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The Relationship Between Intraocular Pressure and Rates of Central Versus Peripheral Visual Field Progression

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Abstract

Purpose—To study the effects of intraocular pressure (IOP) on rates of glaucomatous central versus peripheral visual field (VF) progression.

Methods—The African Descent and Glaucoma Evaluation Study (ADAGES) is a longitudinal prospective cohort study that recruited patients from three centers. A sample of those with established glaucoma were included in this study. Mean peripheral sensitivity (MPS) and mean central sensitivity (MCS) were defined based upon the average total deviation (TD) of the peripheral and central (10 degrees) points of the 24–2 VF, respectively. Progression was based upon central and peripheral change from linear mixed effects models. The relationships between VF progression and IOP mean, maximum, and fluctuation as continuous variables were also investigated. Main outcome measures were MPS and MCS progression rates.

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Results—452 eyes of 344 patients were studied. The mean number of VFs (standard deviation) for each eye was 13.3 (6.4) over 9.1 (3.7) years. Mean baseline MD was −5.1 (3.9) dB and mean rate of MD change was −0.26 dB/year (95% CI: −0.33 to −0.20, P<0.001). Mean rates of MPS (−0.27 dB/year, 95% CI: −0.33 to −0.22, P<0.001) and MCS change (−0.26 dB/year, 95% CI: −0.31 to −0.21, P<0.001) were similar (P=0.351). Mean, fluctuation, and maximum IOP were significantly associated with MPS and MCS (all P<0.025).

Conclusions—The effect of IOP parameters on VF progression was statistically similar between central and peripheral VF regions.

Trial Registration—clinicaltrials.gov Identifier: NCT00221923

PRECIS

In this longitudinal prospective cohort study of open angle glaucoma patients, intraocular pressure parameters (mean, fluctuation, and maximum) had a similar effect on glaucomatous progression in the central and peripheral visual field regions.

Keywords

central visual field damage; intraocular pressure; risk factors; glaucoma; progression

INTRODUCTION

Glaucoma, one of the leading causes of irreversible blindness,[1] is an acquired disease of the optic nerve characterized by the death or impairment of retinal ganglion cells. Treatment for glaucoma is centered on lowering intraocular pressure (IOP), as this is the primary proven modifiable risk factor associated with the halting of glaucoma progression.[2,3] Moreover, glaucomatous damage tends to be focal at least in the earlier stages, often affecting the central field.[4,5]

Our group has previously reported that baseline damage to the 12 central-most points of the 24–2 visual field (VF) is associated with future faster rates of global field progression.[6] Moreover, central damage as measured with standard automated perimetry [7] and optical coherence tomography[8] has been linked to worse vision-related quality of life as measured by the National Eye Institute Visual Function Questionnaire. Therefore, it is important to study not only the predictive value of central field damage on future progression, but also better understand how lowering IOP may play a role in preventing future loss in this important region for daily activities.

Reduction of baseline IOP and decreased fluctuation of IOP has been associated with decreased glaucoma progression in several studies.[3,9–12] This relationship was explored in the Advanced Glaucoma Intervention Study-7 (AGIS-7),[10] which studied the relationship between consistent lowering of IOP and VF progression longitudinally. Patients who were at or below a set level of IOP at 100% of visits did not have significant overall VF progression. [10] Furthermore, IOP was found to be an important predictor of VF improvement in the Collaborative Initial Glaucoma Treatment Study. This report found that lower mean IOP,

lower minimum IOP, and lower sustained levels of IOP were associated with an improvement in VF of ≥ 3 dB.[9]

The present report aims to investigate the association between IOP and VF progression in a cohort with a wide spectrum of damage and treated with current therapeutic options. In addition, we seek to understand the relationship between IOP and the central 10 degrees of the VF. Given that the macula contains 30% of all retinal ganglion cells,[13] we hypothesized that the progression of the central VF (associated with macular function) will respond differently to higher IOP than the peripheral VF.

METHODS

The multi-site African Descent and Glaucoma Evaluation Study (ADAGES) collaboration (clinicaltrials.gov Identifier: NCT00221923) includes the Hamilton Glaucoma Center at the Department of Ophthalmology, University of California-San Diego (data coordinating center), Edward S. Harkness Eye Institute at Columbia University Medical Center, and the Department of Ophthalmology, University of Alabama-Birmingham. The institutional review boards at all sites approved the study methodology, which adheres to the tenets of the Declaration of Helsinki and to the Health Insurance Portability and Accountability Act. All participants gave written informed consent. ADAGES enrollment began in January 2003 and ended in July 2006, and follow-up continued into 2016.

ADAGES was an observational prospective cohort study.[14] Patients were recruited from three sites and the study aimed to identify factors accounting for differences in glaucoma onset and rate of progression between individuals of African descent and European descent. Patients requiring treatment were given topical therapy, oral medications, and glaucoma surgery as determined by their physician. In the present report, only individuals with established glaucoma were included.

Participants

Participants were asked to identify their race by self-report using the National Eye Institute inclusion/enrollment system describing ethnicity and race (http://orwh.od.nih.gov/pubs/outreach.pdf [pages 120–121]). Information regarding a family history of glaucoma (biological mother, father, sibling, aunt, uncle, and grandparent) was also obtained. All participants were recruited from the glaucoma clinics and ophthalmic practices at each of the three recruiting sites, by advertisement and community presentations, and by referral from other ophthalmologists and optometrists in the community.

The ocular testing performed in ADAGES has been described elsewhere.[14] In brief, participants underwent a comprehensive ophthalmic examination, including annual review of medical history, best-corrected visual acuity, slit-lamp biomicroscopy, IOP measurement, dilated funduscopic examination, pachymetry, simultaneous stereoscopic optic disc photography, and standard automated perimetry VF testing with the 24–2 Swedish interactive threshold algorithm (Carl Zeiss Meditec, Inc., Dublin, California, USA). VFs were repeated every 6 months and optic disc photographs were performed every 12 months.

Glaucomatous optic neuropathy

Glaucomatous optic neuropathy was defined as excavation, neuroretinal rim thinning or notching, localized or diffuse retinal nerve fiber layer defect, or vertical cup-disc ratio asymmetry > 0.2 between eyes (not explained by differences in disc size) based on masked grading of stereophotographs by two graders at the Imaging Data Evaluation and Analysis (IDEA) Reading Center. Only photographs of adequate quality were used for evaluation. Disagreements were resolved by consensus or adjudication by a third experienced grader.

Inclusion criteria at baseline

All participants had open angles, a best-corrected visual acuity ≥ 20/40, and a refractive error <5.0 diopters sphere and <3.0 diopters cylinder. At least one high-quality stereophotograph and two reliable (<15% false positives, <20% fixation losses, <33% false negatives) standard automated perimetry Humphrey 24–2 field test results at baseline were required. To minimize the influence of high variability and the floor effect on estimates of rates of change, only eyes with baseline MD better than −15 dB were included. Both eyes were included, except in cases where only one eye met the study criteria. Diabetic participants without evidence of retinopathy were included.

Exclusion criteria

Participants were excluded if they had a history of intraocular surgery (except for uncomplicated cataract surgery or uncomplicated glaucoma surgery), secondary causes of glaucoma (e.g., iridocyclitis, trauma), other systemic or ocular diseases known to affect the VF (e.g., pituitary lesions, demyelinating diseases, etc.), significant cognitive impairment, history of stroke, Alzheimer disease, or dementia, problems other than glaucoma affecting color vision, an inability to perform VF examinations reliably, or a life-threatening disease that precluded retention in the study.

An abnormal 24–2 VF was defined as pattern standard deviation abnormality at P<5% or Glaucoma Hemifield Test result that was “outside normal limits.” Abnormality had to be confirmed with an additional VF test.[14] Only treated subjects with glaucomatous optic neuropathy, abnormal 24–2 VFs, at least five 24–2 VFs, and a minimum of 4 years of follow-up were included in the present report.

Visual field progression

52 test locations of the 24–2 VF were analyzed, after the test points above and below the blind spot were excluded. Progression was defined with trend analysis of the age-corrected mean peripheral sensitivity (MPS), which is the average of the total deviation values of the 40 points outside the central 10 degrees (52 total points – 12 central points), and mean central sensitivity (MCS), which is the average of the total deviation values of the 12 points within the central 10 degrees. We employed linear mixed effects models to measure rates of progression.

Statistical analysis

Measures of center and dispersion are described as mean and standard deviation (SD), respectively. Categorical variables were compared using Fisher's exact-test and continuous variables were compared using one-way analysis of variance with Bonferroni correction for multiple comparisons. Linear mixed effects models were used to evaluate rates of change in MPS and MCS of the 24–2 VF over time. In linear mixed models, the average evolution of the outcome variables (peripheral and central points of the 24–2 VF) are described using a linear function of time, and random intercepts and random slopes introduce subject- and eye-specific deviations from this average evolution. Linear mixed models account for the fact that two eyes from one individual can have different rates of loss over time, while also correcting for correlations between two eyes from one individual and for correlations between measurements over time in the same eyes.

Because IOP has a significant effect on rates of VF progression,[10] we were interested in differences in IOP effects on the central 10 degrees of the 24–2 field as compared to the entire 24–2 field. The central 10 degrees were represented by the central 12 points of the 24–2 field; this model was created by Hood et al[15] and is shown in Figure 1. All analyses were adjusted for baseline sensitivity (MPS and MCS) and central corneal thickness (CCT) by including these variables and their interaction with 'Time'. The following IOP parameters (obtained with Goldmann tonometry at each visit) collected over the course of the VF sequences were tested: mean (average of all measurements), maximum (highest discrete measurement), and fluctuation (standard deviation of all measurements). The coefficient of the interaction term between these parameters and the variable 'Time' describes the effect of each mmHg increase on the rates of change (dB/year). All patient visits over the course of the follow-up period were considered in the mean, maximum, and fluctuation IOP calculations.

Statistical analyses were performed using STATA (version 14; StataCorp LP, College Station, TX). The alpha level (type I error) was set at 0.05.

RESULTS

902 eyes of 600 established glaucoma patients with repeatable VF loss were considered for inclusion. 452 eyes of 344 patients met our inclusion criteria and were studied in this analysis. Mean (SD) age and MD at baseline were 64.2 (11.7) years and −5.1 (3.9) dB, respectively. Mean number of VF tests for each eye was 13.3 (6.4) spanning 9.1 (3.7) years. Demographics are presented in Table 1.

Baseline damage in the study sample of the 12 central-most points of the pattern deviation plot with P<5% is represented in Figure 2. Mean rates of MPS (−0.27 dB/year, 95% CI: −0.33 to −0.22, P<0.001) and MCS change (−0.26 dB/year, 95% CI: −0.31 to −0.21, P<0.001) were similar (P=0.351). Of note, central points were more reproducible than peripheral points, as evidenced by smaller residual variances with MCS than MPS (2.77 [95% CI: 2.67 to 2.88] vs. 3.26 [95% CI: 3.13 to 3.39]).

Tables 2–4 show the results of the linear mixed effects models testing the relationship between IOP mean, maximum, and fluctuation and rates of change of MPS and MCS. For each mmHg higher mean IOP, MPS and MCS rates of change were −0.019 dB/year (95% CI: −0.032 to −0.010; P<0.001) and −0.021 dB/year (95% CI:−0.030 to −0.008; P=0.001) faster, respectively. Similar significant effects were also seen on relationship between fluctuation of IOP and progression (β (MPS): −0.012; 95% CI: −0.023 to −0.001; P=0.028 vs. β (MCS): −0.012; 95% CI:−0.023 to −0.001; P=0.030) and maximum IOP and progression (β (MPS): −0.010; 95% CI: −0.016 to −0.004; P=0.001 vs. β (MCS): −0.007; 95% CI:−0.013 to −0.001; P=0.023).

DISCUSSION

We refuted our initial hypothesis and found that the effect of IOP on rates of VF change is similar between central (macular) and peripheral regions of the VF. Higher mean IOP, maximum IOP, and greater fluctuations in IOP are as likely to damage the central VF as the peripheral VF. Given the known association between macular damage and decreased quality of life as well as overall field progression, our findings underscore the importance of monitoring progression not only globally, but also in the macular region.

While previous studies have demonstrated that lower IOP is important in preventing progression of glaucoma,[10, 16–18] ours is the first to specifically evaluate the association between level of IOP and central versus peripheral VF damage in a population with treated open-angle glaucoma. AGIS 7 found that eyes that maintained IOP <18 mmHg during all study visits for six years had no significant net VF deterioration.[10] In the CIGTS, in the medically-treated group maximum IOP and fluctuation of IOP were significantly associated with lower (worse) MD over a 3- to 9-year period.[9] Despite the different population investigated and distinct endpoints, our report agrees with studies suggesting that lower IOP levels (mean, maximum, and fluctuation) can slow VF progression in glaucoma.

Previous studies have investigated patterns of progression as a function of glaucoma phenotypes. Ahrlich et al showed that progression in normal-tension glaucoma tended to occur more often in the central field, as opposed to findings in high-pressure exfoliative glaucoma, even after adjusting for IOP.[16] Yousefi et al also found that central field progression as well as more asymmetric (superior vs inferior) progression was seen in primary open-angle than primary angle-closure eyes, which could at least in part be explained by differences in disease mechanism and IOP levels at presentation.[17] In a sample of primary open-angle glaucoma, normal-tension glaucoma, and chronic angle-closure glaucoma, Su et al investigated the rate of change of retinal threshold sensitivity in the ten glaucoma hemifield test (GHT) zones and found that rates in the inferior arcuate zone were not associated with IOP levels.[18]

Our findings may have implications on the design of clinical trials investigating IOP-lowering effects on VF progression. Recently, Wu et al investigated whether employing VF endpoints based upon the 24–2 MD, central 24–2 (analogous to our MCS) could improve time to detect significant progression.[19] The group found that the central 24–2 detected progression sooner than the global 24–2,[20,21] probably due to the known lower variability of

the central field. Nonetheless, when estimating treatment effects it is possible that a similar IOP change may result in different reduction in progression slopes when looking at the entire VF versus the macular region (for instance: if each mmHg reduction in IOP was less protective of progression in the macula versus the global VF, than a larger sample size would be required to study IOP effects on the macula). Our findings suggest the effects of IOP are similar on the central and peripheral VF, and it is known that the central field has greater reproducibility. Therefore, clinical trials aiming to detect VF progression due to IOP could use central VF testing (24–2 MCS or 10–2[19]) as a primary outcome measure, as lower variability of the central points will lead to similar detection of VF progression in a shorter duration.

Several theories exist regarding early central VF damage in glaucoma. Hood et al identified that the inferior macular vulnerability zone contributes the nerve fibers responsible for central vision in early glaucoma.[22] Hood et al also identified axonal crowding at the inferior pole of the nerve as a potential risk factor for early glaucomatous damage in this region.[23] The superior and inferior regions of the optic nerve head may also be affected by enlargement of the pores of the lamina cribrosa, paucity of structural support, and consequent loss of the retinal nerve fiber layer.[24]

Our study has some limitations. First, the central VF was studied only using the 24–2 strategy, which may not have adequately sampled the central points.[25,26] A long-term study using both 24–2 and 10–2 testing strategies is needed to validate our results, and may be able to detect a difference between progression in central versus peripheral points. Additionally, setting a target IOP individualized to the patient's disease has been shown to be of importance in the treatment of glaucoma patients[27]; further studies on target IOP and central versus peripheral VF progression are warranted. Furthermore, IOP measurements were based on office-hour checks, which do not capture IOP circadian rhythms and hence may have missed about 60% of the IOP peaks that occur outside this period.[28,29] Additionally, the applicability of our study to advanced glaucoma is limited. Our focus was on those with early or moderate glaucoma with central defects, and eyes with MD worse than −15 dB were excluded. The reasoning behind this exclusion was to minimize floor effect from allowing for the detection of progression. Additionally, a pointwise analysis may have been useful in further detection of damage. However, the high variability of individual points between tests may have limited our ability to draw conclusions using this type of progression analysis. Finally, ADAGES participants were selected based upon specific criteria that may not be generalizable to other populations.

Conclusion

Our findings suggest that the central ten degrees of the 24–2 VF do not have a different association with IOP than the peripheral field. Randomized clinical trials should investigate the effect of personalized target IOP values on rates of central versus peripheral VF progression.

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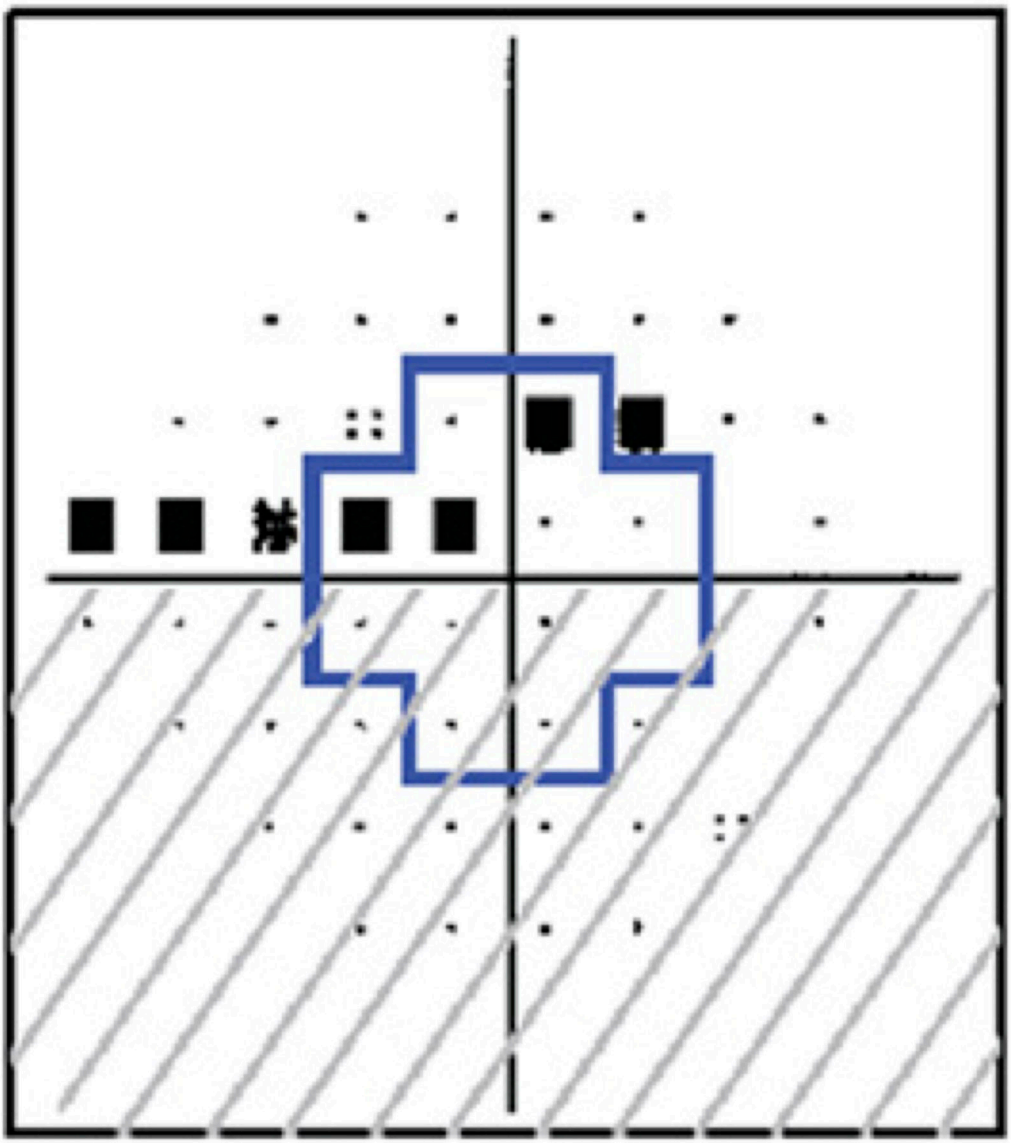

Figure 1. The central visual field within the 24–2 field.

The central 10 degrees of the visual field was defined as the 12 points enclosed by the blue box on the 24–2 field.

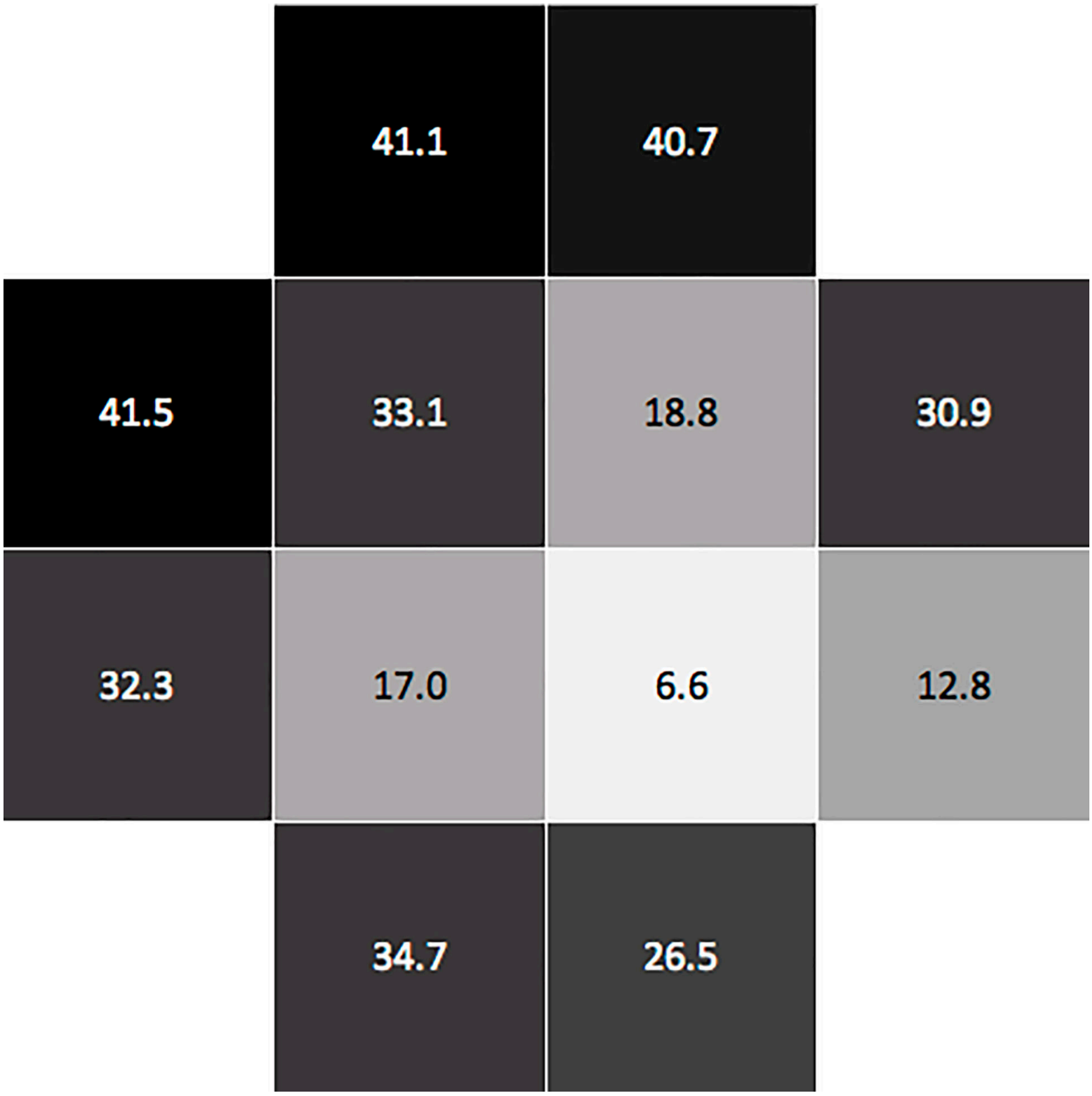

Figure 2. Central damage in the study population.

Percentage of the 12 central-most points of the pattern deviation plot with probabilities less than 5% in the study sample. The left corresponds to the nasal field and the right the temporal field. All eyes were flipped to right eyes projection for visualization.

Table 1:

Demographic and clinical characteristics.

Parameter	Mean
Age (years)	64.2 (11.7)
Baseline Mean Deviation (dB)	−5.1 (3.9)
Number of Visual Field Tests	13.3 (6.4)
Follow-up Time (years)	9.1 (3.7)
Mean IOP During Follow-up (mmHg)	15.7 (4.5)
Mean Baseline IOP (mmHg)	20.7 (8.4)
Mean Maximum IOP (mmHg)	23.9 (8.4)
Mean IOP Fluctuation (mmHg)	5.0 (4.8)
Rate of IOP Change (mmHg/year)	−0.63 (0.8)
Rate of Mean Deviation Change (dB/year)	−0.26 (0.5)
Rate of Mean Peripheral Sensitivity change (dB/year)	−0.27 (0.5)
Rate of Mean Central Sensitivity Change (dB/year)	−0.26 (0.5)

IOP = intraocular pressure.

dB = decibels.

Table 2:

Mean Intraocular Pressure and Mean Central Sensitivity and Mean Peripheral Sensitivity

	Mean Central Sensitivity Deviation				Mean Peripheral Sensitivity Deviation			
	Coef.	95% Conf.Interval		P	Coef.	95% Conf.Interval		P
Time (years)	0.343	−0.041	0.727	0.080	0.137	−0.266	0.540	0.506
Mean IOP (mmHg)	−0.027	−0.064	0.009	0.141	−0.014	−0.050	0.023	0.459
Mean IOP x Time	−0.019	−0.030	−0.008	0.001	−0.021	−0.032	−0.010	<0.001
CCT (microns)	0.001	−0.003	0.005	0.600	0.000	−0.004	0.004	0.965
CCT X Time	−0.001	−0.001	0.000	0.076	0.000	−0.001	0.000	0.475
Baseline (dB)	0.944	0.905	0.983	<0.001	0.895	0.857	0.933	<0.001
Baseline x Time	0.001	−0.011	0.012	0.910	−0.008	−0.019	0.003	0.171

IOP = intraocular pressure.

CCT = central corneal thickness.

dB = decibels.

Table 3:

Intraocular Pressure Fluctuation and Mean Central Sensitivity and Mean Peripheral Sensitivity

	Mean Central Sensitivity Deviation				Mean Peripheral Sensitivity Deviation			
	Coef.	95% Conf.	Interval	P	Coef.	95% Conf.	Interval	P
Time (years)	0.106	−0.241	0.453	0.550	−0.127	−0.497	0.242	0.499
Fluctuation IOP (mmHg)	−0.062	−0.096	−0.028	<0.001	−0.062	−0.095	−0.028	<0.001
Fluctuation IOP x Time	−0.012	−0.023	−0.001	0.030	−0.012	−0.023	−0.001	0.028
CCT (microns)	0.001	−0.002	0.005	0.455	0.000	−0.003	0.004	0.832
CCT X Time	−0.001	−0.001	0.000	0.054	0.000	−0.001	0.000	0.396
Baseline (dB)	0.932	0.894	0.970	<0.001	0.892	0.855	0.929	<0.001
Baseline x Time	0.006	−0.016	0.007	0.432	−0.012	−0.023	−0.001	0.039

IOP = intraocular pressure.

CCT = central corneal thickness.

dB = decibels.

Table 4:

Maximum Intraocular Pressure and Mean Central Sensitivity and Mean Peripheral Sensitivity

	Mean Central Sensitivity Deviation				Mean Peripheral Sensitivity Deviation			
	Coef.	95% Conf.Interval		P	Coef.	95% Conf.Interval		P
Time (years)	0.210	−0.156	0.576	0.260	0.038	−0.348	0.425	0.846
Maximum IOP (mmHg)	−0.030	−0.049	−0.011	0.002	−0.024	−0.043	−0.005	0.013
Maximum IOP x Time	−0.007	−0.013	−0.001	0.023	−0.010	−0.016	−0.004	0.001
CCT (microns)	0.001	−0.002	0.005	0.500	0.002	−0.003	0.004	0.854
CCT X Time	−0.001	−0.001	0.000	0.059	0.000	−0.001	0.000	0.446
Baseline (dB)	0.940	0.902	0.978	<0.001	0.895	0.858	0.932	<0.001
Baseline x Time	−0.003	−0.014	0.009	0.624	−0.010	−0.021	0.001	0.070

IOP = intraocular pressure.

CCT = central corneal thickness.

dB = decibels.