Original Article

Multimodal Imaging of Reticular Pseudodrusen in Turkish Patients

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Abstract

Objectives: To investigate the presence and prevalence of reticular pseudodrusen (RPD) in patients with age-related macular degeneration using multiple imaging modalities and to compare the sensitivity and specificity of these modalities in the detection of RPD.

Materials and Methods: Images from a total of 198 consecutive patients were analyzed prospectively. Color fundus photography, red-free imaging, spectral domain optical coherence tomography (SD-OCT), infrared and blue reflectance (BR) imaging, fundus autofluorescence (FAF), enhanced-depth imaging OCT (EDI-OCT), fundus fluorescein angiography (FFA) and indocyanine green angiography were performed. RPD was diagnosed in the presence of relevant findings in at least two of the imaging methods used.

Results: RPD were detected in 149 eyes (37.6%). In the detection of RPD, color fundus photography, red-free photography, SD-OCT, infrared, FAF, BR, and FFA imaging had sensitivity values of 50%, 57.7%, 91.6%, 95%, 74.6%, 65.7%, and 28.2% and specificity values of 99.6%, 100%, 98.4%, 94.6%, 100%, 99.6%, and 69.8%, respectively.

Conclusion: Infrared imaging had the highest sensitivity. SD-OCT combined with infrared imaging was the most sensitive imaging technique for detecting RPD. The high specificity of FAF, red-free, and BR imaging may be useful to confirm a diagnosis of RPD.

Keywords: Age-related macular degeneration, imaging methods, reticular pseudodrusen, Turkish patients

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Introduction

Reticular pseudodrusen (RPD) were first described by Mimoun et al.[1] in 1990 as "les pseudodrusen visible en lumiere bleue," referring to extramacular yellow deposits with an average diameter of 100 µm which were arranged in an interwoven network pattern and did not fluoresce on fluorescein angiography but became more visible under blue light. Arnold et al.[2] later coined the term "reticular pseudodrusen" and the morphology of RPD was further investigated. Since then, the term RPD has become widely used. Zweifel et al.[3] examined these lesions using spectral domain optical coherence tomography (SD-OCT) and showed in 2010 that they were located between the retinal pigment epithelium (RPE) and the inner segment/outer segment junction (recently referred to as the ellipsoid zone) and called them subretinal drusenoid deposits.

The reported incidence and prevalence of RPD vary based on the stage of age-related macular degeneration (AMD) and the imaging modality used. Very low rates were reported in community-based epidemiological studies based on color fundus images.[4,5] However, the prevalence of RPD cannot be determined accurately because diagnosis is dependent on the imaging modality and they show atypical distribution, are mistaken for typical drusen, and may disappear over time. RPD is associated with poor prognosis in AMD, which is a major cause of irreversible blindness in the older population. Therefore, the ability to detect and evaluate RPD via imaging and to determine their prevalence is of clinical importance.[6,7] The aim of this study was to prospectively investigate and analyze the presence and prevalence of RPD in consecutive patients diagnosed with AMD using multiple imaging modalities.

Materials and Methods

Patients who presented for the first time to the outpatient clinic of the Ege University Medical Faculty Hospital, Department of Ophthalmology and were diagnosed with AMD between September 2015 and September 2016 were

prospectively evaluated. Cooperative patients with AMD who were over 50 years of age, consented to the imaging procedures, had no media opacities that prevented imaging, had not been previously treated for AMD, had no additional retinal pathology, had no contraindication for the imaging methods used in the study, and had no advanced renal or hepatic pathology were included in the study. Patients under 50 years of age, those with media opacity, high myopia (refractive error greater than -6.00 diopters [D]), additional retinal pathology such as pathological myopia, idiopathic choroidal neovascularization (CNV), ocular histoplasmosis, angioid streaks, central serous chorioretinopathy, or retinal macroaneurysm, those who had been previously treated for AMD at another center, and those with fluorescein allergy were excluded from the study.

The study was conducted in compliance with Declaration of Helsinki and was approved by the Ethics Committee of the Ege University Medical Faculty (decision no: 15-11.1/5, date: 18.12.2015). Written informed consent was obtained from all patients enrolled.

The patients underwent a complete ophthalmologic examination including best corrected visual acuity (BCVA, expressed as logarithm of the minimum angle of resolution [logMAR]) assessment, intraocular pressure measurement, slit-lamp anterior segment examination, and posterior segment examination with a 90-D lens. All patients were examined using color and red-free fundus photography, macular SD-OCT, and infrared (IR), fundus autofluorescence (FAF), blue reflectance (BR), and fundus fluorescein angiography (FFA) imaging. In addition, indocyanine green angiography (ICGA) was performed in 66 eyes of 33 patients. Color fundus (50°) and red-free images were acquired with a Topcon 3D OCT-2000 (Topcon Medical Systems, Tokyo, Japan). Multimodal images including IR, BR, FAF (excitation 488 nm, emission >500 nm), macular OCT, ICGA, and FFA were obtained using a confocal scanning laser ophthalmoscope (Spectralis HRA+OCT; Heidelberg Engineering, Heidelberg, Germany). IR images of the macula were obtained at a resolution of 768 x 768 pixels using an excitation wavelength of 820 nm on a 55° area centered on the macula, while BR images were obtained using an excitation wavelength of 488 nm. In OCT image acquisition, 50 horizontal B-scans were obtained from a 30° x 20° or 30° x 25° macular area, depending on the patient. Each acquired B-scan was a composite of 50 B-scans averaged automatically by the device software. Subfoveal choroidal thickness was measured in the enhanced depth imaging mode of SD-OCT using the distance between the choriosclera border and the outer edge of the hyperreflective RPE at the fovea. Patients were classified as early, intermediate, or advanced AMD according to the multicenter Age-Related Eye Disease Study (AREDS) classification for AMD published in 2000.[8] Color fundus, red-free, SD-OCT, IR, FAF, BR, FFA, and ICGA images from each eye were independently assessed by two retina specialists and RPD was diagnosed if both specialists detected relevant findings by at least two of the methods.

RPD were identified as multiple yellowish-white reticular patterns on colored fundus images, and reticular pattern was identified as a bright interwoven network about 125-250 µm in width on red-free images. In addition, reticular lesions were identified as subretinal hyperreflective granular deposits on the RPE in at least one B-scan on SD-OCT, as hyporeflective lesions on a base of slightly increased hyperreflectivity in IR imaging, and as 5 or more small, hypoautofluorescent, round/oval lesions with indistinct margins surrounded by hyperautofluorescence on FAF imaging. RPD were identified as interwoven, hyperreflective lesions on BR imaging, as hypofluorescent dots appearing in the mid-late phase in ICGA, and as hypofluorescent dots in the early phase of FFA. In addition, RPD distribution in the macula was assessed by quadrant based on the Early Treatment Diabetic Retinopathy Study (ETDRS) grid. The ETDRS grid consists of 3 concentric circles 1, 3, and 6 mm in diameter, with the central 1-mm circle showing foveal thickness. The inner ring lying between the 1- and 3-mm circles and the outer ring between the 3- and 6-mm circles are divided into 4 sectors (inferior, superior, nasal, temporal). Finally, RPD were divided in three stages as described by Zweifel et al.[3]

Statistical Analysis

Chi-square, Shapiro-Wilk normality test, and Mann-Whitney U test were used for statistical analyses. The limit for statistical significance was set as $p<0.05$. All statistical analyses were performed with SPSS for Windows version 22 (IBM Corp., Armonk, NY, USA) software.

Results

The study was carried out on 396 eyes of 198 consecutive patients who met the inclusion criteria. The mean age was 72.0±7.74 years (range, 51-96 years); 102 (51.5%) patients were female and 96 (48.5%) were male. Mean BCVA was 0.46±0.56 logMAR (range, 0-3.10 logMAR). Mean subfoveal choroidal thickness was 203.5±75.31 µm (range, 45-436 µm).

Grading with the AREDS classification resulted in 145 eyes (36.6%) with early AMD, 86 eyes (21.7%) with intermediate AMD and 165 eyes (41.7%) with advanced AMD. The mean ages in these groups were 71.06±8.3, 71.59±7.2, and 73.04±7.3 years, respectively. There was no statistically significant difference when the stages were compared in terms of mean age.

Color fundus photography, red-free photography, SD-OCT, IR, FAF, BR, and FFA imaging had sensitivity values of 50%, 57.7%, 91.6%, 95%, 74.6%, 65.7%, and 28.2% and specificity values of 99.6%, 100%, 98.4%, 94.6%, 100%, 99.6%, and 69.8%, respectively, in the detection of RPD (Figure 1, Table 1). IR imaging had the highest sensitivity (95%), followed by SD-OCT (91.6%); however, specificity was higher in SD-OCT compared to IR imaging. Specificity was highest in red-free (100%), color fundus (99.6%), and BR imaging (99.6%), but their sensitivity was lower compared to IR, SD-OCT, and FAF. FFA had the lowest sensitivity and specificity.

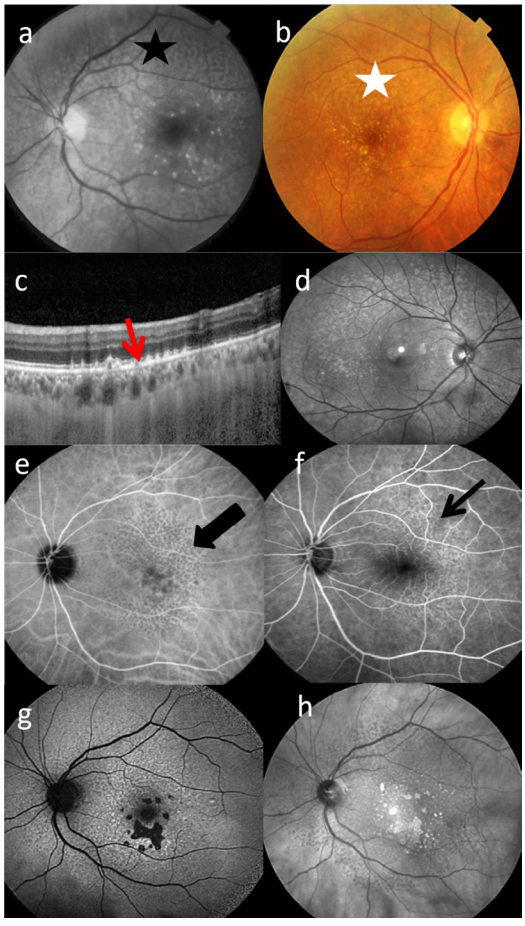

Figure 1. Appearance of reticular pseudodrusen on multimodal imaging. Appearance of the reticular pattern in red-free imaging (black star) (a) and color fundus photograph (white star) (b) Reticular pseudodrusen were identified as granular or triangular hyperreflective deposits located above the RPE in the subretinal space on SD-OCT imaging (red arrow) (c), a bright, interlacing network appearance on BR imaging (d), hypofluorescent dots on ICGA (bold black arrow) (e) and FFA (thin black arrow) (f), a grouping of hypofluorescent lesions with indistinct borders on a base of slightly increased autofluorescence on FAF imaging (g), and groups of hyporeflective lesions on a slightly hyperreflective background on IR imaging (h)

SD-OCT: Spectral domain optical coherence tomography, RPE: Retinal pigment epithelium, BR: Blue reflectance, ICGA: Indocyanine green angiography, FFA: Fundus fluorescein angiography, FAF: Fundus autofluorescence, IR: Infrared

Table 1. Sensitivity and specificity of imaging modalities in the detection of reticular pseudodrusen

Imaging method	Sensitivity (%)	Specificity (%)
Color fundus photography	50	99.6
Red-free photography	57.7	100
SD-OCT	91.6	98.4
Infrared imaging	95	94.6
FAF	74.6	100
BR imaging	65.7	99.6
FFA	28.2	69.8

SD-OCT: Spectral domain optical coherence tomography, FAF: Fundus autofluorescence, BR: Blue reflectance, FFA: Fundus fluorescein angiography

RPD were detected in at least two imaging methods in 149 (37.6%) of the eyes and were not detected in 247 eyes (62.4%). The prevalence of RPD detected in at least three imaging modalities was 30.5% (121 eyes). The mean age of patients with RPD was 73.98±7.33 years, which was significantly higher compared to the patients without RPD, whose mean age was 70.81±7.75 years (p<0.001). RPD were bilateral in 65 patients (77.4%) and unilateral in 19 patients (22.6%).

Forty-four (58.7%) of the patients with RPD were female and 31 (41.3%) were male. Statistical analysis showed RPD to be significantly more common among females. Of the patients without RPD, 58 were female and 65 were male. Statistical analysis revealed no significant sex difference between patients with and without RPD (p=0.038). Mean subfoveal choroid thickness was 167.94±62.7 µm in eyes with RPD and 224.83±74.3 µm among eyes without RPD. Eyes with RPD had significantly lower mean subfoveal choroidal thickness (p<0.001).

Mean BCVA was 0.42±0.49 logMAR in eyes with RPD and 0.48±0.6 logMAR in eyes without RPD. The difference in BCVA between eyes with and without RPD was not statistically significant (p=0.902).

One hundred eighteen eyes (29.8%) had neovascular AMD and 28 eyes (7.1%) had geographic atrophy. Of the 118 eyes with neovascular AMD, RPD was absent in 78 (66.1%) and present in 40 (33.9%). Of the 28 eyes with geographic atrophy, RPD was absent in 8 (28.6%) and present in 20 (71.4%). Among the 149 eyes with RPD, neovascular AMD (26.8%, 40 eyes) was significantly more common than geographic atrophy (13.4%, 20 eyes) (p<0.001). Of the 247 eyes without RPD, 97 had early AMD, 47 had intermediate AMD, and 103 had advanced AMD. Of the eyes with RPD, 48 had early AMD, 39 intermediate AMD and 62 advanced AMD. While RPD were more common in patients with advanced AMD, the difference did not reach statistical significance (p=0.178).

Analysis of the topographic distribution of macular RPD according to the ETDRS grid centered on the fovea showed that RPD was most common in the superior quadrant (100%), followed by the temporal quadrant (66%) (Figure 2). RPD were located nasal of the optic disc in 19.4% of eyes. In terms of area of distribution, RPD were located in at least 1 quadrant in 24

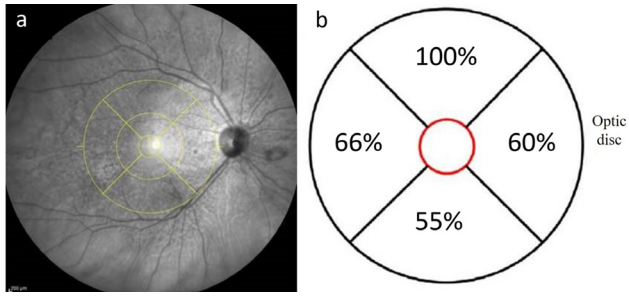

Figure 2. Illustration of the ETDRS grid used to determine the topographic distribution of RPD (a) and the prevalence of RPD in each quadrant (b)

ETDRS: Early Treatment Diabetic Retinopathy Study, RPD: Reticular pseudodrusen

eyes (17.6%), in at least 2 quadrants in 31 eyes (22.8%), in at least 3 quadrants in 32 eyes (23.5%), and in 4 quadrants in 49 eyes (39%). Progression of AMD stage was not associated with higher prevalence of RPD in the macula (p=0.779).

SD-OCT grading of RPD could not be done in 16 eyes because the RPD were located outside the OCT scanning area. Of the 133 eyes that had RPD in the macular area and could be staged, 77 (51.7%) did not exhibit stage 3 RPD, while 56 (37.6%) had stage 3 RPD in addition to stage 1 and stage 2 RPD. In other words, the "target" appearance corresponding to stage 3 was observed in 37.6% of the eyes. Presence of stage 3 RPD was not associated with more advanced AMD stage (p=0.058). ICGA was performed in 66 eyes of 33 patients. Of those 66 eyes, RPD were detected by other imaging modalities in 26 (39.4%) and ICGA was able to detect RPD in 25 eyes (96.2%).

Discussion

Although their clinical significance and pathophysiology are still not fully understood, RPD have been reported to be an early sign of the process leading to neovascular AMD and identified as a high-risk factor in many studies.[4,9,10,11,12] The incidence and prevalence of RPD vary in different studies based on AMD stage and the imaging modality used. Newer imaging modalities such as SD-OCT, IR imaging, FAF, and confocal scanning laser ophthalmoscopy have led to improvements in the diagnosis of RPD.[13] The higher sensitivity and specificity of some of these imaging methods have enabled a more accurate estimate of RPD prevalence based on multimodal imaging in more recent studies. Using blue fundus photography, IR, FAF, BR, ICGA, and SD-OCT, Ueda-Arakawa et al.[13] reported the prevalence of RPD as 20% in Japanese patients. Wilde et al.[14] determined a prevalence of 22.1% in their evaluation of 231 consecutive patients using OCT, color fundus photography, red-free photography, and FFA. Although Hogg et al.[10] concluded in 2014 that IR imaging was the modality that best visualizes RPD, this technique was not used in the study by Wilde et al.[14] In addition, it is reported that some patients may have had RPD prior to developing CNV, and that RPD regression or masking by hemorrhagic gliosis or fluid accumulation associated with CNV may result in a lower RPD detection rate. Ethnicity, sex, and age distribution may also play a role in the prevalence of RPD.[15] Using a wide variety of imaging techniques, we determined the prevalence of RPD to be 37.6% in our study. This high rate is also the result of using a wide SD-OCT scanning area as well as additional multimodal imaging techniques that display a larger area and allow the detection of RPD located outside the central macula. In a study conducted by De Bats et al.[16] using six imaging techniques, including color fundus photography, blue fundus photography, multicolor imaging, IR, FAF, and SD-OCT, RPD was detected in 149 eyes (61.3%) of 86 patients (68.8%). The high prevalence they reported compared to other studies may be attributed to the vast majority of their patients having late-stage AMD and the stronger association between RPD and advanced AMD.[16,17] The same group did not detect a statistical difference in RPD prevalence between the early and late stages of AMD. In our study, RPD were seen at every stage and were not statistically associated with a specific AREDS stage, which is consistent with previous studies.[18,19]

Significantly higher mean age and female preponderance were observed among the patients with RPD in our study. This is consistent with the literature. Lee et al.[15] found that the average age of those with RPD was significantly higher than that of patients without RPD. The same authors reported that the female sex predominated in the RPD patient group. Wilde et al.[14] reported in their study of 231 patients that RPD were more common in females, though they detected no age difference between those with and without RPD. While female sex is associated with a higher prevalence of systemic autoimmune inflammatory diseases, research is currently being conducted to determine whether there are inflammatory markers or pathogens associated with RPD. Although female sex and age were reported to be risk factors for RPD in various studies, other studies have not reported differences in age or sex between patients with and without RPD.[16,20]

Schmitz-Valckenberg et al.[21] reported that confocal scanning laser ophthalmoscopy imaging was superior to fundus photography for the detection of RPD and they recommended IR and FAF as optimal methods for the characterization of RPD. Ueda-Arakawa et al.[13] reported that color fundus photography, IR, FAF, near infrared-FAF, BR, ICGA, and SD-OCT had specificity of 100%, 91.8%, 95.0%, 95.3%, 100%, 100%, and 98.4% and sensitivity of 75.7%, 94.6%, 86.5%, 32.1%, 77.1%, 73.0%, and 94.6%, respectively, in the detection of RPD. In their study, SD-OCT was shown to have the highest sensitivity and specificity for detecting RPD. De Bats et al.[16] also reported that SD-OCT had the highest sensitivity and specificity in detecting RPD. In contrast, in a 2016 study by Gil et al.,[22] IR and FAF were the best imaging modalities for detecting RPD, followed by OCT. In the present study, eight imaging modalities (color fundus photography, red-free photography, BR imaging, IR imaging, FAF, SD-OCT, ICGA, and FFA) were used for a definitive RPD diagnosis. The sensitivity and specificity of ICGA could not be statistically evaluated because we were only able to perform ICGA on a small number of patients, as most of the patients could not purchase ICG stain. Therefore, sensitivity and specificity values were determined for seven imaging modalities. Sensitivity was highest in IR imaging (95%) and SD-OCT (91.6%), while SD-OCT had higher specificity compared to IR imaging. We found that FFA, red-free photography, and color fundus photography were inadequate for the detection of RPD. IR imaging was the most useful method for detecting RPD because it had the highest sensitivity and was less affected by media opacity, such as cataracts, than the other methods.[3] The sensitivity and specificity of SD-OCT were 91.6% and 98.4% in our study, which demonstrates the necessity of using this method when evaluating for RPD.

Because no imaging modality can detect RPD with 100% sensitivity, it is difficult to distinguish RPD from other changes

(soft/hard drusen) using a single imaging modality. Based on our study and others comparing different imaging techniques for visualizing RPD, it seems beneficial to use at least two imaging modalities to detect RPD and confirm the diagnosis, regardless of the techniques used.[13,16,23,24]

Several researchers have suggested a link between RPD and choroidal integrity. Switzer et al.[25] reported reduced subfoveal choroidal thickness in eyes with RPD. Although theories concerning the choroid vary greatly, they share choroidal thinning as an integral component in the appearance of RPD. In our study, subfoveal choroidal thickness was significantly lower in eyes with RPD. Querques et al.[26] found that the choroid was generally thinner in early AMD eyes with RPD compared to those without RPD. A hypothesis regarding the reduced subfoveal choroidal thickness in the presence of RPD and the choroidal etiology of RPD has not been fully clarified.[27] As RPD are associated with an increased risk of advanced AMD, choroidal thinning may be important to our understanding of the process underlying RPD and further research is needed on this topic.

While RPD are seen in every stage of AMD, neovascular AMD was more common than geographic atrophy among the eyes with RPD in our study. This may be related to the generally higher prevalence of CNV in cases of advanced AMD compared to geographic atrophy. The Beaver Dam Study found that eyes with RPD were at similar risk for both neovascular AMD (29%) and geographic atrophy (36%).[4] Smith et al.[23] also reported a high prevalence of both types of advanced AMD in patients with RPD. Although the relationship between RPD and late AMD is clear in the literature, the relative link between RPD and neovascular AMD and geographic atrophy remains uncertain. Lee et al.[15] detected bilateral RPD at a rate of 97.7%. This is higher than bilaterality rates reported in other studies, which range between 54.8% and 75.8%.[15,28] It was proposed that this finding was related to ethnic differences or the lower prevalence of neovascular AMD, which often causes RPD to disappear. In the present study, RPD were bilateral in 65 patients (77.4%) and unilateral in 19 patients (22.6%). Our bilaterality rate is also lower than that reported by Lee et al.,[15] which may be due to the higher prevalence of RPD among patients with neovascular AMD in our study.

In our analysis of the topographic distribution of macular RPD based on a fovea-centered ETDRS grid, RPD were most commonly found in the superior quadrant (100% of eyes), followed by the temporal quadrant (66% of eyes). There are a few other studies in which the topographic distribution of RPD has been analyzed using the ETDRS grid. In a study by Steinberg et al.,[29] RPD were found superior to the fovea in 100% of cases and nasal to the fovea in 81%. As confirmed by our results, RPD are most commonly located superior to the fovea.[4,26,30]

Conclusion

Considering the increasing importance of RPD, we investigated their prevalence in patients with AMD and determined the rate to be 37.6%. While IR imaging had the highest sensitivity of the 7 imaging modalities employed in our study, the combined use of SD-OCT and IR imaging may be beneficial in the detection of RPD. Due to the important prognostic information they provide, further research is needed regarding the detection and analysis of RPD.

Ethics

Ethics Committee Approval: The study was conducted in compliance with Declaration of Helsinki and was approved by the Ethics Committee of the Ege University Medical Faculty (decision no: 15-11.1/5, date: 18.12.2015).

Informed Consent: Obtained.

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Authorship Contributions

Surgical and Medical Practices: S.B.Ç., F.A., J.M., C.A., Concept: S.B.Ç., F.A., C.D., S.N., Design: S.B.Ç., F.A., Data Collection or Processing: S.B.Ç., C.D., Analysis or Interpretation: S.B.Ç., F.A., C.D., S.N., J.M., C.A., Literature Search: S.B.Ç., Writing: S.B.Ç., C.D.

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