• Brief Report •

Diffusion tensor imaging of horizontal extraocular muscles in patients with concomitant and paralytic esotropia

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Abstract

● **AIM:** To assess metrics of diffusion tensor imagining (DTI) in evaluating microstructural abnormalities of horizontal extraocular muscles (EOM) in esotropia.

● **METHODS:** Six adult concomitant esotropia patients, 5 unilateral abducent paralysis patients and 2 healthy volunteers were enrolled. Conventional magnetic resonance imaging (MRI) and DTI were performed on all subjects using 3T MR scanner. Fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) of medial and lateral rectus muscles were measured and compared between patients group and control group.

● **RESULTS:** Medial rectus MD and RD within the adducted eye of concomitant patients was significantly greater than that in unilateral abducent paralysis patients (0.259×10^{-2} mm^2/s *vs* 0.207×10^{-2} mm^2/s, P=0.014; 0.182×10^{-2} mm^2/s *vs* 0.152×10^{-2} mm^2/s, P=0.017). Both strabismus patients showed a significantly decreased MD and AD than that obtained in normal controls for lateral rectus muscles (P<0.05). Medial rectus MD of the adducted eye in concomitant strabismus patients was significantly decreased than that in healthy controls (0.259×10^{-2} mm^2/s *vs* 0.266×10^{-2} mm^2/s, P=0.010). Lateral rectus AD of the adducted eye in concomitant strabismus patients was significantly decreased as compared with that in healthy controls (0.515×10^{-2} mm^2/s *vs* 0.593×10^{-2} mm^2/s, P=0.013). No statistically significant differences were present between the adducted and fixating eyes in concomitant strabismus patients.

● **CONCLUSION:** DTI represents a feasible technique to assess tissue characteristics of EOM. The effects of eye position changes on DTI parameters are subtle. Decreased MD and RD could be evidence for remodeling of the medial rectus muscle contracture. Lower medial and lateral recuts MD of concomitant esotropia patients indicates a thinner fibrous structure of the EOM. Lower MD and AD should be general character of esotropia.

● **KEYWORDS:** diffusion tensor imagining; extraocular muscle; esotropia; strabismus

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INTRODUCTION

Currently, little consensus exists on possible causes of concomitant esotropia. Results, as obtained from electrophysiological experiments on the horizontal motor nerve in primates, have revealed that a disorder of the nerve center controlling binocular motor coordination may serve as a basis for concomitant esotropia[1-2]. It has also been suggested that genes play an important role in the occurrence of strabismus[3-4]. In addition to an involvement of central nervous system diseases, other factors may also play a role in acquired decompensated esotropia[5]. Compared with concomitant esotropia, the cause of abducens nerve palsy is relatively clear. Abducens nerve and nucleus injury, including trauma and tumor, result in denervation of the lateral rectus muscle and eventually to paralytic esotropia. If a lateral rectus muscle remains totally paralyzed for more than 3–4wk, the medial rectus muscle will gradually develop a contracture, presenting as increased esotropia and limited lateral rotation[6]. While this condition of muscle contracture represents a well-known phenomenon, details regarding the functional and structural changes remain elusive. It has been suggested that an increasing number of sarcomels in overcontracted muscle fibers may be responsible for this condition, but direct evidence is still lacking[6].

Extraocular muscles (EOM) may play an important role in the occurrence and development of esotropia. Attempts at evaluating EOM have been limited to the anterior segment of the lateral rectus muscle as EOM are located deep in the orbit and muscle specimens are typically only obtained following surgical treatment of esotropia patients. Accordingly, medial rectus muscle specimens have not been available in these cases due to the recession procedure. Such conditions have limited their use in pathological studies. Due to the high sensitivity for soft tissue and ability to provide a variety of detection sequences, magnetic resonance imaging (MRI) is the preferred method to study EOM under physiological conditions[7]. At present, MRI studies involving EOM have been focussed at the morphological level, including cross-sectional areas, volume and morphological changes of EOM at different eye positions[8-9]. By contrast, few studies have been performed at the tissue level of EOM function.

Due to the varying characteristics of cellular structures and extracellular matrices, water diffusion and direction can differ markedly. Based on this principle and, combined with diffusion weighted imaging, diffusion tensor imaging (DTI) technology has emerged as a novel procedure for evaluating tissue structures and functions. DTI represents the only magnetic resonance technology that can quantitatively analyze water diffusion in tissues and trace three-dimensional (3D) tissue fiber structures. This technique was initially used to evaluate the structure of white matter in the brain and image nerve fiber tracts, such as optic nerve and optic radiation[10-11]. Recently, skeletal muscle has also become a focus of DTI research[12-13]. As EOM comprise a specialized type of skeletal muscle, the combination of MRI+DTI offers the possibility to not only display morphological characteristics of these muscles, but also the opportunity to explore their internal fibrous structure characteristics. Diffusion in skeletal muscles is shown to be highest along the axis of the fibers [axial diffusivity (AD) or λ1] and lowest perpendicular to the axis of the fibers [λ2, λ3 and radial diffusivity (RD)=(λ2+λ3)/2]. The mean diffusivity (MD) is obtained from the mean value of three eigenvalues[12]. Fractional anisotropy (FA) represents an index of the extent of anisotropy, scaling from 0 for isotropic diffusion and approaching 1 for maximum anisotropy[14].

At present, DTI studies involving EOMs have mainly focused on thyroid-related ophthalmopathy. The purpose of this study was to evaluate the value and feasibility of applying DTI for assessing medial and lateral rectus muscles in patients with concomitant and paralytic esotropia. In addition, through evaluating differences in DTI parameters within these muscles, the potential for identifying the development of esotropia may be revealed.

SUBJECTS AND METHODS

Ethical Approval The Ethics Committee of Zhongshan Ophthalmic Center of Sun Yat-sen University approved this retrospective study, which was conducted according to the principles expressed in the Declaration of Helsinki. The approval number was 2019KYPJ120. All subjects provided written informed consent prior to the conduction of imaging.

Adult esotropia patients seen at the Department of Strabismus and Amblyopia, in the Zhongshan Ophthalmic Center of Sun Yat-sen University and normal volunteers were recruited for this study which was conducted over the period from June 2019 to December 2019. A criterion for the normal volunteer subjects was the absence of any eye movement disorders or diplopia. The duration of esotropia in the patients was over one year. Esodeviation of these patients was between 25°-45°. Patients with orbital fracture, orbital tumor, thyroid-related eye disease, vertical strabismus, rotatory strabismus, restrictive strabismus, myasthenia gravis, and previous ocular muscle surgery were excluded.

Imaging Studies Magnetic resonance scans were performed using a 3T MR scanner (Skyra, Siemens Medical Solutions Erlangen, Germany) with a 16-channel head coil. DTI acquisitions were performed on the oblique axial plane using ss-EPI-based DTI. The imaging parameters were as follows: repetition time (TR)/echo time (TE)=5060/76ms, field of view= 256.0×256.0 mm^2, matrix=256×256, slice thickness=2 mm, slice number=30, readout segment=7, non-collinear gradient encoding directions=12, b=0 and 500s/mm^2. Total imaging time was 6min and 20s. Conventional imaging protocols included axial T2-weighted imaging (TR/RE=1700/2.25ms) and axial, coronal, and sagittal T1-weighted imaging (TR/TE=6000/125ms). Other parameters were as follows: field of view=200 mm, slice=1 mm for T1 and 5 mm for T2.

To reduce motion-related errors due to eye movements, each subject was instructed to focus upon a target placed at a distance of 5 meters through a mirror fixed to the head coil. Monocular fixation was used with the dominant eye or unaffected eye as the fixating eye, while the contralateral eye was covered with an ordinary eye-patch. The subject was asked to fixate upon the visual target as steadily as possible during the scanning.

DTI Data Analysis A 3D slicer 4.10.2 (https://www.slicer.org/) was used for "DTI" reconstruction. The "DTI" reconstruction method was used to model the eigenvectors, and pixel-by-pixel maps of FA, MD, AD, and RD were then automatically obtained (Figure 1). Based on the b-0 image, the influence of surrounding unrelated tissues and noise signals were removed. Using the MIPAV 9.0.0 imaging tool (https://mipav.cit.nih.gov/), polygonal regions of interest (ROIs) were carefully selected manually to avoid the inclusion of any surrounding

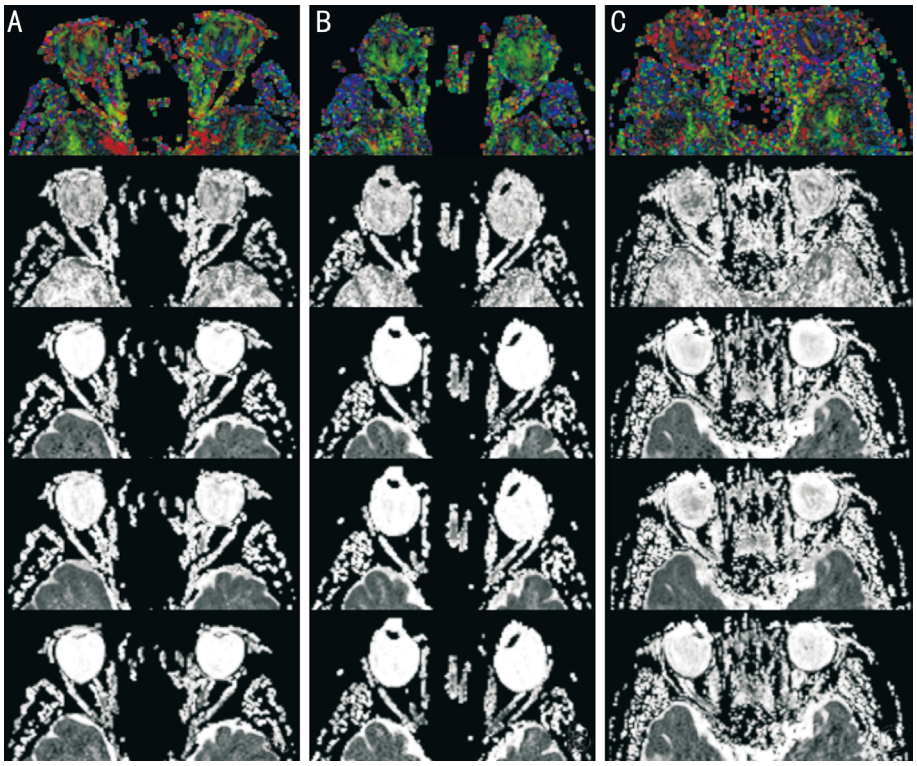

Figure 1 Corresponding color-coded FA, gray-scale FA, MD, AD, and RD maps (from top to bottom) A: Images in a normal volunteer; B: Images in a concomitant esotropia patient with right eye fixating; C: Images in a left abducens palsy patient. FA: Fractional anisotropy; MD: Mean diffusivity; AD: Axial diffusivity; RD: Radial diffusivity.

fatty tissue. ROIs were placed as widely as possible on the selected images. Two consecutive axial images that included the middle levels of medial and the lateral rectus EOM in both orbits on b-0 images were selected from each person. With the exception of one patient with concomitant esotropia, only one plane was selected as the boundary was not clear in the remaining planes. ROIs of lateral rectus muscles in unilateral abducent paralysis were eliminated from analyses as the lateral rectus muscle atrophy made it difficult to clearly image this structure. The average value of each ROI was obtained through the software calculation function.

Statistical Analysis Statistical analyses were performed using the SPSS version 22 program (SPSS Inc, Chicago, IL, USA). One-way analysis of variance was used for comparisons between concomitant strabismus, unilateral abducent paralysis and the control group followed by least-significant difference as post-hoc pairwise comparisons. Independent *t* tests were used to compare difference between eyes within the strabismus group. A *P* value of <0.05 was required for results to be considered statistically significant.

RESULTS

There were 6 patients (4 males and 2 females) with concomitant esotropia. They ranged in age from 21 to 51y (mean age=30.7±10.8y), with a mean±SD esodeviation of 33.7°±7.2°. There were 5 patients (4 males and 1 female) with unilateral abducens nerve palsy. These patients ranged in age from 30 to 65y (mean age=54.6±15.2y), with a mean±SD esodeviation of 33.6°±6.5°. The two normal volunteers were males aged 27 and 43y (mean age=35y). The difference in esodeviation between the strabismus groups was not statistically significant. Of the 6 patients with concomitant esotropia, 2 experienced acute concomitant esotropia, while the onset times of the other concomitant esotropia patients was unknown. Of the 5 abducens nerve palsy cases, 3 resulted from auto accidents and 2 from brain tumors. The average duration of onset was 1.4y.

Medial rectus MD and RD within the adducted eye of concomitant patients was significantly greater than that of the medial rectus of the adducted eye in unilateral abducent paralysis patients (0.259×10^{-2} mm^2/s *vs* 0.207×10^{-2} mm^2/s, P=0.014; 0.182×10^{-2} mm^2/s *vs* 0.152×10^{-2} mm^2/s, P=0.017). Both strabismus patients showed a significantly decreased MD and AD than that obtained in normal controls for lateral rectus muscles (P<0.05). Medial rectus MD of the adducted eye in concomitant strabismus patients was significantly decreased than that of the Medial rectus in healthy controls (0.259×10^{-2} mm^2/s *vs* 0.266×10^{-2} mm^2/s, P=0.010). Lateral rectus AD of the adducted eye in concomitant strabismus patients was significantly decreased as compared with that of the lateral rectus in healthy controls (0.515×10^{-2} mm^2/s *vs* 0.593×10^{-2} mm^2/s, P=0.013). A summary of the details of these results is contained in Table 1. No statistically significant

Table 1 DTI parameters among patients with unilateral abducent paralysis, concomitant esotropia and normal controls

Parameters		Unilateral abducent paralysis	Concomitant esotropia	Normal control	*P*
FA	AM	0.684±0.054	0.660±0.043	0.649±0.061	0.354
	AL		0.634±0.047	0.627±0.043	0.720
	FM	0.677±0.046	0.646±0.076	0.649±0.061	0.495
	FL	0.641±0.064	0.625±0.038	0.627±0.043	0.742
MD[1]	AM	0.207±0.039	0.259±0.061	0.266±0.016	0.015
	AL		0.273±0.058	0.315±0.024	0.070
	FM	0.208±0.038	0.232±0.068	0.266±0.016	0.057
	FL	0.245±0.054	0.260±0.044	0.315±0.024	0.006
AD[1]	AM	0.486±0.059	0.531±0.062	0.523±0.063	0.230
	AL		0.515±0.072	0.593±0.040	0.013
	FM	0.472±0.045	0.486±0.083	0.523±0.063	0.281
	FL	0.505±0.051	0.495±0.046	0.593±0.040	0.000
RD[1]	AM	0.152±0.026	0.182±0.027	0.158±0.028	0.039
	AL		0.184±0.034	0.188±0.016	0.771
	FM	0.150±0.023	0.172±0.040	0.158±0.028	0.293
	FL	0.174±0.039	0.186±0.025	0.188±0.016	0.526

DTI: Diffusion tensor imagining; AM: Medial rectus muscle of the adducted eye; AL: Lateral rectus muscle of the adducted eye; FM: Medial rectus muscle of the fixating eye; FL: Lateral rectus muscle of the fixating eye. [1]The unit is 10^{-2} mm^2/s.

differences were present between the right and the left eyes in either the concomitant strabismus or unilateral abducens nerve palsy groups. A summary of the details of these results is contained in Tables 2 and 3.

DISCUSSION

Use of DTI for assessing EOM is in its infancy. Related studies on EOM using DTI include comparisons as performed between EOM and other muscles[15] and use of DTI for the study of thyroid associated orbitopathy[16-17]. DTI of the lateral rectus muscle in Duane retraction syndrome has also been discussed[18]. However, to our knowledge, no study exists using DTI as related to eye movement and eye position. Currently, the meaning of differences in DTI parameters can only be inferred as based on that of data on skeletal limb muscles. As the structure and function of EOM differ markedly from that of skeletal limb muscles, this extrapolation is tenuous. For example, EOM are more involved with, and responsible for, rapid and precise coordination of eye movements versus that of the weight bearing required of skeletal limb muscles. Moreover, EOM need to respond quickly and accurately and resist fatigue. Thus, they contain more satellite cells, which enables EOM to demonstrate a greater ability for remodeling and are less susceptible to muscular dystrophy[19]. EOM fibers are significantly smaller than that of other skeletal muscle fibers and possess unique histochemical characteristics and mitochondrial distributions[20]. Moreover, EOM are rich in sarcoplasmic reticulum, contain 6 different muscle fiber components, including fast and slow nerve fibers, are stimulated more frequently, contract faster and produce a continuous slow tension contraction as compared with that of skeletal limb muscles. In addition, EOM remain active day and night, with 70% remaining active even in the rest eye position[20]. We found that the medial rectus MD and RD within the adducted eye of concomitant patients was significantly greater

Table 2 DTI parameters between eyes in the concomitant esotropia group

Parameters	Mean	Standard deviation	*P*
AMFA–FMFA	0.026	0.046	0.094
ALFA–FLFA	0.021	0.078	0.396
AMMD–FMMD[1]	-0.014	0.035	0.222
ALMD–FLMD[1]	-0.028	0.051	0.099
AMAD–FMAD[1]	0.016	0.056	0.353
ALAD–FLAD[1]	-0.008	0.068	0.699
AMRD–FMRD[1]	-0.002	0.028	0.835
ALRD–FLRD[1]	-0.015	0.041	0.267

DTI: Diffusion tensor imagining; AM: Medial rectus muscle of the adducted eye; AL: Lateral rectus muscle of the adducted eye; FM: Medial rectus muscle of the fixating eye; FL: Lateral rectus muscle of the fixating eye. [1]The unit is 10^{-2} mm^2/s.

Table 3 DTI parameters between eyes in the unilateral abducens palsy group

Parameters	Mean	Standard deviation	*P*
AMFA–FMFA	0.007	0.050	0.661
AMMD–FMMD[1]	-0.001	0.032	0.925
AMAD–FMAD[1]	0.014	0.059	0.473
AMRD–FMRD[1]	0.002	0.025	0.805

DTI: Diffusion tensor imagining; AM: Medial rectus muscle of the adducted eye; AL: Lateral rectus muscle of the adducted eye; FM: Medial rectus muscle of the fixating eye. [1]The unit is 10^{-2} mm^2/s.

than that of the medial rectus of the adducted eye in unilateral abducent paralysis patients. Since the MD is the sum of 2/3RD and 1/3AD, the increasing of RD could explain the increasing of MD. Since there was no significant difference in the angle of deviation between the two types of strabismus patients, it can be assumed that the change of eye position is not the main cause of the difference. The medial rectus within the adducted eye of unilateral abducent paralysis patients may be thinner than that of concomitant patients. Berry *et al*[14] reported that a close relationship exists between DTI parameters and muscle fiber diameter. The thicker the muscle fiber, the lower the FA and higher the MD values. Conversely, the thinner the muscle fiber, the higher the FA and lower the MD values. Results from Klupp *et al*[21] assessing lumbar paraspinal muscles strength and DTI parameters revealed that MD, λ3, and RD was positively correlated with muscle strength. Based on former research, unilateral abducent paralysis patients tends to have thinner and weaker medial rectus fiber than concomitant patients have. Sarcomere remodeling and increases in perimysium collagen fibers could provide an explanation for this decrease in medial rectus MD within abducens paralysis patients, suggesting a remodeling of the medial rectus muscle contracture.

Concomitant strabismus patients showed lower MD levels in medial rectus muscles of adducted eye as compared with that observed in normal controls. Such effects may be attributable to thinner muscle fibers, which then produces an imbalance in EOM strength in patients with concomitant esotropia. However, this hypothesis is inconsistent with the findings of Schoeff *et al*[22] who found that medial rectus muscles of patients with concomitant esotropia were thicker than that of normal controls, while no significant changes were observed in lateral rectus muscles. Needless to say, the thinness of the fibrous structure does not necessarily lead to muscle atrophy, but may also result from an increase in the number of muscle fibers. Considering the abundance of satellite cells and robust remodeling ability of EOM, the medial rectus muscle of patients with concomitant esotropia may contain more small muscle fibers, showing characteristics of small muscle fibers and large overall size. An alternative explanation may be that medial muscles of patients with concomitant esotropia contain more organelles (*e.g.*, mitochondria) and the resultant crowding of intracellular structures causes limited water diffusion. Further research will be required to determine whether this characteristic change represents a primary or an adaptive change secondary to alterations in innervation.

Both esotropia patients showed a significantly decreased MD and AD than that obtained in normal controls for lateral rectus muscles of the fixed eye. Meanwhile, no difference was found between lateral rectus MD and AD of the fixed eye in concomitant strabismus patients and unilateral abducent paralysis patients. Thus, the difference in MD and AD should be general character of esotropia. Klupp *et al*[21] found in their study of paraspinal muscle that AD and MD value had significant positive correlation with the ratio of extension to flexion. Takao *et al*[23] found a positive correlation of the soleus muscle in the non-contraction state between the maximum power and the AD, λ2, and MD. However, The study of Yamauchi *et al*[24] showed that a lower rectus femoris AD value predicted greater peak knee extension torque, which may lead to the fact that the rectus femoris is a biarticular muscle and includes the highest proportion of fast fiber type. AD was also found associated with fiber size, edema, and fibrosis[14]. Plus the finding that lateral rectus AD of the adducted eye in concomitant strabismus patients was significantly decreased as compared with that of the lateral rectus in healthy controls, decreasing AD of unparalyzed lateral rectus can be a general characteristic of esotropia patients. In that case, the lateral rectus muscles of the esotropia patients tends to be weaker than that of the control. The absence of statistically significant differences in any of the DTI parameters between medial rectus muscles in eyes of the concomitant strabismus group with various angles of esodeviation suggests that eye position exerts little effects on DTI parameters. Moreover, no differences in DTI parameters were found between medial rectus muscles in the concomitant strabismus and unilateral abducens nerve palsy group. Such results suggests that only slight tissue differences exist between contracted medial rectus muscles in paralytic strabismus and medial rectus muscles in concomitant strabismus. Accordingly, contracture of the medial rectus is more likely to represent a lack of muscle relaxation than a definite structural change in the muscle. Based on these findings, the basis for clinical contracture may be diastolic dysfunction of the medial rectus, rather than hyperfunction. The esotropia after chronic abducens paralysis may also represent a combination of paralytic esotropia and restrictive esotropia.

Our study has several limitations. First, the sample size and representation of this study were limited. Second, in patients with abducens palsy, the location of the affected lateral rectus muscle near the lateral orbital wall would affect the DTI imaging and selection of the ROI. At present, the limited number of studies on DTI of EOM along with the effects of eye position change on DTI parameters have yet to reveal any clear results. In order to determine the influence of eye position on DTI parameters, DTI scans will need to be performed in larger samples of concomitant esotropia patients with various angles of deviation.

Here, we report on the feasibilty of DTI for use in assessing tissue characteristics of EOM. Compared with unilateral abducent nerve palsy, the medial rectus muscle MD and

RD within the adducted eye in patients with concomitant strabismus was increased. Sarcomere remodeling and increases in perimysium collagen fibers could provide an explanation for this decrease in medial rectus MD within abducens paralysis patients. The medial rectus muscle MD of the adducted eye in patients with concomitant strabismus was decreased when compared with that of the normal control group, which indicates that a thin fibrous structure of the EOM is present in concomitant esotropia patients exist. Both esotropia patients showed a significantly decreased MD and AD than that obtained in normal controls for lateral rectus muscles of the fixed eye. This finding suggest decreasing AD of unparalyzed lateral rectus can be a general characteristic of esotropia patients. However, the effects of eye position changes on DTI parameters were not obvious. Such effects reflect differences which exist in the function and structure of EOM versus skeletal limb muscles. Further studies directed toward evaluating EOM of strabismus patients with use of MR-DTI are anticipated.

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