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Changes in diffusion tensor imaging indices of the lumbosacral enlargement correlate with cervical spinal cord changes and clinical assessment in patients with cervical spondylotic myelopathy

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ABSTRACT

Objectives: We examined whether changes in diffusion tensor imaging (DTI) indices of the lumbosacral enlargement are similar to those at the cervical level, and correlate with clinical assessments in patients with cervical spondylotic myelopathy (CSM).

Patients and methods: Patients with CSM and healthy volunteers (40–42/group) received DTI scans at both lumbosacral enlargement and cervical spinal cord. Modified Japanese Orthopedic Association (mJOA) score was also recorded for those with CSM. The apparent diffusion coefficient (ADC) and fractional anisotropy (FA) values of DTI in the two groups were compared. We also examined the correlation between DTI indices (ADC and FA) of the lumbosacral enlargement and those of the cervical spinal cord, and between DTI indices and mJOA in the CSM group.

Results: Compared with the values of healthy subjects, the ADC values of patients with CSM were significantly increased, and FA values were significantly decreased at both cervical spinal cord and lumbosacral enlargement. Changes in FA value of the cervical cord showed a positive correlation to those of the lumbosacral enlargement in the CSM group. Importantly, a linear correlation was detected between mJOA score and DTI indices (ADC and FA) of the cervical cord, as well as FA value of the lumbosacral enlargement in the CSM group.

Conclusion: DTI indices, especially FA, of the lumbosacral enlargement correlate with clinical assessments of patients with CSM, and hence may be useful for evaluating the severity of cervical cord injury.

1. Introduction

Cervical spondylotic myelopathy (CSM) is a chronic compression state of the cervical spinal cord. It progresses with time and can eventually result in paralysis if not treated properly. As a relatively new imaging modality, magnetic resonance diffusion tensor imaging (DTI) has advantages over conventional MRI because of its higher sensitivity and quantification characteristics. On DTI scans, acute compression of the spinal cord leads to a focal decrease in apparent diffusion coefficient (ADC) value and an increase in the fractional anisotropy (FA) value, two important DTI indices [11]. In contrast, chronic compression of spinal cord results in detectable microstructural changes that increase the ADC value but decrease the FA value [12,13]. Similar changes also have been observed in animal models [2,14]. Accordingly, DTI is widely used to detect and evaluate structural changes in the central nervous system after spinal cord injury [1–3] and has been suggested as a potential biomarker for functional impairments in patients with CSM [4]. Yet, the role of preoperative DTI indices in the prognosis of patients with CSM remains controversial [5–7].

Because surgical implantation of devices at the cervical spinal cord produces imaging artifacts, DTI of the compression site might not be ideal or reliable for evaluating the neurologic state of patients with CSM. Intriguingly, a recent meta-analysis showed that significant changes in DTI indices occurred not only at the compressed cord, but also at the distal cranial sites [8]. In a preclinical study, FA value at the caudal site could discern mild injuries from moderate and severe

Abbreviations: DTI, diffusion tensor imaging; CSM, cervical spondylotic myelopathy; ADC, apparent diffusion coefficient; FA, fractional anisotropy; mJOA, Modified Japanese Orthopedic Association

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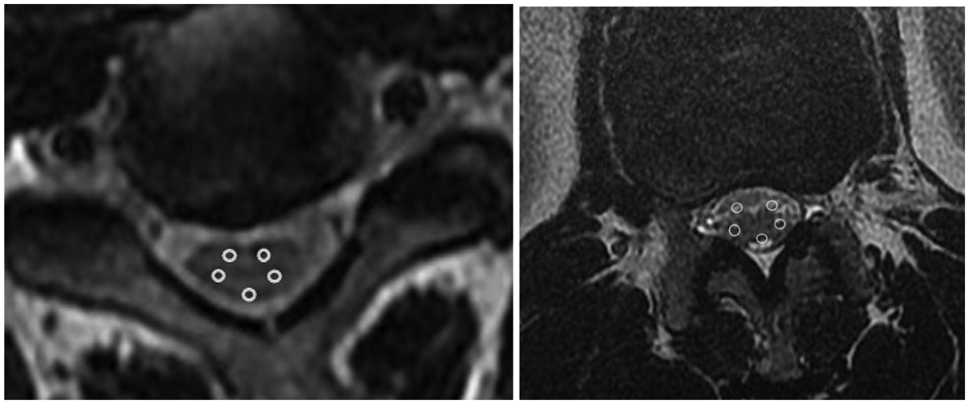

Fig. 1. Representative images of ROI placement. (A) ROI placement in the cervical spinal cord. (B) ROI placement in the lumbosacral spinal cord.

injuries at the rostral sites [9]. Our recent study in rats demonstrated significant changes in DTI indices at the caudal cord after chronic compression of the cervical spinal cord [2]. Based on these findings, we conducted a pilot study in 10 patients with CSM and 10 healthy subjects, and found that FA and ADC values in the lumbosacral enlargement differed significantly between the CSM and healthy groups [10]. Because of the small sample size and potential selection bias in CSM severity, we did not perform correlation analysis of DTI indices between the cervical and lumbosacral enlargement [10]. In the current study, by increasing the sample size and incorporating patients with and without T2-weighted high signal intensity, we tested the hypothesis that changes in DTI indices at the lumbosacral enlargement correlate with those of the compressed cervical cord. Importantly, we further examined whether DTI indices of the cervical spinal cord and lumbosacral enlargement correlate with the clinical assessment of patients using Modified Japanese Orthopedic Association (mJOA) score.

2. Materials and methods

2.1. Eligibility criteria

From February 2011 to February 2015, 40 patients diagnosed with CSM were recruited. All qualifying patients had the following signs and symptoms: neck pain, stiffness, motion dysfunction, upper extremity weakness, sensory symptoms that had persisted for more than 6 weeks, and significant spinal cord compression on radiologic examination (ossification of the ligament flavum, cervical disc herniation, and cervical spinal stenosis). Patients were excluded if they had previous head or brain lesions associated with trauma, cerebral palsy, rheumatoid arthritis, or spine disease, including tumors. The control group consisted of 42 healthy volunteers, without history of neurologic or psychiatric illness, and showed normal signal on MRI: no compressive lesions on T2-weighted MRI, including CSM, ossification of the posterior longitudinal ligament, ossification of the ligament flavum, cervical disc herniation, and cervical spinal stenosis. Informed consent was obtained from both patients and healthy subjects, and the study was approved by the Ethical Committee of Luhe Hospital, Beijing.

2.2. Image acquisition and processing

As described in our previous study [10], all examinations were performed using a 1.5 T MRI scanner (Signa Excite; GE Medical Systems, Milwaukee, Wisconsin). In DTI scans, single-shot spin echo echo-planar image (SS-SE-EPI) with a sense factor of 4 was used for the cervical spinal cord and lumbosacral spinal cord with the following parameters: b-value of 500 mm2/s and 0 mm2/s, 15 diffusion gradient directions, acquisition matrix 128 × 128, and the field of view (FOV) 240 x 240 mm. The conventional MRI sequence parameters of the cervical spinal cord were as follows: (1) sagittal T2WI (repetition time (TR) 3000 ms, echo time (TE) 99 ms, slice/gap 3.0/1.0 mm, matrix 320 × 224, number of excitation (NEX) = 2), ; (2) sagittal T1WI (TR 410 ms, TE 9.9 ms, slice/gap 3.0/1.0 mm, matrix 320 × 192, NEX = 3); (3) axial T2WI (TR 3500 ms, TE 117 ms, slice/gap 4.0/0.5 mm, matrix 288 × 192, NEX = 3). The DTI scan parameters of the cervical spinal cord were as follows: TR 6000 ms, TE 85 ms, slice/gap 6.0/0 mm, matrix 128 × 128, NEX = 4. The conventional MRI sequence parameters of the lumbosacral spinal cord were as follows: (1) sagittal T2WI (TR 2660 ms, TE 106 ms, slice/gap 4.0/0.5 mm, matrix 320 × 256, NEX = 3); (2) sagittal T1WI (TR 400 ms, TE 8.9 ms, slice/gap 4.0/0.5 mm, matrix 320 × 224, NEX = 3); (3) axial T2WI (TR 3500 ms, TE 117 ms, slice/gap 4.0/1.0 mm, matrix 384 × 256, NEX = 2). The DTI scan parameters of the lumbosacral enlargement were as follows: TR 6300 ms, TE 87 ms, slice/gap 5.0/0 mm, matrix 128 × 128, NEX = 4.

A radiologist performed the region of interest (ROI) measurements using the commercially available software ADW 4.3 (GE Medical Systems, Milwaukee, Wisconsin). In CSM patients, 5 ROIs were drawn at the regions with the maximal compression on T2-weighted MRI on axial plane (Fig. 1). For volunteers, ROIs were placed at five levels from C2/C3 to C6/C7, with sagittal T2WI images used as references. All measurements were averaged across 5 ROIs for each subject. When measuring ROIs in the lumbosacral enlargement, 5 ROIs were drawn at the level with the widest diameter.

2.3. Functional assessment

All patients with CSM were evaluated with the mJOA score, which has been validated and widely used as a reliable outcome measurement of CSM. Scores of 15–17, 11–14, and < 11 were defined as mild, moderate, and severe symptomatology, respectively.

2.4. Statistical analysis

Statistical analysis was carried out with SPSS 18.0 (Chicago, IL). We used a Student's *t*-test to compare data between healthy and CSM groups. Correlations between DTI indices from the cervical spinal cord and lumbosacral enlargement, and between DTI indices and mJOA score were calculated with Spearman's correlation analysis. Results were deemed statistically significant at $P \leq 0.05$.

3. Results

3.1. Subject demographics

The CSM group consisted of 22 men and 18 women, with an average age of 55.6 ± 11.9 years (range, 30–69). The healthy group consisted of 25 men and 17 women, and the average age was 51.2 ± 8.6 years (range, 24–69), which was not significantly different from that of the CSM group ($P = 0.674$). In the CSM group, involved segments included

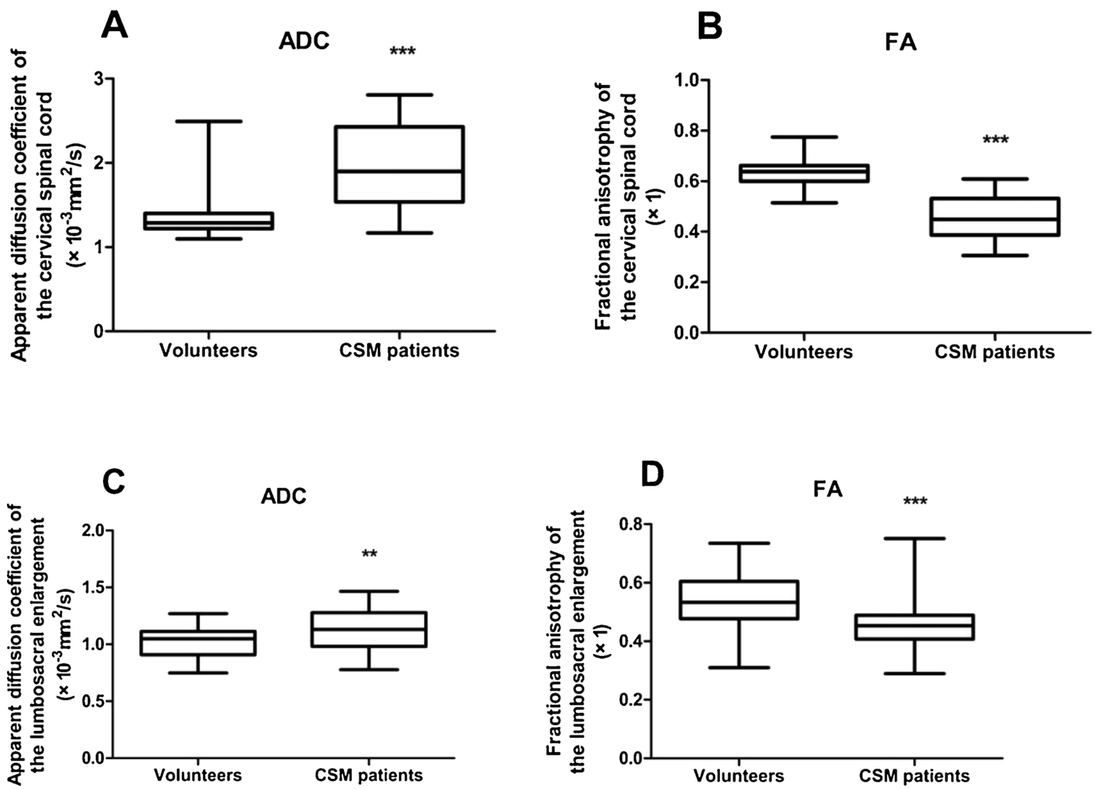

Fig. 2. DTI indices in CSM patients and healthy subjects. (A) The apparent diffusion coefficient (ADC) values at the compressed cervical site in patients with CSM were significantly higher than those of healthy subjects at the corresponding spinal levels (***$P < 0.001$). (B) The fractional anisotropy (FA) values at the compressed site were significantly lower in the CSM group than in the healthy group (***$P < 0.001$). (C) The ADC values of the lumbosacral enlargement in patients with CSM were significantly higher than those of healthy subjects (**$P < 0.01$). (D) The FA values of the lumbosacral enlargement were significantly lower in the CSM group than in the healthy group (***$P < 0.001$). Data are presented as mean ± SD.

C3/4 (9 cases), C4/5 (13 cases), C5/6 (22 cases), and C6/7 (4 cases). Thirty-four patients had compression at one level, four had compression at two levels, and two had compression at three levels.

3.2. DTI indices differ significantly between CSM patients and healthy subjects

ADC values of the cervical spinal cord were significantly higher in patients with compression than in healthy subjects ($P < 0.001$, Fig. 2A). In contrast, FA values of the cervical spinal cord were significantly lower in patients with compression than in healthy subjects ($P < 0.001$, Fig. 2B). Although lumbosacral enlargement was distal to the compressed cervical site, DTI indices at this level were also significantly different between the two groups. Patients in the CSM group had higher ADC values ($P = 0.002$) and a lower FA values ($P < 0.001$) than those in the healthy group (Fig. 2C, D).

3.3. Correlation of DTI indices between the cervical spinal cord and lumbosacral enlargement in CSM patients

No linear correlation in ADC or FA value was detected between cervical spinal cord and lumbosacral enlargement in healthy volunteers ($r = 0.009$, $P = 0.951$ for ADC; $r = 0.128$, $P = 0.421$ for FA; Fig. 3A). However, in CSM patients, FA values of the cervical spinal cord correlated with those of the lumbosacral enlargement ($r = 0.339$, $P = 0.033$, Fig. 3B right). No such correlation was seen for ADC values ($r = -0.216$, $P = 0.179$; Fig. 3B left).

3.4. Correlation between DTI indices and mJOA scores in CSM patients

The neurologic functional deficit of patients with CSM was assessed with the mJOA score. Both FA ($r = 0.5539$, $P = 0.0002$) and ADC ($r = -0.3121$, $P = 0.049$) values at the cervical spinal cord showed a significant positive correlation with mJOA score (Fig. 4A, B). Importantly, FA value at the lumbosacral enlargement also showed a positive correlation with mJOA score (FA: $r = 0.4003$, $P = 0.0105$; ADC: $r = -0.1225$, $P = 0.4513$; Fig. 4D).

4. Discussion

Chronic compression of the cervical spinal cord leads to sustained tissue ischemia that causes white matter degeneration. Pathologic changes that occur subsequent to degeneration include demyelination, damage to the axon transport system, inflammatory cell invasion, and vasogenic edema. These changes result in both functional impairment and changes in DTI indices. Different DTI parameters have different efficacies and sensitivities for neurologic status evaluation. Ellingson et al. [4] suggested that FA has a higher sensitivity and specificity than other DTI parameters for identifying patients with mild-to-moderate cervical spondylosis. Our findings showed an increase in ADC and a decrease in FA value at the compressed cervical cord of patients with CSM. Strikingly, ADC and FA values at the distal and rostral lumbar spinal cord showed changes similar to those at the injured cervical cord in these patients.

Our linear correlation analysis suggests a correlation between mJOA score and FA values not only of the injured cervical spinal cord, but also of the distal uninjured lumbosacral enlargement in patients. A linear correlation between DTI parameters at the injury site and the severity of neurologic deficits in patients with CSM was first reported by Budzik et al. [15]. Jones et al. [16] further compared DTI parameters with clinical assessments in 30 patients with CSM, and found a positive correlation between FA value and mJOA score. A recent meta-analysis

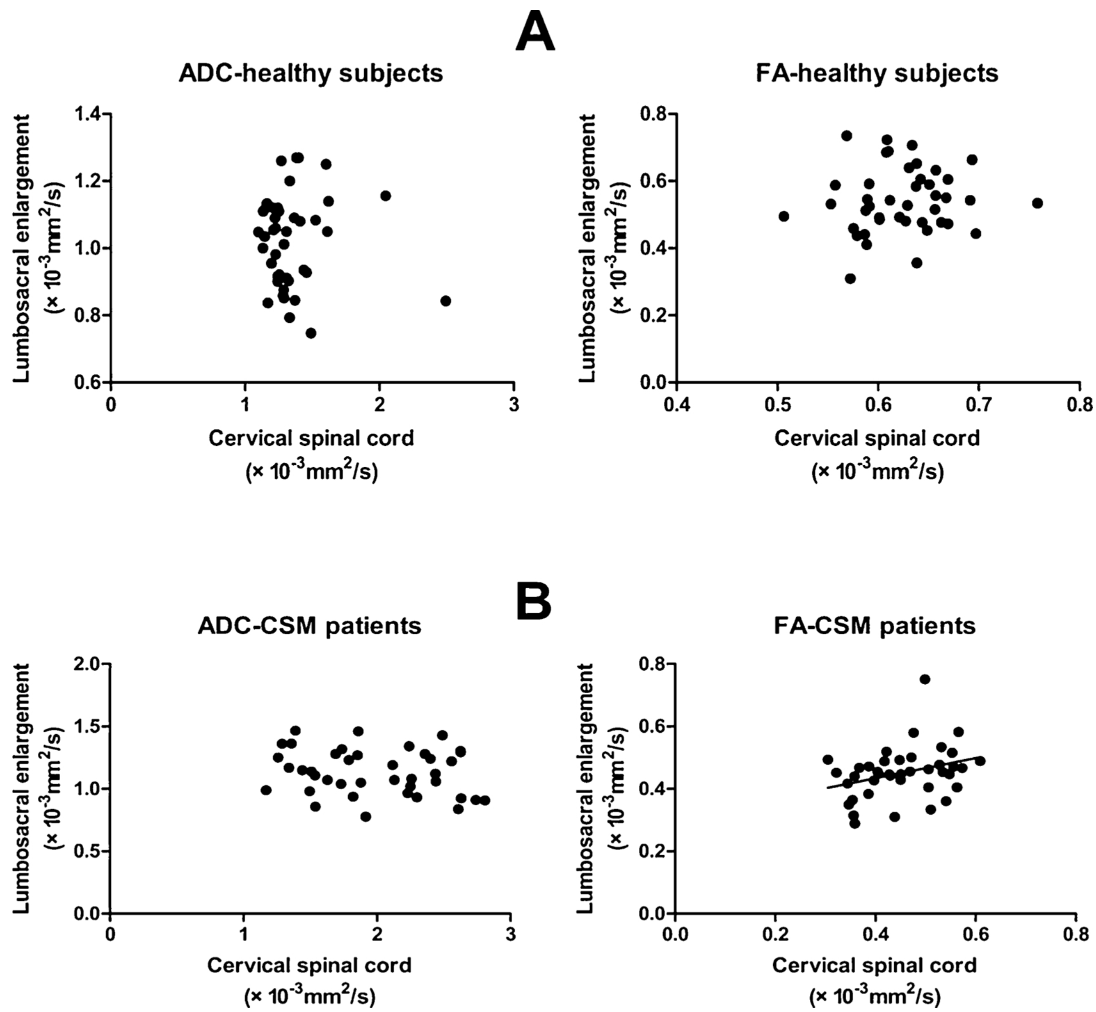

Fig. 3. Correlation analysis of DTI indices between the cervical and lumbosacral spinal cord. (A) Neither apparent diffusion coefficient (ADC; left) nor fractional anisotropy (FA) value (right) of the cervical spinal cord correlated with the corresponding values of the lumbosacral enlargement in healthy subjects. (B) There was no linear correlation in ADC values between the cervical spinal cord and lumbosacral enlargement in patients with CSM ($r = -0.216$, $P = 0.179$, left). However, FA values of the cervical spinal cord correlated with those of the lumbosacral enlargement ($r = 0.339$, $P = 0.033$, right).

also revealed a strong correlation between DTI parameters (ADC and FA) at the compressed level and preoperative mJOA scores [17]. Therefore, our current finding is in line with previous observations.

To establish health care utility, we need to anchor DTI metrics to clinical assessment tools and also use DTI to predict clinical outcomes. Despite its usefulness in evaluating neurologic status, whether preoperative DTI indices correlate with postoperative clinical outcomes remains a debate [16,18,19]. Because individuals differ, it is important to predict the postoperative outcome based on the preoperative baseline score in each patient, for example by incorporating mJOA score as either the change from baseline or recovery rate [18,19]. In this study, we incorporated not only patients with T2-weighted high signal intensity but also those without in an attempt to avoid potential selection bias of patient severity. We found that both FA and ADC values at the cervical spinal cord correlated with mJOA score. Importantly, FA value in the lumbosacral enlargement also showed a linear correlation with mJOA score in these patients. Accordingly, FA values at both sites might be useful for detecting microstructure impairment in patients with CSM. Our findings also suggest that the spinal cord shows wide ranging and remote changes in microstructure after CSM, which may partially explain the differing prognoses of patients.

Shanmuganathan et al. [20] first reported that spinal cord sites remote to the injury, which appear normal on conventional MR imaging, showed significant changes in DTI. Vedantam et al. [21] found that FA of the cervical cord, which is rostral to the injury site in patients after acute cervical spinal cord injury, was associated with motor and sensory function scores of the upper limb. The retrograde microstructural degeneration was also detected in patients with chronic spinal cord injury [22,23]. These findings suggest that DTI indices are useful for evaluating the extent of injury and may better correlate with neurologic deficit than MRI. Furthermore, changes of DTI in distal/remote spinal cord levels might be useful for monitoring recovery after treatment, especially in patients who undergo cervical surgery with internal fixation. In these patients, postoperative neurologic states cannot be reliably assessed by DTI at the cervical level because of extensive imaging artifacts in that region. With that limitation in mind, we performed an animal study that revealed significant changes in DTI parameters in the conus medullaris of rats with chronic compression in the cervical spinal cord [2]. We then conducted a preliminary study in 10 patients with CSM and 10 healthy volunteers, which showed that both FA and ADC at the lumbosacral enlargement differed significantly between patients and healthy volunteers [10]. Our current study extended our previous findings and revealed a linear correlation in FA value between the cervical and lumbosacral spinal cord of patients with CSM.

Possible explanations for these findings may be that chronic compression of the cervical spinal cord leads to secondary degeneration of the distal neuronal elements. Previous studies suggested that this secondary degeneration may be caused by Wallerian degeneration [24,25].

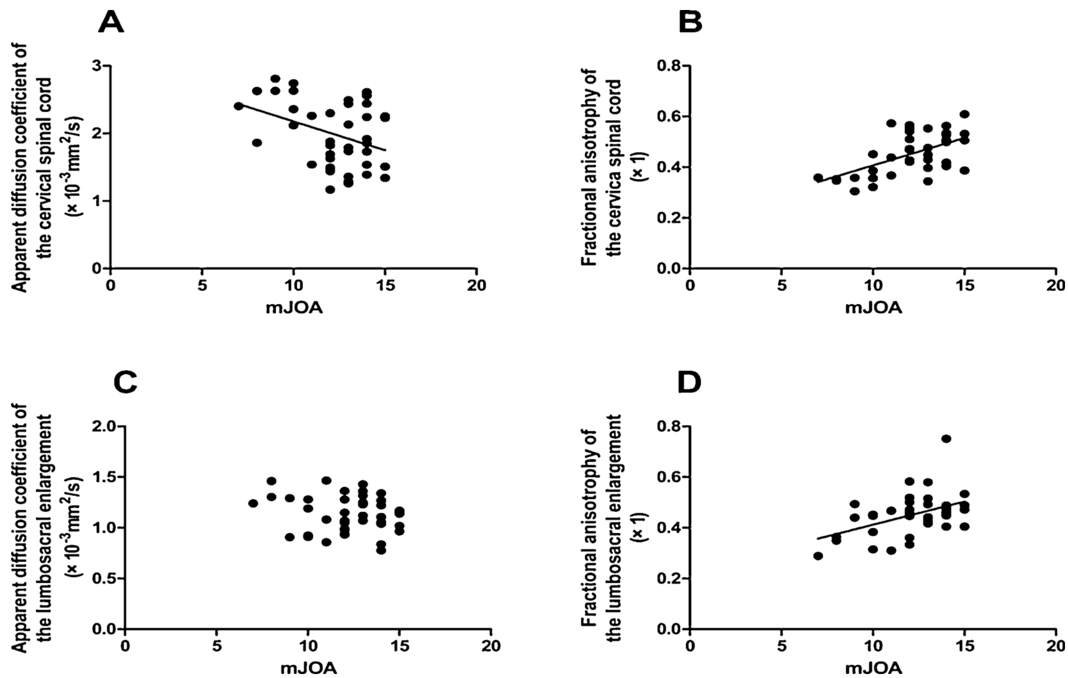

Fig. 4. Correlation analysis of DTI indices and Modified Japanese Orthopedic Association (mJOA) scores in CSM patients. At the cervical spinal cord, (A) the apparent diffusion coefficient (ADC; r = -0.3121, $P =$ 0.049) and (B) fractional anisotropy (FA) value (r = 0.5539, $P =$ 0.0002) showed a significant correlation with mJOA score. (C) There was no correlation between ADC values at the lumbosacral cord and mJOA scores (r = -0.1225, $P =$ 0.4513). (D) However, FA values at the lumbosacral cord showed a positive linear correlation to mJOA scores (r = 0.4003, $P =$ 0.010).

Wallerian degeneration is a process in which axonal injury at a defined site and time simultaneously affects all axons. During Wallerian degeneration, the distal portions of injured axons fragment after a predictable latent phase [25]. The discovery of genetic mutations that delay Wallerian degeneration has provided insight into mechanisms underlying axon degeneration in disease. Rapid Wallerian degeneration requires the pro-degenerative molecules SARM1 and PHR1 [26–28]. Nicotinamide mononucleotide adenylyltransferase 2 (NMNAT2) is essential for axon growth and survival. Its loss from injured axons may activate Wallerian degeneration, whereas NMNAT overexpression rescues axons from degeneration [25]. However, the exact mechanisms are still uncertain.

Together, these findings suggest that DTI changes at distal spinal cord may also reflect the severity of injury at the compressed spinal level. Importantly, we also identified a linear correlation between FA value at both cervical and lumbosacral enlargement and mJOA score. Because FA of the lumbosacral enlargement correlates with clinical assessment in CSM patients, it may be useful for evaluating post-treatment recovery, especially in patients who undergo cervical surgery with internal fixation.

Data archiving

There were no data to deposit.

Funding

No funding was received for this study.

Conflict of interest

The authors declare that they have no conflict of interest.

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.

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