Asymmetric Patterns of Visual Field Loss in Primary Angle Closure Glaucoma, High Tension Glaucoma, and Normal Tension Glaucoma

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Abstract

The data directly comparing the spatial pattern of VF defects between primary angle-closure glaucoma (PACG), high-tension glaucoma (HTG) and normal-tension glaucoma (NTG) is not available. We aim to compare the asymmetric patterns of VF defects in patients with PACG, NTG and HTG across different severity levels. A total of 162 eyes of 114 patients with PACG, 111 eyes of 74 patients with HTG and 148 eyes of 102 patients with NTG were included. VF examinations were performed with standard automated perimetry (HFA, SITA-standard strategy, 24-2), and defects were categorized into 3 stages (early, moderate, and advanced) and each hemifield was divided into 5 regions according to Glaucoma Hemifield Test (GHT). The mean total deviation (TD) of each GHT region was calculated. The relationship between the values of pattern standard deviation (PSD) and mean TD was assessed. In the early stage, nasal region of PACG, central region of HTG and all five regions of NTG in the superior hemifield had significantly worse mean TD than their counterparts in the inferior hemifield. In the moderate stage, three regions of NTG in the superior hemifield had significantly worse mean TD than their inferior counterparts. In the advanced stage, central region of PACG, and central and paracentral regions of HTG in the superior hemifield had significantly worse mean TD than their inferior counterparts. When participants were matched by age, sex and mean deviation, in PACG and HTG eyes, all 5 GHT regions in the superior hemifield had worse mean TD than that of their inferior-hemifield counterparts; however, the differences were not statistically significant. In NTG eyes, the paracentral, nasal, arcuate 1 and arcuate 2 regions in the superior hemifield had significantly worse mean TDs than their inferior counterparts. The superior hemifield is affected more severely than the inferior hemifield in all 3 subtypes of primary glaucoma. This asymmetric tendency was more pronounced in NTG compared to PACG and HTG.

Introduction

Glaucoma is the leading global cause of irreversible blindness, affecting 79.6 million people worldwide in 2020.¹ It is a progressive optic neuropathy with characteristic structural changes and corresponding visual field (VF) defects.² Primary glaucoma is divided into primary angle-closure glaucoma (PACG) and primary open-angle glaucoma (POAG) based on the status of the iridocorneal angle.³ And POAG is subdivided into high-tension glaucoma (HTG) and normal-tension glaucoma (NTG).

PACG, with a crowded anterior segment and narrow anterior chamber angle, is characterized by elevated IOP secondary to the mechanical obstruction of the aqueous outflow by apposition of the iris to the trabecular meshwork.⁴ Pressure-dependent damage is considered to be the major pathogenesis of glaucomatous optic neuropathy in PACG.⁴ By comparison, the mechanism of optic nerve damage in HTG is thought to be a mixture of pressure-dependent and pressure-independent causes. Besides IOP, there are other factors believed to be involved in the development and worsening of HTG, such as choroidal blood flow, vascular dysregulation, and low cerebrospinal fluid pressure.⁵⁻⁷ The pressure-independent vasogenic risk factors are considered to be more important in the development and progression of NTG as compared to HTG.^{6,8,9}

The difference between PACG, HTG and NTG also reflects genetic associations, and glaucomatous structural and functional damage. The genetic associations differ between PACG, HTG and NTG. The MYOC¹⁰ and CAV1/CAV2¹¹ loci have been found to be associated with HTG, and the OPTN gene with NTG,¹² while COL11A1, PCMTD1 and ST18¹³ are associated with PACG. The morphometric features of glaucomatous optic nerve head (ONH) damage also differ between PACG, HTG and NTG. Eyes with NTG tend to have a greater degree of rim thinning, larger cup areas and cup/disc ratios and smaller rim area than eyes with HTG^{14,15} and PACG¹⁶. Smaller optic discs with smaller cup areas and larger rim area are presented in PACG than in HTG eyes.¹⁷

The characteristics of the visual field damage in POAG have been previously reported by several studies using Goldmann perimetry: visual field defects in NTG were found to be more central,^{18,19} more localized,²⁰⁻²² steeper^{18,19,23} and more commonly in the superior hemifield than in HTG.²⁴ In comparison, published data on VF damage in PACG is relatively limited.²⁵ The differences between VF defect in PACG, NTG and HTG have been reported by several studies utilizing automated perimetry: in both PACG and HTG, the superior hemifield is more severely affected than the inferior hemifield,^{26,27} and the VF defects in HTG as compared to PACG tend to be more localized.^{26,28} However, each of these studies included only one or two types of glaucoma, only one prior small study has directly compared the interocular asymmetry of the VF defects between eyes with NTG, PACG and

HTG,²⁹ and one study has compared the VF progression rates among these 3 glaucoma subtypes.³⁰ The data directly comparing the spatial pattern of VF defects between PACG, HTG and NTG is not available. We therefore compared the asymmetric patterns of VF defects in patients with PACG, NTG and HTG across different severity levels.

Methods

Participants

In this cross-sectional study, patients diagnosed with HTG and PACG by a glaucoma specialist (Y.B.L.) were recruited from the glaucoma clinic of the Eye Hospital of Wenzhou Medical University from January 2017 to December 2019. Patients with NTG were recruited from the Wenzhou Glaucoma Progression Study (WGPS), a longitudinal community-based study providing free glaucoma screenings in the Wenzhou area.^{31,32} Written informed consent was obtained from all participants. The current study was approved by the Ethics Committee of the Eye hospital of Wenzhou Medical University, and adhered to the tenets of the Declaration of Helsinki.

All participants in the current study had PACG, NTG or HTG. PACG was defined as the presence of angle closure together with evidence of glaucomatous optic neuropathy and corresponding VF defect, while angle closure was the inability to visualize the posterior trabecular meshwork for $\geq 180^\circ$ on gonioscopy. HTG was defined as the presence of an open anterior chamber angle as assessed by gonioscopy, a single intraocular pressure (IOP) measurement > 24 mmHg, and evidence of glaucomatous optic neuropathy and a corresponding VF defect. NTG included an open anterior chamber angle as assessed by gonioscopy, the presence of glaucomatous optic neuropathy with corresponding VF defect, six median untreated IOP measurements consistently < 21 mmHg, with no single measurement > 24 mmHg and no more than one reading equal to 23 or 24 mmHg.^{8,33} Glaucomatous optic neuropathy was defined as the presence of any of the following: optic disc hemorrhage, retinal nerve fiber layer (RNFL) defect, vertical cup-to disc ratio > 0.7 and/or CDR asymmetry > 0.2 or neuroretinal rim width < 0.1 .³

Additional inclusion criteria were as follows: age ≥ 18 years, presenting visual acuity $\geq 6/18$, and spherical equivalent (SE) refractive error between -6.0 and $+3.0$ diopter (D). Patients were excluded if they had secondary glaucoma, previous laser or incisional surgery of the retina, and/or other conditions potentially affecting the visual field.

Each potential participant underwent a comprehensive ophthalmic examination by a certified ophthalmic technician, including assessment of presenting visual acuity, refraction, IOP, slit-lamp biomicroscopy, gonioscopy, fundus photography (Visucam 200; Carl Zeiss Meditec, Inc., Dublin, CA, USA), and standard automated perimetry (Humphrey Field Analyzer [HFA] II; Carl-Zeiss Meditec, Inc.). IOPs were measured between 8:00 AM and 5:00 PM on one day and the median of two readings was used.

Visual field (VF) examinations were performed with the white-on-white 24–2 Swedish Interactive Threshold Algorithm (SITA) program. VF tests with fixation loss rates $< 20\%$ or false-positive and false negative error rates $< 15\%$ were considered reliable and eligible for analysis; the first VFs test for each participant was excluded from analysis.

VF severity was categorized into 3 stages based on the mean deviation (MD): early glaucoma (≥ -6 dB), moderate glaucoma (< -6 dB and > -12 dB), advanced glaucoma (≤ -12 dB).³⁴ To evaluate the pattern of VF defects, the probability plot was divided into 5 subfield regions in each of the superior and inferior hemifields: central, paracentral, nasal, and two peripheral (arcuate 1 and arcuate 2), derived from the Glaucoma Hemifield Test (GHT).^{27,35,36} When recording pointwise data and dividing regions, VF tests of left eyes were inverted to resemble a right eye for ease of comparison. The mean total deviation (TD) values and mean pattern deviation (PD) values of the 10 visual field regions were calculated, including both superior and inferior hemifields.

Statistical Analysis

Generalized estimating equation (GEE) models were used to adjust for correlations between the two eyes of a participant and clustering within study groups in comparing demographic characteristics. For the pointwise analysis, the mean TD value of each VF test point in the superior hemifield was compared with its corresponding point in the inferior hemifield at each severity level for the three glaucoma groups using GEE model, accounting for mean TD. For the region-wise analysis, the mean TDs and mean PDs of the 5 GHT regions in the superior hemifield were compared with their counterparts in the inferior hemifield at each severity level

for the three groups using the GEE model, adjusting for mean TD/PD and sex. The relationship between TD and PSD was compared in the three groups analyzed using GEE models. Statistical significance was set at $P < 0.05$, and all analyses were performed using SPSS software version 21.0 (IBM., Chicago, IL) and “R” software (R version 4.0.2).

Results

Comparisons Between Glaucoma Sub-type

One hundred and sixty-two eyes of 114 participants with PACG, 111 eyes of 74 participants with HTG and 148 eyes of 102 participants with NTG were enrolled in this study. (Table 1) Participants with HTG were significantly younger than those with NTG and PACG (HTG vs. NTG, $P = 0.012$; HTG vs. PACG, $P < 0.001$). There were more women than men in the PACG and NTG groups, while there were more men in the HTG group. The mean SE refraction in the PACG group was significantly more hyperopic (positive) than that in the NTG and HTG groups (both $P < 0.001$). The mean IOP in the NTG group was significantly lower than that for the HTG groups ($P < 0.001$). LogMAR VA in the PACG group was significantly better than that for the NTG group ($P < 0.001$).

In the early and moderate stages, there was no significant difference in the MD and mean TD among PACG, NTG and HTG eyes. In the advanced stage, the MD and mean TD of HTG and PACG group were significantly worse than that for the NTG group (all $P < 0.05$). There were no significant differences in age and gender across early, moderate, and advanced severity levels among PACG, HTG and NTG group (Table 1). In the PACG group, VA was worst and IOP was highest in the advanced stage (all $P < 0.05$); SE was similar across the severity levels. In the HTG and NTG groups, VA, IOP and SE was similar across the severity levels.

A total of 48 triplets were eyes included in each glaucoma subtype matched based on their age, sex, MD. There was no significant difference in age, sex, MD or degree of VF loss between the PACG, HTG and NTG groups ($P = 0.154, 0.310, 0.272, 0.644$, respectively, Table 2).

Comparisons Between Hemifields

In the early stage, the mean TD of the superior nasal region in the PACG group was significantly worse than its counterpart in the inferior hemifield ($P = 0.032$, Table 3, Fig. 1-A). However, there was no significant difference between the hemifields in the remaining four regions. In the early stage of the HTG group (Fig. 1-D), the central region in the superior hemifield had significantly worse mean TD than its inferior counterpart ($P = 0.022$); the remaining four regions showed no significant difference between the hemifields. In the early stage of the NTG group, all five GHT regions in the superior hemifield had significantly worse mean TD than their inferior counterparts (Fig. 1-G). In the moderate stage, three superior hemifield regions (nasal, central, and peripheral arcuate 2) of the NTG group also had significantly worse mean TD than their corresponding regions in the inferior hemifield (all $P < 0.05$, Fig. 1-H). There was no significant difference in these mean TD of the five regions between the hemifields in both the moderate stage of the HTG and PACG groups (all $P > 0.05$, Fig. 1-B, E). In the advanced stage, the superior hemifield central region of the PACG group had significantly worse mean TD than its inferior counterpart ($P < 0.001$, Fig. 1-C); in the advanced stage of the HTG group, both central and paracentral regions in the superior hemifield had significantly worse mean TD than those in inferior hemifield ($P = 0.015$ and $P = 0.045$, respectively, Fig. 1-F). There was no significant difference in the mean TD for any of the five regions between the hemifields in the advanced stage of the NTG group (Fig. 1-I). The mean TD was significantly worse in the superior hemifield for early and moderate stages in the NTG group (all $P < 0.05$), while there was no significant difference between the hemifields across the severity levels in either the PACG or HTG groups.

In the early stage, one point of the paracentral region, one point of the peripheral (arcuate 1) region and one point of the nasal region in superior hemifield had significantly worse TD than their inferior counterparts in the PACG group. (Figure 2) In the early stage of the HTG group, one point of the nasal region, one point of the central region and a point in the region adjacent to the blind spot had significantly worse mean TD than one in the inferior hemifield. In the early stage of the NTG group, several points clustering in the nasal, paracentral, peripheral (arcuate 1) and peripheral (arcuate 2) regions had significantly worse TD than their inferior counterparts. In the moderate stage, one point in the nasal, paracentral and peripheral (arcuate 1) region, and a point in the region adjacent to the blind spot in superior hemifield had significantly worse mean TD when compared with their counterparts in the inferior hemifield in the PACG group. In the moderate stage of the NTG group, several points clustering in the

nasal, central, peripheral (arcuate 1) and peripheral (arcuate 2) regions in superior hemifield had significantly worse mean TD than their inferior counterparts. In the advanced stage, several points clustering in the central and paracentral regions in the superior hemifield had significantly worse mean TD than their inferior counterparts in the PACG group. In the advanced stage of the HTG group, several points clustering in the nasal, central, and paracentral regions had significantly worse mean TD than their inferior counterparts.

Figure 3 shows the comparisons between the superior and inferior hemifields for the matched subjects. The mean TD of the superior hemifield, as a whole, was worse than that of the inferior hemifield, and this difference was more significant in the NTG eyes ($P = 0.243, 0.250$ and 0.002 for PACG, HTG and NTG, respectively). In PACG and HTG eyes, all 5 GHT regions in the superior hemifield had worse mean TD than that of their inferior-hemifield counterparts; however, the differences were not statistically significant (all $P > 0.05$, Fig. 3-A, B). In NTG eyes, the paracentral, nasal, arcuate 1 and arcuate 2 regions in the superior hemifield had significantly worse mean TDs than their inferior counterparts ($P = 0.045, 0.003, 0.007$ and 0.001 , respectively, Fig. 3-C).

In PACG eyes, a point in the region adjacent to the blind spot had significantly worse TD than its counterpart in the inferior hemifield (TD and P-values are shown in Fig. 3-D). In HTG eyes, 1 point of the nasal region, 1 point of the arcuate 2 region and 1 point in the region adjacent to the blind spot in the superior hemifield had significantly worse TD values than their inferior counterparts (Figure 3-E). In NTG eyes, 1 point of the central region and several points clustering in the nasal, arcuate 1 and arcuate 2 regions had significantly worse TDs than their inferior-hemifield counterparts (Fig. 3-F).

When the comparisons were conducted using PD values, the superior hemifield was also affected more severely than the inferior hemifield (Figure S1 and S2).

Relationship Between PSD and mean TD

The relationship between PSD and mean TD in the three groups followed an inverted-U shape, demonstrating that PSD worsens as mean TD worsens until the damage is so extensive that the PSD begins to decline again. (Figure 4) The best-fit quadratic curves for the NTG, HTG, and PACG groups demonstrated that the NTG group had greater PSD values and the PACG group had lower PSD values for a given mean TD. After controlling for mean TD and $(\text{mean TD})^2$, the PACG group had significantly lower PSD values for a given mean TD than either the NTG or HTG group (all $P < 0.001$).

Discussion

In early stage PACG eyes in the current study, the nasal region in the superior hemifield had significantly worse VF damage than in the inferior counterpart region. These results are consistent with reports by Bonomi et al³⁷ based on 53 eyes with acute angle-closure glaucoma attacks and Lau et al³⁸ in early stage PACG eyes. On the other hand, Gazzard et al²⁷ found that the central region of advanced stage PACG eyes had significantly greater damage in the superior compared to the inferior hemifield. Atalay et al³⁵ reported that five regions in the superior hemifield had significantly worse MDs compared with their inferior counterparts in advanced PACG eyes. Yousefi et al³⁶ also observed more severe damage in the central and peripheral (arcuate 2) regions of advanced PACG eyes. These three studies are in agreement with our finding that the central region in advanced PACG eyes has significantly worse VF damage in the superior than in the inferior hemifield.

In HTG eyes in the current study, the central region in the early stage, and the central and paracentral regions in the advanced stage had significantly greater damage in the superior compared to the inferior hemifield. This is similar to the report from Gazzard and associates,²⁷ who compared the characteristics of VF defect between HTG and PACG eyes. Their early HTG eyes had significantly lower mean pattern deviation in the paracentral region of the superior hemifield than in the inferior hemifield; advanced HTG eyes had significantly lower mean pattern deviation in the superior central region. In the early and advanced HTG eyes in both Gazzard et al²⁷ and the current study, only the central and paracentral region in the superior hemifield was more damaged than the corresponding inferior region. Whereas, in a previous study conducted by Yousefi et al³⁶, almost all superior GHT regions had significantly worse VF damage than the corresponding inferior regions in Japanese POAG patients. The main reason for this disagreement in the asymmetric VF defect patterns among these studies is likely the different criteria used in defining POAG. In the Yousefi³⁶ study, POAG was defined as the presence of glaucomatous optic neuropathy with open anterior

chamber angle, while IOP was not a diagnostic criterion. The proportion of NTG among POAG cases in the Japanese population is as high as 92%,³⁹ and thus a number of NTG cases may be included in the POAG group in the Yousefi study, which may have influenced the VF defect patterns in POAG eyes.

In NTG eyes, five regions at the early stage and three regions at the moderate stage had significantly greater damage in the superior compared to the inferior hemifield. Park et al⁴⁰ evaluated the patterns of VF defects in 34 NTG eyes by dividing probability plots into 2 subfields in each of the hemifields. They found that the depth of VF defects in the superior paracentral area was greater than in the corresponding inferior area, which is consistent with our study. As described above, Yousefi et al³⁶ assessed VF damage among Japanese patients with POAG, among whom many cases were likely NTG. They observed that three GHT regions in the early stage, and five GHT regions in the moderate and advanced stages had significantly worse VF damage than the corresponding inferior regions. This is in agreement with our findings, to a certain extent. Huang et al²⁹ compared VF loss in NTG, POAG, and PACG patients, however, their comparison mainly focused on interocular asymmetry.

In the current study, PACG patients were more likely to be female than patients with HTG. This is consistent with previous studies suggesting that women are at greater risk of PACG than men.⁴¹⁻⁴³ PACG patients were significantly older than HTG patients, also consistent with previous population-based studies suggesting that older age is a strong risk factor for PACG.^{42, 44-46} Patients with NTG in this study were recruited from a community screening for subjects aged 50 years or older.³¹ This may partly explain the finding that NTG patients were significantly older than HTG patients. A more hyperopic SE refraction was observed in PACG than in NTG and HTG, which is in agreement with previous reports describing the strong association between hyperopia and PACG, whereas myopia is reported to be associated with POAG.^{36, 47, 48} Patients with NTG recruited from community screening had significantly better VF parameters, and were more likely to be in the early or moderate stages of glaucoma than patients with HTG and NTG. This finding is in accord with prior reports, including our own on this screening cohort, that glaucoma patients detected by screening had significantly milder VF damage than those diagnosed initially in clinic.^{31, 49}

The MD of regions in the superior hemifield were worse than their inferior counterpart regions in the 3 subtypes of primary glaucoma; this result is in accordance with previously studies. Caprioli et al¹⁹ evaluated the VF of patients with NTG and HTG by computerized perimetry (Octopus programs, 30-degree visual field) and found that the densest scotomas occurred more commonly in the superior hemifield in both groups. Heijl et al⁵⁰ evaluated the distribution of VF loss in HTG patients using automated perimetry and found VF loss to be more common superiorly than inferiorly. McNaught et al⁵¹ also reported similar asymmetric VF damage in patients with PACG. This tendency towards vertically asymmetric VF defects has also been demonstrated in studies using static automated perimetry.^{27, 35, 36} Retinal ganglion cells axons converge at the optic nerve head, travel through the lamina cribrosa, and enter the optic nerve.⁵² The structural changes of the optic nerve head and lamina cribrosa result in a corresponding functional loss of VF, and eyes with lamina cribrosa defects in the inferior half of the optic nerve head have worse VF loss in the superior hemifield.⁵³ Asymmetry of VF defects is likely related to the pattern of susceptibility of the optic nerve head. Previous studies have demonstrated that the inferior temporal ONH has lower collagen density compared to other regions,⁵⁴ rendering it more susceptible to damage during the onset and progression of glaucoma. Consistent with vitro studies, the infero-temporal region of the optic nerve head has greater susceptibility to glaucomatous damage than other areas: Caprioli et al¹⁵ found that patients with POAG had greater thinning of the neuroretinal rim in the inferior and inferotemporal regions. Nouri-Mahdavi et al²⁶ also reported a higher prevalence of localized rim loss in the inferotemporal sector of the optic disc in patients with POAG and PACG. Such structural differences likely underlie the greater vulnerability of the superior VF to glaucomatous damage.

The different patterns of superior-inferior asymmetry in VF defects in the 3 glaucoma subtypes may be associated with their different pathogenic mechanisms. PACG is principally an IOP-dependent glaucoma, due to elevated IOP secondary to angle closure.⁴ The mechanism of HTG is thought to be mixed, but with visual field damage most closely linked to the level of IOP.⁵⁵ IOP-independent mechanism including vasogenic risk factors are likely to play a more significant role in the pathogenesis of glaucomatous optic neuropathy in NTG, compared to HTG.^{6, 8, 9} Mechanisms of visual field damage caused by IOP-dependent factors may differ from those caused by IOP-independent factors, and this may underlie the observed differences in the patterns of VF defects between NTG, PACG or HTG patients in the current and other studies. Furthermore, studies of the

morphologic characteristics of the optic nerve head have also found difference between the 3 subtypes glaucoma: NTG eyes have a larger cup and smaller rim than those with HTG^{14, 15, 56, 57} and PACG¹⁶. These different patterns of glaucomatous optic neuropathy may be a further indication of different pathogenic mechanisms of glaucoma damage in patients with PACG, HTG and NTG.

In the current study, PACG eyes had a lower PSD than those with NTG and HTG. This finding agrees with previous studies reporting that VF loss in PACG eyes is more diffuse than in POAG eyes at the same level of overall field damage.^{26-28, 36} NTG eyes in the current study had higher PSD than those with HTG for a given mean TD, which is consistent with previous reports that POAG with lower IOP tends to have more localized field defects compared to cases with higher pressure.²⁰

Strengths of our study include the fact that it is one of the first to compare the patterns of VF defects between patients with PACG and POAG in China. Over the last two decades, data on this important topic from China are limited to only a few small studies,^{27, 29, 35} only one of which included patients with NTG, focusing only on inter-ocular asymmetry and including few patients (42 NTG, 38 POAG, and 37 CACG).²⁹ NTG patients in the current report were recruited from a longitudinal, community-based study, which may strengthen the generalizability of findings.

Limitations of this study must also be acknowledged. Firstly, the HTG and PACG patients were recruited from clinical settings, which tended to include more severely-affected patients compared to the NTG patients identified in the community. Secondly, although we excluded patients with vision impairment or blindness, prevalent cataract may still have affected the pattern of observed VF defects. Finally, the study was cross-sectional, while a longitudinal design would be needed to determine the pattern of progression in the different sub-types of primary glaucoma.

In summary, we found that the superior hemifield is affected more severely than the inferior hemifield in all three subtypes of primary glaucoma, and this tendency is more pronounced in NTG compared to PACG and HTG. Moreover, the VF damage in NTG and HTG is more localized than that in PACG.

Declarations

Acknowledgments

None.

Authors contributions

Involved in Design of study (L.Y.B, L.F, J.J.H); conduct of study (J.J.H, Y.C, Z.C, Y.W.C); data collection (W.X.Y, S.X, X.X, Z.H.T, Z.J.W); analysis and interpretation of data (Z.C, Z.S.D, Z.J.J, H.J.J); statistical expertise (J.J.H, Z.C); writing the article (J.J.H, C.N); and critical revision of the article (L.Y.B, L.F).

References

1. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. *Br. J. Ophthalmol.* **90**, 262-267 (2006).
2. Weinreb RN, Khaw PT. Primary open-angle glaucoma. *Lancet.* **363**, 1711-1720(2004).
3. Foster PJ, Buhrmann R, Quigley HA, Johnson GJ. The definition and classification of glaucoma in prevalence surveys. *Br. J. Ophthalmol.* **86**, 238-242 (2002).
4. Sun X, Dai Y, Chen Y, et al. Primary angle closure glaucoma: What we know and what we don't know. *Prog. Retin. Eye. Res.* **57**, 26-45 (2017).
5. Drance SM. Some factors in the production of low tension glaucoma. *Br. J. Ophthalmol.* **56**, 229-242 (1972).
6. Flammer J, Orgül S, Costa VP, et al. The impact of ocular blood flow in glaucoma. *Prog. Retin. Eye. Res.* **21**, 359-393 (2002).

7. Wang N, Xie X, Yang D, et al. Orbital cerebrospinal fluid space in glaucoma: the Beijing intracranial and intraocular pressure (iCOP) study. *Ophthalmology*. **119**, 2065-2073.e1 (2012).
8. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. Collaborative Normal-Tension Glaucoma Study Group. *Am. J. Ophthalmol.* **126**, 487-497 (1998).
9. Flammer J, Mozaffarieh M. What is the present pathogenetic concept of glaucomatous optic neuropathy? *Surv. Ophthalmol.* **52**, S162- S173 (2007).
10. Kwon YH, Fingert JH, Kuehn MH, Alward WL. Primary open-angle glaucoma. *N. Engl. J. Med.* **360**, 1113-1124 (2009).
11. Thorleifsson G, Walters GB, Hewitt AW, et al. Common variants near CAV1 and CAV2 are associated with primary open-angle glaucoma. *Nat. Genet.* **42**, 906-909 (2010).
12. Rezaie T, Child A, Hitchings R, et al. Adult-onset primary open-angle glaucoma caused by mutations in optineurin. *Science*. **295**, 1077-1079 (2002).
13. Vithana EN, Khor CC, Qiao C, et al. Genome-wide association analyses identify three new susceptibility loci for primary angle closure glaucoma. *Nat. Genet.* **44**, 1142-1146 (2012).
14. Eid TE, Spaeth GL, Moster MR, Augsburger JJ. Quantitative differences between the optic nerve head and peripapillary retina in low-tension and high-tension primary open-angle glaucoma. *Am. J. Ophthalmol.* **124**, 805-813 (1997).
15. Caprioli J, Spaeth GL. Comparison of the optic nerve head in high- and low-tension glaucoma. *Arch. Ophthalmol.* **103**, 1145-1149 (1985).
16. Zhao L, Wu L, Wang X. Optic nerve head morphologic characteristics in chronic angle-closure glaucoma and normal-tension glaucoma. *J. Glaucoma*. **18**, 460-463 (2009).
17. Sihota R, Sony P, Gupta V, et al. Comparing glaucomatous optic neuropathy in primary open angle and chronic primary angle closure glaucoma eyes by optical coherence tomography. *Ophthalmic. Physiol. Opt.* **25**, 408-415 (2005).
18. Hitchings RA, Anderton SA. A comparative study of visual field defects seen in patients with low-tension glaucoma and chronic simple glaucoma. *Br. J. Ophthalmol.* **67**, 818-821 (1983).
19. Caprioli J, Spaeth GL. Comparison of visual field defects in the low-tension glaucomas with those in the high-tension glaucomas. *Am. J. Ophthalmol.* **97**, 730-737 (1984).
20. Caprioli J, Sears M, Miller JM. Patterns of early visual field loss in open-angle glaucoma. *Am. J. Ophthalmol.* **103**, 512-517 (1987).
21. Chauhan BC, Drance SM, Douglas GR, Johnson CA. Visual field damage in normal-tension and high-tension glaucoma. *Am. J. Ophthalmol.* **108**, 636-642 (1989).
22. Drance SM, Douglas GR, Airaksinen PJ, et al. Diffuse visual field loss in chronic open-angle and low-tension glaucoma. *Am. J. Ophthalmol.* **104**, 577-580 (1987).
23. Levene RZ. Low tension glaucoma: a critical review and new material. *Surv. Ophthalmol.* **24**, 621-664 (1980).
24. Araie M, Yamagami J, Suzuki Y. Visual field defects in normal-tension and high-tension glaucoma. *Ophthalmology*. **100**, 1808-1814 (1993).
25. Douglas GR, Drance SM, Schulzer M. The visual field and nerve head in angle-closure glaucoma. A comparison of the effects of acute and chronic angle closure. *Arch. Ophthalmol.* **93**, 409-411 (1975).
26. Rhee K, Kim YY, Nam DH, Jung HR. Comparison of visual field defects between primary open-angle glaucoma and chronic primary angle-closure glaucoma in the early or moderate stage of the disease. *Korean. J. Ophthalmol.* **15**, 27-31 (2001).
27. Gazzard G, Foster PJ, Viswanathan AC, et al. The severity and spatial distribution of visual field defects in primary glaucoma: a comparison of primary open-angle glaucoma and primary angle-closure glaucoma. *Arch. Ophthalmol.* **120**, 1636-1643 (2002).
28. Boland MV, Zhang L, Broman AT, et al. Comparison of optic nerve head topography and visual field in eyes with open-angle and angle-closure glaucoma. *Ophthalmology*. **115**, 239-245.e2 (2008).

29. Huang P, Shi Y, Wang X, et al. Interocular asymmetry of the visual field defects in newly diagnosed normal-tension glaucoma, primary open-angle glaucoma, and chronic angle-closure glaucoma. *J. Glaucoma*. **23**, 455-460 (2014).
30. Ballae Ganeshrao S, Senthil S, Choudhari N, et al. Comparison of Visual Field Progression Rates Among the High Tension Glaucoma, Primary Angle Closure Glaucoma, and Normal Tension Glaucoma. *Invest. Ophthalmol. Vis. Sci*. **60**, 889-900 (2019).
31. Liang Y, Jiang J, Ou W, et al. Effect of community screening on the demographic makeup and clinical severity of glaucoma patients receiving care in urban China. *Am. J. Ophthalmol*. **195**, 1-7 (2018).
32. Lin S, Cheng H, Zhang S, et al. Parapapillary Choroidal Microvasculature Dropout Is Associated With the Decrease in Retinal Nerve Fiber Layer Thickness: A Prospective Study. *Invest. Ophthalmol. Vis. Sci*. **60**, 838-842 (2019).
33. Leung DY, Iliev ME, Chan P, et al. Pressure-cornea-vascular index (PCVI) for predicting disease progression in normal tension glaucoma. *Br. J. Ophthalmol*. **95**, 1106-1110 (2011).
34. Brusini P, Johnson CA. Staging functional damage in glaucoma: review of different classification methods. *Surv. Ophthalmol*. **52**, 156-179 (2007).
35. Atalay E, Nongpiur ME, Yap SC, et al. Pattern of Visual Field Loss in Primary Angle-Closure Glaucoma Across Different Severity Levels. *Ophthalmology*. **123**, 1957-1964 (2016).
36. Yousefi S, Sakai H, Murata H, et al. Asymmetric Patterns of Visual Field Defect in Primary Open-Angle and Primary Angle-Closure Glaucoma. *Invest. Ophthalmol. Vis. Sci*. **59**, 1279-1287 (2018).
37. Bonomi L, Marraffa M, Marchini G, Canali N. Perimetric defects after a single acute angle-closure glaucoma attack. *Graefes. Arch. Clin. Exp. Ophthalmol*. **237**, 908-914 (1999).
38. Lau LI, Liu CJ, Chou JC, et al. Patterns of visual field defects in chronic angle-closure glaucoma with different disease severity. *Ophthalmology*. **110**, 1890-1894 (2003).
39. Iwase A, Suzuki Y, Araie M, et al. The prevalence of primary open-angle glaucoma in Japanese: the Tajimi Study. *Ophthalmology*. **111**, 1641-1648 (2004).
40. Park JH, Yoo C, Park J, Kim YY. Visual Field Defects in Young Patients With Open-angle Glaucoma: Comparison Between High-tension and Normal-tension Glaucoma. *J. Glaucoma*. **26**, 541-547 (2017).
41. Foster PJ, Baasanhu J, Alsbirk PH, et al. Glaucoma in Mongolia. A population-based survey in Hövsgöl province, northern Mongolia. *Arch. Ophthalmol*. **114**, 1235-1241 (1996).
42. Liang Y, Friedman DS, Zhou Q, et al. Prevalence and characteristics of primary angle-closure diseases in a rural adult Chinese population: the Handan Eye Study. *Invest. Ophthalmol. Vis. Sci*. **52**, 8672-8679 (2011).
43. He M, Foster PJ, Ge J, et al. Prevalence and clinical characteristics of glaucoma in adult Chinese: a population-based study in Liwan District, Guangzhou. *Invest. Ophthalmol. Vis. Sci*. **47**, 2782-2788 (2006).
44. Liang YB, Friedman DS, Zhou Q, et al. Prevalence of primary open angle glaucoma in a rural adult Chinese population: the Handan eye study. *Invest. Ophthalmol. Vis. Sci*. **52**, 8250-8257 (2011).
45. Qu W, Li Y, Song W, et al. Prevalence and risk factors for angle-closure disease in a rural Northeast China population: a population-based survey in Bin County, Harbin. *Acta. Ophthalmol*. **89**, e515-e520 (2011).
46. Sun J, Zhou X, Kang Y, et al. Prevalence and risk factors for primary open-angle glaucoma in a rural northeast China population: a population-based survey in Bin County, Harbin. *Eye (Lond)*. **26**, 283-291 (2012).
47. Shen L, Melles RB, Metlapally R, et al. The Association of Refractive Error with Glaucoma in a Multiethnic Population. *Ophthalmology*. **123**, 92-101 (2016).
48. Gordon MO, Beiser JA, Brandt JD, et al. The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. *Arch. Ophthalmol*. **120**, 714-720; discussion 829-830 (2002).
49. Grodum K, Heijl A, Bengtsson B. A comparison of glaucoma patients identified through mass screening and in routine clinical practice. *Acta. Ophthalmol. Scand*. **80**, 627-631 (2002).
50. Heijl A, Lundqvist L. The frequency distribution of earliest glaucomatous visual field defects documented by automatic perimetry. *Acta. Ophthalmol (Copenh)*. **62**, 658-664 (1984).

51. McNaught EI, Rennie A, McClure E, Chisholm IA. Pattern of visual damage after acute angle-closure glaucoma. *Trans. Ophthalmol. Soc. U K.* **94**, 406-415 (1974).
52. Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. *Jama.* **311**, 1901-1911 (2014).
53. Kiumehr S, Park SC, Syril D, et al. In vivo evaluation of focal lamina cribrosa defects in glaucoma. *Arch. Ophthalmol.* **130**, 552-559 (2012).
54. Winkler M, Jester B, Nien-Shy C, et al. High resolution three-dimensional reconstruction of the collagenous matrix of the human optic nerve head. *Brain. Res. Bull.* **81**, 339-348 (2010).
55. Chauhan BC, Drance SM. The influence of intraocular pressure on visual field damage in patients with normal-tension and high-tension glaucoma. *Invest. Ophthalmol. Vis. Sci.* **31**, 2367-2372 (1990).
56. Yamagami J, Araie M, Shirato S. A comparative study of optic nerve head in low- and high-tension glaucomas. *Graefes. Arch. Clin. Exp. Ophthalmol.* **230**, 446-450 (1992).
57. Kiriyaama N, Ando A, Fukui C, et al. A comparison of optic disc topographic parameters in patients with primary open angle glaucoma, normal tension glaucoma, and ocular hypertension. *Graefes. Arch. Clin. Exp. Ophthalmol.* **241**, 541-545 (2003).

Tables

Table 1. Demographic Characteristics of Participants (Data represent mean +/- standard deviation (SD) except where indicated).						
Subtypes	Characteristics	Total	Early	Moderate	Advanced	P
PACG	Eyes, n	162	57	31	74	
	Age (year)	62.6±9.3	60.9±10.5	64.3±8.1	63.3±8.7	0.501
	Male Gender, n (%)	51(44.7%)	18(41.9%)	9(39.1%)	24(50.0%)	0.275
	VA (logMAR)	0.16±0.16	0.12±0.14	0.11±0.14	0.21±0.16	0.001
	SE (D)	0.16±1.49	-0.01±1.90	0.58±1.11	0.11±1.24	0.127
	IOP (mmHg)	16.63±7.90	14.68±6.31	16.37±5.52	18.25±9.43	0.039
	TD (dB)	-14.21±10.58	-3.46±1.96	-9.14±1.70	-24.61±5.65	< 0.001
	MD (dB)	-13.88±10.77	-3.10±1.81	-8.51±1.69	-24.44±6.00	< 0.001
	PSD (dB)	6.13±3.50	3.12±1.54	7.74±2.74	7.76±3.35	< 0.001
	VFI (%)	61.57±35.13	95.14±3.07	80.87±7.07	27.62±22.09	< 0.001
HTG	Eyes, n	111	24	16	71	
	Age (year)	54.7±15.6	47.6±18.0	63.2±15.1	55.4±13.4	0.002
	Male gender, n (%)	50(67.6%)	14(73.7%)	7(58.3%)	29(67.4%)	0.102
	VA (logMAR)	0.20±0.15	0.14±0.16	0.19±0.17	0.22±0.14	0.126
	SE (D)	-1.36±2.36	-1.63±2.78	-1.36±2.90	-1.27±2.10	0.840
	IOP (mmHg)	18.70±8.14	18.34±5.07	16.68±4.62	19.27±9.48	0.195
	TD (dB)	-16.72±9.93	-2.71±2.35	-9.34±2.10	-23.13±5.55	< 0.001
	MD (dB)	-16.79±10.17	-2.62±2.33	-9.12±1.93	-23.31±5.88	< 0.001
	PSD (dB)	8.01±3.99	3.94±2.51	8.93±4.47	9.18±3.38	< 0.001
	VFI (%)	50.68±32.78	94.08±5.59	77.63±9.23	29.94±20.30	< 0.001
NTG	Eyes, n	148	92	36	20	
	Age (year)	62.8±13.1	63.1±11.9	65.4±11.7	56.8±19.2	0.185
	Male gender, n (%)	49(48.0%)	34(51.5%)	8(34.8%)	7(53.9%)	0.935
	VA (logMAR)	0.20±0.15	0.19±0.14	0.19±0.16	0.25±0.15	0.255
	SE (D)	-1.36±3.00	-1.05±2.81	-1.36±3.25	-2.76±3.15	0.157
	IOP (mmHg)	14.38±3.50	14.66±3.56	14.18±3.27	13.44±3.59	0.443
	TD (dB)	-6.34±5.17	-3.24±2.04	-8.60±1.53	-16.51±4.22	< 0.001
	MD (dB)	-6.17±5.28	-3.00±1.94	-8.42±1.58	-16.72±4.21	< 0.001
	PSD (dB)	6.60±3.98	4.41±2.39	8.98±3.30	12.40±2.39	< 0.001
	VFI (%)	83.75±15.61	92.68±4.92	77.97±6.86	53.05±15.53	< 0.001
VA =visual acuity; SE = spherical equivalent; IOP = intraocular pressure; TD = total deviation; MD = mean deviation; PSD = pattern standard deviation; VFI = visual field index. Data are mean ± standard deviation unless otherwise indicated.						

Table 2. Demographic characteristics of the matched participants.				
Variable	PACG	HTG	NTG	P
Eyes, n	48	48	48	
Age (year)	61.2 (7.98)	56.1 (17.3)	58.8 (15.9)	0.154
Male Sex, n (%)	16 (38.1%)	25 (61.0%)	20 (46.5%)	0.310
MD (dB)	-7.40 (5.99)	-9.76 (8.74)	-8.04 (7.26)	0.272
VF defects severity, n (%)				0.644
Early stage	24(50.0%)	21(43.8%)	24(50.0%)	
Moderate stage	15(31.2%)	14(29.2%)	12(25.0%)	
Advanced stage	9(18.8%)	13(27.1%)	12(25.0%)	
MD = mean deviation; VF = visual field. Data are mean $\pm$ standard deviation unless otherwise indicated.				

Table 3. Glaucoma Hemifield Test Region pattern deviation for participants.								
			Early, n=57		Moderate, n=31		Advanced, n=74	
Glaucoma	Region	Subregion	Mean TD	P	Mean TD	P	Mean TD	P
PACG	Central	Superior	-2.84±3.13	0.850	-7.63±7.33	0.376	-23.28±9.45	<0.001
		Inferior	-2.92±3.77		-6.02±6.60		-19.10±9.47	
	Paracentral	Superior	-2.97±2.31	0.276	-10.44±8.39	0.145	-25.83±8.12	0.187
		Inferior	-2.63±2.16		-7.13±4.37		-24.43±8.98	
	Nasal	Superior	-4.60±4.30	0.032	-14.03±7.53	0.177	-27.12±6.11	0.579
		Inferior	-3.485±2.56		-11.04±6.82		-26.71±6.94	
	Peripheral, arcuate 1	Superior	-3.72±3.32	0.394	-10.23±5.62	0.087	-25.95±5.62	0.856
		Inferior	-3.39±2.80		-7.76±4.49		-25.79±8.00	
	Peripheral, arcuate 2	Superior	-3.65±4.15	0.339	-9.38±6.90	0.259	-24.75±6.38	0.640
		Inferior	-3.15±2.61		-7.69±5.33		-25.23±7.91	
	Hemifield	Superior	-3.65±2.72	0.305	-10.62±4.67	0.150	-25.61±6.18	0.247
		Inferior	-3.17±2.12		-8.14±3.80		-24.74±6.91	
			Early, n=24		Moderate, n=16		Advanced, n=77	
	Region	Subregion	Mean TD	P	Mean TD	P	Mean TD	P
HTG	Central	Superior	-3.51±5.83	0.022	-10.19±9.77	0.767	-23.83±8.55	0.015
		Inferior	-1.35±2.12		-8.98±9.60		-20.22±10.56	
	Paracentral	Superior	-3.21±3.99	0.394	-8.66±8.46	0.775	-27.12±7.69	0.045
		Inferior	-2.63±2.93		-9.73±8.80		-24.53±9.46	
	Nasal	Superior	-4.29±6.33	0.050	-13.56±9.16	0.664	-25.20±6.87	0.253
		Inferior	-1.88±3.13		-12.00±7.43		-23.88±8.53	
	Peripheral, arcuate 1	Superior	-2.54±3.34	0.792	-7.80±6.57	0.643	-24.12±7.98	0.647
		Inferior	-2.36±3.13		-9.19±7.41		-23.48±9.17	
	Peripheral, arcuate 2	Superior	-3.08±5.13	0.814	-6.91±7.11	0.604	-23.21±7.90	0.397
		Inferior	-2.82±3.56		-8.09±6.54		-22.00±10.23	
	Hemifield	Superior	-3.29±3.98	0.214	-9.43±6.46	0.915	-24.71±6.23	0.112
		Inferior	-2.24±2.57		-9.70±6.38		-23.05±8.33	
			Early, n=92		Moderate, n=36		Advanced, n=20	
	Region	Subregion	Mean TD	P	Mean TD	P	Mean TD	P
NTG	Central	Superior	-2.76±4.02	0.039	-10.87±9.32	0.008	-14.38±10.43	0.646
		Inferior	-1.83±2.95		-5.22±4.36		-16.03±11.56	
	Paracentral	Superior	-4.15±4.89	<0.001	-10.70±8.92	0.165	-16.80±12.55	0.666
		Inferior	-2.27±3.27		-7.34±7.55		-18.73±11.37	

Nasal	Superior	-5.32±5.46	0.045	-12.87±9.20	0.028	-20.18±10.71	0.647
	Inferior	-3.77±5.46		-7.84±7.95		-21.83±9.63	
Peripheral, arcuate 1	Superior	-4.89±4.49	<0.001	-10.07±6.54	0.077	-17.33±12.39	0.823
	Inferior	-2.12±2.57		-6.71±6.37		-18.28±9.30	
Peripheral, arcuate 2	Superior	-4.74±5.72	<0.001	-9.84±7.36	<0.001	-14.68±11.98	0.452
	Inferior	-1.13±1.99		-6.31±7.22		-13.41±10.03	
Hemifield	Superior	-4.54±3.63	<0.001	-10.89±5.85	0.028	-17.00±10.47	0.756
	Inferior	-2.30±2.60		-6.80±5.34		-17.98±7.29	

Data represent mean ± standard deviation.

Figures

Figure 1

Between-hemifield comparisons of the GHT regions across severity levels. (A-C) show the superior-inferior asymmetry of VF defects in the PACG group. (D-F) show the HTG group. (G-I) show the NTG group. (A), (D) and (G) represent early stages; (B), (E) and (H) represent moderate stages, and (C), (F) and (I) represent advanced stages, respectively. The shaded regions have significantly worse TD values than their inferior counterparts. ($P < 0.05$).

Figure 2

Between-hemifield comparisons of pointwise locations across the severity levels. (A-C) show the patterns of visual field defect of the PACG group. (D-F) show the HTG group, (G-I) show the NTG group; (A), (D) and (G) represent early stages; (B), (E) and (H) represent moderate stages, and (C), (F) and (I) represent advanced stages, respectively. Black locations have significantly worse TD values compared with their corresponding locations in the inferior hemifield ($P < 0.05$).

Figure 3

Between-hemifield comparisons of the GHT regions and pointwise locations for the matched subjects. (A–C) show the comparisons of regions. (D–F) show the comparisons of pointwise locations. (A) and (D) represent PACG; (B) and (E) represent HTG, and (C) and (F) represent NTG. The dark-shadow regions and dark-shadow points have significantly worse TD values than their inferior hemifield counterparts ($P < 0.05$).

Figure 4

Scatterplot of pattern standard deviation (PSD) versus mean total deviation (TD) for eyes with PACG, HTG, and NTG. Lines represent best-fit quadratic functions for each group. Red squares represent HTG eyes; blue circles represent NTG eyes; yellow triangles represent PACG eyes.

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