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Objective: Fractional anisotropy (FA) of the high cervical cord (C1-C2), rostral to the injury site, correlates with upper limb function in patients with chronic cervical spinal cord injury (SCI). In acute cervical SCI, this relationship has not been investigated. The objective of this study was to identify functional correlates of FA of the high cervical cord in a series of patients with acute cervical SCI.
Methods: Traumatic cervical SCI patients who underwent presurgical cervical spine diffusion tensor imaging at our institution were reviewed for this study. FA of the whole cord as well as the lateral corticospinal tracts (CSTs) was calculated on axial images from C1-C2. Upper limb motor (C5-T1) and sensory (C2-T1) function scores were extracted from the admission American Spinal Injury Association (ASIA) examinations. Correlation analysis for FA with ASIA examinations was performed using a Pearson correlation.
Results: Twelve subjects (9 men, 3 women; mean age 54.7 ± 4.0 years) underwent cervical spine diffusion tensor imaging at a mean duration of 3.6 ± 0.9 days postinjury. No patient had cord compression or intramedullary T2-weighted hyperintensities within the C1-C2 segments. FA correlated with upper limb motor score (whole cord: r = 0.59, *P* = .04; CST: 0.67, *P* = .01) and the ASIA grade (whole cord: r = 0.61, *P* = .03; CST: r = 0.71, *P* = .009). No correlation was found between FA and sensory scores.
Conclusions: FA of the whole cervical cord as well as the CST, rostral to the injury site, is associated with preserved upper limb motor function as well as superior ASIA grades after acute cervical SCI. FA of the high cervical cord is a potential biomarker of neural injury after acute cervical SCI.

Keywords: Diffusion tensor imaging, Fractional anisotropy, Spinal cord, Spinal cord injury

Abbreviations and Acronyms

- ASIA, American Spinal Injury Association;
- CST, Corticospinal tract;
- DTI, Diffusion tensor imaging;
- FA, Fractional anisotropy;
- SCI, Spinal cord injury

Introduction

Traumatic spinal cord injury (SCI) results in partial or complete loss of neuronal function below the neurological level of injury. In addition to anterograde injury, retrograde changes in structure and function are observed within neural pathways.[12,13,22] The characterization of retrograde degeneration is important because it affects neural structures responsible for preserved neurological function and may play an important role in determining the success of rehabilitative strategies. Previous studies have described clinical correlates of these changes in chronic SCI; however, little is known

about the clinical significance of retrograde injury in subjects with acute SCI.

Diffusion tensor imaging (DTI), which measures the diffusion of water molecules within tissues, offers a quantitative assessment of spinal cord microstructure in regions of the cord that appear normal on conventional magnetic resonance imaging (MRI). Retrograde microstructural degeneration in the high cervical cord (C1-C3) is detected by DTI in subjects with chronic SCI.[4,10,11,18] Fractional anisotropy (FA), remote from the injury site, correlates with neurological function, indicating that DTI is a potential biomarker for chronic SCI.[11,18] Although similar changes in FA are observed in acute SCI, few studies have investigated whether FA, rostral to the injury site, correlates with neurological function in the acute setting. The purpose of this study was to evaluate whether FA of the high cervical cord, rostral to the injury site, is associated with neurological function in subjects with acute cervical SCI.

Methods

Subjects

We studied 15 subjects with acute cervical SCI who underwent presurgical DTI and T2-weighted MRI of the cervical spine at our institution between March 2007 and December 2012. Three subjects were excluded from this study: 2 subjects did not have American Spinal Injury Association (ASIA) scores at admission, and 1 subject had high cervical SCI. The final study sample included 12 subjects (9 men, 3 women; mean age 54.7 ± 4.0 years). A chart review was performed to acquire demographic data, neurological level of injury, and ASIA grades. We also recruited 12 neurologically intact subjects (8 men, 4 women; mean age 52.2 ± 4.6 years) within the same age range to undergo cervical spine DTI. All subjects gave written informed consent, and all procedures were approved by the local institutional review board.

Upper Limb Function

Clinical data for motor and sensory function were extracted from the first complete ASIA examination performed on SCI subjects after injury. Upper limb motor function was calculated from the left and right ASIA motor scores for the C5-T1 levels, with a maximum possible score of 50. Upper limb ASIA sensory scores for light touch and pinprick (pain) were calculated for the C2-T1 levels, with a maximum possible score of 32.

DTI

All subjects underwent DTI scanning of the cervical spine (C1-T1) on a 1.5-T MR scanner (Signa Excite; GE Medical Systems, Milwaukee, Wisconsin) with a CTL spine coil. DTI scans of 7 SCI subjects and all healthy subjects were performed with the following protocol: 15 distinct directions, b-value of 600 s/mm^2, TR/TE of 5000/98.2 ms, matrix size of 128 × 128, and FOV of 19 cm^2. Five SCI subjects, who were recruited before May 2011, underwent DTI scanning on an older 1.5-T GE MR scanner along 25 equidistant directions at a b-value of 500 s/mm^2, TR/TE of 4500/80 ms, matrix size of 128 × 128, and FOV of 260 mm × 260 mm. Sagittal T2-weighted images of the cervical spine were also acquired for all subjects using a TR/TE of 4000/102 ms, matrix size of 384 × 224, and FOV of 20 cm^2.

To determine whether there were differences in data output between the old and new MR scanner, we performed cervical spine DTI scans on 4 healthy subjects on both scanners. Mean FA and signal-to-noise ratios of an axial image at the C4-C5 level was compared between scans from the old and new machines. No significant difference in either parameter (old vs. new scanner: mean FA 0.65 vs. 0.62, P = .15; mean signal-to-noise ratio 8.6 vs. 9.2, P = .86) was detected between the scans.

Image Processing

Diffusion images were analyzed using the MedINRIA software package (www.sop.inria.fr/asclepios/software/MedINRIA). Fractional

anisotropy was calculated voxel by voxel from axial FA maps through C1-C2 (high cervical cord), using manually drawn regions of interest. Whole-cord regions of interest were drawn within the perimeter of the cord so as to avoid partial volume effects due to cerebrospinal fluid. Regions of interest also were drawn for the left and right corticospinal tracts (Figure 1) in a manner similar to previous studies.[11,16] Because FA was not significantly different between left and right corticospinal tracts for SCI subjects (Student *t* test, *P* = .68) and control subjects (*P* = .39), the mean FA of the left and right corticospinal tract (CST) was used for analysis.

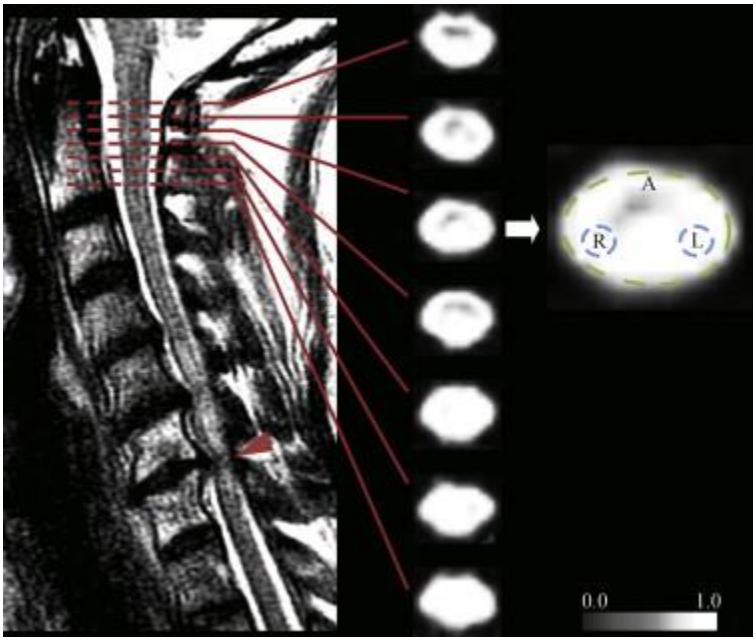

Figure 1. Sagittal cervical spine T2-weighted image of subject 8 showing 7 axial fractional anisotropy maps through the high cervical cord (red dotted line). *Solid arrowhead* shows the injury site at the C6-7 intervertebral disc level. A single fractional anisotropy map is magnified to show the whole cord regions of interest (*green*) and the regions of interest for the corticospinal tracts (*blue*). A, anterior; R, right; L, left.

Statistical Analysis

The Student *t* test was used to compare the mean FA of the whole cord and CST between SCI subjects and control subjects. Correlations between FA and upper limb function and ASIA grades were analyzed using the Pearson correlation. Statistical analysis was performed using SPSS 20.0 (Chicago, Illinois). ASIA grades were converted to numerical values to conduct the correlational analysis.

Means were reported as ± standard error of the mean, and the level of significance was set at $P < .05$.

Results

Clinical Data

Clinical and demographic data for individual SCI subjects are shown in Table 1. All subjects except 1 (subject 7) sustained blunt cervical spine injury. The neurological levels of injury ranged from C2-C7. All SCI subjects except 2 underwent an ASIA examination within 1 week of the DTI scan. All subjects upper limb motor impairment, and the mean upper limb motor score was 26.0 ± 4.2. Upper limb sensory scores were available for 11 SCI subjects, and of these, 6 subjects had intact light touch sensation and 4 subjects had intact pinprick sensation for the C2-T1 levels. The mean score for light touch was 27.2 ± 2.4, and the mean score for pinprick was 23.9 ± 2.7.

Table 1. Demographic and Clinical Features of Acute Spinal Cord Injury Subjects

Subject Number	Age	Sex	Neurological Level of Injury	ASIA Grade	Upper Limb ASIA Motor Score (maximum score = 50)	Upper Limb ASIA Sensory Score for Light Touch (maximum score = 32)	Upper Limb ASIA Sensory Score for Pinprick (maximum score = 32)	Time Interval Between Injury and DTI Scan (days)
1	53	M	C4	D	27	32	15	3
2	62	F	C5	C	10	13	12	10
3	73	M	C5	D	42	31	32	9
4	54	M	C4	A	3	12	8	3
5	60	M	C3	C	21	–	–	2
6	54	M	C7	D	30	21	25	5
7	51	M	C6	D	34	31	32	6
8	43	F	C6	D	29	32	26	2
9†	74	M	C7	D	43	32	18	0*
10	23	M	C4	D	29	32	31	0*
11	65	M	C8	D	44	32	32	2
12	45	F	C5	B	1	32	32	2

ASIA examination was performed at a delayed time point after DTI scan for 2 subjects: patient 2, 14 days; patient 10, 9 days. A dash indicates that sensory scores were unavailable for analysis.
ASIA, American Spinal Injury Association; DTI, diffusion tensor imaging; M, male; F, female.
*Subjects were scanned on the same day as their injury.
†Subject 9 had central cord syndrome at admission.

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Imaging Data

The mean time interval between injury and DTI scan was 3.6 ± 0.9 days (range, 0 to 10 days). No SCI subject had cord compression or T2-weighted intramedullary hyperintensity above the C2-C3 disc space. T2-weighted images of control subjects showed no intramedullary hyperintensity or cord compression at the C1-C2 levels. FA values for individual control subjects are shown in Table 2.

Table 2. Demographic and High Cervical Diffusion Tensor Imaging Data for Control Subjects (n = 12)

Subject Number	Age	Sex	Whole-Cord FA	Corticospinal Tract FA*
1	22	M	0.67	0.72
2	26	F	0.71	0.73
3	40	M	0.72	0.75
4	46	M	0.72	0.72
5	50	F	0.68	0.67
6	55	F	0.63	0.68
7	59	M	0.71	0.71
8	62	F	0.69	0.7
9	64	M	0.65	0.65
10	65	M	0.62	0.65
11	66	M	0.67	0.74
12	72	M	0.63	0.69

FA, fractional anisotropy; M, male; F, female.
*Average FA of the left and right corticospinal tract.

Mean whole-cord FA was significantly lower in SCI subjects as compared to control subjects (0.61 ± 0.01 vs. 0.67 ± 0.01, *P* = .008). SCI subjects demonstrated significantly decreased mean FA within the CST as compared to control subjects (0.66 ± 0.01 vs. 0.70 ± 0.009, *P* = .04).

Correlations Between FA and Clinical Scores

FA of the whole cord correlated with the upper limb motor score (r = 0.59, *P* = .04) as well as the ASIA grade (r = 0.61, *P* = .03). FA of the CSTs also correlated with upper limb motor score (r = 0.67, *P* = .01) and the ASIA grade (r = 0.71, *P* = .009) (Figure 2). The sensory scores for light touch and pinprick (n = 11) did not correlate with whole-cord FA (r = 0.17, *P* = .60; r = 0.17, *P* = .61) or CST FA (r = 0.20, *P* = .55; r = 0.27, *P* = .41).

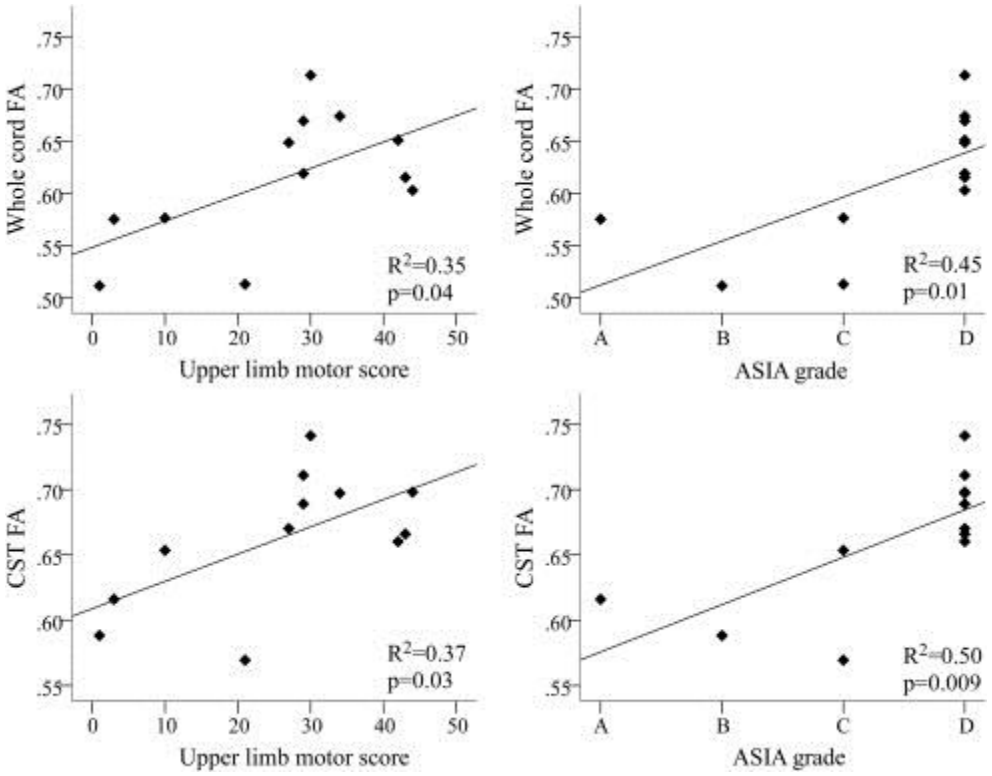

Figure 2. Scatter plots showing high cervical fractional anisotropy of the whole cord and corticospinal tract as a function of upper limb ASIA motor score and ASIA grade for 12 subjects with acute cervical spinal cord injury. ASIA, American Spinal Injury Association; FA, fractional anisotropy; CST, corticospinal tract.

Discussion

The results of this study indicate that DTI of the high cervical cord provides an estimate of white matter integrity and upper limb motor function for patients with acute cervical SCI. In particular, FA of the high cervical cord, rostral to the injury site, may be a useful biomarker of neural injury after acute cervical SCI.

FA, which provides a measure of white matter integrity in the spinal cord, is decreased at the injury site as well as rostral to the injury site in subjects with SCI.[3,4,10,11,18] In chronic SCI, these rostral changes suggest retrograde neural degeneration resulting from axonal loss,[6] demyelination,[2,21] and neuronal atrophy.[15] In acute SCI, the decrease in FA probably indicates impaired axoplasmic flow and axonal swelling, as well as demyelination.[17] Importantly, decreased FA in the high cervical cord is observed in regions of the cord that appear normal on conventional MRI. These changes suggest that neural injury

after acute SCI is more extensive than it appears on conventional MRI. In addition to delineating the true extent of neural injury in acute SCI, rostral DTI metrics may play a role in characterizing preserved neural structures, and thereby assist in planning rehabilitative strategies.

DTI metrics, rostral to the injury site, show strong correlations with locomotor[7,14] and electrophysiological function in animal SCI models.[8] Some of these results have been replicated in studies involving humans with chronic SCI. Petersen et al.[18] showed that high cervical FA of the whole cord and CSTs correlate with ASIA grades in chronic SCI. Cohen-Adad et al.[4] demonstrated correlations between white matter FA, away from the injury site, and total ASIA motor and sensory scores. Freund et al.[11] found associations between upper limb fine motor function and CST FA of the high cervical cord. These results suggest that DTI can potentially link neural structure and function in SCI subjects, and thereby provide a useful noninvasive assessment of neurological function in SCI. In the present study, higher FA values were associated with better upper limb motor function and superior ASIA grades in the acute phase after SCI. The lack of correlation with the sensory scores has been demonstrated in previous studies, and probably relates to the low precision of the clinical sensory examination.[20] In contrast to our results, Cheran et al.[3] showed that FA around the injury site was negatively correlated with ASIA motor scores for subjects with nonhemorrhagic contusions after acute cervical SCI. In that study, higher ASIA motor scores were associated with lower FA, and this paradoxical relationship was believed to be due to microstructural changes at the injury site. These results emphasize the advantage of high cervical DTI, remote from the injury, as a potential marker for neurological function in subjects with acute cervical SCI. We believe that DTI metrics remote from the injury site are less affected by hemorrhage or edema and provide a more accurate assessment of neural structure within the spinal cord.

The results of this study provide data that has clinical utility in the evaluation of subjects with acute SCI. DTI metrics may provide an estimate of neurological function, particularly in acute SCI subjects who cannot undergo a complete neurological examination due to pharmacological sedation, associated injuries, or spinal shock.[9] Because ASIA grades are currently the best predictors of outcome in acute SCI,[1,5] clinical correlates of high cervical FA point to the potential

prognostic value of DTI in acute SCI. DTI also provides data that can supplement conventional MRI in the assessment of subjects with acute SCI. DTI metrics may be particularly useful in determining neural integrity in acute SCI subjects with no intramedullary MR signal change or MR features not consistent with a clinical examination. Subjects with acute SCI often undergo spinal instrumentation around the injury site to stabilize the spine after injury. Repeating high cervical DTI during recovery from SCI may be a feasible option to track neural reorganization in these subjects because high cervical levels are less susceptible to artifacts created by spinal instrumentation. Such studies may delineate changes in neural structure associated with response to physical rehabilitation or biological therapeutic interventions for SCI.[9]

This study is limited by its retrospective design and the small number of subjects included for analysis. The majority of patients in this study were ASIA grade D, and a more uniform distribution of ASIA grades would be expected with larger patient numbers. Inconsistent injury-scan intervals in our study, although a feature of previous studies,[3,19] need to be addressed in future prospective studies. Improvements in image resolution by using 3-T MR scanners may allow for measuring other tract-specific DTI metrics. We intend to take this study forward by determining whether high cervical DTI can predict clinical outcome at mid-term and long-term follow up. Additionally, longitudinal imaging studies may reveal microstructural changes within the cord associated with recovery from SCI.

Conclusions

Greater FA of the whole cervical cord as well as the corticospinal tracts, rostral to the injury site, is associated with preserved upper limb motor function as well as superior ASIA grades after acute SCI. FA of the high cervical cord is a potential biomarker of neural injury after acute cervical SCI.

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