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Title
Surgery of Olfactory Groove Meningiomas: When in Rome, Do as the Romans Do?

Permalink
https://escholarship.org/uc/item/4kg4w2tf

Journal
World Neurosurgery, 83(2)

ISSN
1878-8750

Author
Schaller, Karl

Publication Date
2015-02-01

DOI
10.1016/j.wneu.2014.12.004

Peer reviewed

SPINE

Imaging Techniques in Spinal Cord Injury

Benjamin M. Ellingson[1-3], Noriko Salamon[1], Langston T. Holly[4]

■ BACKGROUND: Spinal imaging plays a critical role in the diagnosis, treatment, and rehabilitation of patients with spinal cord injury (SCI). In recent years there has been increasing interest in the development of advanced imaging techniques to provide pertinent microstructural and metabolic information that is not provided by conventional modalities.

■ METHODS: This review details the pathophysiological structural changes that accompany SCI, as well as their imaging correlates. The potential clinical applications of novel spinal cord imaging techniques to SCI are presented.

■ RESULTS: There are a variety of novel advanced imaging techniques that are principally focused on the microstructural and/or biochemical function of the spinal cord, and can potentially be applied to traumatic SCI, including diffusion tensor imaging, magnetic resonance spectroscopy, positron emission tomography, single-photon emission computed tomography, and functional magnetic resonance imaging. These techniques are presently in various stages of development, including some whose applications are primarily limited to laboratory investigation, whereas others are being actively used in clinical practice.

■ CONCLUSION: Advanced imaging of the spinal cord has tremendous potential to provide patient-specific physiological information about the status of cord integrity and health. Advanced spinal cord imaging is still at early stages of development and clinical implementation but is likely to play an increasingly important role in the management of spinal cord health in the foreseeable future.

INTRODUCTION

Spinal imaging plays an essential role in the diagnosis, treatment, and rehabilitation of patients with spinal cord injury (SCI). Traditionally, these modalities have consisted of plain radiography (**Figure 1A**), computed tomography (CT; **Figure 1B**), and magnetic resonance imaging (MRI; **Figure 1C** and **D**). In combination, these techniques provide excellent macrostructural information regarding the classification and magnitude of the osseous and ligamentous injury, which, coupled with the clinical examination, guides patient management.

Despite their critical importance, these modalities offer comparatively less information regarding the microstructural injury to the spinal cord, and correlations between the radiographic and clinical findings largely have been limited. In part this has lead to the development of novel imaging techniques that are principally focused on the microstructural and/or biochemical function of the spinal cord, including diffusion tensor imaging (DTI), magnetic resonance spectroscopy, positron emission tomography (PET), single-photon emission computed tomography, and functional MRI (fMRI). These techniques are presently in various stages of development, including some whose applications are primarily limited to laboratory investigation,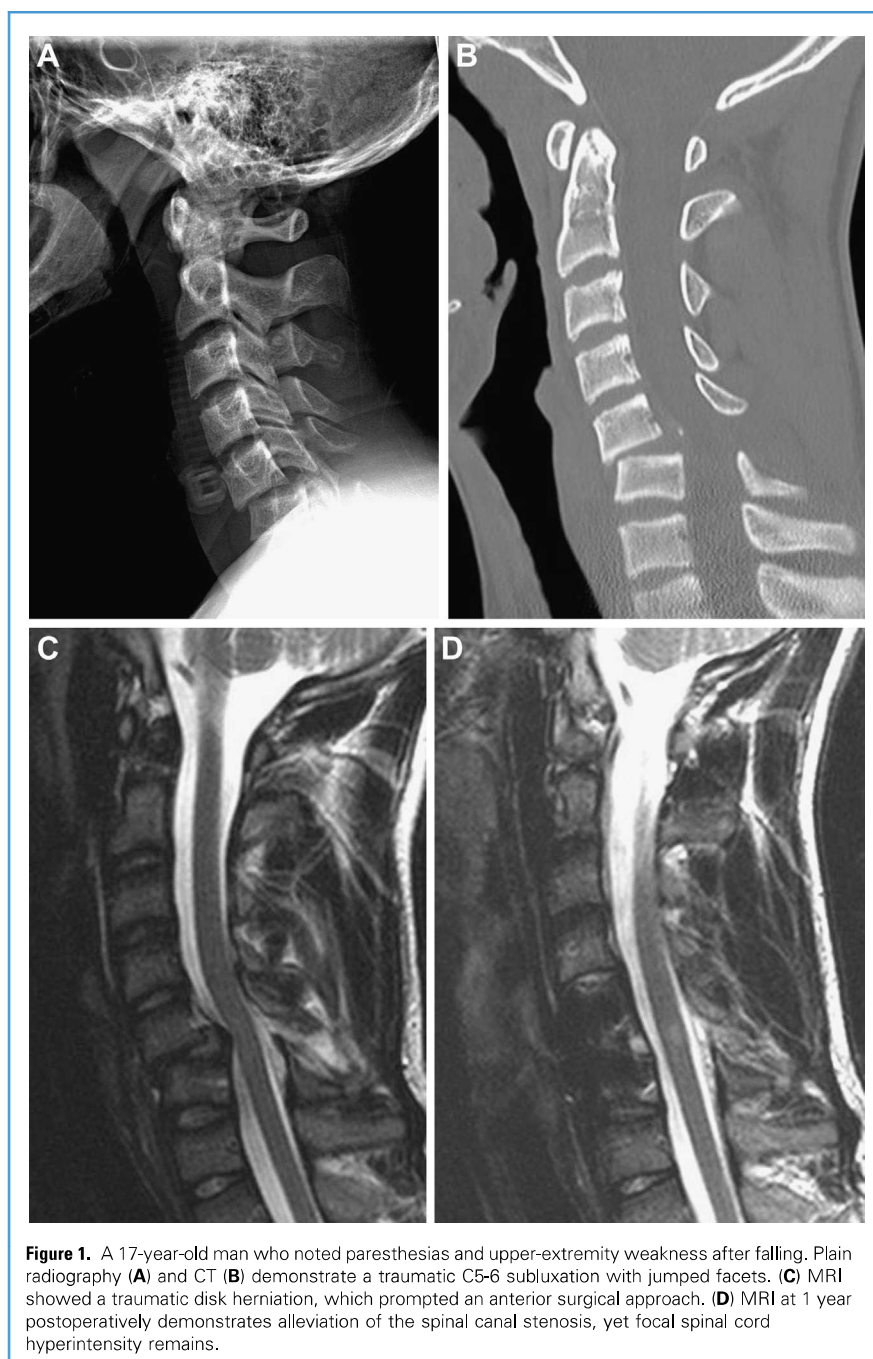 whereas other are being actively used in clinical practice. This review outlines the major structural and vascular changes that are expected to accompany the phases of traumatic injury of the spinal cord, along with the imaging correlates of these physiological changes. The application of conventional and novel imaging techniques to SCI will be discussed.

PHASES OF SCI

Hyper-Acute and Acute Spinal Trauma

The hyper-acute and acute stages of SCI, typically referring from the time of traumatic insult to hours after the initial injury, result in direct mechanical injury as well as other indirect effects including local hypoxia, ischemia, hemorrhage, and edema. Mechanical disruption of neural tissue structure results in immediate death of cells in the region of the insult. The stretching and tearing of large axons results in damage to axonal membranes and an increase in membrane permeability (82). Magnetic resonance spectroscopy clearly demonstrates a decrease in N-acetyl aspartate, a neuronal marker, after traumatic SCI in animal models (69). When diffusion MRI, which is sensitive to the magnitude of water self-diffusion, is used, early axonal

Figure 1. A 17-year-old man who noted paresthesias and upper-extremity weakness after falling. Plain radiography (**A**) and CT (**B**) demonstrate a traumatic C5-6 subluxation with jumped facets. (**C**) MRI showed a traumatic disk herniation, which prompted an anterior surgical approach. (**D**) MRI at 1 year postoperatively demonstrates alleviation of the spinal canal stenosis, yet focal spinal cord hyperintensity remains.

death and the disruption of the cell membranes has been shown to result in elevated apparent diffusion coefficient (ADC) in animal studies (22, 38), numerical simulations (37, 40), and human patients (16, 32, 74, 95). Despite these intriguing observations, hyperacute imaging of SCI is relatively difficult in the clinical scenario because patients often are admitted after this stage of injury.

Some of the earliest imaging changes after SCI are the result of hemorrhages in the central gray matter adjacent to the central canal that spread radially from the central canal into the anterior horns and neighboring white matter regions around the injury epicenter and extend both rostrally and caudally (45, 75, 89). CT is ideally suited for identifying acute hemorrhage after SCI (23, 87) because it shows hyperdense regions in areas of blood products. MRI techniques that are sensitive to changes in magnetic susceptibility, or susceptibility-weighted images, are also useful for identifying hemorrhagic lesions because of the sensitivity to microscopic magnetic perturbations from iron products after spinal trauma (92). Blood products may also be visible as hyper-intensity on precontrast T1-weighted images (36, 59) because the iron within the blood can dramatically shorten tissue relaxation rates.

Compressive or impact-induced spinal trauma often causes restriction of blood flow to the injury site (24, 49, 72). Arterial spin labeling, an MRI technique that uses magnetization tagged blood water in an artery and to quantify blood flow, has been successfully used to quantify blood flow in the mouse spinal cord (16, 25), although similar results in humans have not yet been obtained. Dynamic contrast-enhanced (DCE) MRI, an MR technique that uses a pharmacokinetic model for contrast agent extravasation from the vascular to the extravascular space to quantify blood volume and vascular permeability, also has been used to successfully quantify vascular changes in animal models (7-9, 17), but again analogous studies in human SCI have not yet been performed.

Similarly, the DCE approach has been successfully applied to CT-contrast agents in the spinal cord after injury and demonstrated a decrease in blood flow and volume after acute spinal trauma in animals (44, 54). DCE applied to CT has only recently been shown to be feasible in humans (10); thus, this technique may be useful in the very near future when applied to either CT or MRI data. Other techniques for imaging blood flow can be performed in the spinal cord, including PET imaging using radiolabeled water (H_2-[^{15}O]), single-photon emission computed tomography imaging, xenon-enhanced CT, and phase-contrast MRI; however, these techniques are not yet routinely performed after spinal trauma.

The reduction in blood flow commonly observed often results in a decrease in oxygen tension (24, 48, 83), forcing neural tissue to use anaerobic metabolic pathways in the form of high-energy phosphates, resulting in an overall decrease in metabolism for up to four hours after

the initial insult (76). After a period of anaerobic metabolism lasting from 4 to 24 hours after injury, a shift toward oxidative metabolism occurs in the viable tissue, and the remaining tissue starts to become necrotic (1, 90). PET studies that incorporate [^{18}F]-fluoro-2-deoxy-d-glucose to examine glucose metabolism have clearly demonstrated this decrease in metabolic activity after acute trauma in the rat (64). In addition, investigators all report a decrease in the measured ADC in the early onset of spinal stroke, which is indicative of the ischemic events after infarction (4, 58, 60, 73). Similarly, other investigations have shown a decrease in the ADC within the center of the spinal cord in patients with cervical spondylotic myelopathy (4, 21), which was thought to occur as the result of vascular compromise. Although the precise mechanisms responsible for changes in the diffusion characteristics after acute ischemia are still speculative, it is believed that a shift in water from the greater ADC extracellular compartment to the low ADC intracellular compartment is a result of the decrease in the observed ADC, particularly when one uses clinical scanners that can only measure water mobility at long diffusion times.

Edema occurs relatively abruptly after traumatic injury as a direct result of the mechanical disruption of axon cell membranes, damage to local blood vessels, and electrolytic imbalances (6, 36, 43, 52, 70, 84). This damage to cell membranes increases the amount of extracellular, mobile water, resulting in hyperintensity on T2-weighted (20, 46, 94) or fluid-attenuated inversion recovery MRI (22, 38). ADC in the transverse plane as measured with DTI (38), which is thought to be a result of increased extracellular (fast diffusing) volume fraction. In addition, DTI in acute spinal trauma indicates a decrease in ADC parallel to the spinal cord, resulting in an overall decrease in diffusion anisotropy, or fractional anisotropy (FA), in the lesion sites during the period of severe edema and hemorrhage (79). It has been suggested that this decrease in diffusivity parallel to spinal cord orientation may be attributed to metabolic dysfunction as opposed to specific changes in axon morphology (2); however, this is still currently under active investigation.

Subacute Stage of SCI

After the hyper-acute and acute stages of SCI reactive cells infiltrate near the injury site, axonal degeneration occurs within the regions of injured spinal tracts, and changes in the cellular structure of the neurons occur as a result of change in connectivity. In particular, the initial response to spinal trauma invokes infiltration of inflammatory cells from both the central nervous system and periphery. Activated microglia and astroglia increase in a number of processes (26) relatively proportional to the severity of the injury, and spread from the lesion epicenter into adjacent gray and white matter (65). Activated astrocytes then begin to proliferate and undergo hypertrophy (5), extending long distances into both gray and white matter (3). Polymorphonuclear granulocytes and macrophages are also present in the traumatic cavity in humans (12), as well as Schwann, meningeal, and fibroblast cells (78).

The correlation between these biological changes and structural MRI features is nonspecific, but more advanced MR techniques do show sensitivity to microstructural changes. Regions of local reactive cell infiltration remain hyperintense on T2 as the relative water concentration from edematous processes remain dominant; however, on diffusion MRI, reactive cells such as glia produce collagenous scar tissue that is expected to have a relatively high impact on tissue diffusivity. Schwartz et al. (78) demonstrated that DTI tractography can be used to identify and visualize glial scar orientation. Despite relatively widespread infiltration of reactive cells, the sensitivity of DTI tractography (i.e., DTI eigenvector orientation) appears isolated to regions close to the injury epicenter because microstructural changes must have a sense of "directionality" that is relatively coherent throughout a voxel. Thus, reactive astrocytes may only have an influence on eigenvector orientations close to the injury epicenter, or in relatively close proximity to the forming lesion cavity. The influx of high numbers of astrocytes, microglia, and macrophages are likely to decrease the extracellular volume, which is expected to decrease the overall apparent diffusion coefficient, counteracting the initial increase associated with edema.

Wallerian degeneration (35, 91), or axonal degeneration after traumatic injury,

is also present during the subacute stages of SCI and contributes to changes in both structural and diffusion-weighted MRI, even at locations distant from the injury site. Axon degeneration first manifests as breakdown of the myelin sheath and cytoskeletal proteins such as microtubules and neurofilaments. If the distal segments of damaged axons are not reconnected both structurally *and* functionally, these axons will die and degeneration will continue anterograde. If not connected, the proximal ends of the damaged axons will produce retraction bulbs in order to cleave leaking axoplasm (19). Experimental data suggest apoptosis and necrosis (53, 67, 71) result in extensive retrograde degeneration following injury in humans (3), starting with swelling of neuronal cell bodies (62, 96), nuclear movement within the soma to an eccentric position, then programmed cell death (85). This degenerative process may even continue in presynaptic cells due to loss of target cell signaling, resulting in a cascade of degeneration and total or partial dysfunction of spinal pathways.

Hyperintensity on T2-weighted images arises along affected tracts during Wallerian degeneration (18, 42, 61), which is thought to largely reflect the increased extracellular water fraction during axonal dieback. T1-weighted images show hypointensity within these regions, although the effect is very subtle. Magnetization transfer MRI, a sequence in which the hydrogen on large macromolecules like myelin are excited with radiofrequency energy that is exchanged with the mobile water pool, also has shown sensitivity to these degenerative processes (22, 77). Diffusion MRI shows an elevated ADC in the transverse plane above baseline levels (22) due to the decrease in boundaries to water diffusion during degeneration. Anterograde degeneration results in disintegration of both the axonal membrane and myelin sheath, which decreases the number and extent of transverse boundaries to diffusion and results in a higher transverse ADC. Retrograde degeneration also shows a similar, but slightly larger, increase in transverse ADC in experimental animal models (3), perhaps the subsequent increase in intracellular space from axonal swelling (34).

Gray matter also undergoes morphological changes, many of which have been implicated in severe neurological symptoms including chronic pain (55) and

spasticity (55). Experimental data have shown that the number of dendrites decreases and the length of the remaining dendritic projections increases in motoneurons after injury (88). In a mouse model of spinal injury, similar morphologic changes in spinal neurons have been reported; in addition, an enlargement of the soma during the subacute stages can also occur (29, 39). Despite these quite dramatic changes in gray matter morphology after injury, imaging characteristics resulting from changes are less profound. No real changes in standard MRI have been noted; however, changes on diffusion MRI have been observed. Spinal cord gray matter has been shown to be anisotropic (4, 40, 41), particularly compared with brain gray matter (50). The eigenvalue orientations within spinal gray follow a similar rostral-caudal dominance to white matter, and the particular eigenvector orientation may follow microstructures and the predominant soma orientation (14, 86, 93). Given the sensitivity of diffusion to gray matter microstructures, it is conceivable that large changes in soma morphology after SCI may influence diffusion measurements. Although not thoroughly investigated, an increase in overall apparent diffusion coefficient and a decrease in diffusion anisotropy are likely in spinal gray matter in the acute and subacute stages of injury because of the increase in soma size and decrease in the number of dendritic projections.

Chronic Stage of SCI

Although most of the degenerative processes are stabilized by the chronic stage of injury, which is typically defined from months to years after the initial injury, there is evidence to suggest ongoing degeneration long after the initial response. Progressive demyelination has been documented during the chronic stages of injury (11, 13, 47, 86) and remyelination, when it does occur, results in axons with significantly thinner myelin sheaths (13). Large diameter axons are preferentially at risk for degeneration during chronic injury (51), which often leads to small, unmyelinated axons in damaged axonal tracts. Cysts formed from reactive astrocytes in the subacute stage can spread longitudinally down the spinal cord from the initial site of injury, leading to widespread changes in spinal cord morphology including necrosis (85). In addition, as spinal tracts are left nonfunctional for long periods of time, significant atrophy of the spinal cord also occurs, causing the remaining axons to be compressed and tightly packed. These structural changes all
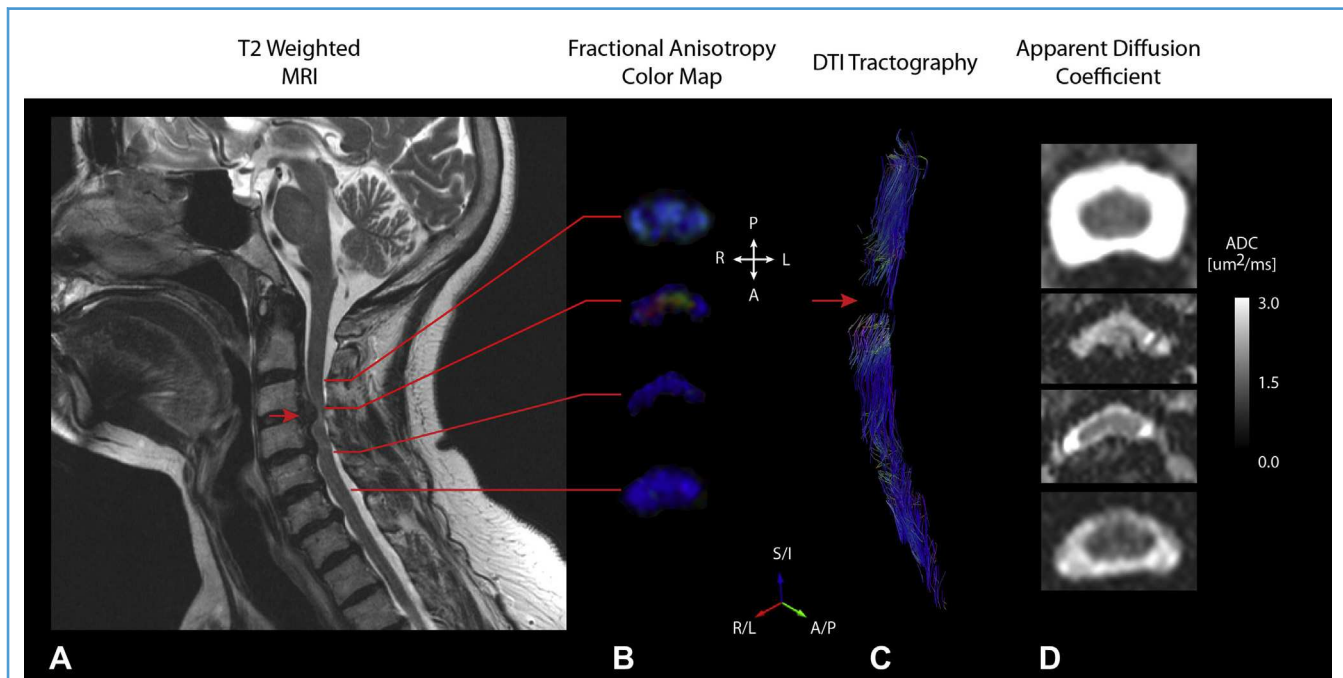
Figure 2. A 77-year-old woman with chronic SCI caused by advanced cervical spondylosis, resulting in myelomalacia and impaired neurological function. (**A**) T2-weighted sagittal MRI showing anterior compression from the intervertebral disk at the C3-4 and C4-5 levels. (**B**) Fractional anisotropy (i.e., FA) color maps showing the relative degree of diffusion anisotropy (brightness) and primary eigenvector orientation (color). *Blue* indicates superior/inferior orientation; *green*, anterior/posterior orientation; *red*, left/right orientation. A greater degree of diffusion anisotropy is observed in healthy white matter tracts due to diffusion being more restricted perpendicular to axon tract orientation. In levels above and below the site of compression, FA color maps are both bright and blue because of high diffusion anisotropy and a rostral-caudal (superior-inferior) orientation, respectively. Color maps at the level of compression show reduced brightness and both red and green colors, reflecting loss of diffusion anisotropy and distorted fiber tract orientation. (**C**) DTI tractography, where pseudoaxon tracts are created based on the information present in the diffusion tensor, shows lack of fiber continuity through the site of compression. This finding reflects disruption in the architecture of the spinal cord such that the tractography algorithm does not propagate fiber tracts through this area. (**D**) ADC, a quantitative measurement of water mobility, is highest within the cerebrospinal fluid within the spinal canal and lower within the spinal tissue. In areas of compression both abnormally high and low ADC can manifest, reflecting the myriad of inflammatory processes and pathogenesis that can alter water diffusivity.

contribute to observed abnormalities on both structural and diffusion MRI (Figure 2). Widespread axonal degeneration results in T2 hyperintensity in affected spinal tracts (69). These tracts also have elevated choline as the result of degenerative changes (27, 30, 31). Diffusion MR characteristics in chronic injury have only recently been explored (37). These studies demonstrate significant changes in diffusion distributions in chronic injury, indicative of expected changes in the spinal cord microstructure. Specifically, ADC measurements taken along the transverse orientation in spinal white matter have shown to be lower than uninjured controls and demonstrate a kurtosis (or flattening) of the diffusion distribution, likely due to loss of large diameter axons because of the known dependence of transverse ADC to axon diameter (6, 36, 43, 52, 66, 70, 81, 84).

CLINICAL CORRELATION

Conventional MRI is considered the "gold standard" imaging modality in the assessment of spinal cord damage (63) yet has not been shown to consistently correlate with the clinical findings after SCI. Consequently, there has been an increasing interest in identifying noninvasive imaging studies that can provide pertinent microstructural and metabolic information about the injured spinal cord, which is theorized to provide more accurate clinical correlation. The potential utility of such imaging modalities and impact on treatment of SCI patients are manifold: (1) the ability to predict functional outcome which can influence rehabilitation strategies, (2) to have a better understanding of the degree of neurologic impairment related to SCI in patients that have concomitant head injury or are otherwise unexaminable, (3) the assessment of neurological injury in children, a patient population in whom the clinical examination is often times unreliable (21), (4) the assessment of spinal cord integrity below the level of injury, and (5) the measurement of cellular changes in response to neural repair or biologic therapies directed towards healing the injured spinal cord.

One such imaging modality, DTI, has been demonstrated to be a more sensitive biomarker of spinal cord damage than standard T2 weighted imaging for both SCI related to cervical spondylosis (15, 33,

68, 80) and traumatic injury (15). For example, Chang et al (68) evaluated 10 chronic SCI patients and 10 healthy controls by using DTI and conventional MRI. Quantitative parameters of DTI (e.g., FA, ADC) were calculated for each cervical spinal cord level, and then DTI tractography parameters were determined for the subaxial levels, which included the number of "tracts" passing through the injury site, or "connection rate." Neurologic function was assessed by use of the International Standards for Neurological Classification of Spinal Cord Injury. Results demonstrated that abnormal appearing cervical levels on conventional MRI were not correlated with clinical findings in SCI patients; however, FA correlated with the motor function, as did the number of DTI tractography fibers and connection rates through the injury site. Specifically, on fiber tractography the one American Spinal Injury Association scale A (i.e., complete) patient demonstrated no visible connections crossing the lesion, and minimal connections were observed in three patients without motor function but spared sensory function. In patients with incomplete injury, the overall imaginary fiber numbers were greater than those with complete or motor complete paralysis. In a separate study, Petersen et al. (68) evaluated 19 chronic cervical SCI patients by using DTI, electrophysiological measures (SSEP, MEP), and neurological examination via the American Spinal Injury Association impairment scale. They found that the FA values were decreased compared to healthy control subjects and that the decrease in DTI values correlated with the clinical completeness of the SCI and with the somatosensory-evoked potential amplitudes.

Another novel imaging techniques for SCI is spinal fMRI. This noninvasive modality relies on changes in blood flow and oxygen levels that occur in metabolically active neural tissue that is responsible for a tested neurological function (57). The signal change is related to both the blood oxygen level–dependent contrast and signal enhancement from extracellular water protons caused by an increase in water content in the area. As such, spinal fMRI is able to map out areas of spinal function related to motor and sensory function. Kornelsen and Macky (56) performed spinal fMRI by using an active and passive lower-limb task

paradigm in a cohort of 12 patients with traumatic SCI. They found that neural activity was present in all patients irrespective of the degree of injury and that both active and passive motion elicited activity below the level of injury.

Future Clinical Applications

Because there are a rapidly increasing number of experimental studies in which authors investigate cellular therapies in animal SCI models, advanced spinal imaging will likely play a critical role in helping to determine the efficacy of these novel treatments. Some potential applications include: (1) serial DTI to initially assess spinal cord integrity and monitor microstructural changes during therapies; (2) perfusion MRI, which may be useful for determining whether blood flow or perfusion has been re-established in the injured cord after therapy; and (3) PET imaging of [^{18}F]-fluoro-2-deoxy-d-glucose, which may be useful for monitoring neural repair, as an increase in glucose uptake might be expected in actively healing spinal tissue.

Several experimental studies have supported the potential role of advanced spinal imaging techniques in the assessment of response to cellular therapy. Schwartz et al. (78) disrupted the rubrospinal tract via cervical funiculotomies in adult rats and then transplanted fibroblasts and vitrogen into the surgical lesion. In addition to discerning between injured and un-injured tracts, DTI was also able to identify glial scarring as well as the orientation of the glial processes. Glial scarring is well recognized as a both a physical and cellular barrier to axonal growth after SCI. Thus, DTI could have a potential role in assessing the efficacy of cellular SCI therapies designed to reduce or inhibit glial scar formation. Ellingson et al. (28) used DTI to monitor the effects of spinal cord regeneration after the transplantation of epidermal neural crest stem cell grafts. Their study showed increased diffusion anisotropy and decreased mean diffusivity at the site of injury in treated animals, suggesting structural and functional improvement of the cord.

Despite the promise of novel imaging techniques for SCI such as spinal DTI and fMRI, there are some limitations to these techniques. Presently, these modalities are not practiced at the vast majority of

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institutions, so their overall impact will be limited until more widely adopted. In comparison with the brain, the spinal cord is very small and has a greater chance of artificial contamination related to the surrounding osseous and ligamentous structures, particularly in the setting of traumatic injury. These techniques are sensitive to patient and physiological spinal cord movement, and methods such as cardiac gating are required to minimize distortion.

CONCLUSION

In summary, advanced imaging of the spinal cord has tremendous potential to provide patient-specific physiological information about the status of cord integrity and health. Advanced spinal cord imaging is still at early stages of development and clinical implementation, but is likely to play an increasingly important role in the management of spinal cord health in the foreseeable future.

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