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Citation

Abstract
Objective: Conventional MRI for the evaluation of cervical spondylotic myelopathy (CSM) may be poorly correlated with a patient's symptoms and prognosis. Interpretation of canal stenosis, contour deformities, and the presence or absence of T2 signal change, can make it difficult to decide who needs decompressive surgery. Diffusion tensor imaging (DTI) provides quantitative measurements that could help clarify the degree and chronicity of spinal cord disease as a result of compression from degenerative spondylosis. DTI can also detect diffusion abnormalities in areas of acute spondylotic compression occurring without T2 signal change. The purpose of this study is to compare these quantitative DTI measures (i.e. metrics) in patients with severe clinical and radiographic evidence of CSM with controls. Methods: DTI of the cervical spine was performed in 11 patients with severe radiographic and clinical multilevel spondylosis who were planned for surgical decompression versus 10 healthy volunteers (as determined by 2 neurosurgeons A.F.B. and P.R.C., and a neuroradiologist M.L.), using pulsed gradient, double spin echo, echo planar imaging. At the C2-3, C3-4 and C4-5 levels, average FA, MD, E1 (longitudinal diffusion), E2 and E3 (transverse diffusion) were calculated within regions of interest at bilateral anterior, lateral, and posterior regions of the cord. Levels caudal to C4-5 were not analyzed due to artifact on DTI. The average age of the spondylosis patients was 67.2±9.8 years vs. 33.4±15.2 years in the control group (p<.001).

Results: Fractional anisotropy (FA) and the minor transverse eigenvalues (E2 and E3) most consistently demonstrated significant differences in values between patients with radiographic and clinical CSM versus controls at C4-5. FA was the most specific in correlating with compression seen on conventional T2 imaging at C4-5; however, the minor eigenvalues showed the greatest degree of significant difference in DTI metrics when compared to controls. At C2-3, significant differences in mean diffusivity (MD) were found at the lateral and central regions as well as minor eigenvalue differences in the posterior, lateral, and central regions. There were no significant differences in the major longitudinal eigenvalue (E1) between patients with CSM versus controls. Conclusion: Minor eigenvalues and fractional anisotropy are significantly different in clinically significant spondylosis with conventional imaging evidence of compression versus controls, with preservation of the major eigenvalue. These values show promise as biomarkers of microscopic injury to the cord, which may help in the early identification of patients who would likely benefit from decompressive therapy. DTI can also provide information on the duration of cord compression in helping to distinguish reversible versus irreversible disease.

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INTRODUCTION
Cervical spondylosis is a common degenerative condition of the spine. While it is present in 75% of people over the age of 65, the vast majority of whom are asymptomatic. Conventional T2-weighted MRI is frequently used to analyze cervical spondylosis. However, prior studies report sensitivities of only 15-65% in predicting myelopathy. Furthermore, T2 signal change, often indicative of severe compression, appears in the late stages of cord compression and cervical myelopathy limiting the benefit of decompressive surgery. It would be of great benefit to the patient if the anatomic and physiologic changes due to cord compression could be identified earlier and treated before.
these changes became irreversible.

Diffusion tensor imaging (DTI) is helpful in assessing white matter abnormalities in various brain pathologies including multiple sclerosis, cancer, infection, and ischemic brain injury. The use of DTI in spinal cord pathology has been limited due to susceptibility effects of CSF motion, cardio-pulmonary cycles, and surrounding bony structures. Several investigators have explored the use of DTI in the evaluation of spinal cord lesions, including trauma, multiple sclerosis, and spondylosis. To our knowledge, there is limited published data on using the major and minor eigenvalues from DTI in characterizing spinal cord damage due to spondylosis.

Using individual eigenvalues for cord diffusion, it may be possible to detect very early changes in cord edema before changes are detectable on conventional T2-weighted imaging. This will be of benefit in triaging patients for earlier decompression. We hypothesize that these DTI metrics will be significantly altered in patients with severe spondylosis versus controls. The major eigenvalue (E1) represents longitudinal white matter diffusion and minor eigenvalues (E2 and E3) represent transverse collateral white matter diffusion perpendicular to the long axis of the cervical spine. The ultimate purpose of our study is to compare these eigenvalues, fractional anisotropy, and mean diffusivity in patients with severe spondylosis versus controls.

TERMINOLOGY

DTI is a relatively new application in spinal cord imaging, not commonly used in the neurosurgical evaluation of cervical spondylotic myelopathy (CSM). In simple terms, DTI provides the ability to detect the direction and ease of water movement in neural tissue. The direction and degree of water movement is not equal in all parts of neural tissues and can also change with age and in pathologic states. Isotropic diffusion describes water diffusion which is equal in all directions (i.e. Brownian motion). Anisotropic diffusion describes highly ordered water movement along one direction. Fractional anisotropy (FA) is a diffusion index measuring the degree of order in the diffusion of water where 0 represents isotropic diffusion and a value of 1.0 represents complete anisotropic diffusion. Mean diffusivity is a measurement of the overall mobility of water. The movement of water can be further described in a series of mathematical terms. Scalar refers to a variable that has magnitude but no direction (e.g. the speed of a water molecule along an axon). A vector has both magnitude and direction (e.g. the speed of a water molecule traveling caudally along an axon). Linear transformation describes the mathematical equation which combines multiple vectors into one where the magnitude of these combined vectors is described by an eigenvalue.

METHODS

STUDY SUBJECTS

Approval for this study was obtained from the Institutional Board of Research Associates. Informed consent was obtained from all study subjects. DTI of the cervical spine was performed in 10 healthy volunteers and in 11 patients with symptomatic myelopathy with severe multilevel spondylosis on conventional MRI imaging, as determined by two neurosurgeons (A.F.B. and P.R.C.) and a neuroradiologist (M.L.) at our institution. The average age of the spondylosis patients was 67.2 ± 9.8 years (average ± standard deviation) vs. 33.4 ± 15.2 years in the control group. There were 4 males and 6 females in the control group and 6 males and 5 females in the spondylosis group.

Control subjects had no history of prior central nervous system disease.

MR IMAGING AND DATA PROCESSING

DTI of the cervical spine was performed at 1.5 Tesla using pulsed gradient, double spin echo, echo planar imaging (repetition time [TR]/echo time [TE], 2000/74; 128x128 matrix; 140x140 mm field of view; 10 contiguous 4 mm slices; b= 1000 s/mm²; 2 minutes, 20 seconds acquisition time, using a parallel imaging with an IPAT factor of 2). Leonardo VD10B software on a Syngo VX49B imaging software platform (Siemens Medical Solutions, Erlangen, Germany) was used to process the images. Fractional anisotropy (FA) and mean diffusivity (MD) were calculated using the following formulas:

\[
FA = \frac{\sqrt{3}}{\sqrt{2}} \frac{\sqrt{(E_1 - E)^3 + (E_2 - E)^3 + (E_3 - E)^3}}{E_1^2 + E_2^2 + E_3^2} \quad [1]
\]

\[
MD = \frac{E_1 + E_2 + E_3}{3} \quad [2]
\]

Six regions of interest (ROIs) were placed at each of the C2-3, C3-4, C4-5 levels, corresponding to the white matter’s left and right anterior, left and right lateral, and left and right
posterior regions (Figure 1).

**Figure 2**

Figure 1

The C5-6 level and below were not able to be analyzed due to artifact. A small distance between the ROIs and the edge of the spinal cord was maintained to avoid CSF partial volume effects. A seventh ROI was placed centrally to cover both the gray and white matter.

**CALCULATIONS**

At the C2-3, C3-4 and C4-5 levels, average FA, MD, and the three principle eigenvalues (E1, E2 and E3) were calculated within paired ROIs at the anterior, lateral, and posterior regions of the spinal cord in the axial plane. These same values were also calculated for the central ROI, which included both gray and white matter. E2 and E3 values were averaged to represent diffusion perpendicular to the axis of the spinal cord. The statistical significances of the computed DTI metrics of gray versus white matter as well as that of the different white matter regions were assessed using a paired, double-tailed Student’s t test (p < 0.05 was considered statistically significant).

**RESULTS**

DTI analysis of the spinal cord was done in the axial plane (E2 and E3). There were no significant differences in laterality (left vs. right). Cranial versus caudal diffusion values (E1) were averaged and were not significantly different. Analysis of longitudinal diffusion (E1) showed no significant differences between spondylosis patients versus controls (Table 1).

**Table 1.** Major Eigenvalue (E1). There were no statistically significant differences in the major Eigenvalue between the normal volunteers and the spondylosis patients in either region of any of the spinal levels.

<table>
<thead>
<tr>
<th>Level</th>
<th>Anterior</th>
<th>Posterior</th>
<th>Lateral</th>
<th>Central</th>
</tr>
</thead>
<tbody>
<tr>
<td>C2-3</td>
<td>Cases</td>
<td>1.97 ± 0.19</td>
<td>1.56 ± 0.21</td>
<td>1.66 ± 0.30</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>1.58 ± 0.24</td>
<td>1.52 ± 0.24</td>
<td>1.62 ± 0.25</td>
</tr>
<tr>
<td></td>
<td>P-value</td>
<td>0.07</td>
<td>0.12</td>
<td>0.12</td>
</tr>
<tr>
<td>C3-4</td>
<td>Cases</td>
<td>1.60 ± 0.46</td>
<td>1.65 ± 0.26</td>
<td>1.68 ± 0.34</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>1.50 ± 0.21</td>
<td>1.58 ± 0.26</td>
<td>1.59 ± 0.29</td>
</tr>
<tr>
<td></td>
<td>P-value</td>
<td>0.3</td>
<td>0.32</td>
<td>0.23</td>
</tr>
<tr>
<td>C4-5</td>
<td>Cases</td>
<td>1.46 ± 0.30</td>
<td>1.51 ± 0.31</td>
<td>1.48 ± 0.32</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>1.42 ± 0.19</td>
<td>1.57 ± 0.26</td>
<td>1.51 ± 0.29</td>
</tr>
<tr>
<td></td>
<td>P-value</td>
<td>0.41</td>
<td>0.46</td>
<td>0.72</td>
</tr>
</tbody>
</table>

The minor eigenvalues (E2 and E3) showed strikingly significant differences between spondylosis patients and controls in all regions of interest at C4-5 (Table 2).

**Table 2.** Minor Eigenvalues (E2, E3). There was a significant difference between the normal volunteers and the spondylosis patients in each of the spinal cord regions at the C4-5 level.

<table>
<thead>
<tr>
<th>Level</th>
<th>Anterior</th>
<th>Posterior</th>
<th>Lateral</th>
<th>Central</th>
</tr>
</thead>
<tbody>
<tr>
<td>C2-3</td>
<td>Cases</td>
<td>0.86 ± 0.21</td>
<td>0.54 ± 0.17</td>
<td>0.52 ± 0.24</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>0.85 ± 0.17</td>
<td>0.46 ± 0.13</td>
<td>0.39 ± 0.14</td>
</tr>
<tr>
<td></td>
<td>P-value</td>
<td>0.62</td>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td>C3-4</td>
<td>Cases</td>
<td>0.81 ± 0.26</td>
<td>0.56 ± 0.15</td>
<td>0.48 ± 0.15</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>0.82 ± 0.18</td>
<td>0.56 ± 0.15</td>
<td>0.43 ± 0.16</td>
</tr>
<tr>
<td></td>
<td>P-value</td>
<td>0.85</td>
<td>0.14</td>
<td>0.51</td>
</tr>
<tr>
<td>C4-5</td>
<td>Cases</td>
<td>0.86 ± 0.21</td>
<td>0.58 ± 0.18</td>
<td>0.54 ± 0.24</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>0.52 ± 0.16</td>
<td>0.38 ± 0.13</td>
<td>0.29 ± 0.12</td>
</tr>
<tr>
<td></td>
<td>P-value</td>
<td>0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

In addition, significant differences were also seen in the posterior, lateral, and central ROIs at C2-3. Significant differences in fractional anisotropy were seen only at the C4-5 level where, like the minor eigenvalues, the ROI’s had the greatest magnitude of difference in the posterior and lateral regions (Table 3).
Table 3. Fractional Anisotropy (FA) There was a significant difference between the normal volunteers and the spondylotic patients in each of the spinal cord regions at the C4-5 level.

<table>
<thead>
<tr>
<th>Level</th>
<th>Anterior</th>
<th>Posterior</th>
<th>Lateral</th>
<th>Central</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>0.51 ± 0.06</td>
<td>0.60 ± 0.07</td>
<td>0.65 ± 0.10</td>
<td>0.52 ± 0.09</td>
</tr>
<tr>
<td>Controls</td>
<td>0.52 ± 0.07</td>
<td>0.64 ± 0.09</td>
<td>0.79 ± 0.09</td>
<td>0.55 ± 0.06</td>
</tr>
<tr>
<td>P-value</td>
<td>0.59</td>
<td>0.06</td>
<td>0.1</td>
<td>0.39</td>
</tr>
</tbody>
</table>

Mean diffusivity measurements showed significant differences between control and spondylotic patients at C2-3 in the lateral and central ROIs and at C4-5 in the anterior and central ROIs (Table 4).

Table 4. Mean Diffusivity (MD). There was a significant difference between the normal volunteers and the spondylotic patients at the lateral and central regions at the C2-3 level and in the anterior and central regions at the C4-5 levels.

<table>
<thead>
<tr>
<th>Level</th>
<th>Anterior</th>
<th>Posterior</th>
<th>Lateral</th>
<th>Central</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>0.56 ± 0.07</td>
<td>0.64 ± 0.08</td>
<td>0.69 ± 0.09</td>
<td>0.59 ± 0.08</td>
</tr>
<tr>
<td>Controls</td>
<td>0.52 ± 0.07</td>
<td>0.63 ± 0.08</td>
<td>0.68 ± 0.08</td>
<td>0.57 ± 0.06</td>
</tr>
<tr>
<td>P-value</td>
<td>0.18</td>
<td>0.08</td>
<td>0.38</td>
<td>0.65</td>
</tr>
</tbody>
</table>

At C4-5, correlations of age as the independent variable and FA or MD as the dependent variable were performed. FA in both groups showed a decrease, which was greater in the spondylotic patients as a function of age (Figures 2 & 3).

Mean diffusivity showed a gradual increase in the normal patients (Figure 4) and a trace decrease as a function of age in the spondylotic patients (Figure 5).
DISCUSSION

Patients who benefit most from surgical decompression for CSM are those who are identified early—before irreversible myelopathy occurs. Unfortunately, on conventional MRI sequences, contour deformities, degree of canal stenosis, or presence of T2 signal change often poorly correlate with a patient’s clinical signs and symptoms. T2 signal change is reported to be present 16-65% of patients with cervical myelopathy and also exists in up to 30% of asymptomatic patients. In a paper by Matsumoto et al., it was shown in 52 patients with mild cervical myelopathy neither signal change nor reduced cross-sectional spinal cord area was predictive of clinical outcome and that early surgical decompression is not necessarily warranted by the presence of either of these factors. The degree of canal stenosis and contour deformity can be rather subjective and should not be used as the sole determinant of who would benefit from decompressive surgery.

Several authors have speculated on the meaning of signal change on conventional MRI stating that it could represent edema, inflammation, gliosis, or myelomalacia depending on the nature and timing of spinal cord disease. DTI of the cervical spinal cord provides quantitative information, which can clarify the nature and chronicity of this signal change. This information in combination with a clinician’s evaluation of stenosis, contour deformity, and signal change (if present) on MRI could improve the sensitivity of using image findings to predict the clinical manifestations of CSM. For instance, DTI can detect abnormal diffusion in areas where T2 signal change is absent potentially allowing clinicians to identify surgical candidates earlier. In a study by Facon et al., DTI provided information regarding the timing of compressive spondylotic spinal cord disease. They reported that FA and ADC (apparent diffusion coefficient) values could differentiate acute versus chronic compression of neural tissue. For example, FA, which measures the degree of anisotropic flow within white matter tracts, was found to be increased in early spinal cord compression and decreased in later stages of compression. In early compression, extracellular water is displaced into cells leading to decreased ADC and higher FA values as a result of cellular edema and tighter packing of axon bundles. These changes model the diffusion changes of the brain in acute versus chronic infarct. With prolonged compression and neuronal death, there is cell lysis, demyelination, gliosis, cystic degeneration, edema, and Wallerian degeneration leading to an outflow of water into the expanded extracellular space leading to increased ADC and lower FA values.

Thus, CSM patients with imaging evidence of compression who present with higher FA and lower ADC values have acute compression may be more likely to recover with surgery than patients with similar imaging with low FA and high ADC values likely representative of gliosis or myelomalacia.

In our study, FA did not differ from controls at C2-3 or C3-4, but showed significant decreases in value versus
controls at the C4-5 level, which most consistently demonstrated radiographic spinal cord compression in the levels analyzed in our disease group. This data is encouraging as it implies that DTI metrics correlate strongly with known location of disease. Mamata et al. made a similar finding and noted that the average ADC increases and FA decreases significantly versus controls in high signal lesions, due to compression, on T2-weighted images. It is important to note that one of the differences between our study and that of others cited in this paper is that we used axial ROIs while others used sagittal images. Using sagittal images, ROIs tend to include more grey matter in measurements of intended white matter diffusion. Hence, depending on the imaging technique (axial versus sagittal), DTI values which significantly differentiate normal from abnormal may vary from study to study.

We found that mean diffusivity significantly differed at the anterior and central ROIs of the C4-5 level. MD also showed significant changes at the lateral and central regions of C2-3. This finding is unusual in that spondylotic compression generally does not occur at this level. These MD values are likely a product of CSF distortion as the naturally widened canal in the upper cervical spine allows for more CSF pulsation artifact to affect volume averaging when making quantitative measurements in the cord. As the canal narrows at C3-4, this effect is minimized. It is also possible that there is an element of retrograde Wallerian degeneration, where spondylodyasis and myelopathy at a lower level within the cervical spine may result in changes along the spinal tracts within the spinal at more rostral levels. Thus, in using DTI of the spine, the clinician must analyze all metrics (i.e. FA, ADC, eigenvalues, etc.) in conjunction with T2 sequences and the clinical exam to avoid being misled by data that may have been distorted by artifact.

The preservation of E1, or longitudinal diffusion, reflects the maintenance of axonal integrity. The often slow microvascular and microstructural changes associated with cervical spondylodyasis may be insufficient to significantly affect longitudinal diffusion along axons. This makes sense as CSM usually manifests insidiously over several years to decades with progressive motor and sensory disturbances and not acute paraplegia. Animal evidence has shown that it takes a powerful neurotoxin like Cuprizone (a copper chelator which destroys myelin) in order to decrease E1 in the mouse corpus callosum. Unlike this toxin, degenerative cord compression causes a lesser and more gradual degree of damage to the white matter tracts and is reflected by significant changes in the minor eigenvalues, E2 and E3, which represent transverse water diffusion within the spinal cord. The magnitude of significant differences in minor eigenvalues at C4-5 was greater than that of any other DTI metric used in this study—again consistent with the presence of maximal spinal cord compression at the C4-5 level in the levels analyzed in our study group.

DTI metrics may provide novel biomarkers in the radiographic evaluation of CSM. The goal of this paper is to examine the relationship between these markers and a group of patients with clinical and conventional MRI findings of CSM. With that in mind, we need to discuss the shortcomings of this study. We were not able to analyze the cervical spinal cord below C4-5 due to coil design and pulsation artifact. Several studies have shown, however, that C4-5 is commonly affected in multilevel cervical spondylodyasis and all 11 patients in our study had compression at that level.

There is also a statistical difference between the ages of the patients in the spondylodyasis group versus the control group (p < 0.001). The mean age for the spondylodyasis patients is 67 years versus 33 years for the controls. When reviewing our database it was not possible to find a 67 year-old patient with a normal spine. There is usually, if not always, an element of spondylodyasis in the aging patient with varying degrees of stenosis. To ensure that we were comparing patients with stenosis with those having nonstenotic canals, our controls had to be younger patients. Investigators have shown a slight age-related decline in FA. However, the degree of change between the two groups in our study is far greater than that seen in prior studies in which the effect of age was examined. As demonstrated in Figures 2 and 3, in both the control and spondylodyasis groups, FA showed an inverse relationship with age. MD showed an age-related trace increase in the control group, but marginally decreased in the spondylodyasis group. This implies that although the average ages between our study groups significantly differ, age does not seem to independently affect the DTI values within the framework of our analysis.

A second limitation is the relatively small number of patients and controls studied. We are in the process of combining multi-center datasets to increase the number of patients and this will be published in a separate paper. Finally, we were not able to accurately analyze the cervical spinal cord below C4-5 (where there is usually maximal cord compression) due

to coil design and pulsation artifact. Improvements in coil design as well as faster-navigated pulse sequences are being developed which will allow examination of the lower cervical spinal cord.

CONCLUSION

The uniform increase in the minor eigenvalues in cervical spondylosis patients represents a novel biomarker of this disease. These biomarkers can help elucidate the anatomic and physiologic changes in the spinal cord parenchyma due to spondylotic compression earlier and describe the nature of spinal cord signal change better than routine T2-weighted imaging. Currently, there are efforts to overcome the technical limitations of DTI imaging of the spine at our institution (e.g. coils to image the entire cervical spine in the axial plane and sequence modification to minimize hardware artifact on post operative imaging). As these limitations are overcome with future innovations, DTI of the spine could become a powerful adjunct in the diagnosis, triage, and surgical treatment of CSM.

References

28. Sun SW, Liang HF, Trinkaus K, Cross AH, Armstrong...


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