Clinical Characteristics of Reticular Pseudodrusen in the Fellow Eye of Patients with Unilateral Neovascular Age-Related Macular Degeneration

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Purpose: To describe associations between reticular pseudodrusen, individual characteristics, and retinal function.

Design: Cohort study.

Participants: We recruited 105 patients (age range, 52–93 years) who had advanced neovascular age-related macular degeneration (AMD) in only 1 eye from 3 clinical centers in Europe.

Methods: Minimum follow-up was 12 months. The eye selected for study was the fellow eye without advanced disease. Clinical measures of vision were distance visual acuity, near visual acuity, and results of the Smith-Kettlewell low-luminance acuity test (SKILL). Fundus imaging included color photography, red-free imaging, blue autofluorescence imaging, fluorescein angiography, indocyanine green angiography, and optical coherence tomography using standardized protocols. These were used to detect progression to neovascular AMD in the study eye during follow-up. All imaging outputs were graded for the presence or absence of reticular pseudodrusen (RPD) using a multimodal approach. Choroidal thickness was measured at the foveal center and at 2 other equidistant locations from the fovea (1500 μm) nasally and temporally. Metrics on retinal thickness and volume were obtained from the manufacturer-supplied automated segmentation readouts.

Main Outcome Measures: Presence of RPD, distance visual acuity, near visual acuity, SKILL score, choroidal thickness, retinal thickness, and retinal volume.

Results: Reticular pseudodrusen was found in 43 participants (41%) on 1 or more imaging method. The SKILL score was significantly worse in those with reticular drusen (mean score ± standard deviation [SD, 38±12) versus those without (mean score ± SD, 33±9) ($P = 0.034$). Parafoveal retinal thickness, parafoveal retinal volume, and all of the choroidal thickness parameters measured were significantly lower in those with reticular drusen than in those without. The presence of RPD was associated with development of neovascular AMD when corrected for age and sex (odds ratio, 5.5; 95% confidence interval, 1.1–28.8; $P = 0.042$). All participants in whom geographic atrophy developed during follow-up had visible RPD at baseline.

Conclusions: Significant differences in retinal and choroidal anatomic features, visual function, and risk factor profile exist in unilateral neovascular AMD patients with RPD compared with those without; therefore, such patients should be monitored carefully because of the risk of developing bilateral disease. *Ophthalmology 2014;■:1–8 © 2014 by the American Academy of Ophthalmology.*

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Deposits within the retina and Bruch's membrane known as drusen are considered a hallmark of age-related macular degeneration (AMD)[1] and have been described historically in terms of size (<63 μm, 63–125 μm, etc.), margins (distinct or indistinct), and texture (soft or hard).[2,3] These are characteristics readily seen on color photographs of the fundus, the primary method of retinal imaging used in the vast majority of clinical and epidemiologic studies of AMD. From these studies, features such as the size and degree of confluence of drusen and presence of areas of hyperpigmentation or hypopigmentation have been deemed as signifying a high risk of progression to advanced sight-threatening stages of AMD.[4,5] Recent developments in imaging over the past 10 years have led to the use of other methods, including fundus autofluorescence (AF) imaging, optical coherence tomography (OCT), confocal scanning laser ophthalmoscopy, and infrared (IR) and red-free (RF) photography, that have revealed other characteristics that are currently evoking interest as potentially better markers of progression to late-stage disease. One such feature is reticular pseudodrusen (RPD), also known as reticular drusen,[6–9] which appear as yellowish interlacing networks in the fundus on biomicroscopy or on color photography.[2] The natural variation in the color of the ocular fundus as

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well as variable quality of photographic capture can result in the failure to identify this drusen type even when present. Despite this, visualization of the fundus using blue or IR wavelengths[10] or by the use of spectral-domain OCT reveal RPD more consistently.[7] Studies correlating spectral-domain OCT and confocal scanning laser ophthalmoscopy findings have suggested that RPD are subretinal deposits located internal to the retinal pigment epithelium (RPE)[7] in contrast to the focal yellowish deposits traditionally described as hard or soft drusen[3] that are located external to the RPE. Therefore, there is an emerging consensus that the term *subretinal drusenoid deposits* should be used to describe this phenotype, rather than reticular drusen.[7]

In older epidemiologic studies that used color fundus photography, reticular drusen were estimated at a very low prevalence (approximately 0.7%).[8] With increasing use of other imaging technologies where their presence is more easily noted, studies have found a high prevalence of RPD.[6] These studies have suggested that RPD is a stronger predictor for progression to late AMD than classical drusen. For example, a prospective study reported that this drusen type was more common in females and that when present, the risk to the fellow eye was more than twice that of eyes with other drusen types.[6] Furthermore, an observational consecutive case series reported reticular drusen in 24% of AMD patients with newly diagnosed choroidal neovascularization.[11] Genetic analysis of those with reticular drusen has shown associations with known risk variants for late AMD, such as *ARMS2* and *CFH Y402H*.[12,13] We undertook a prospective observational study in 3 countries in Europe to identify markers for progression to late AMD in fellow eyes of participants with neovascular AMD in 1 eye. The fellow eyes were examined using stringent tests of macular function and multimethod imaging at 6-month intervals, with grading of the images performed at a reading center. Herein we describe the prevalence of reticular drusen using multimodal imaging. We also describe the relationships between this drusen type and retinal function and the risk of progression to late AMD.

Methods

The study adhered to the tenets of the Declaration of Helsinki on research using human volunteers and was approved by the institutional review board or ethics committees of each of the participating institutions. The protocol was explained in full to all subjects and written informed consent was obtained.

Study Sample

One hundred five participants (age range, 52–93 years) were recruited from 3 centers (Milan, Coimbra, and Belfast) as part of a longitudinal, observational, nonrandomized, noninterventional, multicenter study with the primary aim of identifying early markers of progression from early to neovascular AMD. The study was funded by an educational grant from Pfizer, Inc. (no. A9011051). Patients attending retina clinics at each study site who had a diagnosis of neovascular AMD in 1 eye were approached and invited to take part. Eligibility criteria were as follows: men and women older than 50 years with a confirmed diagnosis of neovascular AMD in 1 eye; study eye (fellow eye) free of any features of late AMD (i.e., no neovascularization or geographic atrophy) with a visual acuity of 20/40 or better; sufficiently clear ocular media and adequate pupillary dilatation to permit good-quality fundus imaging of the study eye; and willing and able to comply with scheduled visits, laboratory tests, and other trial procedures. Exclusion criteria included any of the following: evidence of a neovascular lesion on fluorescein angiography in the study eye or any other feature indicating previous presence of neovascular AMD, such as subretinal or intraretinal fibrosis within the macular region, RPE tear, or both; significant media opacities, including cataracts, that may interfere with visual acuity assessments or fundus imaging in the study eye (lens opacification of sufficient severity that would require cataract surgery within the 2 year follow-up was also an exclusion criterion); presence of other retinal disease such as pathologic myopia (spherical equivalent of −8 diopters or more or axial length of 25 mm or more), ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, or multifocal choroiditis; any ocular progressive disease, for example, glaucoma or diabetic retinopathy, in the study eye; any medical condition that would interfere with the patient's ability to complete the trial; concurrent enrollment in any other observational or interventional clinical study; any treatment with an ocular or systemic investigational agent in the past 60 days for any medical condition; or known serious allergies to the dye used in fluorescein angiography or indocyanine green angiography (ICGA).

Study Procedures

At each study visit, the following procedures were undertaken for the study eye.

Visual Function Assessment. Distance visual acuity was measured at 4 m using an Early Treatment Diabetic Retinopathy Study chart after a protocol refraction using standardized methods. Near visual acuity was measured with a modified Bailey-Lovie near reading chart using the appropriate reading addition over the protocol refractive correction. Charts were translated into the appropriate language for each study site. The charts were presented as transparencies with a black text placed on a portable light box. The chart displayed words of 4, 7, and 11 characters and tested the smallest word size identifiable from 0.0 to 1.6 logarithm of the minimum angle of resolution (Snellen equivalent, 20/10–20/400) at a distance of 25 cm and presented at a tilt of 45°. The words were unrelated and each line contained words of a set character size.

Low-luminance visual acuity was tested using the Smith-Kettlewell low-luminance (SKILL) acuity chart, which was produced by the Smith Kettlewell Eye Research Institute.[14] The SKILL card consists of 2 letter charts mounted back to back. One is a low-contrast chart comprising black letters on a dark gray background (10% of the reflectance of white paper); the other side is a high-contrast (>90%) black-on-white letter chart with a different letter order. The SKILL score was taken as the difference in performance on the low-contrast dark side versus the high-contrast light side. The scoring for each chart was letter by letter. The card was held approximately 40 cm from the eye with the appropriate reading addition in place.

Image Acquisition. The images were obtained using a Spectralis HRA+OCT (Heidelberg Engineering, Heidelberg Germany) and a digital color fundus camera (Topcon 50X; Topcon, Ltd., Tokyo, Japan) with pupil dilation (2 drops: 1 drop of tropicamide 1% and 1 drop of phenylephrine 1% given 10 minutes before the first image acquisition). The minimum pupil dilation accepted was 6 mm.

Color fundus photography. Stereopair color images were captured on a Topcon 50X fundus camera.