

ORIGINAL ARTICLE

Usefulness of conventional magnetic resonance imaging, diffusion tensor imaging and neurite orientation dispersion and density imaging in evaluating postoperative function in patients with cervical spondylotic myelopathy



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KEYWORDS

Anteroposterior diameter;
Cervical spondylotic myelopathy;

Abstract *Objective:* The objective of this study was to evaluate the usefulness of T2 high signal intensity (T2-HSI) and decreased anteroposterior diameter (APD), diffusion tensor imaging (DTI) and neurite orientation dispersion and density imaging (NODDI) in evaluating postoperative cervical cord function.

Methods: The study included 57 postoperative cervical spondylotic myelopathy patients. Clinical evaluation and functional recovery assessments were performed using the modified

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Diffusion tensor imaging;
Neurite orientation dispersion and density imaging;
T2 high signal intensity

Japanese Orthopaedic Association (mJOA) score and recovery rate. The presence of T2-HSI and decreased APD was recorded for exploring the relevance. Spearman correlation was applied to investigate the relationships between DTI and NODDI metrics and mJOA score. Multiple comparisons of T2 signal intensity, APD and diffusion metrics were evaluated by using multiple linear regression.

Results: Only the recovery rate was significantly different between T2-HSI and non-T2-HSI (nT2-HSI) patients ($\chi^2 = 4.466$, $p = 0.045$). Significant differences were not observed between cervical cords with and without decreased APD. Diffusion metrics, including fractional anisotropy ($p = 0.0005$), mean diffusivity ($p = 0.0008$), radial diffusivity ($p = 0.0003$) and intracellular volume fraction ($p = 0.001$), were significantly correlated with mJOA score. The ability of T2 signal intensity ($p = 0.421$) and APD ($p = 0.420$) to evaluate the postoperative function was inferior to that of fractional anisotropy ($p = 0.002$), mean diffusivity ($p = 0.001$), radial diffusivity ($p = 0.001$) and intracellular volume fraction ($p = 0.004$).

Conclusion: Conventional magnetic resonance imaging signs could be considered as a reference to make an approximate assessment, whereas DTI and NODDI could be better quantitative tools for evaluating the postoperative function and may help in interpreting residual symptoms.

The translational potential of this article: DTI and NODDI could provide reliable postoperative evaluation and analysis for cervical spondylotic myelopathy patients.

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Introduction

Cervical spondylotic myelopathy (CSM) is currently a common disease that causes serious nervous lesions. Its low-risk and optimal therapeutic method is posterior cervical laminoplasty that enlarges the spinal canal [1,2]. In clinical practice, some patients show symptoms even after surgery, and their clinical symptoms are inconsistent with conventional magnetic resonance imaging (MRI) signs, including high signal intensity in T2-weighted image or decreased anteroposterior diameter (APD) of the cervical cord, which are often considered to indicate severe myelopathic lesions. However, not all postoperative patients with poor outcomes have such signs. Furthermore, these signs could appear in well-recovered patients. It is troublesome for physicians to convey the interpretations to their patients. Therefore, the usefulness of conventional MRI signs in such circumstances should be evaluated.

The principle of diffusion tensor imaging (DTI) is the measurement of the dispersive anisotropy of water molecules in intravital tissues [3,4]. It can reveal the pathological microstructure of the spinal cord indirectly through a diffusive change in water molecules [5]. Several previous studies have confirmed that DTI is more sensitive than conventional MRI and is capable of identifying lesions of the cervical cord in preoperative CSM patients and thus has diagnostic significance [6–10]. To our knowledge, DTI is rarely used in postoperative studies of CSM patients. However, we believe that DTI is a potential technique to evaluate the postoperative function of the cervical cord.

Neurite orientation dispersion and density imaging (NODDI) was developed from diffusion-weighted MRI. According to the three-compartment model, including intracellular, extracellular and cerebrospinal fluid (CSF) compartments, NODDI can reveal specific morphological

features of neurites, which could account for changes in diffusive anisotropy [11], including neurite orientation distribution [orientation dispersion index (ODI)], neurite density [intracellular volume fraction (Vic)] and fraction of free water [isotropic volume fraction (Viso)]. Although NODDI was originally developed for brain-related applications [12,13], it is considered as a valuable imaging technique for spinal cord diseases [14], for example, multiple sclerosis in the cervical cord [15]. Therefore, this technique may be helpful for providing specific information to patients with poor postoperative outcomes.

The purpose of this study was to verify the efficacy of postoperative signs on conventional MRI and to provide evidence for DTI being a potential evaluation technique for the postoperative function of the cervical cord and NODDI being a potential technique for providing reasoning for residual myelopathic symptoms.

Materials and methods

Patients

The institutional review board of research ethics approved all study procedures. This study enrolled 59 CSM patients with multiple-level cervical stenosis. All patients preoperatively underwent conventional MRI to exclude other spinal diseases (trauma, tumour, infection, cervical spondylotic radiculopathy and so on) and posterior cervical laminoplasty for treatment. The material used to close the enlarged spinal canal or disconnected vertebral plate was biosynthetic bone extracted from coral, which helps avoid the metal susceptibility artifact [16]. All patients provided informed consent. The follow-up MR scan, including conventional MRI, DTI and NODDI, was performed between 12

and 14 months after surgery. Two patients were excluded because of motion artifact. The remaining 57 patients were recruited (14 women and 43 men; mean age, 58.7 years; age range, 36–74 years). The follow-up conventional MRI showed that the multiple-level stenosis of the cervical cord could be almost completely relieved and that there was no new compression away from the surgery site.

Clinical evaluation

For each patient, the standardised modified Japanese Orthopaedic Association (mJOA) score was obtained by senior spinal surgeons (X.H. and N.L., both with 10 years of experience) as clinical functional evaluation before surgery and at follow-up. The mJOA scoring system comprised motor and sensory functions of the upper and lower extremities, trunk and bladder; this system is most frequently used for assessing CSM patients. The Hirabayashi method was used for assessing the function recovery rate after treatment [6,17]. This method is also widely accepted. Recovery rate = $[(\text{postoperative mJOA score} - \text{preoperative mJOA score}) / (17 - \text{preoperative mJOA score})] \times 100\%$. A rate of $\geq 50\%$ indicates a good outcome and that of $< 50\%$ indicates a poor outcome. Considering an mJOA threshold of 15 for differentiating mild and moderate impairment [9], patients were divided into the following two groups according to the follow-up mJOA score: good-score group (mJOA, 15–17) and fair-score group (mJOA, < 15). This grouping could be regarded as mJOA score gradation.

Image acquisition

Conventional MRI, DTI and NODDI were performed using a 3.0-T Ingenia MRI scanner (Philips, Best, The Netherlands) with a 16-channel head-neck coil. Each patient was placed in the supine position during scanning and was informed not to breathe or swallow hard.

Conventional MRI comprised T1-weighted and T2-weighted turbo spin echo sequences in the sagittal view and a T2*-weighted multi-echo fast-field echo sequence in the axial view. The sagittal imaging parameters were as follows: repetition time/echo time, 474/6.3 ms for T1 and 3000/100 ms for T2; field of view (FOV), $160 \times 250 \text{ mm}^2$; slice thickness, 3 mm; slice gap, 0.3 mm; phase-encoding direction, feet to head; resolution, $0.80 \times 1.01 \times 3.0 \text{ mm}^3$ for T1 and $0.7 \times 0.94 \times 3.0 \text{ mm}^3$ for T2 and resolution of reconstruction, $0.58 \times 0.58 \times 3.0 \text{ mm}^3$ for T1 and $0.49 \times 0.49 \times 3.0 \text{ mm}^3$ for T2. A total of 12 sagittal slices covered the entire cervical cord from C1 to C7. The axial imaging parameters were as follows: three echoes were acquired for each slice ($TEs = 8/14/20 \text{ ms}$), which were then combined into one image; TR, 250 ms; FOV, $200 \times 152 \text{ mm}^2$; slice thickness, 4 mm; slice gap, 2 mm; phase-encoding direction, anterior to posterior; resolution, $0.8 \times 0.8 \times 4.0 \text{ mm}^3$ and resolution of reconstruction, $0.78 \times 0.78 \times 4.0 \text{ mm}^3$. A total of 17 axial slices covered the cervical cord from C2 to C7.

DTI data were acquired using a multi-shot echo-planar (EPI) sequence in the axial view to limit susceptibility artifact and eliminate physiological motion artifact in image reconstruction by using phase correction. The DTI parameters were as follows: 15 diffusion directions with a b

value of 800 s/mm^2 ; number of shots, 6; TR/TE, 4701/88 ms; FOV, $180 \times 180 \text{ mm}^2$; slice thickness, 4 mm; slice gap, 2 mm; phase-encoding direction, anterior to posterior; partial Fourier factor, 0.75; resolution, $1.0 \times 1.0 \times 4.0 \text{ mm}^3$ and resolution of reconstruction, $0.63 \times 0.63 \times 4.0 \text{ mm}^3$. The DTI scan time was 6 min and 14 s. NODDI data were acquired by using a single-shot EPI sequence in the axial view. Considering the EPI rate of data acquisition, the effect of physiological motion artifact may be negligible. The NODDI parameters were as follows: 32 diffusion directions with b values of 1000 and 2000 s/mm^2 ; small FOV of $60 \times 160 \text{ mm}^2$ used to reduce image distortion; 2 saturation bands in both anterior and posterior sides applied to suppress the fold-over effect; TR/TE, 4500/77 ms; slice thickness, 4 mm; slice gap, 2 mm; phase-encoding direction, anterior to posterior; resolution, $1.5 \times 1.5 \times 4.0 \text{ mm}^3$; resolution of reconstruction, $0.63 \times 0.63 \times 4.0 \text{ mm}^3$; SENSE factor, 2 and partial Fourier factor, 0.75. The NODDI scan time was 5 min. The slice thickness, gap and locations for DTI and NODDI were the same as those for T2* axial images (Figure 1).

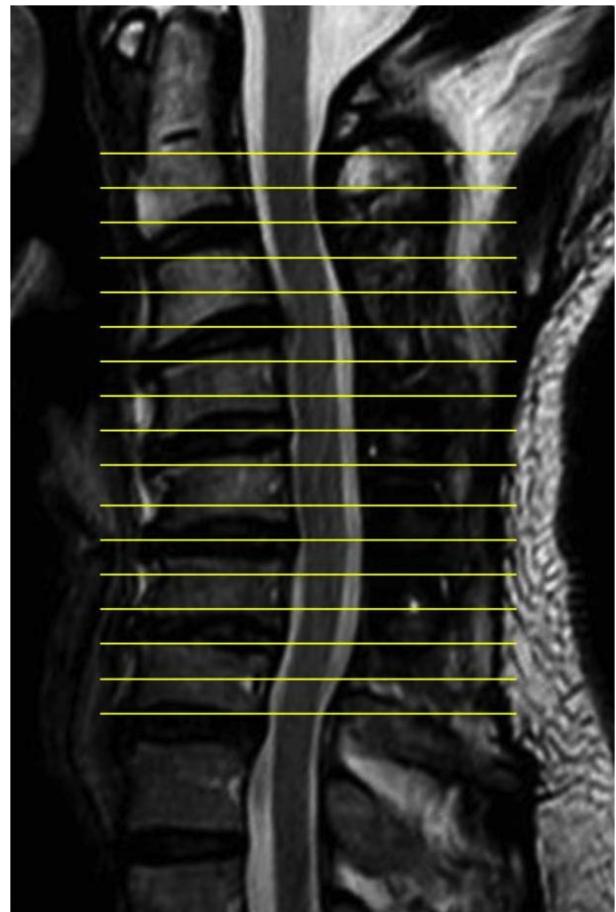


Figure 1 Presentation of the positioning for scanning slices in T2*WI, DTI and NODDI. A total of 17 axial slices cover the cervical cord from C2 to C7. The centre of the axial image is the cervical cord. The slices are placed at the centre of each intervertebral disk as much as possible. DTI = diffusion tensor imaging; NODDI = neurite orientation dispersion and density imaging; T2*WI = T2*-weighted imaging.

Image postprocessing

Two radiologists (W.J. and A.H.Y.) with more than 5 years of experience participated in the image analysis. The most compressed level in the preoperative cervical cord was determined by the lowest compression ratio of the APD divided by the transverse diameter of the cervical cord [6]. The level of interest in the postoperative MRI was the same slice that was the most compressed level on preoperative MRI. According to the postoperative presentation of T2 high signal intensity (T2-HSI) at such levels, patients were divided into the following 2 groups: T2-HSI and non-T2-HSI (nT2-HSI) groups. It should be stated and emphasised that there was no T2 signal change in the other segments of the cervical cord in our patients. Additionally, the postoperative APD at the most compressed level and the proximal normal slice in the cranial direction (prestenotic slice) were measured. Regarding the ratio of the most compressed postoperative APD to the prestenotic APD (Figure 2), a value of ≤ 0.9 indicated decreased APD, whereas that of > 0.9 indicated no decrease [37]. According to the value, patients were divided into the following 2 groups: decreased-APD (dAPD) and normal-APD (nAPD) groups. It should be noted that the change in the left–right diameter of the cervical cord was not considered; therefore, decreased APD did not represent atrophy or volume loss in the cervical cord.

The DTI and NODDI data were first preprocessed using the motion correction function in the Spinal Cord Toolbox (version 3.0.3; NeuroPoly) to align images from different diffusion directions. The image quality was carefully checked. Then, DTI metrics [fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD)] were measured from adjusted data using FMRIB Software Library (FSL) (version 5.0; University of Oxford). Additionally, NODDI metrics (Vic, ODI and Viso) were acquired using the NODDI MATLAB Toolbox (version 0.9; University College London). The region of interest (ROI) was drawn manually in DTI-Studio (version 3.0.3; Johns Hopkins University) in axial MD image and to cover the entire cervical cord possibly at the most compressed level. Although there is a difference in the degree of anisotropy in the grey and white matter, one ROI to include the entire cervical cord was preferred for clinical application and reliable repeatability. To avoid partial volume effect from CSF contamination, ROIs were placed at least 1 voxel around the outline of the cervical cord. Because the compression was relieved by operation, it guaranteed sufficient number of voxels in ROIs for study. A sample ROI is shown in Figure 3. To test the reproducibility of ROI measurement, 15 axial MD images from different patients (approximately 1/4 subjects in our study) were randomly extracted, and two radiologists drew their ROIs. One of the radiologists (A.H.Y.) drew these ROIs twice over 6 months. Intraclass correlation coefficients for inter-observer and intraobserver variability were 0.988 and 0.993, respectively.

Statistical analysis

The follow-up mJOA score was compared between T2-HSI and nT2-HSI patients using the double-tailed independent sample *t* test. The statistical difference of the follow-up

mJOA score between the dAPD and nAPD groups was also assessed using the same statistical method. The Chi-square test (Crosstab) was used for comparing the mJOA recovery rate between the T2-HSI and nT2-HSI groups and the dAPD and nAPD groups. Correlation analyses between DTI and NODDI metrics at the most compressed level and the follow-up mJOA score were performed by using Spearman rank correlation. Multiple comparisons of T2 signal intensity, APD and diffusion metrics in the correlation with follow-up mJOA score were evaluated by using multiple linear regression. The level of significance was set at $p < 0.05$. All data analyses were performed using SPSS software (version 17.0; IBM Corp).

Results

Forty patients (70%) showed T2-HSI. There was no statistically significant difference in the follow-up mJOA score between the T2-HSI and nT2-HSI groups ($t = -1.892$, $p = 0.064$) (Figure 4A), whereas the mJOA recovery rate was significantly higher in the nT2-HSI group than in the T2-HSI group ($\chi^2 = 4.466$, $p = 0.045$) (Table 1). According to mJOA gradation, 12 of 17 (71%) patients with nT2-HSI were included in the good-score group, whereas 24 of 40 (60%) patients with T2-HSI were included in the fair-score group (statistical contrast, $\chi^2 = 4.466$, $p = 0.045$, Table 2).

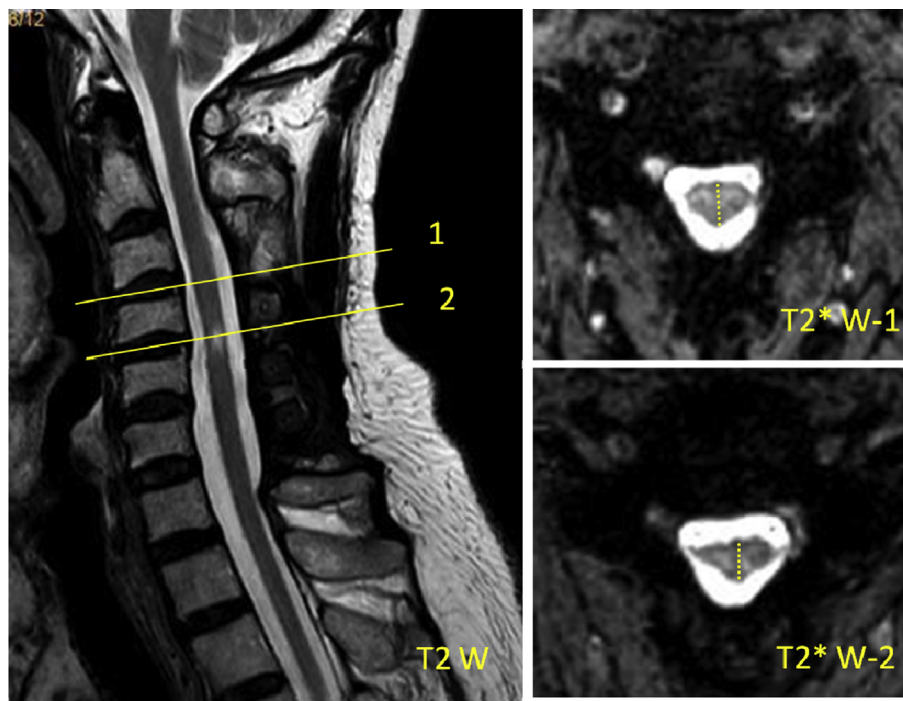
Twenty-six patients (46%) had a cervical cord with decreased APD. Neither the follow-up mJOA score ($t = -0.374$, $p = 0.710$) (Figure 4B) nor the mJOA recovery rate ($\chi^2 = 0.888$, $p = 0.429$) (Table 1) showed significant differences between the dAPD and nAPD groups. We found that 19 of 31 (61%) patients with a cervical cord showing normal APD were included in the good-score group, whereas 17 of 26 (65%) patients with a cervical cord showing decreased APD were included in the fair-score group, although the difference was not statistically significant (statistical contrast, $\chi^2 = 4.026$, $p = 0.064$, Table 2).

With respect to the relationship between DTI and NODDI metrics and the clinical function of the cervical cord, FA, MD, RD and Vic at the most compressed level were significantly correlated with the follow-up mJOA score [FA, $r = 0.448$ ($p = 0.0005$); MD, $r = -0.434$ ($p = 0.0008$); RD, $r = -0.465$ ($p = 0.0003$); Vic, $r = 0.420$ ($p = 0.001$)]. On the other hand, AD, ODI and Viso had no significant correlation with the mJOA score ($p = 0.171$, $p = 0.096$ and $p = 0.765$, respectively). The results of Spearman rank correlation are presented in Figure 5.

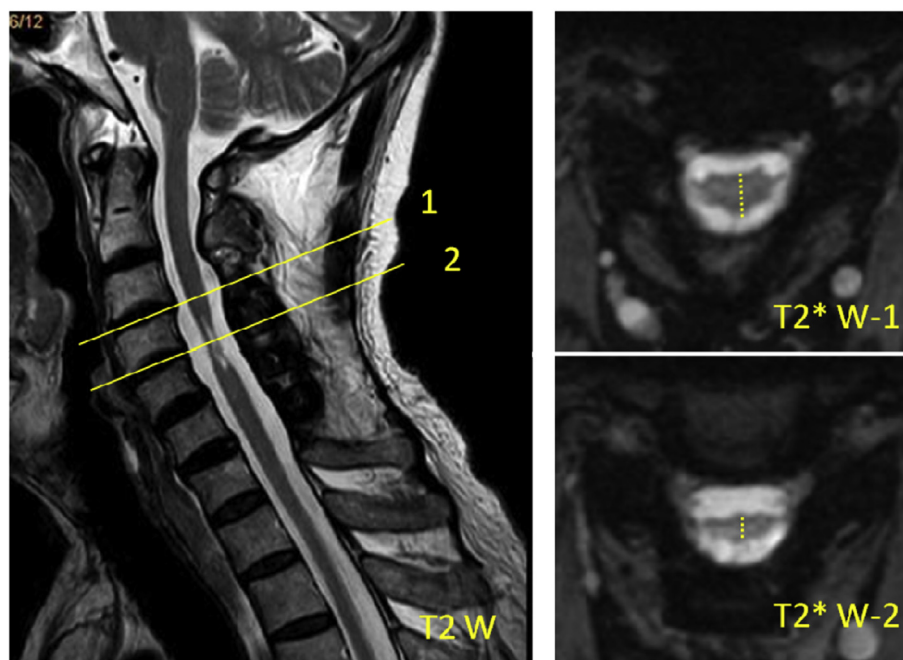
Using multiple linear regression, we observed that there was no correlation between T2 signal intensity and APD and follow-up mJOA score ($p = 0.421$ and $p = 0.420$, respectively) compared with correlation between FA, MD, RD and Vic and follow-up mJOA score ($p = 0.002$, $p = 0.001$, $p = 0.001$ and $p = 0.004$, respectively). This particularly indicated that the ability of T2 signal intensity and APD to evaluate the postoperative function of the cervical cord was inferior to that of some DTI and NODDI metrics. The result of multiple linear regression is presented in Table 3.

Discussion

Physicians often encounter the dilemma that the surgery outcomes are not always good in patients with severe



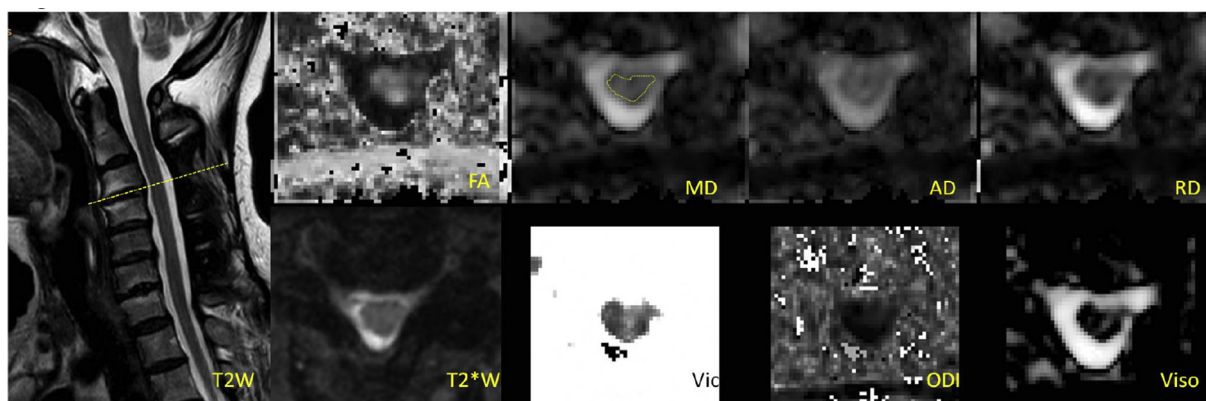
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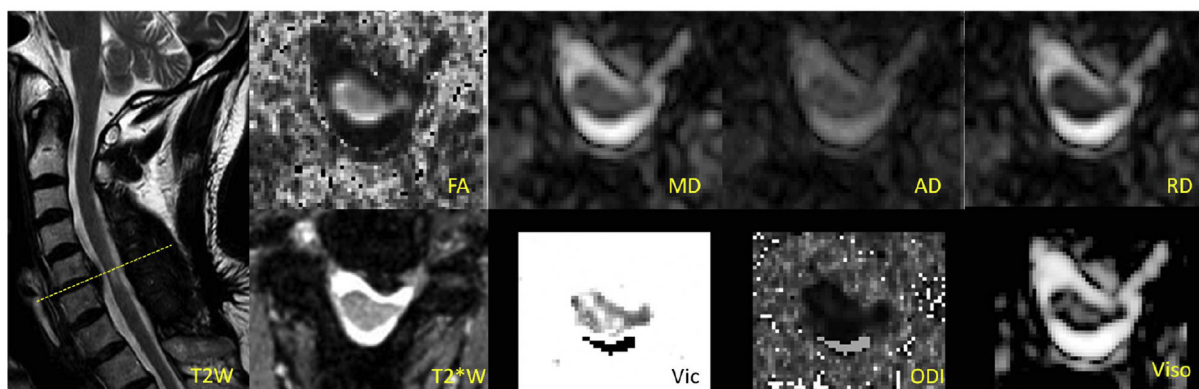
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Figure 2 Demonstration of the measurement of the anteroposterior diameter (APD) of the cervical cord at the proximal normal slice in the cranial direction (Slice 1) and the most compressed level (Slice 2). (A) Cervical cord with a relatively normal APD. The ratio of APD at Slice 2 to APD at Slice 1 is about 0.94. This patient is categorised into the normal-APD group (nAPD). (B) Cervical cord with a decreased APD. The ratio of APD at Slice 2 to APD at Slice 1 is about 0.68. This patient is categorised into the decreased-APD group (dAPD).

T2W = T2 weighted; T2*W = T2* weighted.



A



B

Figure 3 Demonstration of DTI and NODDI metrics and T2*WI at the most compressed slice in two postoperative CSM patients. (A) Cervical cord with relatively normal T2 signal intensity and APD. The ROI is drawn manually on the axial MD image to cover the entire cervical cord and is shown by the yellow dotted line in the MD image. (B) Cervical cord with T2 high signal intensity and decreased APD.

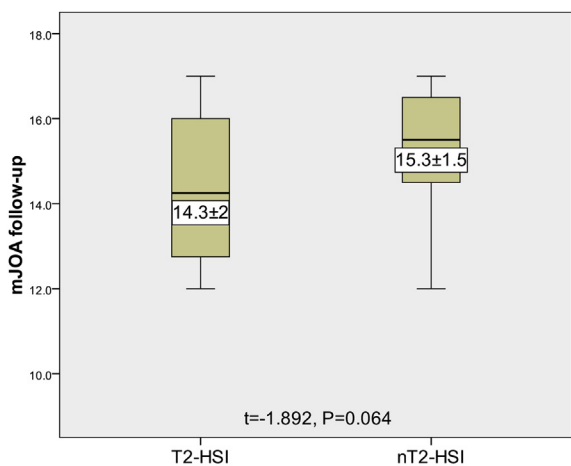
AD = axial diffusivity; APD = anteroposterior diameter; CSM = cervical spondylotic myelopathy; DTI = diffusion tensor imaging; FA = fractional anisotropy; MD = mean diffusivity; NODDI = neurite orientation dispersion and density imaging; ODI = orientation dispersion index; RD = radial diffusivity; ROI = region of interest; T2*WI = T2*-weighted imaging; Vic = intracellular volume fraction; Viso = isotropic volume fraction.

cervical stenosis and that postoperative MRI in patients with poor outcomes cannot provide the requisite reasoning in such conditions even in the absence of abnormalities concerning signal intensity and configuration of the cervical cord. The usefulness of postoperative signs on conventional MRI should be reevaluated, and an alternative imaging technique to quantitatively reflect the postoperative function of the cervical cord should be developed. We hope that our study will be valuable for physicians and postoperative CSM patients.

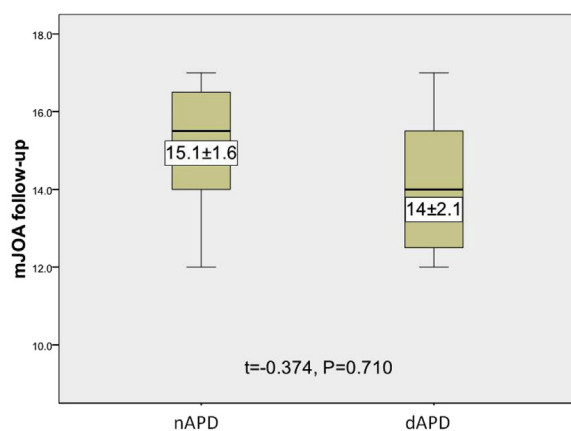
In clinical experience and some previous studies, the presence of T2-HSI in the spinal cord was considered as a sign indicating poor outcome [18,19] because it was presumed to indicate severe impairments, such as malacia and gliosis [20,21]. However, the significance of its correlation with the severity of preoperative myelopathy and surgical prognosis is controversial [6,9,18,22,23]. Our result that postoperative T2-HSI does not necessarily represent postoperative cervical cord dysfunction agrees with the findings

of the studies that disapprove a correlation between these two aspects [6,9]. The reason underlying the inability of using T2-HSI for evaluating myelopathy might be the relatively low sensitivity and no quantification of conventional MRI with respect to microstructural lesions [7]. On the other hand, as mentioned previously, T2-HSI might represent different types of lesions [24,25]. Thus, the influences of the different lesions may differ. However, we should be aware that the probability of a low postoperative mJOA score increases in the presence of T2-HSI. In addition, postoperative T2-HSI might indicate a relatively low rehabilitative efficacy. This is similar to Morio's results that high shrinkage in the T2-HSI area in the postoperative cervical cord is associated with a better recovery efficacy [22]. Therefore, T2-HSI has some clinical implications but is not sensitive and lacks the ability of quantitative assessment. Hence, a sensitive and quantitative imaging technique is needed.

Besides T2-HSI, the cervical cord with decreased APD is another common sign on postoperative conventional MRI.



A



B

Figure 4 Bar plots of the mean value and standard deviation of follow-up mJOA scores in different groups. (A) Patients are divided by the T2 signal intensity (T2-SI). The difference between 2 groups is not statistically significant. (B) Patients are divided by the APD ratio of the cervical cord. The difference between 2 groups is not statistically significant. APD = anteroposterior diameter; dAPD = decreased-APD; mJOA = modified Japanese Orthopaedic Association; nAPD = normal-APD.

Table 1 Postoperative recovery status in groups with and without T2-HSI and with and without decreased-APD cervical cord in the sagittal view.

Group	Recovery rate		Total	χ^2	<i>p</i>
	Good	Poor			
T2-HSI	16	24	40	4.466	0.045
nT2-HSI	12	5	17		
dAPD	11	15	26	0.888	0.429
nAPD	17	14	31		

Note: Except χ^2 and *p* values, the numbers represent the number of people.

APD = anteroposterior diameter; dAPD = decreased-APD; nAPD = normal-APD; nT2-HSI = non-T2 high signal intensity; T2-HSI = T2 high signal intensity.

Table 2 Follow-up mJOA scores in groups with and without T2-HSI and with and without decreased-APD cervical cord in the sagittal view.

Group	mJOA follow-up		Total	χ^2	<i>p</i>
	Good	Fair			
T2-HSI	16	24	40	4.466	0.045
nT2-HSI	12	5	17		
dAPD	9	17	26	4.026	0.064
nAPD	19	12	31		

Note: Except χ^2 and *p* values, the numbers represent the number of people.

APD = anteroposterior diameter; dAPD = decreased-APD; nAPD = normal-APD; mJOA = modified Japanese Orthopaedic Association; T2-HSI = non-T2 high signal intensity; T2-HSI = T2 high signal intensity.

After surgery relieves cervical canal stenosis, the morphology of the cervical cord is supposed to be restored. However, in clinical experience and our study, not all patients showed recovery to the original shape, possibly because atrophy or persistent deformation remains in the cervical cord. Although the proportion of decreased APD with a fair score was as high as that of normal APD with a good score, we could not find a statistically significant difference in the cervical cord function and recovery rate between decreased and comparatively normal APD cords. This finding was similar to the results of previous studies involving preoperative and postoperative patients [9,26]. The reason underlying these findings may be the inability to distinguish atrophy and deformation by only using APD. Therefore, decreased APD is a common but probably not a valuable sign on postoperative MRI. In our future work, we will use the cross-sectional area of the cervical cord to evaluate because the relationship between morphology and function has been determined using this evaluation technique in a previous study on preoperative patients [27].

DTI is the optimal choice for exploring microstructural changes in the postoperative cervical cord for its sensitivity to diffusive changes in water molecules [28]. In the spinal cord, the axonal membrane and myelin sheath are membranous structures that restrict the free diffusion of water molecules [29]. When the spinal cord is compressed for canal stenosis, continuous ischaemia leads to demyelination of white matter and necrosis of neuronal cells, which indicate destruction of membranous barriers; consequently, the diffusion restriction can be reduced [30]. Many previous preoperative studies have confirmed that DTI metrics have a strong correlation with the clinical severity of CSM patients [6,7,9,23]. Regarding postoperative cervical cord, although stenosis is relieved by surgery and oedema is improved, neuronal necrosis and axonal reduction could persist. Thus, diffusion restriction cannot restore, and functional disorders still exist. Our results indicate that DTI can reflect residual abnormality of the postoperative cervical cord quantitatively, and its evaluation efficiency is better than T2-HSI and decreased APD on conventional MRI. The relationship involved a positive correlation of FA [6,7,9,23] and negative correlations of MD

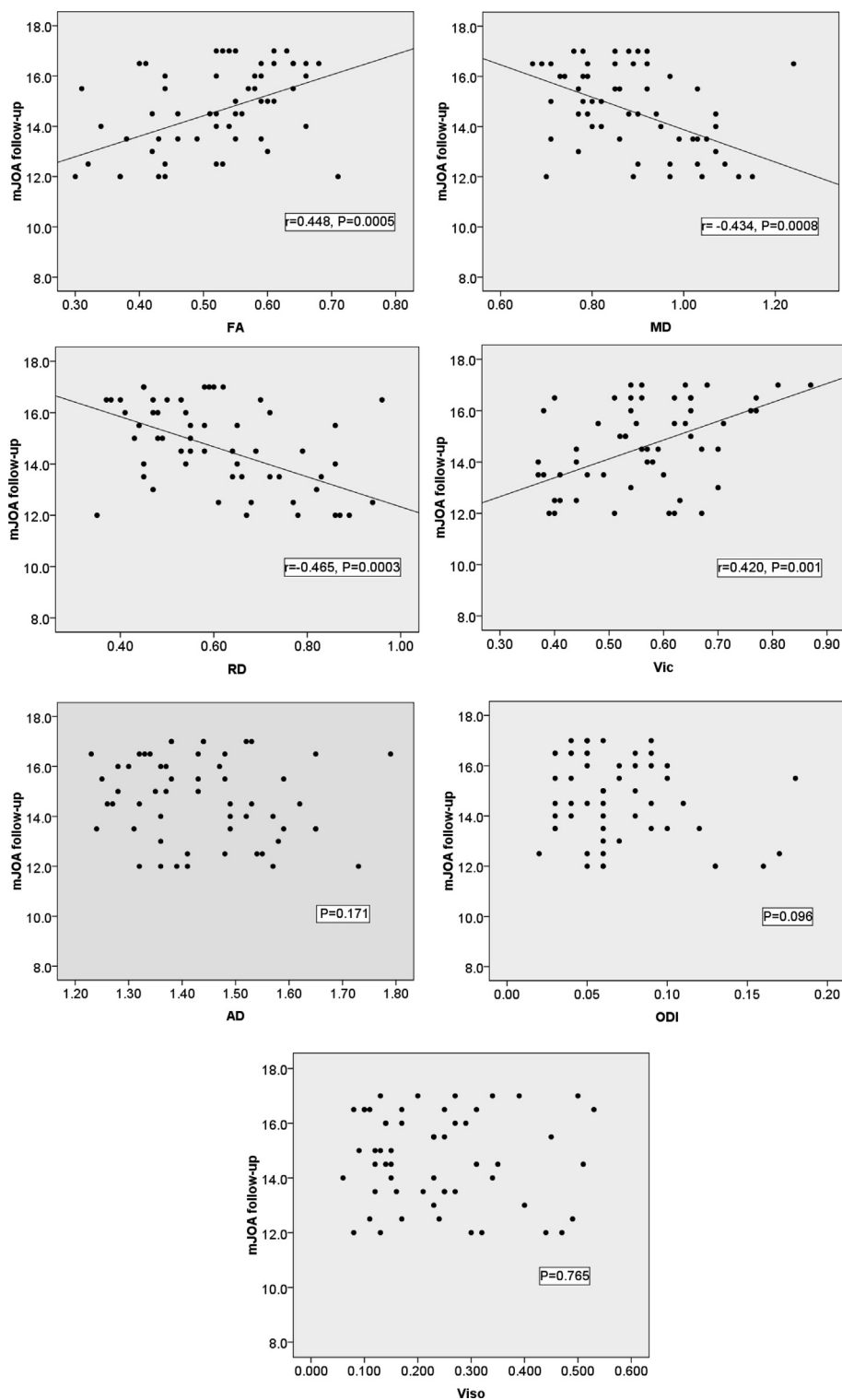


Figure 5 Scatter plots of the correlation between DTI and NODDI metrics at the most compressed level and follow-up mJOA scores. FA, MD, RD and Vic show correlation with the mJOA score.

AD = axial diffusivity; DTI = diffusion tensor imaging; FA = fractional anisotropy; MD = mean diffusivity; mJOA = modified Japanese Orthopaedic Association; NODDI = neurite orientation dispersion and density imaging; ODI = orientation dispersion index; RD = radial diffusivity; Vic = intracellular volume fraction; Viso = isotropic volume fraction.

[31,32] and RD [9]. It agreed with results of a postoperative study. We believe that DTI can help physicians reliably assess the postoperative cervical cord, especially when conventional MRI is inexplicable.

Although DTI provides a more sensitive survey of the cervical cord than conventional MRI, the survey of neurite morphology is still considered as rather macroscopical. Neurite orientation distribution and density are two main

Table 3 The result of multiple comparison of T2 signal intensity, APD and diffusion metrics in the correlation with follow-up mJOA score.

Independent variable	<i>p</i>	Standardised coefficients
Viso	0.959	–
T2 signal intensity	0.421	–
APD	0.420	–
AD	0.369	–
ODI	0.077	–
FA	0.002	–2.039
MD	0.001	2.837
RD	0.001	–4.928
Vic	0.004	0.365

AD = axial diffusivity; APD = anteroposterior diameter; FA = fractional anisotropy; MD = mean diffusivity; ODI = orientation dispersion index; RD = radial diffusivity; Vic = intracellular volume fraction.

features that contribute to neurite morphology and dispersive anisotropy of water molecules [14]. By using biophysical model and orientation distribution, NODDI can specify microstructural abnormalities reflected by DTI. The intracellular compartment refers to the space in a neurite, based on which the neurite density can be acquired. The extracellular one represents glial cells and cell bodies in grey matter and is determined by the density and orientation dispersion of a neurite (Vic and ODI). The CSF one refers to free water or isotropic diffusive area (Viso) [11]. In our study, the neurite density in the postoperative cervical cord of CSM patients was correlated with the follow-up mJOA score. This indicated that neurite density might have an impact on the cervical cord function. However, no relationship with neurite orientation dispersion was observed. The reason for this may be that the cervical cord, especially white matter, is characterised by a highly coherent orientation [29]. Canal stenosis and compression could lead to disordered neurite orientation [33,34]. However, when the compression is relieved by surgery, the disorder may be resolved. However, with regard to neurite density, the lesion caused by compression was much more irreversible. Necrotic neuron and lost neurite cannot regenerate, and thus, they cannot be rescued by surgery. Therefore, declined density rather than disordered orientation may be the reason for postoperative dysfunction and may be associated with residual symptoms. Another metric, Viso, was not correlated with the follow-up mJOA score either. The reason may be the interference caused by isotropic diffusion in the grey matter. However, above all, NODDI could provide the supplemental but specified information for physicians and postoperative CSM patients.

The present study has some limitations. First, because our participants were postoperative patients, the cervical cord restored its shape accordingly after relief of compression. The restoration may have caused shifting of the maximal compression level. Considering this, the slice thickness in our study was 4 mm and was guaranteed to cover a certain volume. Additionally, we did not think that the mean value of DTI or NODDI metrics from 2 or 3 adjacent slices was an optimal solution because it may weaken

the relevance between metrics and functional scores. Second, the population of patients in our study comprised CSM patients with multiple-level cervical stenosis. However, we preferred the most compressed level as the slice of interest for the correlation between diffusion metrics at this level and mJOA score in preoperative research [6,9,23,35]. Additionally, the optimal treatment for simple-level stenosis is anterior cervical surgery. However, this procedure is associated with inevitable susceptibility artifact. Posterior cervical laminoplasty is associated with no such artifact but is ideal for multiple-level stenosis. Third, our ROI covered the entire cross section of the cervical cord. Because NODDI data were acquired with a single-shot EPI sequence to shorten the scan time and allow clinical application, the resolution was inadequate to distinguish grey matter from white matter. Additionally, the drawing method involving entire coverage has relatively reliable repeatability. Furthermore, most DTI studies on CSM in the last 5 years could not make the distinction, and the results were not affected greatly [6,23,35,36]. However, we will take this differentiation into account in our future work.

Conclusion

DTI may quantitatively evaluate the postoperative function of the cervical cord based on parameters such as FA, MD and RD. Additionally, NODDI parameters may help reveal the postoperative microstructure of the cervical cord, and they may have the potential to aid in the interpretation of residual symptoms. The signs revealed through conventional MRI, such as T2-HSI, are still considered as valuable references. We believe that DTI and NODDI have significance in clinical applications and are potential diagnostic techniques for and can offer reliable information to CSM patients and physicians in future.

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Conflicts of interest

The authors declare that they have no conflict of interest relevant to this article.

Ethical approval

All procedures performed in the studies involving human participants were in accordance with the ethical standards

of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

References

- [1] Bernhardt M, Hynes RA, Blume HW, White 3rd AA. Cervical spondylotic myelopathy. *J Bone Joint Surg Am* 1993;75:119–28.
- [2] Lebl DR, Bono CM. Update on the diagnosis and management of cervical spondylotic myelopathy. *J Am Acad Orthop Surg* 2015;23:648–60.
- [3] Basser PJ, Mattiello J, LeBihan D. MR diffusion tensor spectroscopy and imaging. *Biophys J* 1994;66:259–67.
- [4] Thurnher MM, Law M. Diffusion-weighted imaging, diffusion-tensor imaging, and fiber tractography of the spinal cord. *Magn Reson Imag Clin N Am* 2009;17:225–44.
- [5] Sasiadek MJ, Szewczyk P, Bładowska J. Application of diffusion tensor imaging (DTI) in pathologic changes of the spinal cord. *Med Sci Monit* 2012;18:73–9.
- [6] Wen CY, Cui JL, Liu HS, Mak KC, Cheung WY, Luk KD, et al. Is diffusion anisotropy a biomarker for disease severity and surgical prognosis of cervical spondylotic myelopathy? *Radiology* 2014;270:197–204.
- [7] Gao SJ, Yuan X, Jiang XY, Liu XX, Liu XP, Wang YF, et al. Correlation study of 3T-MR-DTI measurements and clinical symptoms of cervical spondylotic myelopathy. *Eur J Radiol* 2013;82:1940–5.
- [8] Rajasekaran S, Janardhan SY, Vishnuprasath SC, Rishi MK, Gopalakrishnan B, Ajoy PS. The assessment of neuronal status in normal and cervical spondylotic myelopathy using diffusion tensor imaging. *Spine* 2014;39:1183–9.
- [9] Benjamin ME, Noriko S, John WG, Langston TH. Diffusion tensor imaging predicts functional impairment in mild-to-moderate cervical spondylotic myelopathy. *Spine J* 2014;14:2589–97.
- [10] Lee S, Lee YH, Chung TS, Jeong EK, Kim S, Yoo YH, et al. Accuracy of diffusion tensor imaging for diagnosing cervical spondylotic myelopathy in patients showing spinal cord compression. *Korean J Radiol* 2015;16:1303–12.
- [11] Zhang H, Schneider T, Wheeler-Kingshott CA, Alexander DC. NODDI: practical in vivo neurite orientation dispersion and density imaging of the human brain. *Neuroimage* 2012;61:1000–16.
- [12] Adluru G, Gur Y, Anderson JS, Richards LG, Adluru N, DiBella EV. Assessment of white matter microstructure in stroke patients using NODDI. *Conf Proc IEEE Eng Med Biol Soc* 2014:742–5.
- [13] Wen Q, Kelley DA, Banerjee S, Lupo JM, Chang SM, Xu D, et al. Clinically feasible NODDI characterization of glioma using multiband EPI at 7 T. *Neuroimage Clin* 2015;9:291–9.
- [14] Grussu F, Schneider T, Zhang H, Alexander DC, Wheeler-Kingshott CA. Neurite orientation dispersion and density imaging of the healthy cervical spinal cord in vivo. *Neuroimage* 2015;111:590–601.
- [15] By S, Xu J, Box BA, Bagnato FR, Smith SA. Application and evaluation of NODDI in the cervical spinal cord of multiple sclerosis patients. *Neuroimage Clin* 2017;15:333–42.
- [16] Wolford LM, Wardrop RW, Hartog JM. Coralline porous hydroxylapatite as a bone graft substitute in orthognathic surgery. *J Oral Maxillofac Surg* 1987;45:1034–42.
- [17] Hirabayashi K. A new method of quantitative determination of vesical urine during excretory cystometry. *J Jpn Obstet Gynecol Soc* 1961;13:1282–4.
- [18] Takahashi M, Yamashita Y, Sakamoto Y, Kojima R. Chronic cervical cord compression: clinical significance of increased signal intensity on MR images. *Radiology* 1989;173:219–24.
- [19] Liu H, Li Y, Chen Y, Wu W, Zou D. Cervical curvature, spinal cord MRI T2 signal, and occupying ratio impact surgical approach selection in patients with ossification of the posterior longitudinal ligament. *Eur Spine J* 2013;22:1480–8.
- [20] Takahashi M, Sakamoto Y, Miyawaki M, Bussaka H. Increased MR signal intensity secondary to chronic cervical cord compression. *Neuroradiology* 1987;29:550–6.
- [21] Kameyama T, Ando T, Yanagi T, Hashizume Y. Neuroimaging and pathology of the spinal cord in compressive cervical myelopathy. *Rinsho Byori* 1995;43:886–90.
- [22] Morio Y, Yamamoto K, Kuranobu K, Murata M, Tuda K. Does increased signal intensity of the spinal cord on MR images due to cervical myelopathy predict prognosis? *Arch Orthop Trauma Surg* 1994;113:254–9.
- [23] Jones JG, Cen SY, Lebel RM, Hsieh PC, Law M. Diffusion tensor imaging correlates with the clinical assessment of disease severity in cervical spondylotic myelopathy and predicts outcome following surgery. *AJNR Am J Neuroradiol* 2013;34:471–8.
- [24] Someya Y, Koda M, Hashimoto M, Okawa A, Masaki Y, Yamazaki M. Postmortem findings in a woman with history of laminoplasty for severe cervical spondylotic myelopathy. *J Spinal Cord Med* 2011;34:523–6.
- [25] Hansen B, Flint JJ, Heon-Lee C, Fey M, Vincent F, King MA, et al. Diffusion tensor microscopy in human nervous tissue with quantitative correlation based on direct histological comparison. *Neuroimage* 2011;57:1458–65.
- [26] Yone K, Sakou T, Yanase M, Ijiri K. Preoperative and postoperative magnetic resonance image evaluations of the spinal cord in cervical myelopathy. *Spine (Phila Pa 1976)* 1992;17:5388–92.
- [27] Karpova A, Arun R, Cadotte DW, Davis AM, Kulkarni AV, O’Higgins M, et al. Assessment of spinal cord compression by magnetic resonance imaging—can it predict surgical outcomes in degenerative compressive myelopathy? A systematic review. *Spine (Phila Pa 1976)* 2013;38:1409–21.
- [28] Kara B, Celik A, Karadereler S, Ulusoy L, Ganiyusufoglu K, Onat L, et al. The role of DTI in early detection of cervical spondylotic myelopathy: a preliminary study with 3-T MRI. *Neuroradiology* 2011;53:609–16.
- [29] Beaulieu C. The basis of anisotropic water diffusion in the nervous system—a technical review. *NMR Biomed* 2002;15:435–55.
- [30] Benjamin ME, Noriko S, Langston TH. Advances in MR imaging for cervical spondylotic myelopathy. *Eur Spine J* 2015;24:197–208.
- [31] Uda T, Takami T, Tsuyuguchi N, Sakamoto S, Yamagata T, Ikeda H, et al. Assessment of cervical spondylotic myelopathy using diffusion tensor magnetic resonance imaging parameter at 3.0 tesla. *Spine (Phila Pa 1976)* 2013;38:407–14.
- [32] Masaaki H, Issei F, Yoshitaka M, Atsushi N, Keigo S, Koji K, et al. New diffusion metrics for spondylotic myelopathy at an early clinical stage. *Eur Radiol* 2012;22:1797–802.
- [33] Takano M, Komaki Y, Hikishima K, Konomi T, Fujiyoshi K, Tsuji O, et al. In vivo tracing of neural tracts in tiptoe walking Yoshimura mice by diffusion tensor tractography. *Spine (Phila Pa 1976)* 2013;38:66–72.
- [34] Wen CY, Cui JL, Lee MP, Mak KC, Luk KD, Hu Y. Quantitative analysis of fiber tractography in cervical spondylotic myelopathy. *Spine J* 2013;13:697–705.
- [35] Ahmadi U, Ulrich NH, Yao YQ, Nanz D, Sarnthein J, Kollias SS. Early detection of cervical spondylotic myelopathy using

- diffusion tensor imaging: experiences in 1.5-tesla magnetic resonance imaging. *Neuroradiol J* 2015;28:508–14.
- [36] Banaszek A, Bładowska J, Szewczyk P, Podgorski P, Sasiadek M. Usefulness of diffusion tensor MR imaging in the assessment of intramedullary changes of the cervical spinal cord in different stages of degenerative spine disease. *Eur Spine J* 2014;23:1523–30.
- [37] Yu YL, Boulay GH, Stevens JM, Kendall BE. Morphology and measurements of the cervical spinal cord in computer-assisted myelography. *Neuroradiol J* 1985;27:399–402.