ORIGINAL ARTICLE

Evaluation of Geographic Atrophy Progression Secondary to Age-related Macular Degeneration Using a Medical Image Processing Software

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ABSTRACT

Introduction: Age-related macular degeneration (AMD) is a multifactorial disease and a major cause of blindness worldwide. Although choroidal neovascularization causes severe acute visual loss in AMD, around 20% of AMD patients who are legally blind have lost central vision due to geographic atrophy (GA). GA pathophysiology and natural history of lesion progression remain unclear. In previous studies, mean lesion progression rates vary widely between individuals. Moreover, different clinical characteristics, namely, history of smoking, hypertension, diabetes, the size of the lesion, its topography, fundus autofluorescence (FAF)-specific lesion AF pattern, and number of lesions have been associated with progression rate. ImageJ software is a straightforward open tool for the analysis of scientific images. Spectral-domain optical coherence tomography (SD-OCT) image processing with ImageJ has been extensively published in the literature. The primary objective of this study was to evaluate GA progression (GAP) rate in SD-OCT using ImageJ processing functions. The secondary objective is to evaluate the progression rate among different GA clinical characteristics. **Methods:** This was a retrospective observational study of patients with GA secondary to AMD. ImageJ v. 1.51 allowed planimetric measurements of areas in SD-OCT and evaluation of lesion progression. Stata software v. 13.1 was used to analyze data. The primary study end point was mean enlargement rate of the atrophic lesion. Secondary and additional end points included assessment of GA lesion size in different disease subgroups as determined by AF pattern (diffuse, banded, focal, and unspecific) and mean change from baseline best-corrected visual acuity (BCVA). **Results:** A total of 40 eyes from 23 patients (mean age 77.9 ± 7.8 years) were included in the study. The difference between BCVA at baseline and at the end of follow-up was statistically significant with $P \leq 0.03$ (mean difference −0.162 ± 0.052; 95% CI 0.057–0.268). Lesion progression rate was 0.558 mm^2/year (±0.944; minimum: 0.0134; maximum: 6.801). Progression rate according to FAF pattern was as follows: Diffuse 0.434 (±0.401; $n = 17$), banded 1.254 (±2.008; $n = 7$), focal 0.407 (±0.707; $n = 6$), and unspecific 0.154 (±0.162; $n = 5$). **Conclusions:** FAF pattern could be a useful predictor of GAP. The banded pattern appears to be associated with a rapid progression. Our methodology using ImageJ is simple and appears to be effective in calculating GA lesion progression rates, and it could be used in different clinical settings and optimize scientific reading center approaches when testing future GA treatment strategies.

Key words: Age-related macular degeneration, geographic atrophy, image processing software, spectral-domain optical coherence tomography

INTRODUCTION

Age-related macular degeneration (AMD) is a multifactorial disease and a major cause of blindness worldwide.[1]

Although choroidal neovascularization (CNV) causes severe acute visual loss in AMD, around 20% of AMD patients who are legally blind have lost central vision due to geographic atrophy (GA).[2]

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GA is a progressive form of dry AMD characterized by permanent loss of retinal photoreceptors, retinal pigment epithelium (RPE), and choriocapillaris.[3]

GA pathophysiology and natural history of lesion progression remain unclear. In previous studies, mean lesion progression rates vary widely between individuals, ranging from 0.38 to 2.8 mm^2 per year.[4] Moreover, different clinical characteristics, namely, history of smoking, hypertension, diabetes, hyperlipidemia, family history, the size of the lesion, its topography, fundus autofluorescence (FAF)-specific lesion AF pattern, and number of lesions have been associated with progression rate.[5]

Recognition and monitoring of GA can be attained with different imaging modalities, including color fundus photography, fluorescein angiography (FA), FAF, near-infrared reflectance, spectral-domain optical coherence tomography (SD-OCT), and more recently optical coherence tomography angiography.[6,7]

Previous studies confirmed SD-OCT feasibility in monitoring GA and determining lesion size progression.[8]

ImageJ software is a straightforward open tool for the analysis of scientific images. SD-OCT image processing with ImageJ has been extensively published in the literature and applied by the authors in different clinical settings.[3,9]

The primary objective of this study is to evaluate GA progression (GAP) rate in SD-OCT using ImageJ processing functions. The secondary objective is to evaluate the progression rate among different GA clinical characteristics. We expect that results from this study provide insights into the natural history of GA and potential identification of relevant clinical features.

METHODS

This was a retrospective observational study of patients from one institution (Department of Ophthalmology, Egas Moniz Hospital, CHLO, Lisbon, Portugal).

The study protocol and procedures followed the tenets of the Declaration of Helsinki.

Inclusion/exclusion criteria

Patients with GA secondary to AMD were included in this study. Patients had to be at least 55 years old. Eyes had to have a GA lesion of at least 1.25 mm^2, evidenced in SD-OCT and FAF using Spectralis HRA+OCT™ (Heidelberg Engineering, Heidelberg, Germany). No signs of early or late CNV could be detectable by SD-OCT, neither signs or history of any other ocular diseases that might confound assessment of the retina.

Parameters and measurements by SD-OCT using ImageJ

ImageJ v. 1.51 (U. S. National Institutes of Health, Bethesda, Maryland, USA, https://imagej.nih.gov/ij/, 1997-2016) allowed planimetric measurements of areas in SD-OCT volume stacks and evaluation of lesion progression [Figure 1].

Lesion progression rate was calculated by dividing the difference between the baseline exam and the follow-up acquisition by the interval of time in months. This value was multiplied by 12 to achieve the annual lesion progression rate.

$$Lesion\ progression\ rate = \frac{Lesion\ area - Lesion\ area\ at\ baseline}{Time\ span\ in\ months} \times 12$$

Lesion progression rates, as determined on SD-OCT images, were calculated and then stratified by lesion subtype according to specific lesion AF, according to the GAP study [Figure 2].[10]

Statistical analysis

The primary study end point was the mean enlargement rate of the atrophic lesion, from baseline as assessed by SD-OCT, using the previously described methodology.

Secondary and additional end points included assessment of GA lesion size in different disease subgroups as determined

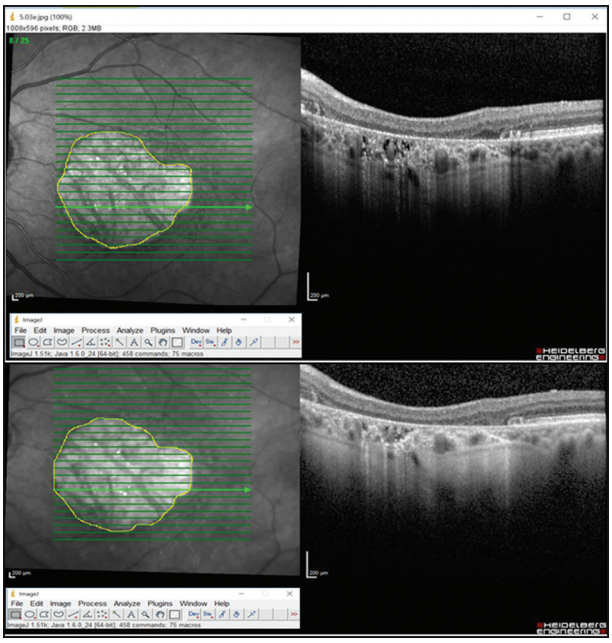

Figure 1: ImageJ printout exemplifying this study methodology. These spectral-domain optical coherence tomography images were acquired 13 months apart. Note the yellow line delimitating the AG lesion, allowing precise area and progression rate calculations

by FAF and mean change from baseline best-corrected visual acuity (BCVA).

Stata software (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC) was used to analyze the data. Participant demographics and baseline characteristics, as well as lesion progression, were summarized with descriptive statistics (n, mean, standard deviation, median, minimum, and maximum).

RESULTS

A total of 48 eyes from 24 patients were analyzed. Eight eyes were excluded from the study, 4 due to the presence of signs indicative of neovascular AMD during the follow-up, 3 due to epiretinal membrane features on SD-OCT, and 1 eye with no evidence of GA.

Descriptive and clinical data for the eyes of the included subjects are summarized in Table 1.

The difference between BCVA at baseline and at the end of follow-up was statistically significant with $P \leq 0.03$ (mean difference −0.162 ± 0.052; 95% CI 0.057–0.268). Of eyes with gradable imaging available, 97.9% had bilateral atrophic lesions.

Lesion progression rate was 0.558 mm^2/year (±0.944; minimum: 0.0134; maximum: 6.801). Table 2 displays the progression rate according to specific FAF characteristics.

DISCUSSION

Unlike active neovascular AMD, there is no effective treatment available for GA, other than visual aids and low vision rehabilitation.[11] Thus, a better understanding of the pathogenesis of GA is imperative.

Postmortem observations have shown that clinical visible areas of GA correspond to areas of RPE and photoreceptor loss and choriocapillaris closure.[12,13]

Consequently, the absence of RPE lipofuscin, containing the dominant fluorophores involved in the FAF signal, determines a markedly reduced AF signal at the site of atrophic lesions.[14]

A striking finding of FAF imaging in GA eyes is the common identification of high-intensity levels of AF at the junctional zone of atrophy.[15] This observation is in accordance with histological studies displaying enlarged lipofuscin-engorged RPE cells surrounding areas of atrophy.[16]

This was the rationale for targeting the detrimental accumulation of lipofuscin in the RPE using visual cycle modulators, namely fenretinide (N-[4-hydroxyphenyl] retinamide). A Phase II multicenter, randomized, double-masked, placebo-controlled study of the safety and efficacy of fenretinide in the treatment of GA displayed reduced lesion growth rates with both 100 mg and 300 mg daily oral fenretinide.[17]

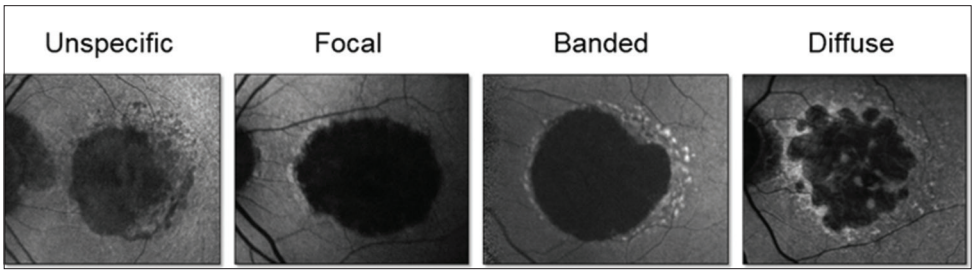

Figure 2: Representative examples from the current study of the four major fundus autofluorescence patterns, according to the geographic atrophy progression study

Table 1: Descriptive and clinical data of the subjects

Subject characteristics	
Number of eyes (subjects)	40 (23)
Age (years)	77.9 (±7.8); minimum: 59; maximum: 91
Sex (men/women)	10/13
Refractive error subjects (myopic/hyperopic)*	8/11
IOP (mmHg)	16.51 (±2.24); minimum: 11; maximum: 20
BCVA (Snellen)	0.322 (±0.244); minimum: 0.05; maximum: 1.0

*Subjects were respectively considered myopic or hyperopic when spherical equivalent was >−1D or>+1D. D: Diopters, BCVA: Best-corrected visual acuity, IOP: Intraocular pressure

Table 2: Progression rate according FAF pattern. Five eyes of the 40 included in this study were unclassified on FAF pattern

Progression rate according to FAF pattern				
FAF pattern	**Diffuse**	**Banded**	**Focal**	**Unspecific**
Number of eyes	17	7	6	5
Rate	0.434±0.401	1.254±2.008	0.407±0.707	0.154±0.162
P	0.669	0.163	0.748	0.349

FAF: Fundus autofluorescence

In addition, genetic studies linked dysfunction of the alternative complement pathway to the pathogenesis of AMD.[18,19] Accordingly, lampalizumab, a monoclonal antibody directed against complement factor D, was considered as a target therapy to GAP. However, a recent Phase III study (Spectri study) evaluating the safety and efficacy of lampalizumab failed to meet its primary end point of reducing the mean change in GA.[20]

The fundus AF in AMD (FAM) study group highlighted the importance of abnormal AF intensities around GA lesions and introduced a morphological classification system for distinct patterns (unspecific, focal, banded, diffuse, and patchy).[10] More recently, the GAP study was designed to identify GAP risk factors, adopting the same FAF patterns.[5]]

These AF distinct phenotypes appear to be of prognostic value for predicting the GAP rate and may reflect the heterogeneity of the underlying disease process.

In the present study, we found that the mean lesion progression, for the included population, was 0.558 mm^2/year. Our results were analogous to previous reports.[10,21,22]

However, as previously reported, there is considerable variability in progression rate among patients. The mechanisms underlying the differences in progression rates among studies are not fully understood and may include variable lesion sizes and locations, different trial methods, imaging techniques, and varying genotype or exposure to environmental factors.

Although FAF is important for the accurate identification of GA lesions, monitoring with SD-OCT appears to be a valid option.[23,24]

Although our small sample size limits conclusions, we also found asymmetric progression rate according to FAF pattern. Progression rate for banded FAF eyes was the highest, 1.254 (±2.008) mm^2/year. Although not statistically significant (P = 0.163), this tendency reproduces the impact of FAF phenotypic features on GAP described on the FAM study.

In conclusion, FAF pattern seems to be an important prognostic marker to predict progression on an individual basis.

Our methodology using ImageJ is simple and appears to be effective in calculating GA lesion progression rates, and it could be used in different clinical settings and optimize scientific reading center approaches when testing future GA treatment strategies. Our approach could be merged with software algorithms offering a breakthrough in understanding and managing GA.

Disclosures

The authors declare no relevant or material financial interests that relate to the research described in this paper.

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REFERENCES

1. Lim LS, Mitchell P, Seddon JM, Holz FG, Wong TY. Age-related macular degeneration. Lancet 2012;379:1728-38.
2. Sunness JS, Gonzalez-Baron J, Applegate CA, Bressler NM, Tian Y, Hawkins B, *et al.* Enlargement of atrophy and visual acuity loss in the geographic atrophy form of age-related macular degeneration. Ophthalmology 1999;106:1768-79.
3. Takahashi A, Ooto S, Yamashiro K, Oishi A, Tamura H, Nakanishi H, *et al.* Photoreceptor damage and reduction of retinal sensitivity surrounding geographic atrophy in age-related macular degeneration. Am J Ophthalmol 2016;168:260-8.
4. Holz FG, Strauss EC, Schmitz-Valckenberg S, van Lookeren Campagne M. Geographic atrophy: Clinical features and potential therapeutic approaches. Ophthalmology 2014;121:1079-91.
5. Schmitz-Valckenberg S, Sahel JA, Danis R, Fleckenstein M, Jaffe GJ, Wolf S, *et al.* Natural history of geographic atrophy progression secondary to age-related macular degeneration geographic atrophy progression study. Ophthalmology 2016;123:361-8.
6. Chaikitmongkol V, Tadarati M, Bressler NM. Recent approaches to evaluating and monitoring geographic atrophy. Curr Opin Ophthalmol 2016;27:217-23.
7. Brunner S, Mora A, Fonseca J, Weber T, Falkner-Radler CI, Oeser R, *et al.* Monitoring of drusen and geographic atrophy area size after cataract surgery using the MD3RI tool for computer-aided contour drawing. Ophthalmologica 2013;229:86-93.
8. Simader C, Sayegh RG, Montuoro A, Azhary M, Koth AL,

Baratsits M, *et al.* A longitudinal comparison of spectral-domain optical coherence tomography and fundus autofluorescence in geographic atrophy. Am J Ophthalmol 2014;158:557-660.
9. Simões, P, Cordeiro M, Silva P, Costa J. Evaluation of Peripapillary Choroidal Thickness in Nonarteritic Anterior Ischemic Optic Neuropathy using a Medical Image-Processing Software. EUNOS; 2017.
10. Holz FG, Bindewald-Wittich A, Fleckenstein M, Dreyhaupt J, Scholl HP, Schmitz-Valckenberg S, *et al.* Progression of geographic atrophy and impact of fundus autofluorescence patterns in age-related macular degeneration. Am J Ophthalmol 2007;143:463-72.
11. Schmitz-Valckenberg S. The journey of "Geographic atrophy" through past, present, and future. Ophthalmologica 2017;237:11-20.
12. Curcio CA. Imaging maculopathy in post-mortem human eyes. Vision Res 2005;45:3496-503.
13. Sarks SH. Ageing and degeneration in the macular region: A clinico-pathological study. Br J Ophthalmol 1976;60:324-41.
14. Lee N, Laine AF, Smith RT. A hybrid segmentation approach for geographic atrophy in fundus auto-fluorescence images for diagnosis of age-related macular degeneration. Conf Proc IEEE Eng Med Biol Soc 2007;2007:4965-8.
15. Holz FG, Bellmann C, Margaritidis M, Schütt F, Otto TP, Völcker HE, *et al.* Patterns of increased *in vivo* fundus autofluorescence in the junctional zone of geographic atrophy of the retinal pigment epithelium associated with age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol 1999;237:145-52.
16. Bearelly S, Khanifar AA, Lederer DE, Lee JJ, Ghodasra JH, Stinnett SS, *et al.* Use of fundus autofluorescence images to predict geographic atrophy progression. Retina 2011;31:81-6.
17. Mata NL, Lichter JB, Vogel R, Han Y, Bui TV, Singerman LJ, *et al.* Investigation of oral fenretinide for treatment of geographic atrophy in age-related macular degeneration. Retina 2013;33:498-507.
18. Yaspan BL, Williams DF, Holz FG, Regillo CD, Li Z, Dressen A, *et al.* Targeting factor D of the alternative complement pathway reduces geographic atrophy progression secondary to age-related macular degeneration. Sci Transl Med 2017;9:eaaf1443.
19. Boyer DS, Schmidt-Erfurth U, van Lookeren Campagne M, Henry EC, Brittain C. The pathophysiology of geographic atrophy secondary to age-related macular degeneration and the complement pathway as a therapeutic target. Retina 2017;37:819-35.
20. ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US). Identifier NCT02247531, a Study Investigating the Safety and Efficacy of Lampalizumab Intravitreal Injections in Participants with Geographic Atrophy Secondary to Age-Related Macular Degeneration (SPECTRI). Available from: https://www.clinicaltrials.gov/ct2/show/NCT02247531. [Last accessed on 2014 Jul 15].
21. Dreyhaupt J, Mansmann U, Pritsch M, Dolar-Szczasny J, Bindewald A, Holz FG, *et al.* Modelling the natural history of geographic atrophy in patients with age-related macular degeneration. Ophthalmic Epidemiol 2005;12:353-62.
22. Allingham MJ, Nie Q, Lad EM, Izatt DJ, Mettu PS, Cousins SW, *et al.* Semiautomatic segmentation of rim area focal hyperautofluorescence predicts progression of geographic atrophy due to dry age-related macular degeneration. Invest Ophthalmol Vis Sci 2016;57:2283-9.
23. Veerappan M, El-Hage-Sleiman AM, Tai V, Chiu SJ, Winter KP, Stinnett SS, *et al.* Optical coherence tomography reflective drusen substructures predict progression to geographic atrophy in age-related macular degeneration. Ophthalmology 2016;123:2554-70.
24. Ebneter A, Jaggi D, Abegg M, Wolf S, Zinkernagel MS. Relationship between presumptive inner nuclear layer thickness and geographic atrophy progression in age-related macular degeneration. Invest Ophthalmol Vis Sci 2016;57:OCT299-306.

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