

Traumatic Spinal Cord Injury; Theranostic Applications of Advanced MRI Techniques

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DOI: <http://dx.doi.org/10.13005/bpj/840>

(Received: September 17, 2015; accepted: October 15, 2015)

ABSTRACT

Imaging technology is an important part of the diagnosis and management of spinal trauma. However, many efforts have been made to develop new diagnostic biomarkers through advanced imaging techniques. Unfortunately, there is still no consensus for practical use of biomarkers in SCI patients. The authors conducted an all-encompassing literature review and relevant images were included as examples. Spinal cord and soft-tissue injuries are best evaluated by magnetic resonance imaging (MRI). However, advanced MRI techniques provide researchers with a non-invasive approach that allows evaluation of physiological and biochemical condition of the spinal cord and the brain at cellular and molecular level. The advent of new rehabilitation and treatment strategies could demand more precise and advanced techniques to approach the pathophysiology and anatomy of the spinal cord, offering more accurate and non-invasive support to research and clinical follow up.

Key words: Spinal trauma, Imaging techniques, Magnetic resonance imaging, Spinal cord injury, Imaging biomarker.

INTRODUCTION

The spinal cord is located in the vertebral canal which starts from the medulla oblongata to the level of the second lumbar vertebrae. It is surrounded by cerebrospinal fluid (CSF) with an average length of about 45 cm in adults¹. Then, nerve roots from the lumbosacral segments descend in the vertebral canal in the form of cauda equina. The spinal cord divides into 31 segments, each of which has an emerging pair of spinal nerves

that transmit information to and from the peripheral nervous system. The spinal cord is divided into; 8 cervical, 12 thoracic, 5 lumbar, 5 sacral and 1 coccygeal nerves². The butterfly-shaped gray matter is located in the inner part of the spinal cord and consists of mainly cell bodies, dendrites and axons, which are surrounded by the white matter; it is organized into three funiculi (anterior, lateral and posterior) in each half of the spinal cord³. The descending and ascending axonal tracts running in these white matter funiculi convey sensory, motor,

and autonomic information between the peripheral nervous system and cerebral regions. When damage occurs to the spinal cord, sensory input, movement of certain parts of the body, and involuntary functions such as breathing can be lost or greatly impacted. When temporary or permanent impairment occurs due to damage to the spinal cord, it is classified as a spinal cord injury (SCI)⁴.

Spinal cord injury (SCI) is a major cause of morbidity due to related neurological conditions such as paraplegia and quadriplegia⁵. Patients with inclusive spinal trauma and poor motor or sensory response may have little chance of improvement⁶. However, patients with incomplete injury could have good prognosis if early diagnosis is made and treatment of fracture and/or hematomas immediately starts⁷. It should be noted that the cause of fracture is different according to age and sex, for example young men mostly suffer from trauma; but elderly female's fractures are due to osteoporosis⁸. In addition to traffic accidents, there are other causes of trauma such as fall, sports or violence. Moreover, treatment of spinal injury may include stabilization and determination of the location and extent of SCI, most of the cases would undergo surgical operation followed by medications such as Methylprednisolone which could have potential side effects as well⁹.

There are two general classes of SCI: Traumatic SCI (TSCI) and non-TSCI (nTSCI) (10). **TSCI** occurs when an external physical impact, such as the one resulting from a motor vehicle accident, a fall, or from violence, damages the spinal cord. TSCI as an acute, traumatic lesion of the spinal cord with varying degrees of motor and/or sensory deficit or paralysis results in motor, sensory and autonomic dysfunction could affect multiple body systems and may cause a life-long risk of various secondary complications¹⁰. In addition, it has a considerable impact on the lives of injured individuals and their social surroundings. In this definition, injuries of the cauda equina, the most caudal part of the spinal cord, were also included. According to instructions from related SCI organizations, TSCI could include fractures, dislocations and contusions of the vertebral column¹¹.

Pathophysiology of TSCI

An acute tear, compression or distortion of the spinal cord by external forces could cause immediate death of the cells at the site of injury, resulting in a secondary injury that exacerbates the tissue damage through intricate mechanisms according to the neuropathological reviews¹². After a primary injury, immediate vascular damage may lead to hemorrhage, ischemic changes and edema. Moreover, an inflammatory response could arise with neutrophil and then macrophage infiltration¹³. In fact, demyelination and death of oligodendrocytes may be associated with neuron necrosis. Macrophages are then responsible for removal of the damaged tissue, leading to the formation of cavities at the level of the lesion¹⁴. Astrocytes form a glial scar, and collagenous fibrosis may also appear in the area of the injury. Some peripheral types of remyelination would occur through schwann cell activity, and varying amounts of spinal cord tissue may be replaced by schwannosis¹⁵. Many destructive responses, such as excitotoxicity, the formation of free radicals and lipid peroxidation, would contribute to additional cell death during the acute and subacute phase following the initial trauma. As a consequence of local neuronal injury in SCI, secondary degeneration can also cause progressive and widespread changes in neural tracts at sites distant from the lesion over several years¹⁶. Histologically, degeneration has been shown to be spread in both anterograde and retrograde directions after SCI in human. Furthermore, axonal changes, such as fragmentation and dying back, could characterize the acute phase of degeneration, as an active process triggered by rises in intracellular calcium levels¹⁷. Moreover, the acute phase of degeneration could follow by slow and progressive myelin degradation, which can continue for a number of years after the initial trauma. Demyelination may also accompany by astrogliosis, which eventually leads to isotropic scarring in regions where degeneration has occurred¹⁸. As an endpoint of neurodegeneration, the spinal cord becomes atrophic after SCI. Secondary degeneration has even been shown to reach cerebral regions, and there would be some histological evidences of the atrophy of corticospinal neurons in human after SCI¹⁹. Furthermore, the grey matter volume and thickness of the sensorimotor cortex as well as the

white matter volume in the corticospinal tract may be decreased after injury²⁰. Such structural changes were shown to be progressive during the first year after injury, although the rate of atrophy could decelerate in the area of the cranial CST after 6 to 12 months²¹. These dynamic atrophic changes were associated with clinical scores, suggesting better clinical outcomes with low volume changes in the cerebral CST after injury²².

TSCI may occur when a pathological process other than external physical force damages the spinal cord such as motor neuron diseases, spondylosis myelopathies, infectious and inflammatory diseases, neoplastic diseases, vascular diseases, toxic, metabolic conditions, and congenital or developmental disorders²³. Also, theranostic agents can be designed to personalize treatment, and minimize damage to normal tissue²⁴.

Classification of SCI into traumatic and non-traumatic and by the severity of the injury is particularly important for the treatment, recovery and rehabilitation of the patients²⁵. When SCI occurs, it can be complete or incomplete, which, in turn, alters whether there is total or partial motor or sensory deficit²⁶. The neurological extent of the injury, or how much motor or sensory function is left intact after the SCI, is measured by a neurological examination. This examination could determine the level of impairment of the patient, reported as American Spinal Injury Association (ASIA) Impairment Scale grade²⁷.

Location of the injury can be diagnosed via imaging methods which can evaluate the spine integrity, or define the repercussion of the trauma on the diameters of the spinal canal and neural foramina²⁸. Radiography is usually used to make diagnosis; however, there are some instances of spinal damage due to fractures which are overlooked on radiography²⁹. Computed tomography (CT) or magnetic resonance imaging (MRI) can ensure diagnosis of spinal fractures in such cases as well as the time which the movement of spinal column is contraindicated due to the probability of neurological damage (Figures 1 and 2)³⁰. Moreover, MRI could play a crucial role in detection and evaluation of spinal trauma. In addition, subtle bone marrow, soft-tissue, and

spinal cord abnormalities, might not be apparent in other imaging modalities, can also be readily detected by MRI³¹. Early detection could lead to prompt and accurate diagnosis, expeditious management, and avoidance of unnecessary procedures, most of the time. Many advantages of MRI such as higher contrast resolution, multiplanar capability, choice of various pulse sequences, and absence of bony artifacts could make it possible to diagnose spinal trauma more accurately than other methods³². In addition, other important findings about neural and extra neural injuries may require surgical interventions, for example, significant disc herniation and epidural hematomas can also be observed. In cases of spinal cord edema, contusion, hemorrhage and ischemia, MRI results may play a role as prognostic indicators too³³.

Why do we use advanced MRI techniques?

Severe central nervous system (CNS) injury is the most common cause of death and disability resulting from trauma. The important factors which could determine the prognosis of patients with CNS injury are the severity of the primary injury followed by secondary cord injury which may begin from the time of traumatic impact³⁴. Although mitigation strategies for the primary injury is not within the scope of this review; however, most treatments of SCI have been focused on accurate diagnosis of primary cord injury and the prevention of secondary, delayed cord injury. Therefore, many efforts have been made to develop new diagnostic biomarkers through advanced imaging techniques. Unfortunately, there is still no consensus for practical use of biomarkers in SCI patients³⁵. In fact, conventional medical imaging techniques are still unable to accurately predict patient's prognosis after a SCI. Although patients with incomplete SCI are able to regain some loss of function, this can be disrupted by immediate physiological response that masks the true extent of the injury²⁵. It is important to fully understand the complexity of a SCI before being able to provide a way to recovery from the disability. Fortunately, physicians are able to offer some insight into the initial diagnosis of SCI; however, extent of injury is difficult to predict because of the initial inflammatory response. The extensive damage that occurs throughout entire axons following neuronal damage in the spinal cord is indeed not limited to the spinal cord³⁶.

A number of studies have demonstrated cortical changes including decreased number of neurons in the motor regions of the cortex as well as corticospinal tract as a result of SCI³⁷. On the other hand, currently advanced MRI techniques provide researchers with a non-invasive approach that allows evaluation of physiological and biochemical condition of the spinal cord and the brain at cellular and molecular level. Although conventional MRI is the imaging modality of choice for guiding management after injury and may appear to be of value in the prediction of prognosis, the provided information is mostly qualitative³⁸. In addition, in emerging clinical trials investigating experimental cell-based, pharmaceutical or rehabilitative interventions, there is a need for more specific and sensitive end-point measures that provide information about the condition of nerve fiber tracts using noninvasive techniques³⁹. To determine the efficacy of agents in a timely and economical manner, biomarkers are required that can be used as surrogate markers of patient's outcome. Recent developments in quantitative neuroimaging of the spinal cord and brain have the potential to detect anatomical, physiological, biochemical, and molecular changes and functional reorganization following SCI⁴⁰. There is now a pressing need to validate the accuracy and sensitivity of these MRI biomarkers, in order to increase the understanding of underlying mechanisms of damage and consequent functional reorganization, to identify potential therapeutic targets, and to track potential treatment-induced changes⁴¹.

Role of advanced MRI techniques in the evaluation of TSCI

Diffusion tensor imaging (DTI)

Diffusion or Brownian motion refers to the completely random displacement of molecules due to thermal energy. The diffusion coefficient, D , characterizes this thermal motion and is usually expressed in units of square millimeters per second (mm^2/s)⁴². This constant is dependent on the temperature, molecular weight and viscosity of the solution. When considering biological tissues, the apparent diffusion coefficient (ADC) is used as a diffusion constant to incorporate the effects of cellular structures and active processes within tissues on diffusion³⁹. If diffusion is equivalent in all

directions, it is called isotropic, whereas the term diffusion anisotropy is used when diffusion is restricted in some directions. In an isotropic medium such as free water, diffusion can be represented as a sphere and characterized by a single scalar ADC that is equivalent in each direction⁴³. In some biological tissues, especially in the white matter of nervous tissue, the ADC depends on the direction in which it was measured. The ADC is higher in parallel with nerve fiber bundles than in the perpendicular direction, indicating anisotropic diffusion³⁹. This asymmetrical diffusion pattern, with different diffusion properties in different directions, can be modeled by a three-dimensional ellipsoid in which the orientation of the longest axis, which has the highest ADC, represents the local fiber orientation. Moreover, the concept of diffusion tensor could provide a simplified mathematical model to estimate microscopic diffusion properties, such as the magnitude, the degree of anisotropy and the principal orientation, by performing six or more diffusion-weighted measurements in independent directions⁴⁴.

Diffusion tensor imaging (DTI) is a relatively new MRI modality with the advantageous feature of using diffusing water molecules to probe the tissue architecture⁴⁵. It can either non-invasively produce quantitative information about the direction and integrity of cerebral and spinal white matter tracts or reveal pathological changes in areas that may appear normal using conventional MRI. DTI has been developed from a technique known as diffusion-weighted imaging, which measures the attenuation of MR signals caused by diffusion, and was initially used for brain imaging. This method can give us unique quantitative information on the microstructural features of white matter in the CNS⁴⁵. Moreover, diffusion properties can be assessed using quantitative indices such as ADC, mean diffusivity (MD) and fractional anisotropy (FA)⁴⁶. The ADC could reflect the average diffusivity of water molecules in all directions; in fact, the stronger water molecules diffuse within a tissue, the larger the ADC is. However, the weaker water molecules diffuse within a tissue, the lower the ADC could be⁴⁷. Thus, tissues with high water mobility and few boundaries to water motion could have high ADC values, such as cerebrospinal fluid and vasogenic edema, whereas tissues with a high degree of complexity and boundaries to diffusion may have a relatively

lower ADC, such as white matter fiber bundles and MD, representing the degree of diffusional motion of water molecules (regardless of direction), is measured in mm^2/s . Furthermore, FA represents a rotationally invariant parameter, where 0 represents completely isotropic diffusion and 1 represents extremely limited diffusion in only one direction⁴⁸ (Figure 3).

Since diffusion barriers within the tissue could change after injury, DTI could act as an invaluable tool to monitor histological changes to the spinal cord after a SCI. Although most researches have focused on diffusion measurements at or within a few segments adjacent to site of injury, DTI parameters of the spinal cord could be sensitive to histological changes occurring after a traumatic injury⁴⁰. However, in addition to the primary injury site, there might be a secondary damage to the spinal cord in regions distant from the (primary) injury site that may result in histological changes which could affect water diffusion, including degeneration of fiber tracts, ischemia, edema, and oxidative damage to the tissue membranes which may act as barriers to diffusion. This inflammatory response could result in impaired medullary circulation as well as changes into spinal cord structure, which may consequently develop necrosis that has been documented throughout the entire length of the spinal cord, up to the brainstem. These physical changes to the cellular microstructure, including axon number and volume changes, and alterations in intracellular and extracellular water balance, may be associated with changes in apparent diffusion, including both longitudinal diffusion (along the tracts) and transverse diffusion (across the spinal tracts)⁴⁹.

Moreover, axon morphometric parameters in various white matter tracts appear to underlie some differences in overall diffusion, which could be useful in the detection of injury to spinal white matter tracts. Thus, as a biomarker for injury severity, DTI measurements of diffusion throughout the spinal cord after an injury might be taken into account. In addition, mean diffusivity could significantly be decreased in regions away from the lesion site consistent with the secondary injury processes such as cytotoxic edema, chronic atrophy and axonal loss. Changes in mean diffusivity have

also been reported in the high cervical spinal cord (rostral to an injury) in patients with chronic SCI⁵⁰. These observations could raise the question of whether changes in diffusivity in regions distant from the injury are correlated to injury severity. Furthermore, it is expected that severity of injury would change the secondary injury processes, as the extent of demyelination and remyelination could depend on the number of axons that are disrupted by the injury. One of the important applications of DTI could be the evaluation of SCI in animal models. In fact, DTI could demonstrate a significant decrease in anisotropy and increase in radial diffusivity at the level of injury and in the areas of the cord that are apparently normal on conventional T2-weighted images⁵¹.

It should be noted that in hyperacute SCI (0-6 hours), diffusion measurements are able to distinguish SCI on the basis of severity. However, the unique feature of DTI may be its ability to detect changes in diffusion metrics at regions rostral and caudal to the lesion. In addition, a decrease in diffusivity remote from the lesion could be observed during recovery from SCI⁵⁰. These findings are possibly related to cytotoxic edema, axonal loss, or chronic atrophy. Interestingly, changes in DTI indexes away from the lesion could be correlated with injury severity, indicating that they may be used as surrogate markers of neural injury. Moreover, DTI of the spinal cord in human was initially inadequate due to the small area of the cord, susceptibility artifacts, and cardiac and respiratory motion artifacts⁵².

However, adequate spatial resolution could still remain an important problem. It is difficult to visualize the individual funiculi on diffusion-weighted images, particularly in the lower thoracic cord. Moreover, the chronic phase of SCI shows wallerian degeneration, astroglial scar formation, and progressive cavitation of the cord with rostral-caudal spreading. Identifying specific changes in DTI metrics to characterize particular histological events during recovery from SCI remains a challenge too. Thus, the use of faster imaging techniques such as parallel imaging and single-shot echoplanar imaging and the use of cardiac pulse gating could help to reduce the artifacts. However, scan acquisition time is still a limitation

for patients with acute SCI because these patients often cannot withstand additional scanning time in the MRI suite⁵³

In general, the most important advantage of tensor imaging could be its ability to show changes in white matter tracts even in cases with normal routine imaging results. In diffuse axonal injury, with normal routine CT scan and conventional MRI, there would be reduction in diffusion anisotropy after 24 h, suggesting axonal injury⁵⁴. It has also been well understood that signal changes seen on routine MRI may not be associated with neurological deficits and clinical findings, whereas DTI has been shown to be correlated with motor deficits. Moreover, in experimental studies, changes in axial diffusivity on DTI in the spinal cord injury as

early as three hours after trauma were reported to be a potential predictor of long-term motor recovery, as DTI can detect early subclinical physiological changes in the cord⁵⁵.

Moreover, Wallerian degeneration above or below the injury level has also been presented on pathological examination. Buss and colleagues have found that there could be a sequential loss of myelin proteins during Wallerian degeneration after spinal cord injury which can be observed (several) years after injury. Similarly, tensor imaging in a rat model with spinal cord contusion has been shown to evolve with changes in the ADC with recovery in ADC values with time, suggesting that recovery from spinal cord injury can be considered as a dynamic process coming after for years. In fact, stem cell therapy for spinal cord injury patients is being tried with the hope of achieving axonal regeneration and recovery. In the future, the use of stem cells in patients with spinal cord injury could probably prove to be a promising therapy. Thus, tensor imaging has the potential to noninvasively identify axonal regeneration after stem cell therapy^{55, 56}.

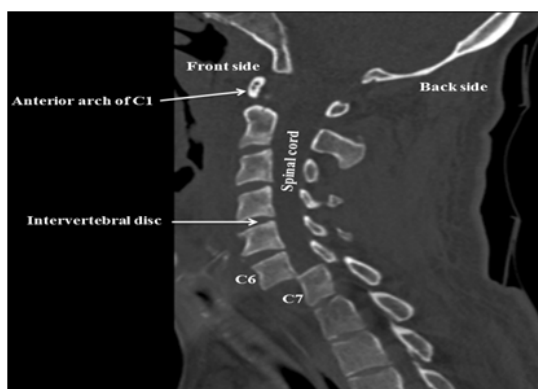


Fig. 1: CT scan of the cervical spine revealing posteriorly displaced C7 vertebral body impressing spinal cord

Magnetic resonance spectroscopy (MRS)

MR spectroscopy (synonymous terms for MRS, including Chemical Shift Imaging (CSI), Spectroscopic Imaging (SI) and Multivoxel Spectroscopy), enables the determination of metabolite concentrations in a predefined region of interest in neurological, psychiatric and metabolic disease, both noninvasively and in vivo. In contrast



Fig. 2: Conventional MRT2-weighted images of the human spinal cord with trauma show characteristic stages of morphological changes during the transition from acute to chronic stages of injury. Images show relatively lower signals at the injured spinal cord at A) acute phase which gradually increased in the time post-injury include B) 2 weeks after SCI, C) 5 months after SCI, and D) 18 months after SCI

to other MR imaging techniques, such as diffusion-weighted imaging, blood oxygen level– dependent contrast imaging, or structural MR imaging methods, MR spectroscopy could provide information about the chemical microenvironment from atomic nuclei in a variety of functional groups. This allows detection of changes in the concentration of various metabolites for investigating healthy tissue and pathologic processes and exercise- or drug-induced changes. The most widely available MRS method, proton (^1H ; hydrogen) spectroscopy is an FDA-approved procedure in the US that can be ordered by clinicians for their patients if indicated. Other methods, such as phosphorous-31 (^{31}P), carbon-13 (^{13}C), or fluorine-19 (^{19}F) MRS, have been successfully applied in humans. But with the ever-increasing importance of clinical MR imaging, these exotic and time-consuming applications have been

push to the side and are only available at a few academic centers. In addition, ^1H MRS does not require any additional hardware beyond what is already being used for MRI. Compared to DTI, the application of MRS to SCI may have more advantages. For instance, MRS can provide metabolic information about the cellular biochemistry and function of the neural structures within the cervical spinal cord. MRS also can be used to assay a series of pertinent biochemical markers, such as N-acetyl aspartate (NAA), lactate, choline (Cho), myo-inositol (Myo-I), glutamine-glutamate complex (Glx) and creatinine (Cr), with particular sensitivity to NAA and lactate⁵⁷.

Metabolites mentioned are including

N-acetyl -aspartate (NAA) produces a large resonance in a H_2O suppressed ^1H spectrum. The peak may contain up to 20% contributions from Aspartyl-glutamate (NAAG). NAA is generally associated with neurons and axons in the adult brain. It has received considerable interest in several disorders where there is neuron loss. However, its function is largely unknown⁵⁸.

The Choline (Cho) peak arises from a mixture of glycerophosphoethanolamine and glycerophosphocholine. Both phospholipids are present in cellular membranes. This resonance can provide information about cell density and membrane integrity (or peroxidation)⁵⁹.

Myo-Inositol (MI) provides a relatively large resonance and is involved in osmotic regulation across the cellular membrane and could be specific for glial cells. The amino acid glycine may also contribute to the myo-inositol resonance. Scyllo-inositol, an isomer of inositol appears also as a singlet peak more downfield. Taurine resonates close to the scyllo-inositol region⁵⁹.

A glutamate and glutamine (Glu, Gln) peak can be detected in the human brain. Glutamine is a precursor of glutamate. Glutamate is involved in neurotransmission. Gamma-aminobutyric acid (GABA), also present but in lower concentrations during normal physiological conditions may overlap with the Glu, Gln resonance at 1.5T field strength⁶⁰.

The creatine (Cr), resonance originates

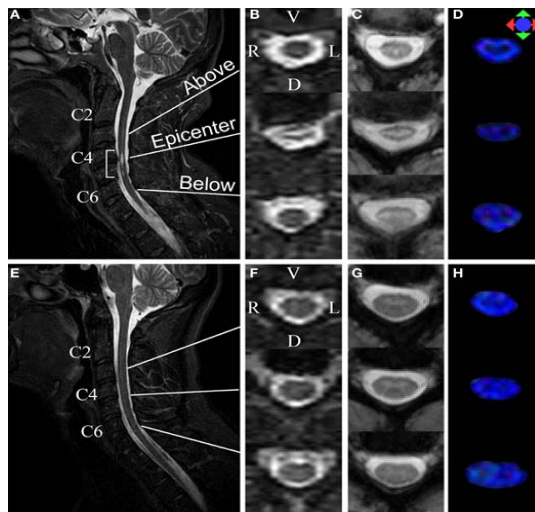


Fig. 3: Top row: Sagittal and axial T2W images (A, B, and C) and axial fractional anisotropy color maps (D) of patient with cervical SCI in above the injury epicenter (D top), injury epicenter (D middle), and below the injury epicenter (D bottom). Note which maps show loss of anisotropy at the injury site. Bottom row: Sagittal and axial T2W images (E, F, and G) and axial fractional anisotropy color maps (H) of cervical spinal cord region from normal volunteer. Control spinal cords showed intact cord structure with normal central gray matter morphology in each three part including above the injury epicenter (H top), injury epicenter (H middle), and below the injury epicenter (H bottom).

from intracellular Cr and PCr. These are involved in the Creatine kinase reaction and consequently in energy metabolism⁶¹.

Some studies have demonstrated that NAA can only be found in axons and neurons and may be considered an indicator of axonal integrity. Although little is known about specific mechanism, lactate is considered to play a central role in metabolic dysfunction after CNS injury and may be correlated to ischemia and mitochondrial dysfunction. In the early changes, the observation of a cervical stenosis patient without spinal cord signal changes showing slightly higher Myo-I and Glx compared to that of the control group suggested Myo-I as a potential early marker for spinal cord inflammation and early stage demyelination in cervical stenosis before neurological impairment⁶². (Figure 4).

In the late changes, while the patient with spinal cord signal changes had a significantly higher Cho/Cr ratio than the control, the patient without spinal cord signal changes had no significant difference compared to the control. These results show that increased Cho levels appear later than the aforementioned cellular metabolic changes in SCI. MR Spectroscopy of the spinal cord is a promising tool for research and diagnosis

because it can provide additional information complementary to other noninvasive imaging methods. Moreover, in neuroresearch MRS is definitely a revolutionary tool that will help understand the biochemistry of brain diseases. Metabolic information obtained from MR spectra is an emerging component in modern neurochemistry and standardized reproducible measurements⁶³.

However, the application of this promising technique to the spinal cord requires comprehensive expertise. The following methodological challenges, related specifically to the application of MR spectroscopy in the human spinal cord, have hindered its application in the clinical settings for many years:

- 1) Strong susceptibility changes, related to the anatomic tissue heterogeneity (vertebral bodies, CSF, muscle tissue, and so forth) around the spinal cord, may lead to spatially periodic distortions of the static magnetic (B₀) field along the spinal cord. This could distort the line shape of the spectra and reduces the signal to noise ratio (SNR).
- 2) The small diameter of the spinal cord (approximately 1 cm in the cervical cord and even lower in the thoracic and lumbar cord⁶) limits the possible voxel size, resulting in a

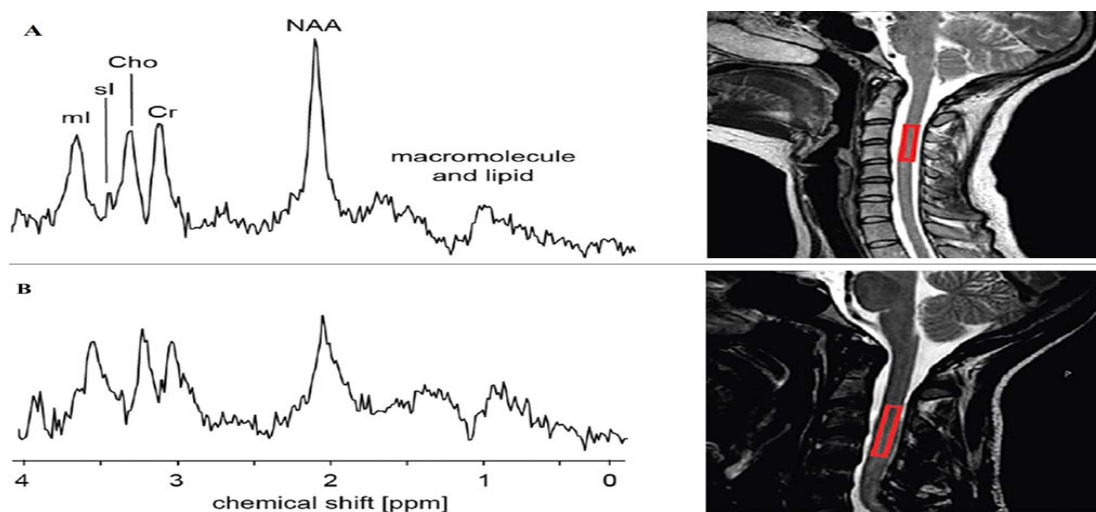


Fig. 4: ¹H-MR spectrum images of the upper cervical spinal cord in healthy volunteer (A) and patient with cervical tSCI (B). The spectrum shows NAA/Cr ratio in patients with tSCI was decreased

- low SNR and potentially imprecise quantification of metabolite concentrations.
- 3) The attainable SNR is also limited by the relatively great distance from the region of interest to the receive coils; for example, in the cervical spinal cord, the distance is approximately 5 cm in all directions and can reach >15 cm in the lower cord regions.
 - 4) The pulsatile flow of the CSF, caused by waves of arterial pressure transmitted via brain contractions due to the fixed total volume inside the skull to the CSF, can reduce the spectral quality (eg, impaired water suppression, distorted line shape and phase). The induced spinal cord motion does not seem to be critical because the maximum transversal displacement in the cervical region is approximately 0.6 mm in the anteroposterior direction.
 - 5) Subject motion is another severe problem because voxel dimensions are in the range of millimeters and are maximized to include as much spinal cord tissue as possible for increasing the SNR. Hence, patient motion in the range of millimeters (which is not unlikely considering the relatively long scanning times needed for spectroscopy) would already move the position of the voxels considerably out of the spinal cord. The result might be the contamination of the spectra with resonances of non-neural tissues, such as lipids, from nearby bone marrow or muscles and a further reduction of the SNR for the metabolites of interest.
 - 6) Anatomic variability, subject motion, or pathophysiologic changes of the electromagnetic tissue properties may affect transmit (B_1) field and hence alter desired flip angles, localization profiles, and SNR.
 - 7) With conventional MR spectroscopy localization techniques such as the point-resolved spectroscopic sequence, the signal of different metabolites could stem from slightly different regions (chemical shift displacement artifact¹). If one considers the small size of the spinal cord, the excitation volumes for some metabolites might be shifted partially out of the cord region. This has to be considered to minimize

measurement errors with regards to relative metabolite concentrations⁶⁴.

Functional MRI (fMRI)

Functional MRI has quickly become the preferred technique for imaging normal structure activity, especially in the typically active tissues such as brain and nerve. The need for a noninvasive method of mapping neural function in the SC, such as fMRI, is related to the fact that clinical decisions about the best treatment course to take following trauma to the SC, or after the effects of diseases such as SCI, may require knowledge of how the cord is functioning according to the ASIA International Standards for Neurological Classification, which involves pin-prick tests across dermatomes and motor tests of various muscle groups. This method is a functional neuroimaging procedure using MRI technology which could measure brain activity by detecting associated changes in blood flow. This technique is based on the coupling of cerebral blood flow and activation of neurons. When an area of the brain is active, the flow of blood in the region also increases⁶⁵.

Two different approaches have been emerged for fMRI of the SC, one based on the established brain fMRI method employing blood oxygenation level-dependent (BOLD) contrast, and the other based on signal enhancement by extravascular water protons (SEEP). The physiological changes underlying the SEEP contrast mechanism are discussed in detail in a separate review in this issue and so are not discussed here. The BOLD contrast mechanism is well known from brain fMRI and also occurs in the SC. Each method has been shown to have specific benefits and drawbacks. SEEP contrast is based on detection of changes in tissue water content and can therefore be obtained with proton density-weighted spin-echo parameters which could provide high-quality images of the SC. Most spinal fMRI studies employing BOLD contrast to date has employed echo-planar spatial encoding to achieve the highest imaging speed. Previous studies indicated that there are some preserved white matter pathways spanning the injury level, and preserved sensory function below the injury, in agreement with clinical assessments based on the ASIA standard. Regardless of the stimulus or the

health of the SC in question, spinal fMRI has been shown to be able to detect neuronal activity in the SC. Thus, without the need for invasive procedures or any changes to existing clinical MRI facilities, this method makes it possible to observe SC function in both patients and healthy subjects. Currently, fMRI is being developed to assess neurological function after surgery⁶⁶.

CONCLUSION

The extension and severity of the spinal trauma injury depends on several factors secondary not only to the features of the primary lesion but also to the treatment strategies and the degree of secondary lesions like demyelination and Wallerian degeneration. DTI as a feasible technique can detect Wallerian degeneration, which is not detected on routine or conventional imaging. Also, as documented in other studies, it may be correlated well with motor deficits and is a predictor of long-term motor recovery.

Currently, advanced MRI techniques could provide unique insight into the pathophysiology and microstructural alterations associated with spinal cord disorders⁶⁷. After SCI injury, the establishment of fast and efficient treatment strategy would depend on specific and detailed anatomical and pathological information that can be precisely provided by CT and MRI. Even in the more severe injuries, some pathways may be preserved and

contribute to functional recovery, which can be achieved by regeneration, remyelination or by neural plasticity, sprouting undamaged pathways. Moreover, although it is well established that cortical reorganization occurs, it remains unclear whether reorganization involves time-dependent anatomical changes. Improving the understanding of the neuronal mechanisms which may subtend clinical recovery during the acute injury phase is the key to develop evidence-based rehabilitation therapy and the tracking of treatment-induced changes. Quantitative neuroimaging of the spinal cord is an advancing field that may increase the understanding of disease progression and facilitate the prediction and monitoring of individual patients following SCI. These new neuroimaging techniques exploit the physical water properties that could define the MR contrasts, which would provide multiple measures of underlying microstructural changes in myelin, iron deposits, and water. Ultimately, quantitative and qualitative advanced MRI techniques in longitudinal multicenter assessments in acute SCI are required to measure central effects and their impact on cortical reorganization as SCI patients recover. This should allow the identification of the most sensitive imaging biomarkers and their applicability in clinical trials. The advent of new rehabilitation and treatment strategies could demand more precise and advanced techniques to approach the pathophysiology and anatomy of the spinal cord, offering more accurate and non-invasive support to research and clinical follow up.

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