Quantitative OCT Analysis of Idiopathic Perifoveal Telangiectasia

Daniel Barthelmes,1 Mark C. Gillies,2 and Florian K. P. Sutter3

PURPOSE. To identify and quantify specific changes in optical coherence tomography (OCT) images of patients with type 2 idiopathic perifoveal telangiectasia (IPT).

METHODS. In a prospectively designed, observational, case-control study, 28 eyes of 14 consecutive patients with IPT were examined with OCT and compared with eyes of 14 unaffected control subjects. Light reflectivity profiles of raw scan data of OCT images were quantitatively analyzed for differences in distance between different retinal reflectivity layers and their respective reflectivities. Maculae were examined in four separate regions: (1) central fovea, (2) nasal perifovea, (3) temporal perifovea, and (4) outside the fovea.

RESULTS. Retinal thinning, shortening of the photoreceptor outer segments and loss of reflectivity of the photoreceptor ellipsoid zone were found in the central foveal area as well as the nasal and temporal perifoveal regions in eyes with IPT. In addition, increased reflectivity of the outer nuclear layer was found in a sharply demarcated area of the inferotemporal perifoveal region in all affected eyes. Retinal tissue located more than 2000 μm away from the foveola was indistinguishable from that in normal eyes.

CONCLUSIONS. Quantitative OCT analysis shows unique and specific changes in the photoreceptors of the central macula in IPT which can be detected from first clinical presentation. These changes may be of use as an additional diagnostic tool. Correlation of the findings in the outer nuclear layer with histologic studies may help identify the nature of the reflectivity increase and define more clearly the type of damage sustained by the photoreceptors in this condition. (Invest Ophthalmol Vis Sci. 2008;49:2156–2162) DOI:10.1167/iovs.07-0478

Idiopathic macular telangiectasia is an uncommon, slowly progressive disease of the macula. A recent revised classification stresses two distinct disease processes: type 1, or aneurysmal telangiectasia with exudation and type 2, idiopathic perifoveal telangiectasia (IPT).1–3 IPT, the most common form, usually occurs bilaterally and is characterized by small telangiectatic vessels characteristically found inferotemporally within 1 disc diameter of the fovea, with staining by fluorescein on angiography but without retinal thickening or exudation. Loss of central macular transparency is a common early feature, discrete superficial white crystals may also be found. The clinical onset of the disease is usually in the fifth decade, with no preference for sex or race.1,2

Optical coherence tomography (OCT) is a noncontact, noninvasive imaging technology, that is already established as a frequently used tool for the diagnosis and follow-up of various retinal diseases.4–5 OCT scans through a normal macula, centered on the foveola, show clearly distinguishable reflective layers. An analysis of the reflectivity of these layers as a function of scan-depth (Fig. 1) results in a curve with several peaks, from now on referred to as P1 to P6.6–7 Corresponding to (similar anatomy), the internal limiting membrane (P3), the outer plexiform layer (P4), the outer nuclear layer (P5), and the nerve fiber layer–vitreoretinal interface (P6). It has been suggested that P2 arises from tightly packed mitochondria in the ellipsoid region of the photoreceptors.8 Because of its unique anatomy, the foveola lacks P4 and P5.

A quantitative analysis of these light-reflection profiles (LRPs) has been used to examine changes in animal models9 and in rare human retinal diseases.10 In this study, quantitative (q)OCT was used to detect and quantify changes in eyes with IPT.

METHODS

Twenty-eight eyes of 14 consecutive patients participating in a natural history study of IPT (see www.mactelresearch.org) and 28 eyes of 14 healthy control subjects were studied. Patients had no other macular diseases, such as diabetic retinopathy or age-related changes. The diagnosis was made by a retinal specialist (MG) based on the unique clinical features of the disease and confirmed by the Reading Center of Moorfields Eye Hospital (London, UK). All patients underwent slit lamp examination, fluorescein angiography, fundus photography, and OCT scanning (Stratus OCT software ver. 4.01; Carl Zeiss Meditec AG, Oberkochen, Germany). Best corrected logMAR visual acuity was measured by certified refractionists using ETDRS (Early Treatment of Diabetic Retinopathy Study) charts. OCT studies were performed twice over a period of 9 months. A custom-designed scan program was used to create a dense raster of data points across the macula. A scan of 12 radial scan-lines of 6-mm length at 15° intervals centered on the fovea (similar to the built-in Macular Thickness Map program) was performed (Fig. 2). Raw scan data were exported from the OCT device for further analysis. For the analysis the raw data from the Stratus OCT were opened as a 32-bit gray-scale image resulting in gray-scale values ranging from 0 to 4095. Since levels of gray were used when analyzing the reflectivity and not decibels, as provided by the Stratus OCT, arbitrary units (AU) were used instead of decibels. Calculation of the LRP was performed with a scientific graphing, data analysis, and visualization software package (IGOR 5.01a; WaveMetrics Inc., Lake Oswego, OR). LRP reflectivity, which ranged from 0 to 4095 AU, was calculated every 50 μm along each scan. Based on the results from healthy control subjects, ranges for detecting peaks in the LRP were defined. The P2 wave in affected eyes was defined as the major positive peak.
deflection of the LRP curve in the region between P1 and the mean position ± 2 SD of the P2 wave in normal eyes. If there was no positive deflection in this region, the value for P2 was recorded as 0. For P3, P4, and P5 in affected eyes, the position was set as the mean position of these waves in normal eyes ± 2 SD in relation to the detection of P6 (the first peak from the vitreous side). A built-in routine in the software for multi-peak detection was used. No manual corrections were made.

Cystoid spaces were identified by their very low reflectivity (about 2 SD of the P2 wave in normal eyes. If there was no positive deflection in this region, the value for P2 was recorded as 0. For P3, P4, and P5 in affected eyes, the position was set as the mean position of these waves in normal eyes ± 2 SD in relation to the detection of P6 (the first peak from the vitreous side). A built-in routine in the software for multi-peak detection was used. No manual corrections were made. OCT images showing heavily distorted retinal architecture were excluded from further analysis, since no reliable results could be obtained.

Conventional OCT
As previously reported,5,10–14 eyes affected by IPT often have hyporeflective spaces in both the inner and outer neurosensory retina. These regions are characterized by cavities without swelling of the surrounding retinal tissue, such as is observed in diabetic macular edema or aneurysmal macular telangiectasia. In our study group 17 (61%) of 28 eyes had hyporeflective spaces that were detectable in 228 of 672 scans. Areas with a disrupted ellipsoid region were seen in 385 of 672 scans (57%). As an interesting finding, three (11%) of the eyes examined showed changes similar to those found in exudative age-related macular degeneration (Fig. 4), including disruption of the highly reflective RPE in association with intraretinal masses of increased reflectivity, probably reflecting gliosis, and pro-

mm centrifugally from the foveola. Zone 4 was located more than 2 mm from the foveal center inferotemporally.

Neuroretinal morphology is comparable in both eyes of healthy control subjects whereas in IPT, despite an often bilateral occurrence, severity may vary between both eyes of an affected patient. Therefore, analysis of LRPs was performed separately in each specified area of the left and right eyes in patients with IPT.

Statistical analyses were performed with commercial software (Statistica 6; StatSoft Inc., Tulsa, OK). One-way ANOVA, bivariate correlation analysis, and unpaired t-test were used when appropriate. Statistical significance was defined as P < 0.05. Statistical differences between the groups were calculated by one-way ANOVA. Post hoc testing revealed no statistical differences between right and left eyes with IPT in equal regions examined.

RESULTS

Patient Characteristics
Of the 14 patients participating, 5 were males. As is characteristic of the disease, all patients with IPT had clinically evident disease in both eyes. The average age of the males was 58 ± 8 years, and that of the females was 56 ± 6.7 years (P = 0.65). Control subjects were matched for sex and age. Mean visual acuities of affected eyes was significantly less than that of control eyes (71.8 ± 12 vs. 92 ± 6 letters; P < 0.05). All eyes were staged for the status of IPT according to Gass’s classification1: 7 eyes were stage 2, 9 eyes were stage 3, 11 eyes were stage 4, and 1 eye was stage 5.

Conventional OCT
As previously reported,5,10–14 eyes affected by IPT often have hyporeflective spaces in both the inner and outer neurosensory retina. These regions are characterized by cavities without swelling of the surrounding retinal tissue, such as is observed in diabetic macular edema or aneurysmal macular telangiectasia. In our study group 17 (61%) of 28 eyes had hyporeflective spaces that were detectable in 228 of 672 scans. Areas with a disrupted ellipsoid region were seen in 385 of 672 scans (57%). As an interesting finding, three (11%) of the eyes examined showed changes similar to those found in exudative age-related macular degeneration (Fig. 4), including disruption of the highly reflective RPE in association with intraretinal masses of increased reflectivity, probably reflecting gliosis, and pro-
announced cystic retinal thickening. These patients had advanced disease with intraretinal pigment migration. During the observation period of 9 months, no changes in the size of the cavities and the disruption of the RPE/Bruch’s membrane lesions were detected.

Two eyes in two patients could not be quantitatively analyzed because of heavily distorted retinal reflectivity curves. Of 672 OCT images, 72 were excluded (including the 48 scans from the two eyes with heavily distorted retinal morphology) for the analysis of zones 1, 2, and 3. The remaining 24 OCT recordings in several patients were excluded because of bad scan quality or intraretinal pigment deposits that made an analysis within zones 1 to 3 impossible. For analysis of zone 4 all OCT images could be used.

**qOCT Characteristics**

There were three specific changes that were found in all three zones of every affected eye examined: (1) decreased reflectivity for the analysis of zones 1, 2, and 3. The remaining 24 OCT recordings in several patients were excluded because of bad scan quality or intraretinal pigment deposits that made an analysis within zones 1 to 3 impossible. For analysis of zone 4 all OCT images could be used.
ity of the photoreceptor ellipsoid region (P2 wave amplitude), (2) shortening of the POS, and (3) thinning of the neurosensory retina. These changes were less pronounced in the temporal parafoveal region, but they were still significant. Post hoc testing revealed no significant differences between left and right eyes with ITP in all three regions (Table 1, Fig. 5). No differences in POS length or reflectivity of P2 were observed outside the regions shown in Figure 5.

A unique finding that was observed only in the inferotemporal region of affected eyes was a significant increase in reflectivity of the outer nuclear layer (Figs. 5C, 5D). There was a significant linear correlation between the extent of changes in the ellipsoid region and the outer nuclear layer on the one hand and areas of reduced macular transparency as well as the regions of early and late hyperfluorescence on fluorescein angiography on the other (Fig. 4). In 12 (43%) of 28 eyes, there was a rough topographic correspondence between the regions of increased ONL reflectivity and areas of capillary telangiectasis, seen as early hyperfluorescence on fluorescein angiography (Fig. 4) in the inferotemporal perifoveal region. Otherwise, the increased ONL reactivities were smaller than the areas of early hyperfluorescence, which often extended into nasal zone 2. In 10 (35%) of 28 eyes, there was a good correspondence between the extent of the defects in the photoreceptor ellipsoid region (P2 wave) and the peripheral margins of the areas of late hyperfluorescence, in other eyes there was poor correspondence of these two phenomena.

Regions 2000 µm beyond the center of the fovea in affected eyes were indistinguishable from those in normal control eyes. There was a strong positive, linear correlation between visual acuity and the degree of shortening of the outer segments (P1–P2), in the central foveolar region (zone 1) of

### Table 1. Summary of Quantitative OCT Data Concerning the Thickness and Reflectivity of Retinal Layers

<table>
<thead>
<tr>
<th>Region</th>
<th>Layer</th>
<th>Reflectivity (AU)</th>
<th>P1–P6 Thickness</th>
<th>ONL Thickness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zone 1 (Foveola)</td>
<td>Control</td>
<td>45.1 ± 10.6</td>
<td>42.0–48.2</td>
<td>194.1</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>37.1 ± 7.3</td>
<td>34.9–39.2</td>
<td>237.9</td>
</tr>
<tr>
<td></td>
<td>ITP</td>
<td>47.1 ± 9.5</td>
<td>45.0–52.0</td>
<td>209.6</td>
</tr>
<tr>
<td>Zone 2 (Nasal)</td>
<td>Control</td>
<td>25.5 ± 16.2</td>
<td>20.5–26.5</td>
<td>118.7</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>35.2 ± 11.8</td>
<td>32.4–18.8</td>
<td>199.4</td>
</tr>
<tr>
<td></td>
<td>ITP</td>
<td>35.6 ± 20.3</td>
<td>34.9–21.0</td>
<td>212.9</td>
</tr>
<tr>
<td>Zone 3 (Temporal)</td>
<td>Control</td>
<td>21.6 ± 10.8</td>
<td>19.1–24.2</td>
<td>144.2</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>24.1 ± 11.2</td>
<td>21.6–26.5</td>
<td>199.7</td>
</tr>
<tr>
<td></td>
<td>ITP</td>
<td>28.4 ± 12.2</td>
<td>24.5–25.6</td>
<td>223.8</td>
</tr>
</tbody>
</table>

**Comparison with Normal Eyes:**

- **Refractive Changes:**
  - POS length in zone 1 was 45.1 ± 10.6 µm (mean ± SD) in normal eyes; 23.5 ± 13.5 µm in eyes with ITP and 26.0 ± 14.9 µm in left eyes with IPT. The measurements taken in normal eyes by OCT imaging were similar to measurements performed on histologic cross-sections of the human foveal centralis which showed lengths of POS centrally of 41 to 65 µm in adults and are comparable with reports on measurements of PROS in OCT images.**

- **Visual Acuity:**
  - Visual acuity and the degree of shortening of the outer segments in zone 1 was 45.1 ± 10.6 µm (mean ± SD) in normal eyes; 23.5 ± 13.5 µm in eyes with ITP and 26.0 ± 14.9 µm in left eyes with IPT. The measurements taken in normal eyes by OCT imaging were similar to measurements performed on histologic cross-sections of the human foveal centralis which showed lengths of POS centrally of 41 to 65 µm in adults and are comparable with reports on measurements of PROS in OCT images.**

- **Correlation with OCT Imaging:**
  - A unique finding that was observed only in the inferotemporal region of affected eyes was a significant increase in reflectivity of the outer nuclear layer (Figs. 5C, 5D). There was a significant linear correlation between the extent of changes in the ellipsoid region and the outer nuclear layer on the one hand and areas of reduced macular transparency as well as the regions of early and late hyperfluorescence on fluorescein angiography on the other (Fig. 4). In 12 (43%) of 28 eyes, there was a rough topographic correspondence between the regions of increased ONL reflectivity and areas of capillary telangiectasis, seen as early hyperfluorescence on fluorescein angiography (Fig. 4) in the inferotemporal perifoveal region. Otherwise, the increased ONL reactivities were smaller than the areas of early hyperfluorescence, which often extended into nasal zone 2. In 10 (35%) of 28 eyes, there was a good correspondence between the extent of the defects in the photoreceptor ellipsoid region (P2 wave) and the peripheral margins of the areas of late hyperfluorescence, in other eyes there was poor correspondence of these two phenomena.

- **Regions 2000 µm beyond the center of the fovea in affected eyes were indistinguishable from those in normal control eyes. There was a strong positive, linear correlation between visual acuity and the degree of shortening of the outer segments (P1–P2), in the central foveolar region (zone 1) of...**

---

**Quantitative Analysis in MacTel 2159**

**Downloaded From: http://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/932950/ on 06/24/2017**
affected eyes \((r = 0.59, P = 0.0085)\). There also appeared to be a correlation between the degree of loss of reflectivity of the photoreceptor ellipsoid region \(P2\) and visual acuity in affected eyes; however, it was not statistically significant \((r = 0.41, P = 0.08)\). There was no correlation between the degree of shortening of the outer segments, the reflectivity of the ellipsoid region, or the reflectivity changes in the outer nuclear layer with the presence or absence of retinal cavities (not shown).

**DISCUSSION**

Patients with IPT show unique features on qOCT analysis that have not been described previously. All three zones (central, nasal perifoveal, and temporal perifoveal) showed shortening of the POS and reduced reflectivity of the photoreceptor ellipsoid region. The inferotemporal zone was most markedly affected, with, additionally, an increase of reflectivity of the outer nuclear layer. These changes were found in all the patients we examined, irrespective of clinical stage, and were significantly different from unaffected eyes. We propose that the qOCT changes in the outer nuclear layer and the photoreceptor ellipsoid region, particularly in the inferotemporal perifoveal zone, may be used as an additional marker for the clinical diagnosis of the disease.

It appears that the reduction of reflectivity of the photoreceptor ellipsoid region \(P2\) and shortening of the outer segments, which were the most consistent findings throughout the foveal and perifoveal regions of affected eyes, may be early events in the course of IPT, since they were found as consistently in eyes with stage 2 disease as they were in eyes with more advanced changes. The regression curve of the correlation of the extent of the ONL reflectivity increase and the degree of outer segment shortening intercepted the vertical axis (corresponding to outer segment shortening) at 0.7 mm (Fig. 6C) suggesting that outer segment damage occurs first to a certain extent and is followed by the development of increased reflectivity of the ONL. Because of the slow nature of

---

**FIGURE 5.** (A, B) Regions affected by decreased P2 reflectivity. The central macula is affected both nasally and temporally with a slight preponderance toward the temporal region. (C, D) Frequency of increase in reflectivity of the ONL of affected eyes. The ONL reflectivity increase is found only in the temporal region and is centered just below the horizontal midline. Difference from normal eyes was defined as a deviation of more than 2 SD from the mean values of controls.

**FIGURE 6.** (A) Control LRP across the temporal perifovea. The peaks representing the RPE \(P1\), the ellipsoid region \(P2\), the ELM \(P3\), and the ONL can clearly be seen. (B) LRP across the temporal perifoveal retina in an eye affected by IPT. Note the significantly lower P2 reflectivity, the decreased distance from P1 to P2, and the decrease in reflectivity of P3 compared to that in control eyes. The ONL is reduced in thickness and shows an increased reflectivity compared to (A). (C) Scatterplot of the maximum linear dimension of the zone of increased ONL reflectivity versus the degree of outer segment shortening \((r = 0.52, P = 0.003)\). (D) Boxplot showing the reflectivities of controls (controls) and left (IPT OS) and right (IPT OD) eyes with IPT. The differences are clearly visible, the increase in reflectivity in IPT is highly significant.
disease progression; however, we were unable to demonstrate this in any individual patient examined over a period of 9 months, nor did we observe the presence of P2 changes in the absence of ONL changes in any affected eye.

This finding concerning P2 is consistent with previous observations,10,13 where a disruption of the inner–outer photoreceptor junction (i.e., the ellipsoid region) line was observed in the temporal perifovea, as well as throughout the whole fovea.15 Disruption of the IS/OS PR junction line accompanied by reduction of ONL thickness in IPT has been proposed as a marker for photoreceptor degeneration previously.12 These changes on OCT are also found in patients with retinal degenerative diseases such as retinitis pigmentosa, where a loss of the P2 signal is accompanied by thinning of the ONL (Fischer MD, et al. IOVS 2006;47:ARVO E-Abstract 5799).

The areas of change detected by quantitative OCT analysis, particularly the reduced P2 wave reflecting photoreceptor damage and the increased reflectivity of the OCT, did not correlate consistently with changes that were discernible on clinical examination, including loss of macular transparency; early hyperfluorescence on angiography, which was confined to the area of telangiectatic change in the normal capillary bed; and late hyperfluorescence, the origin of which is poorly understood (Fig. 4). Loss of retinal transparency may be manifested as a blunted reflexes with grayish discoloration16,17 in other conditions characterized by photoreceptor decay such as cone dystrophies or retinitis pigmentosa. In a minority (43%) of eyes there was a rough correlation between the zones of increased ONL reflectivity and the zones of early hyperfluorescence, as there was also in a smaller proportion of eyes (35%) between the zones of reduced P2 amplitude and late hyperfluorescence. The fact that good correlation between the zones of these respective abnormalities were found only in a minority of cases suggests that each may be associated with the same pathologic process; however, one does not seem to follow the other directly in either comparison.

The decrease in overall retinal thickness in the regions affected by IPT was mainly related to outer segment shortening and the thinning of the outer nuclear layer and therefore represents principally photoreceptor damage. This finding is consistent with previous ones that emphasize the degenerative nature of the disease in the neurosensory retina.12,14 In our study the outer retinal damage was consistent across all affected areas. Particularly in the central fovea, changes in the photoreceptor layer detected by OCT imaging correlated significantly with reduced visual acuity, which is in accordance with previous findings describing a correlation between a disruption of the photoreceptor layer and reduced visual acuity.10 These correlations confirm that the morphologic changes described have functional significance. The thinning is probably of major importance for the understanding of IPT. Other reports on OCT in IPT show reduction of foveal thickness to various degrees. Although previous reports qualitatively described a disruption of the inner–outer photoreceptor junction (P2 signal), this study now adds quantitative data on the extent of damage.10,12,14

A unique finding of the present study is the increased reflectivity in the outer nuclear layer in the perifoveal temporal region. Changes in the ONL located temporally with areas of increased reflectivity were previously interpreted as deep retinal vascularizations.10 Our observations showed ONL reflectivity increase in all patients with IPT, which contrasts with 21% of the sample in a previous report.10 The interpretation of this reflectivity increase is difficult. On the one hand, this change could be the OCT equivalent to deeper retinal vasculatization. On the other, in previous studies with high-resolution OCT, only 21% of the eyes examined showed changes at this level that were supposed to be vascular in origin, whereas all eyes examined had definite IPT. Moreover, histologic reports on IPT do not show a telangiectatic change or an increase of the number of vessels but a thickening of capillary vessel walls, whereas the vessel diameter is within normal ranges.10,25 Also the discrepancy between areas of leakage and areas of ONL (57% poor correlation) changes that we found does not suggest a vascular origin of these changes (Fig. 4).

There are several environmental and genetic defects that could underlie the pathogenesis of IPT. Hypoxic and nutritional diseases have been proposed.12,14,21 A genetic basis is suggested by the fact that the disease almost always affects both eyes, and that it has been described in identical twins.22,23 An environmental contribution is also possible; one such factor that could result in such symmetrical bilateral damage to the photoreceptors is phototoxicity. Light damage would also be expected predominantly to damage the photoreceptors rather than the second- or third-order neurons, which is consistent with the qOCT appearance described. Such damage may lead to reactive gliosis, which could result in the increased reflectivity of the ONL that we observed.

Cystoid spaces, which were observed in 61% of our study sample, did not decrease ONL reflectivity due to their size and spatial distribution. Most frequently, they were located in the innermost retinal layers, and therefore they did not affect the detection of peaks on the LRP curve or the measurement of ONL reflectivity. Previous studies were unable to relate these cavities to hyperfluorescence or leak on fluorescein. The area affected by hyperfluorescence was usually much larger than the area occupied by the cavities.10,12,14

It would be very helpful in further understanding IPT to establish the temporal relationship of the neuronal changes described with the more easily recognized vascular features of the disease. Since IPT progresses slowly, a certain degree of damage has already presumably occurred by the time the patient presents to an ophthalmologist. Examination of patients in the preclinical phase, which may be possible if a large number of unaffected first-degree relatives of affected individuals were targeted, might identify the earliest changes and shed light on the initiating events in the disease.

Some limitations of this study should be considered when assessing the data. The resolution of the Stratus OCT may be insufficient to detect the P2 wave in some patients with advanced disease, leading to miscalculation of the width of the photoreceptor layer. This problem did not appear to occur with any of the eyes we examined. The automated algorithm to measure P2 used in this study worked reliably in most OCT images, though images showing heavily distorted morphology could not be analyzed (Fig. 4). This problem should be addressed in the further development of the software. Another factor that could influence the qOCT analysis of IPT is photoreceptor density. Reliable OCT analysis may not be possible in IPT if photoreceptor density were reduced below a critical level.

The results presented herein shed light on IPT, since they demonstrate that previously undetected changes in the neural retina, particularly in the photoreceptor region, occur consistently and in the early phases of the disease. Further research is warranted to correlate the changes observed in qOCT with functional (multifocal ERG, microperimetry) and histologic studies. Follow-up of the patients over time and examination of family members of affected individuals may provide insights on the temporal course of the changes, which in turn may suggest hypotheses concerning the pathogenesis of the disease.

Acknowledgments

The authors thank Emily Chew and Alan Bird for helpful discussion and critical comments on the manuscript.
References


