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Metabolic Correlates in Spinal Cord Compression Measured by Magnetic Resonance Spectroscopy in the Motor and Sensory Cortices

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A thesis submitted in partial fulfillment of the requirements for the degree in Master of Science

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METABOLIC CORRELATES IN SPINAL CORD COMPRESSION MEASURED BY MAGNETIC RESONANCE SPECTROSCOPY IN THE MOTOR AND SENSORY CORTICES

(Thesis format: Integrated Article)

by

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Graduate Program in Medical Biophysics

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science

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Abstract

Surgical outcome for patients suffering from cervical myelopathy (CM) is unpredictable with varying motor and sensory symptom recovery. Previous *in-vivo* magnetic resonance spectroscopy (MRS) studies of patients surgically treated for CM have demonstrated decreased *N*-acetylaspartate (NAA)/creatine levels in the motor cortex indicating reduced neuronal function. The goal of this thesis was to determine whether absolute NAA changes in the motor and sensory cortices mirror the pattern of motor and sensory functional change observed in patients post surgical treatment.

MRS data were acquired on a 3.0 Tesla Siemens MRI along with clinical outcome measures at baseline, 6-weeks and 6-months post-surgery. The results showed that absolute NAA levels declined in both cortices in a similar temporal pattern but opposite in direction to clinical motor and sensory functional recovery. Findings suggest that low NAA levels may be a trigger for functional recovery although the neural mechanisms involved have not been elucidated.

Keywords:

Cervical myelopathy, magnetic resonance spectroscopy, 3 Tesla, *N*-acetylaspartate, NAA, surgery, motor cortex, sensory cortex
Co-Authorship Statement

Dr. Neil Duggal and Dr. Robert Bartha conceived, designed, and supervised all aspects of this project. Dr. Todd K. Stevens assisted in the magnetic resonance spectroscopy data processing and data analysis. Dr. Duggal performed all clinical assessments. Sandy Goncalves managed subject recruitment and scheduling, and performed all data analyses including the assembly of clinical outcome measurements, magnetic resonance spectroscopy data analysis, and statistical analyses. Sandy Goncalves, Dr. Duggal and Dr. Bartha authored the first draft of the manuscript (Chapter 2), which was then revised with critical input by all co-authors.
Dedication

To my twin sister, Stephanie, for her endless encouragement, love and support in all that I do. For having the wisdom to let me make mistakes when I needed to make them, but always being there to catch me before I fell. For teaching me to never have regrets because each experience teaches us a lesson - it is up to us to “remember what we have learned.” I cannot express how much you mean to me and how much I could not have done this without you.
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I would like to acknowledge all the participants who contributed their time to the completion of this thesis. Without them, none of this work would be possible.

Thank you to my supervisors, Dr. Neil Duggal and Dr. Robert Bartha, for believing in me. I’ve had the privilege of learning and growing as your student through your endless patience, guidance and support. I am grateful for the opportunities and countless words of advice that I will never forget.

I am also greatly indebted to the 3T MRI technician, Oksana Opalevych, at Robarts Research Institute. Thank you for your time, your sacrifice and above all for making endless hours of scan time not seem like work at all. I cannot thank you enough for the last minute scans and “making it happen” – you truly are a team player.
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Chapter 1

1 Introduction to Cervical Myelopathy and Magnetic Resonance Spectroscopy

Chapter 1 of this thesis is divided into three parts. The first part describes the background and motivation of this thesis. The second provides a general overview of the anatomy and physiology of the brain and spinal column as it relates to cervical myelopathy. Finally, the third part of this chapter provides an introduction to proton-magnetic resonance spectroscopy (MRS) for the measurement of brain metabolites in-vivo. This method is used in Chapter 2 to measure metabolite levels in the brain in people with Cervical Myelopathy.

1.1 Background and Motivation

As humans age, otherwise healthy, functioning joints begin to slowly deteriorate over time. In 1956, Clarke and Robinson presented the first study to characterize the natural progression in the degenerative disease known as cervical myelopathy (CM).\(^1\) This slow, progressive process is the most prevalent form of spinal cord disorder in adults over the age of 55.\(^2, 3\) CM is a consequence of the narrowing of the spinal canal and eventual compression of the spinal cord due to various, naturally occurring, arthritic changes in the spinal column.\(^4\) Depending on the severity of the spinal cord compression, symptoms of CM will vary accordingly.

Symptoms of CM manifest in the form of gait dysfunction, numbness and paresthesia in the upper limbs, disturbances in overall hand function, as well as bowel and bladder dysfunction.\(^5, 6\) Surgical intervention to alleviate the compression of the spinal cord is the most widely accepted form of treatment to improve motor and sensory deficits.\(^1, 3, 6-9\)

Unfortunately, studies investigating the efficacy of surgery report high variability with symptom improvement in only one third of patients, 40% remaining neurologically stable, and the remaining 25% of patients continuing to worsen with the passage of time.\(^1, 8\)

Numerous studies have examined the epidemiology of the disease, yet little is understood about the exact mechanism of progression and which patients will truly benefit from
Moreover, the accepted standard of care that suggests that CM requires operative intervention, regardless of disease severity, is beginning to lose support.

It seems that there are two main gaps in the literature.

The first gap in the literature is the lack of studies in the clinical setting demonstrating the tendency of patients with CM to have an earlier recovery of the motor deficits following surgery when compared to sensory dysfunction. A widely accepted clinical outcome measure used to assess motor and sensory function in patients with CM is the modified Japanese Orthopaedic Association questionnaire (mJOA) (Appendix 1-2). The mJOA includes two questions assessing motor dysfunction in the upper and lower limbs and two questions assessing sensory dysfunction in the same fashion. The first two questions report a sub score out of 12 points (Q1 out of 5 and Q2 out 7) where the latter two report a sub score out of 6 (Q3 out of 3 and Q4 out of 3) for a maximum global score of 18 points indicating no dysfunction.

Multiple studies have demonstrated a significant improvement in global mJOA scores following decompressive surgery. A recent non-controlled observational study published by Moussellard et al assessing sixty seven patients with CM demonstrated that at first follow-up, as well as subsequent time points, a significant improvement was reported when compared to baseline. Upon further analysis of the data, an important detail was observed when interpreting the evolution of mJOA scores over time. Global mJOA scores could be divided into two intervals, an early stage with significant improvement (p<0.01) between the date of surgery and first follow up (one month post-surgery), and a second stage with a slight, but significant decrease (p<0.01) between initial follow up and final follow up (24 months post-surgery). It is also important to note that global mJOA scores in this study remained relatively stable during the second stage of recovery until final follow up where the decrease was observed. Although still subjectively improved when compared to baseline, patients reported a worsening of symptoms as compared to initial follow up. These results leave a few questions unanswered. Which symptoms improved, which symptoms continued to worsen, and how did these symptoms change between subsequent follow ups? The authors did not report the evolution of subgroup scores over time for all time points. Global mJOA scores alone
can be misleading due to the uneven weight placed on each subgroup where the combined total value of the sensory symptom questions equals less than one motor question alone. Results reported by Moussellard et al\textsuperscript{17} are difficult to interpret given that no information is provided on how each symptom evolved at each time point.

Al-Tamimi and colleagues published a study\textsuperscript{20} in 2013 evaluating 204 patients surgically treated for CM. Sixty five of those patients were followed for a series of four visits at three, 12, 24 and 60 months post-treatment. Each patient was asked to complete a series of outcome questionnaires including a visual analogue scale (VAS) for two sensory symptoms of arm paresthesia as well as hand paresthesia. Significant improvements (p<0.05) were reported in arm paresthesia between baseline and three months and between 24 months and 60 months. Similarly, VAS scores in hand paresthesia also demonstrated significant improvements (p<0.05) between baseline and three months, 12 months and 24 months, as well as 24 months and 60 months post-treatment. These results contrast those of Moussellard et al\textsuperscript{17} reporting that symptom recovery is very rapid within the first month following surgery but stabilizes afterwards as described by global mJOA scores; a score heavily weighted in favour of motor function assessment. Both studies present important results with respect to the time course of recovery in patients with CM that highlight how rapidly motor function gains can be observed and the delayed response in sensory symptoms.

A second gap in the literature is the lack of studies with consistent follow up intervals across patients beginning with an early time point immediately after treatment along with continued longitudinal follow-up. A characteristic, post-treatment model based on functional and clinical outcome measures outlining the behaviour of CM at both early and long term follow up to determine efficacy of treatment has not been established. As mentioned above, one exceptional study by Moussellard et al\textsuperscript{17} evaluated neurological recovery in CM patients at one month, six, 12, 18, and 24 months post-surgical treatment. This study was the first to establish the relevance of early neurological recovery following surgical decompression in patients with CM demonstrating a rapid improvement at one month with subsequent stabilization in later time points - a finding that would have otherwise been lost had the authors neglected an early follow up.
However, one limitation of this study was that a control group was not provided to compare conservative treatment in patients suffering from the same disease. Kadanka et al\textsuperscript{14} reported a three year follow-up study evaluating 68 patients with CM to compare the efficacy of surgery to conservative treatment in CM patients. Patients were randomized into two groups and evaluated at baseline, six months, one, two and three years post-treatment. The first group was treated conservatively (non-surgically) and the second with surgical intervention. Conservative treatment included immobilization of the neck using a soft collar, the use of anti-inflammatory medications, intermittent bed rest for patients with pain, and avoiding physically overloading activities, getting too cold, manipulation therapies as well as prolonged flexion of the neck. Interestingly, the results demonstrated that on average, surgical intervention was not superior to conservative treatment.

Despite this growing scepticism, recent reports\textsuperscript{21, 22} suggest that the above mentioned study\textsuperscript{14} advocating for non-operative treatment demonstrates insufficient evidence to support the belief that non-operative treatment has a role in the management of CM. In a consensus statement, Fehlings et al\textsuperscript{23} further validate this claim by citing a recent multi-centre study completed by their group that included 278 patients from twelve different centres throughout North America.\textsuperscript{22} Findings from this study demonstrate that on average, operative intervention can offer improvements in both function and quality of life at twelve months post-surgery when compared to baseline. Although both studies are relevant in comparing outcome of surgery, it is important to note that the time points described by each study are starkly different. Kadanka et al\textsuperscript{14} describe results from a three-year follow-up while Fehlings et al\textsuperscript{22} describe results from a twelve month follow-up. Another important feature is that the study by Fehlings et al\textsuperscript{22} did not include a control group in its methodology. A similar group of patients with non-operative treatment was not assessed with the justification that non-operative treatment was both unethical and impractical.\textsuperscript{22}

Given the wide variability of surgical outcome,\textsuperscript{14, 24, 25} uncovering mutually exclusive features between patients who improved following surgery compared to those who did not would aid in tailoring treatment for patients with CM. Numerous studies have been
published finding no link between demographic information, symptomatology, and spinal column abnormalities of those affected by CM with surgical outcome.\textsuperscript{5, 8, 26-29} Previous work by our group\textsuperscript{19, 30} demonstrated changes in the motor cortex of the brain \textit{in-vivo}, a region \textit{distal} to the site of injury at the spinal cord. More specifically, Kowalczyk et al\textsuperscript{30} used non-invasive magnetic resonance spectroscopy (MRS) to measure metabolic changes in the motor cortex of CM patients compared to control subjects. The results showed that the ratio of $N$-acetylaspartate (NAA) to creatine (Cr) was lower in CM patients indicating impaired mitochondrial function distal to the site of injury. In a follow-up study examining motor cortex metabolite levels in CM patients six months following spinal decompression surgery, Kowalczyk et al\textsuperscript{31} showed the NAA/Cr level remained low in spite of recovery in motor symptom function. This finding suggests continued impairment of mitochondrial function.

The purpose of this thesis is to expand on this finding while addressing two gaps in the literature. To our best knowledge, there has been no study of CM patients that has addressed the role of the sensory cortex in the progression and recovery of function following surgery, or examined how sensory symptom recovery differs from motor symptom recovery over time. Because patients experience both motor and sensory functional deficits, we expect to see changes in the sensory cortex similar to those observed in the motor cortex in previous studies.\textsuperscript{31} The second gap in the literature is the lack of studies reporting at early follow-up times. The only other study to evaluate early neurological recovery was Moussellard et al.\textsuperscript{17} Neurological status in early follow-up demonstrated rapid gains in function with typical plateau while paresthesia and numbness persisted into later time points.\textsuperscript{17} Validating these studies and demonstrating metabolic and clinical profiles of patients in terms of sensory and motor deficit will aid in tailoring individualized patient care and post-surgical rehabilitation.

1.2 Anatomy and Physiology of the Cervical Spine

1.2.1 The Cervical Vertebrae

The cervical spine consists of the smallest and lightest bones of the vertebral column and is susceptible to degeneration causing abnormalities in shape as well as size. The most
superior portion of the vertebral column forms the neck and can be categorized into three subgroups defined by morphological and functional characteristics; the atlas, the axis, and the sub axial spinal column. The atlas (C1) is the most superior vertebra and cradles the base of the skull. The second vertebra known as the axis (C2), serves as a pivot for C1 to aid in rotation and support of the head. The final section of the neck is the cervical column that consists of cervical vertebrae three through seven. The cervical vertebrae include the body, the vertebral arch (pedicles, laminae), facets and spinous processes.

The vertebral arch arises posteriorly from the vertebral body and consists of the pedicles, facets and laminae. The pedicles, directed in the posterior-lateral direction, straddle the vertebral foramen and function to protect the spinal cord. On either side of the vertebral foramen are the laminae that converge posteriorly to form the spinous process, the most posterior point of the vertebra. Bony spurs may result from degeneration of the vertebral arch as well as vertebral body. These spurs can impinge into the spinal canal or neural foramen, causing compression of the spinal cord or nerve roots, respectively. The laminae are also the site of attachment of the ligamenta flava that assist in the maintenance of upright posture and overall stability of the neck. Degeneration of the ligamentum flavum results in hypertrophy of this ligament, with resulting spinal cord compression. A combination of degenerative changes, anteriorly and posteriorly, result in narrowing of the spinal canal and spinal cord compression (Figure 1-1).
Figure 1-1: Sagittal T2-weighted MR image showing a cervical spine compression and signal change in the spinal cord the between cervical vertebrae 3 (C3) and cervical vertebrae 4 (C4).

1.2.2 Intervertebral Discs

In between all vertebral bodies lies an intervertebral disc. Each disc secures adjacent vertebrae in place to form a joint to allow for flexibility and an even distribution of load across the disc.\(^{33}\) An intervertebral disc includes three major components. The first component, the outer annulus fibrosus, consists of densely packed concentric rings of collagen fibril lamellae and fibrocartilage.\(^{33}\) The fibres of the outer layer are arranged obliquely where, in each successive ring, the corresponding fibres are perpendicular to its adjacent ring, giving the intervertebral disc tensile strength and elasticity.\(^{34}\) The second component of the intervertebral disc is the nucleus pulposus that is found on the inside of the disc surrounded by the annulus fibrosus. This layer is gelatinous in nature and is mainly composed of chondrocyte-like cells, proteins fibres such as collagen, and proteoglycan aggrecans that combine to form a three-dimensional matrix in the form of a
gel lattice where the loose fibres are suspended in a mucoprotein gel.\textsuperscript{34} The third and final component of the intervertebral disc is the cartilaginous plate.

Over time, cartilaginous fibres begin to lose elasticity. In order for a disc to function properly, it must have high water content. A well hydrated disc is both strong and pliable to be able to withstand axial load. As the disc dehydrates, it loses ability to support the axial load causing a weight bearing shift from the nucleus pulposus, outward, onto the annulus fibrosus, outer vertebral body, and facets. Ultimately, increased forces on the annulus lead to fissuring, tearing, disc bulging and herniations.

1.2.3 The Spinal Cord

The spinal cord is the main route for all information linking the brain and the peripheral nervous system and is an integral part of the central nervous system. The most important roles the spinal cord has in the body are autonomic, motor function control and sensation perception. This complicated network of bundled neurons contains different tracts and pathways. More specifically, the ascending and descending tracts of the nervous system form the sensory and motor pathways of communication to and from the brain.

1.2.4 Principal Descending Tracts

Within the spinal cord there are two types of descending motor tracts: the corticospinal tracts and the subconscious tracts. The corticospinal tracts consist of three pairs of descending tracts. The first pair, the corticobulbar tracts, is responsible for conscious control over the face, jaw and eye muscles. The remaining two and most relevant to cervical myelopathy, the lateral and anterior corticospinal tracts, are both responsible for the conscious control over skeletal muscles. These two pathways are known as the pyramidal tracts (Figure 1-2). When damaged, atrophy and muscle weakness is observed. The second of the two types of descending tracts, are the subconscious motor pathways. They consist of four different tracts that are responsible for unconscious motor control: the tectospinal tracts, reticulospinal tracts, vestibulospinal tracts and rubrospinal tracts. The tectospinal tracts are responsible for the coordination of information and movement of the head and neck, while the reticulospinal tracts are responsible for the coordination of the eyes and respiratory muscles. Similar to the tectospinal tracts, the vestibulospinal
tracts also monitor the position of the head, but more importantly, alter neck muscle contraction, muscle tone as well as the limbs for the maintenance of posture and balance. Deterioration of this spinal tract results in ataxia, the loss of full control of muscle movements with clinical manifestations in loss of balance and posture. Finally, the rubrospinal tract relays information to the flexor and extensor muscles. This tract is thought to be smaller and less densely packed with axons often cited as a relatively minor pathway in humans.\textsuperscript{35, 36}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{example.png}
\caption{Example of the pyramidal tracts of the principal descending (motor) pathways from the brain to the spinal cord.}
\end{figure}

\subsection{1.2.5 Principal Ascending Tracts}
Sensory neurons from the ascending tracts deliver information from the spinal cord to the brain. The posterior column tract, the spinothalamic tract, and the spinocerebellar tract are the three major sensory tracts of the ascending pathway. The posterior column tracts consist of two components, the fasciculus gracilis that transmits information from areas below thoracic vertebra six (T6), and the fasciculus cuneatus that transmits information from areas above T6 that travel to the brain via the posterior section of the spinal cord, medially to the posterior gray horn. The fasciculus cuneatus is more relevant to this work.
as it includes information being transmitted via the cervical spinal cord. Proprioception, pressure, fine touch and vibration sensation information are transmitted to the brain via these tracts. The spinothalamic tracts are responsible for transmitting pain, temperature, crude touch as well as pressure sensations first to the thalamus via the spinal cord and finally to the sensory cortex with decussation in the medulla (Figure 1-3).

![Diagram of the brain pathways](image)

**Figure 1-3:** Example of the posterior pathways of the principal ascending (sensory) pathways to the brain via the spinal cord from the right side of the body.

1.2.6 Motor and Sensory Cortex

The motor cortex, located in the most posterior part of the frontal lobe, is one of the most important areas of the brain in controlling voluntary movements. This area of the brain receives information from different parts of the brain and spinal cord to aid in communication via descending tracts for voluntary movements. The sensory cortex, located directly posterior to the motor cortex, is the main area of the brain responsible for tactile sensation perception.

Researchers have reliably depicted how the body is cortically represented along the motor and sensory cortex.\(^{37}\) The cortical homunculus, a somatic representation of the body in the cortex, was first described by Penfield and Boldrey\(^ {37} \) in 1937 by electrically
stimulating the brain and observing its affects. More recently, studies\textsuperscript{38, 39} have been able to reproduce findings by Penfield and Boldrey\textsuperscript{37} with non-invasive and more accurate techniques. More specifically, Yousry et al\textsuperscript{39} identified a new landmark specific to the hand region of the motor cortex using functional MRI. This result was of particular interest to CM researchers, as some of the main complaints of patients suffering from the disease relate to weakness, numbness, paresthesia and loss of dexterity in one or both hands.\textsuperscript{4, 10-12, 40} Yousry et al\textsuperscript{39} localized the hand region of the brain to a shape resembling a “knob” visible in the sagittal view of the motor cortex in the precentral gyrus indicated by the red circle in Figure 1-4. The same landmark can also be observed in the axial view of the brain in the form of an omega. The hand region of the sensory cortex is located directly posterior to the hand region of the motor cortex. Landmarks in the axial and sagittal view used to locate the hand area of the motor cortex are also used to locate the hand area of the sensory cortex.

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{sagittal_mri.png}
\caption{Sagittal T\textsubscript{1}-weighted MRI outlining the characteristic “knob” region of motor cortex controlling hand function.}
\end{figure}

Previous studies have demonstrated cortical plasticity\textsuperscript{41-44} as well as cortical atrophy\textsuperscript{45, 46} in patients with spinal cord injury. Results from these studies demonstrated that patients who suffered from damage to the spinal cord were not only affected by motor, sensory
and limb impairment below the site of injury, but measurable changes upstream from the injury.

1.3 Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy (MRS) is a non-invasive imaging technique that allows the measurement of low concentration mobile metabolites in the brain.\textsuperscript{47} It is a valuable clinical and research-applicable tool\textsuperscript{47-49} that is used to study a variety of different pathologies including epilepsy,\textsuperscript{50} traumatic brain injury,\textsuperscript{51} amyotrophic lateral sclerosis (ALS),\textsuperscript{52} and cancer.\textsuperscript{53} Measurements are made from predefined volumes of tissue called voxels.\textsuperscript{54}

\textbf{Figure 1-5:} Three plane MR images with a voxel outlined in yellow. Saturation bands are placed around the voxel to null signal from outside the volume of interest.
MRS spectra are typically acquired from a small, localized volume of interest in the brain. Operationally on the scanner, this voxel is placed over the area of interest and positioned using three frames of reference; sagittal, axial, and coronal images. Saturation bands are placed near the boundaries of the voxel to exclude signal from the surrounding tissue. Localization of signal from a region of interest is achieved using gradients that selectively excite three orthogonal planes. Only signal from the intersection of all three excited planes is properly refocused and forms the signal we measure from the selected region of interest. The pulse sequence used to acquire data in this thesis is called “Point-Resolved Spectroscopy” (PRESS). The PRESS pulse sequence is composed of three slice selective radiofrequency pulses – a 90°, followed by two 180° pulses. These radiofrequency pulses select slabs in orthogonal directions and the intersection of all three slabs define the voxel.

Since approximately 80% of the brain is occupied by water, this signal may conceal smaller metabolite peaks and therefore must be suppressed prior to measurement of the low concentration metabolites. The water signal is suppressed at the time of the MRS data acquisition. Water suppression involves a chemical shift selective (CHESS) element. CHESS employs a 90° Gaussian shaped radiofrequency pulse that allows for only a specific range of frequencies in the sample to be selected with a narrow bandwidth followed by a dephasing gradient pulse. Optimization of this technique is achieved by repeating this technique with varying radio frequency pulse amplitudes. Water suppression techniques reduce the water signal significantly but do not eliminate it. To remove the water completely from the spectrum before quantifying metabolite levels, we can fit the water peak using a Lanczos Singular Value Decomposition and subtract its contribution from the spectrum.

Macromolecules from within the brain and lipid signals from outside the brain in the dermis and epidermis can also contaminate the in-vivo spectrum and may interfere and overlap with metabolite peaks. These macromolecule and lipid signal should also be removed to clean the data prior to metabolite concentration quantification. Unwanted
signals from lipids are visible between 0 and 1 ppm in the spectrum. Unwanted lipid signals are first minimized during acquisition by careful placement of the MRS voxel, being diligent to exclude as much lipid containing substances, such as skin, as possible. A second technique to suppress lipid signals is the placement of selective saturation bands around the voxel in each orthogonal direction to null the lipid signal (Figure 1-5). Despite these techniques, lipid signals are sometimes still detected during data acquisition. Remaining signal can be subtracted using a technique such as the Lanczos Singular Value Decomposition fitting of the spectrum and subsequent removal of peaks within a predefined frequency range.\textsuperscript{57}

Eddy currents are induced by changing magnetic fields. In the case of MRS, successive rapid switching of gradient magnetic fields creates eddy currents that introduce signal artefacts in the MRS spectrum. Eddy current artefacts are corrected by using the unsuppressed water signal as a reference. An eddy current correction (ECC) is used, which applies a point by point phase correction of the time domain signal of the spectra acquired.\textsuperscript{58} Another technique, quantification by conversion to Lorentzian type deconvolution\textsuperscript{59} (QUALITY) can be applied by dividing the spectra by the unsuppressed water signal. This method also removes eddy current distortions. A combined QUALITY/ECC approach was used in the current study to optimize results.

1.3.1 Characteristics of a $^1$H MR Spectrum

An \textit{in-vivo} spectrum contains multiple characteristic frequencies that correspond to different metabolites. Magnetic resonance spectra are characterized by one or more peaks with each peak having an associated resonant frequency, line width, phase, and area.\textsuperscript{61} Each metabolite molecule contains one or more specific hydrogen chemical environments that lead to unique resonant frequencies for the hydrogen nuclei in the molecule. In the case of NAA, the dominant peak in the spectrum is produced by the methyl protons (CH$_3$) shown in Figure 1-6.
The area under a particular peak is directly proportional to the concentration of the corresponding metabolite that it represents as shown in Figure 1-7. NAA generates the largest metabolite peak (largest amplitude) in the MRS spectrum and its CH$_3$ methyl group is located at 2.02 ppm.

1.3.2 Measurement of Metabolite Concentration

Spectra are analyzed by fitting linear combinations of known metabolite line shapes to the in-vivo spectrum. Prior knowledge of in-vitro metabolite spectra are derived from spectra of metabolites in aqueous solution measured at 37 degrees Celsius and pH 7 to replicate the conditions that would be experienced in-vivo.$^{62}$
In this thesis there were six metabolites that were modeled and measured in the brain by long echo-time proton spectroscopy: N-acetylaspartate (NAA), creatine (Cr), choline (Cho), glutamine (Gln), glutamate (Glu), and myo-inositol (mI).

NAA is one of the most abundant amino acids found in the human brain with an average concentration of 9.2 mmol/g. It is considered a marker of neural health and integrity and has been shown to be distributed throughout the neuron and axon. NAA is the focus of the work described in this thesis. Studies have related NAA to brain metabolism by investigating different brain pathologies. By characterizing the areas of the brain that demonstrate consistent NAA abnormalities and correlate with disease progression MRS provides non-invasive metabolic information that no other tool is currently capable of matching. For example, NAA has been found to be decreased in many degenerative, neurological diseases including forms of dementia, multiple sclerosis, epilepsy, post traumatic stress disorder, and stroke. Patients with Canavan’s disease as well as children with sickle cell disease have been shown to have increased NAA in the brain. Although the exact function of NAA has still not been established, synthesis of NAA is known to be in the mitochondria of the neuron. Dautry and colleagues demonstrated the involvement of NAA in brain metabolism by treating rats and primates with a mitochondrial toxin that significantly reduced the amount of NAA in the brain. Ciccarelli et al also found that as mitochondrial activity decreased, NAA levels also decreased demonstrating an association. In 2005, Madhavarao and colleagues suggested a model that linked NAA with the production of energy and NAA’s path into cytosol.

Shown in Figure 1-8, L-aspartate N-acetyltransferase catalyzes the synthesis of NAA using acetyl-Co-enzyme A (Ac-CoA) and L-aspartate (Asp). NAA then cycles from the neuronal mitochondria through extracellular space into the oligodendrocyte where it is hydrolyzed to Asp and acetate with the release of water by available aspartoacylase that the neuron otherwise lacks. NAA is able to cycle into extracellular space (cytosol) due to the high intracellular-extracellular gradient created by the extremely high concentration of NAA in the intracellular space compared to that of the extracellular space (1000:1). Studies have also proposed that NAA may be an osmolyte where the mechanism involved in removing NAA from the neuron involves the movement of
water as well (Figure 1-8). This theory suggests that the cycle of NAA synthesis would also serve as a molecular water pump where water produced by metabolic neuronal processes in myelinated neurons would be actively removed as a water-NAA unit against a water gradient in the direction of aquaporin-4 (AQP4) water channel proteins. AQP4 water channel proteins are readily available in astrocytes where the water will ultimately cross the blood brain barrier (Figure 1-8). To support this theory, data collected in humans has shown that for every 1 mol of NAA transport into extracellular space, at least 121 moles of metabolic water is transported alongside it. Thus, NAA may be used as a marker of neuronal viability as well as energy metabolism because of its link to mitochondrial function.

**Figure 1-8** - Proposed synthesis and cycle of NAA. NAA is synthesized with the substrates acetyl-coenzyme A (Ac-CoA) and L-aspartate (Asp) catalyzed by L-aspartate N-acetyltransferase (Asp-NAT). Metabolic water (H$_2$O) and NAA move out of the neuron and NAA becomes hydrolyzed by aspartoacylase (ASPA) with a by-product of acetate (Ac) and Asp. H$_2$O moves toward AQP4 eventually crossing the blood brain barrier. Delta ($\Delta$) denotes the catalyst of the associated chemical reaction.
The metabolites glutamine (Gln) and glutamate (Glu) are abundant in the brain and involved in neurotransmission. Glu is an excitatory neurotransmitter involved in memory, learning, and cognition\textsuperscript{84} and has been shown to be decreased in Alzheimer’s disease patients.\textsuperscript{85} Glu is present in most of the brain but concentrated in areas such as the spinal cord, outer layers of the cerebral cortex as well as the hippocampus.\textsuperscript{86} Gln is a precursor to Glu found in presynaptic terminals of the neuron. Gln is metabolized into Glu creating the most abundant neurotransmitter in the brain.\textsuperscript{87} Due to their spectral overlap Glu and Gln are often evaluated as the sum of Glu+Gln, referred to as Glx.

In MRS, the measured Cr signal is the combined total concentration of phosphocreatine (PCr) and Cr expressed as total Cr.\textsuperscript{88} Total Cr is used as a marker of energy metabolism in astrocytes as well as neurons due to the involvement of phosphocreatine with ATP synthesis.\textsuperscript{88} Specifically, PCr is a readily available substrate for ATP synthesis from ADP through the creatine kinase reaction. PCr provides an energy store for fast regeneration of ATP. The total Cr signal is assumed to remain relatively constant\textsuperscript{47} in the normal, healthy brain and has therefore been used in many studies as a reference standard to scale metabolites. This approach eliminates the need to quantify cerebral spinal fluid (CSF) fraction within the voxel to account for changes in tissue partial volume between subjects. However the concentration of Cr has been shown to change in pathological conditions such as liver diseases.\textsuperscript{89} Cho is involved in pathways of phospholipid synthesis. The vast majority of chemicals in the brain containing choline are non-soluble.\textsuperscript{47} Alterations in choline create large increases in MRS visibility of choline-containing compounds such as phosphatidylcholine, phosphoryl choline, and glycerophosphoryl choline.\textsuperscript{90} MI is considered to be a marker of gliosis and contributes to very specific diseases such as dementia.\textsuperscript{89} In general, ml alone has not been reliably used as a diagnostic measure, but one that is used in conjunction with other metabolite changes.\textsuperscript{47}

1.3.3 Thesis Objectives

The overall goal of this thesis is to determine whether metabolite level changes in the motor and sensory cortices mirror the pattern of motor and sensory functional change observed in cervical myelopathy patients following surgery. Since there have not been
any studies published to date exploring the relationship between metabolic changes in the motor and sensory cortices and the temporal recovery of symptoms, this thesis will test the following specific hypothesis: that changes in metabolite levels, specifically N-acetylaspartate, will lag in the sensory cortex compared to the motor cortex, emulating the time course of functional recovery.
References


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37. W. Penfield and E. Boldrey, Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation, Brain (60), 389-443 (1937).


determination of basal levels and changes evoked by high K+, Journal of neurochemistry 62 (6), 2349-2355 (1994).


Chapter 2

2 Magnetic Resonance Spectroscopy in the Motor and Sensory Cortices Following Surgery for Cervical Myelopathy

2.1 Introduction

Degenerative changes in the cervical spine are part of the natural ageing process. Subtle progression is often asymptomatic in most people over 40 years of age.1 Cervical myelopathy (CM) is the most prevalent form of spinal cord dysfunction in adults over 55 and is characterized by a sequence of changes occurring in the spinal column including intervertebral disc degeneration, collapsing of disc space, degenerative narrowing of the spinal canal, formation of osteophytes, and hypertrophy of the ligamentum flavum, lamina and facets.2-4 As a result, symptoms begin to develop in a gradual but progressive step-wise manner.3, 5, 6

Clinically, CM manifests itself in patients with upper limb sensory loss, loss of dexterity, numbness, paresthesia and weakness in upper and lower limbs, loss of proprioception and in more severe cases, bowel and bladder incontinence.7-9 Following decompressive surgery, patients typically experience motor function improvement at early follow-up. For example, strength in upper limbs and gait dysfunction improve both subjectively and in objective measures along with improvements in overall balance.10, 11 Gains in motor function typically plateau while paresthesia and numbness persist with slow improvements in neurological status later in recovery.11

Previous work completed by our group showed significantly decreased \(N\)-acetylaspartate (NAA)/creatine (Cr) ratio in the motor cortex of CM patients compared to healthy control subjects using proton-magnetic resonance spectroscopy (MRS).12 MRS is a non-invasive imaging technique that enables the measurement of high-concentration mobile metabolites in a given volume of tissue in the brain.13 Such metabolites include \(N\)-acetylaspartate, choline, creatine, myo-inositol, glutamate (Glu), and glutamine.

The two primary metabolites of interest in this study are NAA and Glu. NAA is found exclusively in neurons as well as neuronal processes and is therefore a marker of
neuronal integrity.\textsuperscript{14, 15} NAA has also been found to be decreased in several other disease conditions such as Alzheimer’s disease, bipolar disorder, stroke and schizophrenia.\textsuperscript{16} NAA is a free amino acid synthesized in neuronal mitochondria from L-aspartate and acetyl-coenzyme A in reactions that are catalyzed by \textit{N}-acetyltransferase.\textsuperscript{17-19} It is then later transported to the cytosol by translocase and hydrolyzed by the amidohydrolase, \textit{N}-acetyl-L-aspartate.\textsuperscript{20} Physiologically, however, the role of NAA is still unknown. Presently, studies have proposed that NAA may be a precursor for the neurotransmitter NAAG, a neurotransmitter itself, an osmolyte involved in fluid homeostasis, and may incite protein synthesis, among other suggestions.\textsuperscript{21} Glutamate (Glu) is a major excitatory amino acid neurotransmitter that is derived by local synthesis of glucose and can also be formed directly from glutamine. Glu, among other amino acid transmitters, is used for excitatory synaptic transmission in the brain and is crucial in cellular metabolism. Decreased Glu levels have been found in other diseases states such as Schizophrenia, amyotrophic lateral sclerosis and Alzheimer’s disease.\textsuperscript{22}

The goal of this study was to determine whether metabolite level changes in the motor and sensory cortices mirrored the pattern of motor and sensory functional change observed in patients following surgery. Specifically, we hypothesized that at six weeks after surgery, the concentration of NAA would be increased in the motor cortex while remaining unchanged in the sensory cortex. We also hypothesized that at six months after surgery, NAA would be increased in both the motor and sensory cortices compared to baseline values.

2.2 Methodology

2.2.1 Patient Population

Twenty-four patients (20 males, 23 right handed, age range: 34 to 67 years, mean age ± standard error of the mean; 52 ± 2 years) with CM including a clinical MRI to support the diagnosis and no other neurological impairments or previous surgical treatment in the brain or spinal column were recruited and participated in this study. All participants provided written informed consent according to the Declaration of Helsinki and this study was approved by the University of Western Ontario’s Human Subjects Research Ethics
Board. At the time of enrolment, all patients demonstrated progressive symptoms manifesting no longer than 24 months. All patients had a baseline MRI scan. 17 patients underwent surgical treatment and completed two follow-up MRI exams at six weeks and six months post surgery that coincided with early and late clinical follow-up visits. Eleven out of seventeen (11/17) patients were treated for focal single-level cervical disc herniations, while the remaining six patients were treated for multi-level spondylotic disease causing myelopathy. Eight control subjects of similar age were recruited (5 males, 8 right handed, 48 ± 3 years) with no past clinical history of cervical myelopathy or previous surgery in the brain or spinal column. Control subjects also completed three MRI scans; one at baseline, then repeated at six weeks and six months.

All patients completed validated clinical outcome measures including the modified Japanese Orthopaedic Association Score (mJOA), and the Neck Disability Index (NDI). All patients suffering from CM were also assessed using the American Spinal Injury Association Impairment Classification scale (ASIA) by a licensed physician.

### 2.2.2 Magnetic Resonance Imaging

All magnetic resonance imaging (MRI) was performed using a 3.0 Tesla Siemens (Erlangen, Germany) Magnetom Tim Trio (N=15) or a 3.0 Tesla Siemens Magnetom Prisma Fit (N=2) MRI, using a 32-channel head coil. Each exam (total scan time = 48 minutes) included the acquisition of sagittal 3D T1-weighted inversion prepared (inversion time = 900 ms) rapid gradient echo anatomical images (192 slices, 1mm isotropic resolution, repetition time/echo time = 2300/3.42 ms) over the whole brain. These images produced high grey matter/white matter/cerebral spinal fluid contrast and were used for measurement of tissue partial volume within the spectroscopy voxel.

A 20mm isotropic voxel was positioned in the precentral gyrus over the area of the motor cortex that controls hand function as defined by Yousry et al\textsuperscript{23} using functional activation studies. Anatomical landmarks were also used to place the voxel. For example, in the sagittal view, the hand region of the motor cortex has the characteristic hook or “knob” type appearance while in the axial view the cortex appears in the shape of an omega. A second spectroscopy voxel was placed in the sensory cortex, directly posterior to the
voxel placed in the motor cortex. Three-dimensional images of the position of both voxels were saved for each participant to aid in placing the voxel over the same area during follow-up visits. Voxels were placed in the motor and sensory cortices in the contralateral hemisphere to the side of increased clinical deficit (n = 3 on the right, n = 14 on the left side of the brain) while in data acquired for control subjects, spectra were acquired in the motor and sensory cortices on both sides of the brain. Data were not acquired on both sides of the brain in patients due to discomfort in the arms and neck as a result of cervical myelopathy. Water suppressed spectroscopic data were localized using point resolved spectroscopy (PRESS, repetition time/echo time = 2000/135 ms, 192 averages, voxel size = 8 cm$^3$) and water unsuppressed spectroscopic data were acquired from the same voxel (PRESS, repetition time/echo time = 2000/135 ms, 8 averages, voxel size = 8 cm$^3$).

Prior to spectral analysis, residual water signal is removed by subtraction using a LSVD. Resultant spectra were fitted in the time domain using a Levenberg-Marquardt minimization routine incorporating a template of prior knowledge of each acquired metabolic lineshapes. In house analysis software (fitMAN), created in our laboratory in the IDL (Version 5.4 Research Systems Inc.) programming language, was used to model each metabolic peak after derived prior knowledge of in-vitro metabolite models. An example of the fitting is shown in Figure 2-1 where the top line represents the residual difference between the in-vivo spectrum and the fitted spectrum. Each metabolite is displayed at the bottom of the figure demonstrating its contribution to the spectrum.
**Figure 2-1:** An example spectrum from $^1$H MR spectroscopy of the area in the motor cortex controlling hand function. Top line above the spectrum is the residual line showing the result of fitting superimposed on the spectrum acquired from the data. Each metabolite is displayed on the bottom half of the figure demonstrating its contribution to the spectrum.

Tissue partial volume analysis was performed using the T$_1$-weighted anatomical images for each individual subject to determine the fraction of tissue and CSF within the voxel. Metabolite levels were normalized to the total tissue water signal and adjusted to account for water and metabolite specific T$_1$ and T$_2$ relaxation. Relaxation time constants obtained from the literature from measurements made at 3 Tesla. Based on previous studies that have shown specific metabolite involvement in neurological disorders such as CM, the following metabolites were measured and reported: NAA, choline, creatine, myo-inositol, Glu and glutamine.

### 2.2.3 Statistical Analysis

Absolute concentrations of metabolites were compared between groups using a two-tailed Student’s t-test with alpha error of 0.05. For comparisons at different time points (baseline, six weeks and six months) in patients, a two-tailed paired Student’s t-test with
an alpha error of 0.5 was also used. Correlations between clinical scores and absolute metabolite concentrations were determined by the Pearson Correlation Coefficient (r). Statistical analysis does not account for multiple comparisons due to the exploratory nature of this study as well as the planned comparisons made during the conception of this study.

2.3 Results

2.3.1 Clinical Outcome Measures

Table 2-1 summarizes patient and control demographic information as well as the clinical outcome measurements made using the NDI, mJOA, and ASIA neurological classification scales. Patients that participated in the study demonstrated a significantly decreased NDI (Table 2-1) score (p<0.05) from baseline to six months indicating an improvement in neck pain and its effect on daily activities. A significant increase was also observed in mJOA scores (Table 2-1) from baseline to six months (p<0.001) and from six weeks to six months (p<0.05) indicating improvement in both motor and sensory function. A trend toward an increase (p=0.07) was also found in the mJOA when comparing baseline to six week scores. Patients also showed a significant increase in the ASIA scores (Table 2-1), the only objective clinical measure. The ASIA can be subdivided into two categories, a motor section and a sensory section. In the motor section, there was a significant improvement between baseline and six weeks (p<0.05) and between baseline and six months (p<0.05). In the sensory portion of the ASIA, specifically with respect to light touch, there was a significant improvement between baseline and six months (p<0.01) and between six weeks and six months (p<0.05).
Table 2-1: Demographic and Clinical Data for Patients and Controls

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>17</td>
<td>8</td>
<td>n/a</td>
</tr>
<tr>
<td>Age</td>
<td>52 ± 2</td>
<td>48 ± 3</td>
<td>0.230</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>16 / 1</td>
<td>5 / 3</td>
<td>0.136</td>
</tr>
<tr>
<td>Handedness (right/left)</td>
<td>16 / 1</td>
<td>8 / 0</td>
<td>0.332</td>
</tr>
<tr>
<td>NDI scores</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>19.2 ± 2.0</td>
<td>2.3 ± 0.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>6 weeks</td>
<td>15.9 ± 1.8</td>
<td>2.5 ± 0.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>6 months</td>
<td>12.8 ± 2.1</td>
<td>2.9 ± 1.0</td>
<td>0.0002</td>
</tr>
<tr>
<td>mJOA scores</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor questions</td>
<td>8.3 ± 2.5</td>
<td>12 ± 0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sensory questions</td>
<td>4.2 ± 0.8</td>
<td>6 ± 0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>6 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor questions</td>
<td>9.4 ± 2.1</td>
<td>12 ± 0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sensory questions</td>
<td>4.5 ± 1.0</td>
<td>6 ± 0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>6 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor questions</td>
<td>9.7 ± 1.8</td>
<td>12 ± 0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sensory questions</td>
<td>4.8 ± 0.6</td>
<td>6 ± 0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ASIA scores</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper motor</td>
<td>23.5 ± 0.4</td>
<td>24.2 ± 0.4</td>
<td>25 ± 0</td>
</tr>
<tr>
<td>Lower motor</td>
<td>23.8 ± 0.4</td>
<td>24.3 ± 0.3</td>
<td>25 ± 0</td>
</tr>
<tr>
<td>Light touch</td>
<td>24.5 ± 1.3</td>
<td>25.8 ± 1.2</td>
<td>30 ± 0</td>
</tr>
<tr>
<td>Pin prick</td>
<td>24.5 ± 1.2</td>
<td>25.2 ± 1.3</td>
<td>30 ± 0</td>
</tr>
<tr>
<td>6 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper motor</td>
<td>24.7 ± 0.2</td>
<td>24.8 ± 0.1</td>
<td>25 ± 0</td>
</tr>
<tr>
<td>Lower motor</td>
<td>24.6 ± 0.3</td>
<td>24.8 ± 0.1</td>
<td>25 ± 0</td>
</tr>
<tr>
<td>Light touch</td>
<td>26.8 ± 1.0</td>
<td>28.2 ± 0.7</td>
<td>30 ± 0</td>
</tr>
<tr>
<td>Pin prick</td>
<td>27.0 ± 1.0</td>
<td>28.5 ± 0.7</td>
<td>30 ± 0</td>
</tr>
<tr>
<td>6 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper motor</td>
<td>24.7 ± 0.2</td>
<td>24.9 ± 0.1</td>
<td>25 ± 0</td>
</tr>
<tr>
<td>Lower motor</td>
<td>24.8 ± 0.1</td>
<td>24.8 ± 0.2</td>
<td>25 ± 0</td>
</tr>
<tr>
<td>Light touch</td>
<td>29.3 ± 0.3</td>
<td>28.8 ± 0.5</td>
<td>30 ± 0</td>
</tr>
<tr>
<td>Pin prick</td>
<td>29.0 ± 0.7</td>
<td>28.8 ± 0.5</td>
<td>30 ± 0</td>
</tr>
</tbody>
</table>
2.3.2 Metabolic Changes in the Motor and Sensory Cortices

When compared to healthy, age matched control subjects at baseline, patients had significantly lower concentration of NAA in both the motor (p<0.01) and sensory (p<0.05) cortices (Figure 2-2). At baseline, there were no other significant metabolite differences between patients and healthy control subjects. The absolute concentration of NAA remained stable in control subjects across all three time points, baseline, six weeks and six months in both the motor and sensory cortices. Table 2-2 describes the absolute metabolite levels in patients with CM at each time point (baseline, six weeks and six months post-surgical treatment) in both the motor and sensory cortices. For all three time points, there were no significant differences detected (p>0.05) when comparing the absolute concentrations of metabolites between the motor and sensory cortices. However, the concentration of NAA changed over time in both the motor and sensory cortices (Table 2-2, Figure 2-3). Specifically, NAA showed a significant decrease in the motor cortex from baseline to six weeks (p<0.05) and from baseline to six months post-operatively (p=0.05). Interestingly, a different profile was observed in the sensory cortex with NAA showing a significant decrease from baseline to six months (p<0.05) and from six weeks to six months (p<0.05) post-operatively. There were no other metabolite changes in the motor cortex after surgery. In contrast, in the sensory cortex, there was a significant change observed in Glx, the sum of glutamate and glutamine. The change was observed between baseline and six months (p<0.05) and between six weeks to six months (p<0.01). No other changes were observed in absolute metabolite concentrations in the sensory cortex.
Figure 2-2: Average absolute concentration of NAA in patients (n=24) and controls (n=8) at baseline in both the motor and sensory cortices. The error bars represent the standard error of the mean and the asterisks represent significant differences between groups (p<0.05).
Table 2-2: Absolute Metabolite Concentrations (mM) for Patient Group

<table>
<thead>
<tr>
<th></th>
<th>Motor Cortex</th>
<th>Sensory Cortex</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>6 Weeks</td>
</tr>
<tr>
<td>NAA</td>
<td>15.7 ± 0.4</td>
<td>14.9 ± 0.6*</td>
</tr>
<tr>
<td>Glu</td>
<td>4.4 ± 0.3</td>
<td>3.8 ± 0.3</td>
</tr>
<tr>
<td>Gln</td>
<td>1.3 ± 0.2</td>
<td>1.2 ± 0.1</td>
</tr>
<tr>
<td>Glx</td>
<td>5.6 ± 0.4</td>
<td>5.1 ± 0.3</td>
</tr>
<tr>
<td>Cr</td>
<td>8.6 ± 0.4</td>
<td>8.3 ± 0.4</td>
</tr>
<tr>
<td>Cho</td>
<td>2.5 ± 0.1</td>
<td>2.5 ± 0.1</td>
</tr>
<tr>
<td>mI</td>
<td>2.6 ± 0.3</td>
<td>2.4 ± 0.1</td>
</tr>
</tbody>
</table>

NAA = N-Acetylaspartate; Glu = Glutamate; Glx = Glutamate + Glutamine; Cr = Creatine; Cho = Choline; mI = Myo-Inositol

*Significantly different compared to baseline (p<0.05)
†Significantly different compared to 6 weeks (p<0.05)
± represents standard error of the mean
Figure 2-3: The change in average absolute concentrations of NAA in patients with CM following surgery. The error bars represent standard error of the mean and asterisks represent significant differences between time points.
Examining the change in NAA levels with change in clinical scores, a significant correlation was found between the change in the motor portion of the mJOA after six months and the corresponding change in the absolute concentration of NAA ($r=0.44$, $p=0.040$, Figure 2-4). Correlations between Glu and NAA were performed between all time points in both the motor and sensory cortices. Significant correlations were found in the motor cortex between the change in absolute concentrations of NAA and Glu from baseline to six weeks ($r=0.750$, $p=0.0003$), baseline to six months ($r=0.721$, $p=0.006$), and six weeks to six months ($r=0.599$, $p=0.006$) (Figure 2-5). Similarly, significant correlations were also found in the sensory cortex between the change in absolute concentrations of NAA and Glu from baseline to six weeks ($r=0.528$, $p=0.018$), baseline to six months ($r=0.905$, $p<0.0001$) and six weeks to six months ($r=0.631$, $p=0.006$) (Figure 2-5). No other correlations were found when comparing absolute concentrations with clinical outcome measures but a similar pattern was observed in significant changes between time points in the motor portion of the ASIA questionnaire and the concentration of NAA in the motor cortex (Figure 2-6). Similarly, significant changes between time points in the concentration of NAA in the sensory cortex and the sensory portion of the ASIA questionnaire when testing light touch (Figure 2-7).
Figure 2-4: Correlation between the change in scores on the motor portion of the modified Japanese Orthopaedic Association questionnaire and the change in the absolute concentration of N-acetylaspartate (NAA) in the motor cortex six months after surgery. A linear regression line is shown superimposed on the data.
Figure 2-5: Correlations between the change in absolute concentration of N-acetylaspartate and the change in glutamate between two time points. Plots A and B are correlations of the change in concentration between baseline and six weeks post-operatively, plots C and D between baseline and six months, and E and F between six weeks and six months. Plots A, C and E are all concentrations in reference to the motor cortex and plots B, D, and F are all concentrations in reference to the sensory cortex. In each graph, a linear regression line is shown superimposed on the data.
Figure 2-6: The change in average absolute concentrations of NAA and average motor ASIA scores in patients with CM following surgery. The error bars represent standard error of the mean and asterisks represent significant differences between time points.

Figure 2-7: The change in average absolute concentrations of NAA and average sensory (light touch) ASIA scores in patients with CM following surgery. The error bars represent standard error of the mean and asterisks represent significant differences between time points.
2.4 Discussion

This study is the first to characterize the metabolic profile in the motor and sensory cortices in patients with CM at baseline, six weeks and six months post-surgery. Clinical outcome measures were also collected at all three time points providing a functional context for the metabolite level measurements. Our findings demonstrated a decreased absolute concentration of NAA in both the motor and sensory cortices in patients compared with healthy control subjects at baseline. After surgery, absolute NAA levels in the motor cortex decreased at six weeks and six months compared to baseline, but no difference was found when comparing six month levels with six week levels. In the sensory cortex, patients demonstrated a decrease in absolute NAA concentrations between baseline and six months and between six weeks and six months post-treatment. A similar pattern was evident in the absolute concentration of Glx (a sum of glutamine and glutamate) where there was a significant decrease between baseline and six months as well as six weeks and six months. The mJOA, ASIA, and NDI clinical outcome measures all showed a significant improvement across time points. Patients consistently improved in motor as well as sensory function in both patient-subjective and physician-objective measures. We found a significant correlation between the decrease in the absolute concentration of NAA in the motor cortex between baseline and six months and the improvement in patient scores between over the same time interval measured by the ASIA neurological classification scale of motor function.

A previous study by our group Kowalczyk et al.\textsuperscript{12} found decreased NAA/Cr levels in the motor cortex in CM patients compared to controls. Decreases found in this ratio were attributed to a decrease in NAA rather than an increase in creatine. The current study supports the initial finding and provides further evidence to support the notion that it is NAA that is declining. The current study is the first to report absolute metabolite concentrations in the cortex to evaluate patients with cervical myelopathy. In addition, the current study also indicates that decreased NAA may be more widespread in the brain as lower levels were also observed in the sensory cortex at baseline. This decrease suggests neuronal damage or axonal loss is present in both cortices. It is unclear whether these changes are permanent (suggesting neuronal/axonal loss) or whether reduced NAA
indicates there is a decline in mitochondrial function that is potentially reversible.\textsuperscript{26} When comparing the decreases in the absolute concentration of NAA between the motor and sensory cortices, a temporal difference was observed.

The current study also characterized the changes in NAA at six weeks and six months following surgery. The decline in NAA levels observed in the motor cortex at six weeks and six months post surgery was consistent with a previous study by our group\textsuperscript{27} that showed decreased NAA/Cr levels six months after surgery. The current study confirms that NAA is declining while creatine levels are constant. The significant correlation between the decrease in NAA and the improvement in motor function six months following surgery (Figure 2-4) indicates that individuals with the greatest improvement also had the least decline in NAA levels. A decline in NAA level was also observed in the sensory cortex, but only six months after surgery. Therefore the NAA decline in the motor cortex preceded that observed in the sensory cortex.

Although there were no other significant correlations between decreases in metabolites and improvement in functional scores, we have seen an interesting pattern in the physician-objective ASIA neurological impairment scale that mimics that of NAA in the motor and sensory cortices. There was a significant improvement observed between baseline scores and six week scores, baseline scores and six month scores, and a lack of significant improvement between six weeks and six months. This pattern is identical to that of the decrease in the absolute concentration of NAA in the motor cortex (Figure 2-6). A pattern was also observed between the sensory portion of the ASIA neurological impairment scores, specifically the portion testing light touch, and the absolute concentration of NAA in the sensory cortex (Figure 2-7). A significant improvement between baseline and six months, six weeks and six months, but no significant improvement between baseline and six weeks directly emulates the pattern observed in metabolic changes in the sensory cortex. Although this pattern was not observed among the patient-subjective scores and only demonstrated in physician-objective scores, this suggests that patients may not be accurately assessing their own function. The lack of symptom specific questions among outcome measures as well as patients not having the
ability to compare previous answers before completing the questionnaires may be misrepresenting true results.

The only other metabolic measure to change was the sum of glutamine and glutamate (Glx), in the sensory cortex, which was decreased at six months following surgery compared to baseline and six weeks post surgery. Changes were not observed in Glu and Gln independently likely due to the higher relative error in these measurements. Glutamate, the major excitatory neurotransmitter in the nervous system is the main contributor to the Glx along with glutamine, a glutamate precursor.\(^{28}\) It is noteworthy that there was a significant correlation between changes in NAA levels and changes in Glu levels at all time points in both the motor and sensory cortices (Figure 2-5). This correlation is commonly observed in the brain and suggests that decreased mitochondrial function (NAA) neuronal activation is accompanied by decreased neurotransmitter activity (Glx).

Although this study demonstrates that metabolite level changes can be detected as early as six weeks following surgery, future studies are needed to determine whether the decreases in absolute NAA levels continue beyond six month after surgery, or whether NAA levels eventually normalize.

2.5 Conclusion

Levels of NAA are decreased in the motor cortex as early as six weeks after spinal decompression surgery in patients with cervical myelopathy and remain decreased at six months. NAA levels in the sensory cortex also decrease in the sensory cortex after surgery, but not until six months post surgery. This decrease in NAA levels is observed despite improvement in patient function over the same interval.
References


17. F. B. Goldstein, Biosynthesis of N-acetyl-L-aspartic acid, Biochimica et biophysica acta 33 (2), 583-584 (1959).


24. M. N. Kassem and R. Bartha, Quantitative proton short-echo-time LASER spectroscopy of normal human white matter and hippocampus at 4 Tesla incorporating


Chapter 3

3 Conclusions, Limitations and Future Work

3.1 Summary

Cervical myelopathy (CM) is a common, debilitating disease in adults and little is known about how the disease progresses or how the spinal cord and brain recover after treatment. Previous studies have demonstrated significant functional and metabolic differences in the brain in CM patients compared to healthy control subjects. The overall goal of this thesis was to evaluate patients with CM before and after surgery to establish a metabolic profile in both the motor and sensory cortices. In particular, our aim was to relate motor and sensory function at both early and later time-points following surgery to metabolic changes. This work was motivated by the clinical observation that motor function returns prior to sensory function in many patients.

This study evaluated patients before surgery, at early recovery following surgery (at six weeks post-treatment) and also at later follow-up (six months post-treatment). We hypothesized that at six weeks after surgery, the concentration of N-acetylaspartate (NAA) would be increased in the motor cortex while remaining unchanged in the sensory cortex. Our second hypothesis was that at six months after surgery, NAA would be increased in both the motor and sensory cortices compared to baseline values.

Results showed that at baseline, patients had a significantly lower (p<0.05) absolute concentration of NAA in both the motor and sensory cortices when compared to control subjects suggesting mitochondrial dysfunction of affected neurons. It is unlikely that decreased NAA levels are due to neuronal death as the levels of other metabolites were mostly unaffected. The absolute concentration of NAA in control subjects remained stable across time points in both the motor or sensory cortices. In the motor cortex, the absolute concentration of NAA in patients was significantly decreased between baseline and six weeks (p<0.05) and between baseline and six months (p<0.05). There was no significant decrease between six weeks and six months. Motor symptom recovery, as described by the motor portion of the American Spinal Injury Association (ASIA)
impairment classification scale, was significantly better (p<0.05) between baseline and six weeks and between baseline and six months (p<0.05). There were also no significant changes in function between six weeks and six months.

In the sensory cortex, the absolute concentration of NAA in patients was significantly lower between baseline and six months (p<0.05) and between six weeks and six months (p<0.05). With respect to sensory function, as described by the sensory portion (light touch) of the ASIA impairment classification scale, patients had significant sensory improvement between baseline and six months (p<0.05) and six weeks and six months (p<0.05).

We originally hypothesized that NAA levels would increase after surgery – indicating a reversal of metabolic dysfunction. However, the opposite was observed. The reason for declining NAA levels in conjunction with functional recovery is unclear. One possibility is that the decrease in NAA is a trigger for cortical plasticity where the brain recruits surrounding areas of the cortex to regain lost function. In group average analyses, decreases in the absolute concentration of NAA in the motor cortex mirrored the pattern of motor function recovery. Similarly in the sensory cortex, decreases in the absolute concentration of NAA mirrored the pattern of sensory symptom recovery. However, no correlation was observed between the absolute change in NAA and functional recovery when examining individual patients. The reason why the observed decline in NAA levels lags in the sensory cortex remains unclear because the cause of the decline in NAA has yet to be understood.

To the best of our knowledge, this study is the first to characterize metabolic changes in the motor and sensory cortices following surgery in patients with cervical myelopathy. The results will aid clinicians in counseling patients following surgery to focus early rehabilitation on regaining motor symptom loss such as strength of the arms and legs while delaying sensory symptom rehabilitation to a later time in post-surgical recovery.
3.2 Limitations

One limitation of our study was the heterogeneity of our patient group. Although stringent criteria were used to recruit study participants, the symptoms of cervical myelopathy in patients ranged in severity. It is unclear how the variability of symptom severity affects the absolute concentration of NAA in both the motor and sensory cortices. Another limitation of our study was the reproducibility in the placement of the magnetic resonance spectroscopy (MRS) voxel in both the motor and sensory cortices. To minimize placement error in follow-up scans, we employed projections of the position of the voxel in three orientations from the baseline scan for each patient as a reference. However, differences in head orientation as well as subject motion between the short time that the T2-weighted localizer scans were acquired and the voxel placement and spectroscopy acquisition could have lead to small errors in voxel placement. It is also unclear what effects, if any, surgical intervention had on the cortex and absolute metabolite concentrations.

3.3 Future work

This thesis was the first to report significant differences in absolute metabolite concentrations in patients surgically treated for cervical myelopathy and healthy control subjects. Further studies are needed to determine whether decreases in the absolute concentration of NAA continue beyond the six month time point. Continued studies are needed in order to determine whether longitudinally, patients with cervical myelopathy continue to experience metabolic changes in the cortex that can be influenced by rehabilitation or whether metabolite levels stabilize over time. Studies have shown that at three years following surgery, patients who were conservatively treated are functionally the same as patients who were treated surgically. Moreover, similar studies evaluating the absolute metabolite levels of patients conservatively managed are needed to establish a metabolic profile for these patients at baseline, six weeks and six months following the introduction of conservative treatment.

Further studies would also benefit from the use of an animal model. With animal studies, histology can be used to identify cellular changes caused by the disease at various time
points. Histological data as well as advanced imaging techniques, such as positron emission tomography (PET), could give us further insight into the different processes of the mitochondria of the affected neurons of the brain allowing us to determine whether NAA is a culprit in the degenerative changes of the disease or a by-product of another process we are currently unable to detect.
Appendix 1-1: Ethics Approval

Use of Human Participants - Ethics Approval Notice

Principal Investigator: Dr. Neil Duggal
Review Number: 18118
Review Level: Full Board
Approved Local Adult Participants: 46
Approved Local Minor Participants: 0
Protocol Title: Metabolic and Functional Correlates in Spinal Cord Compression Measured by Magnetic Resonance Imaging
Department & Institution: Clinical Neurological Sciences, London Health Sciences Centre
Sponsor: Canadian Institutes of Health Research
Ethics Approval Date: August 24, 2011
Expiry Date: March 31, 2015

Documents Reviewed & Approved & Documents Received for Information:

<table>
<thead>
<tr>
<th>Document Name</th>
<th>Comments</th>
<th>Version Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>UWO Protocol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Letter of Information &amp; Consent</td>
<td>2011/07/25</td>
<td></td>
</tr>
<tr>
<td>Advertisement</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

This is to notify you that the University of Western Ontario Health Sciences Research Ethics Board (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced study on the approval date noted above. The membership of this HSREB also complies with the membership requirements for REB’s as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB’s periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the UWO Updated Approval Request form.

Member of the HSREB that are named as investigators in research studies, or declare a conflict of interest, do not participate in discussions related to, nor vote on, such studies when they are presented to the HSREB.

The Chair of the HSREB is Dr. Joseph Gilbert. The UWO HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Ethics Officer to Contact for Further Information

This is an official document. Please retain the original in your files.
Appendix 1-2: mJOA Questionnaire

JAPANESE ORTHOPAEDIC ASSOCIATION SCALE FOR CERVICAL SPONDYLOTIC MYELOPATHY
To be completed by the patient

Study Name ________________________
Unique ID ________________________
Date Completed ______________ (yy/mm/dd)

MARK ONE:
☑ pre-op   ☐ 6 weeks   ☐ 6 months   ☐ Other,,,,,,

Please answer every section and mark in each section only the ONE box that applies to you. We realize you may consider that two of the statements in any one section relate to you, but please just mark ONE box that most closely describes your problem.

<table>
<thead>
<tr>
<th>☐</th>
<th>Score</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Motor Dysfunction score for upper extremities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Inability to move hands</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Inability to eat with a spoon but able to move hands</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Inability to button shirt but able to eat with a spoon</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Able to button shirt with great difficulty</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Able to button shirt with slight difficulty</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>No dysfunction</td>
<td></td>
</tr>
</tbody>
</table>

| **Motor Dysfunction score for lower extremities** | | |
| 0 | Complete loss of Motor sensory function | |
| 1 | Sensory preservation without ability to move legs | |
| 2 | Able to move legs but unable to walk | |
| 3 | Able to walk on flat floor with a walking aid (i.e., cane or crutch) | |
| 4 | Able to walk up and/or down stairs with handrail | |
| 5 | Moderate to significant lack of stability but able to walk up and/or down stairs without handrail | |
| 6 | Mild lack of stability but able to walk with smooth reciprocation unaided | |
| 7 | No Dysfunction | |

| **Sensory Dysfunction score for upper extremities** | | |
| 0 | Complete loss of hand sensation | |
| 1 | Severe sensory loss or pain | |
| 2 | Mild sensory loss | |
| 3 | No sensory loss | |

| **Sphincter dysfunction score** | | |
| 0 | Inability to micturate voluntarily | |
| 1 | Marked difficulty with micturation | |
| 2 | Mild to moderate difficulty with micturation | |
| 3 | Normal micturation | |
Appendix 1-3: Neck Disability Index (NDI)

**NECK DISABILITY INDEX**

[To be completed by the patient!]

Unique ID: __________________ Date Completed: ________________

**MARK ONE:** □ Pre-op □ 3 months □ Other

This questionnaire has been designed to give the doctor information as to how your neck pain has affected your ability to manage in everyday life. Please answer every section and mark in each section only the ONE box that applies to you. We realize you may consider that one of the statements in any one section relate to you, but please just mark ONE box that most closely describes your problem.

<table>
<thead>
<tr>
<th>Section 1 – Pain Intensity at the moment</th>
<th>Section 4 – Reading</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ I have no pain at the moment</td>
<td>□ I can read as much as I want to:</td>
</tr>
<tr>
<td>□ The pain is very mild</td>
<td>□ with no pain in my neck</td>
</tr>
<tr>
<td>□ The pain is moderate</td>
<td>□ with slight pain in my neck</td>
</tr>
<tr>
<td>□ The pain is fairly severe</td>
<td>□ with moderate pain in my neck</td>
</tr>
<tr>
<td>□ The pain is very severe</td>
<td>□ I can’t read as much as I want to because of moderate pain in my neck</td>
</tr>
<tr>
<td>□ The pain is the worst imaginable</td>
<td>□ I can hardly read at all because of pain in my neck</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Section 2 – Self Care (washing dressing)</th>
<th>Section 5 – Headaches</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ I can look after myself normally without causing extra pain</td>
<td>□ I have no headaches at all</td>
</tr>
<tr>
<td>□ I can look after myself normally but it causes extra pain</td>
<td>□ I have slight headaches that come frequently</td>
</tr>
<tr>
<td>□ It’s painful to look after myself if I am tired and careless</td>
<td>□ I have moderate headaches that come frequently</td>
</tr>
<tr>
<td>□ I need someone help to manage most of my personal care</td>
<td>□ I have severe headaches that come frequently</td>
</tr>
<tr>
<td>□ I cannot work, Due with difficulty and starvation</td>
<td>□ I have headaches almost all the time</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Section 3 – Lifting</th>
<th>Section 6 – Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ I can lift heavy weights without extra pain</td>
<td>□ I can concentrate fully:</td>
</tr>
<tr>
<td>□ I can lift heavy weights but it gives extra pain</td>
<td>□ when I want to with no difficulty</td>
</tr>
<tr>
<td>□ Pain prevents me from lifting heavy weights off the floor, but I can manage if conveniently positioned. (on a table)</td>
<td>□ when I want to with little difficulty</td>
</tr>
<tr>
<td>□ Pain prevents me from lifting heavy weights, but I can manage light to medium weights if conveniently positioned on a table</td>
<td>□ I have a fair degree of difficulty in concentrating when I want to</td>
</tr>
<tr>
<td>□ I can lift very light weights</td>
<td>□ I have a great deal of difficulty in concentrating when I want to</td>
</tr>
<tr>
<td>□ I cannot lift or carry anything at all</td>
<td>□ I cannot concentrate at all</td>
</tr>
</tbody>
</table>
# Neck Disability Index

*To be completed by the patient*

## Section 7 - Work
- I can do as much work as I want to
- I can only do my usual work, but no more
- I can do most of my usual work, but no more
- I can do some of my usual work, but no more
- I can hardly do any work at all
- I can't do any work at all

## Section 8 - Driving
- I can drive my car without any neck pain
- I can drive my car as long as I want with slight pain in my neck
- I can drive my car as long as I want with moderate pain in my neck
- I can hardly drive as long as I want because of moderate pain in my neck
- I can hardly drive at all because of severe pain in my neck
- I can't drive my car

## Section 9 - Sleeping
- I have no trouble sleeping
- Slightly disturbed (less than 1 hour sleeplessness)
- Moderately disturbed (1-2 hours sleeplessness)
- Severely disturbed (2-3 hours sleeplessness)
- Completely disturbed (3+ hours sleeplessness)

## Section 10 - Recreation
- I am able to engage in all my recreation activities with no neck pain at all
- I am able to engage in all my recreation activities with some pain in my neck
- I am able to engage in most but not all of my usual recreational activities because of neck pain
- I am able to engage in a few of my usual recreational activities because of pain in my neck
- I can hardly do any recreation activities because of pain in my neck
- I can't do any recreation activities at all
Appendix 1-4: American Spinal Injury Association (ASIA) Impairment Classification Scale
Curriculum Vitae

Name: Sandy Goncalves

Post-secondary Education and Degrees:

Master of Science
Department of Medical Biophysics
University of Western Ontario
London, Ontario, Canada
2011-2014


Supervisors: Neil Duggal, MD, MSc, FRCSC, FACS
Robert Bartha, PhD

Bachelor of Health Science
The University of Western Ontario
London, Ontario, Canada
2007-2011

Honours and Awards:
Western Research Graduate Scholarship
2011-2013

Related Work Experience
Research Coordinator
Department of Clinical Neurological Sciences
University Hospital - London Health Sciences Centre
2011 - present

Presentations and Abstracts: (*presenter)


1st Place Poster Category Prize