Multidisciplinary Ophthalmic Imaging

Longitudinal Analysis of Reticular Drusen Associated With Geographic Atrophy in Age-Related Macular Degeneration

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See the appendix for the principal investigators in the Geographic Atrophy Progression (GAP) Study Group.

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Purpose. To characterize longitudinal changes of reticular drusen (RDR) in subjects with geographic atrophy (GA) secondary to age-related macular degeneration in the multicenter, prospective natural history Geographic Atrophy Progression Study.

Methods. Three-field confocal scanning laser opthalmoscopy fundus autofluorescence (cSLO FAF) excitation [exc.] = 488 nm; emission [em.] 500–800 nm, Heidelberg Retina Angiograph/Spectralis) of 44 eyes of 22 patients with RDR (median age 77.6 years; range, 61–90 years) at baseline were identified in the study population and included for further analysis. Two independent readers determined the presence, topographic distribution, and pattern of RDR at baseline and at 18 months. Furthermore, the convex hull of the extent of RDR as the minimum polygon encompassing the entire area of RDR involvement was quantified.

Results. RDR lesion boundaries were clearly detectable in all directions within three-field FAF composite images in 16 eyes of 10 patients at both baseline and final visits. Over time, RDR-affected retinal area and RDR density increased. Quantitative analysis showed a mean average RDR extent of 53.7 mm² (95% confidence interval [95% CI]; 40.7; 66.8) at baseline. The mean differences for intraobserver agreements were 2.4 mm² (95% CI; −0.1; 4.9) for reader 1 and −0.6 mm² (95% CI; −2.3; 1.1) for reader 2. The mean difference of interobserver agreement was 0.9 mm² (95% CI; −0.8; 2.7). A mean growth rate of the RDR extent within the three-field FAF composite image of 4.4 mm²/y (95% CI; 1.9; 6.9) was measured.

Conclusions. In vivo cSLO FAF imaging allows for both qualitative and quantitative mapping of longitudinal changes of RDR areas within a relatively short time period. Continuous enlargement of the affected retinal area indicates disease progression with regard to this phenotypic characteristic associated with GA in AMD. Systematic recordings of RDR progression appears warranted in future natural history and interventional studies in dry AMD. (ClinicalTrials.gov number, NCT00599846.)

Keywords: age-related macular degeneration, reticular drusen, fundus autofluorescence, scanning laser opthalmoscopy

AMD is a complex chronic, progressive disease with both genetic and environmental factors. It is the most common cause of legal blindness in industrialized countries. Genetic risk variants of the ARMS2 gene and polymorphisms in complement genes, including factor H, have been implicated with AMD.2–9

Drusen are a hallmark in the early and intermediate stages of the disease. On fundus biomicroscopy or fundus photography, drusen have been classified as hard, soft, cuticular (or basal laminar) or calcified drusen.10,11 More recently, reticular drusen (RDR), also called “reticular pseudodrusen,” have been implicated as associated with AMD.12–14 The term “reticular pseudodrusen visible en lumière bleue (the pseudo-drusen visible in blue light)” was introduced by Mimoun and colleagues in 1990.10 They initially described “retinal lesions with a variable diameter of approximately 100 microns that did not appear hyperfluorescent on fluorescein angiography.”10 In 1991, Klein et al. included reticular drusen in the Wisconsin age-related maculopathy grading system and specified them as “ill-defined networks of broad, interlacing ribbons.”11 Arnold and colleagues published an extensive study on the morphological appearance of reticular pseudodrusen in 1995.15 They reported “a yellowish interlacing network of oval shaped or roundish lesions with a diameter of approximately 125 to 250 microns, readily seen in red-free light or with the infrared wavelengths of the scanning laser ophthalmoscope.” Other studies, for instance the Beaver Dam Eye study, identified RDR as a risk factor for the development of late-stage AMD.16,17

Using fundus autofluorescence (FAF) imaging, several authors have reported that RDR correspond to multiple ill-defined areas of decreased fundus autofluorescence surrounded by areas with brighter intensities.18–20 This characteristic appearance is defined as the “reticular pattern” in the classification of fundus autofluorescence patterns in early age-related macular disease.20

The development of new imaging methods, such as confocal scanning laser ophthalmoscopy (cSLO) and spectral-domain optical coherence tomography (SD-OCT), has led to improvements in visualization of RDR. In this context, the analysis of the geographic atrophy study (GAP)-population (n = 458
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patients) revealed a high RDR prevalence of 62%, using cSLO imaging, as compared with a detection rate of 18% by fundus camera photography.12,14,21 The exact histopathological correlate of RDR remains unclear, and is a matter of debate. While some studies favor an origin within the choroid, other findings that are based on simultaneous SD-OCT and cSLO imaging suggest alterations at the level of the photoreceptors.22-25 Sarks et al. demonstrated in one clinicopathological examination that RDR might be located in the subretinal space on the internal surface of the RPE.24 Sohrab localized the reticular pattern of RDR to the intervascular choroidal stoma on SD-OCT scans.25 On the other hand, Spaide and colleagues showed on histological examination and SD-OCT scans, that RDR—also called subretinal drusenoid deposits—seems to be located above the RPE.22 Querques et al. demonstrated on follow-up SD-OCT scans the possible progression of individual RDR above the RPE.25

To the authors’ knowledge, until today most discussions deal with the question of the RDR location or RDR and SD-OCT changes at one point and over time; changes of the size of the area with RDR have not been systematically investigated yet. While it appears to be well conceivable that the RDR area enlarges over time, the rate of progression and the required time for observation to measure any sort of progression remains unclear. According to preliminary own observations, we felt that a clear enlargement of the RDR area could not be reliably assessed within 6 months. As previously reported, RDR detection and analysis required superior image quality. In this context, we felt that the analysis of the RDR involvement by en face imaging and its progression over time had to be based on a reliable dataset with a standardized and well-defined imaging protocol.

The purpose of this study was to record longitudinal structural changes and the extension rate of the area covered with RDR by cSLO FAF imaging in patients with geographic atrophy (GA) secondary to AMD.

METHODS

Study Population

Patients were recruited from the natural history of Geographic Atrophy Progression (GAP) study (www.clinicaltrials.gov, NCT00599846). This was a prospective, multicenter, non-interventional, observational study with no masking or randomization that was originally designed to quantify atrophic lesion growth in patients with GA secondary to AMD. It was an international study with clinical centers in the United States, Europe, Israel, and Australia. The study followed the tenets of the Declaration of Helsinki and was approved by the local ethics committees. Informed consent was obtained from each patient after explanation of the nature and possible consequences of the study. The primary and secondary study objects are not the aim of the current publication and will be reported elsewhere. Scheduled study visits were at baseline and every 6 months for up to 18 months. At each visit, all subjects underwent a complete ophthalmic examination including assessment of best-corrected visual acuity (BCVA) using Early Treatment Diabetic Retinopathy Study (ETDRS) charts and dilated fundus exam; retinal images were collected using cSLO imaging and fundus camera photography. Patient enrollment started in January 2008 and ended in August 2009. With the initiation of the Geographic Atrophy Treatment Evaluation (GATE) study in April 2009 in Europe, Israel, and Australia, patients were allowed to exit early from the GAP study and enroll in the GATE study, assuming that they met entry criteria. In December 2009, the GAP Study was finally terminated and the data file subsequently locked.

For inclusion, patients had to be aged 50 years with a well-demarcated area of GA secondary to AMD in the study eye. The total GA lesion size had to be ≤17.5 mm² (ca. 7 disc areas [DA]) with one single lesion of at least 1.25 mm² (0.5 DA). BCVA in the study eye had to be ≥55 letters. In the fellow eye, drusen ≥63 μm or GA had to be present. Patients were not eligible if any signs of choroidal neovascularization (CNV) were seen in either eye. The investigator at each participating clinical center initially determined eligibility and then imaging data were sent to the central reading center for analysis.

Imaging Protocol

Retinal imaging and data submission were performed according to standardized reading center operating procedures. These procedures included certification of each photographer prior to the initiation of the study at his/her clinical site. All patients underwent cSLO retinal imaging (Heidelberg Retina Angiograph, HRA classic, HRA2, or Spectralis; Heidelberg Engineering, Heidelberg, Germany) and included acquisition of near-infrared reflectance (IR 820 nm); blue reflectance (BR 488 nm [HRA2 and Spectralis] or 512 nm [HRA classic]); and FAF (excitation [exc.] 488 nm; emission [em.] 500–700 nm) using the high-speed mode. Images were recorded with a minimum resolution of 512 × 512 pixels. The field of view was set at 30° × 30° and centered on the macula. For the FAF modality, two additional fields were obtained, one temporal to the macula, the other one nasal to the macula with the temporal aspect of the optic disc in the center. cSLO images were separately uploaded by each clinical site through a secure website to an electronic database for immediate analysis at the reading center of predefined grading parameters. This grading did not include the qualitative and quantitative analysis of RDR for each imaging modality.

Procedures

For the current analysis of the natural history of RDR, the database of the GAP study was screened for patients that had a complete 18-month review period and who had RDR present at baseline by FAF imaging. Given that no change of RDR area involvement by en face imaging—at least to the best of our knowledge—has been available so far and also based on our own initial observations, that no clear change in the RDR pattern may be visible within 6 months, we aimed to include only GAP subjects with maximum available follow-up of 18 months. Secondly, we limited the quantitative analysis of RDR area involvement to FAF imaging because RDR area involvement typically exceeds the central macular field (30° × 30°, centered on the fovea). According to the standardized protocol of the GAP study (as mentioned above), only three-field imaging had been obtained for the FAF imaging, while all other modalities were limited to the central field, including near-infrared reflectance imaging.

Because of early termination of the GAP study (as mentioned above), only 42 of the 413 initially recruited subjects completed the study (while the remaining 371 patients had an early termination). The presence of RDR in the entire GAP study population has been reported previously following a two-independent reader system with senior arbitration in case of discrepancy.26 For FAF imaging, RDR had been found to be present in at least one eye in 56% of subjects. A similar RDR detection rate of 52% (22 subjects) was found in the selected 42 subjects with complete follow-up. These 22 subjects were included in the current analysis.
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This representative example for a right eye with GA secondary to AMD shows marked reticular drusen within the retinal FAF montage image that was calculated using the “compute composite” mode of the Heidelberg Eye Explorer (left). The RDR area was quantified using the CH (as shown by white color) that was defined as the minimum polygon encompassing the entire area with RDR (right). For illustration purposes, the white outline of the CH has been intensified.

To evaluate the topographic RDR extent for each eye with definitive RDR, a retinal FAF montage image was automatically compiled with the “compute composite” mode of the commercial software used (Heidelberg Eye Explorer; Heidelberg Engineering), which merged the three captured FAF fields. Retinal FAF montage images were exported as bitmaps and processed using image analysis software (Image); National Institutes of Health, Bethesda, MD). To enhance images, brightness and contrast were optimized by stretching the pixel histogram using the entire range of available pixel values (0–255). Image contrast was manually adjusted to enhance maximally RDR identification. In the following, two independent readers (JSS and JA) assessed the processed composite baseline and 18-month visit imaging data. A senior reader (SSV) arbitrated discrepancies. The RDR pattern and possible changes over time were qualitatively described. In addition, the visibility of the lesion boundaries in all directions was assessed. It has been previously reported that superior image quality is required for RDR detection. Uneven illumination of the image frame (that may be due to improper orientation of the camera during acquisition and/or limited pupil dilatation) or shading effects (that may be due to vitreous floaters or tear film artifacts) may allow for assessment of the pure presence of RDR in at least some part of the image, but may lead to the inability to grade for RDR presence in other parts of the image. As a proper evaluation of the RDR area involvement is not possible in this scenario, these eyes were excluded from the following quantitative analysis. To determine the RDR area, the convex RDR hull (CH) was outlined using the polygon tool at both the baseline and the 18-month visits (Fig. 1). The images were processed by the two independent readers in a random order. For the assessment of intrarater variability, all images were evaluated again after 2 weeks. The CH was defined as the minimum convex polygon (no corner had an angle over 180°) encompassing the entire RDR area. If RDR boundaries were not visible in at least one quadrant (i.e., inadequate image quality due to uneven illumination of the scan field), no quantitative analysis was performed. If the RDR boundaries were found to be at any part at the edge of the FAF composite image, the convex hull was drawn at the border of the image. While it cannot be ruled out in this latter scenario—that the RDR area involvement extended partly beyond the image frames—the convex hull area and its progression rate must be regarded as the minimum RDR polygon extent and its enlargement rate over time. Finally, the CH area of all eyes with clearly delineable borders within the three-field FAF composite was quantified using the CH (as shown by white color) that was defined as the minimum polygon encompassing the entire area with RDR (right). For illustration purposes, the white outline of the CH has been intensified.

FIGURE 1. Number and percentage of eyes with detectable RDR, and clearly defined RDR extent.

The median age of the included 22 subjects of the GAP study with complete follow-up of 18 months and visible RDR in at least one eye at baseline was 77.6 years (range, 61–90 years). There were 7 men and 15 women. Among these 44 eyes, the distribution of FAF patterns according to the previously reported classification system of abnormal FAF patterns in the junctional zone of GA in patients with AMD was as follows: none, n = 1; focal, n = 1; banded, n = 1; diffuse, n = 36; patchy, n = 3; not determinable, n = 2.57 Due to shading effects or uneven illumination, 28 eyes were excluded from the quantitative analysis. In the remaining 16 eyes of 10 subjects (median age 78.8 years; range, 71–90 years), the extent of RDR area involvement within the three-field FAF composite was delineable both at the baseline and at the month 18 visit (Fig. 2). In 11 of these 16 eyes, RDR lesions were partly in contact with the image borders.

Qualitative Analysis

RDR were detected in five eyes within the three-field composite FAF image (i.e., without any contact to the image borders) at the baseline and at the follow-up examination (Fig. 3A). In four of the remaining 11 eyes, the complete border of the RDR area was only entirely visible at baseline, whereas in follow-up images, the RDR involvement exceeded the image frames particularly superior and temporal to the foveal center. In the other seven eyes, RDR involvement exceeded the image frames at both the baseline and at the follow-up examination (Fig. 3B). In accordance with previous reports, the diameter of single RDR lesions was being confirmed to vary in between 50 to 400 μm by random measurements of several lesions, while no systematic quantification of all visible individual RDR

RESULTS

Measured data were manually transferred to a computer database (Excel; Microsoft Corporation, Redmond, WA). Pixel area values were converted to square millimeters for each eye by using the scale factor given by the commercial software (Heidelberg Eye Explorer; Heidelberg Engineering) used. This factor is based on a Gullstrand model eye assuming standard corneal radii and taking into account the individual spherical refraction as adjusted by the operator during acquisition. The CH RDR area at the baseline visit RDR was subtracted from the month 18 visit CD RDR area (assuming a linear growth rate) to calculate the RDR area progression rate over time per year.

Bland-Altman statistics and Wilcoxon analysis were used to assess both intra- and interrater reliability.

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lesions was performed.\textsuperscript{10,15} By appearance and qualitative assessment of the readers, the individual RDR size and the number per area declined with increasing eccentricity (Fig. 4).

Within the observation period, the retinal area involved by RDR, and the RDR density increased. In some eyes, single RDR coalesced in the central macula and there was an associated laminar, mottled decreased FAF signal (Fig. 4). As previously described, RDR were most commonly seen superior and temporal to the foveal center and also often nasal to the optic disc. When RDR were located nasal to the disc, the area adjacent to the optic nerve head was relatively devoid of RDR. Just above and below the optic disc at the vascular arcade origin, few RDR lesions were found, while their number increased toward more nasal retinal areas (Fig. 3B).

**Quantitative Analysis**

At baseline, the average RDR extent by three-field FAF composite imaging was 53.7 mm\textsuperscript{2} (95% confidence interval [95% CI; 40.7--66.8]). For reader 1, the average RDR extent was 51.9 mm\textsuperscript{2} (95% CI; 39.7--64.3); and for reader 2, it was 55.6 mm\textsuperscript{2} (95% CI; 42.0--69.3). The mean baseline differences for intraobserver agreement were 2.4 mm\textsuperscript{2} (95% CI; −0.1--4.9) for reader 1 and −0.6 mm\textsuperscript{2} (95% CI; −2.3--1.1) for reader 2. The mean interobserver agreement difference was 0.9 mm\textsuperscript{2} (95% CI; −0.8--2.7). The RDR area at baseline did not differ significantly between eyes ($P = 0.137$).

An RDR mean growth rate of 4.4 ± 5.1 mm\textsuperscript{2}/y (95% CI; 1.9--6.9, min −0.8, max 17.7) was measured within the three-field FAF composite montage. For reader 1, the mean growth rate was 3.3 mm\textsuperscript{2}/y (95% CI; 0.8--5.8); and for reader 2, it was 5.6 mm\textsuperscript{2}/y (95% CI; 2.9--8.4). The mean intraobserver agreement differences of the growth rate were −0.7 mm\textsuperscript{2}/y (95% CI; −2.8--1.2) for reader 1 and 0.9 mm\textsuperscript{2}/y (95% CI; −0.6--2.4) for reader 2. The mean interobserver agreement difference was 0.1 mm/ y$^2$ (95% CI; −1.0--1.2; Fig. 5). When one includes only the 5 eyes with delineable RDR boundaries that had no contact to the composite image borders at both visits, the mean RDR extent at baseline was 25.1 mm\textsuperscript{2} (95% CI; 13.2--36.9) and the average progression rate was 2.7 mm\textsuperscript{2}/y (95% CI; −1.2--6.6).

The RDR area progression rate did not differ significantly between eyes ($P = 0.197$). When one considers all eyes with manifest GA at baseline (total atrophy size of at least 1.25 mm\textsuperscript{2}), the GA progression rate in eyes without RDR averaged
1.9 mm²/y (95% CI; 1.6–2.4) and was not statistically significant compared to eyes with RDR, which had an average progression rate of 1.5 mm²/y (95% CI; 1.1–2.0; \( P = 0.112 \)). In the latter group, there was a statistically significant correlation between GA progression (mean 1.5 mm²/y) and RDR area progression (mean 4.4 mm²/y) (Fig. 6) (\( P = 0.011 \)).

**DISCUSSION**

This study demonstrates both qualitative and quantitative changes of the RDR pattern over time using cSLO FAF imaging. These observations are compatible with an underlying dynamic process that accompanies disease progression. Furthermore, the findings of decreased density and reduced size of individual RDR lesions with increasing eccentricity suggest a centrifugal spread of RDR from the posterior pole. Quantification of the RDR extent within an 18-month period can be used to estimate long-term progression rates and help in the design of future studies.

To detect subtle changes in RDR extent and density, sufficient image quality obtained with rigorous imaging protocols are necessary. Furthermore, when individual lesions become confluent over time, described in this study as a mottled RDR pattern, it may be more difficult to identify RDR in eyes with an advanced RDR phenotype. Of note, only a limited number of eyes could be included in this study and the RDR boundaries exceeded the image frames in several subjects. However, to the best of our knowledge, this is the first study demonstrating progressive changes of RDR extension over time using retinal in vivo imaging. Querques et al. showed longitudinal changes of RDR in SD-OCT images. In would be interesting to assess RDR evolution with combined cSLO and SD-OCT imaging in a future study.

Because most RDR extent exceeded the image border in most eyes, the actual RDR progression rate might be even higher than that measured in this study. It remains unclear if and how far outside three-field composite images individual RDR lesions may be present. The visualization of more peripheral retinal areas is challenging using current imaging technology, at least at high-resolution and in a standardized fashion that would be mandatory for RDR analysis. Of note, averaging of several frames to a mean FAF or IR image is required for accurate RDR area visualization, while single SLO images or fundus camera photography is inferior in terms of RDR detection. The use of the convex hull to determine the extent of RDR involvement and its progression over time is only an estimation for the actual involvement. It is obvious that the definition of the exact border of the RDR area that is composed of single subtle lesions is challenging. The strategy to apply the convex hull in the study was chosen merely because of practical considerations and with regard to previous investigations that have reliably analyzed ill-defined lesion boundaries in retinal imaging using this approach. It would be conceivable that the “bulges” above and below the optic disc may add to the inaccuracy of the convex hull for the analysis of RDR area involvement. Overall, we believe that exact determination of the RDR area involvement remains challenging. Improvements in retinal imaging technology along with the development of image analysis software algorithms would be beneficial in the future.

**Figure 4.** Shows a highly-magnified cutout of an FAF image temporal superior to the fovea at the border of the RDR area in a right eye of a patient with GA. Toward the fovea (right-lower corner), single RDR lesions appear to coalesce and are associated with a laminar, mottled decreased FAF signal. Furthermore, it appears that toward the edge of the involved RDR area (upper-left corner), the size of single RDR lesions is smaller and that their density (distance to each other or number of individual RDR per involved retinal area) is greater.

**Figure 5.** Demonstrates the Bland-Altman plot for reader 1, reader 2, and the interrater measurements for the area with reticular drusen at baseline (left) as well as the progression over time (right).
that was conducted without extra funding by the sponsor. The manuscript was approved by the sponsor.

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The results show that RDR are dynamic structures undergoing changes over time. As the extension of the area with RDR seems to be higher than the GA rate, there might be a different disease mechanism involved. The more rapid progression of RDR affected area as compared with atrophic lesion enlargement may indicate that RDR lesions are not a direct precursor of atrophy development. Further studies with a larger GA cohort are required to evaluate if the analysis of RDR growth patterns may be helpful to predict rates of future atrophy progression. One wonders whether the enlargement of existing atrophy or the development of new atrophic satellites is spatially confined to retinal areas that have been previously affected by RDR. Interestingly, it has been reported that both RDR lesions and GA presence are more prevalent in the superior macula.26,29–30 However, a prospective longitudinal study will be required to establish a direct association. We observed, to the best of our knowledge for the first time, a relative sparing of RDR above and below the optic nerve head when RDR were localized nasal to the optic disc. A possible explanation for this observation may be a challenging detection of RDR lesions at the side of concomitant large retinal vessels or that these large vessels may be protective for the development of RDR lesions.

The main limitation of the study is the relatively small number of eyes examined longitudinally. In addition, the dataset is based on a natural history on GA. Therefore, we cannot exclude any possible differences in the RDR progression between different AMD phenotypes. Expanded natural history studies are needed to validate the findings herein. Previously, we have reported that both cSLO FAF and IR imaging are most sensitive for RDR detection, particularly compared with standard fundus photography.12,14 Notably, in order to include peripheral areas in the analysis, the quantification of RDR area involvement was limited on three-field FAF imaging in this study as only central images of other modalities were available. Furthermore, the approach of using the convex hull obviously represents an estimation of the area involvement of RDR. We have initiated development of retinal imaging processing software that may allow automated detection of RDR which may be helpful in this respect.

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**APPENDIX**

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