Spectral-Domain Optical Coherence Tomography Staging and Autofluorescence Imaging in Achromatopsia

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IMPORTANCE Evidence is mounting that achromatopsia is a progressive retinal degeneration, and treatments for this condition are on the horizon.

OBJECTIVES To categorize achromatopsia into clinically identifiable stages using spectral-domain optical coherence tomography and to describe fundus autofluorescence imaging in this condition.

DESIGN, SETTING, AND PARTICIPANTS A prospective observational study was performed between 2010 and 2012 at the Edward S. Harkness Eye Institute, New York-Presbyterian Hospital. Participants included 17 patients (aged 10-62 years) with full-field electroretinography-confirmed achromatopsia.

MAIN OUTCOMES AND MEASURES Spectral-domain optical coherence tomography features and staging system, fundus autofluorescence and near-infrared reflectance features and their correlation to optical coherence tomography, and genetic mutations served as the outcomes and measures.

RESULTS Achromatopsia was categorized into 5 stages on spectral-domain optical coherence tomography: stage 1 (2 patients [12%]), intact outer retina; stage 2 (2 patients [12%]), inner segment ellipsoid line disruption; stage 3 (5 patients [29%]), presence of an optically empty space; stage 4 (5 patients [29%]), optically empty space with partial retinal pigment epithelium disruption; and stage 5 (3 patients [18%]), complete retinal pigment epithelium disruption and/or loss of the outer nuclear layer. Stage 1 patients showed isolated hyperreflectivity of the external limiting membrane in the fovea, and the external limiting membrane was hyperreflective above each optically empty space. On near infrared reflectance imaging, the fovea was normal, hyporeflective, or showed both hyporeflective and hyperreflective features. All patients demonstrated autofluorescence abnormalities in the fovea and/or parafovea: 9 participants (53%) had reduced or absent autofluorescence surrounded by increased autofluorescence, 4 individuals (24%) showed only reduced or absent autofluorescence, 3 patients (18%) displayed only increased autofluorescence, and 1 individual (6%) exhibited decreased macular pigment contrast. Inner segment ellipsoid line loss generally correlated with the area of reduced autofluorescence, but hyperautofluorescence extended into this region in 2 patients (12%). Bilateral coloboma-like atrophic macular lesions were observed in 1 patient (6%). Five novel mutations were identified (4 in the CNGA3 gene and 1 in the CNGB3 gene).

CONCLUSIONS AND RELEVANCE Achromatopsia often demonstrates hyperautofluorescence suggestive of progressive retinal degeneration. The proposed staging system facilitates classification of the disease into different phases of progression and may have therapeutic implications.
Achromatopsia is a congenital cone photoreceptor disorder with autosomal recessive inheritance and an estimated prevalence of 1 in 30,000. Affected individuals usually have congenital nystagmus, poor visual acuity, photophobia, and lack of color discrimination. Funduscopic examination is often normal, although pigmentary mottling and atrophic changes may be observed in the macula. Electoretinography (ERG) reveals absent or profoundly reduced cone responses with normal or mildly subnormal rod function. These features establish the clinical diagnosis of achromatopsia. Causative mutations have been identified in the CNGB3 (Chr. 8q21.3), CNGB3 (Chr. 2q11.2), GNAT2 (Chr. 1p13.3), PDE6C (Chr. 10q23.3), and PDE6H (Chr. 12p12.3) genes, with CNGB3 being the most commonly affected. All of these genes encode functionally important components of the cone phototransduction cascade.

Achromatopsia has traditionally been thought of as a stationary disease and was classified as part of the cone dysfunction syndromes rather than the cone dystrophies. However, findings in animal models and in human studies have suggested that achromatopsia is rather a progressive degeneration. Mouse models of achromatopsia have demonstrated a progressive loss of the cone cells with age, canine models have shown detectable cone ERG function in young pups that becomes nonrecordable in mature dogs, and human studies of achromatopsia have revealed deterioration in cone ERG function over time. Recently, studies have used spectral-domain optical coherence tomography (SD-OCT) to show age-dependent correlations with reduced outer nuclear layer (ONL) and total retinal thicknesses, disruption of the inner segment ellipsoid (ISE) line, the presence of an optically empty space (OES) (also called a bubble or hyporeflective zone) in the cone photoreceptor layers, and retinal pigment epithelium (RPE) disruption. Most recently, a longitudinal study evidenced progressive structural degeneration in children younger than 10 years with achromatopsia. Over a mean follow-up period of 16 months, these individuals showed a decrease in central macular and ONL thicknesses as well as new or enlarging disruption of the ISE line.

Treatments for achromatopsia are on the horizon. Cone-targeted gene therapy has shown success in mouse and canine studies, in which it improved cone survival, recovered cone ERG amplitudes to near-normal levels, and corrected visual acuity. Another promising treatment is the use of neuroprotective compounds, most notably ciliary neurotrophic factor (CNTF), which has been shown to inhibit progressive degeneration of rod and cone photoreceptors in a variety of animal models and clinical trials. It also induced cone outer-segment regeneration in a rat model of retinal degeneration and improved cone ERG function and vision in dogs with achromatopsia. Therefore, long-term treatment with CNTF starting at early stages of degeneration could be a viable strategy for preservation and rescue of cone photoreceptors. However, success with either gene- or CNTF-based therapy would require that cone photoreceptors are present and viable within the macula. Although there are still many hurdles to overcome, stem cell-based therapy is being pursued as a potential treatment of retinal degenerative diseases and may become an option for patients who have already lost their foveal cones. However, if RPE atrophy is also present, replacement of the RPE would be an additional consideration and may result in more challenging treatment.

Another imaging modality, which is widely used in the diagnosis, characterization, and follow-up of many retinal disorders, is fundus autofluorescence (AF). This technique enables visualization of the distribution of lipofuscin across the posterior pole. Lipofuscin contains a complex mixture of fluorescent molecules that are by-products of the visual cycle and are accumulated in the RPE through phagocytosis of photoreceptor outer segments. Although the diffuse increase of lipofuscin with aging is physiologic, abnormal distributions are common in many retinal diseases and result in topographic changes in intensity on AF images. Decreased AF is typically considered to be a marker of RPE atrophy, but it may also indicate photoreceptor loss (arrested bis-retinoid deposition) combined with photodegradation of RPE lipofuscin. For example, adenosine triphosphate binding cassette A4 (ABCA4)-related disease and cone-rod dystrophies of other origins can present with hyperautofluorescent rings that surround decreased or absent foveal AF and progressively expand with time. These rings colocalize with reduced visual sensitivity and, across the annulus, the ISE line may not be visible on SD-OCT. Given the mounting evidence for the progressive nature of achromatopsia, one may expect to observe AF features similar to those seen in other progressive degenerations. We describe these features and compare them with structural changes as observed on SD-OCT.

### Methods

Seventeen patients (11 [65%] males, 6 [35%] females; mean [SD] age, 31 [16] years; range, 10-62 years) with achromatopsia were included in this study. There were 4 sibling pairs. The study was performed between February 2010 and May 2012 at the Edward S. Harkness Eye Institute. The research adhered to the tenets of the Declaration of Helsinki, institutional review board approval was granted, written informed consent was obtained from participants or parents/guardians, and Health Insurance Portability and Accountability Act compliance was maintained. Participants received no monetary compensation. Experienced electrophysiologists performed full-field ERGs according to the International Society for Clinical Electrophysiology of Vision standards. The diagnosis was based on clinical presentation of poor visual acuity since birth, congenital nystagmus, photophobia, severe color vision defects, and absent or residual cone responses with normal rod re-
sponses on ERG. Participants were screened in a step-by-step strategy for mutations in the \( CNGB3 \) (OMIM 605080), \( CNGA3 \) (OMIM 600053), \( GNAT2 \) (OMIM 139340), \( PDE6C \) (OMIM 600827), and \( PDE6H \) (OMIM 601190) genes, as previously described.\(^4,6\)

All patients underwent a detailed ophthalmic examination; imaging included color fundus photography as well as near-infrared reflectance (NIR), AF, and SD-OCT imaging performed with a confocal scanning laser ophthalmoscope (Spectralis HRA+OCT, Heidelberg Engineering). Autofluorescence images (488 nm excitation, 500-680 nm barrier filter) were composed of at least 9 single frames (30° × 30° field, high-speed setting), which were computationally averaged to improve signal to noise ratio. However, fewer frames were used in some cases when image acquisition was difficult. Spectralis OCTs were performed as single horizontal line scans across the foveal center. The high-resolution setting was used, and 40 to 100 frames per scan were obtained; however, these were adjusted when severe nystagmus and poor fixation impaired OCT tracking. Each SD-OCT scan was correlated in real time with either an NIR (NIR-OCT) or AF (AF-OCT) image (Eye Explorer software; Heidelberg Engineering). The NIR-OCT images were obtained for all participants; however, AF-OCT imaging was possible only with 6 individuals (35%) because of difficult image acquisition. For the remaining 11 cases (65%), aligning AF to NIR images with software written in MATLAB, version 7.10 (http://www.mathworks.com/products/matlab/) enabled accurate correlation between AF and SD-OCT.

## Results

Clinical characteristics of the patients are summarized in **Table 1**. All participants had photophobia and congenital nystagmus. Snellen best-corrected visual acuity ranged from 20/80 to 20/200 (mean, 20/150) and was generally symmetrical.

Participants demonstrated largely symmetrical findings on all imaging modalities. On color fundus photography, 7 pa-

<table>
<thead>
<tr>
<th>Patient/Sex/Age, y</th>
<th>Sibling Pair</th>
<th>BCVA, R, L</th>
<th>SD-OCT Stage(^a)</th>
<th>Color Fundus Photography</th>
<th>Near-Infrared Reflectance</th>
<th>AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/24</td>
<td>1</td>
<td>20/200, 20/200</td>
<td>1</td>
<td>Normal</td>
<td>Normal</td>
<td>Increased AF in superior and nasal fovea and parafovea</td>
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<tr>
<td>2/I/15</td>
<td>20/80, 20/80</td>
<td>1</td>
<td>Normal</td>
<td>Normal</td>
<td>Decreased macular pigment contrast</td>
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</tr>
<tr>
<td>3/M/17</td>
<td>20/150, 20/150</td>
<td>2 (Intermittent ISe line disruption)</td>
<td>Normal</td>
<td>Hyporeflective fovea</td>
<td>Increased AF in temporal parafovea</td>
<td></td>
</tr>
<tr>
<td>4/F/45</td>
<td>20/80, 20/80</td>
<td>2 (Focal ISe line disruption)</td>
<td>Normal</td>
<td>Hyporeflective fovea</td>
<td>Reduced foveal AF; increased AF in inferior and temporal parafovea</td>
<td></td>
</tr>
<tr>
<td>5/M/23</td>
<td>1</td>
<td>20/160, 20/200</td>
<td>3</td>
<td>Dark fovea</td>
<td>Hyporeflective fovea</td>
<td>Reduced foveal AF surrounded by increased AF</td>
</tr>
<tr>
<td>6/M/23</td>
<td>20/200, 20/200</td>
<td>3</td>
<td>Dark fovea</td>
<td>Hyporeflective fovea</td>
<td>Reduced foveal AF surrounded by increased AF</td>
<td></td>
</tr>
<tr>
<td>7/M/25</td>
<td>20/200, 20/200</td>
<td>3</td>
<td>Hypopigmented foveola</td>
<td>Normal</td>
<td>Increased AF resulting in foveal stippling</td>
<td></td>
</tr>
<tr>
<td>8/M/34</td>
<td>20/100, 20/150</td>
<td>3</td>
<td>Hypopigmented foveola</td>
<td>Hyporeflective fovea</td>
<td>Reduced foveal AF</td>
<td></td>
</tr>
<tr>
<td>9/M/62</td>
<td>20/150, 20/150</td>
<td>3</td>
<td>Normal</td>
<td>Hyporeflective fovea</td>
<td>Reduced foveal AF</td>
<td></td>
</tr>
<tr>
<td>10/F/48</td>
<td>20/150, 20/150</td>
<td>4</td>
<td>Mottled RPE changes</td>
<td>Mixed hyporeflective and hyperreflective features</td>
<td>Greatly reduced foveal AF</td>
<td></td>
</tr>
<tr>
<td>11/M/24</td>
<td>2</td>
<td>20/100, 20/100</td>
<td>4</td>
<td>Mottled RPE changes</td>
<td>Mixed hyporeflective and hyperreflective features</td>
<td>Greatly reduced foveal AF surrounded by increased AF</td>
</tr>
<tr>
<td>12/M/35</td>
<td>2</td>
<td>20/150, 20/150</td>
<td>4</td>
<td>Mottled RPE changes</td>
<td>Mixed hyporeflective and hyperreflective features</td>
<td>Greatly reduced foveal AF surrounded by increased AF</td>
</tr>
<tr>
<td>13/F/10</td>
<td>3</td>
<td>20/150, 20/150</td>
<td>4</td>
<td>Well-defined area of RPE atrophy</td>
<td>Hyporeflective fovea with central hyperreflective area</td>
<td>Greatly reduced foveal AF surrounded by increased AF</td>
</tr>
<tr>
<td>14/M/13</td>
<td>3</td>
<td>20/150, 20/150</td>
<td>4</td>
<td>Well-defined area of RPE atrophy</td>
<td>Hyporeflective fovea with central hyperreflective area</td>
<td>Greatly reduced foveal AF surrounded by increased AF</td>
</tr>
<tr>
<td>15/F/21</td>
<td>20/100, 20/100</td>
<td>5 (Complete RPE disruption)</td>
<td>Well-defined area of RPE atrophy</td>
<td>Hyporeflective fovea with central hyperreflective area</td>
<td>Reduced foveal AF (greatly reduced centrally) surrounded by increased AF</td>
<td></td>
</tr>
<tr>
<td>16/M/52</td>
<td>4</td>
<td>20/200, 20/200</td>
<td>5 (Complete RPE disruption and ONL loss)</td>
<td>Atrophic macular lesion</td>
<td>Mixed hyporeflective and hyperreflective features</td>
<td>Absent foveal AF; increased AF around larger lesion</td>
</tr>
<tr>
<td>17/M/56</td>
<td>4</td>
<td>20/200, 20/200</td>
<td>5 (Coloboma-like macular lesion)</td>
<td>Excavation of macula down to sclera</td>
<td>Predominantly hyperreflective with hyporeflective features</td>
<td>Absent central macular AF</td>
</tr>
</tbody>
</table>

Abbreviations: AF, autofluorescence; BCVA, best-corrected visual acuity; ISe, inner segment ellipsoid; L, left; ONL, outer nuclear layer; R, right; RPE, retinal pigment epithelium; SD-OCT, spectral-domain optical coherence tomography.\(^a\) Stage 1, intact outer retina; stage 2, ISe line disruption; stage 3, optically empty space; stage 4, optically empty space with partial RPE disruption; and stage 5, complete RPE disruption and/or loss of the ONL.
tients (41%) showed RPE alterations; 3 of these (18%) were mottled RPE changes and 4 (23%) were a distinct area of RPE atrophy. Another patient had bilateral coboloma-like atrophic macular lesions, with excavation down to the sclera (further detail is available in the Supplement [eAppendix 1]). Of the patients with no visible RPE changes, 2 had a darkened fovea (12%), 2 showed a hypopigmented foveola (12%), and in 5 cases, the fovea appeared normal (29%). On NIR imaging, 9 patients (53%) had a hyporeflective fovea, with a distinct central zone of hyperreflectance in 3 of these cases (18%). The fovea in 5 patients (29%) showed mixed hyporeflective and hyperreflective features, and in 3 individuals (18%) appeared normal.

Autofluorescence imaging was more sensitive for detecting pathologic features than both color fundus photography and NIR imaging and demonstrated abnormalities in all patients. An area of reduced AF was observed in the central macula of 13 participants (76%). It was often in the shape of a horizontal oval and was limited to the fovea, although 2 patients (12%) had larger lesions extending into the parafovea. In 8 cases (47%), a region of hyperautofluorescence surrounded the reduced AF, and 1 case (6%) showed bordering hyperautofluorescence limited to the inferior and temporal parafovea. Of the 4 patients (24%) without reduced AF, 3 individuals (18%) demonstrated hyperautofluorescence and 1 patient (6%) showed decreased macular pigment contrast. The area of hyperautofluorescence was generally greater in horizontal than vertical extent and ranged in width from a thin rim surrounding reduced AF to a wider region that extended into the parafovea.

On SD-OCT, 13 participants (76%) had foveal hypoplasia. The ISe line was disrupted in 15 patients (88%), and 8 of these (47%) showed varying degrees of RPE disruption. Achromatop-

Discussion

One objective of our study was to evaluate the AF features of achromatopsia. Being a primary cone photoreceptor disorder, the area of hyperautofluorescence found in most (71%) of our patients likely reflects increased cone outer segment turnover, which is marked by intensified bisretinoid deposition in the RPE. Low calcium levels in CNAG3 and CNBG3-deficient cones may affect endoplasmic reticulum metabolism and outer segment biogenesis. Given the evidence from previous studies that achromatopsia is a progressive disorder, our finding of hyperautofluorescence is not surprising. However, the observed hyperautofluorescence was often subtle and, in 3 patients (18%) with early-stage disease, was visible...
only on one side of the fovea. For the cases without hyperautofluorescence, the slow rate of photoreceptor damage in combination with masking of the AF signal by macular pigment may have resulted in the AF images not manifesting the abnormalities in outer segment turnover. Green light AF, which excludes macular pigment, and estimation of macular pigment density could be helpful for a more precise degree of autofluorescence derived from RPE lipofuscin in the macula. This assessment may be further aided by AF quantification.

Patients with RPE disruption demonstrated on SD-OCT displayed a corresponding area of greatly reduced or absent AF. However, 5 (29%) of the 7 individuals (41%) who had ISe line disruption but no RPE damage also showed reduced AF (less marked than in those with RPE atrophy), which was localized to regions of photoreceptor loss. This suggests that the reduced AF in these patients arises from arrested deposition of bisretinoids in the RPE (due to the absence of photoreceptors) coupled with lipofuscin depletion due to photodegradation. The area of hyperautofluorescence was generally observed in regions where the ISe line was present, indicating that it preceded photoreceptor loss. However, in 2 patients (12%; both with stage 3 achromatopsia) it extended into the region of ISe loss, likely reflecting areas where photodegradation had not yet substantially reduced AF intensity. Longitudinal data in future studies would be helpful to
evidence changes in AF intensity over time and correlate them with features observed on SD-OCT.

We believed SD-OCT to be the optimal modality with which to stage achromatopsia because it provides high-resolution imaging of retinal architecture and is widely available and easy to perform. In contrast, other techniques, such as adaptive optics and multifocal ERG, are difficult to perform in achromatopsia because of the nystagmus and poor fixation inherent to this condition. These techniques are therefore not practical for a clinically accessible staging system, but may be useful to perform. In contrast, other techniques, such as adaptive optics and multifocal ERG, are difficult to perform in achromatopsia because of the nystagmus and poor fixation inherent to this condition. These techniques are therefore not practical for a clinically accessible staging system, but may be useful.
ful adjunctive measures for tracking structural and functional responses to treatment in clinical trials. Our system relies on SD-OCT alone for simplicity but also because no other imaging modality in our study reliably differentiated between all stages. It is primarily based on the integrity of cone photoreceptors, but also takes into account damage to the RPE. The degree of structural degeneration categorized by this staging system may guide selection of optimal treatment strategies not only for clinical trials, but in clinical settings as well. Although our study was limited by its cross-sectional design and fairly small sample size, our assessment of the clinical course of achromatopsia was guided by the age-dependent correlations demonstrated in previous cross-sectional SD-OCT studies and by the dynamic retinal changes evidenced in a recent longitudinal study.

Patients with stage 1 achromatopsia had an intact outer retinal structure, with only subtle discontinuities in the IS line and a relatively preserved cone outer segment tip layer in the fovea. This indicates that the cone photoreceptors maintained structural integrity; these patients would therefore be ideal candidates for gene therapy. They would also be most likely to benefit from treatment with CNTF, which may arrest cone degeneration and possibly also recover their function, as it did in dogs with CNGB3 mutations. An interesting feature that we observed in these cases was increased reflectivity of the foveal ELM. This was observed in the absence of hyperreflective foveal cone outer segments, which was shown to be a transitional phase toward IS line disruption, and thus the ELM appears to be the first structure to demonstrate hyperreflectivity. Although this feature was subtle in one patient, it was more prominent and extended over a larger region in the other patient, where it corresponded to the region of cone outer segment tip thinning. The observed ELM hyperreflectivity may be explained by a greater difference in refractive index as tissue below it breaks down, for which it appears to be a sensitive indicator. Therefore, isolated hyperreflectivity of the ELM may represent an early sign of cone degeneration detectable on SD-OCT.

Stage 2 was defined by disruption of the IS line. Although these patients had loss of the photoreceptor outer segments, the photoreceptor inner segment layer was relatively spared. Gene therapy has not been shown to regenerate cone cells, but long-term treatment with CNTF induced cone outer segment regeneration in a rat model of retinal degeneration. Therefore, there may be potential for CNTF to not only arrest the degenerative process but also to regenerate the focal cone damage in these patients.

Photoreceptor damage was more extensive in patients with stage 3 and 4 disease, who showed loss of both the photoreceptor inner and outer segments in the OES. It is suspected that many cone nuclei are ectopically located in these patients (Supplement [eAppendix 4]). However, the ONL was still present, which suggests that these patients retain some viable and correctly located nuclei. They may therefore experience some success with treatments aimed at photoreceptor regeneration, although photoreceptor replacement with stem cell therapy may be the most suitable treatment. Of note are 2 reported cases of patients who presented with an OES beneath an only intermittently disrupted IS line (Supplement [eAppendix 5]).

Patients with stage 4 achromatopsia demonstrated partial RPE disruption within the region of the OES. Previous studies found RPE atrophy only in older age groups, and we observed several patients with an OES but with no signs of RPE disruption. This suggests that RPE disruption is a late manifestation in achromatopsia. The secondary RPE damage may be explained, at least in part, by the toxic effects of lipofuscin accumulation in these cells. When considering an optimal treatment protocol for patients with RPE disruption, regeneration or replacement of the RPE would be an additional consideration and may result in more challenging treatment.

Conclusions

Achromatopsia often exhibits AF features that suggest progressive retinal degeneration. Autofluorescence imaging pro-
vides a modality to topographically visualize the pathologic changes and reveals features that are not otherwise appreciated; it may therefore provide some additional clinical usefulness, as suggested by the observations in this report. The foveal ELM appears to be the first structure to develop hyper-reflectivity and may be an early sign of cone degeneration in patients with intact outer retina. The proposed SD-OCT staging system may be used to guide therapeutic decisions.

ARTICLE INFORMATION
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REFERENCES


