Reticular Pseudodrusen

A Risk Factor for Geographic Atrophy in Fellow Eyes of Individuals with Unilateral Choroidal Neovascularization

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Purpose: To determine whether reticular pseudodrusen (RPD) confer an increased risk of progression to late-stage age-related macular degeneration (AMD) in fellow eyes of those recently diagnosed with unilateral choroidal neovascularization (CNV).

Design: Retrospective study.

Participants: Two hundred consecutive participants with CNV secondary to AMD in 1 eye and no signs of late-stage AMD in the fellow eye.

Methods: Clinical examination and comprehensive retinal imaging, including spectral-domain optical coherence tomography, near-infrared reflectance (NIR), and color fundus photography, at baseline and every follow-up visit.

Main Outcome Measures: Incidence of geographic atrophy (GA) and CNV in the fellow eye.

Results: Mean age ± standard deviation was 77±7 years, and 61% of the cohort were female. Fifty-eight percent (n = 116) had RPD, 68% had drusen of 125 μm or more, 36% had pigmentary changes, 10% had both drusen of 125 μm or more and pigmentary changes, and 17% had only RPD in their fellow eyes. After a mean follow-up of 2.3 years, CNV developed in 36% of patients and GA developed in 14% of patients. Those with RPD demonstrated late-stage AMD (61% vs. 33.4%; $P < 0.001$) and GA (22.4% with RPD vs. 2.4% without RPD; $P < 0.001$) more often. The presence of reticular pseudodrusen was an independent risk factor for the development of GA (hazard ratio [HR], 4.93; $P = 0.042$), but not for CNV (HR, 1.19; $P = 0.500$), at least within the follow-up of this study. Both drusen of 125 μm or more and pigmentary changes at baseline were significant risk factors for the development of CNV and GA (HR, 1.96−11.73; $P \leq 0.020$).

Conclusions: Reticular pseudodrusen seem to confer an increased risk of progression to GA, in addition to drusen and pigmentary changes. The presence of RPD needs to be taken into account when discussing a patient's prognosis and planning management. *Ophthalmology 2014;■:1−5 © 2014 by the American Academy of Ophthalmology.*

Age-related macular degeneration (AMD) is phenotypically diverse, and a number of risk factors are associated with progression to sight-threatening, late-stage disease.[1] It is important both clinically and scientifically to characterize the nature and impact of risk factors on progression to enable appropriate patient management and targeted clinical research.

Clinical classification systems, based on color fundus images, have enabled risk stratification based on the appearance of early AMD signs of drusen and pigmentary changes.[2] Reticular pseudodrusen (RPD), seen clinically or on color images as a reticular pattern of small yellow-white lesions most often in the superior macula, also have been considered a high-risk sign for late AMD.[3] New retinal imaging methods, in particular near-infrared reflectance (NIR) using a confocal scanning laser ophthalmoscope and spectral-domain optical coherence tomography (SD OCT), are much more sensitive at detecting RPD than clinical examination and have revealed a higher prevalence of AMD than previously assumed.[4−6] To date, however, all studies assessing the impact of RPD on the progression of AMD lacked appropriate imaging and did not include both NIR and SD OCT, which have been shown to have the highest sensitivity in detecting RPD when used in combination.[6]

The presence of choroidal neovascularization (CNV) in the first eye places individuals at high risk of late-stage disease developing in their fellow eye.[2,7] This risk may be exacerbated considerably by the presence of RPD.[3,8] Against this background, we assessed the impact of the presence of RPD on the progression to late-stage AMD in fellow eyes of patients with CNV in their first eye using NIR and SD OCT imaging as part of a very comprehensive retinal imaging protocol.

Methods

The prospective inclusion of participants into a study of neovascular AMD that allowed this retrospective analysis was

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Table 1. Sample Characteristics at Baseline and Progression to Late-Stage Disease

	Total Sample (n = 200)	RPD (n = 116)	No RPD (n = 84)	P Value*
Age (yrs)	76.77±7.10	77.38±6.96	75.93±7.25	0.154
Follow-up (yrs)	2.33±1.66	2.48±1.60	2.12±1.73	0.123
Sex				
Male	79 (39.5)	45 (38.8)	34 (40.5)	0.811
Female	121 (60.5)	71 (61.2)	50 (59.6)	
Risk factors				
None	20 (10)	0 (0)	20 (24)	
Drusen and/or pigment only	64 (32)	0 (0)	64 (76)	
RPD only	34 (17)	34 (29)	0 (0)	
RPD, drusen, and/or pigment	82 (41)	82 (71)	0 (0)	
Progression				
No progression	101 (50.5)	45 (38.8)	56 (66.6)	<0.001
CNV	71 (35.5)	45 (38.8)	26 (31.0)	0.015
GA	28 (14)	26 (22.4)	2 (2.4)	<0.001

CNV = choroidal neovascularization; GA = geographic atrophy; RPD = reticular pseudodrusen.
Data are n (%) or mean ± standard deviation unless otherwise indicated.
*Either independent samples *t* test or Mann–Whitney *U* test.

approved by the Human Ethics Committee of the Royal Victorian Eye and Ear Hospital and the institutional review board of the University of Utah and adhered to the tenets of the Declaration of Helsinki. All participants included in this study provided consent before participation.

Participants

Participants were recruited from the medical retina clinic at the Royal Victorian Eye and Ear Hospital at the University of Melbourne, Melbourne, Australia, and the John A. Moran Eye Center at the University of Utah, Salt Lake City, Utah, from 2010 through 2012. All consecutive subjects with newly diagnosed CNV secondary to AMD were recruited into longitudinal studies of neovascular AMD at both the Melbourne and Utah sites. They gave informed consent for their retinal images and medical records to be assessed. We retrospectively reviewed their data to address the question of the fellow eye by including only those participants with non–late-stage AMD in their fellow eye and follow-up for at least 1 year, unless late-stage AMD developed in the fellow eye in less than 1 year, in which case they were not excluded from analyses.

Exclusion criteria for all participants based on the assessment of all images included the presence of late-stage AMD (including any geographic atrophy [GA] and CNV) or other retinal pathologic features, such as diabetic retinopathy or significant epiretinal membrane in the fellow study eye, and any corneal or media opacity that obscured the macula and prevented the assessment of disease state. Participants had to have undergone all required imaging, that is, SD OCT, NIR, and color fundus photography. Using color fundus photographs, AMD was graded in accordance with a recently revised international classification.[9] The presence of RPD was defined as groups of hyporeflective lesions against a background of mild hyperreflectance on NIR with corresponding hyperreflective signal above the retinal pigment epithelium on SD OCT.[4,6,10,11]

Image Acquisition

All participants underwent imaging with color fundus photography, NIR, and a 20°×20° volume scan with at least 19 B-scans on SD OCT. These were performed using a mydriatic fundus camera (Topcon TRC-50EX; Topcon Corporation, Tokyo, Japan) and a Spectralis HRA+OCT (Heidelberg Engineering, Heidelberg, Germany). Fluorescein angiography was performed at baseline presentation, and indocyanine green angiography and fundus autofluorescence were performed as clinically indicated.

End Points

All participants were followed up for a mean ± standard deviation of 2±1.3 years (median, 2 years; range, 7.4 years), and the time to the development of either GA or CNV was determined. End-stage disease was classified as either GA or CNV depending on whichever late stage developed first. Choroidal neovascularization was defined based on clinical examination and was confirmed by SD OCT and fluorescein angiography. Geographic atrophy was defined based on clinical examination and color photography with lesions larger than 175 μm and within 2 disc diameters of the fovea and confirmed on SD OCT and NIR.

Statistical Analyses

Univariate and multivariate survival analyses (Kaplan-Meyer and Cox) were performed to investigate the influence of baseline characteristics (including age, sex, presence of RPD, drusen, and pigmentary changes) on hazard rates of late-stage AMD. These were performed first combining all cases of late-stage AMD and then separately for the occurrence of CNV and GA, adjusting the level of significance according to the number of factors tested in the model. All analyses were performed with SPSS software version 19.0 (IBM, New York).

Results

A total of 200 participants (61% female) with unilateral CNV without late AMD in the fellow eye fitted the inclusion and none of the exclusion criteria at the 2 sites and were included in our analysis (Table 1). All participants underwent anti–vascular endothelial growth factor treatment for CNV. Participants had a mean age ± standard deviation of 77±7 years. Overall, the prevalence of RPD in fellow eyes was 58%; 68% had drusen of 125 μm or more, and 36% had pigmentary changes. Twenty patients (10%) did not have any risk factors observed in the fellow eye, 44 patients (22%) had only either drusen of 125 μm or more or pigmentary abnormalities, 20 patients (10%) had both drusen of 125 μm or more and pigmentary abnormalities, and 34 patients (17%) had only RPD. Forty-one patients (20.5%) had