

# Identifying the injury in demyelinating cervical spinal cord disease: A diffusion tensor imaging and tractography study

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## Abstract

**Background & Objectives:** Multiple sclerosis (MS), neuromyelitis optica (NMO) and acute transverse myelitis (ATM) are common diseases in neurology; however their corresponding cervical spinal cord involvements are still ambiguous. The purpose of this study was to demonstrate the utility of diffusion tensor imaging (DTI) and diffusion tensor tractography (DTT) in identifying the injury in cervical spinal cord. **Methods:** Nine patients and nine healthy volunteers were enrolled in this study. Conventional sequences and DTI scan were performed on each participant. **Results:** The average fractional anisotropy (FA) values of the cervical cord in patients with acute cerebral type MS, acute or stationary cerebrospinal type MS, acute NMO, or acute ATM were all significantly decreased relative to the control group ( $p < 0.05$ ). As to the cerebrospinal type MS, the changes in acute-stage patients were more apparent ( $p < 0.05$ ). The average FA value of the cervical cord in acute NMO was decreased more extensively, involving the normal-appearing spinal cord ( $p < 0.05$ ). In patients with MS or NMO, The lesions showed significantly hypointense on FA images and directionally encoded color (DEC) images, nevertheless the pathological areas on DTI images were no significantly different from those on routine sequences. On DTT, the fiber tracts in the lesion-involved regions were all sparser than that in control regions, nevertheless interruption or impairment of fiber tracts could only be noted in NMO patients. Bilateral differences of average FA values in the cervical cord was noted in one case with ATM and another case with MS ( $p < 0.05$ ), and the decrease of FA values was significant in the main side of clinical presentations.

**Conclusion:** DTI and DTT may be a sensitive measure for early cervical injury in MS, NMO and ATM.

## INTRODUCTION

Myelopathy is frequent in demyelinating diseases of central nervous system where acute inflammatory response and cervical spinal involvement is common.<sup>1-2</sup> In the spectrums of demyelinating diseases, multiple sclerosis (MS), neuromyelitis optica (NMO) and acute transverse myelitis (ATM) are common particularly among Asians, often resulting in significant disability.<sup>1-3</sup> The commonly occurring lesions in cervical spinal cord can be detected with conventional sequences of MRI in acute-onset patients. However, differential diagnosis often depends upon laboratory tests to demonstrate the absence of associated systemic diseases.<sup>2,4</sup> Besides differential diagnosis, quantitative analysis of the disease severity as well as the prognostic evaluation based

on the current radiological examinations is still unavailable.<sup>5,6</sup> Diffusion tensor imaging (DTI) and diffusion tensor tractography (DTT) are advanced MRI techniques that enables the measurement of the anisotropic restricted diffusion of water in tissue in order to produce neural tract images. It enables the quantification of diffusion anisotropy, and detection of subtle changes in the white matter which is normally not observed on conventional MRI images.<sup>7</sup> Recently, the application of DTI in cerebral diseases, especially MS, have been reported.<sup>8,9</sup> However, evidence on the clinical value of DTI in spinal cord diseases, especially in patients with NMO or ATM is lacking.<sup>10,11</sup> In the present study, we used DTI and clinical functional assessment systems to quantitatively evaluate the severity of disease in patients with MS, NMO and ATM.

## METHODS

### *Patient selection*

Subjects were consecutively recruited in the period of January 2013–January 2014 from the neurology department of the First Affiliated Hospital of Jilin University. Three patients had first episode NMO according to the diagnostic criteria of Wingerchuk.<sup>12</sup> Two patients had first episode ATM according to the diagnostic criteria of ATM.<sup>13</sup> Two patients had first episode acute cerebral type MS and 2 patients were third episode cerebrospinal type MS according to the diagnostic criteria of McDonald.<sup>14</sup> The demographic characteristics of the patients are presented in Table 1.

Nine healthy volunteers who were matched for age and sex were enrolled as the control group. The unenhanced MRI images of all the volunteers were normal, and none of the controls had a previous history of neurological or psychiatric diseases. The controls also had no past history of anti-neuropathic or psychotropic medication.

The study was approved by the Institutional Review Board and Ethics Committee of the First Affiliated Hospital of Jilin University. All participants gave written consent.

### *Neurological assessments*

All participants underwent a comprehensive neurological assessment by an experienced neurologist who was blinded to the diagnosis of the participants. The assessment was performed within 24 hours following the conventional MRI and DTI scan. They were evaluated for the severity of the neurological deficit by grading systems as suggested by American Spinal Injury Association (ASIA) scoring system. The result is summarized in Table 1.

### *MR image acquisition*

All the patients and control subjects underwent MR imaging on a Siemens Trio 3.0 Tesla scanner with a 12-channel staged-array whole-neck coil (Magnetom Tim Trio, Siemens Medical Solutions, Erlangen, Germany). The protocol included localizing sagittal and coronal T1-weighted images, followed by turbo spin-echo axial T1- and T2-weighted images (Gradient strength: 45 mT/m). Axial DTI of the cervical spinal cord was then performed using pulsed gradient, spin-echo, double-shot, echo-planar imaging with the following parameters: 56 axial slices, repetition time (TR)=7600 ms, echo time (TE)=93 ms, slice thickness (ST)=3 mm, the

number of diffusion-encoding gradient directions (NDGD)=64, field of view (FOV)=230 mm×230 mm (the upper limit over brain stem, and the lower limit exceeding the level of T3), and acquisition matrix (AM)=320×320. The DTI imaging plane was parallel to the conventional axial images, and perpendicular to the long axis of the spinal cord. The duration of DTI acquisitions lasted for 6 minutes and 42 seconds per patient study, during which, time the patients were asked to hold still and avoid swallowing. In addition, every patient underwent MRI of the brain on the same MR scanner using standardized head coils and the following sequences: Axial FLAIR-weighted images, coronal T2-weighted images, and axial T1-weighted images.

### *MR image analysis*

The DTI data were post-processed on a dedicated workstation (Leonardo, Siemens Medical Solutions, Erlangen Germany). After an initial correction of geometric distortions, the following two-dimensional color or gray-scale images were generated: directionally encoded color (DEC) maps and fractional anisotropy (FA) maps. The specific regions of interest (ROIs) were manually set on the FA images, and then copied to the other created DTI maps (diameter=1.8 mm). The ROIs included: a) The acute-stage cervical spinal lesions, b) The stationary-stage cervical spinal lesions, and c) The normal-appearing spinal white matter regions. For each patient, FA values were measured in ROIs.

For the reconstruction of DTT, the NEURO 3D software from Siemens was utilized on the Leonardo console. The orientation and distribution of cervical spinal white matter fiber tracts were intuitively displayed.

## RESULTS

### *Demographic and clinical manifestations*

The patients consisted of 7 women and 2 men, with a mean age of 37.8±14.8 years (range, 22–61 years). Five patients presented with motor deficits, 6 with sensory deficits, and one patient with NMO had sphincter dysfunction. In all patients, the symptoms onset was more than one month preceding the DTI scanning. The neurological evaluations were performed at onset of symptom, admission to hospital, discharge, and at follow-up (one year later). Their clinical features are summarized in Table 1.

**Table 1: The clinical features and neurological assessments in the study patients**

Patient	Age (y)	Sex	Symptoms	Duration (week)	Diagnosis	ASIA Score	
						Sensory (Total 22)	Motor (Total 100)
1	23	F	Weakness, sensory change	1	ATM	162/152/182/212	92/90/96/100
2	56	M	Weakness, sensory change	1	ATM	125/112/144/202	60/51/78/89
3	33	F	Blurring vision	1	NMO	224/224/224/224	100/100/100/100
4	49	F	Weakness, sensory change, sphincter dysfunction	1	NMO	180/168/200/224	63/55/80/93
5	61	F	Weakness, sensory change	1	NMO	162/148/185/220	83/75/92/95
6	29	F	Blurring vision, Vertigo	1	MS	224/224/224/224	100/100/100/100
7	22	F	Blurring vision, diplopia	1	MS	N.A.	
8	25	M	Sensory change	1	MS	N.A.	
9	42	F	Weakness, sensory change	1	MS	184/168/205/221	76/67/89/93

F: Female; M: Male; N.A.: Not available; ATM: Acute transverse myelitis; NMO: Neuromyelitis optica; MS: Multiple sclerosis; ASIA: American Spinal Injury Association

Duration: The interval between onset of symptoms and diffusion tensor imaging (DTI);

ASIA Score is presented as "onset/admission/discharged/1 year follow-up"

#### *Differences between patient and the age-sex-matched controls*

The average FA values of the cervical cord in patients with acute cerebral type MS, acute or stationary cerebrospinal type MS, acute NMO, or acute ATM were significantly decreased as

compared to the control group ( $P<0.05$ ). With regards to the cerebrospinal type MS (Patients 8 and 9), the changes were more apparent in the acute-phase patient than the stationary-phase patient ( $P<0.05$ ). The average FA values as compared to controls are summarized in Table 2.

**Table 2: Fractional anisotropy (FA) differences between patients and the age-sex-matched control**

Patient	Diagnosis	Location of the lesions	Fractional anisotropy		P value
			Patient	Control	
1	ATM	C2-7	0.54±0.059	0.69±0.041	0.00
2	ATM	C2-7	0.47±0.065	0.69±0.058	0.00
3	NMO	C2-7	0.57±0.012	0.70±0.060	0.002
4	NMO	C2-3	0.43±0.094	0.69±0.053	0.00
5	NMO	C2-3	0.57±0.064	0.64±0.055	0.003
6	MS	N*	0.57±0.061	0.73±0.053	0.018
7	MS	N*	0.62±0.091	0.72±0.052	0.003
8	MS	C2-6	0.59±0.085	0.71±0.060	0.00
9	MS	C2-6	0.50±0.082	0.66±0.057	0.00

\* N: No visible lesion was noted on conventional magnetic resonance images

ATM: Acute transverse myelitis; NMO: Neuromyelitis optica; MS: Multiple sclerosis

**Table 3: Lateralization analysis of decrease in FA value in study patients**

Patient	Level *	Left-side FA	Right-side FA	P value
1	C4	0.45±0.005	0.47±0.029	0.211
2	C4	0.57±0.044	0.53±0.055	0.037
3	C4	0.52±0.116	0.53±0.149	0.704
4	C2	0.50±0.061	0.43±0.119	0.151
5	C2	0.62±0.064	0.62±0.056	0.844
8	C4	0.53±0.083	0.53±0.042	0.764
9	C4	0.46±0.091	0.56±0.046	0.004

\* Level: The level of the center of lesions on T2-weighted images

# The data of Patient 6 and Patient 7 was not available as no visible lesion was observed on T2-weighted images  
 FA: Fractional anisotropy

*Lateralization analysis of decrease in FA values*

In the corresponding level of the cervical spinal lesion, bilateral differences of average FA values in the cervical cord was only noted in two cases, *i.e.*, Patient 2 with ATM and Patient 9 with MS. The decrease was significant ( $P<0.05$ ) in the more symptomatic side. No significant decrease ( $P<0.05$ ) in lateralization of the FA values was observed in other patients (Table 3).

*The FA changes in the distal normal-appearing white matter (NAWM)*

Besides the lesions, the average FA values of the distal normal-appearing white matter were also decreased in patients with acute NMO ( $P<0.05$ ) (Table 4).

*Imaging appearance*

No significant difference was observed in FA and DEC images of control group (Figure 1) and the patient with ATM (Figure 2). In patients with NMO (Figure 3) and those with MS (Figure 4), the lesions showed significantly hypointense FA and DEC images. Nevertheless, the pathological areas on DTI images were not significantly different

from those on routine sequences. On DTT, the fiber tracts in the lesion-involved regions were all sparser than that in control regions. However, interruption or impairment of fiber tracts could only be noted in NMO patients (Figure 3).

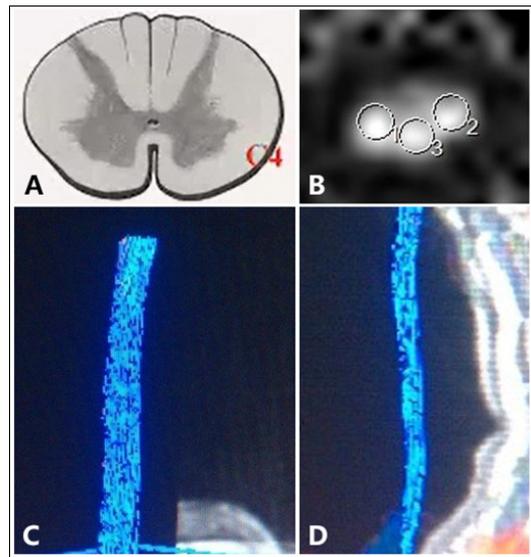


Figure 1. The cross-sectional diagram of the cervical spinal cord (A), fractional anisotropy (FA)map (B), and diffusion tensor tractographic (DTT) images (C&D) in a normal volunteer.

**Table 4: The FA changes in the distal normal-appearing white matter in study patients as compared to control**

Patient	FA(Patient)	FA(Normal)	P value
4	0.589±0.086	0.663±0.083	0.009
5	0.625±0.079	0.704±0.056	0.002

FA: Fractional anisotropy

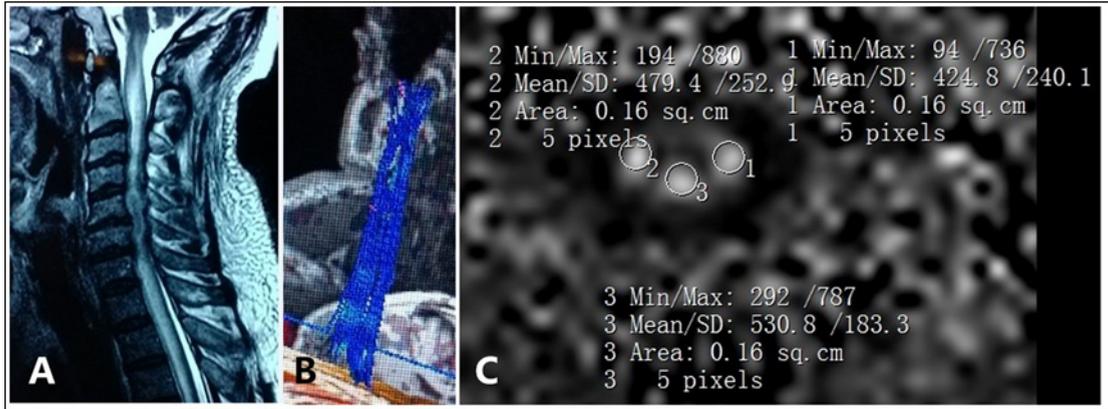


Figure 2. Patient 2 with acute transverse myelitis. The T2-weighted images show a hyperintense cervical spinal lesion (A). On diffusion tensor tractography (DTT), the fiber tracts in the lesion-involved regions are sparser (B). FA values are significantly decreased (C).

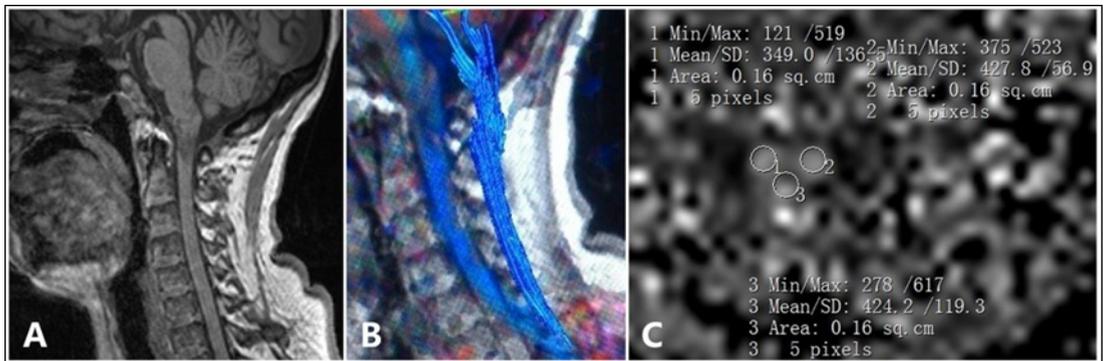


Figure 3. Patient 5 with neuromyelitis optica. The T1-weighted images show a hypointense cervical spinal lesion (A). The DEC images showed significantly hypointense lesions and the diffusion tensor tractographic (DTT) images show interruption of fiber tracts (B). FA values are significantly decreased (C).

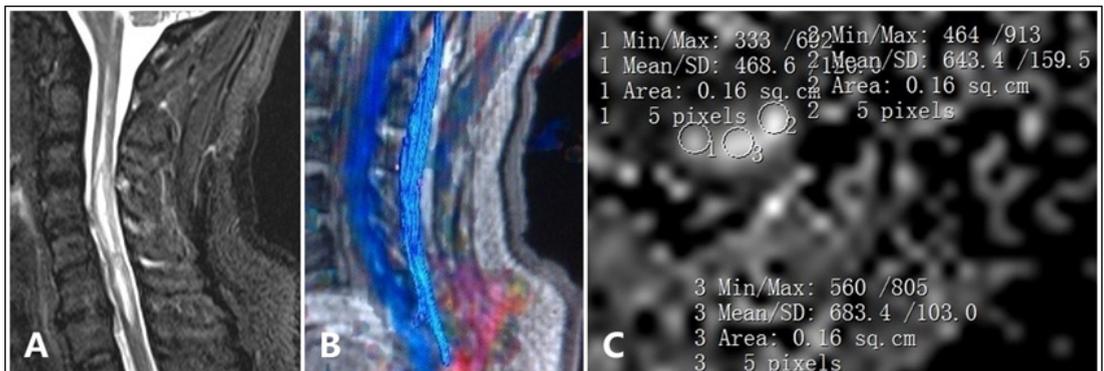


Figure 4. Patient 9 with multiple sclerosis. The T2-weighted images show a hyperintense cervical spinal lesion (A). The DEC images showed significantly hypointense lesions and the fiber tracts in the lesion-involved regions are sparser on diffusion tensor tractography (DTT)(B). FA values are significantly decreased.

## DISCUSSION

MS is an acquired chronic immune-mediated inflammatory condition of the central nervous system, affecting both the brain and spinal cord.<sup>6,9</sup> In the present study, 4 patients were enrolled, and 2 of them had cerebral type MS whose spinal MRI images were normal on conventional sequences (T1, T2 and Gd-DTPA enhanced). However, the average FA values were found to be decreased in these patients, indicating the presence of occult injury which may be invisible on conventional MR images in cervical spinal cord. Previous studies have confirmed the existence of occult injuries in the NAWM and normal-appearing gray matter (NAGM) regions in patients with MS, supporting that MS is a diffuse disease involving the whole central nervous system including brain and spinal cord, rather than being just a focal lesion.<sup>15,16</sup> NAWM is thought to be a balance between inflammation and neuroprotection, and water diffusion may increase when the balance is disrupted.<sup>17</sup> The abnormality of NAWM may also be observed secondary to the Wallerian degeneration of dominant cerebral lesion.<sup>18</sup> Previous reports have also found some obvious pathological changes, which include decrease in FA value and increase in radial diffusivity (RD) index in the normal-appearing spinal cord (NASC) regions of cervical spinal cord in patients with MS.<sup>25</sup> In a DTI study, Hesseltine *et al* proposed that the abnormal changes of NASC may be due to Wallerian degeneration, focal ischemic change, or local demyelination.<sup>19</sup> Our Patient 8 had third episode clinical relapse of MS, and the pathological region (C2-6) in the cervical cord was almost isointense on T1-weighted images. However, the average FA value was lower compared to the control; this was less in magnitude than Patient 9, who had an active-stage lesion on conventional MRI in the cervical cord. This may be related to the myelin repair and regeneration in the late-stage lesion. Besides, Patient 8 had a relatively milder neurological deficiency and more functional improvement clinically during the follow-up period of 6 months DTI and tractography. DTI and tractography may be a sensitive modality for early detection of cervical occult injury, thus, facilitating the evaluation of prognosis. In addition, there are studies on ATM indicating that the decrease in FA values in the caudal NASC region is closely associated with the prognosis<sup>20</sup>; nevertheless, the correlation analysis did not work for the MS patients as the NASC regions were unrecognizable.

Cervical cord involvement is most frequent

clinical site of involvement in spinal MS, and is usually asymmetric. Previous studies have demonstrated that the right-side of the cervical cord was more vulnerable to injury, and right-sided injury was usually more severe.<sup>21</sup> This right-side predominance might be related to the left-side location of the dominant hemisphere in majority of patients, though there is insufficient evidence to support the hypothesis.<sup>22</sup> The present study also did not provide this as our sample size was small.

Previous studies have shown that the decreasing degree of FA values in early-stage lesions or NASC region is parallel to the clinical prognosis with lesser change being correlated with better prognosis.<sup>23,24</sup> The decrease in FA value reflects axonal injury, correlation with clinical recovery has been seen; the lower the FA values, the more severe is the injury, with the more serious neurological dysfunction and the worse outcome.<sup>25</sup> On the other hand, early remyelination could result in the reconstruction of fasciculus anisotropy, leading to an increase in FA values and decrease in RD values, which implies a better prognosis.<sup>26</sup> Furthermore, the decreasing of apparent diffusion coefficient (ADC) values in acute lesions might be related to the proliferation of astrocytes and oligodendrocytes, which can represent remyelination and clinical recovery, also suggesting a more favorable outcome.<sup>27,28</sup> In the present study, Patient 9 had acute spinal-type MS with significantly decreased average FA value, and poor prognosis, which is also consistent with this theory.

NMO is an inflammatory disease of the central nervous system characterized by severe attacks of optic neuritis and myelitis, which exhibits some similarities to MS in clinical manifestations and imaging and has long been considered as a variant of MS.<sup>23,29</sup> Compared to MS, conventional MRI of the spinal cord in NMO exhibits greater longitudinal extension (usually more than three spinal segments), T1 hypointensities, T2 hyperintensities, significant enhancement and central gray matter involvement.<sup>29</sup> However, early NMO lesions may be invisible on conventional MRI images. Some previous investigations have reported the diffusion characteristics of normal-appearing white matter in NMO, and found significant changes in ADC.<sup>30</sup> Comparative studies of DTI between NMO groups and MS groups showed that the FA values of both the anterior and posterior columns were decreased in comparison to controls, where FA value was lower in NMO than in MS, and there was more

extensive demyelination-related NASC damage in NMO patients.<sup>29</sup> Similar studies also supported that NMO is more severe than MS.<sup>29,31,32</sup> On this basis, relevant DTI studies have identified NMO, including the relapsing-remitting subgroup, as a new spinal cord lesion pattern with more severe occult injury in comparison to MS.<sup>23</sup> In the present study, the clinical and radiological profiles were consistent with that reported in the previous studies. The changes in DTI parameters were parallel to the follow-up evaluation scores, suggesting DTI as a sensitive method for predicting prognosis. However, further studies with larger cohort are required to confirm this.

ATM is an autoimmune response that induces segmental demyelination or necrosis at several spinal cord levels, which is thought to be more severe than MS or NMO.<sup>20</sup> Patients with ATM usually present with pain, fever, and a combination of motor, sensory, and sphincter dysfunctions. Studies of DTI on patients with ATM are sparse.<sup>20</sup> Previous reports pointed out that FA values in lesions and in distal NASC regions were significantly decreased in patients with ATM and the decrease in FA values in distal normal-appearing spinal cord is probably related to clinical outcome.<sup>20,33</sup> The mechanism of change in FA value in NASC regions is still unclear. Renoux *et al.* observed specific variations in FA pattern in patients with ATM. They proposed that FA values might depend upon the water diffusivity in the extracellular space along the axon fibers, where a decreased FA values might be related to an increase in the extracellular space induced by demyelination, axonal loss, and unpacking of white matter fibers.<sup>33</sup> In the present study, both patients with ATM had whole cervical segments involvement, thus, no NASC could be identified. However, the FA values decreased in both when compared to the controls, and the amplitude of variations was consistent with the clinical severity and prognosis.

In conclusion, the results of our study suggest that DTI has a potential role in the assessment of the spinal involvement in patients with MS, NMO or ATM. The decreased average FA values could reflect the cervical occult injury in patients with cerebral type MS or NMO. Furthermore, it is noteworthy that the extent of lesions is symmetric in some cases, which is parallel to the clinical manifestations. Further, studies are necessary to establish a better correlation between molecular biology and neuroimaging findings, as well as to define the role of DTI as a clinical and prognostic marker in these patients.

## DISCLOSURE

Conflict of interest: None

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