Progressive Loss of Cones in Achromatopsia: An Imaging Study Using Spectral-Domain Optical Coherence Tomography

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PURPOSE. Achromatopsia (ACHM) is a congenital autosomal recessive cone disorder with a presumed stationary nature and only a few causative genes. Animal studies suggest that ACHM may be a good candidate for corrective gene therapy. Future implementation of this therapy in humans requires the presence of viable cone cells in the retina. In this study the presence of cone cells in ACHM was determined, as a function of age.

METHODS. The appearance and thickness of all retinal layers were evaluated by spectral-domain optical coherence tomography (SD-OCT) in 40 ACHM patients (age range, 4–70 years) with known mutations in the CNGB3, CNGA3, and PDE6C genes. A comparison was made with 55 healthy age-matched control subjects.

RESULTS. The initial feature of cone cell decay was loss of inner and outer segments with disruption of the ciliary layer on OCT, which was observed as early as 8 years of age. Cone cell loss further progressed with age and occurred in 8 (42%) of 19 patients below 30 years and in 20 (95%) of 21 of those aged 30+ years. Retinal thickness was significantly thinner in the fovea of all patients (126 µm in ACHM vs. 225 µm in the control; P < 0.001) and correlated with age (β = 0.065; P = 0.011). Foveal hypoplasia was present in 24 (80%) of 30 patients and in 1 of 55 control subjects.

CONCLUSIONS. ACHM is not a stationary disease. The first signs of cone cell loss occur in early childhood. If intervention becomes available in the future, the present results imply that it should be applied in the first decade. (Invest Ophthalmol Vis Sci. 2010;51:5952–5957) DOI:10.1167/iovs.10-5680

Achromatopsia (ACHM) is a congenital cone photoreceptor disorder with a presumed stationary course. The estimated prevalence is 1 in 30,000. ACHM is characterized by low visual acuity, photophobia, nystagmus, severe color vision defects, and a presumably normal macular appearance. The inheritance is autosomal recessive, and the known responsible genes are CNGA3, CNGB3, GNAT2, and PDE6C. Together, these genes explain the majority (>90%) of all ACHM cases. Although it is known that these genes code for essential proteins in the cone phototransduction cascade, repair of the gene defects is not feasible as yet.

A promising therapy that is currently under investigation is cone-targeted gene therapy. The first results of animal studies showed that CNGB3, CNGA3, or GNAT2 knockout mice and dogs responded well to adenoassociated virus gene therapy. In these rescued animals, cone ERG amplitudes recovered to nearly normal levels. The next step in this development will be gene therapy in humans with cone dysfunction. For that purpose, it is crucial to know whether the nonfunctional cones are present and still viable in the macula.

The purpose of this study was to investigate the presence of cone cells as a function of age in ACHM. We compared foveal morphology in 40 ACHM patients of various ages with that in 55 healthy age-matched control subjects using a new spectral-domain optical coherence tomography system (SD-OCT; Spectralis; Heidelberg Engineering, Heidelberg, Germany). This device has high reproducibility and better resolution than conventional OCT, and its images correlate well with histopathology in vivo.

METHODS

Study Population

ACHM patients (n = 40; n = 77 eyes) were ascertained from the Dutch ACHM patient organization (AchroNed) as well as from various ophthalmogenetic centers in The Netherlands (Erasmus Medical Centre, Rotterdam; The Rotterdam Eye Hospital, Radboud; Nijmegen Medical Centre, Nijmegen; and Caroline C. W. Klaver, Department of Ophthalmology and Department of Epidemiology, Erasmus Medical Centre, P.O. Box 2040, NL-3000 CA Rotterdam, The Netherlands; c.c.w.klaver@erasmusmc.nl.)
Centre, Nijmegen; and Sensis Institute, Grave). Diagnostic criteria were poor visual acuity since birth, congenital nystagmus, photophobia, color vision disturbances in three axes, and absent or residual cone responses with normal rod responses on full-field electroretinogram (ERG). All patients were screened for mutations in the CNGA3, CNGB3, GNAI2, and PDE6C genes. Control subjects (n = 55; n = 110 eyes) were unrelated persons accompanying patients or healthcare workers derived from the Erasmus Medical Centre who had best corrected visual acuity (BCVA) of 0.8 (20/25) or higher and no eye diseases. Control subjects were age-matched with patients per decade. The study was approved by the Medical Ethics Committee of Erasmus Medical Centre and adhered to the tenets of the Declaration of Helsinki. All patients provided signed, informed consent for participation in the study, retrieval of medical records, and use of blood and DNA for research.

Clinical Examination and OCT
All ACHM patients underwent a complete ophthalmic examination, including best corrected Snellen visual acuity, refractive error, color vision testing (HRR, Ishihara), ERG, and 35° fundus photography centered on the macula (TRC 50IX, Topcon, Tokyo, Japan). We performed SD-OCT on all eyes with the Heidelberg Spectralis (HRA+OCT ver. 4.0, with TruTrack eye tracking and Heidelberg Noise Reduction; Heidelberg Engineering) according to published procedures.11

Allied software (Eye Explorer, ver. 1.61; Heidelberg Engineering) was used for all measurements. We performed a single-section scan (one B-scan, 30°, 768 pixels) to obtain a longitudinal section across the center of the macula, and we performed a volume scan (19 B-scans, 20° × 15°, 512 pixels, 12 frames per B-scan) to ensure capturing the center of the fovea. When the nystagmus in the ACHM patients was so severe that it impaired the tracking system of the OCT, settings for resolution, speed, the number of B-scans, and the number of frames per B-scan were adjusted.

Retinal thickness measurements in the fovea included the following structures: outer nuclear layer (ONL), inner and outer segments of the cone cells, and retinal pigment epithelium (RPE). Measurements were determined per ETDRS area12 using the automated measurements from the software. We calculated retinal thickness in the fovea manually by searching the thinnest point in the fovea (Eye Explorer tool; Heidelberg Engineering). We placed points to outline the boundaries of the foveal pit and then used the system’s measurement tool to calculate depth and width of the fovea. In subjects with foveal hypoplasia or a hypodense area (bubble), measurements were performed manually as well. In these cases, we placed points to outline the boundaries of the extra retinal layers or the bubble, measured these with the system’s measurement tool, and then subtracted the results from the total retinal thickness given by the automated measurements.

Statistical Analysis
Frequency differences between ACHM patients and control subjects were compared by using Student’s t-test for continuous variables and one-way ANOVA for categorical variables. First, we calculated between-eye correlations for the OCT measurements. Correlations between continuous variables (e.g., foveal thickness and disease status; ACHM and control) were calculated with a bivariate Pearson’s correlation test; correlations between categorical variables (e.g., macular appearance) were analyzed with the Spearman correlation analysis. Differences in the presence of cone and RPE cell disruptions were analyzed with the χ² test. In the cases, we further examined, by linear regression analysis, whether age, visual acuity, and/or macular appearance influences foveal thickness.

Results
Clinical Features
Baseline characteristics of the study population are presented in Table 1.

<table>
<thead>
<tr>
<th>Variable</th>
<th>ACHM n = 40</th>
<th>Control n = 55</th>
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<tbody>
<tr>
<td>Mean age (SD), y</td>
<td>34 (19)</td>
<td>32 (18)</td>
</tr>
<tr>
<td>0–9 y</td>
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<tr>
<td>10–19 y</td>
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<td>23</td>
</tr>
<tr>
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<td>32</td>
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<td>17*</td>
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<tr>
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<td>14*</td>
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<tr>
<td>Hypermetropia</td>
<td>13</td>
<td>4*</td>
</tr>
<tr>
<td>Molecular defect</td>
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</tr>
<tr>
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<td></td>
</tr>
<tr>
<td>PDE6C mutations</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>No mutations</td>
<td>0</td>
<td>55*</td>
</tr>
</tbody>
</table>

Data are the number of subjects to whom the variable applies, unless otherwise stated. * P < 0.05 for the difference between ACHM patients and control subjects.

We examined 77 eyes of 40 patients with ACHM and all 110 eyes of 55 control subjects. All patients showed pendular nystagmus, were photophobic, and had BCVA of 0.05 to 0.20. Refractive errors (≤2 D or ≥2 D) were significantly more present among the patients (24/16 vs. 18/37; P = 0.004). Gene defects in the patients were mostly present in the CNGB3 gene (83%; 33/40). We did not find a genotype-phenotype correlation (i.e., the genes were equally distributed among those with and without OCT abnormalities).

OCT Findings
All OCT parameters correlated highly between the right and left eyes (R² ≥ 0.90). To ensure the best images for analysis, we used the eye that was least affected by congenital nystagmus for all subsequent measurements. Observations on OCT and macular appearance are summarized in Table 2.

Loss of cone inner and outer segments (IS and OS) with interruption of the ciliary layer (the connecting cilium of the photoreceptors) was the most frequent retinal abnormality among the patients (Figs. 1A, 1B). This feature was present in 28 (70%) of 40 of the ACHM patients and showed a strong association with age. In the age group 0 to 10 years, only one (1/7; 14%) examined child had this feature, whereas in the oldest age group, all patients (7/7; 100%) showed this characteristic (Fig. 2).

Fundus photographs of patients with only loss of IS and OS (n = 2) showed no abnormalities.
A bubble, an optical empty cavity, was visible in the cone cell layer in 24 (60%) of 40 of the ACHM patients (Figs. 1C, 1D). Smaller bubbles coincided with loss of OS, whereas bigger bubbles also involved the IS of cone photoreceptor cells. Fundus photographs of patients with a bubble and intact RPE layer on OCT (n = 19) showed RPE mottling (n = 11), no foveal reflexes (n = 2), or no abnormalities (n = 6). The presence of a bubble on OCT was not significantly related to BCVA.

Disruption of the RPE cell layer was visible in 7 (18%) of 40 of the ACHM patients (Figs. 1E, 1F) and was present only in those beyond 40 years of age. Fundus photographs evidenced the RPE disruption in the majority of cases (6/7; 86%). BCVA was not significantly reduced.

TABLE 1. Clinical Characteristics of Patients with ACHM and Age-Matched Control Subjects

- Frequency differences between ACHM patients and control subjects. All patients showed pendular nystagmus, were photophobic, and had BCVA of 0.05 to 0.20. Refractive errors (≤2 D or ≥2 D) were significantly more present among the patients (24/16 vs. 18/37; P = 0.004). Gene defects in the patients were mostly present in the CNGB3 gene (83%; 33/40). We did not find a genotype-phenotype correlation (i.e., the genes were equally distributed among those with and without OCT abnormalities).

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We determined the total thickness of the ONL, IS, and OS of the cone photoreceptors and the RPE layer in the fovea and of all retinal layers in the nine ETDRS areas. These layers were significantly thinner in the patients (mean thickness of 126 μm in foveas of the patients; 225 μm in foveas of the control subjects, \( P < 0.001 \)), and the reduction correlated significantly

<table>
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<tr>
<th>Table 2. Measurements of the Macular Appearance on Fundus Photographs and on OCT in ACHM Patients and Control Subjects</th>
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<tbody>
<tr>
<td>ACHM ( n = 40 )</td>
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<tr>
<td><strong>Macular appearance on fundus photographs, ( n )</strong></td>
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<tr>
<td>No aberrations</td>
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<td>Foveal reflex absent</td>
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<tr>
<td>(Subtle) RPE alterations</td>
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<td>Bull’s eye with RPE degeneration</td>
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<td>Area of RPE atrophy</td>
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<tr>
<td><strong>Macular appearance on OCT (by age group), ( n )</strong></td>
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<td>Retinal thickness of ETDRS area 1 (fovea), mean (SD), μm</td>
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<tr>
<td>( 0–9 ) (( n = 6 ))</td>
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<td>( 20–29 ) (( n = 5 ))</td>
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<td>Retinal thickness of ETDRS area 2–9 (parafovea), mean, μm</td>
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<tr>
<td>Total</td>
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<tr>
<td>Loss of cone inner- and outer segments</td>
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<tr>
<td>( 60–70 )</td>
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<tr>
<td>Total</td>
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Data are the number of subjects who exhibited each feature, unless otherwise stated. The number of subjects in each age group (\( y \)) was the same for all OCT findings.
with age (1.2 μm [SE 0.33]) decrease per year; \( \beta = 0.065; P = 0.011 \). The patients without any signs of retinal degeneration (all layers intact on OCT; \( n = 12 \)) also had thinner layers (mean thickness, 179 μm in foveas of the patients; 225 μm in foveas of the control subjects; \( P = 0.05 \)). The control subjects all had a foveal thickness of at least 215 μm and showed no reduction with age. Refractive error did not correlate with foveal thickness (\( P = 0.822 \)).

**Foveal Hypoplasia**

In the fovea of 80% (24/30) of the ACHM patients, we noted multiple ganglion cell layers. These extra layers indicate a lack of formation of the foveal pit (i.e., foveal hypoplasia). This phenomenon was always present bilaterally. It occurred in all age groups of patients and in one 51-year-old control subject with a Snellen visual acuity of 1.25 in both eyes, no color vision defects, and a normal macular appearance. Those with foveal hypoplasia had a less steep foveal slope than those with a normal fovea (92 μm vs. 135 μm; \( P = 0.02 \)), but had no differences in foveal width (2004 μm vs. 2126 μm; \( P = 0.20 \)) (Fig. 3). Fundus photographs showed absent foveal reflexes in only 50% of patients with hypoplasia and revealed normal macular appearance in the remaining half.

**FIGURE 1.** Fundus photographs and OCT images showing progressive loss of cones in patients with ACHM. (A) Normal OCT in a 9-year-old patient with mutations in the CNGA3 gene (c.847C>T/c.1709G>T). (B) Loss of cone photoreceptor inner and outer segments with disruption of the ciliary layer on OCT and normal macular appearance on the fundus photograph in an 8-year-old patient. Mutations were detected in the CNGB3 gene (c.1148delC/c.991-3T>G). (C) Small bubble with absent cone photoreceptors in the fovea on OCT and normal macular appearance on the fundus photograph in a 15-year-old patient with mutations in the CNGB3 gene (c.1148delC/c.1148delC). (D) Large bubble with absent cone photoreceptors in the fovea on OCT and normal macular appearance on the fundus photograph in a 21-year-old patient with mutations in the CNGB3 gene (c.1148delC/c.1148delC). (E) Foveal bubble and moderate RPE cell layer disruption on OCT and macular RPE atrophy on the fundus photograph in a 49-year-old patient with mutations in the CNGA3 gene (p.D260N/p.D162V). (F) Complete cone and RPE cell layer disruption in the fovea on OCT and macular RPE atrophy on the fundus photograph in a 56-year-old patient with mutations in the CNGB3 gene (c.1148delC/c.886–896del11insT). NFL, nerve fiber layer; GCL, ganglion cell layer; IPL, inner plexiform layer; INL, inner nuclear layer; OPL, outer plexiform layer; ONL, outer nuclear layer; IS/OS, inner segments and outer segments of the cones; CC, ciliary layer (connecting cilium); RPE, retinal pigment epithelium.

**FIGURE 2.** The proportion of ACHM patients with cone cell degeneration (gray) and RPE atrophy (black) per age group in percentages. The total number of patients per stratum is given below the age range. The youngest patient with signs of cone cell decay was 8 years old.
DISCUSSION

Our study provides evidence that cone cells die progressively in ACHM. The first signs of decay were loss of IS and OS with a disruption of the ciliary layer on OCT, followed by appearance of an evolving bubble with cell loss in the cone photoreceptor layer. The end stage was characterized by atrophy of the RPE. This cascade of events had its onset predominantly in the second decade and showed a strong association with age thereafter. Before any signs of decay were visible, the foveal and parafoveal regions were already significantly thinner in the ACHM patients than in the age-matched control subjects. With the appearance of cone cell degeneration, thinning of the retina became more pronounced.

A strength of this study was the use of the recently developed Spectralis SD-OCT (Heidelberg Engineering). The resolution of this device is 50 times higher than that of the conventional Stratus OCT (Carl Zeiss Meditec, Oberkochen, Germany), making it possible to distinguish the different retinal layers and to analyze changes on a cellular level. Moreover, the SD-OCT has settings that are adjustable for the individual patient, facilitating measurements in patients with congenital nystagmus and in young children. A limitation of the study was the relatively small sample size and its cross-sectional design. Only larger studies with longer follow-up can overcome the problems.

Investigations of retinal morphology in ACHM have been scarce. Former histopathology studies of individual patients contradict each other on the presence and number of cones in the fovea. Falls et al. described a normal number of foveal cones with aberrant morphology in one ACHM patient. In contrast, Glickstein and Heath reported a patient who had no detectable foveal cones. Two in vivo imaging studies in which the Stratus OCT was used had disparate results, as well. One reported a normal macular thickness, whereas the other showed a significant decrease. We believe that these contradictory findings may result from differences in the age of the patients. In favor of this view are the results from a study of knockout mice that had no CNGB3 channels. Cones were present at the age of 2 months, but no cones were detected at 8 months.

Foveal hypoplasia was a frequent phenomenon in the ACHM patients in our study (24/30; 80%). It has been reported in histology studies, but not yet confirmed in in vivo imaging studies. Vopal hypoplasia is not specific for ACHM, but is present in other congenital eye disorders, such as ocular albinism and aniridia. In the healthy eye, foveal development takes place at 24 to 36 weeks of gestation by thinning of the ganglion cell layers and thickening of the ONL. The final relocation of the inner nuclear and ganglion cell layers to the periphery takes place at 4 months after birth, resulting in uncovered foveal cone nuclei thereafter. Our ACHM patients with foveal hypoplasia appeared not to have had these early foveal developments. They showed no thickening of the ONL, persistent ganglion cell layers, and a significantly less steep foveal slope (Fig. 3). Remarkably, one control subject also had foveal hypoplasia with extra ganglion cell layers. The difference from the ACHM patients was that this person had a normal thickness of the ONL. We do not know the exact mechanism behind this aberrant retinal development. However, the range in the measurements of the width (range, 1665–2629 μm; SD: 257) and the slope of the fovea (range, 91–173 μm; SD: 20) was large in our healthy control subjects, indicating that normal foveal development varies considerably among subjects with normal visual acuity. The diagnosis of foveal hypoplasia was by far more sensitive on OCT than on fundus photographs, suggesting that aberrant foveal development may be more common than presumed. Half of the ACHM patients with foveal hypoplasia on OCT showed a normal macular appearance. In these patients, a minor slope was often present, giving the impression of a normal foveal reflex (Fig. 3).

What do our results indicate for the application of future therapies? They imply that the foveal cones of ACHM patients, although reduced in number, are morphologically intact at birth. However, after the first decade, cone cell loss occurs progressively in a relatively short time. Therefore, our results suggest that if gene therapy becomes available in the future, earlier application may be preferable to later application.

In conclusion, our study provides profound evidence that ACHM is not a stationary disease, but a disorder that shows progressive loss of cone photoreceptors. SD-OCT is a valuable, noninvasive tool for visualizing the severity of cone decay and a helpful means of giving insight to the cellular changes present in ACHM.

References


