Voxel-Based Morphometric Features of Dysthyroid Optic Neuropathy

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Abstract

Background: Dysthyroid optic neuropathy (DON) is a serious complication of thyroid-associated ophthalmology (TAO), leading to loss of vision or blindness. Numerous studies had reported thyroid dysfunction affects a wide range of visual pathways in adults, from the retina to the visual center. We aimed to explore if there were abnormalities of gray matter density (GMD) in DON patients.

Methods: We collected patients with TAO from The Eye Hospital of Wenzhou Medical University. All patients underwent routine ophthalmic examination, Clinical Activity Score (CAS), intraocular pressure (IOP), exophthalmos, visual field, OCT, and orbital CT scan. 16 patients with DON and 16 patients without DON (N-DON) were enrolled in this study. Age, gender, orbital congestion index and degree of education of patients were matched between the two groups. High-resolution magnetization-prepared rapid acquisition with gradient echo (MPRAGE) scans was performed on all patients. Voxel-based morphometry (VBM) was applied to analyze the T1 weighted images of the brain, based on functional magnetic resonance imaging (fMRI) integrated VBM (FSL-VBM).

Results: GMD was significantly decreased in the right middle temporal gyrus, left middle frontal gyrus, left superior frontal gyrus, and right middle frontal orbital gyrus in the DON when compared to N-DON.

Conclusions: The DON can result in reduced GMD in specific areas of the brain. This finding suggests that there may be other mechanisms in Don

1. Background

Thyroid associated ophthalmology (TAO) is an autoimmune disease, always comorbid with dysfunction of thyroid^[1, 2]. The physical manifestation of TAO includes proptosis, upper and lower eyelid retraction, periorbital edema, diplopia, photophobia. The most serious complication is DON, which may lead to blindness

At present, it is generally accepted that the main pathogenesis of Don is orbital apex crowding and edema. Numerous studies have documented the differences in muscle index^[3, 4], superior ophthalmic vein enlargement^[4], and intracranial fat prolapse^[5] between DON and non-DON (N-DON). However, overlap and even contradictory findings of these indices exist between DON and N-DON^[4–6]. Anderson et al.^[7] reported three atypical cases of DON with normal-sized or minimally enlarged extraocular muscles. Therefore, optic compression is not the only etiology responsible for the pathogenesis of the DON.

Numerous studies have reported that thyroid dysfunction impacts a wide range of optic pathways in adults, involving the retinal cone^[8], myelination in optic nerve^[9–11], and visual gyrus^[12, 13]. Primary hypothyroidism has significantly increased the risk of open-angle glaucoma^[14], which eventually results in visual field defects^[15]. Additionally, hypothyroidism has a high incidence of color contrast sensitivity impaired^[16] and visual evoked potential (VEP) disorders^{[17],[18]}. Higher baseline thyroid-stimulating

hormone could be associated with faster cognitive decline over-time among US adults in the urban area, specifically in domains of working memory and visuospatial and/or vasoconstriction abilities^[19]. Consistently, hypothyroidism contributes to a reduction in granular cells in the cerebellum and hippocampus in rats during adulthood^[20–23]. Neuroimaging identified that patients with dysfunction of thyroid had reduced grey matter volume in particular regions of the brain^[24]. Thus, dysfunction of thyroid might directly impact the central nervous system.

It is well accepted that thyroid dysfunction is closely related to the development and in proportion to the severity of TAO. Recent research has shown that thyroid-stimulating immunoglobulin (TSI) was associated with new-onset DON^[25]. Accordingly, we hypothesize that thyroid dysfunction contributes to DON. We aimed to explore if there were abnormalities of gray matter density (GMD) in DON patients.

2. Methods

2.1 Participants

This research conforms to the principles of the Helsinki Declaration. Patients with TAO were recruited from The Affiliated Eye Hospital of Wenzhou Medical University. Those with CAS ≥ 3 were excluded. The patients who concurrently affected other ophthalmologic diseases, such as exposure keratitis, multiple sclerosis, ischemic or inflammatory neuritis, cataract, glaucoma, macular diseases, high astigmatism, high myopia, and congenital dyschromatopsia, were excluded since they could significantly affect visual function. The diagnostic criteria of TAO are according to thyroid hormone level, clinical features, and MRI finding. The diagnosis of DON was made based on the presence of at least two clinical signs suggestive of optic neuropathy, such as a reduction in best-corrected visual acuity (BCVA), altered visual fields, relative afferent pupillary defect (RAPD), and unexplained optic disc swelling^[26].

2.2 Ophthalmologic examination

All patients underwent complete ophthalmologic examination according to the European Group On Graves' Orbitopathy (EUGOGO) criteria and obtained a CAS score. The BCVA was assessed with Snellen charts and expressed as a decimal fraction. Automated perimetry was performed with Humphrey's visual field analyzer (HFA; Humphrey Instruments, Inc., San Leandro, CA). The resultant readout is based on Swedish Interactive Threshold Algorithm Fast Test (30–2 SITA Fast) with a Goldmann size III stimulus on a dim background (31.5 apostilbs) and foveal threshold turned on. During visual field testing, each patient was provided with adequate near-vision correction and necessary rest. Visual fields with reliability indices exceeding normal limits (fixation losses $>15\%$, false positive or false negative $>15\%$) were repeated thrice. The readout was excluded from data analysis if it was considered unreliable. All patients received orbital computer tomography (CT) scan to determine rectus muscle index (Barrett L 1988^[27]) and medial rectus maximal diameter (Weis E 2012^[28])

2.3 Groups

Among TAO patients, 16 with DON and 16 without DON (N-DON) were enrolled in this study. Age, gender, muscle index, medial rectus maximal diameter, and degree of education were match between the two groups.

2.4 Image acquisition

MRI was performed by using a 3.0T GE Signa HDx scanner (GE Healthcare, Milwaukee, Wisconsin) with an 8-channel head coil. Three-dimensional T1-weighted images were acquired in the sagittal plane through the 3D SPGR sequence. Scan parameters were as follows: repetition time = 8.8 ms, echo time = 4.02 ms, flip angle = 15°, field of view = 256 × 256, voxel size = 1 mm³, 160 slices without gap.

2.5 Voxel-based morphometry analysis

Structural features were evaluated by FMRIB Software Library (FSL) to achieve FSL-VBM, an optimized VBM-style analysis. This yields a measure of the difference in the local grey matter volume. Firstly, brain structural images were extracted by the Brain Extraction Tool (BET). Then, tissue types were segmented by FSL, FLIRT, and FNIRT to obtain images for grey matter partial volume, which were aligned to MNI152 standard space. The resulting images were averaged to create a study-specific template, which could be applied to nonlinearly re-register native images on grey matter. These images were modulated (to correct for local expansion or contraction) by being divided by Jacobians of the warp field, and subsequently smoothed by an isotropic Gaussian kernel with a sigma of 3 mm. Finally, comparisons between two groups were carried out with permutation-based nonparametric tests. Randomized functions were implemented in FSL, using a threshold-free cluster-enhancement method, for proper statistical inference of spatially distributed patterns.

3. Results

3.1 Demographic findings

Demographic characteristics are summarized in Table 1 and Table 2. Two groups were matched in age, sex, muscle index, inner rectus thickness, and education degree. Thyroid function is described in Table 2. No significant difference in levels of T3, T4, or TSH was observed between the two groups. but Six (18.75%) patients were diagnosed with hypothyroidism. Five patients in the DON group, and a patient in N-DON group.

Table 1. Demographic and neuropsychological characteristics

	DON	N-DON	<i>P-value</i>
Gender, n (M/F)	16 (6/10)	16 (10/6)	1.000
Age, years	50.7 ± 6.2	46.3±7.0	0.076
IOP	18.27±4.24	17.45±5.03	0.265
MD (VF od)	-13.44 ±10.11	-1.58 ±1.81	0.000
MD (VF os)	-10.66 ±6.95	-1.32 ±1.42	0.000
Muscle index (V)	57.03	51.18	0.56
Muscle index (H)	50.48	48.66	0.64
Inner rectus thickness	6.40mm	6.24mm	0.15

Data were represented as mean ± SD when appropriate and analyzed using independent-samples t-tests.; M, Male; F, Female; VF, visual field; MD, mean deviation. V, Vertical; H, Horizontal

Table 2. Thyroid function of different groups

	DON	N-DON	<i>P-value</i>
T3	2.20±0.96	1.97±0.58	0.27
T4	134.08±46.01	122.02±20.38	0.19
FT3	6.73±2.10	5.53±2.11	0.21
FT4	23.79±16.83	19.33±3.85	0.16
TSH	3.50±5.91	2.20±3.85	0.33

T3:3,5,3' triiodothyronine; T4 thyroxine: ; FT3:free-triiodothyronine;

rT4: Free thyroxine; TSH: thyrotropic stimulating hormone.

3.2 VBM

Significant differences were observed in 4 brain regions between the two groups (Figure 1 and Table 3). These brain regions are located on the left middle frontal gyrus, left superior frontal gyrus, right middle frontal gyrus, right middle frontal orbicular gyrus and right middle temporal gyrus,

Table 3. Significantly different values of gray matter density in brain regions between the two groups

Brain regions	Voxels	BA	MNI coordinates			<i>P</i> -value
			x	y	z	
Temporal_Mid_R	254	54	-28	-12		0.978
Frontal_Mid_Orb_R	662	12	62	0		0.994
Frontal_Mid_L	135	-18	56	2		0.978
Frontal_Sup_L	59	-18	26	58		0.978

MNI—Montreal Neurological Institute; *BA*—Brodmann area—Temporal_Mid_R—the right middle temporal gyrus—Frontal_Mid_L—the left middle frontal gyrus, Frontal_Sup_L—the left superior frontal gyrus, Frontal_Mid_Orb_R—right middle frontal orbicular gyrus

4. Discussion And Conclusion

In this study, we investigated alteration in GMD among representative TAO patients with or without DON. Compared to N-DON, GMD was decreased significantly in DON, mainly in the right middle temporal gyrus, left middle frontal gyrus, left superior frontal gyrus, and right middle frontal orbicular gyrus. The cortical visual processing network includes dorsal and ventral pathways. The middle temporal gyrus is a key node in the dorsal pathway, which involves in visuospatial functions and visual motion^[29-31]. The middle frontal gyrus and superior frontal gyrus take part in the oculomotor control, which is closely related to dorsal and ventral pathways.^[32-34]

Thyroid dysfunction could influence a wide range of visual pathways, including retina cone opsin expression^[8], myelination in optic nerve^[9-11], and visual gyrus^[12, 13]. Besides, abnormal limbic regions caused by dysfunction of thyroid are mostly temporal and frontal lobes^[36, 37], which is consistent with our findings.

Previous studies have indicated that both hypothyroidism and hyperthyroidism can lead to brain abnormalities in structure and function^[12, 40]. A study on 2557 individuals suggested that patients with hypothyroidism had significantly lower total brain volume than the normal^[40]. Hypothyroidism could cause a reduction in grey matter volume (GMV) in the left postcentral gyrus and cerebellum. Reduction in white matter volume was also observed in the cerebellum, right superior frontal gyrus, middle frontal gyrus, right anterior central gyrus, and right temporal gyrus^[38]. Through VMB analysis, hyperthyroid patients exhibit reduced GMV in the hippocampus, parahippocampal gyrus, calcarine, lingual gyrus, and left temporal pole, which are critical for memory, attention, emotion, vision, and motor planning^[39].

For brain connection, thyroid dysfunction also leads to abnormal functional connectivity (FC) in the brain. Resting-state magnetic resonance imaging (rs-MRI) identified a significant decrease in hippocampus

volume and functional FC in regions of the right front-parietal network, medial visual network, and motor network in hypothyroid patients^[13]. Compared with healthy controls, patients with hyperthyroidism exhibited increased FC in the bilateral anterior insula (AI), bilateral posterior insula (PI) and left anterior lobe of the cerebellum (ALC); whereas decreased FC in the bilateral lateral prefrontal cortex (LPFC), right medial temporal gyrus (MTG) and bilateral posterior cingulate cortex (PCC)^[41]. Even more, short-term hyperthyroidism could lead to abnormal connection in brain^[37].

No study on the effect of dynamic thyroid function on brain structure has been reported. Krausz Y et al. compared regional cerebral blood flow (rCBF) between hypothyroid patients and health subjects during euthyroid state after treatment. Compared with controls, rCBF in hypothyroid patients before treatment was lower in the right parietooccipital gyri, cuneus, posterior cingulate, lingual gyrus, fusiform, insula, and pre- and postcentral gyri. Perfusion failed to recover to normal when the thyroid function returns to normal state^[42]. These findings were validated by later researches^{[43][44][45]}. According to the above discussion, the brain function of patients with hypothyroidism can not be completely recovered after a thyroid hormone supplement, which indicates that the dynamic abnormality of thyroid hormone may lead to brain dysfunction.

The pathogenesis of DON remains unclear. The DON was caused by compression associated with edema and increased volume of orbital tissue. Muscle index^[3, 4] was applied to evaluate crowded orbital apex, with several contradictions in the follow-up studies^[4-6]. Recently, researchers proposed that the maximum diameter of rectus muscle was an important quantifiable predictor of compressive optic neuropathy in TAO^[28]. In our study, the difference in orbital apex crowding between the two groups was minimized. Therefore, under the circumstance of excluding crowded orbital apex, the DON group experienced a decrease in gray matter density in different brain areas, which was similar to that caused by dysthyroid function. It is well accepted that thyroid dysfunction is closely related to the development and in proportion to the severity of TAO. So, Thyroid abnormalities might be related to abnormal changes in the brain regions of patients with DON. In this study, there was no significant difference in T3, T4, and TSH between the two groups, but 6 patients (18.75%) had been diagnosed with hypothyroidism. This may be because we can not reflect the long-term dynamic changes of thyroid hormone levels when we detect thyroid hormone levels at a time point. Therefore, it is necessary to further study the long-term dynamic thyroid hormone level of large sample.

This study had several limitations. First, the sample size of each group was relatively small. Further studies are required to reproduce our findings by recruiting a large cohort of patients. Second, this study was cross-sectional, which made it difficult to evaluate if increased GMD of the higher vision cortex could be influenced by prolonged illness duration.

5. Conclusions

In this study, we apply VBM analyses to examine dynamic changes in GMD among representative patients with or without DON. The DON group exhibits significantly lower GMD in the right middle

temporal gyrus, left middle frontal gyrus, left superior frontal gyrus, and right middle frontal orbital gyrus. Therefore, DON might have multiple pathogenic mechanisms.

List Of Abbreviations

Dysthyroid optic neuropathy DON

thyroid-associated ophthalmology TAO

gray matter density GMD

Clinical Activity Score CAS

intraocular pressure IOP

magnetization-prepared rapid acquisition with gradient echo MPRAGE

Voxel-based morphometry VBM

functional magnetic resonance imaging FMRIB

visual evoked potential VEP

thyroid-stimulating immunoglobulin TSI

best-corrected visual acuity BCVA

altered visual fields, relative afferent pupillary defect RAPD

EUropean Group On Graves' Orbitopathy EUGOGO

grey matter volume GMV

functional connectivity FC resting-state magnetic resonance imaging rs-MRI anterior insula AI posterior insula PI

anterior lobe of the cerebellum ALC

lateral prefrontal cortex LPFC

medial temporal gyrus MTG posterior cingulate cortex PCC

regional cerebral blood flow rCBF

Declarations

Ethical approval—Ethical approval was waived by the local Ethics Committee of Wenzhou medical university and all the procedures being performed were part of the routine care.

Consent for publication: Not applicable

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests—The authors have no conflicts of interest to declare.

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Author Contributions—YHT and JLG conceived and designed the study.BXM —CWM and TTC performed the experiments.YHT wrote the paper. YHT, XZL, JLG eviued and edited the manuscript. All authors read and approved the manuscript

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Figures

Figure 1

Two-sample t-test on alteration of gray matter density between two groups. Decreased gray matter density is mainly located in the right middle temporal gyrus, left middle frontal gyrus, left superior frontal gyrus, and right middle frontal orbital gyrus. DON, dysthyroid optic neuropathy; N-DON, non-dysthyroid optic neuropathy;