Predictive Value of Outer Retina En Face OCT Imaging for Geographic Atrophy Progression

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Purpose. We determined if the ellipsoid zone (EZ) disruption pattern could be predictive of the geographic atrophy (GA) pattern at 1 year in dry age-related macular degeneration (AMD).

Methods. A retrospective study was done of dry eyes in patients with AMD and GA from July to November 2013. Eyes with previous choroidal neovascularization were excluded. Based on spectral domain optical coherence tomography (SD-OCT), the GA was assessed at each timepoint, using a sub-RPE slab derived from the Cirrus Advanced RPE Analysis software encompassing the RPE (sub-RPE slab). Disruption of the EZ also was assessed at baseline, using en face extraction of a 20-µm-thick slab, 20 µm above the RPE (EZ slab) encompassing the EZ band using two different algorithms (RPE and RPE-fit). The EZ disruption area surrounding GA at baseline was quantified using ImageJ software. Primary endpoint was to identify en face pattern similarities between the baseline EZ disruption and the 1-year GA. Secondary endpoint was to correlate the baseline EZ disruption area surrounding GA with the GA enlargement over 1 year. Statistical analysis was performed using a correlation test (Pearson) and a *t*-test.

Results. We included 37 eyes of 31 patients with dry AMD. En face EZ disruption pattern correlated in two-thirds of cases with the 1-year GA pattern using both algorithms. The EZ disruption area surrounding GA at baseline and GA enlargement over 1 year were poorly correlated when RPE-fit algorithm ($R = 0.17$) was used. The correlation was still poor using an RPE algorithm ($R = 0.38$), but increased after selection of eyes without reticular pseudodrusen ($R = 0.79$).

Conclusions. The EZ disruption pattern could be an indicator for GA pattern progression, but is not a good quantitative tool to predict the size of GA in the overall population over a 1-year period except for patients without reticular pseudodrusen. The results in this specific population must be confirmed by further studies.

Keywords: age-related macular degeneration, en face optical coherence tomography, geographic atrophy

Geographic atrophy (GA) is a significant cause of progressive visual impairment defined by the progressive loss of the RPE. Unfortunately, no reliable method can predict an area in the macula where GA is likely to appear or GA growth over 1 year once it has appeared.

Whether GA results from an initial abnormality of the photoreceptors, RPE, or choriocapillaris remains unknown. Fundus autofluorescence (FAF) imaging has identified different hyperautofluorescence patterns[1] of the RPE, which have been associated with different growth characteristics of the GA, incriminating an RPE dysfunction before RPE atrophy. An electrophysiologic dysfunction of the photoreceptors has been detected away from the GA edge, which suggests that photoreceptor abnormalities could occur before GA appearance.[2] In addition to electroretinographic abnormalities around GA, microperimetric,[3,4] dark adaptation,[5] and low luminance abnormalities also have been detected.[6–8]

However, despite all these findings, the mechanisms of GA appearance and progression remain unclear and there currently is no good reliable test to predict the exact GA pattern and enlargement rate (ER) over 1 year.

The aim of this study was to determine if the ellipsoid zone (EZ) disruption pattern could be predictive of the GA pattern at 1 year in dry age-related macular degeneration (AMD).

Methods

All patients who underwent a clinical examination for dry AMD from July to November 2013 in a referral retinal practice in Paris (France) were included retrospectively. This clinical

examination was called T+1. All corresponding patients were seen once a year for a clinical examination in the private practice. Data from the examination performed 1 year earlier between June and December 2012 were collected, and corresponded to T0. All patients underwent macular optical coherence tomography (OCT) scans with en face analysis, and had a follow-up longer than 1 year. This study was conducted in accordance with the tenets of the Declaration of Helsinki, and an informed consent was obtained from subjects. Approval was obtained from the France Macula Federation ethical committee.

Inclusion criteria were patients with dry AMD with unifocal or multifocal GA, and a follow-up $\geq$1 year. Both eyes of the same patient could be included. Exclusion criteria were all eyes with any sign or previous history of choroidal neovascularization or eyes with confusing retinal conditions, such as retinal detachment, severe nonproliferative diabetic retinopathy, retinal vascular occlusion, macular edema, evidence of inherited retinal degeneration, or a history of pars plana vitrectomy.

All patients underwent a complete ophthalmologic examination including best-corrected visual acuity (BCVA), slit-lamp, and noncontact fundus examination (Superfield; Volk Optical, Inc., Mentor, OH, USA). Fundus autofluorescence, fluorescein angiography (Topcon TRC-50DX Retinal Camera; Topcon Medical Systems, Inc., Tokyo, Japan), and OCT (macular cube) were performed at baseline. Geographic atrophy was diagnosed based on color fundus imaging, FAF, fluorescein angiogram, and OCT. Based on these examinations and patient age, one of the six retina specialists in the retinal clinical practice made the diagnosis of GA secondary to AMD. Lesions totally contained within the scan area only were included.

Spectral domain-OCT (SD-OCT) was performed using the Cirrus HD-OCT instrument (Cirrus 2; Carl Zeiss Meditec, Inc., Dublin, CA, USA). Each eye was imaged using a 200 $\times$ 200-raster scan pattern. Eye tracking was not used for acquisition. For each patient, based on SD-OCT, the GA was assessed at each timepoint, using a sub-RPE slab derived from the Cirrus Advanced RPE Analysis software (sub-RPE slab). Ellipsoid zone disruption, but not all the area affected (Fig. 1), also was assessed at baseline, using en face extraction of a 20-μm-thick slab, 20 μm above the RPE (EZ slab) using two algorithms (RPE as previously described[9] and RPE-fit).

We created and used a visual analogic scale (VAS) as a measurement tool for assessing and comparing baseline EZ disruption area pattern on the EZ slab, and GA area pattern on the sub-RPE slab at 1 year. A score of 0 was assigned when there was no similarity at all between both patterns (progression of atrophy in a location without any baseline EZ disruption), 1 when both patterns showed a few similarities (fragmented progression of atrophy only in one location with baseline EZ disruption), 2 when the patterns were highly but not completely similar (all the atrophy that developed over the year was contained in the baseline EZ disruption), and 3 when the patterns were strictly superimposable (the whole baseline EZ disruption had progressed toward atrophy). Two independent retina physicians (SYC, AGA) scored all the images and when there was no consensus, one of the investigators (FF) adjudicated the disagreement.

We carefully reviewed all the acquisitions and distinguished patients for whom the growth of atrophy over the 1-year period was completely present within the margins of the baseline EZ disruption and patients for whom GA grew outside of the margins of the baseline EZ disruption. We also calculated the total surface covered by GA on the baseline EZ disruption slab. Calculation was done for baseline and 1-year GA. Furthermore, we quantified the percentage of border of GA consisting of an EZ disruption, and we classified patients depending on whether the percentage of the border of GA consisting of an EZ disruption zone was lower than 25%, between 25 and 50%, between 50 and 75%, or higher than 75%. We also determined how far from the edge of GA, EZ typically extended and if patches of EZ disruption arose de novo, not connected to the existing GA.

Using Adobe Photoshop CS2 image analysis software (Adobe Photoshop CS2, San Jose, CA, USA), we superimposed the GA area selected on the sub-RPE slab at baseline on the EZ slab as described previously[9] (Fig. 1). Limits of the EZ disruption area on the EZ slab surrounding GA at baseline (with both algorithms, RPE and RPE-fit) and GA area on the sub-RPE slab at each timepoint were delimited by one of the clinicians (AGA), and quantified with ImageJ software (http://imagej.nih.gov/ij/; provided in the public domain by the National Institutes of Health, Bethesda, MD, USA) using the same pixel scale for all pictures. These measurements were possible because the size of the en face OCT extractions obtained was the same for all patients (6 $\times$ 6 mm). In all cases, the GA was contained in the 6 $\times$ 6 scan area at baseline and at 1 year of follow-up. We determined surfaces in pixels and converted them into square millimeters (mm^2). The enlargement rate of GA was determined as the difference in the square root GA area measurements between baseline and 1 year, and expressed in mm per year. Finally, we selected, using multimodal imaging, the cases without reticular pseudodrusen, for subanalysis. Two clinicians selected patients without reticular pseudodrusen, and when there was no consensus, one of the investigators (SYC) adjudicated the disagreement.

For FAF, the GA areas were measured after one of the clinicians (AGA) had delimited manually the surface to be quantified using the LediOPH 2k2 image processing system (Lheritier, Cergy-pontoise, France).

The primary endpoint was to determine pattern similarities between the baseline EZ and the 1-year GA. The secondary endpoint was to correlate the GA enlargement over 1 year on en face OCT images with the EZ disruption surface surrounding GA at baseline. Statistical analysis was performed using a correlation test (Pearson), and a *t*-test with GraphPad software (GraphPad Software, Inc., La Jolla, CA, USA). A P value <0.05 was considered statistically significant.

Results

We included 37 eyes of 31 patients (5 men and 26 women; mean age, 84.9 years) with GA due to dry AMD. All patients had GA at baseline. The mean interval between each visit was of 12.85 months. The BCVA was 64.5 (20/50) $\pm$ 17 letters at baseline and 58.8 (20/63) $\pm$ 18 letters at 1 year. Among the 37 cases, GA involved the fovea in 14 cases (37.8%) at baseline and in 17 cases (45.9%) at 1 year.

To determine if the baseline EZ disruption surface surrounding GA progressed toward GA after 1 year, the baseline EZ disruption pattern surface was compared to the 1-year GA pattern. Two independent physicians (SYC, AGA) examined the patterns. A VAS was used and 70% of complete correlation was found between both physicians; in the remaining 30% of cases we used the adjudication of a third investigator (FF). The en face EZ disruption pattern correlated in two-thirds of cases (64.86%) with the 1-year GA pattern: completely in 24.32% of cases, and partially in 40.54% of cases. Visual analogic scale results used to compare the baseline EZ disruption with the 1-year GA are shown in the Table.

We distinguished patients for whom the growth of atrophy over the 1-year period was completely present within the margins of the baseline EZ disruption (this was the case in 28 of 37 eyes or 75.7%), and patients for whom GA grew outside

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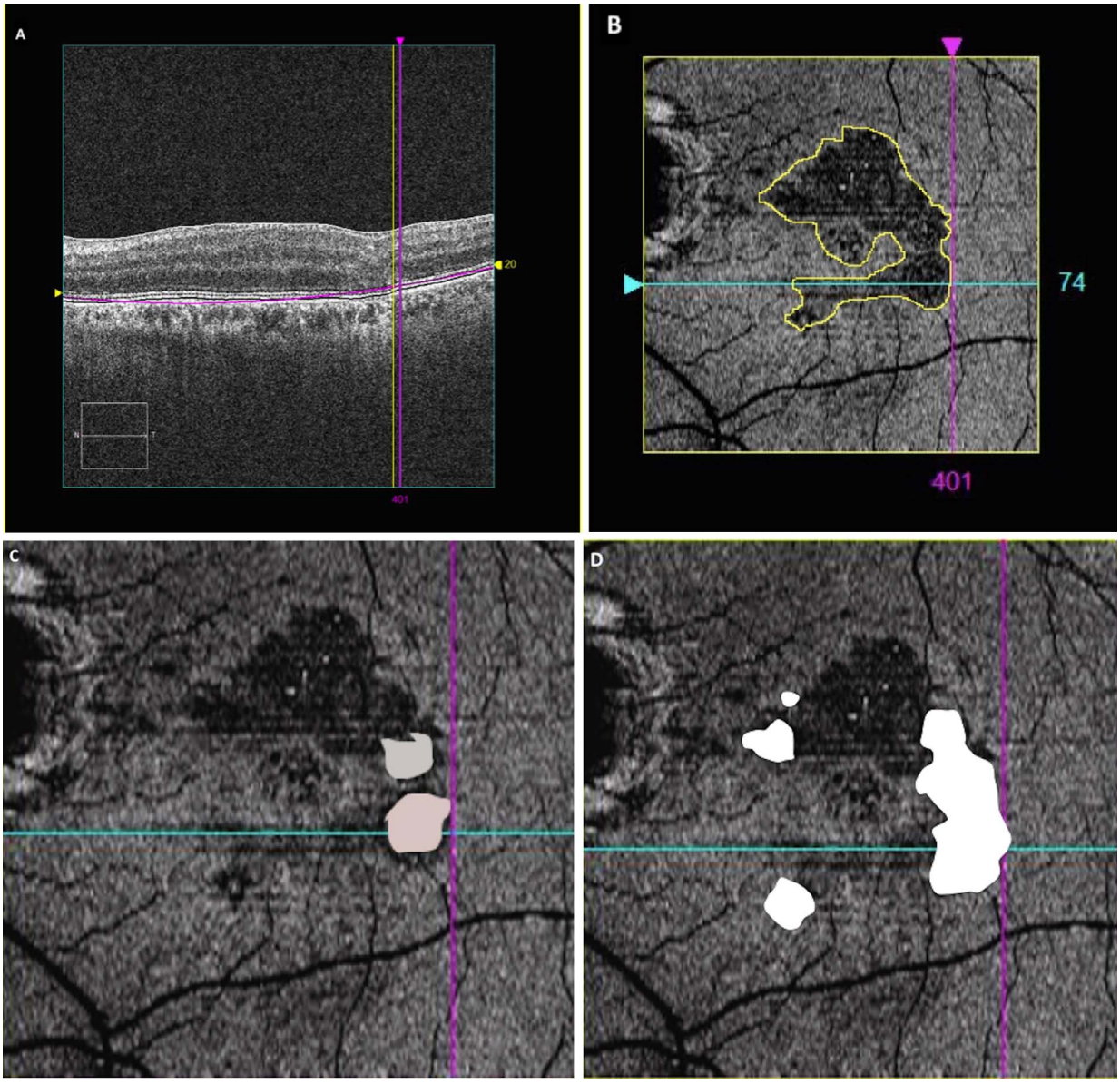

FIGURE 1. Correlation between individual B-scan and pattern observed on the en face EZ slab at baseline. (**A**) B-scan of a patient from the cohort. The RPE disruption on the B-scan is marked by a *yellow vertical line* and that of the EZ line by a *purple vertical line*. The two *solid black lines* are encompassing the RPE, one below and one above. *Black dotted lines* represent the 20-μm area above the RPE and a 20-μm-thick slab from which the EZ slab is taken using the RPE algorithm. The *purple horizontal line* shows RPE using the RPE-fit algorithm. (**B**) En face EZ slab at baseline. The EZ disruption on the B-scan (*purple vertical line*) shown in (**A**) corresponds to the boundary of the *black area* on the en face image derived from the EZ slab (intersection of *purple* and *blue lines*). The B-scan (**A**) was taken out along the *blue horizontal line* of (**B**), and the *vertical purple line* is at the same position in (**A**, **B**), allowing us to locate the B-scan in the retina. In (**B**), the *blue* and *purple lines* were manually moved to be located at the edges of the EZ disruption in *black*. The *yellow line* surrounds the EZ disruption surface. (**C**) En face EZ slab at baseline, with the baseline GA superimposed in *white*. (**D**) En face EZ slab at baseline, with the 1-year GA superimposed in *white*. Note that GA grew, at 1 year, within the area of the baseline EZ disruption. The visual analogic scale score in this patient was 1. Baseline and 1-year GA areas were, respectively, 0.84 and 1.41 mm and the size of the baseline EZ disruption was 2.17 mm.

of the margins of the baseline EZ disruption (9 eyes or 24.3%). We also calculated the total surface covered by the GA on the baseline EZ disruption slab and found that GA covered 54.8% of the total surface at baseline and 71.6% at 1 year. The average percentage of border of GA consisting of an EZ disruption was 63.6%. The percentage of border of GA consisting of an EZ disruption was lower than 25% in 7 of 37 eyes (18.9%), between 25% and 50% in 4 (10.8%), between 50% and 75% in 8 (21.6%), and higher than 75% in 18 (48.7%). The mean maximal distance of EZ extension from the border of GA was 0.9 ± 0.44 mm (minimum-maximum, 0.03–2.1), and the mean minimal distance was 0.03 ± 0.04 mm (minimum-maximum, 0–0.18) and there was no patch of EZ disruption arose de novo, not connected to the existing GA.

A quantitative study of the relationship between the baseline EZ disruption surface size surrounding GA area and the GA enlargement over 1 year was done by looking for a correlation using a Pearson correlation test with RPE and RPE-fit algorithms.

The mean square root of the GA area was 2.48 ± 0.74 mm at baseline (T0; minimum-maximum, 0.32–3.86), and 2.86 ± 0.65 mm at T+1 (minimum-maximum, 1.09–4.02). The mean

Table. En Face Pattern Similarities Between Baseline EZ Disruption and 1-Year GA

Score of Visual Analogic Scale	% of Patients
0	5.4
1	29.79
2	40.54
3	24.32

A visual analogic scale was created and used as a measurement tool for assessing and comparing the hyporeflective area pattern on the EZ slab (EZ disruption) and the hyperreflective area pattern on the sub-RPE slab (GA). The baseline EZ disruption shape and pattern were compared to the 1-year GA pattern. A score of 0 was assigned when there was no similarity at all between both patterns (progression of atrophy in a location without any baseline EZ disruption), 1 when both patterns showed a few similarities (fragmented progression of atrophy only in one location with baseline EZ disruption), 2 when the patterns were highly but not completely similar (all the atrophy that developed over the year was contained in the baseline EZ disruption), and 3 when the patterns were strictly superimposable (the whole baseline EZ disruption had progressed toward atrophy). Two independent retina specialists (SYC, AGA) analyzed images.

enlargement rate of GA was 0.38 ± 0.17 mm per year (minimum-maximum, 0.05–1.39). At baseline, the total EZ disruption surface was systematically larger than the GA surface. The Pearson coefficient between the EZ disruption surrounding GA at baseline and the GA enlargement area over 1 year was 0.17 with the RPE-fit algorithm.

When we used the RPE algorithm, the Pearson correlation coefficient between the baseline EZ disruption area surrounding GA and the percentage of baseline EZ disruption surface covered by 1 year GA was $R = -0.65$ ($P < 0.01$). The Pearson coefficient between the EZ disruption surrounding GA at baseline and the GA enlargement area over 1 year was $R = 0.38$ ($P < 0.05$, Fig. 2). Without the higher enlargement rates (3 eyes) of the series that clearly forced the curve, this latter correlation became $R = 0.1$ ($P > 0.05$).

In cases without reticular pseudodrusen (19 of 37 eyes), the Pearson coefficient remained statistically significant between the baseline EZ disruption area surrounding GA and the percentage of baseline EZ disruption surface covered by 1-year

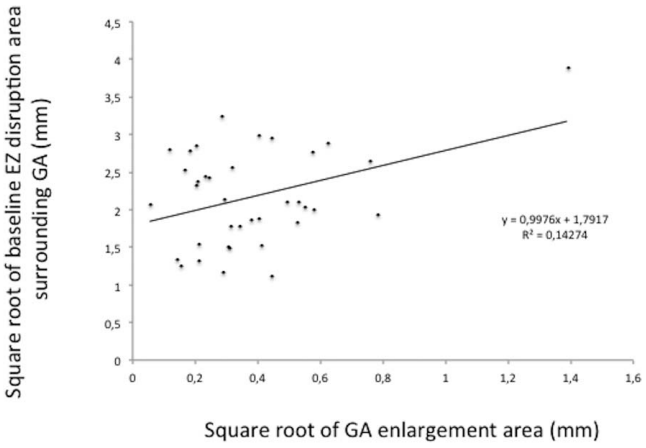

Figure 2. Correlation between the GA enlargement rate over 1 year and the baseline EZ disrupted surface alone surrounding GA area (RPE algorithm) considering the square roots areas. A significant linear correlation was found with a Pearson coefficient $R = 0.38$ ($P < 0.01$). The *line* is clearly forced by the three outliers with higher enlargement rates. When we withdrew them the coefficient became $R = 0.1$ ($P > 0.05$).

Figure 3. Correlation between the GA enlargement over 1 year and the baseline EZ disrupted surface alone surrounding GA area (RPE algorithm) in patients without reticular pseudodrusen considering the square roots areas $R = 0.79$ ($P < 0.01$).

GA ($R = -0.47$, $P < 0.01$). The Pearson coefficient between the EZ disruption surrounding GA at baseline and the GA enlargement area over 1 year was $R = 0.63$, $P < 0.01$ (Fig. 3) and higher when considering the square root area $R = 0.79$ ($P < 0.01$). Without the higher enlargement rate (1 eye) of the series that clearly forced the curve, this latter correlation became $R = 0.69$ ($P < 0.01$).

Fundus autofluorescence confirmed the diagnosis of GA (RPE atrophy) in all cases, and the GA pattern on FAF was systematically comparable to the GA pattern on the en face sub-RPE slab. To confirm this finding, the correlation between the baseline GA surface area measured on FAF images and that measured on the sub-RPE slab was studied and was strongly significant with a Pearson correlation coefficient of 0.9 ($P < 0.0001$, Fig. 4). There was no statistical difference between both GA measurement methods ($P = 0.09$).

Discussion

In this study, we compared the baseline EZ disruption surface pattern with the 1-year GA surface in dry AMD and found a correlation in two-thirds of cases. These results are consistent

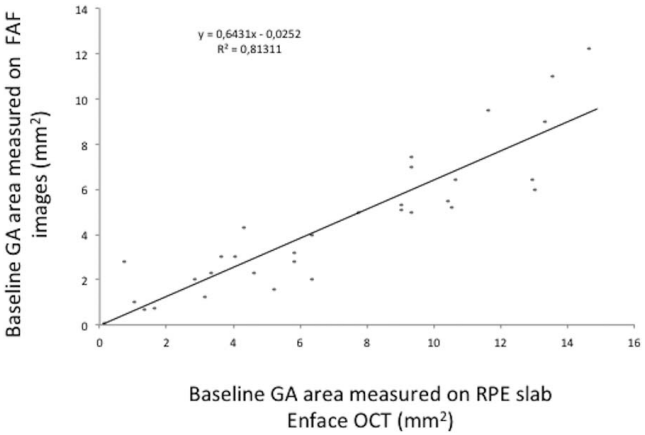

Figure 4. Correlation between the baseline GA size measured manually on en face RPE extraction with ImageJ software and the baseline GA size measured manually with Ledioph 2k2 image processing system on Topcon FAF images. A linear correlation was found between these values with a Pearson coefficient $R = 0.9$ ($P < 0.0001$).

with those found by Nunes et al.,[9] who have shown that en face SD-OCT imaging of the IS/OS region revealed a bilaterally symmetrical pattern of the outer retinal disruption extending beyond the GA edges, which accurately predicted GA progression over 1 year in 13 of 30 eyes (43.3%). The appearance of the EZ disruption area before the onset of the GA (RPE atrophy) suggests that photoreceptors could be impaired before the onset of the RPE atrophy and that the EZ disruption area could progress toward RPE atrophy after 1 year. Moreover, in our study, the baseline total EZ disruption surface was systematically larger than the GA surface at baseline, which also could suggest that a photoreceptor dysfunction could occur before RPE atrophy. Nunes et al.[9] already have described the existence of outer retinal damages in area without geographic atrophy, but we described here precisely for the first time to our knowledge the characteristics of these outer retinal damages as they appeared in en face OCT. We assessed the percentage of patients for whom the growth of atrophy over the 1-year period was completely present within the margins of the baseline EZ disruption, and patients for whom GA grew outside of the margins of the baseline EZ disruption. We also described the total surface covered by GA on the baseline EZ disruption slab, the percentage of the border of GA consisting of EZ disruption, of how far from the existing GA does EZ disruption typically extend, and also whether patches of EZ disruption arise de novo not connected to the existing GA.

Moreover, we also provided a quantitative analysis of the relationship between size of the baseline EZ disruption surrounding GA and the growth of GA over 1 year. For this purpose, the surface sizes were studied and a weak linear correlation was found between the GA enlargement rate over 1 year and the EZ disruption surface surrounding GA at baseline using the RPE-fit algorithm. The correlation was slightly higher using the RPE algorithm, as shown by Nunes et al.[9] Because reticular pseudodrusen may induce a diffuse pattern on the EZ slab as previously suggested,[9] we assessed the correlation between the GA enlargement rate and the baseline EZ disruption only in cases without reticular pseudodrusen, and the correlation increased significantly when considering the square root of the area ($R = 0.79$, $P < 0.01$).

In this study, the enlargement rate of the GA over 1 year and the EZ disruption surface surrounding the GA area at baseline were not strongly correlated when considering the area measured in square millimeters. One explanation could be that the choice of a 1-year follow-up interval was arbitrary. A longer follow-up may be needed to assess the variability of GA progression rates that should be taken into account to evaluate the relevance of the en face EZ disruption surface size to predict GA progression. We considered the square root areas to reduce the variability of GA progression rates, but the correlations still were weak except for cases without pseudodrusen when using the RPE algorithm. Our quantitative analysis does not seem very accurate to predict GA enlargement over a 1-year follow-up period, probably because the progression rate is patient-dependent. Moreover, a small change in settings (slab height, contrast) for EZ slab selection, or the presence of eye-tracking, can completely change the en face image. The RPE algorithm seems to be much more appropriate to assess GA progression. To date, two methods can be used to quantify GA, FAF, and en face sub-RPE slab OCT that recently has been found as precise as fundus images[10] and comparable.[11] We used the latter method, which was more convenient for quantification. To validate this method, we compared the values found for GA quantification using FAF to those found using en face OCT on the sub-RPE slab, and a highly significant linear correlation was found, suggesting that both methods can be used. There was no statistical difference between both types of measurement, but the area measured on the RPE slab was systematically larger than that measured on FAF. This could be due to the different software used for quantification (ImageJ for OCT and Liedioph for FAF), but also to the large number of multifocal atrophy patterns that can multiply the small errors in measurements, and at last to the difficulties in identifying the boundaries of GA, in particular in the vicinity of the fovea and in the presence of cataract. This was particularly the case on FAF images, although the same clinician (AGA) was assigned to delineate the edges of atrophy in both cases.

In conclusion, the en face EZ disruption pattern could be useful to assess the future pattern of GA progression in two-thirds of cases, but is not a good quantitative tool to predict the size of atrophy in the overall GA population over a 1-year period except probably for patients without reticular pseudodrusen. The results in this specific population need further studies to be confirmed. The morphologic characteristics of the EZ disruption that we described could be helpful in the assessment of en face OCT in the evaluation of GA progression, especially in an era when retina specialists attempt to identify surrogate endpoints for clinical analysis and assessment of new therapeutics since the BCVA does not correlate well with GA progression.

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