• Clinical Research •

Predictive parameters on CT scan for dysthyroid optic neuropathy

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Abstract

● **AIM:** To evaluate the value of parameters on CT scan in predicting dysthyroid optic neuropathy (DON) and to provide guidance for early diagnosis of DON accordingly.

● **METHODS:** A total of 67 eyes of 35 patients with thyroid-associated ophthalmopathy (TAO) were included in this study. Patients were divided into 2 groups (DON group and non-DON group). Parameters were measured on high resolution CT, including muscle index (MI), superior ophthalmic vein (SOV) dilatation, extraocular muscle volume/orbit volume (MV/OV), and intracranial fat prolapsed, and be compared between these 2 groups. The relation between those parameters and visual function [visual acuity (VA) and visual field defect (VF defect)] were also evaluated.

● **RESULTS:** MI and MV/OV were significantly higher in DON group (P=0.00035 and P=0.00026). No significant difference was detected regarding intracranial fat prolapse existence and SOV dilatation (P=0.37 and P=0.15). MV/OV was found to have significant negative correlation with both VF defect (R=-0.332, P=0.0273) and VA (R=-0.635, P=0.00) while MI was found to have negative linear correlation with VA only (R=-0.456, P=0.00017). The area under receiver operating characteristic curves was 0.82 for MV/OV and 0.75 for MI. The best performance in detecting DON was achieved when MV/OV is set at 0.20 with 72% sensitivity and 87% specificity and MI is set at 0.52 with 64% sensitivity and 80% specificity.

● **CONCLUSION:** MI and MV/OV are predictive parameters for DON. Together with clinical manifestations, MV/OV≥0.2 can be used as a good indicator for DON in TAO patients.

● **KEYWORDS:** dysthyroid optic neuropathy; muscle index; superior ophthalmic vein dilatation; intracranial fat prolapse; muscle volume/orbital volume

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INTRODUCTION

Thyroid-associated ophthalmopathy (TAO) is an autoimmune inflammatory process affecting both orbital and periorbital tissues, like extraocular muscles and retrobulbar fat[1]. TAO may occur before, during, or after the onset of hyperthyroidism, or less frequently in euthyroid or hypothyroid patients[1-2]. Dysthyroid optic neuropathy (DON), as the most severe complication of TAO, affects 4%-8% of TAO patients, which can result in permanent and irreversible severe visual loss[2]. Once DON is diagnosed, prompt treatment (large dose hormone or orbital decompression surgery) is needed to prevent permanent visual damage[2-3].

The pathogenesis of DON is still unclear. Several possible theories have been raised in previous researches[2-4]. Direct compression to optic nerve at the orbital apex caused by enlarged extraocular muscles is the most plausible and widely accepted one[2,4-7], which is proved by the presence of orbital apex crowding on CT images in most patients with DON[8]. Several parameters on CT images reflecting this crowding have been mentioned in previous studies, including muscle index (MI), superior ophthalmic vein (SOV) dilatation, intracranial fat prolapse, and extraocular muscle volume/orbit volume (MV/OV)[5-6,9-10]. Barret *et al*[5] found out that MI of greater than 67% is indicative of compressive optic neuropathy. Significant SOV enlargement was specifically noted in orbits with optic neuropathy[6] and intracranial fat prolapse correlated closely to the presence of optic neuropathy in Graves' ophthalmopathy[9]. MV/OV was thought to be a real response of the compressed orbital apex[10]. However, it has not been fully explored which parameter has the strongest power in predicting DON.

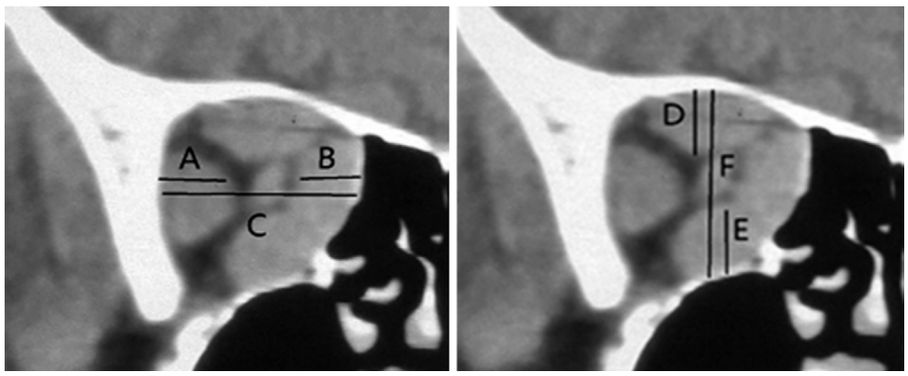

Figure 1 MI calculation Measurements were taken halfway between the posterior globe and orbital apex. The horizontal MI=(A+B)/C; The vertical MI=(D+E)/F. The greater one of these two numbers was taken as final MI.

In this study, we aim to evaluate and compare the value of these parameters (MI, SOV dilatation, intracranial fat prolapse, and MV/OV) in predicting DON and provide guidance for early diagnosis of DON accordingly.

SUBJECTS AND METHODS

Ethical Approval This study conformed to the principles outlined in the Declaration of Helsinki and was approved by the Institutional Ethics Committee [No.KYK(2016)16; Medical Ethics Committee, Wenzhou Medical University, Wenzhou, Zhejiang Province, China]. Written informed consent was taken from all participants before the investigation.

Clinical Data Altogether 35 patients (67 eyes) presented as TAO in Eye Hospital of Wenzhou Medical University from March 2015 to November 2018 were enrolled in this study. The diagnosis of TAO was based on clinical manifestation and signs according to previously established criteria[11]. All of the patients underwent a complete set of ophthalmic examination, including best corrected visual acuity (BCVA), standard automated perimeter, non-contact tonometer and eye slit lamp examination. High-resolution computed tomography (HRCT) was performed on each subject. The CT slice thickness ranged from 0.75 to 1 mm. The tissue assessment was limited between -1024 and +1024 Hounsfield unit. All cases were divided into DON group and non-DON group. The clinical diagnosis of DON was confirmed if two or more of the following criteria were met[12]: 1) reduced BCVA not attributable to other eye disease; 2) visual field (VF) defect ＜ -5.0 decibel; 3) impaired color vision; 4) relative afferent papillary defect (RAPD); 5) optic disc swelling/atrophy. Patients younger than 20y were excluded to avoid ongoing growth influence. Patients with following conditions were also ruled out, including pregnancy, ocular disease other than TAO, history of eye injury or surgery and previous TAO treatment of radiotherapy, immunosuppressive therapy or surgery.

Imaging Analysis

Muscle index calculation MI was calculated according to the method described by Barrett *et al*[5] (Figure 1). Measurements were made at the CT plane halfway between the posterior globe and orbital apex. The transverse dimensions of the lateral rectus muscle (A), medial rectus muscle (B), and orbital width (C) were measured along a horizontal line through the optic nerve. Similarly, the longitudinal dimension of superior rectus/levator complex (D), inferior rectus muscle (E) and the orbital height (F) were obtained along a vertical line through the optic nerve. The horizontal MI was expressed as the percentage of orbital width occupied by the lateral and medial rectus muscles [(A+B)/C]. The vertical MI was expressed as the percentage of the height of the orbit occupied by the inferior rectus muscle and the superior muscle complex [(D+E)/F]. The larger one of these two indexes was taken as the final MI.

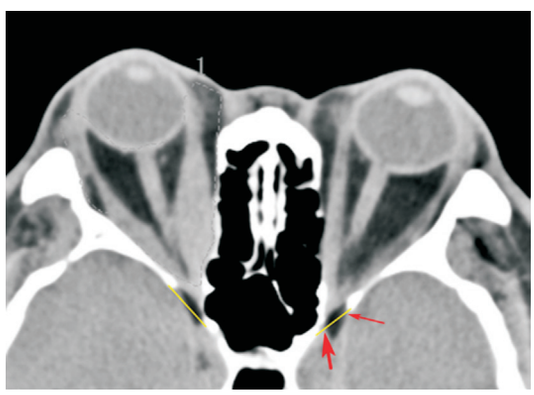

Figure 2 Intracranial fat prolapse was present in left eye but absent in right eye Thin arrow indicates the most inner border of the sphenoid wing and thick arrow indicates the most anterior border of sphenoid body groove.

Intracranial fat prolapse Intracranial orbital fat prolapse was examined according to the method described by Birchall *et al*[9]. The posterior extent of orbital fat was defined relative to the boundary of the superior ophthalmic fissure, which were measured on axial CT images. The lateral margin of the superior ophthalmic fissure was the most inner border of the sphenoid wing (Figure 2, thin arrow). The medial margin was the most anterior border of sphenoid body groove formed by internal carotid artery (Figure 2, thick arrow). The fissure was

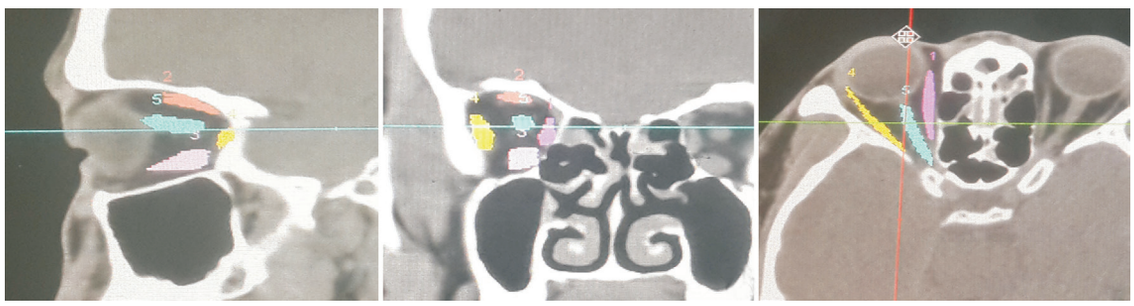

Figure 3 Muscle and orbital volume measurements Yellow area, pink area, orange area, and white area stand for external rectus muscle, medial rectus muscle, superior rectus, and inferior rectus respectively. Blue area stands for optic nerve.

Table 1 Clinical characteristics of DON group and non-DON group

Characteristic	DON group	Non-DON group	*P*
Eyes (*n*)	36	31	
Gender (M:F)	10:26	11:20	0.50
Age (y)	46.42±12.08	41.42±12.08	0.10
Parameters of orbital			
MV/OV	0.22±0.07	0.16±0.42	<0.01
MI	0.54±0.12	0.43±0.11	<0.01
Diameter of SOV (cm)	0.19±0.05	0.17±0.06	0.15
Presence of intracranial fat prolapsed	13 (36.1%)	8 (25.8%)	0.37

seen as a line joining these two points. Intracranial fat prolapse was confirmed if fat was seen 2 mm or more posterior to this line.

Superior ophthalmic vein dilatation SOV dilatation was assessed by SOV diameter. The SOV diameter was measured in axial planes[6] and the maximum one was taken into comparison.

Muscle volume/orbit volume calculation A software computer program (syngo Volume Evaluation; Siemens AG, Forchheim, Germany) was used to measure the MV/OV on CT scans. The areas of extraocular muscles and orbital space behind the globe were drawn along the margins of every structure in all axial slices. Coronal and sagittal slices were shown on the same screen, which helped increase the accuracy of the muscle marking and monitor three-dimensional views (Figure 3). Since the superior rectus muscle and levator palpebrae superior muscle are too closely located to be distinguished from each other, we measured these two muscles together as a superior rectus group. The volume within the marked space was then calculated by the syngo Volume Evaluation software. MV/OV is the ratio of extraocular muscle area to total orbital area. All measurements were performed by a single reader and repeated 3 times.

Statistical Analysis Statistical analyses were performed by using the Statistical SPSS 21.0. Descriptive statistics like mean value±standard deviation (SD) were used for normally distributed variables. The independent Sample *t*-test was used to compare the age, MI, SOV dilatation, MV/OV between the two groups. The Chi-square test was used to compare the gender, intracranial fat prolapse between the two groups. The relation between predictive parameter (MV/OV, MI) and visual function [VF defect, visual acuity (VA)] were further evaluated by Pearson linear correlation analysis. Receiver operating characteristic (ROC) curves were applied to describe the ability of these parameters to discriminate between cases with and without DON. Statistical significance was defined at $P<0.05$.

RESULTS

Thirty-five TAO patients (67 eyes) were included in the study, with 12 males and 23 females. The age ranged from 22 to 60y, with a mean age of 44.10±9.86y. Three of them were suffered unilaterally while the other 32 suffered bilaterally. Thirty-six eyes were enrolled in DON group and the other 31 eyes were in non-DON group. No statistical differences were detected in age and gender between 2 groups (both $P>0.05$). MI and MV/OV were significantly higher in DON group than that in non-DON group ($P=0.00035$, $P=0.00026$). However, no statistical difference was observed in SOV diameter between 2 groups ($P=0.15$). Intracranial fat prolapse was seen in 13 of 36 eyes in DON group (36.1%) and 8 of 31 eyes in non-DON group (25.8%), with no significant difference shown ($P=0.37$). The clinical characteristics of 2 groups were listed in Table 1.

Pearson linear correlation analysis was used to analyze the relation between predictive parameter (MV/OV, MI) and visual function (VF defect, VA). MV/OV was found to have significant negative correlations with both VF defects and

VA (*R*=-0.332, *P*=0.0273; *R*=-0.635, *P*=0.00). MI was found to have negative linear correlation with VA only (*R*=-0.456, *P*=0.00017; Table 2).

ROC curves were used to describe the ability of the MV/OV and MI to discriminate between cases with and without DON. The area under ROC curve of MV/OV and MI were 0.82 and 0.75 respectively. The best performance in diagnosing DON was achieved at MV/OV=0.2 with 72% sensitivity and 87% specificity, and at MI=0.52 with 64% sensitivity and 80% specificity (Figure 4).

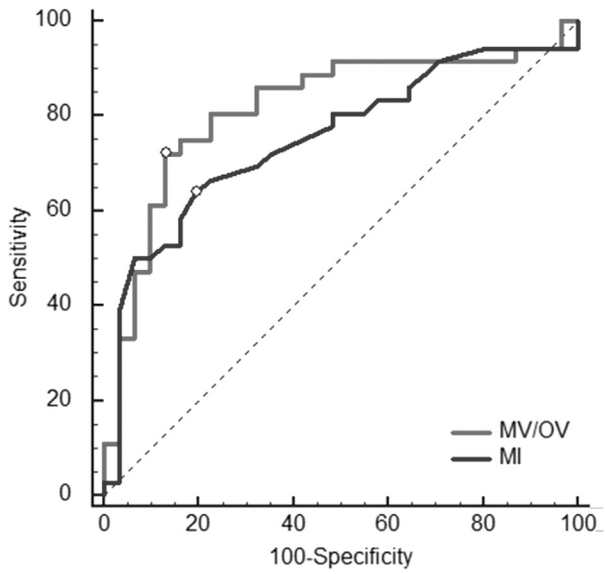

Figure 4 Ability of the MV/OV and MI to discriminate between cases with and without DON in ROC curves.

Table 2 Pearson liner-correlation analysis to predict VA and VF defect

Variables	*R*	*P*
VF defects		
MV/OV	-0.322	0.0273
MI	-0.190	0.20
VA		
MV/OV	-0.635	0.00
MI	-0.456	0.00017

DISCUSSION

DON is one of the most severe complications of TAO, which requires prompt diagnosis and treatment to prevent permanent damage to visual function[13]. The diagnosis of DON usually depends on clinical features, including decreased VA, abnormal VF, impaired color and brightness perception, RAPD and optic papilla edema or atrophy[1]. Nevertheless, DON is often subclinical and undetected until visual function is severely compromised. It is even more so in euthyroid or hypothyroid patients[1,3,12]. Differential diagnosis is also confusing from other causes of visual impairment secondary to TAO, such as exposure keratopathy or secondary glaucoma[12] .Therefore, it is highly desirable to develop imaging technique to facilitate the early diagnosis of DON[5-7,14-17].

CT scan is the preferred imaging technique for investigating DON in previous studies[1,5-6,14,18-19]. It has been proved to be excellent in visualizing the detailed structure of orbit, like extraocular muscles, orbital fat, and vein[18-19]. Parameters on CT scan are useful in quantitative measurement of extraocular muscle enlargement and orbital apex crowding[2,4-7].

MI was considered as an indicator of DON by many studies before[5,8]. In our study, we confirm that DON patients had higher MI than non-DON patients, which is consistent with findings from previous studies[5,8], and supports the theory that direct compression by enlarged extraocular muscles is a major culprit in optic nerve dysfunction in patients with DON. Meanwhile, we find out that MI is an independent indicator for VA but not for VF defect. According to the way of MI calculation, which is derived from the CT plane half way between the posterior globe and orbital apex, MI cannot directly reflect the orbital apex crowding caused by enlarged muscles[20] but only tells DON of late-stage rather than early-stage. VF defect usually shows earlier than VA decrease for optic nerve damage and it will become worth or even tubular vision in most cases with DON of late-stage. Thus, the VF field may remained the same at the late-stage of DON.

The SOV is valveless and directly connected to the cavernous sinus[21]. Causes of dilatation include carotid cavernous fistula, inflammation at the apex of the orbit, orbital pseudotumor, and thyroid eye disease[22]. Apical crowding and increased intraorbital pressure in TAO patients may lead to SOV dilatation. However, in our study, no difference was detected in SOV diameter between TAO patients with and without DON. One plausible reason is that venous outflow is normalized by blood compensation mechanism during chronic compression[8]. Another explanation is that SOV dilatation may have existed in TAO patients before they developed into DON.

Intracranial fat prolapse through the superior ophthalmic fissure was first mentioned by Birchall *et al*[9] as an indicator of DON, while other researches believed this radiographic feature was not a reliable risk factor for DON[1,23]. We revisited the method described by Birchall and showed DON group and non-DON group do not differ statistically with regards to intracranial fat prolapse. This implies that intracranial fat prolapse may have existed in TAO patients before they developed into DON, just like SOV dilatation.

MV/OV is a parameter that not only takes extraocular muscle but also orbit volume into consideration. Chan *et al*[23] highlighted the importance of both extraocular muscle enlargement and bony orbit volume as predictors of DON. Some researches pointed out that orbital parameters, like orbital volume, extraocular MV and fat volume (FV), were affected by many factors, such as gender, age, race and

etc[10,24-26]. For example, men usually have larger orbit, more fat tissue, and bigger MV than women, but the ratio of FV/OV and MV/OV shows the same trend in both genders[10,27]. Thus, MV/OV represents the relative amount of volume that extraocular muscles occupy in the orbit and can effectively offset the gender or age or race differences. Therefore, we believed MV/OV is more valuable and credible in predicting DON. In our study, we find out that MV/OV was much higher in patients with DON than those without, which is consistent with the previous researchers[10,28]. Furthermore, we proved that MV/OV is an independent predictor for both VA and VF defect, implying its use in early diagnosis of DON. As an independent criterion, MV/OV shows a relative satisfactory diagnostic capability with 72% sensitivity and 87% specificity at a cut-off of 0.2, much better than that of MI. If combined with clinical symptoms and signs, it can definitely help increase the diagnostic efficiency for DON.

In conclusion, MI and MV/OV are predictive parameters for DON, while SOV dilation and intracranial fat prolapse are not. MV/OV is most effective among these parameters in predicting DON. Together with other clinical features, MV/OV ≥20% can be used as another important criterion in diagnosis of DON.

Whereas, limitations were existed in this study. Patients included in this study with DON as a cross sectional study. Predictive value is more important in early stage or before DON development. Thus a large-sampled controlled prospective research should better be evaluated in patents before DON development in another longitidional study to prove predictive values before DON development.

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