·Letter to the Editor·

High sensitivity of diffusion tensor imaging in discriminating idiopathic demyelinating optic neuritis

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Dear Sir,

I am Dr. Yan Zhang, from Zhongshan Ophthalmic Center, State Key Laboratory of Ophthalmology Sun Yat-sen University, Guangzhou, Guangdong Province, China. I write to present a report concerning that diffusion tensor imaging has high sensitivity in discriminating idiopathic demyelinating optic neuritis.

Idopathic demyelinating optic neuritis (IDON) is the most common type of idiopathic optic neuritis. It is an acute or subacute demyelinating disease with unilateral or bilateral optic nerve involved [1]. One third to half of the IDON patients have the tendency to develop multiple sclerosis (MS)[2]. Because the lack of direct examination, the diagnosis of IDON is quite complicated, most of which depends on the results of visual functional tests.

Conventional magnetic resonance (MR) scanning sequences can not investigate the destruction of tissue in demyelinating disease like IDON adequately [2-6]. But diffusion tensor imaging (DTI) can noninvasively evaluate the white matter integrity and fiber connectivity *in vivo*. The alternations of diffusion indices, including fractional anisotropy (FA), mean diffusivity (MD), primary diffusivity ($\lambda_{//}$) and transverse diffusivity ($\lambda_{\perp}$), provide information about the break down of myelin and axons within the optic nerve [7-10]. There were several reports that accessing optic neuritis (ON) with DTI in recent years [11-14]. These results show the great potential and capacity of DTI measures as useful biomarkers and indicators for the evaluation of myelin injury in the visual pathway[15-16].

In this study, sixteen IDON patients and fifteen healthy controls matched in age and gender underwent conventional MR scanning sequences and DTI to investigate whether DTI has higher sensitivity in discriminating IDON. We also compared the diffusion indices of optic nerves between the two groups, which may indicate the demyelization of optic nerves.

The research protocol was approved by the ethics committees for clinical research. All of the procedures involving the participants were conducted following the Declaration of Helsinki and institutional guidelines in compliance with the stated regulations. Written informed consent was obtained from all of the participants.

The study group included sixteen patients (3 males and 13 females; age: 36.5 ±3.6y, range: 17-53) with IDON in unilateral or bilateral eyes. Demographics of the study group were listed in Table 1. Fifteen healthy volunteers (3 males and 12 females; age: 38.3±3.3y, range: 20-50) who recruited

Table 1 Demographics and characteristics of patients

Characteristics	Values
Sujects, *n*	16
Age [a, mean (range)]	36.5 (17-53)
Gender, *n* (%)	
F	13 (81.3)
M	3 (18.7)
Diagnosis, *n* (%)	
Clinically isolated syndrome	14 (87.5)
Multiple sclerosis	2 (12.5)
Clinically involved optic nerves	29
Disease duration prior scanning [d, mean (range)]	8 (3-34)
Median visual acuity [mean (range)]	0.4 (0.3-1.2)
Color vision abnormality, *n* (%)	4 (25)
Contrast sensitivity abnormality, *n* (%)	5 (31.3)
Visual field testing abnormality, *n* (%)	14 (87.5)
VEP abnormality, *n* (%)	14 (87.5)
Papillitis, *n* (%)	11 (68.9)
Cerebrospinal fluid examination, *n* (abnormality)	6 (0)

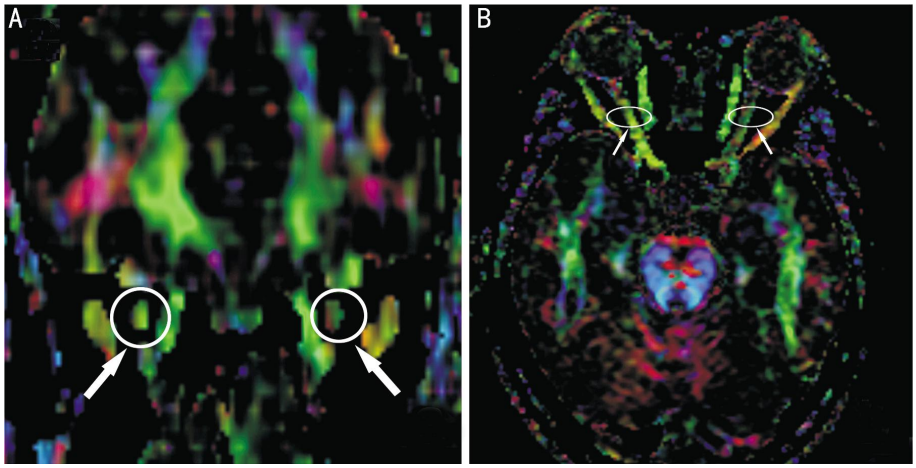

Figure 1 In coronal plane DEC maps, select the anterior, moderate, and posterior segment of the orbital part of optic nerve as the ROIs by the same reader (A). The axial DEC maps were taken as reference (B).

Table 2 The parameters of each acquisition sequence in MRI scanning

Acquisition sequences	TR/TE (ms)	Matrix size	FOV (cm)	NEX	Slice thickness/inter-slice separation (mm)	Acquisition time (min:s)
T_1WI	140/2.0	320×272	24×20	3	6.5/0.8	1:32
T_2WI	4900/99.3	320×224	24×18	2	5/1.5	1:42
T_2-FLAIR	8500/128	320×192	24×24	1	5/1.5	2:24
STIR- T_2WI	2500/60	256×224	24×20	2	6.5/0.8	2:30
DTI SE-EPI	6000/60.1	128×128	24×24	2	3/0	6:52

from the out-patients were taken as controls. Inclusion criteria consisted of 1) right handed; 2) the best corrected visual acuity is 1.0 in each eye without history of ocular disease; 3) there is no occupied lesion or abnormal findings in conventional MR scanning; 4) no history of neurological diseases including cerebrovascular disease, neurodegenerative disease and trauma *etc*; 5) no drug, alcohol or addictive substance abuse.

Magnetic resonance imagings (MRI) were performed using a 1.5-Tesla scanner (Signa Twin, GE, USA) with an 8-channel head-phased array coil. The baseline scan was in the axial plane. Head movement was limited by vacuum fixation cushions.

All the subjects underwent conventional sequence scanning, including T_1WI, T_2WI, T_2-fluid-attenuated inversion recovery imaging (T_2-FLAIR), short T_2 inversion recovery (STIR)-T_2 WI imaging and T_1WI with gadolinium (Gd-DTPA) enhancement. Consecutive slices were acquired in all sequences. DTI was performed in a spin echo-echo planar imaging (SE-EPI) diffusion tensor sequence in the axial plane right after the conventional sequences scanning (b=0/1000 s/mm^2; diffusion-sensitive gradient direction=13; voxel size=0.9 mm ×0.9 mm ×0.9 mm). The acquisition parameters of each sequence were listed in Table 2.

Primary DTI data were post-processed using the Volume One 1.72 software (GE Healthcare, USA), directional encoded color (DEC) maps and black-white FA maps were obtained. The criteria for selecting the region of interest (ROI) of optic nerve was as follows: 1) in recombined coronal plane DEC maps, select the anterior, moderate, and posterior segment of the orbital part of optic nerve as the ROIs by the same reader (Figure1A). The axial DEC maps were taken as reference (Figure 1B). 2) The FA value, MD value, $\lambda_{//}=\lambda_1$ and $\lambda_{\perp}=(\lambda_1+\lambda_2)/2$ of each ROI were measured in three continuous slices. Obtain the mean value of all the measurements as the final result of each value in each ROI. 3) The partial volume effect was avoided as much as possible in the ROI selection.

Chi-square test was used to compare the sensitivity of each scanning sequence in discriminating IDON. Two-sample t-test was used to compare diffusion tensor indices values between groups. $P<0.05$ was used to determine statistical significance. All analyses were performed using the Statistical Package for the Social Sciences software, Version 13.0 (SPSS, Chicago, Illinois, USA).

In the study group, all nerves manifested as iso-intense in T_1WI maps. The sensitivity of T_2WI, T_2-FLAIR, STIR-T_2WI, T_1WI with Gd-DTPA enhancement and DTI sequence in discriminating IDON was different ($\chi^2=17.584$, $P=0.000$) (Table 3). DTI had higher sensitivity than other conventional MRI sequences in discriminating IDON.

When compared with healthy controls, the FA values of optic nerve decreased ($P=0.000$) while the MD values, $\lambda_{//}$ and $\lambda_{\perp}$ increased ($P=0.000$) in IDON patients (Table 4).

Conventional MRI scanning can detect optic nerve's size, pattern, signal intensity and enhancement with contrast

Table 3 The sensitivity of each acquisition sequence in discriminating IDON *n* (%)

Acquisition sequences	Positive	Negative	Total	Sensitivity
T_2WI	11	18	29	37.9
T_2-FLAIR	15	14	29	51.7
STIR-T_2WI	17	12	29	58.6
T_1WI Gd-DTPA	18	11	29	62.1
DTI SE-EPI	27	2	29	93.1
Total	88	57	145	60.1

Table 4 Diffusion indices of optic nerves in both groups ($\bar{x} \pm s$, MD, $\lambda_{//}$, $\lambda_{\perp}$ is $\times 10^{-3}mm^2/s$)

Group	*n*	FA	MD	$\lambda_{//}$	$\lambda_{\perp}$
Patients	29	0.343±0.053	1.457±0.180	2.325±0.161	1.367±0.126
Controls	30	0.592±0.066	0.940±0.100	1.925±0.187	0.668±0.098
t		16.106	8.693	2.897	11.591
P		0.000	0.000	0.000	0.000

medium. Its sensitivity in detecting ON differed according to reports, though not being satisfied in most situations. The sensitivity of T_2WI, T_2 -FLAIR, STIR-T_2WI and T_1WI with Gd-DTPA enhancement in discriminating IDON was 37.9%, 51.7%, 58.6% and 62.1% respectively in our study, which was similar to previous reports (Table 3)[5-6,8]. Some authors attempted to improve the imaging technique. The sensitivity of fat suppression technique in discriminating ON was 57% to about 83%[8]. With three times dosage of Gd-DTPA, the sensitivity of T_1WI in discriminating ON increased to 75% (21 of 28 affected eyes)[16]. The sensitivity of T_1WI with Gd-DTPA enhancement in discriminating ON reached 94% in Kupersmith *et al*'s [6] report. The result of Rizzo *et al* [2], which obtained from a relatively large number of patients, revealed that increased STIR signal appeared in 84% cases, while the sensitivity of T_1WI with Gd-DTPA enhancement reached 97%. However, we established that DTI has higher sensitivity than other conventional MRI sequences in discriminating IDON (Table 3).

When compared with healthy controls, the FA values of optic nerve decreased while the MD values, $\lambda_{//}$ and $\lambda_{\perp}$ increased in IDON patients (Table 4). The changes of diffusion indices provide information for the underlying micro-anatomic changes or pathological changes of white matter (WM) fiber bundles[17-21]. They include two categories, the diffusion anisotropy and the diffusivity. Diffusion anisotropy, which uses FA as the measurement index, reflects the directionality of water diffusion in each voxel. The change of FA suggests alteration in axonal density and axonal arrangement. Diffusivity reflects the speed of water diffusion in each voxel. Its measurement indexes include MD, $\lambda_{//}$ and $\lambda_{\perp}$. MD reflects the average amplitude of water diffusion. $\lambda_{//}$ represents the diffusivity parallel to the principle axis of the fiber, reflects the changes of restricted barriers along the direction of the fiber tract and the changes of extracellular space. $\lambda_{\perp}$ represents the diffusivity perpendicular to the principle axis of the fiber, reflects the changes of axonal membrane, myelin sheath and extracellular space [22-23]. Loss of myelin and axons, for instance in demyelinating optic neuritis, leads to reduced anisotropy. This result in increased diffusion perpendicular to the white matter tract, increased overall diffusivity (MD) and decreased tissue directionality (FA). If the ON relieved after therapy, the FA value would increase and the MD value would decrease. Therefore the FA and MD value also can be indicators to estimate the effectiveness and prognosis of ON. Naismith *et al*'s [11] study supported the ability for DTI to assess tissue injury by demonstrating a proportional relationship to functional outcomes in remote ON. $\lambda_{\perp}$ can discriminate among categories of visual recovery within affected eyes[24]. In our study $\lambda_{//}$ did no decrease but increase, which was different from Naismith *et al*'s result[11]. $\lambda_{//}$ could either decrease or increase since axons had been damaged, distorted and regenerated with plaques in $\lambda_{//}$'s decrease, while optic nerve mostly stayed in edema when it increased[25]. However, the sample size of this study was quite small and we did not perform a serial study following treatment to look for the utility of the techniques in monitoring therapy, for instance, to compare the visual outcomes, which was certainly a disadvantage of this study.

In conclusion, DTI has higher sensitivity than other MR scanning sequence in discriminating IDON. Diffusion indices of optic nerve change significantly when compared with healthy controls, which illustrating the demyelization of optic nerve in IDON.

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