Patients With Normal Tension Glaucoma Have Relative Sparing of the Relative Afferent Pupillary Defect Compared to Those With Open Angle Glaucoma and Elevated Intraocular Pressure

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Purpose. We determined whether there is relative sparing of pupil function in glaucoma patients with normal pressures compared to those with high pressures.

Methods. A cross-sectional study was done of 68 patients with primary open angle glaucoma (POAG): 38 had normal IOPs on all-day phasing before treatment (never >21 mm Hg), with confirmed progression of glaucomatous optic neuropathy (NTG) and 30 had glaucomatous optic neuropathy associated with elevated intraocular pressures (>25 mm Hg; HP-POAG). The relative afferent pupillary defect (RAPD) was quantified with the RAPDx device, and mean deviation of visual field loss was obtained from reliable Humphrey visual fields. Outcomes measures evaluated were difference in slope between NTG and HP-POAG when plotting: (1) RAPD score against difference in mean deviation (MD) between eyes, and (2) RAPD score against difference in RNFL thickness between eyes.

Results. The slopes for magnitude of RAPD versus difference in MD were −0.06 (95% confidence interval [CI], −0.076, −0.044) for patients with NTG and −0.08 (95% CI, −0.109, −0.067) for those with HP-POAG. Fitting the interaction term showed a statistically significant difference between the slopes (0.023; 95% CI [0.0017, 0.0541]; *P* value = 0.037; HP-POAG reference group). Thus, for difference in MD, the slope for patients with NTG was flatter than the slope for those with HP-POAG.

Conclusions. Glaucoma patients with NTG have a lesser RAPD for a given level of intereye difference of HVF MD, compared to patients with high IOPs. This suggests that damage to intrinsically photosensitive retinal ganglion cells (ipRGCs) differs between the normal and high-pressure forms of open-angle glaucoma (OAG), and supports the theory that mitochondrial optic neuropathies may have a role in the group of diagnoses currently termed normal tension glaucoma.

Keywords: low-tension glaucoma, mitochondria, pupils

The collaborative normal tension glaucoma (NTG) study demonstrated that IOP reduction reduces progression in NTG.[1] However, speculation remains that factors other than pressure have a role in NTG pathogenesis. Evidence for this includes the relatively large prevalence difference of NTG among different genetic populations,[2] and a possible association between NTG and migraine,[3] Raynaud's phenomenon,[4] and sleep apnea.[5] It has been suggested that NTG is at least partly a mitochondrial optic neuropathy.[6–8]

Recent work has identified melanopsin containing intrinsically photosensitive retinal ganglion cells (ipRGCs) as part of the input into the afferent arm of the pupillary light reflex.[9] While ipRGCs are intrinsically photosensitive, they also are activated by stimulation of retinal rods and cones.

A number of studies have found relative preservation of ipRGCs compared to other RGCs in a range of mitochondrial optic neuropathies.[10,11] A mouse model of OPA1 found complete preservation of ipRGCs.[12] A histologic study of two human patients with Leber's hereditary optic neuropathy (LHON) and one with dominant optic atrophy found that the melanopsin-containing RGCs were relatively spared compared to pronounced loss of total RGCs.[10] Two studies have confirmed preservation of ipRGCs in LHON with pupillometry.[13,14] While these observations strongly suggest that ipRGCs resist neurodegeneration caused by mitochondrial dysfunction, the mechanism of this protection is not known.

This finding provides an explanation for the clinical observation that patients with LHON had relative preservation

of their pupil function for a given level of visual loss.[15] Similarly, if NTG were a mitochondrial optic neuropathy, the pupil response in NTG compared to high pressure primary open angle glaucoma (HP-POAG) should be relatively spared due to survival of ipRGCs in mitochondrial optic neuropathies.[10] ipRGCs have been shown to be damaged in HP-POAG.[16] Therefore, if the pathogenesis of NTG relates more strongly to mitochondrial dysfunction than in HP-POAG, patients with NTG should have relative sparing of their pupil function.

One method of assessing pupil function is to compare the pupil response between the patient's two eyes. Asymmetrical disease is reflected in asymmetrical pupil responses in the form of a relative afferent pupil defect (RAPD). The difference between eyes in white-on-white standard automated perimetry Humphrey Visual Field (HVF) mean deviation (MD) is a measure of intereye asymmetry of glaucoma damage. When the magnitude of the RAPD is plotted against intereye difference in MD, then the magnitude of the pupil defect correlates with the difference in glaucomatous visual field (VF) loss between the two eyes.[17] We investigated whether there was a significant difference in slope in patients with NTG versus those with HP-POAG for: (1) RAPD versus difference in MD between eyes and (2) RAPD versus difference in RNFL between eyes.

Method

Subjects

Two subgroups of patients were recruited: patients with NTG and those with HP-POAG. The NTG group underwent all day phasing before commencing any glaucoma treatment, and never had any IOP reading above 21 mm Hg. They also had evidence of glaucomatous VF progression as determined by Progressor software (Medisoft, Leeds, United Kingdom).

The HP-POAG group included patients with a measured IOP of at least 25 mm Hg in the eye with the worse VF defect, but no IOP reading above 40 mm Hg. They required the same disc and VF parameters as the NTG group, but without the requirement for VF progression. A pressure of at least 25 mm Hg was selected to have a clear distinction concerning IOP between the two study groups.

Patients were included only if they had a reliable HVF (false-positive [FP] <15%, false-negative [FN] <33%, fixation loss [FL] <20%), had completed at minimum of two HVFs before the field used for the study, and had a glaucomatous field defect in at least one eye that matched the site of optic disc cupping. All patients had the same lens status in each eye (either bilaterally phakic or bilaterally pseudophakic); the pupil assessment compared the left and right pupils and, therefore, having no potential confounder between the two eyes was considered important.

Exclusion criteria for both groups were any retinal or optic nerve disease other than glaucoma, or any other ocular disease likely to alter VF or pupil assessment. Individuals were excluded if they were using a topical α2 agonist or pilocarpine, both of which are known to affect pupil size. Similarly, patients using systemic medications known to alter pupil size, such as opiates, also were excluded.

For each patient, RAPD magnitude was quantified by the Konan RAPDx system (Konan Medical USA, Irvina, CA, USA). For each eye of each patient, MD was determined using a 24-2 HVF with the SITA-standard strategy. Retinal nerve fiber layer (RNFL) thickness was measured using the Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany), with the global RNFL thickness parameter used. Informed consent was obtained from all participants and the research adhered to the tenets of the Declaration of Helsinki. Ethical review and approval was obtained through the United Kingdom NHS national research ethics committee (approval number 14/EM/1011).

RAPDx Pupillometry

The commercially available RAPDx device provides automated pupillometry with output of an "RAPD score." The RAPD score has been shown to have a strong correlation with the difference in MD between each eye of glaucoma patients.[17,18] The instrument is Food and Drug Administration (FDA; Washington, DC, USA) approved.

Each subject was dark-adapted for at least 1 minute before undergoing pupillometry. The RAPDx presents visual stimuli monocularly, alternately to each eye, with the fellow eye continuing to view a nominal background and fixation target as a cyclopean scene.[17] Bright full-field white stimuli were presented for durations of 0.2 seconds alternating with 1.9 seconds of nominal background illuminance. The amplitude of change in dimensions of each pupil is calculated from baseline under nominal illumination. After one practice stimulus pair, pupil responses elicited by a series of stimulus pairs are averaged to assess the relative afferent pupillary defect value. A log magnitude comparing the difference of pupil constriction amplitudes between the two eyes was calculated automatically. This was defined as the RAPD score in this study.

There are two methods by which the ipRGCs may be stimulated by the RAPDx. The first is directly; that is, the threshold retinal irradiance for ipRGC activation has been determined as approximately 5×10^{11} photon/cm^2/s at 500 nm,[19] which is at the threshold of the luminance provided by the RAPDx. Second, ipRGCs also are stimulated by retinal rods and cones[20,21] and, therefore, loss of ipRGCs is likely to diminish the pupil response at a range of luminance levels.

Data Analysis and Statistics

Summary statistics for the outcome measures are presented as mean and standard deviation (SD) for right/left eyes separately. Differences were computed as left eye minus right eye values, as the RAPD score is positive when the right eye is worse than the left and vice versa. Plots of RAPD magnitude against difference in HVF MD between eyes and of RAPD magnitude against difference in RNFL between eyes are presented with separate fitted regression lines for the NTG and HP-POAG groups separately—R^2 values from univariable linear regression are provided as a measure of fit. Significance level was set at 5%.

To compare the slopes of RAPD magnitude between NTG and HP-POAG, two separate linear regression models, one with an interaction term between group and difference in HVF MD between eyes and other with an interaction term between group and difference in RNFL thickness between eyes, were fitted. Coefficients are presented with respective 95% confidence intervals (CIs). Sensitivity analysis, excluding observations below −1.5 and above 1.5 RAPD units, was conducted to investigate the impact of outliers on the main findings. The criteria for defining outliers was guided by Chang et al.[18] (beyond 1.5 log units RAPD, in either direction, data points diverge from the line of best fit and correlation is less tight).

Results

We recruited 68 patients with open angle glaucoma (OAG): 38 with progressive NTG and 30 with glaucomatous optic

Table 1. Summary Statistics for Outcome Measures by Patient Group

	NTG Group, $N = 38$		HP-POAG Group, $N = 30$	
	Mean	**SD**	**Mean**	**SD**
RAPD*	−0.06	0.7	−0.09	0.7
MD – Left Eye	−8	5.5	−4.7	4.1
MD – Right Eye	−7.5	7.1	−5.6	5.2
MD Difference	−0.5	8.6	0.9	6.9
RNFL – Left Eye	67.2†	15†	73.7‡	15.1‡
RNFL – Right Eye	67.2‡	16.8‡	70‡	19.6‡
RNFL Difference	−0.6†	18.5†	3.8‡	26.9‡
CCT – Left Eye	539	33	544	36
CCT – Right Eye	536	30	541	34
Max IOP before treatment – Left Eye	18	2	29	5
Max IOP before treatment – Right Eye	18	2	28	5

* One patient with NTG had RAPD values above 1.5 log units and two with NTG had RAPD values below −1.5 log units.
† Missing for five patients.
‡ Missing for four patients.

neuropathy associated with elevated IOPs. The mean age (SD) of participants was 66 (11) and 65 (14) years in the NTG and HP-POAG groups, respectively. Summary statistics for the outcome measures are presented in Table 1 by patient group.

In Figures 1 and 2, the individual univariable regression lines cross, suggesting that there might be a difference in the slopes between the two groups. The R^2 values indicate good fit; that is, 61% of the variation in the magnitude of RAPD can be explained by the difference in MD for the NTG group and, 74% of the variation in the magnitude of RAPD can be explained by the difference in MD for the HP-POAG group.

The slopes for magnitude of RAPD versus difference in MD were –0.06 (95% CI [– 0.076, –0.044]) for patients with NTG and –0.08 (95% CI [–0.109, –0.067]) for those with HP-POAG. Fitting the interaction term showed a statistically significant difference between the slopes (0.023; 95% CI [0.0017, 0.0541]; P value = 0.037; HP-POAG reference group). Thus, for difference in MD, the slope for patients with NTG is flatter than the slope for patients with HP-POAG. When removing outliers (i.e., observations with RAPD below −1.5 and above 1.5 log units), this result remained significant.

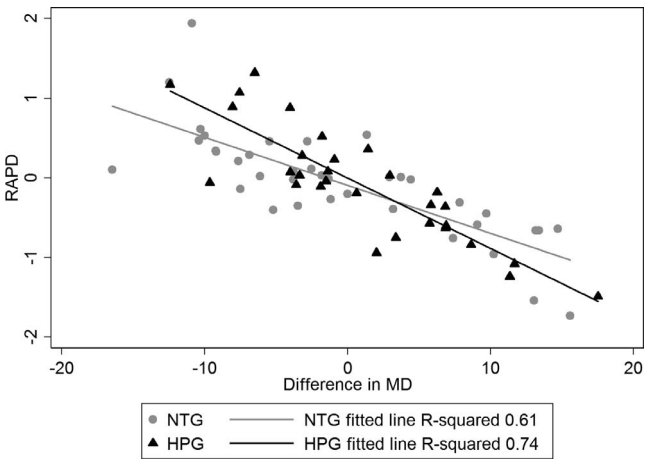

Figure 1. Univariable regression lines. Plot of RAPD magnitude against difference in HVF MD between eyes in respective individual patient groups.

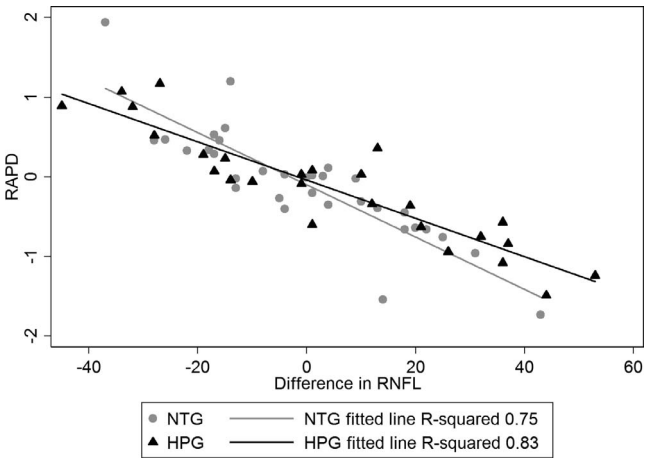

Figure 2. Univariable regression lines. Plot of RAPD magnitude against difference in RNFL thickness between eyes in respective individual patient groups.

The slopes for magnitude of RAPD versus difference in RNFL thickness were –0.03 (95% CI [–0.039, –0.025]) for patients with NTG and –0.02 (95% CI [–0.028, –0.019]) for patients with HP-POAG. Fitting the interaction term showed a statistically significant difference between the slopes (–0.009; 95% CI [–0.0167, –0.0006]; P value = 0.036; HP-POAG reference group). Thus, for difference in RNFL, the slope for patients with HP-POAG is flatter than the slope for patients with NTG. However, when removing outliers (i.e., observations with RAPD below –1.5 and above 1.5 log units) as shown in Figure 3, there was no longer evidence of a difference in slopes between NTG and RAPD (interaction term coefficient 0.001; 95% CI [–0.006, 0.009]; P value 0.73) suggesting that the detected difference might be driven by outliers.

Discussion

Our results suggested that for a given level of VF asymmetry, patients with NTG have a lesser magnitude RAPD compared to those with HP-POAG. This suggested relative sparing of pupil

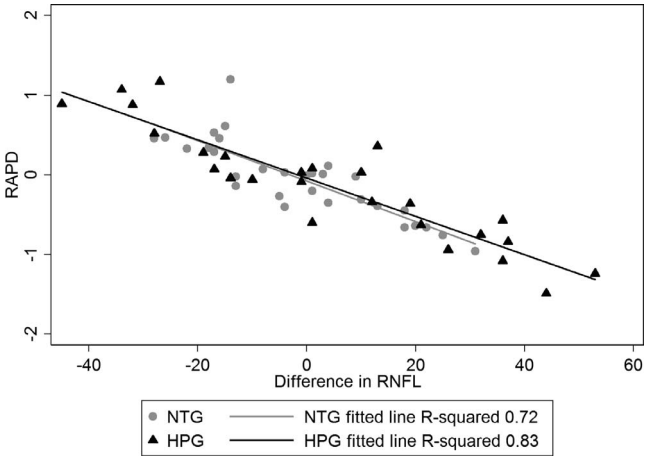

Figure 3. Plot of RAPD magnitude against difference in RNFL thickness between eyes in respective individual patient groups. Univariable regression lines removing outliers (i.e., observations with RAPD below −1.5 and above 1.5 log units).

function for a given level of field defect in patients with NTG that most likely represents relative sparing of ipRGCs in NTG.

Several investigators have demonstrated that ipRGCs are damaged in patients with POAG and elevated IOPs.[16,22,23] Our study suggested that NTG behaves differently and that damage to ipRGCs may be less for patients with NTG compared to those with elevated pressures. There is evidence that ipRGCs are spared preferentially in mitochondrial optic neuropathies. The term "NTG" may include individuals with varying susceptibility to different optic nerve stressors, and this study supports the idea that mitochondrial disorders may have a role in at least a subset of these patients.

There also is evidence that damage to ipRGCs has broader relevance to patient outcomes.[24] Glaucoma is associated with alterations of the circadian system with associated sleep disorders.[24] Light has an important role in synchronizing the circadian system, and therefore, loss of ipRGCs compromises the circadian rhythm.[24] This is the postulated mechanism of the finding of sleep disturbance in glaucoma patients. Although the findings from this study may suggest that relative sparing of ipRGCs in NTG may lead to less sleep disturbance, there also is evidence that sleep pathology may be an underreported complication of primary mitochondrial disease.[25] A number of groups are investigating sleep disturbance in glaucoma, but these results suggest that attention should be given to NTG subgroups within these studies. These findings raise the possibility that a noninvasive technique may be able to identify patients in whom mitochondrial dysfunction had a significant role. However, this clearly would need extensive further work.

At present IOP-lowering is the only proven intervention for any glaucoma, yet many patients continue to deteriorate despite medical IOP-lowering, and go on to have surgical lowering of IOP with all its attendant risks.[26] This applies equally to patients with NTG, but the lower pretreatment IOP leads to a higher risk of harm from hypotony.[27] The ability to identify patients with mitochondrial dysfunction may influence surgical decisions by reassessing whether there is a different risk–benefit profile of IOP lowering surgery in this subgroup. Further, it may be that patients with a greater influence of mitochondrial dysfunction could be targeted to better identify the most appropriate patients in whom to assess neuroprotective therapies.

Finally, this study also confirms previous findings of a tight correlation between RAPD magnitude and visual function measured with automated perimetry. Any apparent uncoupling of this tight correlation has implications for clinical practice: a disproportionately large RAPD in symmetrical glaucoma, or no RAPD in apparently asymmetrical glaucoma should prompt consideration of an alternative (or additional) diagnosis to glaucoma.

There are limitations to our study. Although our finding was positive for HVF MD versus RAPD, it was unexpected to find that there also was a significant difference in slope between groups on the structure outcome. To maximize recruitment, we included all patients irrespective of the magnitude of the RAPD. However, results of other investigators have suggested an uncoupling of the linear relationship between RAPD and intereye MD difference once the RAPD magnitude is >1.5 log units,[18] a finding in keeping with our results. This may be because of the RNFL thickness "floor." It does not fall below 30 μm even in eyes with end-stage optic neuropathies with no light perception.[28] Data points with a large difference in RNFL thickness between eyes are most likely to be affected by this floor effect: if there was no floor effect we would expect a larger RNFL difference. Once we limited the analysis to patients with RAPD magnitude <1.5 log units, the difference between the slopes for HVF versus RAPD remained significant, while for RNFL versus RAPD there was no longer evidence of a difference in slopes between groups. Finally, we required evidence of progression for patients with NTG, but not for those with high pressures. Patients with NTG likely have a higher probability of harboring an alternative or additional diagnosis to glaucoma, and we wanted to be confident of the NTG phenotyping. Although this was a difference between the groups, we believe it unlikely to have led to any significant bias.

A possible alternative hypothesis to explain our results relates to the suggestion that NTG affects the central VF more commonly than HP-POAG,[29] and that the macula appears be to affected relatively early in the glaucomatous disease process.[30] These observations raise the possibility that undetected central field defects may lead to a greater RAPD for the same level of measured MD, which potentially would lead to a flatter curve when plotting RAPD against MD, which was observed in our study. Although evidence for early macula involvement in glaucoma is relatively strong, evidence that the central field is affected more in NTG is conflicting.[29] For central field changes to explain our findings, they would need to be predominantly unilateral; however, only 8 of the 38 patients with NTG had an eye with a MD that was less than −1 dB and, therefore, most participants had bilateral glaucoma. As the study compares difference between eyes (rather than investigating absolute values), it is likely that this effect would be somewhat mitigated, should it, indeed, be present.

One strength of this study is its extremely tight phenotyping with documented normal pressures on phasing, correlated field loss, and disc damage, and confirmed VF progression in the normotensive group. This minimizes the chance that we have included subjects with nerves damaged by prior ischemic events or compressive lesions that might masquerade as NTG. That there is no significant difference in central corneal thickness between groups suggests that we have captured "true" NTG, rather than "apparent" NTG due to artificially low IOP measurements.

Different wavelengths and light intensities will lead to different ratios of stimulation of ipRGCs and photoreceptors,[31] and the relatively low luminance of the RAPDx stimulus means that it is unlikely to have activated directly the ipRGCs through melanopsin, but rather via activation of rods and cones. However, the preferential preservation of the ipRGCs nonetheless would produce the same result as we present here.

In summary, patients with HP-POAG have a greater RAPD for a given level of intereye VF asymmetry, compared to patients with normal pressure glaucoma. One interpretation of this result is that damage to ipRGCs differs between the normal and high-pressure forms of OAG, which would support the theory that mitochondrial optic neuropathies may have a role in the group of diagnoses currently termed NTG.

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