

## Guest Editorial

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### ***Reticular Pseudodrusens: An alternative marker of outer retinal dysfunction in AMD***

Reticular pseudodrusen (RPD), an entity described almost 30 years ago, has recently come into focus of attention as an additional clinical characteristic of age-related macular degeneration (AMD). AMD is a chronic condition causing irreversible loss of vision in a significant proportion of the elderly population and is a leading cause of blindness in industrialized countries.<sup>1</sup> Drusen, being the distinctive feature of AMD, has been described histo-pathologically as focal deposits of extracellular material between the retinal pigment epithelium (RPE) and the inner collagenous layer of Bruch membrane (BM).

The differentiation between conventional drusen and pseudo-drusen was made first by Mimoun and co-workers in 1990. They described these RPD as 'pseudodrusen visible en lumière bleue'.<sup>2</sup> In 1995, Arnold and co-workers characterised them as "yellow interlacing network 125–250  $\mu\text{m}$  wide" and coined the term reticular pseudodrusen.<sup>3</sup> This had been alternatively called as "reticular drusen", "reticular macular disease" and "subretinal drusenoid deposits (SDDs)".

Incidence and prevalence of RPD depends upon a slew of factors like stage of AMD, cohort of patients enrolled, risk factors and most importantly, the imaging modality used. Prevalence of RPD in the elder population was assessed by two large, prospective studies, namely, Beaver Dam Eye study and Blue Mountains Eye study using colour fundus photographs (CFP). In these studies, the prevalence of RPD turned out to be 0.7% – 3.0% and 1.95% – 4% at baseline and 15 years respectively. They also found a 4 fold to 6 fold higher rate of progression to late AMD with RPD compared to eyes without RPD.<sup>4</sup> Studies done by Marsiglia and colleagues found RPD as a key factor in the progression to geographical atrophy. Prevalence rate of 29% was found as per the AREDS2 study using fundus auto-fluorescence (FAF), more frequently seen with intermediate AMD compared to early AMD.<sup>5</sup> Therefore, depending on the imaging modality used, stage and type of AMD, prevalence of RPD in patients with AMD may change.

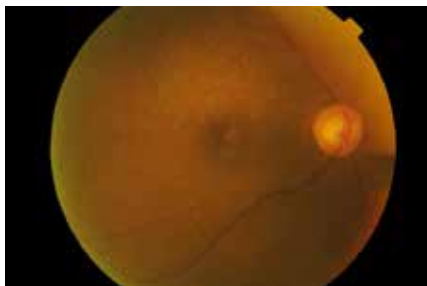
AMD and RPD share several common non-ocular risk factors, including older age, female sex, current smoking and high body mass index. Association with factors such as coronary artery disease, diabetes mellitus, hypertension and decreased renal function are still under debate.<sup>3,4</sup> Some large studies have shown role of two major AMD risks alleles, namely, Complement Factor H (Y402H and I62V variants) on chromosome 1q32 and the Age-related Maculopathy Susceptibility 2 (ARMS2 A69S) on chromosome 10q26. Due to discrepancies, the exact role of genetic involvement yet need to be elucidated.<sup>5,6</sup> Besides AMD, RPD have also been described in association with conditions like acquired vitelliform lesions, Sorsby's fundus dystrophy, pseudoxanthoma elasticum.

Numerous imaging modalities have been used alone or in combination to study the details of RPD with the highest sensitivity of infra-red (IR), near infra-red and short wavelength FAF (NIR-FAF, SW-FAF), SD-OCT and wide field En face SS-OCT, whereas late phases of indocyanine green angiography (ICGA), blue channel of CFP and confocal blue reflectance (CBR) having almost perfect specificity. However, there is no gold standard investigation and use of at least 2 imaging modalities has been advocated. Suzuki and colleagues described 3 types of RPD on the basis of IR imaging- dots type, ribbon type and an uncommon third type presenting as yellow white globules. In the first type, IR reveals perifoveal hypo-reflective dots often showing a target configuration, the second type is characterized by perifoveal faint hypo-reflective ribbons; and the third subtype is featured by mid- peripheral hyper-reflective spots.<sup>7,8</sup>

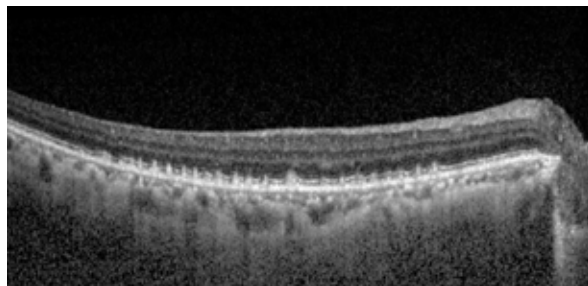
The blue channel of CPF allows better contrast of RPD since the short wavelength of blue light is preferably absorbed by RPE. RPD manifest as hypofluorescent dot, may be surrounded by area of hyperautofluorescence on SW-FAF. Possible explanations can be either an absence of retinoids within the RPE or a blockage effect by the subretinal material which prevents excitation light from reaching the RPE. The exact mechanism is still not known. In NIR imaging, RPD appear as individual or groups of hyporeflective dots, often with a target configuration (a central reflective round area with a surrounding hyporeflective annulus). IR imaging should be considered among

choice of imaging RPD due to its reliability.<sup>7,8</sup>

RPD on indocyanine green angiography appears as hypo-cyanescent dots in the mid-to-late phases which correlates with dots seen at IR and FAF, suggesting a pathology internal to RPE. 7SD-OCT shows RPD as discrete accumulation of hyper-reflective material above the RPE in the subretinal space. Zweifel et al categorised RPD in 3 different stages: 1) diffuse accumulation of granular hyper-reflective material between RPE and EZ, 2) collection of material bowing and distorting EZ profile and 3) conical appearance with focal interruption of EZ. A typical case is highlighted (Figure 1a, b). Fading of the material due to reabsorption and migration within the inner retinal layers was identified as stage 4 by Querques and co-workers. Since SD-OCT has excellent diagnostic properties and reliability in identification of RPD, it holds a very promising role in future.<sup>8,9</sup>



**Figure 1a:** A case with typical Reticular Pseudodrusen in the posterior pole with the characteristic yellow punctate morphologic pattern.



**Figure 1b:** OCT of the case showing multiple, conical subretinal drusenoid deposits abutting the ellipsoid zone.

Drusen are histologically characterized by the accumulation of lipids gathering in the BM (basal deposits). In contrast, RPD are seen as material in the subretinal space extending up to the outer segment and even in the outer nuclear layers. Involvement of neighbouring structures like photoreceptor disruption and reactive gliosis can be an associated feature. Subsequent histological studies of RPD established that they consist of membranous debris, as well as unesterified cholesterol, apolipoprotein E (apoE), complement factor H and vitronectin. In comparison to conventional drusen, RPD have been found to consist of different lipid constituents. Immunohistochemical staining of regions surrounding RPD has found increased expression of the intermediate filament glial fibrillary acidic protein in Muller cells, an indicator of retinal stress indicating the role of inflammation.<sup>10</sup>

Unlike subtypes of drusen, RPD present as a different morphological pattern in the retina making its appearance above RPE. Although linked to many pathological conditions, its role in AMD holds a clinical significance to correlate with subtypes of AMD and its progression. To conclude, the role of RPD in retinal diseases, particularly AMD which leads to irreversible loss of vision, has become an area of interest. From simple colour fundus photographs to advanced imaging like IR, FAF, SD-OCT, it is advisable to use at least 2 different imaging modalities to discern the role of RPD in AMD patients and may form the basis of future clinical trials and epidemiological studies.

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