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Progression of Retinitis Pigmentosa as Measured on Microperimetry: The PREP-1 Study

Mustafa Iftikhar, MD,[1] *Saleema Kherani, MD,*[1] *Ramandeep Kaur,*[1] *Marili Lemus,*[1] *April Nefalar,*[1] *Bushra Usmani, MD,*[1] *Nadia Junaid, MD, MPH,*[1] *Peter A. Campochiaro, MD,*[1] *Hendrik P.N. Scholl, MD,*[1,2] *Syed M. Shah, MD*[1]

Purpose: To evaluate yearly progression of retinitis pigmentosa (RP) using microperimetry (MP) performed on Nidek MP1 (NAVIS Software v1.7; Nidek Technologies, Padova, Italy).

Design: Retrospective longitudinal study.

Participants: RP patients with consecutive MP tests (using the same test settings).

Methods: Data were collected as part of the Photoreceptor Cell Death in Retinitis Pigmentosa Retrospective (PREP-1) study. Visual acuity, fixation stability, mean sensitivity, and regional sensitivity were assessed at baseline and at yearly follow-up appointments. Regional sensitivity was calculated based on 2 methods. Method 1 involved topographical division into central macula (CM) and paracentral macula (PM). Method 2 involved functional division into the edge of scotoma (ES) and the seeing retina (SR). Linear mixed-effects models were used to assess the annual rate of change for each parameter, adjusted for disease duration.

Main Outcome Measures: Annual rate of change of visual acuity, fixation stability, and retinal sensitivities (mean sensitivity and regional sensitivities using methods 1 and 2).

Results: In total, 75 eyes of 39 patients (median age, 56 y; males, 57%) with a follow-up period ranging from 1 to 4 years were reviewed. Visual acuity at baseline was positively correlated with all retinal sensitivity parameters, most strongly with CM sensitivity ($r = 0.545$, $P < 0.001$). There was no change in visual acuity ($P = 0.075$) or fixation stability ($P = 0.371$) per year. All retinal sensitivity parameters had a significant decline per year ($P < 0.001$), with a decline of 0.4 decibel (dB) for mean sensitivity, 0.6 dB for CM, 0.3 dB for PM, 1.3 dB for ES, and 1.1 dB for SR. Method 2 identified the greatest number of cases, with a significant decline in regional sensitivity.

Conclusion: MP can detect significant changes in regional sensitivity over a 1-year period in patients with RP, even as visual acuity and fixation remain stable. An individualized approach to analyzing retinal sensitivity derived from MP may offer a useful outcome measure for future clinical trials. *Ophthalmology Retina 2017;■:1–6* © *2017 by the American Academy of Ophthalmology*

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Retinitis pigmentosa (RP) is an inherited retinal disease that causes degeneration of the rod and cone photoreceptors, leading to progressive visual impairment. The disease is characterized by nyctalopia and peripheral visual field constriction that eventually involves the macula, resulting in gradual deterioration of central visual acuity at advanced stages.[1–4] Although there are no effective interventions now, several clinical trials are underway that aim to slow down the progression of the disease.[5–7]

Traditionally, progression in RP has been evaluated using Goldmann visual fields and electroretinography.[8–12] More recently, spectral-domain OCT (SD-OCT) has also been used to evaluate progression by assessing the changes in retinal structure.[13–16]

Microperimetry (MP) is a visual field test that integrates computerized threshold perimetry with real-time fundus imaging, allowing precise localization of the functional defects.[17] MP has been proven to accurately and reliably test fixation stability and identify the extent of retinal light sensitivity losses.[18] It has also gained widespread acceptance as a tool for investigating the functional consequences of structural changes of the macula in retinal diseases,[17] which have already been established in RP.[19,20]

Not only does MP benefit from a relatively low test-retest variability as compared with conventional visual field tests such as Humphrey Field Analyzer (HFA),[21–23] it has also been demonstrated to be more sensitive in detecting a change in function in RP.[24,25] This makes it especially useful as an outcome measure in clinical trials evaluating retinal dystrophies. In slowly progressive diseases such as RP, visual acuity may not be the best outcome as it is affected late in the disease, and it is difficult to determine rate of progression over a short period of time, making clinical trials longer and expensive. Furthermore, MP results have also been shown to directly correlate with vision-related quality of life in patients with RP.[26]

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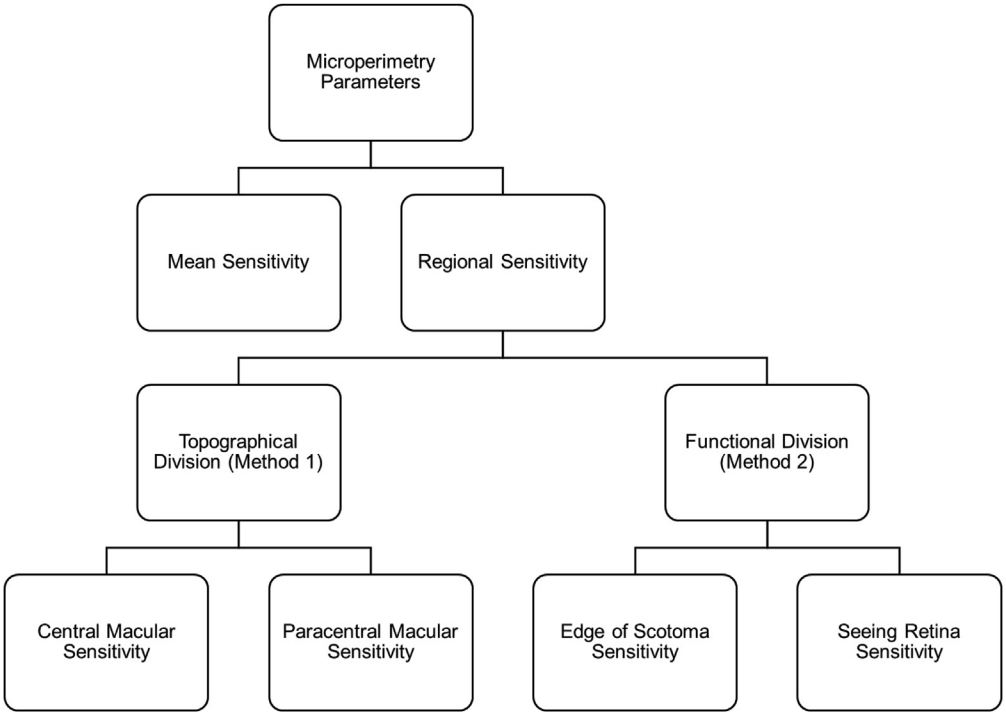

Figure 1. Microperimetry parameters measured in patients with retinitis pigmentosa.

Therefore, the purpose of this study was to investigate the use of MP as a reliable outcome measure in RP by estimating the annual rate of change in retinal sensitivity, along with visual acuity and fixation stability. In particular, we sought to investigate 2 methods of evaluating changes in regional retinal sensitivity that have been previously reported for atrophic macular disease.[27]

Methods

Data were collected as part of the Photoreceptor Cell Death in Retinitis Pigmentosa Retrospective (PREP-1) study. The study adhered to all tenets of the Declaration of Helsinki and was approved by the institutional review board of the Johns Hopkins Medical Institutions.

Patients with a diagnosis of RP (based on clinical history, funduscopic examination, visual field testing and other diagnostic modalities including, in certain cases, genetic testing) and with multiple MP tests as part of their routine clinical care were identified using the electronic health records system. Patients who had at least 2 MP tests performed 1 year apart using the same test grid and settings were included in the study.

A total of 75 eyes of 39 patients met the inclusion criteria, with follow-up periods ranging from 1 to 4 years. Patient demographics and best-corrected Snellen visual acuity at each visit were recorded, and the visual acuity measurements were converted to Early Treatment Diabetic Retinopathy Study (ETDRS) letter scores.

All MP tests had been performed using the Nidek MP1 (NAVIS software version 1.7; Nidek Technologies, Padova, Italy) with our institution's standardized acquisition protocol for RP patients, as described below. A 10-2 Humphrey test grid was used, comprising 68 test loci covering the central 20° of the fovea. The fixation target was a 2° red cross. The test stimulus was white and was set to Goldmann size III (approximately 0.4° in diameter) with a duration of 200 milliseconds. A 4-2 threshold strategy was used. Subsequent microperimetry tests were performed using the follow-up protocol that automatically aligns the infrared image from the follow-up test with that of the initial test so that the test stimuli are projected at the same retinal loci.

Each baseline MP test was graded for fixation stability and retinal sensitivity parameters that were then compared with those of the follow-up tests. Fixation stability was quantified using the bivariate contour ellipse area (BCEA) calculated by the MP1 machine, encompassing 68% of all fixation loci (representing values within 1 standard deviation of the mean). Retinal sensitivity was quantified as mean sensitivity and regional sensitivities (Fig 1). Mean sensitivity (MS) was measured as the average of retinal sensitivity values from all 68 test loci. Regional sensitivities were measured by grouping test loci using 2 methods—method 1 and method 2 (Fig 2).

Method 1 involved dividing the test loci into 2 regions based on topographical features—central macula (CM) and paracentral macula (PM). CM included test loci within a 5° radius of the fovea (central 16 loci), whereas PM included the remaining test loci located from 5° to 10° of the fovea (peripheral 52 loci).

Method 2 involved dividing the test loci into 2 regions based on functional features—edge of scotoma (ES) and seeing retina (SR). ES included test loci that were directly adjacent (horizontally or vertically) to a point of absolute scotoma (defined as a test locus where the brightest stimulus could not be seen). If the scotoma was noncontiguous, ES included all the test loci adjacent to each separate scotoma. SR included all the remaining test loci.

MP tests were graded at baseline and at each yearly follow-up visit (Fig 2). The average annual rate of change was calculated for each parameter, including visual acuity and fixation stability.

All data were analyzed using Stata, version 14.1 (Stata Corp, College Station, TX). The Shapiro-Wilk test was used to determine normality of data. Descriptive statistics were calculated for