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Role of orbital magnetic resonance imaging in early detection of Graves' Orbitopathy and disease activity

Mohamed Roshdi
Endocrinology Unit, Internal Medicine department, Faculty of Medicine, Mansoura University, Egypt

Mohamed Ghonem
Endocrinology Unit, Internal Medicine department, Faculty of Medicine, Mansoura University, Egypt

Amany Abdel Hamid
Endocrinology Unit, Internal Medicine department, Faculty of Medicine, Mansoura University, Egypt

Azza A Baiomy
Clinical pathology department, Faculty of Medicine, Mansoura University, Egypt

Ahmed AK Abdel Razek
Radiology department, Faculty of Medicine, Mansoura University, Egypt

Manar Mansour
Radiology department, Faculty of Medicine, Mansoura University, Egypt

***Abstract*---** Background and aim: we aim to evaluate feasibility of using diffusion tensor imaging (DTI) "A new technique of magnetic resonance imaging (MRI)", of extraocular muscles (EOMs) in patients with Graves' orbitopathy (GO) versus clinical activity score (CAS) in early detection of GO activity. Methods and materials: This case control study was conducted on 20 patients with moderate to severe active GO (10 males & 10 females with a mean age of 35.50±13.65 years) and 10 age and sex-matched volunteers without any thyroid abnormality as a health control (HC). Patients and HCs underwent DTI of the orbit in coronal plane. Mean diffusivity (MD) of each of the EOMs was calculated. CAS, according to the standardized criteria recommended by European Group on Graves' Orbitopathy (EUGOGO), was calculated for the patients. Results: GO patients' EOMs showed significantly higher MD values compared to HCs' (P < 0.001). Median CAS was 4. A statistically

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***Corresponding author**: Mohamed Roshdi; Email: mohamedroshdi154@gmail.com*
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significant positive correlation was only detected between CAS and MD of the inferior rectus muscle (r=.360, p=.023). Conclusion: DTI is a useful tool for detecting microstructural changes in GO and superior to CAS in early detection of GO activity.

***Keywords*---** Diffusion tensor imaging, Mean diffusivity, Graves' orbitopathy, Clinical activity score.

Introduction

Autoimmune thyroid diseases (AITD) are the most frequent autoimmune disorders **(Antonelli et al., 2015)**. Autoimmune thyroiditis (AT) and Graves' disease (GD) were reported to be the main clinical presentations included **(Cui et al., 2019)**. Presence of TSH receptor antibodies (TRAbs), resulting in hyperthyroidism, thyroid eye disease (Graves' orbitopathy, GO) and – very rarely – localized dermopathy (pretibial myxedema, PTM), characterizes GD**(Smith and Hegedus, 2016)**.

TRAbs act as agonist, stimulate thyroid gland to over secrete excessive thyroid hormone and uncouple the thyroid from pituitary control**(Davies et al., 2020)**. They also induce thyroid gland growth. TRAb stimulation of fibroblasts expressing TSH receptor (TSHR), induces hyaluronan production, facilitated by crosstalk between TSHR and insulin-like growth factor 1 receptors. This is associated with retro-orbital inflammation, extraocular muscle fiber disruption and tissue edema**(Krieger et al., 2020)**.

The prevalence of GD in the general population was in the order of 1% to 1.5%**(Perros et al., 2017)** Nearly 3% of females and 0.5% of males developed GD throughout their lifetime**(Nyström et al., 2013)**. Approximately 25–50 % of GD patients showed clinical manifestations of GO **(Bartalena et al., 2020).** Active inflammatory stage followed by a static stage are two subsequent stages in the natural course of GO **(Hiromatsu et al., 2014).** Therefore, duration of GO, its clinical activity and severity determine treatment decisions **(Bartalena et al., 2021).** The first-modality of therapy for active and moderate-severe cases recommended, is intravenous glucocorticoid (GC)**(Bartalena et al., 2016)**. However, Its effect is significantly low after 18 months of disease duration**(Terwee et al., 2005).**

Clinical activity score (CAS) was established for accurate evaluation of GO activity**(Menconi et al., 2017)** and was correlated with the treatment response, and if CAS ⩾ 3, immunosuppressive therapy is recommended **(Mourits et al., 1989)** The CAS was also recommended by the European Group on Graves' Orbitopathy (EUGOGO) consensus.**(Negro et al., 2016)** However, CAS has significant limits including, inappropriate evaluation of the various levels of inflammation activity, so the score does not change with any improvement or exacerbation until it completely resolves, and low sensitivity and subjectivity owing to the operator dependence**(Tachibana et al., 2010)**.

Thus, there is growing interest to find appropriate quantitative markers or more reliable imaging features to further validate CAS. Orbit Magnetic resonance imaging (MRI) was widely applied for diagnosing thyroid associated orbitopathy (TAO) and further staging TAO**(Siakallis et al., 2018)**. Main parameters evaluated in previous imaging studies of GO, were expanded extraocular muscles and orbital fat tissues, which were thought to be significant contributors to proptosis in GO**(Gontarz-Nowak et al., 2021)**.

Diffusion tensor imaging (DTI), which provides quantitative information about the microstructural integrities of highly oriented tissues, was applied for assessing various orbital diseases, such as glaucoma, optic neuritis, and others**(Min et al., 2018)**. However, studies that applied DTI to assess microstructural changes in TAO patients, were limited**(Lee et al., 2018).**

Main parameters of DTI are fractional anisotropy (FA) and mean diffusivity. The FA determines the directionality of a diffusion signal, **(Sundgren et al., 2004)** whereas Diffusivity measures the magnitude of diffusion of water molecules within the tissue, which is dominated by interstitial space**(Sotak, 2004)** Diffusivity could increase in edematous muscle and decrease in fibrotic and fatty infiltrated tissue**(Kilicarslan et al., 2015).**

Methods and Materials

The Institutional Ethics Committee approved the protocol of the study and informed consent was given by all participants. This Case control study included 20 patients with moderate to severe active graves' orbitopathy (GO) and 10 health control (HC) subjects without any thyroid abnormality. Both patients and HCs were recruited from outpatient Endocrinology clinic in Specialized Medical Hospital, Mansoura University over a period of 20 months from November 2019 to August 2021.

The inclusion criteria: Patients with moderate to severe, active GO. The control group consisted of age- and sex-matched healthy volunteers with negative results of any thyroid abnormality. The exclusion criteria were presence of other ophthalmological disease such as glaucoma, history of any chronic illness such as diabetes and hypertension, history of previous exposure to radiation and radioactive iodine, history of previous eye surgery and history of prior immune therapy such as corticosteroid in the previous 6 months.

Thyroid stimulating hormone receptor antibody (TRAb) was measured, for both patients and HCs, using third generation thyroid binding inhibiting immunoglobulin (TBII) with Enzyme-Linked Immunosorbent Assay (ELISA) method supplied by Bioassay technology china.

Principle

This kit is sandwich ELISA. The plate has been pre-coated with Human TRAb antibody. TRAb present in the sample is added and binds to antibodies coated on the wells. And then second Human TRAb Antibody is added and binds to TRAb in the sample. Then Streptavidin- Horse Radish Peroxidase (HRP) is added and binds to the Biotinylated TRAb antibody. After incubation unbound Streptavidin-HRP is washed away during a washing step. Substrate solution is then added and color develops in proportion to the amount of human TRAb. The reaction is terminated by addition of acidic stop solution and absorbance is measured at 450 nm.

Magnetic resonance imaging & clinical activity score

The magnetic resonance imaging of the orbit was done for patients and HCs and the clinical activity score (CAS) was obtained for patients. The CAS was calculated by one endocrinologist with 10 years' experience. A score of three or more on CAS is classified as active GO. The time between magnetic resonance imaging and CAS score was 3–7 days.

Firstly, all subjects, patients and control group underwent conventional MR protocol of the orbit which was done using a 1.5-T machine (Ingenia, Philips. Netherland) using dStream Head and Neck 20 channel coil. Then subjects were exposed to diffusion tensor imaging (DTI).

DTI data were obtained using a single shot echo planar imaging sequence (TR/TE = 3118/93 ms). The scanning parameters were, field of view of 230 × 177 mm2, data matrix of 92 × 88, and voxel dimensions of 2.43 × 2.54 × 2.5 mm3. Parallel imaging [SENSitivity Encoding (SENSE) reduction factor P 2 was used. Diffusion gradients were applied along 32 axes, using a b value of 0 and 1000 s/mm2. Thin section forty-eight slices were obtained, with a thickness of 2.5 mm, no gap, and total scan duration of about 7–8 min.

Image analysis

Processing of DTI data were carried out by dedicated workstation (Philips Extended MR Workspace 2.6.3.2 with DTI functional tool software). Analysis was done by expert radiologist in head and neck imaging, since10 years, who was blinded to patients' laboratory and clinical data. Regions of interest (ROI) single-pixel seed were placed in the extra ocular muscles to calculate mean diffusivity.

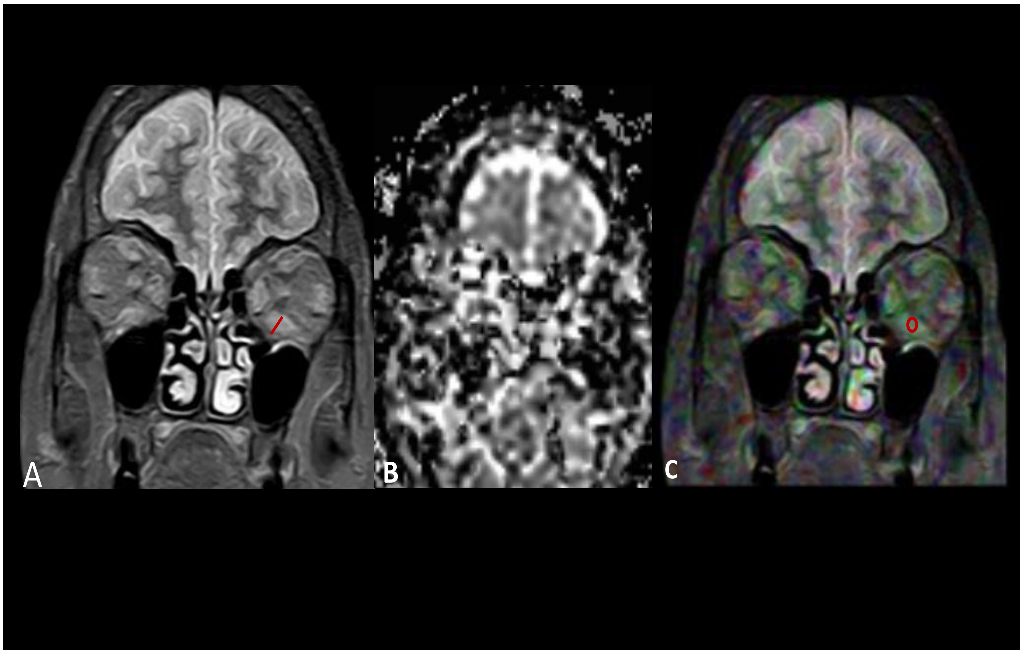

Figure (1): (A) coronal Short-TI Inversion Recovery (STIR) of both orbits (red line) refers to thickness measurement of inferior rectus (IR). (B) coronal apparent diffusion co-efficient (ADC) map, (C) coronal diffusion tensor imaging (DTI) image, (red circle) refers to region of interest (ROI) for measurement of mean diffusivity (MD).

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. Qualitative data were described using number and percent. Quantitative data were described using median (minimum and maximum) and mean, standard deviation for parametric data after testing normality using Kolmogrov-Smirnov test. Significance of the obtained results was judged at the (0.05) level.

Results

Table (1): Socio-demographic characteristics of the studied groups

	Patients group N=20	**Health control (HC) group N=10**	**P-value**
Age/years	35.50±13.65	31.90±9.61	0.428
Sex			
Male	10(50)	5(50)	1.0
Female	10(50)	5(50)	

Smoking **NO** **YES**	14(70) 6(30)	9(90) 1(10)	0.222

Table (1) shows that there was no statistically significant difference between studied groups regarding socio-economic data including age and sex. Among studied groups; 50% of each group were males. Prevalence of smoking did not show statistically significant difference between studied groups.

Table (2): Clinical activity score (CAS) in patients' group.

CAS **Median (range)**	**4 (3-6)**

Table (2) Median Clinical activity score (CAS) was 4 ranging from 3 to 6 in patients' group.

Table (3): Thyroid stimulating hormone receptor antibody (TRAb) of the studied groups.

	Patients group	HC group	P
TRAb (unit/ml)	95.6 (65-445)	34.5 (23.8-47.4)	<0.001*

Health control (HC)

Table (4): Mean diffusivity (MD) of extraocular muscles among the studied groups.

	Patients group	HC group	P
SR MD(x 10-3 mm2 /s)	1.48±0.10	1.05±0.13	<0.001*
IR MD(x 10-3 mm2 /s)	1.73±0.13	1.09±0.13	<0.001*
MR MD(x 10-3 mm2 /s)	1.76±0.16	1.14±0.11	<0.001*
LR MD(x 10-3 mm2 /s)	1.48±0.147	1.17±0.10	<0.001*

Superior rectus (SR), Inferior rectus (IR), Medial rectus (MR), Lateral rectus (LR), Mean diffusivity (MD), Health control (HC)

Table (4): Mean diffusivity (MD) of each of extra-ocular muscles was higher in patients' group compared to health control group, the highest MD was found in medial rectus (MR) muscle in patients' group.

Table (5): Correlation between Clinical activity score (CAS) & orbital muscle mean diffusivity (MD) in patients' group.

		CAS
SR MD	r	.289
	p value	.071
IR MD	r	**.360***
	p value	**.023**
MR MD	r	.165
	p value	.308
LR MD	r	.255
	p value	.113

Superior rectus (SR), Inferior rectus (IR), Medial rectus (MR), Lateral rectus (LR), Mean diffusivity (MD), Clinical activity score (CAS), r: Spearman correlation co-efficient

Table (5): The only statistically significant correlation was found between MD of inferior rectus (IR) muscle and CAS and they were positively correlated (r=.360, p=.023).

Table (6): Correlation between Thyroid hormone receptor antibody (TRAb) & orbital muscle mean diffusivity (MD) in patients' group.

		TRAb
SR MD	r	.424
	p value	.006
IR MD	r	.427
	p value	.006
MR MD	r	.588
	p value	.001
LR MD	r	.605
	p value	.001

Superior rectus (SR), Inferior rectus (IR), Medial rectus (MR), Lateral rectus (LR), Mean diffusivity (MD), Thyroid hormone receptor antibody (TRAb), r: Spearman correlation co-efficient

Table (6): A statistically significant positive correlation was detected between TRAb level and MD of each of extra-ocular muscles in patients' group.

Discussion

Graves' orbitopathy (GO) is also known as thyroid-associated ophthalmopathy (TAO) and thyroid eye disease (TED). It is the most frequent extra thyroidal manifestation of Graves' disease (GD) **(Garrity and Bahn, 2006)**. Approximately 25–50 % of GD patients showed clinical manifestations of GO **(Bartalena et al., 2020).**

GO is characterized by an inflammatory process and subsequent tissue expansion, remodeling, and/or fibrosis of fibroadipose tissues and extraocular muscles in the orbit **(Pouso-Diz et al., 2020)**. Although the exact pathogenesis of GO, is incompletely understood, most studies agreed with an abnormal immune response to thyroid-stimulating hormone receptor (TSHR) and insulin-like growth factor-1 receptor (IGF-1R) in the orbit, where orbital fibroblasts appear to be the major effector cells **(Khong et al., 2016)**.

TAO patients' orbital soft tissues were thought to experience two phases: the initial acute inflammatory phase, characterized by hyaluronic acid accumulation and mononuclear inflammatory cell infiltration, and subsequent chronic inactive phase featured with interstitial fibrosis, and fatty infiltration **(Taylor et al., 2020)**. This pattern was identified as Rundle's curve **(Hales and Rundle, 1960)** Therefore, duration of GO, its clinical activity and severity determine treatment decisions **(Bartalena et al., 2021).**

Clinical activity score (CAS) was established for accurate evaluation of GO activity **(Menconi et al., 2017).** However, it has many limitations such as its binary (yes/no) feature, **(Mourits et al., 1989)** low sensitivity and subjectivity owing to the operator dependence **(Tachibana et al., 2010).**

Thus, there was growing interest to find appropriate quantitative markers or more reliable imaging features to further validate CAS. Orbit Magnetic resonance imaging (MRI) was widely applied for diagnosing TAO and further staging TAO **(Siakallis et al., 2018)**

Diffusion tensor imaging (DTI) is a non-invasive MRI technology which is very sensitive to water molecules' micromovement. Thus, it can provide quantitative information of water molecule diffusion movement **(Jeon et al., 2018)**. Common parameters of DTI include fractional anisotropy (FA) and mean diffusivity (MD) values. The MD can reflect the magnitude of water diffusion dominated by interstitial space **(Razek et al., 2019)**. Diffusivity could increase in edematous muscle and decrease in fibrotic and fatty infiltrated tissue **(Kilicarslan et al., 2015)**. FA can represent the directionality of water molecules, hence it can reflect tissues' integrity of microstructural architectures **(Gholizadeh et al., 2019)**

Our study was a case control study that was carried out on 20 patients with moderate to severe active GO and 10 normal subjects without thyroid abnormality as health control group. Socio-demographic characteristics (age & sex) as well, the prevalence of smoking did not show any statistically significant difference among the studied groups.

In terms of microstructural changes in extra-ocular muscles (EOMs), MD of each of extraocular muscles (superior rectus (SR), inferior rectus (IR), medial rectus (MR), and lateral rectus (LR)) was statistically significantly higher in patients' group compared to health control (HC) group ($p<0.001$ for each). This was consistent with **Kilicarslan et al., (2015)** who demonstrated significantly higher MD value of all the EOMs (IR, MR, LR and SR) in patients with GO versus healthy control ($p = 0.0001$). This result was in agreement with the findings of previous studies demonstrating higher MD of medial and lateral recti in patients with GO compared to healthy control **(Chen et al., 2020, Chen et al., 2021).**

Higher MD in patients with active GO, may be attributed to infiltration of the EOMs with hyaluronic acid formed by fibroblasts. Hyaluronic acid is hydrophilic glycosaminoglycan that retains water causing edematous muscles **(Hiromatsu et al., 2015)**. These changes result in increasing the diffusion space of the water protons in the extracellular and intracellular dimensions with a resultant increase in the MD value **(Razek et al., 2010)**.
Clinical activity scales, such as the CAS **(Mourits et al., 1997)** and vision, inflammation, strabismus and appearance (VISA), **(Dolman and Rootman, 2006)** could be very helpful in assessing disease activity. Although the combination of MRI studies and clinical scores would improve diagnostic accuracy, the results were conflicting. Some researchers found no clear correlation between MRI findings and CAS indexes **(Vlainich et al., 2011).** In terms of microstructural changes detected by DTI, **Kilicarslan et al., (2015)** reported that there was no correlation between the CAS and apparent diffusion co-efficient value of all EOMs. However, other researchers reported significant positive correlations **(Tachibana et al., 2010).** In our study, CAS score showed a statistically significant positive correlation only with IR MD (r=.360, p=.023).

There are a few limitations of this study. First, our study population was relatively small, and did not include patients with mild GO. Second, we didn't conduct post-treatment assessment because complete follow-up information was not available for every patient. However, we believe that our results could be a strong basis for further larger prospective studies.

To conclude, Mean diffusivity (MD) as a parameter in Diffusion tensor imaging (DTI) "new technique of magnetic resonance imaging (MRI)" reflected microstructural changes in Graves orbitopathy (GO), and was found superior to clinical activity score (CAS) in early detection of GO activity. However, use of DTI MRI in combination with CAS score could be more beneficial.

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