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Pupillary Responses to Full-Field Chromatic Stimuli Are Reduced in Patients with Early-Stage Primary Open-Angle Glaucoma

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Purpose: To evaluate the ability of chromatic pupillometry to reveal abnormal pupillary responses to light in patients with early-stage primary open-angle glaucoma (POAG) and to test whether the degree of pupillometric impairment correlates with structural hallmarks of optic nerve damage in the disease.

Design: Cross-sectional study.

Participants: Forty-six patients with early-stage POAG (63.4±8.3 years, 63% male, 87% ethnic-Chinese) and 90 age-matched healthy controls (61.4±8.6 years, 34% male, 89% ethnic-Chinese). Patients with POAG had a visual field mean deviation (VFMD) of −6 decibels or better on automated perimetry.

Methods: Each participant underwent a monocular 2-minute exposure to blue light (462 nm) followed by another 2-minute exposure to red light (638 nm) using a modified Ganzfeld dome equipped with a light-emitting diode lighting system. The light stimuli intensity was increased logarithmically to evaluate the combined extrinsic and intrinsic response of intrinsically photosensitive retinal ganglion cells (ipRGCs). Light-induced changes in horizontal pupil diameter were assessed monocularly using infrared pupillography.

Main Outcome Measures: Baseline-adjusted, light-induced pupillary constriction amplitudes were calculated, and individual irradiance-response curves were constructed for each stimulus. Pupillary constriction amplitudes were compared between groups and across light intensities using a linear mixed model analysis. The linear relationship between pupillometric parameters and different structural and functional features of glaucoma was assessed using Pearson's correlation analysis.

Results: Light-induced pupillary constriction was reduced in patients with early-stage POAG compared with controls at moderate to high irradiances (≥11 Log photons/cm^2/s) of blue ($P = 0.003$) and red ($P < 0.001$) light. Maximal pupillary constriction amplitude was correlated with retinal nerve fiber layer thickness (RNFL) thickness (blue: $r = 0.51$, $P < 0.001$; red: $r = 0.45$, $P = 0.002$) in patients with POAG but not in controls. Conversely, pupillometric parameters were not correlated with visual field scores in patients with early-stage POAG.

Conclusions: Patients with early-stage POAG exhibit reduced pupillary responses to moderate and high irradiances of blue and red lights. This wavelength-independent functional alteration correlates with structural thinning of the RNFL and could be the consequence of dysfunction or loss of melanopsin expressing ipRGCs in the early stages of the disease. *Ophthalmology 2018;■:1−10 © 2018 by the American Academy of Ophthalmology.*

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Glaucoma is the leading cause of irreversible blindness, with a global prevalence of 3.5% and an expected increase rate of 74% between 2013 and 2040.[1] Primary open-angle glaucoma (POAG) accounts for the majority of glaucoma cases worldwide.[1] It is characterized by a progressive and painless loss of retinal ganglion cells and their axons, leading to a gradual, yet irreversible, visual field (VF) loss.[2] Early detection of POAG is critical for vision preservation and consequently reduction of health economic burden,[3,4] yet even in developed countries such as Singapore, 81.6% of patients with primary glaucoma are unaware of their condition.[4]

Although OCT is efficient in detecting early structural changes associated with the onset of POAG,[5] VF testing by standard automated perimetry (SAP) remains the sole functional and clinically adopted assessor of vision loss and progression of the disease.[6] Although SAP is essential to evaluate visual declines associated with POAG, the test remains subjective and demanding in time and effort for patients and medical personnel alike,[7] and does not always

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reflect the severity of structural decrements observed in glaucoma.[8,9]

Retinal photoreception is not exclusive to rods and cones but is also dependent on intrinsically photosensitive retinal ganglion cells (ipRGCs) expressing the blue-sensitive photopigment melanopsin.[10] The ipRGCs integrate inputs from rods and cones,[11] along with their sluggish intrinsic photo-responses to moderate and high intensities of light (above 11 Log photons),[12] and convey the nervous signal to brain regions such as the suprachiasmatic nucleus for circadian photo-entrainment,[13] the olivary pretectal nuclei controlling the pupillary light response (PLR),[11] and other image-forming and nonimage-forming structures.[14] The discovery of these inner retina photoreceptors offers a potential way for glaucoma screening with animal and human histological and electrophysiological studies asserting a loss or disruption of ipRGCs in this disease.[15-17]

Pupillometry is a simple, noninvasive, and objective procedure that consists of measuring pupil size and reactivity. Pupillary light responses are dependent on the integrity of ipRGC projections and the interplay between the outer (red/green-shifted peak sensitivity) and inner (blue-shifted peak sensitivity) retinal photoreception.[18] Such interplay lays the foundation for the use of chromatic pupillometry as a tool to evaluate the integrity of visual functions and localize retinal dysfunctions in various ocular diseases,[19-21] including glaucoma.[22-25]

Whether using direct or consensual pupillometry,[26,27] concomitantly with full-field, regional, or multifocal chromatic illumination paradigms,[22-25,27,28] previous studies have shown that the PLR, and particularly the intrinsic melanopsin-mediated postillumination pupillary response (PIPR), is altered in moderate and advanced stages of glaucoma. These pupillometric alterations correlate with structural (e.g., cup-to-disc ratio) and functional (e.g., VF mean deviation [VFMD]) defects across disease severities.[24,26,27] Recently, Adhikari et al[25] reported a dysfunction in the PIPR subsequent to a 1-second high-intensity light pulse of blue light delivered in the superonasal quadrant field of patients with early-stage glaucoma and glaucoma suspects.

With the use of chromatic pupillometry and ramping-up lighting stimuli designed to sequentially test the functional integrity of retinal photoreceptors without isolating the melanopsin-mediated pupillary response, previous research from our group revealed a reduction in PLR to both blue and red lights in patients with moderate and severe POAG.[27] Using a similar light stimulation design, we evaluate the ability of chromatic pupillometry to reveal abnormal pupillary responses to light in patients with early-stage POAG and test whether the degree of pupillometric impairment correlates with structural and functional markers of glaucomatous optic nerve damage.

Methods

Participants

A total of 136 participants (46 patients with bilateral or unilateral early-stage POAG and 90 age-matched healthy controls) took part in this cross-sectional study. Patients with POAG were recruited from the glaucoma clinics at the Singapore National Eye Center, whereas control participants were recruited from the general population through local advertisement and word-of-mouth referrals. All participants underwent a comprehensive ophthalmological assessment that comprised slit-lamp and gonioscopic examinations, best-corrected visual acuity (BCVA) (logarithm of the minimum angle of resolution chart, Lighthouse International, New York, NY), color vision testing (Ishihara plates, Kanehara & Co, Tokyo, Japan), automated refraction (Canon RK 5 Auto Ref-Keratometer, Canon, Tochigiken, Japan), ocular biometry (IOLMaster, Carl Zeiss Meditec, Jena, Germany) to measure ocular axial length (AxL) and anterior chamber depth (ACD), intraocular pressure (IOP) measurement using Goldmann applanation tonometry, and peripapillary retinal nerve fiber layer (RNFL) thickness assessment via high-definition OCT (Cirrus version 6.0, Carl Zeiss Meditec, Dublin, CA). The OCT results were validated only if the recorded signal strength had a value of 6 or better. Participants also underwent SAP (Humphrey VF analyzer II model 750, Carl Zeiss Meditec). The Humphrey VF testing was performed with near refractive correction using the 24-2 Swedish Interactive Thresholding Algorithm (Fast) with stimulus size III. Repeat testing was performed if false-positive or false-negative responses exceeded 33% or if the fixation loss rate was greater than 20%. Subjects who could not achieve these reliability criteria were excluded. Patients were diagnosed as having POAG, in the absence of any other causes of secondary optic neuropathy, on the basis of abnormal optic disc cupping (vertical cup-to-disc ratio over 0.7 or an inter-eye asymmetry over 0.2) or neuroretinal rim notching, with thinning of the RNFL on high-definition OCT, compatible glaucomatous VF defect based on the criteria reported by Hodapp et al,[6] and open angles on gonioscopy. Patients with VFMD scores of −6 decibels or better were graded as having early-stage POAG.[6]

Patients and controls were excluded if they had any associated ophthalmic conditions such as myopia worse than −6 diopters, dense cataracts, retinopathies, other causes of optic neuropathy and ocular motor disorders, or pupillary abnormalities except for relative afferent pupillary defects. Patients with clinically diagnosed psychiatric or neurologic disorders, including cognitive impairment or dementia, were also excluded, as were patients who had previously undergone intraocular surgery or were taking psychotropics or other medications that could affect the PLR or alertness. Demographic information and medication and smoking history were collected using interviewer-administered questionnaires. The study was approved by the SingHealth Centralized Institutional Review Board, and written informed consents were obtained from all participants. Research procedures adhered to ethical principles outlined in the Declaration of Helsinki.

Chromatic Pupillometry

Subsequent to ophthalmic examinations, participants' PLRs were evaluated in a dedicated dark room at the Singapore Eye Research Institute clinics. Each subject underwent two 4-minute pupillary assessment blocks that consisted of 1 minute of darkness to measure baseline pupil size followed by 2 minutes of light exposure and another 1 minute of darkness to assess pupillary redilation to baseline (Fig 1). Participants were first exposed to a blue light stimulus (peak wavelength = 462 nm, full width at half maximum = 25.2 nm) then to a red light stimulus (peak wavelength = 638 nm, full width at half maximum = 15.5 nm). The order of light exposures was fixed because our intent was to evaluate the usefulness of our protocol as a standardized clinical screening procedure. Light was administered to the study eye, with the fellow eye covered by an eye patch, using a modified Ganzfeld dome (Labsphere, Inc, North Sutton, NH) equipped with narrow-bandwidth light-emitting