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Percentage of Foveal vs Total Macular Geographic Atrophy as a Predictor of Visual Acuity in Age-Related Macular Degeneration

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Abstract

Purpose: This article investigates the relationship between visual acuity (VA), total area of geographic atrophy (GA), and percentage of foveal GA.

Methods: A multicenter, retrospective, cross-sectional study was conducted of patients with GA due to age-related macular degeneration. Demographics, VA, fundus autofluorescence (FAF), and spectral-domain optical coherence tomography (SD-OCT) images were collected. Using FAF images aided by SD-OCT, fovea-sparing status, GA pattern, total GA size, and percentage of GA covering the foveal area—within a 1.5-mm-diameter circle centered on the fovea centralis—were assessed. Univariable and multiple linear regression analyses were performed.

Results: Fifty-four eyes (mean age, **78.7** ±**7.7** years [SD], 60.0% female) were studied. Mean VA was 0.8 ± 0.6 logarithm of the minimum angle of resolution (Snellen equivalent 20/126 ± 20/80), mean total GA 8.8 ± 6.7 mm^2, and mean percentage of foveal GA was 71.5 ± 30.9%. Of all assessed eyes, 48.2% (n = 26) presented with multifocal GA, and 18.5% (n =10) had foveal sparing. Multiple regression analysis revealed that, controlling for age and GA pattern, the percentage of foveal GA presented a statistically significant association with VA (ß =0.41, P = .

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The research protocol was conducted in accordance with Health Insurance Portability and Accountability Act requirements and the tenets of the Declaration of Helsinki. The institutional review boards of Massachusetts Eye and Ear and Coimbra University Hospital approved this study.

Statement of Informed Consent
Informed consent was obtained when required.

004). No significant associations were observed with mean total GA size, while controlling for the same variables (ß=0.010, P = .440).

Conclusions: Percentage of foveal GA was significantly associated with VA impairment, although the same was not verified for total GA area. These findings suggest that percentage of foveal GA may represent a more useful tool for assessing the impact of GA on VA. Further validation is needed in larger cohorts.

Keywords

dry AMD (nonneovascular); fovea; fundus autofluorescence; geographic atrophy; imaging; macula; OCT

Introduction

Age-related macular degeneration (AMD) is the leading cause of visual disability in elderly patients in industrialized countries.[1] Geographic atrophy (GA) represents the late stage of dry AMD, and it is characterized by the irreversible loss of macular retinal tissue, retinal pigment epithelium (RPE), and choriocapillaris.[2] Although this process is a slowly progressing one, it causes decreases in central vision over time,[3] which rapidly accelerate when GA covers the foveal center.

GA is responsible for severe vision loss in approximately 20% of all patients with AMD, and more than 8 million people are affected worldwide.[2,4] For not-well-understood reasons, atrophic macular diseases such as GA due to dry AMD can spare the foveal center until late in the disease course, and this so-called *foveal sparing* has been reported in about 20% of representative GA populations enrolled in clinical trials.[5]

Color fundus photography, fundus autofluorescence (FAF), and optical coherence tomography (OCT) imaging can be used to identify and follow GA lesions. However, FAF is considered by most to be the imaging of choice that allows a sharp discrimination of a lesion's boundaries. This is primarily because FAF provides a good visualization of the high contrast between atrophic (hypofluorescent) and normal areas.[4,6] On OCT, GA is typically characterized by thinning of the hyperreflective external bands due to attenuation/loss of the photoreceptors, ellipsoid zone, and RPE/Bruch complex, as well as deeper hyperreflectivity in the sub-RPE layers due to increased laser light penetration through the atrophic RPE.[2]

The total area of GA lesions is often used as an indicator of severity in late-stage dry AMD. However, this measure does not readily predict residual visual acuity (VA) nor VA decline rates.[7] Fovea-sparing status has been shown to correlate better with VA than total GA size; nevertheless, its binary nature prevents it from being used to quantify the relationship between the continuous shrinking of the spared foveal area and the worsening of VA over time.[8]

To explore more sensitive anatomical predictors of VA in GA, we defined and analyzed the percentage of foveal GA and its association with VA. This approach may lead to more accurate outcome measures for clinical trials as well as for patient counseling.

Methods

Study Design

This is a multicenter, retrospective cross-sectional study. The research protocol was conducted in accordance with Health Insurance Portability and Accountability Act (HIPAA) requirements and the tenets of the Declaration of Helsinki. The institutional review boards of Massachusetts Eye and Ear and of Coimbra University Hospital approved this study. Informed consent was obtained when required.

Study Population and Study Protocol

We identified and reviewed the medical records and images of eyes with GA. We adopted the most recent Age-Related Eye Disease Study (AREDS) definitions,[9] namely that GA is present if the lesion has a diameter of 433 μm or more (AREDS circle I-2) and has at least 2 of the following features: absence of RPE pigment, circular shape, or sharp margins.

Individuals from 2 centers were considered. At Massachusetts Eye and Ear, we identified patients seen between September 2011 and June 2017 as part of the AMD biomarkers study and from the attending clinic (DV).[10] We also considered individuals from Portugal participating in the AMD biomarkers study developed by the faculty of medicine, University of Coimbra, in collaboration with the Association for Innovation and Biomedical Research on Light and Image and the Centro Hospitalar e Universitário de Coimbra, Portugal.

For all considered participants, exclusion criteria included GA with choroidal neovascular membranes; diagnosis of any other vitreoretinal disease, active uveitis, or ocular infection; significant media opacities that precluded observation of the ocular fundus; refractive error equal to or greater than 6 diopters of spherical equivalent; history of any ocular surgery or intraocular procedure such as laser or intravitreal injections within 90 days prior to enrollment; and diagnosis of diabetes mellitus. Additionally, only eyes with FAF as well as OCT images according to a predefined protocol, available on at least one visit, were considered for this study. For FAF, we considered eyes with high-resolution 30° FAF, centered on the fovea. For OCT, we used high-resolution 30° spectral domain-optical coherence tomography (SD-OCT).

For the final included eyes, we reviewed medical records and collected the following information: age, sex, smoking status, AREDS supplementation, and Snellen VA at the same date as the considered images.

Imaging Analysis

We reviewed FAF and SD-OCT images of the eyes considered for this study. The foveal area was defined by a 1.5-mm-diameter circle, centered on the fovea centralis with the Heidelberg built-in circle tool (Heidelberg Engineering, GmbH). For determining the fovea centralis, SD-OCT cross-sectional images combined with the corresponding infrared images were used in parallel with the FAF images to help determine the location of the umbo/fovea centralis and the GA areas, and the pointer tool was used to mark points on the infrared image for the fovea centralis.

Using the Heidelberg built-in free-hand draw tool that automatically computes the enclosed area in square millimeters (mm^2), 2 masked graders (S.B. and R.S.) independently measured the GA lesion within the foveal area of 1.77 mm^2 ($A=\pi r^2 = \pi(1.5\ mm/2)^2 = 1.77\ mm^2$), and calculated its value in percentage of the total foveal area (Figure 1). The total macular GA area was measured by the same graders. For marking of the GA areas, the pointer tool was used to mark points on the lesion borders for which SD-OCT cross-sectional scans showed loss of the RPE and ellipsoid zone. This was then transferred to the corresponding FAF image, which was subsequently connected via the free-hand draw tool in a multimodal approach.[11] For analysis, average values of the 2 graders were used, except when values disagreed by more than 10%, in which case a third grader (I.L.) was used for adjudication. We graded for fovea-sparing status and GA pattern (focal or multifocal) in addition to collecting demographic information on age, sex, study eye, smoking status, and AREDS supplementation.

Statistical and Data Analysis

Traditional descriptive methods such as mean and SD for continuous variables, and percentages for dichotomous/categorical variables, were used to describe the clinical and demographic characteristics of the study population.

Regarding the inclusion of 2 eyes of the same patient for some cases, our statistical assessments were performed using multilevel mixed-effect models. By definition, these models are appropriate for research designs in which data for participants are organized at more than one level (ie, nested data). In this study, the units of analysis were considered the eyes (at a lower level), which are nested within patients who represent the contextual/aggregate units (at a higher level).[12]

Univariate analyses were initially performed for all the potential confounders such as age and GA pattern, and all variables with a P value less than or equal to .250 were included in the initial multiple model. A backward elimination procedure was then performed to achieve the multivariable models presented for the variables that were statistically significant in the univariate analysis.

For univariate and multivariable analyses, we report P values and beta coefficients. The beta coefficients represent the change in the outcome variable for one unit of change in the predictor variable (while holding other predictors in the model constant, in the case of multivariable analyses).[13] This means, for example, given a continuous variable such as age, beta coefficients represent the change in VA per year increase in age. For binomial variables, such as smoking, AREDS supplementation, or foveal sparing, their absence was considered the reference term, so beta coefficients refer to the change in their presence. The reference term for the study eye was the right eye; for GA pattern, unifocal GA; and for sex, female sex.

All statistics were performed using Stata version 14.1 (StataCorp LP) and P values less than .05 were considered statistically significant.

Results

Study Population

We included 54 eyes from 35 patients (mean age, 78.7 ± 7.7 years, 60.0% female [n = 21]) with GA due to nonneovascular AMD. Mean VA was 0.81 (Snellen equivalent, 20/129) ± 0.63 (range, 0–2.60) logarithm of the minimum angle of resolution, mean total GA 8.79 ± 6.66 mm^2 (range, 0.84–25.36 mm^2), mean percentage of foveal GA was 71.53 ± 30.94% (range, 0%−100%). A total of 48.15% (n = 26) of assessed eyes presented with multifocal GA, and 18.52% (n = 10) had foveal sparing (see demographics in Table 1).

In all eyes, SD-OCT images allowed a clear identification of the umbo/fovea centralis as well as the GA lesion borders. Figure 1 presents an example of measurement of percentage of foveal GA.

The results of the univariate analysis considering all variables of interest and their association with VA are shown in Table 2.

Percentage of Foveal GA

The mean percentage of foveal GA was statistically significantly associated with VA in univariate analysis (ß = 0.01, P < .001) (Table 2). This association remained significant on multivariable analysis, controlling for age and GA pattern (ß = 0.41, P = .004).

Total Macular GA

Univariate or multivariable analysis for total macular GA revealed there were no statistically significant associations with VA (ß= 0.02, P = .054, for univariate), (ß = 0.010, P = .440 for multivariable).

GA Pattern and Foveal Sparing

GA pattern presented a statistically significant association with VA (ß = −0.507187 9, P = .001) and so did foveal sparing (ß=−0.539212 7, P = .009).

Conclusions

We present a retrospective, cross-sectional study of 54 eyes diagnosed with GA due to nonneovascular AMD in which we used FAF and SD-OCT to examine the association of percentage of foveal GA and total macular GA lesion size with VA. Our results revealed that, after accounting for potential confounders such as age and GA pattern, the percentage of foveal GA was significantly associated with VA, although the same was not observed for total GA lesion size.

In GA clinical studies, the most common outcome measures for GA are changes in total GA, changes in square-root GA, or other phenotypic refinements.[14,15] As our results show, total GA poorly correlates with VA, and potentially with patients' overall quality of life. This finding is in agreement with previously published literature, which showed no relationship of total GA size with VA and has been investigated by multiple groups.[8,16]

Efforts have been made to study the association between VA and the distance between the edges of GA and the fovea,[16,17] or to examine residual visual function in the presence of fovea-sparing lesions.[16–19] Fovea-sparing status has been shown to have a stronger correlation with VA than total GA size; however, it does not quantify the extent to which the foveal area is affected nor the worsening of VA over time since it measures only presence or absence of GA in the anatomic foveola centralis.[8,16,17] A recent investigation of the associations of VA with total GA size as well as fovea-sparing status in 65 eyes found no relationship between VA and total GA size as well as foveal island size.[20] The same group also evaluated the width of the bridge—defined as the minimal linear dimension of intact RPE located within the residual foveal island— and found only a suggestion of a positive relationship in the range of 300 to 550 μm of bridge width and no relationship at all outside this range, leading to the conclusion that this measurement might not be an ideal outcome parameter for GA clinical trials.

Our study results suggest that using the percentage of foveal GA is potentially a more sensitive outcome parameter for association with VA. Our study is limited, however, by its modest size and retrospective design. As such, our results should be validated in larger, more representative populations before changes in percentage of foveal GA can be used more widely in clinical trials or clinical practice. Further studies should examine more precise evaluation of affected areas as well as evaluate the progression rate of percentage of foveal GA over time and examine predictive ability of such a tool on future VA changes.

In conclusion, here we propose for the first time the use of percentage of foveal GA as a possible predictor of VA in GA. Our data suggest such a measure may have a stronger association with VA impairment than total GA size. Therefore, with future research, it might represent a better tool to measure VA decline over time compared with fovea-sparing status. Nonetheless, VA has limitations as a tool to assess visual function in patients with GA, and other outcomes may be better suited.[21]

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Declaration of Conflicting Interests

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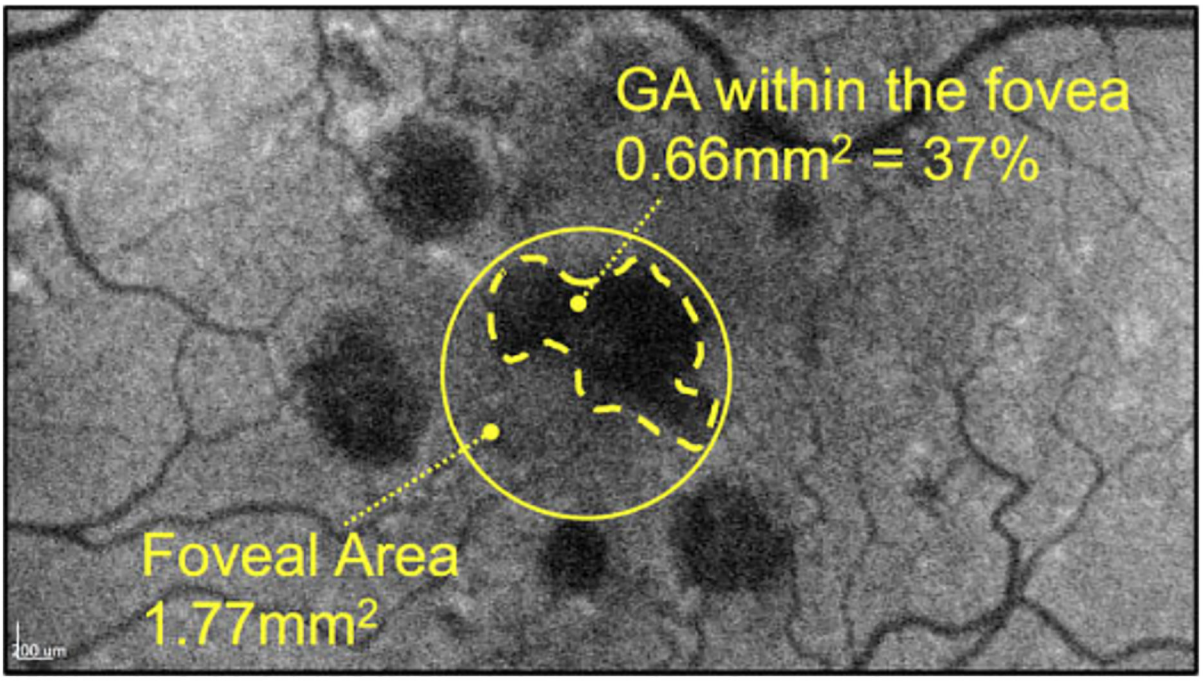

Figure 1.

Illustration of calculation of percentage of foveal geographic atrophy (GA). A 1.5-mm-diameter circle centered on the fovea centralis was determined with the use of optical coherence tomography cross-sectional and infrared images (see Methods). The outline of the GA within the foveal area was performed by 2 independent graders using the Heidelberg built-in free-hand draw tool (Heidelberg Engineering, GmbH), which automatically computes the enclosed area in square millimeters, and the percentage was calculated after division by the area defined by the standard foveal area of 1.5 mm diameter.

Table 1.

Demographic and Clinical Characteristics of the Included Study Eyes.

Age at date of imaging, y (n = 54)	
Mean ± SD (range)	78.7 ± 7.7 y (62–96 y)
Sex (n = 35)	
Female	21 (60.0%)
Male	14 (40.0%)
Smoking (n = 30)	
No	27 (90.0%)
Yes	3 (10.0%)
AREDS (n = 38)	
No	14 (36.8%)
Yes	24 (63.2%)
Study eye (n = 54)	
OD	29 (53.7%)
OS	25 (46.3%)
GA pattern (n = 54)	
Unifocal	28 (51.9%)
Multifocal	26 (48.2%)
Foveal sparing (n = 54)	
No	44 (81.5%)
Yes	10 (18.5%)
VA in logMAR (n = 54)	
Mean ± SD (range)	0.8 ± 0.6 (0–2.6)

Abbreviations: AREDS, Age-Related Eye Disease Study; GA, geographic atrophy; logMAR, logarithm of the minimum angle of resolution; OD, right eye; OS, left eye; VA, visual acuity.

Table 2.

Univariable Linear Regression Analysis Considering VA as the Outcome.

	β	*P*	95% CI
Age, y	0.017	.113	−0.00409, 0.038529
Sex[a]	−0.285	.097	−0.621 5504, 0.051 2273
Study eye[b]	−0.226	.178	−0.554347 1, −0.102 713
Smoking[c]	−0.319	.398	−1.058263, 0.420522 6
AREDS[c]	−0.412	.051	−0.826 5572, −0.001 8414
GA pattern[d]	−0.507	.001*	−0.811 8193, −0.202 5564
Foveal sparing[c]	−0.539	.009*	−0.944041 5, −0.134 384
Total GA (mm^2)	0.024	.054	−0.0004198, 0.048712
Foveal GA (mm^2)	0.536	<.001*	−0.262 5702, 0.8104187
% of foveal GA	0.010	<.001*	0.0049928, 0.0149448

Abbreviations: AREDS, Age-Related Eye Disease Study; GA, geographic atrophy; VA, visual acuity.

*P <.05.

[a]Female sex considered the reference term.

[b]Right eye considered the reference term.

[c]Reference term considered the absence of these variables.

[d]Unifocal GA considered the reference term.