Feasibility of diffusion kurtosis imaging in evaluating cervical spinal cord injury in multiple sclerosis

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Abstract

Background and purpose

At present, it is a difficult problem to evaluate cervical spinal cord (CSC) injury in multiple sclerosis (MS). To assess gray matter (GM), white matter (WM), lesions of MS and the therapeutic effect using diffusion kurtosis imaging (DKI).

Material and Methods

A total of 78 subjects (48 of MS and 30 of health) perform routine MR scan and DKI of CSC. DKI-metrics were measured in the lesions, normal-appearing GM and WM. The MS patients were divided into two groups according to the presence or absence of T2 hyperintensity. The disability of the two groups was assessed by the extended disability status scale (EDSS) before and after treatment.

Results

- 1) Significant differences were detected in DKI metrics between MS and healthy ($P < 0.05$) and between patients with CSC T2-hyperintense and without T2-hyperintense ($P < 0.001$);
- 2) Compared to healthy, GM-MK, GM-RK and WM-FA, WM-AD were statistically reduced in patients without T2-hyperintense ($P < 0.05$).
- 3) Significant differences were observed in DKI metrics between patients with T2-hyperintense after therapy ($P < 0.05$), as well as GM-MK and WM-FA, WM-AD in patients without T2-hyperintense ($P < 0.05$);
- 4) EDSS was correlated with MK values, as well as EDSS scores and MK values after therapy.

Conclusions

- 1) DKI-metrics can detect and quantitatively evaluate the changes in cervical spinal cord micropathological structure;
- 2) MK and RK values are sensitive metrics to detect the damage of gray matter;
- 3) MK values quantitatively evaluate the clinical disability progression and the therapeutic effect in MS patients.

Introduction

Multiple sclerosis (MS) is the most common neuroimmunological demyelinating disease and the most common non-traumatic disability in young adults[1, 2]. The cervical spinal cord (CSC) is a vulnerable region. Extensive abnormalities in CSC are correlated with neurological deficits and the development of clinical disability in MS patients[3, 4]. However, there is a clinicoradiological contradiction that clinical disability and routine MR parameters, including the number and volume of T2-hyperintense CSC lesions, show poor correlation and the so-called normal-appearing of CSC in MRI[5–11]. Fortunately, new quantitative imaging, such as diffusion tensor imaging (DTI)[12] and diffusional kurtosis imaging (DKI)

[13], assessed microstructural CSC abnormalities in MS patients, which could surmount this paradox and provide novel biomarkers to monitor disease progression. DTI is based on the assumption that diffusing water molecules follow a Gaussian distribution and is a significant MRI used to observe the displacement of water molecules at a microscopic level[13]. Spinal cord DTI (typical b-value = 0, 1000, 1500s/mm²) has now been used in MS research for almost a decade[14]. DTI metrics include fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity(AD) and radial diffusivity (RD). FA, an index of diffusion anisotropy and integrity, could be biomarkers of WM damage[12]. MD, AD and RD are diffusion metrics calculated along the averaged eigenvectors, the principal and the perpendicular, respectively[15]. Typically, the displacement of water molecules is restricted by barriers, such as cell membranes and organelles. Hence, DTI of CSC may be inappropriate in the biological structures. In addition, DTI modeled on single fiber orientation in each voxel has limited reliability for crossing fibers and provides less valuable information in tissues such as GM because the microstructure of GM is characterized as isotropic. Although several correlations have been established between quantitative MR metrics of CSC and clinical disability in MS, the gray matter of CSC is rarely observed[16, 17]. DKI (typical b-value = 0, 500, 1000, 1500, 2000, 2500s/mm²) is an advanced form of diffusion analysis, which enables the quantification of non-Gaussian diffusion through the estimation of the diffusional kurtosis[12]. Thus, DKI may accurately reflect subtle micropathological abnormalities in GM in vivo compared to DTI[18]. DKI metrics include mean kurtosis (MK), axial kurtosis (AK) and radial kurtosis (RK). MK, a index of tissue microstructural complexity, has been shown to be sensitive to microstructural pathological changes in both anisotropic and isotropic tissue compared to FA and MD. AK are kurtosis in the direction of the principal diffusion tensor eigenvector. RK are kurtosis averaged over all diffusion directions perpendicular to the principal diffusion tensor eigenvector[15].

As the Expanded Disability Status Scale (EDSS)—the clinical scale most frequently used to quantify disability in MS—is heavily weighted toward motor disability. The measurement of spinal cord damage provides clinically relevant information than the assessments of brain damage.

Through DTI of cervical spinal cord, Oh J found that the FA, MD values were more abnormal in the high- vs low-disability subgroup of MS patients[11]. One study showed that the DTI metrics in AD and RD show a pathological increase, and FA shows a pathological decrease in cervical spinal cord T2-hyperintense lesions[14]. Through DKI of cervical spinal cord in patients with MS, Raz E found that cervical cord white matter FA and gray matter MK value were significantly decreased compared with controls[12]. The present study aimed to: 1) quantitatively evaluate microstructural damage of lesion and normal-appearing GM and WM in the CSC of MS patients compared to healthy subjects using MK, MD, and FA value; 2) determine whether MK provides additional information about GM abnormalities compared to MD and FA values; 3) assess the association between DKI metrics of CSC and clinical disability assessed by EDSS score before and after therapy.

Material And Methods

Study population

From January 2018 to October 2019, 48 consecutive patients with MS diagnosed by 2017 McDonald criteria[19] in our institution were subjected to cervical spinal cord MRI before and after therapy. The exclusion criteria were as follows: 1) other related diseases, such as cervical trauma and neuromyelitis optica; 2) contraindications to performing MRI; 3) steroid treatment in the 3 months before MRI. After MS patients had undergone a disease modifying therapies (DMTs)[19], MR scans were performed again when no corticosteroids treatment during the last month. The following demographic and clinical variables were acquired for each patient: age, sex, disease duration, and degree of disability assessed by EDSS score. An experienced neurologist recorded the EDSS score before and after one course of treatment. According to CSC T2-hyperintense, MS patients were divided into patients with T2-hyperintense lesions and patients with no T2-hyperintense lesions. Moreover, 30 healthy sex- and age-matched adults comprised the control group.

MRI acquisition

All images were acquired by a 3.0T MR scanner (Philips Ingenia; Philips Medical Systems, Best, The Netherlands) using a 16-channel head and neck coil. The examinee was placed in the supine position and informed not to move the body as much as possible, breathe calmly, and avoid swallowing movements and cough to reduce motion artifacts. For each subject, cervical spinal cord MRI protocol was as follows:

1. Sagittal T1-weighted, by using a spin-echo MR imaging sequence, 15 contiguous sections was acquired (TR/TE = 550/6.4ms; echo-train length = 4; section thickness/gap = 3/0mm; FOV = 240mm; matrix = 256×256).
2. Sagittal T2-weighted, by using a fast spin-echo MR imaging sequence, 15 contiguous sections were acquired and used to plan axial imaging such that the axial slice stack was centered on the C4-C5 vertebral disc and perpendicular to the spinal cord (TR/TE = 3263/95ms; echo-train length = 36; section thickness/gap = 3/0 mm; FOV = 240 mm; matrix = 256×256).
3. Axial T2*-weighted, centered on the C4-C5 vertebral disc, were acquired using an averaged multiple fast-field echo (mFFE) sequence with 5 echoes and 35 contiguous axial sections was acquired (TR/TE = 700/7.2 0 ms, 4 additional echoes where $\Delta TE = 8.83\text{ms}$; flip angle = 28°; section thickness/gap = 3/0 mm; FOV = 150×150 mm²; matrix = 512×512). The mFFE sequence provided high-resolution detail of the cervical spinal cord, including GM, WM, and was used to delineate structures of regions of interest[20].
4. Axial DKI sequence, the center position is the same as axial T2-weighted, using a twice-refocused spin-echo diffusion sequence with an echo-planar imaging readout with 32 different diffusion-encoding directions and 35 contiguous axial sections. For each direction, 4 b-values (0, 700, 1400, and 2100 s/mm²) were used (TR/TE = 3100/101 ms; section thickness/gap = 3/0 mm; FOV = 80×80 mm²; matrix = 512×512). The gradient length (δ) and time between the two leading edges of the diffusion gradients (Δ) were 9.8 and 44.1 ms, respectively. F.O.S. is on, one RF pulse is collected

within FOV, and the other RF pulse is collected in the area of 50% FOV on both sides of the phase coding direction.

Image analysis

All DKI data were imported in the in-house software (Diffusion Kurtosis Estimator) in MATLAB to spatial smoothing, correct for eddy distortions, median filtering, denoising and correction for Gibbs ringing artifacts, which has been validated and reported before[12, 15]. We use the two-dimensional (2D) rigid-body algorithm reported in the literature to coregistering all diffusion weighted image to T2*-weighted image and obtain FA, MD and MK maps of DKI-derived indices[12, 21]. DKI metrics included FA, MD, and MK values. First, the FA and MD values were calculated in the DTI model. Second, the diffusion kurtosis was calculated on a voxel-by-voxel basis as described previously [18]. Four b values were used in the following equation:

$$\ln [S(b)] = \ln [S(0)] - b \cdot D_{\text{app}} + 1/6 \cdot b^2 \cdot D_{\text{app}}^2 \cdot K_{\text{app}}$$

where D_{app} is the apparent diffusion coefficient for the given direction, and K_{app} is the apparent kurtosis coefficient that is dimensionless. Then, region of interest (ROI) was used to measure the DK metrics of the spinal cord between C1 and C7 levels, generating 35 values for each of the DKI metrics in each subject (1680 spinal cord sections for 48 patients and 1050 spinal cord section for 30 controls). Of the 2730 sections, 205 included T2*-weighted visible lesions, whereas the remaining were classified as normal-appearing CSC. The lesions were outlined on the T2*-weighted images using the MIPAV (Medical Image Processing, Analysis, and Visualization) application for quantitative analysis and visualization of medical images (<http://mipav.cit.nih.gov>). Then, the outlined ROIs were automatically transferred onto the corresponding DKI maps by the dTV II FZR software to obtain quantitative values from each parameter[22]. In addition, normal-appearing GM and WM from patients and healthy controls were measured using rectangular ROIs (size: 2 voxels, 3.0 mm²) placed on the T2*-weighted images in the right and left anterior gray horns and the dorsal column (reduce artifacts caused by the flow of the cerebrospinal fluid, the data within the WM had to be measured as close to the inner side of the spinal cord as possible) in 35 contiguous sections at the C1–C7 level, as described in Fig. 1. Then, the dTV II FZR software allowed for copying of the ROIs and guaranteed the evaluation of the same region with corresponding DKI maps. The normal-appearing GM/WM metrics were calculated by averaging the results obtained in all ROIs (70 ROIs for GM and 35 ROIs for WM). Thus, each subject contributed one value for each of MK, MD, and FA for the total spinal cord, including lesions and normal-appearing GM/WM. ALL image data processing and evaluation were performed by a neuroradiologist who specialized in neuroimmunology. Sagittal T2-weighted and axial T2*-weighted were used to identify and count the lesions in the CSC by a neuroradiologist who worked for 15 years.

Statistical Analysis

SPSS software (version 21.0; SPSS, Chicago, IL, USA) was used for statistical analysis. Intra-class correlation coefficients were used to evaluate the agreement between the two readers for each DKI parameters. All demographic, clinical, and EDSS scores were examined with the non-parametric Wilcoxon rank-sum test or the Kruskal-Wallis test because the values did not follow normal distributions. An ANOVA model, adjusted for age and sex, was used to assess the differences in DKI metrics among the study groups. A χ^2 test was used for patient sex comparison. Before and after therapy, the DKI metrics in the MS group were compared by paired-sample t-test. The correlations between EDSS score and DKI metrics from the lesions and the GM and WM were determined using Pearson's correlation coefficient. $P < 0.05$ indicated statistical significance.

Results

Demographics

Subject demographics and clinical data for our patient and control groups are provided in Table 1. No significant differences were detected in sex ($P = 0.632$) among the three groups. Among 48 patients with MS, 31 had relapsing-remitting (RR) MS, 10 had secondary progressive (SP) MS, and 7 presented primary-progressive (PP) MS. A total of 25 T2 hyperintense lesions were identified in 15/ 48 (31%) patients with MS (10 with SPMS, 4 with PPMS, and 1 with RRMS). A median of 2 (range: 1–3) lesions was noted in each patient. One cervical spinal cord T2 hyperintense lesion was detected in 8/48 (17%) patients with MS (5 with SPMS, 2 with PPMS, and 1 with RRMS), two cord lesions were detected in 4/48 (8%) patients (2 with SPMS and 2 with PPMS), and three cord lesions were detected in 3/48 (6%) patients (2 with SPMS and 1 with PPMS). T2-weighted images, appearing normal, were found in the other 33/48 (69%) patients (30 with RRMS, 2 with PPMS, and 1 with SPMS). The MS patients with T2 hyperintense lesions were older, had prolonged disease duration and had higher EDSS scores than the patients with no T2 hyperintense (all $P < 0.001$).

Table 1
Main demographic of clinical data of the study groups

Parameter	Healthy Subjects (<i>n</i> = 30)	Patients with T2 hyperintense (<i>n</i> = 15)	Patients with no T2 hyperintense (<i>n</i> = 33)	<i>P</i> value
Sex				.632*
Men	11	7	12	
Women	19	8	21	
Mean age (y)	44.2 (19–55)	45.7 (21–56)	39.6 (17–44)	.001†
Median no. of CSC T2 hyperintense lesions	—	2 (1–3)	—	
Median disease duration (y)	—	21 (2–44)	12 (0.25–41)	.001††
Median EDSS score	—	6.0 (1.5–8.0)	3.0 (1.0–6.0)	.001††
<p>Note.—Data in parentheses are range. Abbreviation: EDSS = Expanded Disability Status Scale.</p> <p>*Determined with χ^2 test.</p> <p>†Determined with AVNOA.</p> <p>††Determined with <i>Kruskal-Wallis</i> test.</p>				

Comparison of DKI metrics between healthy subjects and MS patients

Inter-rater agreement for DKI metrics between the two readers was found to be good (range 0.8 to 0.9). Figure 2 shows the distribution of DKI metrics in CSC of MS patients and healthy subjects. Compared to healthy subjects (*n* = 30), FA, AD, MK, RK were significantly decreased (all *P* < 0.05) and MD, RD, AK value were increased (*P* < 0.05) in MS patients (*n* = 48).

Table 2 shows that DKI metrics of GM placed the ROIs in bilateral ventral horns and WM placed the ROIs in the dorsal column, which were compared at the C1–C7 level in healthy subjects (*n* = 30) and MS patients with no T2 hyperintense lesions at that level (*n* = 33). In MS patients, normal-appearing GM-MK, GM-RK and WM-FA, WM-AD values were significantly decreased compared to those in healthy subjects (*P* = 0.018, < 0.001 and < 0.001, 0.0211 respectively), while other DKI parameters were not significantly different across the two groups of subjects.

Table 2

Comparison of DKI metrics between MS patients with no T2 hyperintense and healthy subjects

Metrics [§]	Location	Patients with no T2 hyperintense (<i>n</i> = 33)	Healthy subjects (<i>n</i> = 30)	Parameter	<i>P</i> value [†]
MK	GM	1.08 ± 0.02	1.15 ± 0.04	<i>t</i> = -9.807	.018
	WM	1.12 ± 0.13	1.11 ± 0.03	<i>t</i> = -1.789	.079
MD	GM	0.71 ± 0.01	0.70 ± 0.02	<i>t</i> = 0.899	.372
	WM	0.90 ± 0.02	0.89 ± 0.07	<i>t</i> = -1.059	.294
FA	GM	0.80 ± 0.12	0.81 ± 0.07	<i>t</i> = -1.828	.073
	WM	0.52 ± 0.04	0.63 ± 0.03	<i>t</i> = -17.749	< .001
AD	GM	1.54 ± 0.02	1.55 ± 0.01	<i>t</i> = -1.021	.284
	WM	1.67 ± 0.03	1.78 ± 0.04	<i>t</i> = -8.904	.0211
RD	GM	0.65 ± 0.04	0.64 ± 0.05	<i>t</i> = -2.104	.081
	WM	0.68 ± 0.02	0.67 ± 0.02	<i>t</i> = -1.504	0.231
AK	GM	0.59 ± 0.01	0.58 ± 0.02	<i>t</i> = 0.922	0.512
	WM	0.60 ± 0.02	0.59 ± 0.03	<i>t</i> = 0.899	0.458
RK	GM	0.91 ± 0.03	1.27 ± 0.02	<i>t</i> = -16.904	< .001
	WM	0.94 ± 0.01	0.95 ± 0.02	<i>t</i> = -0.904	0.436
<p>Note.—Abbreviation: MK = mean kurtosis (unitless); MD = mean diffusivity ($\times 10^{-3}$ mm² /s); FA = fractional anisotropy (unitless); AD = axial diffusivity ($\times 10^{-3}$ mm² /s); RD = radial diffusivity ($\times 10^{-3}$ mm² /s); AK = axial kurtosis (unitless); RK = radial kurtosis (unitless). GM = gray matter; WM = white matter. DKI metrics from GM and WM for patients with no T2 hyperintense and healthy subjects.</p> <p>[§]Data are ± standard deviation.</p> <p>[†]Determined with AVNOA.</p>					

Table 3 shows that DKI parameters of sections from lesions were compared to the values of sections from normal-appearing CSC in MS patients with T2 hyperintense (*n* = 15) and MS patients with no T2 hyperintense lesions (*n* = 33). The six metrics differed significantly: MK, FA, AD, RD, AK and RK values were lower and MD values were higher in lesions than in normal-appearing CSC (all *P* < 0.001).

Table 3
Comparison of DKI metrics between MS patients

Metrics [§]	Patients with T2 hyperintense (<i>n</i> = 15)	Patients with no T2 hyperintense (<i>n</i> = 33)	Parameter	<i>P</i> value [†]
MK	0.91 ± 0.03	1.06 ± 0.02	<i>t</i> = -23.109	< .001
MD	1.14 ± 0.01	0.80 ± 0.01	<i>t</i> = 93.275	< .001
FA	0.42 ± 0.01	0.66 ± 0.02	<i>t</i> = -41.311	< .001
AD	2.03 ± 0.03	2.27 ± 0.02	<i>t</i> = -35.271	< .001
RD	0.75 ± 0.02	0.97 ± 0.03	<i>t</i> = -55.311	< .001
AK	0.56 ± 0.01	0.86 ± 0.01	<i>t</i> = -44.834	< .001
RK	0.67 ± 0.03	0.91 ± 0.02	<i>t</i> = -64.167	< .001
<p>Note.—Abbreviation: MK = mean kurtosis (unitless); MD = mean diffusivity ($\times 10^{-3}$ mm² /s); FA = fractional anisotropy (unitless); AD = axial diffusivity ($\times 10^{-3}$ mm² /s); RD = radial diffusivity ($\times 10^{-3}$ mm² /s); AK = axial kurtosis (unitless); RK = radial kurtosis (unitless). DKI metrics from lesion for patients with T2 hyperintense and from gray/white matter for patients with no T2 hyperintense.</p> <p>[§]Data are ± standard deviation.</p> <p>[†]Determined with AVNOA.</p>				

DKI metrics and therapeutic effect

Tables 4 and 5 showed that DKI parameters of sections from lesions and the values in sections of normal-appearing GM/WM were compared before and after one course of treatment in MS patients with T2 hyperintense (*n* = 15) and MS patients without T2 hyperintense lesions (*n* = 33), respectively. After the end of the treatment, MK, FA, AD, RD, AK and RK values were increased while the MD value was decreased compared to that before the treatment; the difference was statistically significant (all *P* < 0.001) in MS patients with T2 hyperintense, although no significant change was noted in the number, location, and signal intensity of T2-hyperintense lesions. In MS patients without T2 hyperintense, normal-appearing GM-MK and normal-appearing WM-FA and WM-AD increased significantly (all *P* < 0.001), while normal-appearing WM-MD decreased (*P* = 0.019) after treatment compared to that before treatment.

Table 4

Comparison of DKI metrics before and after treatment in MS patients with T2 hyperintense (n = 15)

Metrics [§]	Before treatment	After treatment	Parameter	Pvalue [‡]
MK	0.91 ± 0.03	0.98 ± 0.05	$t = 10.800$	< .001
MD	1.14 ± 0.01	1.12 ± 0.01	$t = 6.441$	< .001
FA	0.42 ± 0.01	0.45 ± 0.02	$t = 10.247$	< .001
AD	2.03 ± 0.03	2.06 ± 0.02	$t = 11.156$	< .001
RD	0.75 ± 0.02	0.77 ± 0.01	$t = 5.566$	< .001
AK	0.56 ± 0.01	0.58 ± 0.02	$t = 7.122$	< .001
RK	0.67 ± 0.03	0.71 ± 0.02	$t = 12.564$	< .001
<p>Note.—Abbreviation: MK = mean kurtosis (unitless); MD = mean diffusivity ($\times 10^{-3}$ mm² /s); FA = fractional anisotropy (unitless); AD = axial diffusivity ($\times 10^{-3}$ mm² /s); RD = radial diffusivity ($\times 10^{-3}$ mm² /s); AK = axial kurtosis (unitless); RK = radial kurtosis (unitless). GM = gray matter; WM = white matter. DKI metrics from lesion for patients with T2 hyperintense.</p> <p>[§]Data are ± standard deviation.</p> <p>[‡]paired-sample t-test.</p>				

Table 5

Comparison of DKI metrics before and after treatment in MS patients with no T2 hyperintense (n = 33)

Metrics [§]	Location	Before treatment	After treatment	Parameter	Pvalue [‡]
MK	GM	1.08 ± 0.02	1.09 ± 0.04	$t = 5.200$	< .001
	WM	1.12 ± 0.13	1.11 ± 0.03	$t = 1.153$	.258
MD	GM	0.71 ± 0.01	0.71 ± 0.12	$t = 1.153$	.59
	WM	0.90 ± 0.02	0.88 ± 0.02	$t = 2.141$	.019
FA	GM	0.80 ± 0.12	0.81 ± 0.03	$t = 1.391$	.174
	WM	0.52 ± 0.04	0.53 ± 0.03	$t = 4.983$	< .001
AD	GM	1.54 ± 0.02	1.54 ± 0.03	$t = 1.168$	.877
	WM	1.67 ± 0.03	1.71 ± 0.04	$t = 6.145$	< .001
RD	GM	0.65 ± 0.04	0.64 ± 0.02	$t = 1.213$	.644
	WM	0.68 ± 0.02	0.67 ± 0.03	$t = 1.225$	.678
AK	GM	0.59 ± 0.01	0.59 ± 0.02	$t = 1.247$	.358
	WM	0.60 ± 0.02	0.60 ± 0.04	$t = 1.328$	.558
RK	GM	0.91 ± 0.03	0.90 ± 0.02	$t = 1.928$	.093
	WM	0.94 ± 0.01	0.93 ± 0.02	$t = 1.557$	.107
<p>Note.—Abbreviation: MK = mean kurtosis (unitless); MD = mean diffusivity ($\times 10^{-3}$ mm² /s); FA = fractional anisotropy (unitless); AD = axial diffusivity ($\times 10^{-3}$ mm² /s); RD = radial diffusivity ($\times 10^{-3}$ mm² /s); AK = axial kurtosis (unitless); RK = radial kurtosis (unitless). GM = gray matter; WM = white matter. DKI metrics from GM and WM for patients with no T2 hyperintense.</p> <p>[§]Data are ± standard deviation.</p> <p>[‡]paired-sample t-test.</p>					

DKI metrics and disability as determined by the EDSS

In the MS patients of CSC of T2-hyperintense lesion, a significantly converse correlation was established between the EDSS score and MK value before and after treatment ($r = -0.634$, $P = 0.011$ and $r = -0.645$, $P = 0.009$, respectively). In addition, significant converse correlations were established between the EDSS score and MK value of normal-appearing GM before and after the treatment ($r = -0.630$, $P = 0.011$ and $r = -0.377$, $P = 0.031$, respectively) (Fig. 3). No significant correlations were established between the EDSS score and other DKI parameters in MS patients.

Discussion

CSC injuries detected on MRI have critical diagnostic and prognostic value for MS[23]. Routine MRI of CSC could detect lesions with only limited micropathological change. Ozturk showed that T2*-weighted gradient-echo scans in the spinal cord reveal MS lesions with greater regularity compared to routine T2-weighted spin-echo imaging[24]. Thus, we used T2*-weighted imaging to count and outline all T2-hyperintense lesions in MS patients, which is consistent with the sequence used by Chuhutin et al[25].

In the current study, MS patients with normal-appearing GM and WM had damage likely due to CSC microscopic injuries that were not detected by routine MRI. The MS pathology of CSC included axonal loss, inflammation, demyelination, and gliosis; each of these features could be inferred with quantitative MR metrics of tissue structure[26–29]. Therefore, the micropathological changes of CSC for MS patients played a critical role in determining the therapeutic plans and evaluating prognosis. In line with previous DKI studies[12], our DKI metrics from T2-hyperintense lesions and normal-appearing GM and WM suggested extensive microscopic damage of CSC in MS patients compared to healthy subjects, suggesting that quantitative MR of CSC overcomes clinical-radiology paradox. Demyelination seems to play a part in the early phase, while other processes, such as axonal loss, are prominent in the later course of the disease[12]. Both axonal loss and demyelination decrease FA and AD, inflammation, and gliosis, increasing in MD[23, 30].

Accumulating evidence indicated that CSC injury in MS patients is not only limited to WM but also involves the GM[31–34]. High annualized spinal cord atrophy rates were correlated with reductions in gray matter volume. The study by Kearney et al[17]. and Schlaeger et al[16]. suggested that loss of GM is the main contributor to progressive disability. The current study showed that only the MK and RK values of normal-appearing GM were significantly reduced in MS patients compared to the healthy participants, indicating that GM injury persists below the resolution of routine T2-weighted imaging, MK and AK could serve as a more sensitive potential biomarker for evaluating the GM than DTI-metrics in the early diagnosis of the disease. Subsequently, MK and AK may provide more information that is different and complementary to that obtained with DTI on the evaluation of GM damage. Decreased MK is likely associated with neuronal shrinkage, pronounced gliosis, and demyelination of the spinal cord GM[16]. This phenomenon was consistent with muscular atrophy (especially in the intrinsic hand muscles) for the majority of MS patients assessed at autopsy.

Additionally, we found severe lesions than in normal-appearing GM and WM for MS patients. Lukas et al. implied that patients suffering from disease progression during the follow-up period had significantly higher rates of CSC atrophy than patients with a stable disease course[7]. One of the main features of progressive patients with MS was the severe and extensive spinal cord involvement. A large number of lesions of CSC were observed in progressive MS than in relapsing MS phenotypes[37, 38]. In 15 MS patients with T2-hyperintense lesion, 14 were progressive MS, including 10 SPMS and 4 PPMS, confirming a greater number of lesions in patients with SPMS and PPMS vs. RRMS patients[39, 40]. This might be correlated with a greater axonal loss in this PPMS phenotype.

In the initial MR studies, a converse association was found between MK from the lesions and normal-appearing GM and the EDSS score in MS patients, implying that potential biomarkers of MK monitor the disability in MS. Also, MK might help to improve the monitoring of disease progression and prediction of disease evolution.

The variability of axon and dendrite orientations—termed neurite orientation dispersion—is reduced in the spinal cords of patients with MS[41]. This finding could provide a novel biomarker for MS prognosis and therapeutic efficacy. Axonal loss in the CSC is a key source of monitoring disease progression in patients with MS. Although no increase was detected in the number of lesions after the treatment in the current study. FA and AD values originated from lesions and normal-appearing WM are significantly increased (all $P < 0.001$), which might indicate regeneration of neural axons. Similarly, MK is increased (all $P < 0.001$) at lesions and normal-appearing GM, indicating that MK may assess therapeutic efficacy[38].

Limitations

First, the number of MS patients was low and not selected according to MS phenotypes. Reportedly, FA and MD of CSC are differences among different subtypes of MS patients[38]. However, the differences in MK have not been reported among various subtypes of MS patients, necessitating in-depth research. Second, the FA and MD estimated inside DKI framework may be more accurate in Thaler's study, which is what we need to improve in the future[42]. Third, the resolution and SNR of the DKI acquisition are not sufficiently high to differentiate the gray/white matter, future research needs to use a high in-plane resolution of DWI acquisitions (e.g. 1 mm^2). Fourth, transferring the ROIs does not correct for the distortion from the EPI readout, low SNR and resolution in DKI images. Fifth, this cross-sectional study could not demonstrate how DKI-metrics dynamically change as MS advances continually. Future longitudinal studies are warranted to examine whether the current approach could be used to monitor the disease progression of MS. Sixth, our study was limited to the cervical spinal cord. Regina et al. demonstrated that remarkable GM atrophy is present at lower thoracic levels, which might affect the EDSS[43].

Conclusion

Spinal cord micropathological abnormalities at disease onset have critical implications for diagnosis and prognosis. Quantitative DKI metrics of CSC could be sensitive to the axonal loss and other pathological processes of lesions and normal-appearing GM and WM, assigning quantitative MRI a key role to elucidate the association between disability and spinal cord abnormalities in MS patients.

Declarations

Acknowledgments

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Authors' contributions

BBY conceived and designed the study, LD supervised the research. BBY, SZQ and ZBX collected and analyzed data. ZZN, JYG interpreted data. LD substantively revised it. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets collected and analyzed during the current study are available from the corresponding author upon reasonable request.

Ethical Approval

The study was approved by the Medical Research Ethics Committee and the Institutional Review Board of the First Hospital of Jilin University (2020-485) and was performed in accordance with the principles expressed in the Declaration of Helsinki. All study participants provided written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Figures

Figure 1

Axial T2* weighted image (a) of the cervical spinal cord at C2/C3 disk level shows the location of ROIs placed in the gray matter of the bilateral ventral horns (yellow) and white matter of the dorsal column (red). Corresponding mean kurtosis (b), mean diffusivity (c), and fractional anisotropy (d) maps. Images are from a healthy subject.

Figure 2

The box-and-whisker plots shows the distribution of FA, MD, AD, RD, MK, AK and RK value in cervical spinal cord of MS patients and healthy subjects. Patients with MS had a significantly smaller FA, AD, MK, and RK value as well as higher MD, RD and AK value than healthy subjects (all $P < .005$).

Figure 3

Scatterplots of the relationship between EDSS score and MK. **a.** shows that the MK value of patients with T2-hyperintense lesions is negatively correlated with the EDSS score; **b.** shows that the MK value of patients with T2-hyperintense lesions is negatively correlated with the EDSS score after treatment; **c.** shows that the MK value of patients without T2-hyperintense lesions is negatively correlated with the EDSS score; **d.** shows that the MK value of patients without T2-hyperintense lesions is negatively correlated with the EDSS score after treatment.