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Chromatic Multifocal Pupillometer for Objective Perimetry and Diagnosis of Patients with Retinitis Pigmentosa

Ron Chibel, MSc,[1,2] Ifat Sher, PhD,[1,2] Daniel Ben Ner, BA,[1,2] Mohamad O. Mhajna, MD,[1] Asaf Achiron, MD,[3] Soad Hajyahia, MD,[1] Alon Skaat, MD,[1,2] Yakir Berchenko, PhD,[4] Bernice Oberman, MSc,[4] Ofra Kalter-Leibovici, MD,[2,5] Laurence Freedman, PhD,[4] Ygal Rotenstreich, MD[1,2]

Purpose: To assess visual field (VF) defects and retinal function objectively in healthy participants and patients with retinitis pigmentosa (RP) using a chromatic multifocal pupillometer.

Design: Cross-sectional study.

Participants: The right eyes of 16 healthy participants and 13 RP patients.

Methods: Pupil responses to red and blue light (peak, 485 and 625 nm, respectively) presented by 76 light-emitting diodes, 1.8-mm spot size at different locations of a 16.2° VF were recorded. Subjective VFs of RP patients were determined using chromatic dark-adapted Goldmann VFs (CDA-GVFs). Six healthy participants underwent 2 pupillometer examinations to determine test–retest reliability.

Main Outcome Measures: Three parameters of pupil contraction were determined automatically: percentage of change of pupil size (PPC), maximum contraction velocity (MCV; in pixels per second), and latency of MCV (LMCV; in seconds). The fraction of functional VF was determined by CDA-GVF.

Results: In healthy participants, higher PPC and MCV were measured in response to blue compared with red light. The LMCV in response to blue light was relatively constant throughout the VF. Healthy participants demonstrated higher PPC and MCV and shorter LMCV in central compared with peripheral test points in response to red light. Test–retest correlation coefficients were 0.7 for PPC and 0.5 for MCV. In RP patients, test point in which the PPC and MCV were lower than 4 standard errors from the mean of healthy participants correlated with areas that were indicated as nonseeing by CDA-GVF. The mean absolute deviation in LMCV parameter in response to the red light between different test point was significantly higher in RP patients (range, 0.16–0.47) than in healthy participants (range, 0.02–0.16; $P < 0.0001$) and indicated its usefulness as a diagnostic tool with high sensitivity and specificity (area under the receiver operating characteristic curve (AUC), 0.97, Mann–Whitney–Wilcoxon analysis). Randomly reducing the number of test points to a total of 15 points did not significantly reduce the AUC in RP diagnosis based on this parameter.

Conclusions: This study demonstrates the feasibility of using a chromatic multifocal pupillometer for objective diagnosis of RP and assessment of VF defects. *Ophthalmology 2016;■:1–14 © 2016 by the American Academy of Ophthalmology.*

Visual field (VF) testing is part of the current clinical standard for evaluating retinal degeneration and optic nerve damage.[1,2] Dark-adapted Goldmann perimetry and automated perimetry are used most commonly for detecting and monitoring patients with retinitis pigmentosa (RP).[2,3] These methods bear significant limitations because they are subjective by nature and rely heavily on subject cooperation and attention. Hence, testing of young children, the elderly, and individuals with impaired communication skills is doomed to yield unreliable results. These tests also may be stressful for patients because they need to make conscious decisions on identification of near-threshold stimuli that appear rapidly and disappear.[4] Moreover, test results may be affected by the patient's fatigue, wakefulness, and attentiveness during the long procedure. Therefore, constant monitoring and instruction of participants by qualified personnel are needed to obtain reliable results.[4] Furthermore, test–retest variability, in particular in peripheral locations and in regions of VF deficits, makes it difficult to determine whether the VF is worsening over the course of serial examinations.[5–8] Hence, frequent examinations are needed and misdiagnosis of early stages is common.[7,9–11]

Several attempts have been made to establish objective perimetry based on pupil light response to perimetric light stimuli. Harms[12] was the first to report pupilloperimetry in 1949. More studies followed using perimetric white-light stimuli with some success. However, specificity and sensitivity were not sufficiently high to be of clinical use.[13–23] More recently, multifocal pupillographic perimetry using

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white and chromatic stimuli arranged in a dartboard pattern was developed (nuCoria Field Analyzer; nuCoria Pty. Ltd., Acton, Australia).[24–27] This method analyzes both eyes simultaneously, and although it is promising, it cannot differentiate between the rod and cone systems.

Retinitis pigmentosa encompasses a group of progressive retinal degeneration diseases that predominantly affect the rod photoreceptor system, resulting in night blindness in the early phase of the disease and loss of peripheral vision that progresses to tunnel vision. In later stages of RP, degeneration of cone photoreceptors causes progressive decline of visual acuity.[28] Disease progression is monitored by electroretinography and perimetry.[3,29,30] However, poor test–retest repeatability in patients with RP, specifically in areas with VF deficits,[5,6,30,31] limits the ability to assess disease progression and particularly to design and interpret clinical trials of potential therapeutic agents.

We recently demonstrated a proof of concept for using a chromatic multifocal pupillometer for detection of VF defects in RP patients. The pupil responses of healthy volunteers and RP patients were recorded at 13 different locations of the 30° VF in response to blue- and red-light stimuli (peak, 485 and 640 nm, respectively; light intensity, 40 cd/m^2; target size, 64 mm^2).[32] Retinitis pigmentosa patients demonstrated a significantly reduced percentage of pupil contraction (PPC) compared with healthy participants in testing conditions that emphasized rod contribution (blue light) in nearly all VF locations. By contrast, the PPC in responses to red light (which emphasizes cone contribution) was reduced significantly in RP patients compared with healthy participants, mostly in peripheral locations. In central locations, there was no significant difference between the PPC of RP patients and healthy participants in response to red light. In a second study, we demonstrated that RP patients demonstrated significantly lower PPC in response to blue light in peripheral locations of the central VF than healthy participants.[33] Furthermore, in both studies, minimal PPC was recorded in RP patients in areas that were not detected in dark-adapted chromatic Goldmann perimetry.[32,33] In these studies, we evaluated only a single parameter of the pupil response, the PPC. These studies suggested that VF defects as well as rod and cone function may be assessed in RP patients using a chromatic multifocal pupillometer.

In the current study, we examined the dynamics of the pupil response in the central VF of RP patients and healthy participants. We analyzed additional parameters of the pupil light response, the maximal contraction velocity (MCV), and the latency of MCV (LMCV) to determine the effect of retinal degeneration on these parameters. To the best of our knowledge, this is the first report of evaluation of the LMCV parameter in pupillometry studies. The central VF of RP patients was assessed using a chromatic multifocal pupillometer and was compared with the patients' chromatic dark-adapted Goldmann VF (CDA-GVF)[2] results as well as the pupillometry results of healthy participants. We report that RP patients demonstrated significantly lower PPC and MCV in areas that were reported as nonseeing by CDA-GVF and that the mean absolute deviation in the LMCV parameter between different test point locations was significantly higher in RP patients and may present a valuable parameter as a diagnostic tool for RP.

Methods

Participants

The Sheba Medical Center Institutional Review Board Ethics Committee approved this trial. The study was conducted according to the tenets of the Declaration of Helsinki and was registered at www.clinicaltrials.gov (identifier, NCT02014389). Informed written consent was obtained from all participants. Sixteen healthy volunteers, age matched with patients (see below; 6 men and 10 women; mean age ± standard deviation, 38.4±15.6 years; range, 26–77 years) were included in the study. Inclusion criteria were normal eye examination results, best-corrected visual acuity of 20/20, normal color vision, no history of or current ocular disease, no use of any topical or systemic medications that could adversely influence efferent pupil movements, and normal 24-2 Swedish interactive threshold algorithm results, developed for the Humphrey standard perimeter (Humphrey Field Analyser II, Swedish interactive threshold algorithm 24-2; Carl Zeiss Meditec, Inc., Jena, Germany).

The study patient group comprised 13 patients with RP (3 women and 10 men; mean age ± standard deviation, 36.15±14.6 years; range, 20–65 years). Inclusion criteria for RP patients were typical abnormal fundus appearance and previously recorded electroretinography results that were abnormal under scotopic or photopic conditions or both (in compliance with the protocol of the International Society for Clinical Electrophysiology of Vision)[34] and typical abnormal kinetic chromatic Goldmann test results (loss of VF that is either concentric or that began superiorly and subsequently demonstrated an arcuate scotoma that progressed either from the nasal or the temporal side; incomplete midperipheral ring scotoma that broke through into the periphery; or a residual central VF, with blue and red isopters that were either superimposed or in which the isopter in response to the red stimulus was larger than that in response to the blue stimulus[2,3]).

Exclusion criteria were a concurrent ocular disease and any other condition affecting the pupil response to light. Data recorded for all patients included gender, diagnosis, and electroretinography responses. Patients were tested for best-corrected visual acuity and for color vision by the Farnsworth D15 test. The right eyes of both healthy and RP participants were examined.

Light Stimuli

Light stimuli were presented using a Ganzfeld dome apparatus (Accutome, Inc, Malvern, PA; Fig 1) placed 330 mm from the patient's eye. All tests were performed in a dark room. The untested eye was covered. Participants were asked to fixate on a white-light fixator (0.9 cd/m^2; Fig 1B, white arrow) at the center of the dome. Stimuli were presented from 76 targets (light-emitting diodes) with diameter of 1.8 mm^2 in a VF of 16.2°. The wavelength and intensity of light stimuli selected for this study were 625±5 nm and 1000 cd/m^2 for long-wavelength stimuli (red light) and 485±5 nm and 200 cd/m^2 for short-wavelength stimuli (blue light). The light intensities were chosen after preliminary calibrations that enabled us to identify the minimal stimulus intensity that yielded a substantial pupil response in 5 healthy participants. Background luminance was 0.05 cd/m^2. Light intensities were determined by measurement with the LS-100