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Diffusion Tensor Imaging in a Large Longitudinal Series of Patients With Cervical Spondylotic Myelopathy Correlated With Long-Term Functional Outcome

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Abstract

BACKGROUND

Fractional anisotropy (FA) of the high cervical cord correlates with upper limb function in acute cervical cord injury. We investigated the correlation between preoperative FA at the level of maximal compression and functional recovery in a group of patients after decompressive surgery for cervical spondylotic myelopathy (CSM).

OBJECTIVE

To determine the usefulness of FA as a biomarker for severity of CSM and as a prognostic biomarker for improvement after surgery.

METHODS

Patients received diffusion tensor imaging (DTI) scans preoperatively. FA values of the whole cord cross-section at the level of maximal compression and upper cervical cord (C1-2) were calculated. Functional status was measured using the modified Japanese Orthopedic Association (mJOA) scale preoperatively and at follow-up up to 2 yr. Regression analysis between FA and mJOA was performed. DTI at C4-7 was obtained in controls.

RESULTS

Forty-four CSM patients enrolled prior to decompression were compared with 24 controls. FA at the level of maximal compression correlated positively with preoperative mJOA score. Preoperative FA correlated inversely with recovery throughout the postoperative period. This was statistically significant at 12 mo postoperation and nearly so at 6 and 24 mo. Patients with preoperative FA <0.55 had a statistically significant difference in outcome compared to FA >0.55.

CONCLUSION

In the largest longitudinal study of this kind, FA promises a valid biomarker for severity of CSM and postoperative improvement. FA is an objective measure of function and could provide a basis for prognosis. FA is particularly useful if preoperative values are less than 0.55.

Keywords

Biomarker, Cervical spine, DTI, Fractional anisotropy, mJOA, Myelopathy, Spondylosis

ABBREVIATIONS

- **CSM** cervical spondylotic myelopathy
- **DTI** diffusion tensor imaging
- **DWI** diffusion-weighted images

- **FA** fractional anisotropy
- **FOV** filed-of-view
- **LMC** level of maximal cord compression
- **mJOA** modified Japanese Orthopedic Association
- **MRI** magnetic resonance imaging
- **ROIs** regions of interest

Cervical spondylotic myelopathy (CSM) is a degenerative disease of the spinal cord caused by chronic compression.[1] It is the leading cause of spinal cord injury in individuals over 55 yr of age[2] and cervical spondylosis is a major cause of neck pain. Symptoms most commonly include neck stiffness, arm and shoulder pain, unsteady gait, and sensory loss, along with numbness or tingling in the extremities, bladder control problems, and, rarely, loss of sphincter control.[3],[4]

Assessing the severity of CSM, where the symptoms are largely patient reported and difficult to measure objectively, presents a challenge. Currently, the most commonly used scale is the modified Japanese Orthopedic Association (mJOA) score, which is a validated questionnaire administered to patients that determines motor dysfunction in the upper and lower extremities, sensation, and sphincter dysfunction.[5] There is no valid method to incorporate quantitative radiological findings into the assessment of the patient's condition and prognosis, particularly when considering surgical intervention.

Magnetic resonance imaging (MRI) (T2-weighted images) of the cervical spine is the imaging modality of choice in patients with suspected CSM.[6] MRI provides a clear picture of the spinal canal, delineating stenosis and ruling out other potential pathologies. CT scans can be used as a supplement to MRI to better assess the bony structures around the area of stenosis.[7] Both of these modalities, however, provide only qualitative data. To date, there has been no quantifiable radiological method of assessing the microstructural damage in the cord, especially in chronic cases,[8-10] or providing a patient with an expected postsurgical recovery prognosis.

Diffusion tensor imaging (DTI) has the advantage of evaluating microstructural changes in the nervous system by measuring the diffusion characteristics of water within the tissue[11-13] through various radiographic markers, including fractional anisotropy (FA). FA ranges from 0 to 1, with higher values indicating greater spatial asymmetry of diffusion, as might be expected in a water impermeable cylindrical structure such as an intact axon.[14] Essentially, FA measures the coherence of diffusion that can be used to infer changes in tissue microstructure, particularly in the white matter of the central nervous system. Prior work with acute cervical cord injury has established a correlation between FA of the high cervical cord and upper limb function.[15]The relationship is less clear in chronic conditions such as CSM. To our knowledge, there has been no large-scale longitudinal study exploring preoperative FA and postoperative improvement in CSM patients. This study investigates the relationship between preoperative FA at the level of maximal cord compression (LMC), severity of symptoms at baseline, and functional recovery after surgical decompression for CSM. Each of the patients was followed clinically for 2 yr postoperation.

METHODS

Subjects

We conducted a prospective nonrandomized study of patients who underwent elective decompression of the cervical spine following the diagnosis of CSM. All procedures were in compliance with the principles of the Declaration of Helsinki and are approved by our Institutional Review Board (ID number PRO00009624, Predicting the outcomes of CSM using diffusion tensor imaging, Medical College of Wisconsin/Froedtert Hospital Institutional Review Board). All subjects involved provided written consent and received incentives for travel,

time, and completion of surveys. Patients presenting with CSM were enrolled from March 2010 through September 2015. The determination of myelopathy was based on the definition of the surgeon treating the patient and included the presence of 1 or more symptoms and signs localized that were localized to the cervical spine such as overresponsive reflexes or hyperreflexia, clonus, clumsiness of hands, positive Hoffmann's reflex, positive Babinski sign, dysfunction of the bowel or bladder, and/or gait dysfunction. The exclusion criteria for the study included patients with surgery of the cervical spine in the past, nondegenerative or coexisting pathology for example trauma, multiple sclerosis or rheumatoid arthritis, and central cord syndrome. Prior to the surgery, a cervical spine MRI with DTI was obtained. Baseline functional status was determined using the mJOA scale for the purpose of correlation analysis. The data regarding the demographics, surgery, and outcomes were recorded at 6, 12, and 24 mo. A cohort of asymptomatic healthy subjects was recruited after a normal MRI of the cervical spine for comparison of DTI markers.

Magnetic Resonance Imaging

T2-Weighted MR Images

In each patient with CSM, the LMC was identified with the help of T2-weighted sagittal MRI. More specifically, T2-weighted sagittal scans were used for determining the presence of intramedullary T2-weighted hyper intensity at the LMC in the CSM group. This was achieved by 2 separate evaluators blinded to the radiology reports, using the picture archiving and communication system. Any discrepancy was resolved by consensus.

Diffusion Tensor Imaging Patients were imaged using a Cervical-Thoracic-Lumbar spine coil (GE Medical Systems, Milwaukee, Wisconsin) in a 1.5 T MR scanner (Signa Excite; GE Medical Systems). A standard single-shot, twice-refocused, spin-echo EPI pulse sequence was used to obtain DWI of the cervical spine (C1-T1, Figure 1). The scanning protocol for obtaining DTI involved directional resolution of 15 directions with axial slices of dimensions 3 mm × 3 mm and a gap of 3 mm between slices, and a b-value of 600 s/mm^2 and a single T2-weighted image with a b-value of 0 s/mm^2.[38] Sagittal T2-weighted images were obtained with a TR, 4000 ms; TE, 102 ms; filed-of-view (FOV), 20 cm^2; and matrix size, 384 × 224. DWI were obtained with a TR = 5000 ms; TE = 98.2 ms; FOV of 19 cm × cm; number of excitations = 2; and matrix size of 128 × 128.[38]

FIGURE 1. Axial, whole-cord DTI image taken at C5.

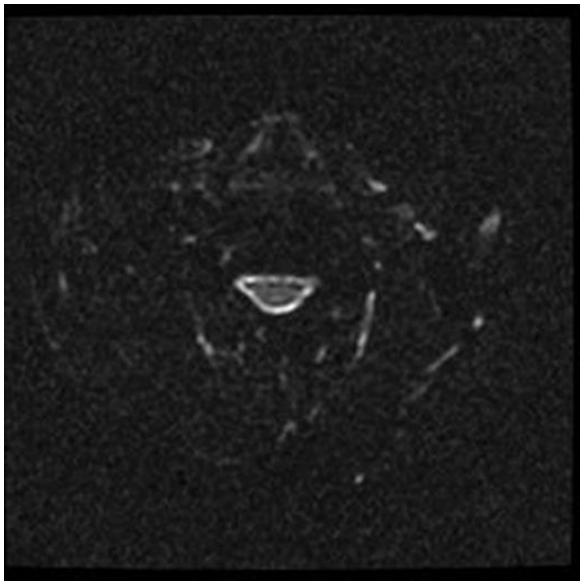


Image Processing

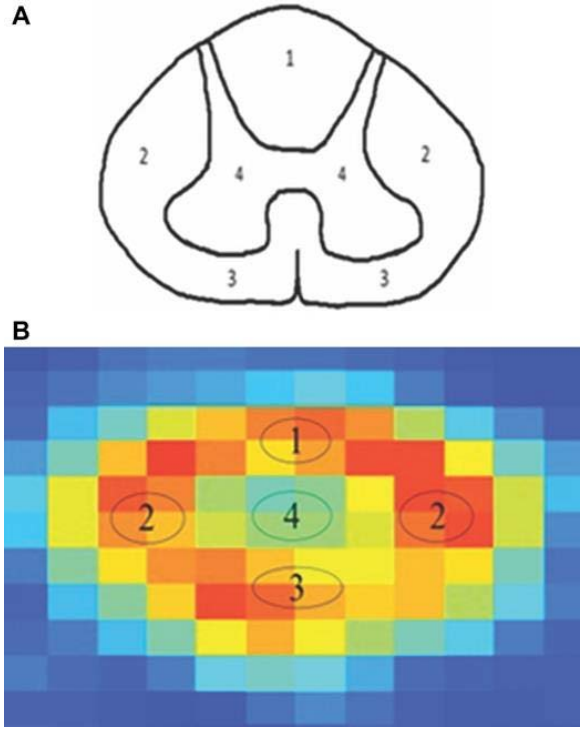
The processing of diffusion data was carried out with Analysis of Functional NeuroImages (http://afni.nimh.nih.gov/afni) software. First, the registration of the 15 DWIs to the T2-weighted image was

carried out with an affine registration based on Fourier transform to correct for geometric distortions induced by Eddy currents, subject motion inside the scanner, and susceptibility effects.[38] Following the registration of the diffusion images, a symmetric 3 × 3 diffusion tensor along with the eigenvalues of this tensor was calculated at each voxel using a nonlinear tensor-fitting algorithm.[39] The diffusion images were then checked for outliers, which were removed from further analysis. The optimization was completed using a gradient descent method. DTI indices were calculated from the eigenvalues as follows: FA (based on the definition of Basser and Pierpaoli[16]), mean diffusivity (MD [10^3 mm^2 s^1], the average of all 3 eigenvalues), longitudinal apparent diffusion coefficient ([10^3 mm^2 s^1], the largest of the 3 calculated eigenvalues), and transverse apparent diffusion coefficient ([10^3 mm^2 s^1], the average of 2 smallest eigenvalues).[39]

Regions of Interest

The axial maps at the LMC that were based on FA were selected for the analysis (Figure 2).[38] Then, custom software written in MATLAB (MathWorks, Natick, Massachusetts) was utilized for manually drawing the regions of interest (ROIs) on axial FA maps. The manual ROIs were drawn keeping in mind to include the whole cord but excluding at least 2 voxels at the periphery of the cord to minimize the risk of partial volume effects due to the surrounding cerebrospinal fluid.[38] For the control group, an axial FA selection is made at the levels C4 to C7 for comparison. DTI metrics are calculated using the measured eigenvalues as previously described to derive FA and MD.

FIGURE 2. A, Axial layout of the spinal cord gray and white matter tracts. **B**, Example of postprocessing input to our MATLAB (MathWorks) program. Blue regions indicate cerebrospinal fluid, excluded from the final analysis.



Statistical Analysis

Statistical analysis of the metrics is performed using 2-sample *t*-tests and linear regression analysis in Excel (Microsoft, Redmond, Washington), using its built-in data analysis tools. Linear analysis was performed to segregate the CSM group by FA value to identify a cut-off value for likelihood of functional improvement at 12 mo. This was defined as a point after which FA was not clearly correlative with changes in mJOA following

decompressive surgery, likely due to approaching values seen in normal subjects. A *P*-value of .05 was prospectively chosen to indicate statistical significance.

RESULTS

Forty-four patients presenting with CSM met the study criteria and were enrolled in this study before decompressive surgery. The average age was 53.9 yr (standard deviation = 9.8, range 33–81); 18 were male and 26 were female. Thirty-nine patients completed follow-up at 6 mo, 34 at 12 mo, and 26 at 24 mo, at the time of writing. The control group consisted of 24 healthy subjects: 13 males and 11 females, with an average age of 52.3 yr (standard deviation = 16.7, range 22–85).

FA calculated values were lower in the patient group, compared to the controls, at the LMC (0.51 ± 0.06 vs 0.57 ± 0.04, $P < .001$). FA at the LMC was also found to have a positive correlation with baseline preoperative mJOA (mJOA = 9.94*FA + 8.43, $R^2 = .09$, $P = .05$, Figure 3). There was no statistically significant correlation with postoperative mJOA values. There was an inverse relationship between preoperative FA at the LMC and postoperative improvement in mJOA (lower preoperative FA predicted higher improvement in postoperative mJOA) at 6, 12, and 24 mo. This was statistically significant in 34 patients at 12 mo postoperation (ΔmJOA = −20.49*FA + 11.14, $R^2 = .24$, $P = .003$) and near statistical significance at 6 and 24 mo ($P = .08$ and .09, respectively; Figures 4-6). However, when looking at absolute mJOA values using a 2-sample *t*-test, there was no significant difference between pre- and postoperative values at 12 mo (mean preop = 13.55 ± 2.14, postop = 14.15 ± 2.44, *P*-value = .26). This finding did not change when looking at subsets of patients above and below an FA of 0.55. Preoperative FA at C1-2 was also lower in the patient group compared to the controls (0.56 ± 0.05 vs 0.61 ± 0.04, $P < .001$). However, FA at C1-2 did not correlate with changes in mJOA in follow-up in this group of patients.

FIGURE 3. Linear regression analysis demonstrating the relationship between preoperative mJOA score and FA values at the level of maximal compression. Greater functional status is associated with higher FA values.

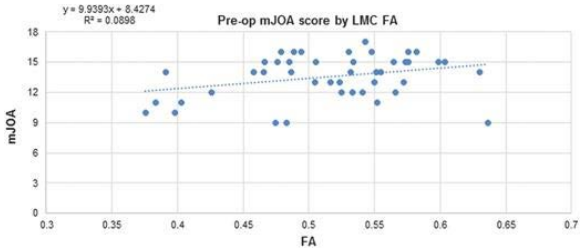
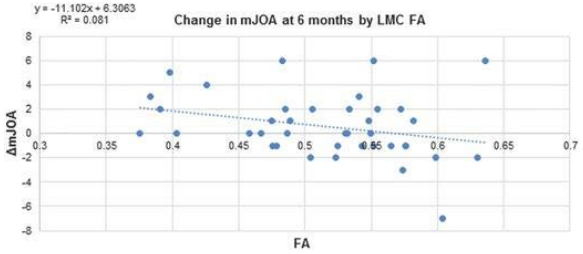


FIGURE 4. Linear regression analysis demonstrating the relationship between the change in mJOA score at 6-mo follow-up and preoperative FA values at the level of maximal compression. Lower FA values are associated with a greater functional improvement following surgery.



In the 22 CSM patients whose FA values were less than 0.55, postoperative mJOA scores improved by an average of 1.45 points. The 12 CSM patients with FA values above 0.55 declined, on average, by −0.92 points,

although the absolute mJOA values at 12 mo varied from +6 to −5. The difference in improvement between these 2 groups was statistically significant (*P* = .042).

DISCUSSION

CSM is a major cause of disability in the population above 55 yr of age. Delivering both cost-effective and efficient care is paramount in patients presenting with CSM. The generally accepted management for CSM has been decompression, either anterior or posterior, with or without fusion, depending on the level and origin of pathology.[17] The occasional futility of surgical decompression in some cases of CSM has also been described.[18] Patient selection for decompressive surgery remains a challenge, given the chronic progressive nature of the disease and the constellation of presenting symptoms, some of which are not quantifiable or amenable to objective evaluation on a neurological exam.[19]

The mJOA score has been proposed as a widely accepted clinical predictor of severity of CSM as well as outcome. In previously published work,[20] there is a positive correlation between higher baseline mJOA values and the improvement in postdecompression mJOA. Other work substantiated this finding in addition to other clinical prognosticators like age, smoking, symptom duration, and gait impairment.[21] A recent review of literature suggests symptom severity and duration are the most significant predictors of postdecompression outcomes.[22] While 17 of the papers support a positive relationship between baseline mJOA scores and the postdecompression increase in mJOA, 5 papers suggest a negative relationship and 12 showed no significant relationship at all.[22] In studies analyzing good outcomes based on reaching a minimum mJOA score of 16, the same conclusion is postulated: High initial mJOA score indicated a higher chance of achieving a postdecompression score of 16 or more.[23] In our study, we reached a statistically significant negative correlation between baseline mJOA values and the extent of improvement postdecompression (*P* = .001, Figure 7).

The lack of conclusive data and limitations in clinical exam as a marker for recovery underline the need for a noninvasive objective marker for CSM. MRI-derived T2 and T1 signal change in the spinal cord tissue had been the main focus of such work, starting with the qualitative detection of an intra-axial signal change to the more recent attempts at quantification of signal intensity, or signal change ratios. While some correlation exists from a qualitative standpoint for T1[24] and T2,[25] the quantitative results in both regards are inconsistent.[26-28] Some studies did show correlation with baseline functional status, but not with outcomes.[20],[29]

A relatively new technique is using DTI indices as a method of quantifying the degree of neurological injury and offering prognosis after decompression. This represents ongoing work by several groups starting in the early 2000s and culminating in about 14 small-sample sized studies with validated data.[30] The earlier results were also inconsistent,[31] with no correlation between the DTI indices and mJOA in CSM. More recently, such a correlation was established between FA values and baseline mJOA scores.[29],[32] The FA values from DTI showed a negative correlation with disease severity in CSM as indicated by baseline mJOA scores,[29],[33] both at the LMC and at the high cervical cord. These findings were confirmed by Guan's meta-analysis.[30]

The development of 3T scanners, reduction in artifact, and improvement in ROI selection methods and processing are yielding DTI indices that are better reflective of the microstructure of the spinal cord and its functional status.[34],[35] Although we were able to note significant association between baseline mJOA scores and FA values obtained at both the LMC and high cervical cord at C1-2, other studies have noted a lesser relationship at the LMC.[29] This could be due to the aforementioned progress in DTI scanning technology.

One prior study postulated a positive relationship between baseline FA values and the postdecompression improvement using the Neck Disability Index, but this was a small sample of 15 patients followed only for 12 mo and did not reach statistical significance. In addition, no correlation was found when mJOA was used as an alternative functional marker.[29]

With 44 enrolled patients to date, ours is the largest longitudinal study correlating preoperative DTI indices to functional recovery over 24 mo. The sample size might be responsible for not reaching statistical significance at 6 and 24 mo, despite maintaining the same trend as the 12-mo data (P = .003, Figure 5). At 6 mo, patients may still be recovering from their decompressive surgery. We present our finding of an inverse relationship between preoperative FA values at the LMC and functional improvement postdecompressive surgery: the lower the preoperative FA value, the higher the likelihood of mJOA increase postdecompression. At presentation, FA at the LMC and high cervical cord both positively correlated with mJOA scores reflecting severity of disease, and could therefore be utilized as an objective marker for disease severity. An analysis of mJOA scores at baseline and at 12 mo post decompression reveals an inverse correlation, ie, a lower presenting mJOA score predicts a greater increase in mJOA (functional improvement) postsurgery (Figure 7). This correlation is currently quite weak, but the consistency from 6 to 12 to 24 mo encourages further investigation. The study is ongoing and sample size continues to grow. The need for further investigation is highlighted by the lack of a statistically significant difference between preoperative and postoperative absolute mJOA values. Finally, patients with lower preoperative FA values experienced the greatest increases in mJOA scores following decompressive surgery, indicating that, in this large series with long-term follow-up, preoperative FA could be a prognostic biomarker for clinical improvement after surgical decompression. Above an FA value of 0.55, its usefulness as a predictive biomarker may be insignificant, likely due to approaching values seen in normal subjects. When the 2 groups of patients above and below this number were compared, there was a statistically significant difference in outcomes at 12 mo following decompressive surgery, although the group of patients with an FA score of >0.55 was small and demonstrated variable outcomes. Considerable further investigation is required to solidify the utility of FA as a determining factor in whether or not to offer surgery to a patient.

FIGURE 5. Linear regression analysis demonstrating the relationship between the change in mJOA score at 12-mo follow-up and preoperative FA values at the level of maximal compression. Lower FA values are associated wit h a greater functional improvement following surgery.

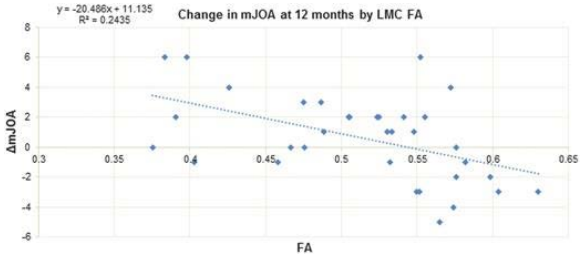


FIGURE 6. Linear regression analysis demonstrating the relationship between the change in mJOA score at 24-mo follow-up and preoperative FA values at the level of maximal compression. Lower FA values are associated with a greater functional improvement following surgery.

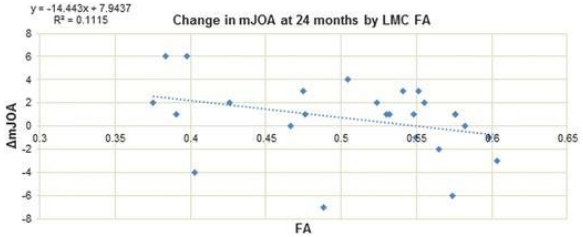
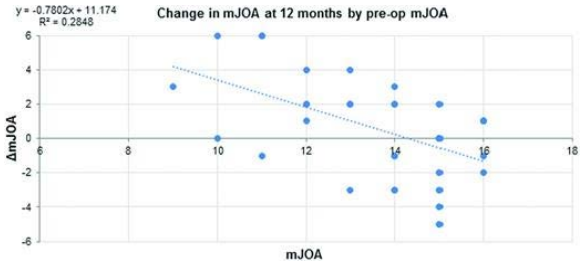


FIGURE 7. Linear regression analysis demonstrating the relationship between the change in mJOA score at 12-mo follow-up and preoperative mJOA scores. Lower preoperative mJOA values are associated with a greater increase in mJOA following surgery.



Future studies are being conducted to examine FA at C1-2 as a predictor of function postdecompression, based on a 2015 meta-analysis by Guan.[30] Additionally, exploration of newer, more refined indices including double diffusion encoding by our group[36] and diffusion basis spectrum imaging[37] might help further develop DTI to yield more accurate biomarkers predictive of outcome after decompressive surgery.

CONCLUSION

Our results demonstrate that FA has the potential to be utilized as a biomarker for the prediction of improvement following decompressive surgery of the cervical spine in CSM. There is need for additional investigations to strengthen the argument concerning the use of FA as an objective measure for measuring functional status in myelopathic conditions. It could also provide a basis for clinical decision making regarding surgical candidates and to explain to patients their expected recovery following surgery.

Disclosures

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Notes

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