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

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Abstract

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—200 consecutive participants with CNV secondary to AMD in one 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 (SD-OCT), near-infrared reflectance (NIR), and colour 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 was 77 (± 7) years, and 61% of the cohort were female. 116 (58%) had RPD, 68% had drusen $\geq 125 \mu\text{m}$, 36% pigmentary changes, 10% had both drusen $\geq 125 \mu\text{m}$ and pigmentary changes, and 17% had only RPD in their fellow eyes. After a mean follow-up of 2.3 years, 36% developed CNV and 14% GA. Those with RPD developed late-stage AMD more often (61% versus 33.4%, $p < 0.001$), and more often GA (22.4% with RPD versus 2.4% without RPD,

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Conflict of interest: RHG is on the advisory board of Bayer Australia and Novartis Australia. GSH is a member CAB, Sequenom; member SAB, AGTC; shareholder, Ophtherion, Inc; shareholder, Voyant Biopharmaceuticals LLC; and receives research funding, Allergan.

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$p < 0.001$). RPD 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 $\geq 125\mu\text{m}$ and pigmentary changes at baseline were a significant risk factor for the development of CNV and GA (HR 1.96 – 11.73; $p = 0.020$).

Conclusions—RPD appear to confer an increased risk of progression to GA, additive to drusen and pigmentary changes. The presence of RPD needs to be taken into account when discussing a patient's prognosis and planning management.

Keywords

Reticular pseudodrusen; age-related macular degeneration; progression

INTRODUCTION

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, in order to enable appropriate patient management and targeted clinical research.

Clinical classification systems, based upon colour 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 colour images as a reticular pattern of small yellow-white lesions most often in the superior macula, have also 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 (cSLO) and spectral-domain optical coherence tomography (SD-OCT), are much more sensitive at detecting RPD than clinical examination and have revealed a higher prevalence in 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 neovascularisation (CNV) in the first eye places individuals at high-risk of developing late-stage disease 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, which allowed this retrospective analysis, was approved by the Human Ethics Committee of the Royal Victorian Eye and Ear Hospital (RVEEH) and 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 prior to participation in this study.

Participants

Participants were recruited from the medical retina clinic at the Royal Victorian Eye and Ear Hospital at the University of Melbourne, Australia, and the John A. Moran Eye Center at the University of Utah, USA from 2010 until 2012. All consecutive subjects who presented with a 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 one year, unless they developed late-stage AMD in the fellow eye in less than one year, in which case they were not excluded from analyses.

Exclusion criteria, for all participants, based upon the assessment of all images, included the presence of late-stage AMD (including any geographic atrophy (GA) and CNV) or other retinal pathology 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 all required imaging, i.e. 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 hyper-reflectance on NIR with corresponding hyperreflective signal above the retinal pigment epithelium (RPE) 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 (FA) was performed at baseline presentation, and indocyanine green angiography (ICGA) and fundus autofluorescence (FAF) were performed as clinically indicated.

Endpoints

All participants were followed up for an average of two years (± 1.3 years standard deviation, 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 was developed first. CNV was defined based on clinical examination and confirmed by SD-OCT and FA. GA was defined based on clinical examination and color photography with lesions larger than 175 μm and within two 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, gender, presence of RPD, drusen and pigmentary changes) on hazard rates of developing late-stage AMD. These were performed firstly combining all 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 version 19.0 (IBM, NY, USA).

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 (VEGF) treatment for their CNV. Participants were on average 77 years old (± 7 years standard deviation (SD)). Overall, the prevalence of RPD in fellow eyes was 58%, and 68% had drusen $\geq 125 \mu\text{m}$ and 36% pigmentary changes. 20 (10%) patients did not have any risk factors observed in the fellow eye, 44 (22%) had only either drusen $\geq 125 \mu\text{m}$ or pigmentary abnormalities, 20 (10%) had both drusen $\geq 125 \mu\text{m}$ and pigment, and 34 (17%) had only RPD. 41 (20.5%) patients had RPD with either drusen $\geq 125 \mu\text{m}$ or pigment, and another 41 (20.5%) had RPD with both, drusen and pigment.

After a mean follow-up of 2.3 years, 36% of fellow eyes progressed to CNV and 14% to GA in the overall sample. Persons who did not develop late stage had the longest follow up (2.6 ± 1.9 years, compared to 2.4 ± 1.5 in GA ($p=1.000$) and 1.9 ± 1.2 in CNV ($p=0.023$)). Persons with RPD and without RPD did not differ in age, gender, follow-up or presence of drusen $\geq 125 \mu\text{m}$ and pigmentary changes at baseline (Table 1). More persons with RPD, however, developed late-stage AMD during follow-up (61% versus 33.4%, $p<0.001$), and most of this discrepancy was due to a much higher occurrence of GA compared to persons with no RPD (22.4% versus 2.4%, $p<0.001$, Table 1).

Based on Kaplan Meier survival analysis, (Figure 1) the estimate for the mean time from presentation with a CNV in the first eye until onset of GA in the fellow eye in participants with RPD was shorter (4.54 ± 0.38 years) compared to those without RPD (7.11 ± 0.27 years, $p < 0.001$, log rank test; Kaplan-Meyer survival plots in Figure 1). The difference in the estimate of mean time to development of CNV was not significantly different between the two groups (3.69 ± 0.32 years and 4.62 ± 0.43 years respectively, $p = 0.355$ log rank test; Kaplan-Meyer survival plots in Figure 1).

Stratifying the development of late-stage AMD by number of macular risk factors (drusen $\geq 125 \mu\text{m}$, pigmentary changes and RPD), having just drusen and pigmentary changes or just RPD cause CNV and GA to occur earlier compared to no risk factors. Having both, drusen and/or pigmentary changes as well as RPD, conveys the highest risk of developing late-stage AMD ($p<0.001$ for any late-stage AMD, $p<0.001$ for GA and $p=0.015$ for CNV; Kaplan-Meier plots in Figure 2). No patients without any macular risk factors, and 31% (25 of 82) of patients with all risk factors developed GA. Four out of 20 patients (20%) with no macular

risk factors in the fellow eye developed CNV and 40% (33 of 82) with all risk factors developed CNV.

In multivariate COX regression analysis, both drusen $\geq 125\mu\text{m}$ and pigmentary changes at baseline were a significant risk factor for the development of CNV and GA (Table 2). RPD, however, was only a significant risk factor for the development of GA and not CNV (Table 2).

Discussion

In this sample, we found RPD to be an independent risk factor for GA development, but not CNV, in the fellow eye of patients being treated with anti VEGF treatment for CNV in the first eye. Both, drusen $\geq 125\mu\text{m}$ and pigmentary changes at baseline were significant risk factors for the development of CNV and GA, with additional presence of RPD exacerbating this risk to develop both forms of late-stage AMD. Our findings have implications for monitoring and counseling high-risk patients with RPD, who will require close follow up. Furthermore, being at high risk of developing GA in their fellow eye, although having no signs of late AMD at baseline, makes this group of great interest for future clinical trials of interventions to prevent or slow the development of GA.

In agreement with a number of previous studies, we found RPD to be a risk factor for the development of late-stage AMD, particularly GA, in our cohort of patients with CNV in their first eye, i.e. a high risk for progression in the fellow eye.^{3, 8, 12} A French study demonstrated RPD to be a risk factor for CNV as well as GA in a very similar group of patients with CNV in their first eye, but only used blue reflectance photography and FA to detect RPD.⁸ However, a combination of SD-OCT and NIR has been shown to have the highest sensitivity in detecting RPD⁶, and thus was used in our study. In fact, blue reflectance photography has been shown to have a low inter-observer agreement in detecting RPD compared to NIR.¹² Therefore participants in that study may have been misclassified with respect to their RPD status. This is highlighted by a previous study which investigated the prevalence of RPD in a group of patients who presented with newly diagnosed CNV.¹³ RPD were determined on the basis of fluorescein angiography, blue reflectance and red-free photography, and OCT or NIR imaging were not performed. The proportion of patients found to have RPD was considerably lower (24%)¹³ compared to studies using SD-OCT (35-38%)¹⁴, NIR (62%)¹², or NIR combined with SD-OCT (58% in our sample) in very similar samples of high risk patients. Against this background, we are confident that the imaging employed in this study reliably detected RPD, as the sensitivity and specificity of combining NIR and SD-OCT has been shown to be superior to other imaging techniques.⁶

A number of risk factors for the development of late-stage AMD in the second eye have been described.⁷ Presence of drusen $\geq 125\mu\text{m}$ and pigmentary changes, in association with late-stage disease in the fellow eye, confer a risk of progression of about 50% over five years, as demonstrated by the Age-related Eye Disease Study (AREDS).² In a systematic review of all available studies, the cumulative incidence of late-stage AMD in fellow eyes of persons with unilateral CNV was found to be 11-12% at 1-2 years, 21% at 3 years and 27% at 4 years.⁷ The overall rate of progression to late-stage AMD in patients with RPD

observed in our study (61% over 2.5 years) is similar to the only other study assessing progression to late-stage AMD in patients with RPD and unilateral CNV (56% over 3 years).⁸ Both are considerably higher than the overall progression rates reported for pooled samples including persons with and without RPD, and highlights once more the high risk for the development of late-stage AMD conferred by RPD.³ This risk seems to be additive to the risk conveyed by the conventional macular risk factors drusen and pigmentary changes as demonstrated by our Kaplan-Meier plots. However, due to sample size restrictions and censored follow-up, RPD was not confirmed as an independent risk factor for CNV development in fellow eyes in subsequent Cox survival analyses. Given the importance of establishing risk factors for the progression to late-stage AMD, future studies should aim to clarify these associations.

To our knowledge, this is the first study assessing the influence of RPD on progression of AMD in high-risk patients, employing a combination of SD-OCT and NIR. Limitations of this study are its moderate size and limited follow up and the selection bias inherent in all clinical case series recruited pro- or retrospectively at tertiary eye hospitals. However, it is a representative group of patients with neovascular AMD presenting to two medical retina departments for treatment, and who are at a high risk of suffering bilateral visual loss when developing late-stage disease in their second eye. Results can be generalized to patients seen at these specialist clinics and the information can be carefully extrapolated. Further strengths of this study are its comprehensive and highly appropriate retinal imaging. Based on a number of previous studies we are confident that we detected RPD with the highest possible accuracy. Similarly, the regular – up to monthly – follow-up inclusive of NIR and SD-OCT imaging allowed for a very precise definition of the two endpoints, CNV and GA, as well as an accurate timing of its occurrence.

In conclusion, we have demonstrated RPD to be an independent risk factor for GA in high risk AMD, in addition to other risk factors such as drusen > 125µm and pigmentary changes. With the ubiquity of OCT, which usually includes infrared imaging, clinicians should keep RPD at the forefront of their minds when discussing patients' prognosis and the risk of developing late-stage disease in fellow second eyes.

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Figure 1.

Kaplan-Meier plots for time until progression to choroidal neovascularization (CNV, panel A) and geographic atrophy (GA, panel B). Those with reticular pseudodrusen (black line) had a significantly shorter time to progression to GA compared to those without (grey line; $p < 0.001$). No difference was found for progression to CNV ($p = 0.355$).

Figure 2.

Kaplan-Meier plots for time until progression to late-stage age-related macular degeneration (AMD; A), geographic atrophy (GA; B) and choroidal neovascularization (CNV; C), stratified by number of risk factors (RF; none, drusen and/or pigment, reticular pseudodrusen (RPD), and RPD + drusen and/or pigment). For both, CNV and GA, patients with all risk factors (RPD, drusen and/or pigment) progress the fastest ($p < 0.001$ for any late-stage AMD, $p < 0.001$ for GA and $p = 0.015$ for CNV). Please note that no patient with no risk factors develops GA while a number of patients with no risk factors develop CNV in their fellow eye during follow up.

Table 1
Sample characteristics at baseline and progression to late-stage disease, as n (%) or mean $\pm$ standard deviation

	Total sample n= 200	RPD n=116	No RPD n=84	p [*]
Age (years)	76.77 $\pm$ 7.10	77.38 $\pm$ 6.96	75.93 $\pm$ 7.25	0.154
Follow up (years)	2.33 $\pm$ 1.66	2.48 $\pm$ 1.60	2.12 $\pm$ 1.73	0.123
Gender				
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	20(24%)	
Drusen and/or pigment only	64 (32%)	0	64(76%)	
RPD only	34 (17%)	34(29%)	0	
RPD, drusen and/or pigment	82 (41%)	82(71%)	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

* Either independent samples t-test or Mann-Whitney-U tests; RPD= reticular pseudodrusen; CNV= choroidal neovascularization; GA= geographic atrophy

Table 2
COX regression analysis results for hazard rates of late-stage AMD, controlling for age and gender

Late AMD	Risk Factors	Hazard Ratio (HR)	95% Confidence Interval (CI)	p-value
CNV	RPD	1.19	0.72-1.94	0.500
	Drusen 125µm	1.96	1.14-3.36	0.015
	Pigmentary Changes	2.49	1.51-4.10	<0.001
GA	RPD	4.93	1.06-22.93	0.042
	Drusen 125µm	11.73	1.47-93.81	<0.020
	Pigmentary Changes	5.75	2.09-15.84	0.001
CNV or GA	RPD	1.20	0.76-1.89	0.433
	Drusen 125µm	2.08	1.25-3.49	0.005
	Pigmentary Changes	2.55	1.64-3.96	<0.001

AMD= age-related macular degeneration, CNV= choroidal neovascularisation, GA= geographic atrophy, RPD= reticular pseudodrusen