A New Method to Monitor Visual Field Defects Caused by Photoreceptor Degeneration by Quantitative Optical Coherence Tomography

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PURPOSE. To correlate the dimension of the visual field (VF) tested by Goldman kinetic perimetry with the extent of visibility of the highly reflective layer between inner and outer segments of photoreceptors (IOS) seen in optical coherence tomography (OCT) images in patients with retinitis pigmentosa (RP).

METHODS. In a retrospectively designed cross-sectional study, 18 eyes of 18 patients with RP were examined with OCT and Goldmann perimetry using test target 14e and compared with 18 eyes of 18 control subjects. Ascans of raw scan data of Stratus OCT images (Carl Zeiss Meditec, AG, Oberkochen, Germany) were quantitatively analyzed for the presence of the signal generated by the highly reflective layer between the IOS in OCT images. Starting in the fovea, the distance to which this signal was detectable was measured. Visual fields were analyzed by measuring the distance from the center point to isopter 14e. OCT and visual field data were analyzed in a clockwise fashion every 30°, and corresponding measures were correlated.

RESULTS. In corresponding alignments, the distance from the center point to isopter 14e and the distance to which the highly reflective signal from the IOS can be detected correlate significantly (r = 0.75, P < 0.0001). The greater the distance in VF, the greater the distance measured in OCT.

CONCLUSIONS. The authors hypothesize that the retinal structure from which the highly reflective layer between the IOS emanates is of critical importance for visual and photoreceptor function. Further research is warranted to determine whether this may be useful as an objective marker of progression of retinal degeneration in patients with RP. (Invest Ophthalmol Vis Sci. 2008;49:3617–3621) DOI:10.1167/iovs.08-2003

Retinitis pigmentosa (RP) is a hereditary disease with a worldwide prevalence of approximately 1.5 million affected persons.1 Night blindness is a prominent feature in the early stages of the disease. Later, a progressive centripetal destruction of the photoreceptors leads to concentric constriction of the visual field (VF). Several electrophysiological, psychophysical, and imaging techniques, such as the full-field electroretinogram (ERG), the multifocal ERG, fine matrix mapping, microperimetry, and autofluorescence imaging have been established to document and quantify retinal changes related to photoreceptor loss in retinal degeneration.2,3 Although there are many established techniques, the evaluation of VF constriction and amplitudes in the ERG have been adopted as standards in observing and documenting progression of retinal damage in patients with RP. Once the disease has progressed to the point that no amplitudes are recordable in the ERG, the VF measurements are the best parameters left to monitor the disease.

Optical coherence tomography (OCT) is a noncontact, noninvasive imaging technology that is frequently used to diagnose and follow up various retinal diseases.4,5 OCT scans through a normal macula show clearly distinguishable reflective layers. Analyzing the reflectivity of these layers as a function of scan depth (Fig. 1) results in a curve with several peaks, from here on referred to as P1 to P6.7,8 Corresponding to retinal anatomy,9 these peaks (P1–P6) represent the retinal pigment epithelium (P1), a highly reflective layer between the inner and outer segments of photoreceptors (P2), the external limiting membrane (P3), the outer plexiform layer (P4), the inner plexiform layer (P5), and the nerve fiber layer–vitreoretinal interface (P6). The P2 signal has been suggested to arise from tightly packed mitochondria in the ellipsoid region of the photoreceptors (Fischer MD, et al., IOVS 2006;47:ARVO E-Abstract 5799). The human fovea, with its unique anatomy, lacks the outer and inner plexiform layers (i.e., P4 and P5 are not found in the fovea). A quantitative analysis (qOCT) of these light reflection profiles (LRPs) has been used to examine changes in animal models10 and in rare human retinal diseases.7,11

Histopathologic studies have reported on characteristic changes in the ultrastructure of the diseased retina in RP and have pointed to a close morphologic–functional correlation.12 Based on these observations, we tested the hypothesis that within the same orientation, the distance to which P2 can be detected in OCT images correlates with the dimension of the visual field.

MATERIAL AND METHODS

Patients

This was a prospectively designed, retrospective cross-sectional study in 18 eyes of 18 control subjects and 18 eyes of 18 patients with RP, who were referred to the University Hospital Zurich. All subjects underwent slit lamp examination, measurement of best corrected visual acuity (BCVA), and VF testing with Goldmann kinetic perimetry. Full-field ERG recordings (UTAS 3000: LKC Technologies Inc., Gaithersburg, MD) were performed according to the standard protocol of the International Society for Clinical Electrophysiology of Vision.13,14 Inclusion criteria were confirmed RP in the patients or good health in the control subjects. To exclude progression of disease as a variable in

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the correlation study, only study subjects in whom all examinations were performed on a single day were included. Exclusion criteria were the presence of any other ocular disease or any opacities of the optical media affecting OCT imaging and analysis, such as cataract or cystoid macular edema. The diagnosis of RP was established based on biomicroscopy, full-field ERG results and VF test results. The clinical appearance of RP was heterogeneous, including young patients with severe disease, older patients with mild forms, and vice versa. The study was performed in accordance with the tenets of the Declaration of Helsinki 1975 (1983 revision). Institutional review board approval was not required for this retrospective study.

Visual Fields
Goldmann perimetry (Goldmann Perimeter; Haag-Streit, Bern, Switzerland) was performed with test targets V4e, I4e, I2e, and I1e. Only test targets V4e and I4e were reliably detected by all patients with RP. Digitized Goldmann visual field charts were analyzed (Photoshop 9.02; Adobe Systems Inc., San Jose, CA). The dimension from the center point (fovea) to the radial limit of the isopter (I4e) was measured in degrees with the calibrated line tool. Measurements were taken every clock hour (12 measurements, each 30° apart) on each VF (12 readings per patient; Fig. 1).

Optical Coherence Tomography
OCT scanning was performed with Stratus OCT 3 software version 4.01 (Carl Zeiss Meditec AG, Oberkochen, Germany). The built-in macular thickness scan program, consisting of six radial line scans of 6 mm in length (Fig. 1) centered on the foveola with 512 A-scans/line scan, with each line scan consisting of 1024 pixels, was used. The area covered by this scan program corresponds to approximately 25° in the visual field.
VF. Each scan was recorded carefully and visually checked to ensure the exact intersection with the foveola. In patients with fixation problems, the scans were repeated until a correct cross-section of the foveola was obtained. Raw scan data were exported from the OCT device and opened as a 32-bit gray-scale image, resulting in grayscale values ranging from 0 to 4095. Since levels of gray were used in analyzing the amplitude of light reflection and not decibels, as provided by the Stratus OCT, arbitrary units (AU) were used instead of decibels. Light reflectivity profiles (LRPs) were calculated (IGOR 5.0ia; Wavemetrics Inc., Lake Oswego, OR). LRP amplitudes, which ranged from 0 to 4095 AU, were calculated every 43.5 µm along each line scan. Based on the results in healthy control subjects, ranges for P2 were defined as the major positive deflection of the LRPs and each of the six peaks in control subjects were highly reproducible inter- and intraindividually and showed narrow 99% confidence intervals (CIs) (Fig. 3). Analysis of LRPs of control subjects showed that P2 was clearly detectable in all A-scan profiles along the full lengths of the scans (3 mm), whereas in patients with RP the P2 signal could only be detected to a distance of 0.83 ± 0.69 mm from the foveal center (Fig. 4).

Correlation Analysis

The distance (millimeters) at which P2 was detected in the OCT images was correlated with the matching dimension of the VF in degrees (same orientation; i.e., the OCT measurement at 6 o’clock in the inferior retina correlated with the dimension of the 12 o’clock superior visual field extent). Bivariate correlation analysis and linear regression were performed (Statistica 6; StatSoft Inc., Tulsa, OK). Statistical significance was defined as $P < 0.05$.

**RESULTS**

**ERG and Clinical Data**

All patients with RP had pathologic cone- and rod-driven responses in full-field ERG recordings. Control subjects had normal cone- and rod-driven ERG responses. Age was comparable between patients with RP and control subjects. Patients with severe RP phenotypes (flat ERG, severely constricted VF) showed pronounced bone spicules and attenuated vessels, whereas patients with recordable ERG responses and less constricted visual fields showed only minor attenuation of the vessels and only discrete bone spicules. The dimension from the foveola to the detection of isopter 14e was 58.18 ± 12.4° (mean ± SD) in control subjects and 11.76 ± 6.69° in patients with RP. Clinical data are shown in Figure 2.

**OCT Analysis**

LRPs and each of the six peaks in control subjects were highly reproducible inter- and intraindividually and showed narrow 99% confidence intervals (CIs) (Fig. 3). Analysis of LRPs from control subjects showed that P2 was clearly detectable in all A-scan profiles along the full lengths of the scans (3 mm), whereas in patients with RP the P2 signal could only be detected to a distance of 0.83 ± 0.69 mm from the foveal center (Fig. 4).

**Correlation Analysis**

Correlating the distance to which P2 can be detected in all OCT scans with the respective dimension of the visual field (14e) resulted in a correlation coefficient of $r = 0.746$ at a significance level of $P < 0.0001$. A scatterplot illustrating these data is shown in Figure 4. Data from control subjects (P2 detectability versus extent of visual fields) were omitted in the correlation analysis, because in healthy control subjects, the P2 signal extends beyond the retina studied (with the exception of the optic nerve). Hence, when considering the OCT scan length (maximum, 5 mm centrifugal of the foveola), a detectable P2 of 5 mm in all control subjects correlated with a much larger VF would strongly bias the analysis due to a ceiling effect in the quantitative OCT analysis.

**DISCUSSION**

In the present study, we tested the hypothesis that the distance to which the P2 signal in OCT, emerging from the photoreceptors correlates with the dimension of the visual field constriction in patients with RP. We showed a close and highly significant correlation of these parameters. The greater the remaining visual field in patients with RP, the greater the distance to which P2 could be detected in OCT. We propose that quantitative OCT analysis (qOCT) could be used as an additional objective measure of disease progression and hence is a useful tool during clinical follow-up of patients with RP.

While ERG and OCT give objective test results, Goldmann perimetry, a psychophysical test method, is strongly dependent on observer and patient alertness and cooperation. Furthermore, the reproducibility of visual field testing in patients...
with RP is reduced significantly compared with that in healthy subjects, with intraobserver and interobserver variation of from 11% to 13% and from 10% to 16%, respectively. Even though caution was taken to calibrate the Goldmann device and correct adequately for refractive errors, additional variables such as patient–investigator alertness and response time cannot be standardized.

In addition, other factors have to be considered when correlating the OCT data with the VF data. In contrast to the usual way Goldmann kinetic perimetry is performed (i.e., moving the test target from the periphery to the center), the extent of the VF was analyzed analogous to the algorithm used to quantify the eccentricity of the P2 signal in the radial scan lines of the OCT (i.e., from the center to the periphery). Even though the algorithm can detect P2 peripheral to the first cutoff point (where P2 is no longer present), which is expected in cases with a ring scotoma, we could not find this in our measurements. Because of the technical limitations of the Stratus OCT, a reliable scan to analyze the periphery correctly (beyond the temporal vessel arcades) could not be performed. This obstacle made it impossible to include in our analysis some of the peripheral VF islands that were found in some of the patients. Still, in cases of a peripheral island in the VF, the reappearance of P2 was seen in single test scans. The obvious difference between the measured VF extension in the Goldmann recordings and the quantitative analysis of P2 detectability in OCT recordings is also evident under the assumption that 25° of VF correspond to an area of approximately 6 mm in diameter. The average eccentricity of a P2 signal of 0.83 mm would correspond to approximately 3.46°, whereas the measured average was 11.76°.

An explanation for this discrepancy could be that current OCT technology may not be sensitive enough to account for dissociation of function and morphology in the degenerative process. In RP, diffuse decay of the photoreceptors generates a gradient in photoreceptor density from the periphery to the fovea. In areas with low photoreceptor density, OCT may not show P2, but the patient could still detect the test target with the remaining photoreceptors. Newer OCT devices, such as spectral domain OCTs, with higher resolution and faster recording, giving a higher resolution image of the neuroretina, could reduce this problem and decrease the discrepancy between the OCT and VF findings by allowing much more accurate measurements. Another factor that may help to explain...
the difference is the phenomenon that patients with a small remaining VF have difficulties suppressing optokinetic reflexes and may reorient the remaining VF to the moving test target thus, artificially enhancing the VF size.

Despite these differences, the highly significant correlation is proof of a robust and functional method and indicates high reproducibility. The fact that correlation of VF extent and eccentricity of valid P2 signal follows a linear relationship gives rise to the assumption that the method of quantifying P2 eccentricity could be used as an additional tool to monitor objectively the centripetal photoreceptor decay in patients with RP. However, the method cannot replace the current standards, including VF testing and ERG recordings. Combining the information from the quantitative OCT analysis with data acquired from other modalities, such as multifocal ERG, fundus autofluorescence, or fine matrix mapping, would make it possible to establish criteria for the design of treatment trials in the future.

The successful application of quantitative analysis of OCT images indicates the potential to move from pure, experience-based pattern recognition to quantitative analysis. With the advent of new OCT devices with faster recording capabilities and higher resolution, this new quantitative approach would be predicted to further our understanding not only of the degenerative process in RP but of other retinal diseases as well.

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