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Optical Coherence Tomography–Defined Changes Preceding the Development of Drusen-Associated Atrophy in Age-Related Macular Degeneration

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Purpose: To characterize the pathological changes preceding the development of drusen-associated atrophy in eyes with age-related macular degeneration (AMD) using spectral-domain optical coherence tomography (SD-OCT).

Design: Longitudinal and cross-sectional retrospective observational study.

Participants: A total of 181 participants with intermediate AMD in at least 1 eye (141 unilateral, 40 bilateral) were assessed longitudinally. A total of 230 participants with bilateral intermediate AMD (40 longitudinal participants with an additional 190 participants) were analyzed cross-sectionally.

Methods: Spectral-domain OCT, color fundus photography (CFP), near-infrared reflectance, and fundus autofluorescence imaging were performed in all participants at cross-section and every 3 months for up to 30 months in the longitudinal study. Spectral-domain OCT volume scans were examined for features that portend the development of drusen-associated atrophy, and the topography, prevalence, and risk factors of these features were determined through cross-sectional analysis.

Main Outcome Measures: The pathological features on SD-OCT preceding the development of drusen-associated atrophy and the characteristics of these features.

Results: Twenty areas from 16 eyes of 16 participants developed drusen-associated atrophy after an average of 20 months (range, 8–30 months). Spectral-domain OCT features unique in these areas included: subsidence of the outer plexiform layer (OPL) and inner nuclear layer (INL), and development of a hyporeflective wedge-shaped band within the limits of the OPL. These characteristics were termed "*nascent* geographic atrophy" (nGA), describing features that portend the development of drusen-associated atrophy. Cross-sectional examination of participants with bilateral intermediate AMD revealed that independent risk factors for the presence of nGA included the presence of pigmentary changes (odds ratio [OR], 16.84; 95% confidence interval [CI], 2.42–117.24) and nGA in the fellow eye (OR, 4.15; 95% CI, 1.12–15.34); nGA was present in 21.9% of participants with drusen >125 μm and pigmentary changes in both eyes.

Conclusions: This study identified pathological changes occurring before the development of drusen-associated atrophy using SD-OCT, which we defined as nGA. Although nGA is undetectable on CFP, it is important for determining the risk of future vision loss in AMD and could be used as an earlier surrogate end point in interventional trials targeting the early stages of AMD. *Ophthalmology 2014;■:1–8 © 2014 by the American Academy of Ophthalmology.*

Video and supplemental materials are available at www.aaojournal.org.

Drusen and pigmentary changes within the macula are recognized as early clinical signs of age-related macular degeneration (AMD) that can be present for many years before there is a loss of central vision. Severe vision loss can subsequently occur as a consequence of the development of geographic atrophy (GA), a late-stage phenotype of AMD characterized on color fundus photography (CFP) by a sharply delineated area of hypopigmentation due to retinal pigment epithelium (RPE) loss with visible choroidal vessels at its base.

A lack of sensitive, specific, and evolving structural and functional biomarkers of the early stages of disease, which can be used to monitor progression and severity of disease before vision is lost, has been a major impediment for the evaluation of novel interventions that target early stages of AMD. Thus, there is an urgent need to identify robust

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markers of disease state and risk of progression, which develop within a predictable and clinically relevant time frame, so that they can be used as surrogate end points of disease severity and used in clinical trials to evaluate the efficacy of therapeutic interventions.

With recent major advances in in vivo imaging techniques, commercially available optical coherence tomography (OCT) devices using spectral-domain (SD) technology are capable of non-invasively visualizing the retina with high resolution.[1] In particular, SD-OCT has been used extensively to detail pathological features and longitudinal changes in existing areas of GA and its margins,[2–9] as well as correlating with changes on other imaging modalities.[10–13] Recent studies have used SD-OCT alone to identify areas of atrophy when examining risk factors for their subsequent development,[13,14] with one study considering atrophy to be present when there was a loss of the RPE band with increased choroidal signal reflectivity on SD-OCT.[14] However, these studies have not documented prior pathological changes on SD-OCT that were specific to the development of these areas of atrophy.

The purpose of this study was to examine the structural features as seen on SD-OCT, which identify distinctive characteristics that portend the development of drusen-associated atrophy. Because the presence of these nascent features may represent significant risk for the development of drusen-associated atrophy, we wanted to determine their prevalence cross-sectionally in eyes graded as having intermediate AMD on CFP.

Methods

Participants

Participants who were involved in human ethics or institutional review board–approved AMD research studies that adhered with the Declaration of Helsinki from 2 different sites, the Centre for Eye Research Australia, Melbourne, and the John A. Moran Eye Center, University of Utah, were retrospectively analyzed in the longitudinal study if they met the inclusion criteria. The inclusion criteria required participants to be older than 50 years of age and to have multiple drusen >125 μm (intermediate AMD), as determined on CFP, and best-corrected visual acuity of ≥20/40 in at least 1 eye. The exclusion criteria for a study eye included any evidence of advanced AMD, including any evidence of GA or choroidal neovascularization (CNV) at the baseline examination on CFP and SD-OCT, and any past treatment for CNV or any other disease that would affect vision or prevent longitudinal evaluation of the pathologic features of AMD. For this longitudinal analysis, only participants whose eyes were not found to have drusen-associated atrophy detected on SD-OCT at the initial visit and were seen at least every 3 months for a minimum of 12 months were included. Drusen-associated atrophy was defined in a similar manner to previous studies,[14,15] as a loss of the RPE and inner-segment ellipsoid (ISe) bands, resulting in increased signal transmission below Bruch's membrane (BM) that is also accompanied by loss of the external limiting membrane (ELM) and outer nuclear layer (ONL) in this area (Fig 1). These participants were examined longitudinally to determine pathological features preceding the development of drusen-associated atrophy on SD-OCT.

Once these features were determined from the longitudinal study, participants at the 2 sites with bilateral intermediate AMD, as determined on grading of CFP, who met the same inclusion and exclusion criteria for intermediate AMD in both eyes and seen at a minimum of 1 time point were examined in a cross-sectional analysis. Images from these participants, including those with bilateral intermediate AMD from the longitudinal cohort, were analyzed to determine the prevalence of these features and their associated risk factors at cross-section.

Imaging

Combined near-infrared reflectance (NIR) and SD-OCT (Spectralis HRA+OCT, Heidelberg Engineering, Heidelberg, Germany) was performed on all participants during all visits. For SD-OCT, all participants had volume scans performed using 49 B-scans of the central 20°×20° area, with 25 frames averaged for each B-scan (Melbourne), or 19 horizontal B-scans of the central 15°×20° area with 10 frames averaged for each B-scan (Utah), using the automatic scan alignment feature for follow-up scans. For all participants, CFP and fundus autofluorescence were also performed at both sites.

Grading and Image Analysis

The grading of CFP was performed using OptomizePro (Digital Healthcare Image Management System, Digital Healthcare Ltd, Cambridge, UK) by an experienced grader (Melbourne) to determine eligibility for this study. Geographic atrophy was defined as a sharply delineated area of RPE hypopigmentation that was >175 μm with the underlying choroidal vessels visible. The grader was masked to SD-OCT, NIR, or fundus autofluorescence images.

Spectral-domain OCT images were reviewed for the presence of drusen-associated atrophy, and all previous scans were examined by 4 investigators (Z.W., C.D.L., L.N.A., and R.H.G.) together once these areas were identified, to determine which features uniquely preceded the development of the atrophic areas. The 4 investigators then reached a consensus on these features and labeled them as "*nascent* geographic atrophy" (nGA), which were then examined cross-sectionally in all participants with bilateral intermediate AMD, using the first visit in this longitudinal cohort, in addition to another group of participants who were seen at only 1 time point. The presence of reticular pseudodrusen (RPD) was also identified using NIR and SD-OCT in all participants.

Statistical Analysis

To investigate the risk factors for the presence of nGA while adjusting for age and accounting for within-subject, between-eye correlations, an analysis using generalized estimating equations was prepared using a binary logistic model. Univariate analyses were first performed for each risk factor, and then all significant risk factors were included in a multivariate analysis.

Results

Development of Drusen-Associated Atrophy on Spectral-Domain Optical Coherence Tomography

A total of 221 eyes from 181 participants with intermediate AMD (without any atrophy detected on SD-OCT at the initial visit) were included in the retrospective longitudinal analysis and consisted of 141 participants with intermediate AMD in 1 eye and CNV in the fellow eye and 40 participants with bilateral intermediate AMD. Participants were on average 75 years of age (range, 50–96 years). They were followed longitudinally with all imaging modalities for an average of 32 months (range, 12–90 months). During the follow-up, 20 areas of drusen-associated atrophy were detected using SD-OCT in 16 eyes of 16 participants after an average