Magnetic resonance spectroscopy

Magnetic resonance spectra were successfully acquired in all patients and controls. The positioning of the magnetic resonance spectroscopy voxel is shown as a white box on the motor cortex in Fig. 2. Figure 3 shows the spectrum acquired in one patient along with the fitted result and the residual (the difference between the fit and the spectrum). The individual metabolite components for N-acetylaspartate, choline, creatine, myo-inositol, glutamate and glutamine are also provided in Fig. 3.

No differences in any metabolite ratios were detected between the right and left side of the motor cortex in the control subjects (P > 0.05). Since there were no lateralized differences in controls, it was reasonable that metabolite data were combined for all patients with cervical myelopathy (10 right side, 14 left side). The average metabolite ratios are shown in Fig. 4 for all study groups. There was a significant decrease in the N-acetylaspartate/creatine metabolite ratio in the cervical myelopathy group (1.16 ± 0.07) compared to right side (1.37 ± 0.03; P = 0.01) and left side controls (1.38 ± 0.03; P = 0.007) in the motor cortex. There was no significant difference in the myo-inositol/creatine metabolite ratio in the cervical myelopathy group (0.30 ± 0.02) compared to right side (0.28 ± 0.02; P = 0.50) and left side controls (0.31 ± 0.02; P = 0.73) in the motor cortex. No other metabolite ratio differences were observed.

Tukey’s post hoc analysis was completed in our exploratory study between patients with cervical myelopathy and control groups to determine patterns that were not specified a priori. The patient group was divided into two groups based on the side of the brain that was studied. There were no differences in metabolite ratios between 13 patients with cervical myelopathy and controls when comparing the left side directly. There was a significant decrease in the N-acetylaspartate/creatine (P = 0.008), ratio in the 11 patients with cervical myelopathy who had the voxel placed on the right side of the motor cortex compared with the right side controls.
Correlations

There were no significant correlations between any of the metabolite ratio and questionnaire scores ($P < 0.05$). There was also no correlation between the duration of symptoms (7.5 ± 1.4 months) in the cervical myelopathy group and the $N$-acetylaspartate/creatinine ratio ($r = 0.008$, $P = 0.48$). The presence of spinal cord signal change was found in 87.5% (21/24) of the patients with cervical myelopathy and did not correlate with the $N$-acetylaspartate/creatinine ratio ($r = 0.05$, $P = 0.40$).

Discussion

The overall goal of this study was to investigate the effects of cervical myelopathy secondary to degenerative disease on the neuronal metabolism and activity of the motor cortex, specifically, to characterize the metabolic correlates of spinal cord compression in the brain. This pilot study is the first to perform magnetic resonance spectroscopy in the motor cortex to evaluate metabolite levels in patients with reversible spinal cord compression. Our
findings demonstrated a decrease in the N-acetylaspartate/creatine ratio in the hand area of the primary motor cortex in patients with cervical myelopathy compared with healthy controls. Although previous studies (Holly et al., 2007; Nagashima et al., 2010) have examined local metabolite changes in the spinal cord, our study demonstrated altered metabolite levels remote to the site of injury. Remote injury of the sensorimotor cortex in patients with cervical myelopathy could be a critical factor underlying recovery.

Given that cortical synaptic plasticity has been shown in a variety of neurological disorders, we focused our efforts on the metabolite changes in the hand region of the motor cortex instead of local changes occurring in the cervical spinal cord. Recent studies have described changes in cortical activation during sensory and/or motor tasks in cervical myelopathy and patients with spinal cord injury (Curt et al., 2002a, b; Holly et al., 2007; Jurkiewicz et al., 2007; Dong et al., 2008; Duggal et al., 2010; Tam et al., 2010). Our group has previously reported an increased volume of activation within the primary motor cortex and a decreased volume of activation within the primary sensory cortex in patients with cervical myelopathy followed by cortical reorganization after decompressive surgery on the spinal cord (Duggal et al., 2010). Based on these results, we hypothesized that cortical metabolic changes, particularly changes in N-acetylaspartate/creatine and myo-inositol/creatine, may result from spinal cord compression.

The current study found significant decreases in N-acetylaspartate/creatine ratio in the motor cortex of patients with cervical myelopathy. Studies into the physiological relationship between N-acetylaspartate and neuronal cells have suggested that N-acetylaspartate/creatine is a marker of neuronal density and/or viability (DeStefano et al., 1995; Geurts and van Horssen, 2010). Reduced N-acetylaspartate/creatine may imply neuronal death or neurometabolic impairment (DeStefano et al., 1995; Geurts and van Horssen, 2010). Additional support for N-acetylaspartate/creatine as a neuronal health marker comes from several in vivo studies that found N-acetylaspartate/creatine levels can reversibly decline after treatment in neurological disorders such as acute brain injury (DeStefano et al., 1995) and amyotrophic lateral sclerosis (Rooney et al., 1998). The metabolic abnormalities of N-acetylaspartate/creatine detected using magnetic resonance spectroscopy may precede anatomical degeneration found using structural MRI.

Our results of a decreased N-acetylaspartate/creatine ratio are consistent with a previous study by Holly et al. (2006) who found patients with cervical myelopathy (n = 21) had a significantly lower average N-acetylaspartate/creatine ratio than healthy controls at the C2 level of the spinal cord. Decreases in N-acetylaspartate/creatine are more likely to be attributed to decreases in N-acetylaspartate than increases in creatine, suggesting axonal or neuronal damage/loss. It remains controversial whether neuronal damage, as suggested by N-acetylaspartate levels, is permanent or reversible in the setting of incomplete injury secondary to degenerative spinal cord compression. Puri et al. (1998) performed proton magnetic resonance spectroscopy on the motor cortex of the dominant hand/cortical hemisphere unless motor function was lateralized, in which case the weaker side was assessed, in six patients recovering from incomplete spinal cord injury and five healthy controls. They found the N-acetylaspartate/creatine ratio was higher in the motor cortex of recovering patients than of the motor cortical area in controls (Puri et al., 1998). These results have clinical implications in determining the role of potential surgery. If it is confirmed that increases in N-acetylaspartate/creatine accompany recovery in patients with cervical myelopathy after the initial decrease as observed in our study, magnetic resonance spectroscopy could provide a non-invasive method for prognosis and monitoring of patients with cervical myelopathy.

We found no significant change in the myo-inositol/creatine ratio. Myo-inositol regulates osmotic pressure in neuroglial cells and is found specifically in astrocytes (Bains and Oliet, 2007; Barres, 2008; Allen and Barres, 2009). It has been shown to increase in neurodegenerative diseases such as Alzheimer’s disease (Chen et al., 2009) and multiple sclerosis (Fernando et al., 2004; Vrenken et al., 2005) and is considered a glial marker. Astrocytes provide neurons with energy, substrates for neurotransmission and are required for neuronal repair following injury (Bains and Oliet, 2007; Barres, 2008; Allen and Barres, 2009). However, they can also suppress repair (Barres, 2008; Allen and Barres, 2009) by forming a scar and producing molecules that inhibit regrowth of damaged or severed axons (Allen and Barres, 2009). In spinal cord injury, a glial scar may act as a local barrier to the regeneration of damaged axons (Silver and Miller, 2004; Barres, 2008; Allen and Barres, 2009). Lebrun-Julien et al. (2009) disrupted the signalling events surrounding retinal glial cells and found they could protect the majority of neurons and confirmed that glial cell events play a key role in death triggered by glutamate. The lack of any changes with myo-inositol may indicate that reversible spinal cord compression does not trigger glial activation and proliferation in the motor cortex. Glial activation and scarring may only occur in the setting of irreversible neuronal cell death.

Past research has found >60% of patients with cervical myelopathy have a T2 signal change in the spinal cord on MRI (Matsumoto et al., 2000; Suri et al., 2003). Spinal cord signal change is most commonly found in the more severe cervical myelopathy and can be associated with changes such as myelomalacia (Wada et al., 1995). The presence of signal intensity changes on MRI has been suggested as a possible criterion for surgery (Naderi et al., 1998; Morio et al., 2001). Even though the presence of spinal cord signal change was found in 87.5% of the subjects with cervical myelopathy in this study, there was no correlation with the decrease in N-acetylaspartate/creatine. The lack of correlation could be suggestive of a disconnect between significant spinal cord injury and the neuronal integrity or viability in the motor cortex.

We hypothesized that there may be correlations between changes in the N-acetylaspartate/creatine and myo-inositol/creatine metabolite ratios and the neurological functional scores. However, no significant correlations were observed between any metabolite ratios and the Neck Disability Index, modified Japanese Orthopaedic Association or American Spinal Injury Association Impairment scale questionnaires. Since the N-acetylaspartate/creatine ratio was significantly decreased in the patient group and the clinical scores were also found to be significantly worse in the patient group, the lack of a correlation between the metabolite ratio and clinical scores suggests that functional
changes may be dominated by the local insult to the cord, not damage to the cortex. Future work will determine whether alterations in the cortex correlate with or limit functional recovery following spinal decompression surgery.

Stringent inclusion criteria, along with rigorous acquisition and post-processing methods are required to reduce data variance. Our pilot study included a sample size of 24 patients, with an attempt to select a homogeneous population of patients with a similar clinical history. We performed high magnetic field magnetic resonance spectroscopy at 3.0 T, which provides greater signal-to-noise ratio and greater spectral separation of multiplets that tend to overlap at lower field strength (Gonen et al., 2001; Bartha et al., 2002a). A larger cohort will be necessary to determine whether magnetic resonance spectroscopy findings have prognostic significance. Prospective studies should include patients with both short and long term pathology to determine how cortical metabolite levels are altered during the course of cervical myelopathy. Other regions of the motor cortex may also be of interest. A limitation of our study was that spectra were acquired only from the contralateral motor cortex of the weaker side in patients with cervical myelopathy rather than on both sides as done in the control subjects. Spectroscopy data were only acquired from a single side in patients due to time constraints, as patients could not tolerate the long scan times required to obtain spectroscopy data from both sides. The pooling of spectroscopy data in the patient group from the side of the motor cortex with the greatest functional deficit as previously described (Puri et al., 1998) was a reasonable approach as lateralized spectroscopy measurements in the control group did not show metabolite level differences. However, future studies would benefit from lateralized spectroscopy measurements in patients with cervical myelopathy to evaluate potential heterogeneity, and correlation of metabolite level changes in the cortex with findings on cervical MRI.

Conclusion

This study demonstrates decreased N-acetylaspartate/creatine in the motor cortex of patients with cervical myelopathy secondary to degenerative disease, indicating the presence of neurological damage or dysfunction likely caused by neuronal and/or axonal injury.

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