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MUSCULOSKELETAL

Diffusion tensor imaging and fibre tracking in cervical spondylotic myelopathy

Jean-François Budzik · Vincent Balbi · Vianney Le Thuc · Alain Duhamel · Richard Assaker · Anne Cotten

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Abstract
Objectives To (1) obtain microstructural parameters (Fractional Anisotropy: FA, Mean Diffusivity: MD) of the cervical spinal cord in patients suffering from cervical spondylotic myelopathy (CSM) using tractography, (2) to compare DTI parameters with the clinical assessment of these patients (3) and with information issued from conventional sequences.
Methods DTI was performed on 20 symptomatic patients with cervical spondylotic myelopathy, matched with 15 volunteers. FA and MD were calculated from tractography images at the C2-C3 level and compressed level in patients and at the C2-C3 and C4-C7 in controls. Patients were clinically evaluated using a self-administered questionnaire.
Results The FA values of patients were significantly lower at the compressed level than the FA of volunteers at the C4-C7 level. A significant positive correlation between FA at the compressed level and clinical assessment was demonstrated. Increased signal intensity on T2-weighted images did not correlate either with FA or MD values, or with any of the clinical scores.
Conclusion FA values were significantly correlated with some of the patients' clinical scores. High signal intensity of the spinal cord on T2 was not correlated either with the DTI parameters or with the clinical assessment, suggesting that FA is more sensitive than T2 imaging.

Keywords Diffusion tensor imaging · Cervical spondylosis · Tractography · Clinical correlation · Fractional nisotropy

Abbreviation

DTI	Diffusion Tensor Imaging
DT	Diffusion Tensor
CSM	Cervical Spondylotic Myelopathy
MR	Magnetic Resonance
FA	Fractional Anisotropy
MD	Mean Diffusivity
ADC	Apparent Diffusion Coefficient
JOACMEQ	Japanese Orthopaedic Association Cervical Myelopathy Evaluation Questionnaire
ROI	Region of Interest
DTI-FT	Fibre Tracking (with Diffusion Tensor Imaging)

Introduction

Cervical spondylotic myelopathy (CSM) is a common disease caused by chronic segmental compression of the spinal cord due to spondylotic changes. It can lead to severe functional impairment, requiring surgery. MR imaging represents the best imaging technique for the assessment of this disorder.. However, discrepancies between clinical features and signal intensity of the spinal cord on both T1-

J.-F. Budzik · V. Balbi · V. Le Thuc · A. Cotten (✉)
Service de Radiologie et d'Imagerie Musculosquelettique,
Hôpital Roger Salengro,
59037 Lille, France
e-mail: anne.cotten@chru-lille.fr

A. Duhamel
Université de Lille,
UDSL, EA2694,
59037 Lille, France

R. Assaker
Département de Neurochirurgie, Hôpital Roger Salengro,
59037 Lille Cedex, France

and T2-weighted sequences have been reported [1–3]. The transverse area measurement of the cervical canal has been found useful [4], but the measurement method has some influence on the clinical correlation [5] and this technique does not assess the functional reduction of the canal during the cervical spinal motion, which has a predominant role in the natural course of myelopathy [6, 7].

For these reasons, a new imaging approach is required for the assessment of CSM. Several studies using diffusion-tensor imaging (DTI) [8–10] have reported changes in the DTI parameters in patients with CSM. Indeed, this technique may show microstructural parameters abnormalities that are beyond the resolution of conventional MR techniques for spinal cord impairment assessment, but to the best of our knowledge there are no series using tractography amongst this population. Only one study performed on volunteers has evaluated the intra-and inter-observer agreement of region of interest (ROI) and tractography for the measurement of DT parameters [11]. They were low with ROI and excellent with tractography. Moreover, as far as we know, there are no studies correlating DTI parameters with clinical parameters.

The aims of this study were to (1) demonstrate how microstructural parameters (FA and MD) of the cervical spinal cord in patients suffering from cervical spondylotic myelopathy can be obtained by means of tractography, (2) compare DTI parameters with the clinical assessment of these patients and (3) compare DTI parameters with the signal intensity of the spinal cord achieved with conventional MRI sequences.

Materials and methods

The study was approved by the local ethics committee. Each volunteer or patient gave written consent.

Subjects

Patient inclusion criteria were (a) clinical symptoms of cervical myelopathy and (b) qualitative evidence of cervical canal narrowing on conventional radiographs, computed tomographic (CT) or MR images. Exclusion criteria were (a) other known neurological diseases and/or (b) absence of cervical canal narrowing on conventional radiographs, CT or MR images and/or (c) cervical spine surgery. Patients were selected by a neurosurgeon. A total of 20 patients met our criteria and were included (10 men, 10 women; mean age: 57.3 years; range 34 to 78 years). All were from the neurosurgery outpatient clinic. The severity of their myelopathy was evaluated according to the Japanese Orthopaedic Association Cervical Myelopathy Evaluation Questionnaire (JOACMEQ) [12, 13]. Twenty-four questions assessed five different functional areas, defined as follows: the upper limbs, the lower limbs, the cervical spine, the bladder and quality of life. Each patient completed the questionnaire on the day of the MRI examination. A score was assigned to each of the five areas. The overall score ranged from a minimum of 0 to a maximum of 100, with a low score indicating a high level of dysfunction.

The patients were matched to 15 volunteers according to age and sex (eight men, seven women; mean age: 54.8 years; range: 35–73 years). All volunteers were asymptomatic, did not suffer from any disease and had not received any drugs liable to alter sensory or motor function.

MR imaging parameters

All MRI were performed on a 1.5 T full-body system (Achieva, Philips, The Netherlands). Sense spine coils were used for all images. The MRI protocol consisted of a sagittal T1-weighted (TR = 390 ms; TE = 12 ms) sequence and sagittal and axial T2-weighted (TR = 3500 ms; TE = 120 ms) sequences. A sagittal DTI sequence was then acquired. The DTI acquisition was based on single-shot Echo Planar Imaging (EPI factor = 111). SPIR (Spectral Presaturation with Inversion Recovery) was used to suppress the fat signal. Diffusion was measured in 25 directions; the b-factor was 900 mm^2/s. The image acquisition parameters were as follows: TE = 94 ms, TR = 2010 ms, FOV = 200 × 200 × 36 mm, partial Fourier acquisition (half-scan factor = 0.6179), recon matrix = 128 × 128, phase encoding AP. The bandwidth in the frequency direction was 1595 Hz/pixel. Twelve transverse slices were acquired without any spacing. The in-plane image resolution was 1.56×1.56 mm with a 3-mm-thick slice. This sequence lasted 3 min and 33 s. Another sagittal T2-weighted acquisition was used to match the anatomical location of the DT images; the same FOV, slice thickness, gap and slice number as for the DT images were used.

Diffusion registration

Eddy current and motion-related misalignment of the diffusion tensor MR images were corrected off-line using Automated Image Registration software (Philips pride Diffusion Registration and IDL, ITT, Boulder, CO, USA). All diffusion-weighted images were reorientated to match the b0 images. This preliminary co-registration procedure helped to minimise distortions and artefacts, and to achieve proper alignment before image analysis.

Data analysis

Two radiologists, both experienced in DTI analysis, independently performed the data analysis.

DTI post-processing was performed by successively using two different software programs. First, the data were analysed using MEDINRIA (Asclepios Research Project—INRIA Sophia Antipolis—http://www-sop.inria.fr/asclepios/). The first step consisted of determining the b0 threshold in order to eliminate artefactual voxels corresponding to noise. The FA map was then automatically calculated. Several parameters had to be determined. We chose 200 (corresponding to 0.2) as the FA threshold, with the aim of excluding as many extra-spinal voxels as possible without excluding the voxels of the diseased spinal cords. The minimum fibre length was 10 mm (smaller fibres were excluded). The volume under study was then manually restricted to the spine using a cropping box. The algorithm was based on an extraction of the principal diffusion direction (PDD) of the tensor field in the regions where the diffusivity was highly linear and a vector based tracing scheme [14, 15]. The resulting fibre was saved.

The second step consisted of obtaining DTI values from the fibre at the levels of interest. To achieve this, we used FiberViewer 1.2.3 software (http://www.ia.unc.edu/dev/index.php; http://www.ia.unc.edu/dev/download/fiberviewer/index.htm). This second software program was used to extract the FA and MD from the tractography images. No ROI positioning was necessary as a semi-automatic axial stratified analysis calculation of FA and MD was made (Mean Diffusivity corresponds to one third of the trace of the diffusion tensor [16]). These values could be visualised on a curve next to the Fibre Tracking (DTI-FT) 3D image.

In patients, we studied the spinal cord at the narrowed level, identified on T1 and T2 sequence. In controls, we studied C4-C7 corresponding to the narrowed levels in patients. The values corresponding to each volume were reported on a chart, thanks to which the average MD and FA could be calculated for each volume studied. We obtained average MD and FA values for compressed level and C2-C3 level in patients, and for the C2-C3 and C4-C7 volumes in volunteers. FA and MD measurements were compared by two radiologists to assess inter- and intra-observer agreement.

The presence of increased signal intensity on T2-weighted sequences or of decreased signal intensity on T1-weighted sequences in the spinal cord was also systematically analysed.

Statistical analysis

Statistical tests were performed with SAS software (SAS Institute Inc., Cary, NC 25513).

We compared FA and MD values between the C2-C3 and C4-C7 levels in volunteers, and between the C2-C3 and pathological levels in patients. We also compared the FA and MD values of the pathological level in patients with those obtained at the C4-C7 level in volunteers. In addition, FA and MD values in C2-C3 were compared in volunteers and patients. Mann-Whitney *U* test for independent samples and Wilcoxon test for paired samples were used to perform non-parametric analysis.

In patients, we looked for a correlation between DT values obtained at both levels and age, sex, JOACMEQ clinical scores, number of pathological levels and abnormal signal intensity on T1-/T2-weighted images with Spearman correlation coefficient. The threshold values for FA and MD were outlined by a ROC curve to better separate patients from controls.

Fermanian and Fleiss methods were used to assess the intra- (Ro) and inter (R)-observer agreement of FA and MD measurements [17]. A measurement was deemed highly reproducible for Ro >0.91. The reproducibility was considered good in the case of 0.71< Ro <0.91; moderate for 0.51< Ro <0.71. Ro <0.51 was interpreted as being poorly reproducible. $P<0.05$ was considered statistically significant.

Results

DTI-FT images provided a good depiction of the cervical spinal cord in all controls and patients. Spinal cord compression sites were clearly identified (Figs. 1, 2, 3). FA and MD values could be extracted from DTI-FT images in all controls and patients. These values are indicated in Tables 1 and 2.

Comparison of FA and MD in patients and volunteers

In healthy volunteers, FA was significantly lower ($p=0.0006$) at C4-C7 than at C2-C3, with a mean difference of 0.03, but there was no significant difference in MD between the two levels.

In patients, the FA was significantly lower at the pathological level than at the C2-C3 level ($p<0.0001$) with a mean difference of 0.106. The FA at the pathological level was also significantly lower ($p=0.0003$) than that of volunteers at the C4-C7 level (mean difference=0.094). The MD was significantly higher ($p<0.0001$) at the narrowed level than at the C2-C3 level with a mean difference of 0.140. No significant difference in MD was found between patients and volunteers. No significant difference in either FA or MD at C2-C3 was found between patients and volunteers.

Correlation between DTI parameters and clinical findings

The average scores of the JOACMEQ evaluation are given in Table 3. There was a significant positive correlation between FA at the narrowed level and respectively at lower

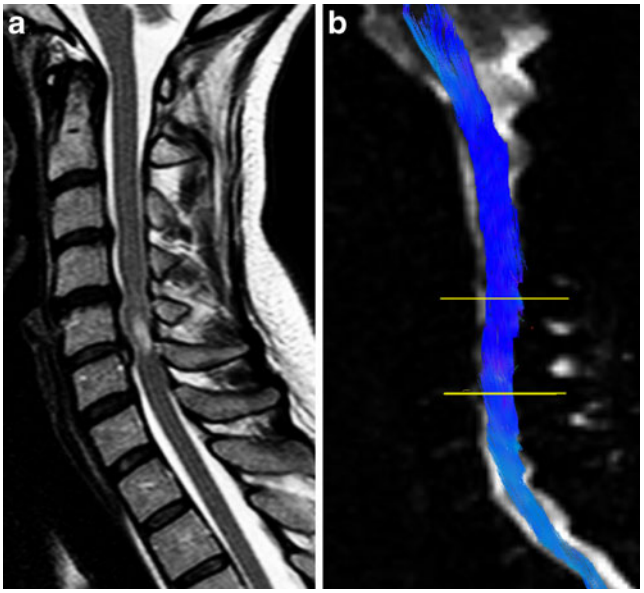

Fig. 1 MR image of the spine in a 39-year-old woman. Sagittal T2-weighted image shows ill-defined increased signal intensity of the spinal cord (**a**); DTI-FT image shows limited stenosis contrasting with the high signal intensity seen on the sagittal T2-weighted image (**b**). Mean FA in this area is measured 0.47, which is one of the highest FA values in our patients. This case illustrates that, despite a high signal intensity of the spinal cord on T2, tractography and FA suggest that the microstructure of the spinal cord is preserved. These findings are in agreement with the moderate clinical impairment (JOACMEQ scores of 95/100 for upper limbs and 59/100 for lower limbs)

(p=0.0002) and upper (p=0.0009) extremity function. Such a correlation was also observed at the C2-C3 level (p=0.0001 and p=0.0081 respectively). FA was not correlated with the other clinical scores, nor was MD.

Correlation between DTI parameters and conventional imaging findings

On conventional sequences, the average number of narrowed levels was two (minimum 1, maximum 4); 10 patients (50%) had increased signal intensity of the spinal cord on T2-weighted images; 2 patients (10%) had decreased signal intensity on T1-weighted images; no abnormal signal intensity was identified at C2-C3 level on T1/2-weighted images. Increased signal intensity on T2-weighted images did not correlate either with FA or MD values. Increased signal intensity on T2-weighted images or decreased signal intensity on T1-weighted images did not correlate with any of the clinical scores. The two patients with decreased signal intensity on T1-weighted images clearly had lower FA values at the pathological site compared with healthy volunteers (0.34 and 0.38 versus 0.503), but with such a small number of patients that no statistical analysis could be carried out.

A significant negative correlation was found between FA and the number of narrowed levels (p=0.0263 at C4-C7 and p=0.011 at C2-C3), and between FA at C4-C7 and the age of the patients (p=0.0166). No correlation was found between MD and the previous two elements. Sex was not correlated with either FA or MD.

Inter-observer agreement was excellent, with R=0.95 and 0.98 respectively for FA and MD. Intra-observer agreement was excellent as well, with Ro=0.97 and 0.99 respectively for FA and MD.

Discussion

Diffusion Tensor Imaging has already proved to be able to identify microstructural changes in cervical spondylotic myelopathy [8–10], as in other various cervical spine disorders [18–21] thanks to changes in DT parameters. However, to the best of our knowledge, there are no studies correlating DTI parameters with clinical scores, and no studies using tractography for extracting the DTI parameters in this population of patients. Nevertheless, this measurement method seems more reliable [11].

Extracting DT values using tractography

As far as we know, this is the first study performed in patients suffering from CSM that measures FA and MD values on tractography images instead of using Regions of Interest (ROI). Indeed, most DTI studies carried out on the

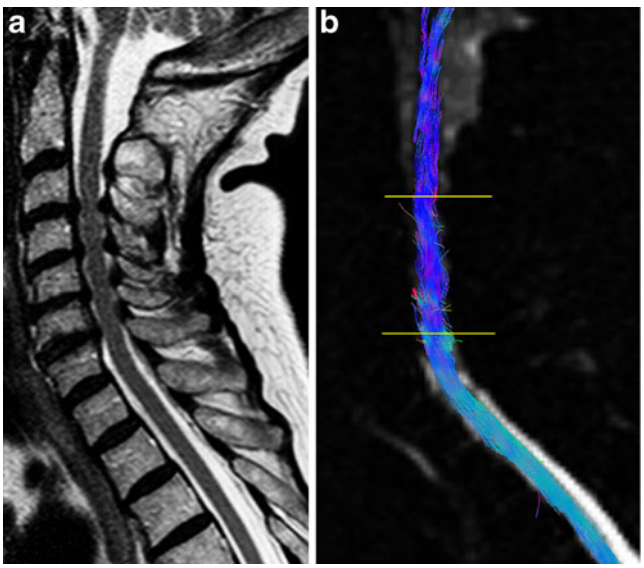

Fig. 2 MR image of the spine in a 52-year-old man. Sagittal T2-weighted image shows no abnormal signal intensity on T2-weighted (**a**). DTI-FT shows ill-defined spine outline (**b**). Histogram shows that FA drops on the whole compressed segment, with a mean value of 0.38. The JOACMEQ scores for upper and lower limbs are low (68 and 55 respectively). This example shows that, despite a normal signal on T2, the FA of the spinal cord is lower than that of the patient in Fig. 1

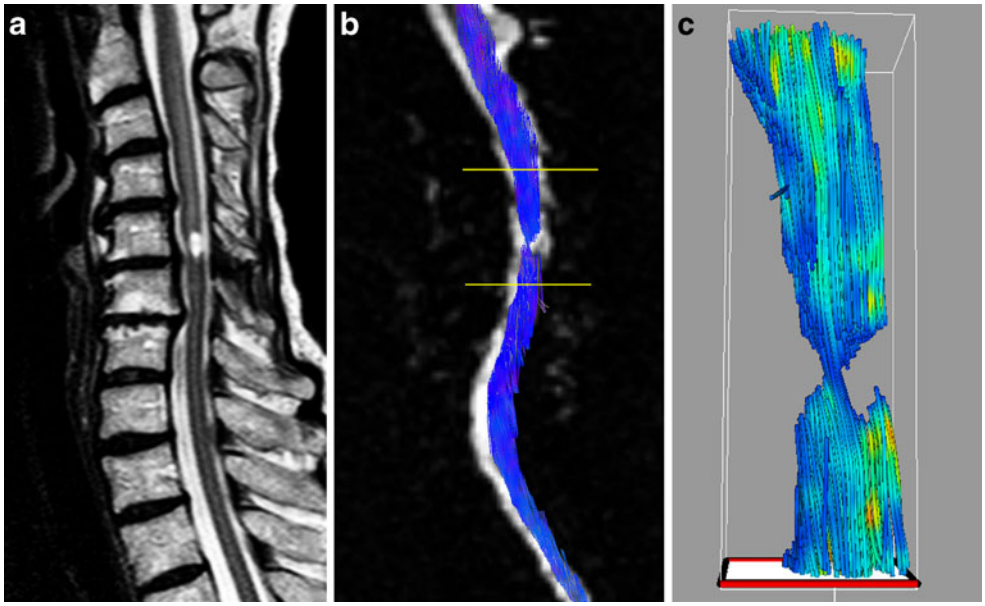

Fig. 3 MR image of the spine in a 59-year-old woman. Sagittal T2-weighted image shows increased signal intensity of the spinal cord (**a**); fibres interruption (suggesting that the tissue became isotropic) and spinal narrowing on DTI-FT images (**b**); A blown-up image of the tractography in the area of compression is seen on (**c**) with an important FA drop at the compressed site (FA = 0.35) on the FA histogram of the segmented spinal cord. The patient has severe functional impairment with JOACMEQ scores of 16/100 for the upper extremities and 9/100 for the lower extremities. In this other example, tractography and FA suggest that the high signal on T2 images represents cavitations and necrotic changes

spinal cord use ROI measurements [8, 10, 13, 22, 23]. The latter method involves manually drawing a circle or ellipsoid representing the ROI on DT images. Partial volume effects have to be avoided, as the inclusion of adjacent highly isotropic cerebrospinal fluid in the ROI can dramatically decrease FA and increase MD values. The use of ROIs smaller than the spinal cord appears to be a good solution to avoiding this problem [8, 18, 22]. However, histopathological studies have demonstrated that the distribution of the lesions is not homogeneous inside the spinal cord. As a consequence, excluding the peripheral part of the spine may imply losing essential information. Moreover, as far as we know, only one study performed on volunteers has evaluated the intra- and inter-observer agreement of both techniques for the measurement of DT parameters [11]. They were low with ROI and excellent with tractography. This is the reason why we chose a DTI-FT-based approach rather than a ROI method. As in the former study, we obtained excellent intra- and inter-observer agreement. The b value of 900 s/mm^2 was chosen on the basis of a recent study [24]. MD was used because it is independent of the choice of directions made for the measurements, contrary to ADC [16].

Table 1 Healthy volunteers

Level	C2-C3	C4-C7
FA	0.537±0.035	0.503±0.039
	0.549 [0.47–0.59]	0.51 [0.42–0.545]
MD	0.782±0,17	0.824±0.13
	0.77 [0.44–1.03]	0.816 [0.56–0.99]

First line: FA and MD mean values at C2-C3 and C4-C7 levels, associated with standard deviation. Second line: Median value and range

FA and MD in control subjects

In agreement with previous studies [10, 11, 22], we found a significant decrease in FA in C4-C7 compared with C2-C3 in healthy volunteers. Several hypotheses have been suggested to explain this difference: a higher percentage of large-diameter axons in the proximal spine [22], a higher grey/white matter ratio at the C4-C7 level or different partial volume effects resulting from different spinal calibre [10]. The technique we used probably explains the lower values (0.51–0.53) we found in healthy volunteers compared with other studies using ROI measurements (0.55–0.745) [18]. Indeed, the FA values depend on several factors, including the number of gradient directions, the voxel size and the number of acquisitions [25]. Our results are rather close to one DTI-FT-based study (0.65 in C2-C3 and 0.6 in C4-C7) [11]. This persistent discrepancy can be explained by the lower FA threshold we used to apply the DTI-FT algorithm. As our study involved both volunteers and patients with stenotic changes, we decided to use a low

Table 2 Patients. First line: FA and MD mean values at C2-C3 and C4-C7 levels, associated with standard deviation. Second line: Median value and range

Level	C2-C3	Compression site
FA	0.507±0.06	0.401±0.05
	0.532 [0.41–0.58]	0.395 [0.32–0.48]
MD	0.796±0.12	0.937±0.16
	0.805 [0.58–0.99]	0.94 [0.67–1.26]

FA threshold (0.2) in order to avoid excluding voxels where spinal lesions might be the most significant.

FA and MD in patients

In patients, a significant decrease in FA was also observed at the stenotic level compared with the upper cervical spine, but this decrease was more important than the FA decrease observed in volunteers between the proximal and distal levels. MD was also significantly increased at the stenotic site, but only when comparing the patient with himself (stenotic level versus C2-C3). Such changes in FA and MD values have already been reported in cervical spondylotic myelopathy on the basis of ROI measurements [8–10, 18]. They may be related to changes in the microstructural organisation of the spinal cord. Indeed, different lesions have been histopathologically described in CSM [26, 27]. They include oedema, gliosis, decrease in the number and diameter of fibres and axons, cavitations, and thinning of the myelin sheaths. The diffusional motion of water is impeded by tissue structures such as cell membranes, myelin sheaths and white matter fibre tracts. Any lesions of these cellular barriers, which physiologically restrict water motion, may be associated with a decreased FA and increased diffusivity. This hypothesis is reinforced by the fact that we found a significant negative correlation between FA and the number of stenotic levels: as the latter increased, the pathological phenomenon is supposed to extend, causing FA values to drop.

FA and MD in patients and clinical correlation

One of the striking results of our study was that it showed a positive correlation between decrease in FA and functional impairment of the upper and lower limbs. As far as we know, this is the first time that a correlation between the severity of the clinical impairment and DTI microstructural parameters has been reported in patients with cervical spondylotic myelopathy. Indeed, previous studies using DTI in such patients did not use detailed clinical scores [8–10, 18]. The use of a precise clinical score was an important goal of our study. As the Japanese Orthopaedics Association score has been shown to be both a valid and a reliable functional outcome measure in patients with cervical spondylotic myelopathy [1, 28–30], we decided to use the optimised classification, which was recently published [12, 13]. In our patients, the worse the upper and lower limb scores, the lower the FA values. This decrease in the FA values may reflect the degree of microstructural disorganisation of the spinal cord, suggesting either local extracellular oedema or a smaller number of fibres matching a larger extracellular space, or both [23]. We may also assume that minor lesions and oedema with a roughly preserved fibrillary microstructure of the spinal cord are not associated with major FA changes (Fig. 1), contrary to demyelination, cavitations and necrotic changes (Figs. 2, 3).

However, it is interesting to note that a decreased FA could be noticed in mildly affected patients. Indeed, the patients included in our study were from the neurosurgery outpatient clinic. This explains the rather high JOACMEQ scores for the upper and lower limbs (76.1±28.6 and 63.4± 27.7 respectively).

Interestingly enough, FA was negatively correlated with age in our patients (p=0.0375). As far as we know, in the cervical spine, this correlation has only been established in healthy subjects [10, 11]. We may assume that older subjects are more likely to develop severe CSM lesions as a result of their long-term illness, physiological decrease in the number of myelinated fibres or histopathological changes due to vascular aging [31, 32].

FA and MD in patients and conventional imaging findings

The significant positive correlation between FA at the compressed level and lower and upper limbs function is especially important, as conventional sequences are usually not reliable for the assessment of the clinical consequences of the stenotic lesions. Decreased signal intensity on T1-weighted images is linked with severe histopathological alterations [27] and poor surgical prognosis [2, 3, 33], but

Table 3 Mean scores issued from the JOACMEQ in each domain. The figures in brackets indicate the standard deviation

Domain	Cervical Function	Upper extremity function	Lower extremity function	Bladder function	Quality of Life
Scores	70.5 [25.3]	76.1 [28.6]	63.4 [27.7]	78.5 [23.3]	43.95 [14]

this feature lacks sensitivity, as it is generally encountered in fewer patients than are T2 abnormalities [1, 2, 30]. In our study, only two patients showed decreased signal intensity on T1-weighted sequences, and both of them had severely decreased FA. Increased signal intensity on T2-weighted images is more frequently encountered, but its significance is still controversial [2, 3]. Several studies [1, 2, 30] have shown that there is no correlation between the presence or absence of increased signal intensity on T2-weighted images and the severity of the clinical symptoms before surgery. Our study confirms these results, as the presence of increased signal intensity on T2 was not correlated with any of the clinical scores. The high signal intensity of the spinal cord probably represents a broad spectrum of lesions [33], from reversible lesions (oedema) to more severe lesions (demyelination or cavitation) (Figs. 1, 3). Furthermore, the presence of increased signal intensity on T2-weighted images was correlated neither with the FA nor with the MD changes (Fig. 2). Former studies have already concluded that DT parameters are more sensitive than T2 signal analysis in assessing patients with CSM [8, 10, 34], as well as other cervical spinal cord diseases [23]. Our study confirms that this feature can also be found in patients with moderate CSM.

The assessment of FA appeared to be more useful than that of MD in our study. Indeed, MD was significantly increased at the narrowed level compared with the C2-C3 level in the same patient, but no difference was found when the patients were compared with healthy volunteers. A higher sensitivity of FA compared with MD for the identification of microstructural changes has been suggested by other studies dealing with spinal compression of infectious or tumoral origin [18]. This also seems to be the case in patients with CSM. One explanation could be greater inter-individual variability for MD than for FA, as we found a smaller standard deviation for the latter. In any event, MD values were not correlated with any of the clinical scores.

Limitations

We acknowledge that our study has several limitations. The first limitation is the small number of patients included. The inclusion of more patients might have improved our statistical analysis, especially with regard to MD values. However, significant statistical differences in FA values were in fact obtained in our study. Secondly, as we were dealing with symptomatic patients subject to movements related to pain, we decided to use a fast imaging sequence. The DTI acquisition lasted only 3 min 33 s and so was compatible with clinical practice. As a consequence, spatial resolution of our sequence was limited and partial volume effect with the LCS or peri-medullary structures may have occurred in our measurements, especially in patients with severe cervical stenosis. The use of a 3 T magnet might be interesting to obtain a short sequence with a higher spatial resolution. Third, we did not correlate our microstructural parameters with spinal cord/spinal canal measurements.

Conclusion

FA values were significantly correlated with some of the patients' clinical scores. This study also confirmed that high signal intensity on T2 of the spinal cord is not correlated either with the DTI parameters or with clinical assessment, suggesting that FA is more sensitive than T2 imaging in this disease. These conclusions appear extremely interesting, as DTI could become a new tool for the assessment of CSM. Further studies are required to confirm these results and to pinpoint the usefulness of such measurements. A follow-up of these patients must now be performed in order to determine whether these FA changes have prognostic significance.

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