IJO-2019-0414

Comparisons of ganglion cell-inner plexiform layer loss patterns and its diagnostic performance between normal tension glaucoma and primary open-angle glaucoma: a detailed, severity-based study

Running title: GCIPL thickness in normal and high tension glaucoma

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Abstract

AIM: To evaluate the patterns of macular ganglion cell-inner plexiform layer (GCIPL) loss in normal tension glaucoma (NTG) and primary open-angle glaucoma (POAG) in a detailed, disease severity-matched way; and to assess the diagnostic capabilities of GCIPL thickness parameters in discriminating NTG or POAG from normal subjects.

METHODS: A total of 157eyes of 157subjects, including 57 normal eyes, 51eyes with POAG and 49eyes with NTG were enrolled and strictly matched in age, refraction, and disease severity between POAG and NTG groups. The average, minimum, superotemporal, superior, superonasal, inferonasal, inferior, and inferotemporal GCIPL thickness, and the average, superior, temporal, inferior, and nasal retinal nerve fiber layer (RNFL) thickness were obtained by Cirrus optical coherence tomography (OCT). The diagnostic capabilities of OCT parameters were assessed by area under receiver operating characteristic (AUROC) curves.

RESULTS: Among all the OCT thickness parameters, no statistical significant difference between NTG group and POAG group was found (all P>0.05). In discriminating NTG or POAG from normal subjects, the average and inferior RNFL thickness,and the minimum GCIPL thicknesshad better diagnostic capabilities. There was no significant difference in AUROC curve between the best GCIPL thickness parameter (minimum GCIPL) and the bestRNFL thickness parameterin discriminating NTG (inferior RNFL; P = 0.076) and indiscriminating POAG (average RNFL;P = 0.913) from normal eyes.

CONCLUSION: Localized GCIPL loss, especially in the inferior and inferotemporal sectors, was more common in NTG than in POAG. Among all the GCIPL thickness parameters, the minimum GCIPL thickness had the best diagnostic performance in differentiating NTG or POAG from normal subjects, which was comparable to that of the average and inferior RNFL thickness.

KEYWORDS: normal tension glaucoma; primary open-angle glaucoma; spectral domain optical coherence tomography; ganglion cell-inner plexiform layer thickness; pattern.

INTRODUCTION

Glaucoma is an optic neuropathy with progressive loss of retinal ganglion cells (RGCs) and their axons that lead to peripapillary retinal nerve fiber layer (RNFL) loss and glaucomatous visual field damage[1]. Of all the glaucoma cases worldwide, approximately 74% are primary open-angle glaucoma (POAG)[2-3]. Although rise in intraocular pressure (IOP) is regarded as the primary risk factor of glaucoma progression[4], RGC loss and glaucomatous optic neuropathy can occur partially independently of IOP in normal tension glaucoma (NTG), usually known as a subset of POAG.

Conventionally, an IOP of less than 22 mm Hg is considered as the cut-off value for defining NTG. POAG and NTG probably represent a continuum of optic neuropathy with considerable overlap of disease characteristics and causative factors. However, the IOP level is not the only difference between NTG and POAG. NTG seems to progress much slower than POAG. Many studies have also demonstrated that disc hemorrhage, localized RNFL defects, thinner neuroretinal rims, and vascular or perfusion abnormalities are more common in NTG patients compared with POAG patients[5-9]. In spite of these findings, the mechanism and risk factors of NTG progression remain unidentified. Moreover, how to define and diagnose NTG using objective measures in its early stage is also a major concern to be resolved.

Spectral domain optical coherence tomography (SD-OCT) enables measurements of both peripapillary RNFL and macular thickness parameters, which has been widely accepted as a standard of care in managing glaucoma. The enhanced scanning speed, better image resolution, and improved retinal layer segmentation ability of the ganglion cell algorithm (GCA, Cirrus Version 6.0; Carl Zeiss Meditec, Dublin, CA) enable the measurement of the macular ganglion cell-inner plexiform layer (GCIPL) thickness. The glaucomatous diagnostic ability of macular GCIPL thickness has been confirmed to be comparable to or better than that of the peripapillary RNFL thickness by multiple studies[10-14]. One of the explanations is that the GCIPL thickness is expected to target at the RGCs, which are primarily affected by glaucoma, directly in an area of their highest concentration[15-18]. However, there is a paucity of studies on the differences in the distribution and the discriminating capability of macular OCT measurements between NTG and POAG. The aims of this study were to compare macular GCIPL parameters

measured by Cirrus OCT between age-, refraction-, and severity-matched NTG and POAG, and to investigate and compare the diagnostic performance of GCIPL and RNFL thickness parameters in differentiating NTG and POAG from normal eyes.

SUBJECTS AND METHODS

Ethical Approval All study subjects were consecutively recruited at Zhongshan Ophthalmic Center of Sun Yat-sen University, Guangzhou, China from August 2014 to May 2015. The study was approved by the Institutional Review Board (IRB) and followed the tenets of the Declaration of Helsinki. Written informed consent was obtained from each subject.

Study Subjects All subjects were performed complete ophthalmic examinations including visual acuity (uncorrected and best-corrected), refraction examination (cycloplegic refraction test was performed if the participant was of <30y of age, whereas manifest refraction test was performed if the participant was of ≥30y of age), central cornea thickness (CCT) measurement (Ultrasonic Pachymetry DGH-1000, Storz Inc, Louis, MO, USA), slit lamp biomicroscopy, angle evaluation using gonioscopy, fundus examination, fundus photography (Kowa nonmyd a-D III; Kowa Optimed Inc, Aichi, Japan), Humphrey perimetry (SITA standard 24-2; Carl Zeiss Meditec, Dublin, CA, USA), and Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA, USA). Intraocular pressure (IOP) was measured by the same well-trained investigator using the calibrated Goldman applanation tonometer (Haag-Streit, Bern, Switzerland) in the day time (8 a.m. to 8 p.m.), or a well-calibrated TonoPen tonometer (TonoPen XL; Bio-Rad, Glendale, CA, USA) during the night (10 p.m. to 6 a.m.).

Eyes with BCVA of at least 20/20, peak IOP of <21 mm Hg, normal appearance of the optic disc, normal and reliable visual field results, no RNFL defects, no previous ocular surgeries, and without any known history of ocular and/or systemic diseases other than mild age-related cataract were considered normal eyes.

Glaucoma diagnosis was made if characteristic structural changes to the optic disc and RNFL defects accompanied by glaucomatous visual field defects were found. Glaucomatous visual field defect was defined as: glaucoma hemifield test outside the normal range, pattern standard deviation with a *P* value of <5%, or a cluster of >3 points in the pattern deviation plot in a single hemifield (superior or inferior) with a *P* value of <5%, and at least one of these should have a *P* value of <1%. A reliable visual field testing should have a false-positive error, a false-negative error, and a fixation loss of less than 20%, simultaneously. Eyes with these features were diagnosed as POAG when IOP of >21 mm Hg at any time point was recorded and was further confirmed on at least 2 more measurements taken on different days, or NTG when untreated peak IOP was 21mm Hg or lower based on IOP measurements taken every 2 hours over a 24-hour period using the above-mentioned devices. Early glaucoma and moderate glaucoma were classified based on the mean deviation (MD) of visual field testing of ≥ -6 dB and from -6 dB to -12 dB, respectively.

The inclusion criteria of this study included: age ≥18y, refractive diopters (spherical equivalence) between -3 to +3, 360-degree open angle, reliable visual field results, and OCT scans with good quality. The exclusion criteria were unsuccessful image acquisition, history of ocular trauma, usage of medications that could cause elevation of IOP or optic neuropathy, and any life-threatening diseases. For eyes with glaucoma, they also included: any known history of ocular disorders other than age-related cataract, diseases that might affect retina health and visual field results, and history of intraocular surgery. If both eyes of a subject met the criteria, only one randomly selected eye was enrolled.

Optical Coherence Tomography Scanning Eyes were dilated with 0.5% tropicamide and 0.5% phenylephrine before OCT scans. OCT scans of Macular Cube 512×128 protocol and Optic Disc Cube 200×200 protocol were performed with the same Cirrus OCT device by a well-trained ophthalmologist (XX). Images with signal strength of less than 7 or those with visible motion or blinking artifacts and segmentation failure were considered of poor quality and discarded immediately.

The average, minimum, and sectoral (superior, superonasal, inferonasal, inferior, inferotemporal, and superotemporal) macular GCIPL thickness was calculated using the GCA algorithm within a 14.13 mm^2 elliptical annulus area centered on the fovea (horizontal inner and outer radius of 0.6 and 2.4 mm, respectively; vertical inner and outer radius of 0.5 mm and 2.0 mm, respectively). The outer boundaries of the RNFL and the IPL were identified and the segmentation of "GCIPL" (a combination of the GCL and the IPL) was yielded. The minimum GCIPL thickness was the minimum measurement of the 1-degree interval among the 360 spokes. The average, superior, temporal, inferior and nasal RNFL thicknesses parameters and optic nerve head (ONH) parameters (rim area, disc area, and vertical cup-to-disc diameter ratio) were generated by the Cirrus internal analysis algorithm.

Statistical Analysis SPSS version 22.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Kolmogorov-Smirov test and Levene test were conducted to test the normality and homogeneity of variance, respectively. Chi-square test was used to evaluate the differences of gender distribution among groups. Age, refractive diopters, values of mean deviation, CCT, IOP, GCIPL and RNFL thickness were compared with one-way analysis of variance (ANOVA), with Bonferroni adjustments used for further pairwise multiple comparisons. Independent *t*-test was used for comparisons between the anti-glaucoma drops being used, OCT parameters and visual field mean deviation between early NTG and early POAG groups, and moderate NTG and moderate POAG groups. The diagnostic ability of each OCT parameter was determined by the area under the

receiver operating characteristic (AUROC) curve, which were then compared using MedCalc 18.0 (Med-Calc Statistical Software bvba, Mariakerke, Belgium) based on the method of DeLong et al[19]. A *P* value of <0.05 was considered to be significant statistically.

RESULTS

A total of 157 eyes were included. The baseline demographic and clinical characteristics of subjects in all 3 groups were showed in Table 1. There were no significant differences in age, gender, refractive diopters or CCT among NTG, POAG, and normal groups. Base-line IOP was significantly different among the 3 groups, while the difference between NTG and normal group was insignificant in pairwise comparisons (*P*=0.767). Although the value of mean deviation was significantly different among the 3 groups, no significant difference was found between NTG and POAG groups in pairwise comparisons (*P*=0.812).

Table 1 Demographic and clinical characteristics of the study population mean±SD

Parameters		NTG (*n*=49)	POAG (*n*=51)	Normal (*n*=57)	*P*
Age (y)		62.2±13.2	60.7±12.1	61.9±12.5	0.819
Gender (male/female)		19/30	28/23	29/28	0.244
Spherical equivalent (diopter)		-1.87±1.81	-1.81±1.37	-1.58±1.66	0.118
Central corneal thickness (μm)		547.8±30.7	558.2±33.6	554.1±27.1	0.440
Baseline intraocular pressure		13.10±3.80	24.93±4.12	14.30±3.51	<0.001
Anti-glaucoma drops		1.33±0.47	1.55±0.40	-	0.041
Disease Stage (early/moderate)		28/21	29/22	-	0.977
Mean deviation (dB)	Total	-6.04±3.77	-6.20±3.96	-0.87±0.82	<0.001
	Early stage	-3.26±1.65	-3.30±1.77	-	0.933
	Moderate stage	-9.75±2.27	-10.04±2.48	-	0.692

NTG: Normal tension glaucoma; POAG: Pimary open angle glaucoma; GCIPL: Ganglion cell-inner plexiform layer; RNFL: Retinal nerve fiber layer. Comparisons among 3 groups (NTG, POAG and normal control groups) were performed using one-way ANOVA. Comparisons between 2 groups (NTG and POAG groups) were performed using independent *t*-test.

The GCIPL and RNFL thickness of each group were displayed in Table 2, with the NTG and POAG groups further subdivided into 3 categories of total (patients of all severity stages), early stage and moderate stage. Though the differences in all GCIPL and RNFL thickness and ONH parameters were of statistical significance among 3 groups except that of disc area, no statistically significant difference between the NTG and the POAG group was found in all parameters using pairwise comparisons with Bonferroni adjustments.Pairwise comparisons of the differences of all parameters between NTG and normal, and POAG and normal showed significant differences (all *P*< 0.001, not shown in Table 2) except that of disc area (between NTG and normal, *P*=0.064; between POAG and normal, *P*>0.999). OCT parameters between early NTG and POAG, and moderate NTG and POAG were also compared and displayed in Table 2.

Table 2 Macular GCIPL and peripapillary RNFL thickness in all study groups mean±SD

Parameters	NTG			POAG			Normal (*n*=57)	*P* values			
	Total (*n*=49)	Early (*n*=28)	Moderate (*n*=21)	Total (*n*=51)	Early (*n*=29)	Moderate (*n*=22)		P^a	P^b	P^c	P^d
GCIPL thickness (μm)											
Average	69.78±10.04	72.71±9.61	65.48±9.13	70.43±8.06	73.72±7.14	65.33±7.37	83.96±5.43	<0.001	>0.999	0.653	0.928
Minimum	58.16±13.72	62.75±13.18	52.13±11.66	60.78±10.28	64.24±10.11	55.50±8.73	80.84±5.86	<0.001	>0.999	0.633	0.207
Superotemporal	70.49±10.71	72.54±10.75	66.70±10.43	70.12±11.26	74.52±9.86	63.33±10.59	82.58±5.45	<0.001	0.612	0.471	0.283
Superior	72.18±13.03	74.50±11.46	68.57±14.09	72.67±10.35	75.66±9.81	67.67±10.14	84.79±6.14	<0.001	>0.999	0.684	0.924
Superonasal	75.88±11.81	78.00±9.84	72.52±13.27	76.22±10.05	77.52±9.77	73.75±10.23	86.33±5.98	<0.001	>0.999	0.853	0.699
Inferonasal	71.04±13.48	74.07±12.44	66.61±13.49	70.35±9.21	73.69±8.16	65.33±8.67	83.88±6.14	<0.001	>0.999	0.891	0.773
Inferior	64.65±12.51	68.75±11.34	59.09±11.59	66.33±9.75	70.07±9.02	60.71±8.63	82.26±5.67	<0.001	>0.999	0.628	0.494
Inferotemporal	64.37±11.26	68.11±11.29	59.65±8.95	66.33±10.47	70.66±9.81	60.13±8.35	83.68±6.26	<0.001	0.900	0.367	0.648
Peripapillary RNFL thickness (μm)											
Average	74.61±9.91	78.29±6.52	68.26±12.05	73.22±11.90	77.79±10.54	66.38±11.13	96.93±8.67	<0.001	>0.999	0.833	0.468
Superior	92.22±21.73	96.75±17.34	83.78±25.79	91.14±19.03	97.86±16.81	80.71±18.43	119.60±14.62	<0.001	>0.999	0.807	0.571
Temporal	61.67±11.52	63.96±12.03	57.13±11.11	56.96±10.82	58.34±10.02	53.58±12.43	69.68±9.03	<0.001	0.076	0.060	0.307
Inferior	81.27±17.10	88.57±13.54	70.70±16.18	84.10±23.49	93.34±21.97	71.83±19.83	127.98±17.15	<0.001	>0.999	0.330	0.945
Nasal	63.20±9.42	63.93±8.59	61.13±10.77	60.20±8.49	61.28±7.55	58.83±9.87	70.26±9.73	<0.001	0.318	0.220	0.267
Optic nerve head parameters											
Rim area (mm^2)	0.893±0.147	0.939±0.122	0.807±0.174	0.910±0.258	0.997±0.192	0.795±0.281	1.367±0.252	<0.001	>0.999	0.178	0.618

Disc area (mm^2)	2.202±0.542	2.195±0.481	2.225±0.606	2.056±0.432	2.067±0.434	2.058±0.424	1.992±0.416	0.064	0.351	0.296	0.311
Vertical cup-to-disc ratio	0.738±0.086	0.707±0.096	0.788±0.052	0.710±0.127	0.676±0.118	0.765±0.127	0.462±0.185	<0.001	0.964	0.285	0.395

GCIPL: Ganglion cell-inner plexiform layer; RNFL: Retinal nerve fiber layer; NTG: Normal tension glaucoma; POAG: Primary open angle glaucoma. [a]Comparisons were performed using one-way ANOVA among NTG, POAG and normal control groups. [b]Comparisons of NTG and POAG were performed using Bonferroni adjustments based on one-way ANOVA. [c]Comparisons were performed using independent *t*-test between early NTG and early POAG groups. [d]Comparisons were performed using independent *t*-test between moderate NTG and moderate POAG groups.

The differences of the 6 sectoral GCIPL thickness parameters and the average GCIPL thickness were calculated and compared between NTG and POAG groups, whose result as well as the proportions of the average, minimum, and 6 sectoral GCIPL thickness of NTG group and POAG group to normal group were showed in Table 3.

Table 3 Patterns of ganglion cell-inner plexiform layer loss in NTG and POAG mean±SD

Parameters	Differences between each sectoral GCIPL thickness and the average GCIPL thickness			Thickness percentage (glaucomatous/normal eyes)	
	NTG (μm)	POAG (μm)	*P* values	NTG (%)	POAG (%)
Average	-	-	-	83.10	83.88
Minimum	-	-	-	71.95	75.19
Superotemporal	0.71±6.67	-0.31±6.02	0.420	85.36	84.91
Superior	2.41±6.50	2.23±6.16	0.892	85.13	85.70
Superonasal	6.10±6.03	5.78±7.00	0.809	87.89	88.28
Inferonasal	1.27±6.46	-0.08±4.74	0.237	84.70	83.88
Inferior	-5.12±6.33	-4.10±6.37	0.422	78.59	80.64
Inferotemporal	-5.41±9.27	-4.10±6.54	0.418	76.92	79.27

NTG: Normal tension glaucoma; POAG: Primary open angle glaucoma.

Table 4 showed the AUROC curves with 95% confidence interval (CI) of the OCT parameters and MD values of visual field testing. In discriminating NTG from normal eyes, the minimum GCIPL thickness and the inferior RNFL thickness were the parameters with the best diagnostic capability in all GCIPL and RNFL parameters, respectively. There was no significant difference of AUROC curve between the minimum GCIPL thickness and the inferior RNFL thickness (Z=-1.776, P=0.076). For diagnosing eyes with POAG from normal eyes, the best parameters were the minimum GCIPL thickness and the average RNFL thickness, respectively. Also, no significant difference in AUROC curve was found between these two parameters (Z=0.109, P=0.913). In each OCTparameter as well as the MD value, there was no statistically significant difference in AUROC curve between NTG and POAG.

Table 4 Diagnostic capabilities of OCT Parameters and visual field mean deviation for discriminating NTG from normal subjects and for discriminating POAG from normal subjects

Parameters	NTG		POAG		*P* value
	AUROC	95%CI	AUROC	95%CI	
GCIPL thickness					
Average	0.917	0.857-0.977	0.933	0.879-0.988	0.697
Minimum	0.950	0.908-0.993	0.960	0.924-0.997	0.731
Superotemporal	0.874	0.797-0.950	0.866	0.788-0.943	0.886
Superior	0.856	0.774-0.938	0.856	0.776-0.936	1.000
Superonasal	0.838	0.747-0.929	0.847	0.759-0.936	0.889
Inferonasal	0.835	0.747-0.923	0.905	0.838-0.973	0.220
Inferior	0.916	0.853-0.979	0.939	0.883-0.996	0.594
Inferotemporal	0.924	0.866-0.981	0.918	0.856-0.980	0.890
RNFL thickness					
Average	0.982	0.961-1.000	0.957	0.917-0.996	0.273
Superior	0.867	0.789-0.945	0.886	0.816-0.956	0.724
Temporal	0.731	0.617-0.844	0.828	0.738-0.917	0.191
Inferior	0.991	0.978-1.000	0.948	0.902-0.994	0.086
Nasal	0.626	0.500-0.751	0.728	0.617-0.838	0.230
Mean deviation	0.944	0.891-0.998	0.925	0.864-0.987	0.644

NTG: Normal tension glaucoma; POAG: Primary open angle glaucoma; GCIPL: Ganglion cell-inner plexiform layer; RNFL: Retinal nerve fiber layer; AUROC: Area under the receiver operating characteristic; CI: Confidence interval.

DISCUSSION

In this study, the GCIPL and RNFL thickness parameters between age-, refraction-, and severity-matched NTG and POAG were evaluated. No significant difference was found in all OCT parameters but the temporal RNFL thickness. The diagnostic performance of the GCIPL and RNFL thickness parameters in discriminating eyes with NTG or POAG from normal eyes were also investigated and compared. In discriminating NTG and POAG from normal eyes, the minimum GCIPL thickness and the average RNFL thickness were the best parameters among all GCIPL and RNFL parameters, respectively, and they also demonstrated comparable diagnostic performance in discriminating NTG and POAG.

It is widely accepted that NTG is a subtype of the spectrum of POAG and it accounts for a significant percentage of open-angle glaucoma[20-21]. NTG was defined as progressive optic neuropathy and glaucomatous visual field defects, with an untreated maximum IOP of 21 mm Hg or less. With the prevalence of POAG rising continuously, the impacts of NTG from individual patient management to public healthcare policies need to be properly estimated. There was a racial variation in the proportion of NTG in POAG. In white European populations, it was from 30% (Italy)[22] to 38.9% (Netherland)[23], compared to 57.1% in South Africa black population[24]. In American white and black population, it was 31.7% (the Beaver Dam Eye Study)[25], and 30% (Barbados Eye Study)[26], respectively. In the population-based Baltimore Eye Survey involved white and black Americans, the proportion of NTG among all POAG was 24%[27]. The proportion of NTG among POAG is much higher according to multiple Asian population-based studies, with the highest percentage reported in Japan (92%)[28] and Singapore (84.6%)[29], followed by South Korea (77%)[30] and India (52.3%-67.2%)[31-32]. In a systematic review and Meta-analysis of estimated NTG prevalence in Chinese population, the overall pooled proportion of NTG among POAG was 70.0%[33]. However, the percentage of NTG among patients with POAG in glaucoma clinics is estimated to be <30% worldwide, which is much lower than the results of population-based studies, suggesting that the underdiagnosis of NTG is a global healthcare problem. Given the high prevalence and high underdiagnosis rate, it is crucial to study the variation patterns of quantitative parameters which are potentially beneficial for earlier diagnosis of NTG and identify the useful diagnostic tools, including the GCIPL thickness measured by OCT.

While the IOP-independent causative factors are commonly associated with the development of NTG, the risk factors are not yet completed verified. Older age, being females, thinner central corneal thickness, myopia, genetic background, and systemic vascular diseases including migraine, low blood pressure, low diastolic ocular perfusion pressure, Alzheimer disease, primary vascular dysregulation, Flammer syndrome, metabolic syndrome, obstructive sleep apnea syndrome and others are known risk factors of NTG[33-35]. Previously published literatures suggested that eyes with NTG tend to have greater RNFL thinning inferiorly and inferotemporally than superiorly and more preserved temporal RNFL quadrant[36]. Some studies showed RNFL thinning was more localized in NTG patients compared to POAG patients[36-37]. Kim *et al*[38] also found that ganglion cell complex (GCC, which is the sum of macular RNFL, GCL, and IPL thickness) loss was more localized in NTG group and more diffuse in POAG group. However, the relationship of the risk factors and the characteristics of NTG including the susceptibility of the inferior RNFL fibers and the localized thinning pattern of RNFL and GCC remained unclear.

In our study, the minimum GCIPL thickness was thinner in NTG group than in POAG group, although not necessarily be statistically significant, which indicated an obvious localized thinning of GCIPL in eyes with NTG. It could be the inferior and/or inferotemporal sectoral GCIPL that account for the major localized thinning effect among all sectoral GCIPL locations, which was consistent to the previous findings showing the more localized inferior or inferotemporal peripapillary RNFL defects in NTG than in POAG[38]. The more obvious localized thinning of GCIPL in NTG may indicate more diffuse thinning of GCIPL in POAG group, especially in the superior hemisphere. In NTG group and POAG group with similar visual field mean deviation, Kim *et al*[38] and Jung *et al*[39] found that GCC or GCIPL in the superior hemisphere was significantly thinner in POAG group, serving as a compensation of the thinning in the inferior hemisphere in NTG group. Some other studies found no significant thinning in certain locations between NTG and POAG groups[40-41]. Although our study did not show significant sectoral GCIPL thinning, the discretization in each sectoral GCIPL parameters, however, were greater than that of POAG, supporting the facts of localized thinning that other observations have showed.

The introduction of “minimum” GCIPL thickness (any one of the 360 degrees) in our study may suggest that the pattern of GCIPL thinning in NTG group does not necessarily mean that the localized thinning has to occur in inferior and/or inferotemporal sector. The location where localized GCIPL thinning occurs could be highly variable between cases. Therefore, minimum GCIPL thickness may preserve more information about the localized thinning, being more sensitive than those averaged sectoral GCIPL thickness parameters (averaged thickness of 60 degrees) for eyes with NTG, which can interpret why the difference of the minimum GCIPL thickness was more significant than other sectoral GCIPL thickness between NTG and POAG group. Despite this difference, other sectoral GCIPL thickness parameters were similar between NTG and POAG, suggesting that these two subtypes of glaucoma have similar distribution pattern of ganglion cells in the macular.

Using a strict age-, refraction-, and disease severity-matching strategy, it was not surprising that the diagnostic capabilities of OCT parameters didn’t show much difference in discriminating NTG or POAG from normal

subjects in this study. Like other studies[10-14,39], our results also suggested that the minimum GCIPL thickness, the average and the inferior RNFL thickness were the parameters with the best glaucoma diagnostic capabilities. The disability of the use of IOP makes diagnosing NTG much more challenging than diagnosing high-tension glaucoma in the early stage, leading to its potentially severe underdiagnosis rate. Although there are a number of studies have investigated and compared the OCT parameters, such as RNFL thickness, macular thickness, GCC thickness between NTG and POAG, to the best of our knowledge, only one of these studies were specifically focusing on the diagnostic ability of GCIPL thickness in discriminating NTG and POAG and found that the diagnostic performance was comparable in differentiating these two subtypes of glaucoma[39]. Given the fact that we included only early and moderate stage glaucoma patients in this study, the AUROC curves of all GCIPL thickness parameters were higher than 0.80, showing that the macular GCIPL thickness could be considered as a reliable objective parameter in diagnosing NTG. Among these, the minimum, the inferotemporal, the average, and the inferior GCIPL thickness had AUROC curves higher than 0.90, which was in consistent with the findings that the average and the inferior peripapillary RNFL thickness had better ability in diagnosing glaucoma than RNFL thickness in other locations[11].

It is important to introduce a multivariable model combining valuable information for making diagnosis from all available OCT parameters, visual field parameters, as well as blood flow/retina vessel density information revealed by OCT angiography into clinical use. The application of artificial intelligence (AI) algorithms after deep learning could be ideal for glaucoma detection which demands a highly personalized data combination and analysis strategy. Future explorations including the improvement in understanding and extracting the existing knowledge and optimization of data selection for AI analysis will be one of the key steps in revolutions of glaucoma diagnosing methodology.

There were several limitations of this study. First, this was a hospital-based retrospective study. All NTG patients were treated with anti-glaucoma drugs shortly after the diagnosis was made. Longer observation was not allowed, while probably being ethically beneficial, may potentially result in selection bias because those might eventually develop to high-tension glaucoma if left untreated could be included as NTG at this point. Second, the relatively small sample size and the lack of golden standard for diagnosing extreme early stage glaucoma may miss preperimetric glaucoma, making the distribution of GCIPL thickness analysis not representative enough for the whole cohort. Investigations with a larger cohort are expected in the future. Last, the disease severity evaluation was based on the cutoff points of the mean deviation of visual field testing. Such classification criteria may be too rough to make the NTG group and the POAG group compatible in a precise severity-matched way.

In summary, localized GCIPL loss, especially in the inferior and inferotemporal sectors was more commonly seen in NTG patients than in POAG patients. While there was no significant difference in macular GCIPL thickness between the NTG group and the POAG group that were strictly matched in age, refraction, and disease severity, the minimum GCIPL thickness, the average and inferior RNFL thickness were the OCT parameters with better diagnostic capabilities. Future investigations on an integral, AI-based glaucoma diagnostic platform are needed to optimize early glaucoma detection and management.

ACKNOWLEDGEMENTS

Foundation: Supported by National Natural Science Foundation of China (No.81800879); Natural Science Foundation of Guangdong Province (No.2017A030310372); Fundamental Research Funds of the State Key Laboratory of Ophthalmology, China (No.2018KF04; No.2017QN05); Sun Yat-Sen University Clinical Research 5010 Program (No.2014016).

Conflicts of Interest: None.

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