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Major review

Perspectives on reticular pseudodrusen in age-related macular degeneration

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ABSTRACT

Drusen have been considered the clinical hallmark of age-related macular degeneration (AMD). Reticular pseudodrusen (RPD), although first described about 25 years ago, have only been recently recognized as an additional clinical phenotype of AMD with distinct characteristics on multimodal imaging and significant impact on visual function. Eyes with RPD are at greater risk of progression to advanced AMD when compared with eyes with drusen only. RPD can also occur in the absence of drusen. Unlike features external to the retinal pigment epithelium that have received most attention in AMD, evidence suggests that RPD are associated with changes internal to the RPE. Therefore, new avenues regarding the pathogenesis of AMD are highlighted by these recent observations. We summarize the current knowledge regarding the histology, imaging, and functional changes in eyes with RPD in AMD and offer concepts of future research for the AMD community to discuss.

1. Introduction

Age-related macular degeneration (AMD), a chronic and progressive retinal degenerative disease that manifests as impairment of central vision as a result of dysfunction and/or death of the photoreceptors and retinal pigment epithelium (RPE),[8,59] is one of the main causes of visual impairment and legal blindness in the older age group.[27] The established clinical hallmark of AMD is the appearance of drusen, histopathologically described as focal deposits of extracellular material between the RPE and the inner collagenous layer of Bruch membrane.[101,114,135] Multimodal imaging has

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confirmed the well-established funduscopic grading of drusen morphology as hard, soft, calcified, and cuticular drusen.[114] Approximately 30 years ago, the Wisconsin Age-Related Maculopathy grading system included reticular drusen as an additional phenotype[52]; however, it is only with recent advances in retinal imaging that interest in this entity, which is now more commonly termed reticular pseudodrusen (RPD),[10] increased, leading to further scrutiny of the contribution of the photoreceptors, RPE, and choroid in the pathogenesis of AMD.[6,106,111,136,150] Moreover, advances in psychophysics have also directed further attention to RPD.[86,120] Several reports confirm that RPD is an independent risk factor for progression of AMD.[57,64] Eyes with RPD have a 4–8 fold greater risk of 5-year progression to late AMD than eyes with drusen alone,[49] and RPD may coexist with both geographic atrophy (GA)[64,106,150] and neovascular AMD.[11,21] Although there is a steep increase in the number of reports on several aspects of RPD, some observations are conflicting. In light of the above, we review the literature on RPD—particularly in respect of epidemiology, pathophysiology, histology, morphological, and functional changes—and provide perspectives on possible further research in AMD based on the association of RPD with AMD.

2. Nomenclature

The first question is whether "reticular pseudodrusen or RPD" is the correct terminology to address these lesions. The entity RPD was first described in 1990 by Mimoun and colleagues as "*les pseudodrusen visible en lumiere bleue*," having a yellow interlacing pattern in the outer macula with variable diameter of about 100 μm that did not fluoresce on fluorescein angiography, but demonstrated enhanced visibility in blue light.[69] A similar description of "*ill-defined networks of broad interlacing ribbons*" on color fundus photography was labeled by the Wisconsin Age-Related Maculopathy grading scheme as reticular soft drusen.[52] The morphology of RPD was further assessed when Arnold and colleagues described them as "*yellow interlacing network 125-250 μm wide, appearing first in the superior outer macula and extending circumferentially and beyond*," in contrast with drusen, which are mainly at the center of the macula, and made the first reference to "*reticular pseudodrusen.*"[10] Since then, the nomenclature "*RPD*" became widely used despite the fact that the lesions are not universally reticular and are neither pseudo (false) nor drusen.[24] Other terms used to describe these lesions are "*reticular drusen*"[24] and "*reticular macular disease.*"[111]

The phenotypic characterization of these lesions on spectral domain optical coherence tomography (SD-OCT) scans illustrates hyper-reflective deposits internal to the RPE.[114] Curcio named this material deposition as subretinal drusenoid deposits (SDDs).[24] The nomenclature may continue to change as new knowledge is gathered.

3. Imaging characteristics of RPD

Although multimodal imaging has improved the visualization of RPD, it is perplexing that the anatomical characteristics of RDP vary depending on the imaging modality. In color fundus photographs they are visualized as a yellow-white, ill-defined network of broad, interlacing ribbons that may have a more punctate appearance closer to the center. They may also appear slightly paler than soft drusen. Better visualization is possible using red-free light,[5,10,89] especially green reflectance[77] supporting the concept that these lesions are located internal to the RPE. Blue channel photography also has a higher detection rate of RPD than standard color photograph because the RPE preferentially absorbs short-wavelength light allowing a dark background to increase the contrast of RPD.[102] Spaide and Curcio accounted for the differences in appearance of cuticular drusen, RPD, and typical soft drusen on the basis of differences in location, morphology, and optical filtering effects of the RPE and the drusenoid material.[114] As RPD are located internal to the RPE, they appear light gray when viewed with blue light, as they are not subjected to the double-pass short-wavelength attenuation of cuticular or soft drusen given their sub-RPE location, and hence appear more yellow-white than RPD.[114]

On confocal scanning laser ophthalmoscopy (cSLO), RPD can be seen using infrared reflectance (IR), short-wavelength fundus autofluorescence (SW-FAF), and confocal blue reflectance (Fig. 1). On IR, RPD may be seen as "dots," "targets," or "ribbon" hyporeflective lesions at the macula[107,109,111,114] confirming that not all RPD lesions are reticular. Suzuki and colleagues categorized RPD into 3 types depending on their IR appearance. The most common variety termed "dots" is defined as an orderly array of whitish discrete accumulations principally located in the perifovea.[124] The exact reason for foveal sparing is unclear; however, this distribution may represent the distribution of the choroidal blood flow or the topography of the photoreceptors.[121] These dots appear as hyporeflective spots but may manifest as target lesions also. The "ribbon" types are described as interconnected bands of yellowish-white material forming a reticular pattern and are also located in the perifovea. An uncommon third type of pseudodrusen—yellow-white globules primarily located peripheral to the perifoveal region—appear hyper-reflective on IR-SLO and are called peripheral pseudodrusen.[124] Dot lesions are most common, whereas the target lesions are the largest. These lesions do coexist in some eyes, dot and target lesions appearing within the first 2 years of disease evolution and dots may progress to target; however, there is insufficient information on the evolution of ribbon lesions. The multicolor mode of spectralis SD-OCT (Heidelberg Engineering, Heidelberg, Germany) allows the simultaneous acquisition and overlay of 3 reflective images with distinctive wavelengths on cSLO that includes blue reflectance (488 nm), green reflectance (518 nm), and IR reflectance (815 nm). RPD are seen as yellow-green on multicolor with higher visibility on green and IR reflectance indicating the lesions are internal to RPE.[7,90,124,132]

On SW-FAF, RPD are seen as small, ill-defined hypoautofluorescent dots, and these dots may be surrounded by areas of hyperautofluorescence[58,111] (Fig. 2). Marsiglia and colleagues showed with serial IR imaging and SW-FAF that areas of RPD are at risk of development of geographic atrophy.[64] SW-FAF originates mainly from the lipofuscin within the RPE so the relative "increased" autofluorescence may be interpreted as RPE disease. Another explanation, however, may be that