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Directional Kinetics of Geographic Atrophy Progression in Age-Related Macular Degeneration with Foveal Sparing

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Purpose: To describe the directional kinetics of the spread of geographic atrophy (GA) spread in eyes with age-related macular degeneration and foveal sparing.

Design: Prospective, noninterventional natural history study: Fundus Autofluorescence Imaging in Age-Related Macular Degeneration (FAM; clinicaltrials.gov identifier, NCT00393692).

Subjects: Participants of the FAM study exhibiting foveal sparing of GA.

Methods: Eyes were examined longitudinally with fundus autofluorescence (FAF; excitation wavelength, 488 nm; emission wavelength, >500 nm) and near infrared (NIR) reflectance imaging (Spectralis HRA+OCT or HRA2; Heidelberg Engineering, Heidelberg, Germany). Areas of foveal sparing and GA were measured by 2 independent readers using a semiautomated software tool that allows for combined NIR reflectance and FAF image grading (RegionFinder; Heidelberg Engineering). A linear mixed effect model was used to model GA kinetics over time.

Main Outcome Measure: Change of GA lesion size over time (central vs. peripheral progression).

Results: A total of 47 eyes of 36 patients (mean age, 73.8±7.5 years) met the inclusion criteria. Mean follow-up time was 25.2±16.9 months (range, 5.9–74.6 months). Interreader agreement for measurements of GA and foveal-sparing size were 0.995 and 0.946, respectively. Mean area progression of GA toward the periphery was 2.27±0.22 mm^2/year and 0.25±0.03 mm^2/year toward the center. Analysis of square root–transformed data revealed a 2.8-fold faster atrophy progression toward the periphery than toward the fovea. Faster atrophy progression toward the fovea correlated with faster progression toward the periphery in presence of marked interindividual differences.

Conclusions: The results demonstrate a significantly faster centrifugal than centripetal GA spread in eyes with GA and foveal sparing. Although the underlying pathomechanisms for differential GA progression remain unknown, local factors may be operative that protect the foveal retina–retinal pigment epithelial complex. Quantification of directional spread characteristics and modeling may be useful in the design of interventional clinical trials aiming to prolong foveal survival in eyes with GA. *Ophthalmology 2015;122:1356-1365 © 2015 by the American Academy of Ophthalmology.*

*Supplemental material is available at www.aaojournal.org.

Geographic atrophy (GA) represents the late stage of dry age-related macular degeneration (AMD).[1–5] Geographic atrophy is present in 3.5% of people older than 75 years[6,7] and becomes the predominant type of AMD in the population 85 years of age and older.[8] In industrial countries, late-stage neovascular or dry AMD is the leading cause of legal blindness in the elderly.[9,10] Although various pathways have been proposed to be involved in the atrophic disease phenotype, the exact underlying pathophysiologic mechanisms are incompletely understood.

Typically, patches of GA initially occur in the parafoveal retina. With spread over time, multifocal atrophic areas may coalesce, and new atrophic areas may occur. In advanced stages, GA areas may form a ring surrounding the intact and still functioning fovea. On clinical examination, the fovea may remain uninvolved by the atrophic process until late in the course of the disease, a phenomenon referred to as *foveal sparing*.[4,11,12] Geographic atrophy areas are associated with a corresponding absolute scotoma. Thus, the foveal-sparing pattern of disease evolution corresponds with progressive visual impairment that is characterized initially by reading difficulties resulting from parafoveal scotomata while the central visual acuity is still preserved.[4,13–17] When the fovea finally becomes involved, a dramatic loss in central visual acuity occurs. However, visual impairments such as decrease in reading speed may start much earlier, putatively correlating with the size of the spared fovea.[16,17]

With the advent of confocal scanning laser ophthalmoscopy fundus autofluorescence (FAF) imaging it is possible to identify and quantify GA areas readily.[18,19] Because of the

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absence of fluorophores in the retinal pigment epithelium (RPE), atrophic areas in GA eyes are associated with a severely reduced signal, resulting in high contrast between the atrophic and nonatrophic retina. Image analysis software has been developed and validated to quantify the size of atrophic areas and the spread over time.[20,21] Because of luteal pigment, blue-light FAF (excitation, 488 nm) intensities typically are decreased in the fovea. Although atrophic patches exhibit an even lower FAF intensity than the central macula, judgment on foveal involvement based on FAF images only can be challenging (Figs 1 and 2). Additional use of near infrared (NIR) reflectance confocal scanning laser ophthalmoscopy imaging, spectral-domain optical coherence tomography imaging, or both have proven helpful in determining foveal involvement (Fig 1).[21,22] A novel imaging analysis tool incorporated in the RegionFinder software (Heidelberg Engineering, Heidelberg, Germany) allows for combined NIR reflectance and FAF image grading. Using the region growth algorithm, the area of foveal sparing is outlined semiautomatically in the NIR reflectance image. Subsequently, the constraint delineating the foveal island is registered automatically to the corresponding FAF images to quantify GA areas outside the residual foveal island in the usual fashion.[21]

Recent studies have addressed the natural history of GA in detail, and several agents that may affect GA progression are in preclinical or clinical development (reviewed in Holz et al[23]). Patients in whom the fovea is affected by the atrophic process still would benefit because eccentric fixation abilities may be preserved and the enlargement of the scotoma size may be reduced. In patients with foveal sparing, preservation of both the fovea and parafoveal retina, even for a limited period, would have an enormous impact on the quality of life. Certain visual tasks necessary for activities of daily living, including recognizing faces and reading, are dependent on the fovea and parafoveal retina. If these areas could be preserved, patients would be able to maintain independent living, and quality of life, for longer.

For the design of interventional trials aiming to preserve the foveal island in eyes with GA, the availability of natural history data is essential. Furthermore, a reliable technique that assesses GA progression toward the fovea is crucial. Therefore, the aim of this study was to quantify the directional kinetics of GA with foveal sparing using a semiautomated software tool that allows for combined NIR reflectance and FAF image grading.

Methods

Patients

Patients were recruited from the Fundus Autofluorescence Imaging in Age-Related Macular Degeneration (FAM) study (clinicaltrials.gov identifier, NCT00393692). This noninterventional, prospective natural history study followed the tenets of the Declaration of Helsinki and was approved by the institutional review boards of the participating centers. Informed consent was obtained from each participant after explanation of the study's nature and possible consequences of participation.

Patients were included in the current analysis with (1) unilateral or bilateral GA resulting from AMD with clear ocular media that allowed for good-quality FAF and NIR reflectance imaging, (2) foveal sparing of GA in at least 1 eye, and (3) serial examinations of at least 6 months.

Definition of Geographic Atrophy Resulting from Age-Related Macular Degeneration

Geographic atrophy was defined funduscopically as 1 or more well-defined, usually more or less circular patches of partial or complete depigmentation of the RPE, typically with exposure of underlying large choroidal blood vessels.[24]

In the FAM study, GA resulting from AMD was defined further as a sharply demarcated lesion with clearly reduced FAF of an extent of 0.05 mm^2 or more (approximately 178 μm in diameter) that does not correspond to exudative retinal changes (e.g., bleeding, exudates, fibrous scar) in an eye with funduscopically visible soft drusen, retinal pigment abnormalities consistent with AMD, or both.[25]

Definition of Foveal Sparing in Geographic Atrophy

In the current analysis, eyes were defined as having foveal sparing in GA if the residual foveal island was more than 270° surrounded by well-demarcated areas of GA. An eye was classified as having complete foveal sparing if GA surrounded the fovea in ring configuration. If there were bridges between the residual foveal island and the surrounding retina, an eye was classified as having incomplete foveal sparing. The definition and classification of foveal sparing were based on FAF and NIR reflectance images. Functional data were not included in this definition.

If the 2 eyes of a patient met the inclusion criteria, both eyes were included in the analysis. Exclusion criteria included the presence of other retinal diseases such as diabetic retinopathy, present or past exudative AMD in the study eye, and retinal dystrophy, as well as a history of laser photocoagulation or retinal surgery. Furthermore, patients in whom the area of atrophy exceeded the 30°×30° confocal scanning laser ophthalmoscopy images were excluded.

Best-corrected visual acuity was determined with Early Treatment Diabetic Retinopathy Study charts on a quasilogarithmic ordinal scale. Before fundus examination, the pupil of the study eye was dilated with 1% tropicamide eye drops.

Image Acquisition, Processing, and Grading

Fundus autofluorescence and NIR reflectance images were acquired using HRA 2 or Spectralis (Heidelberg Engineering). Fundus autofluorescence images were acquired with an excitation wavelength of 488 nm and an emission spectrum of 500 to 700 nm using the high-speed mode. Near infrared reflectance images were obtained at a wavelength of 820 nm. The field of view was set to 30°×30° with a minimum resolution of 512×512 pixels and was centered on the fovea. Single FAF images were aligned automatically and averaged to maximize the signal-to-noise ratio using the manufacturer's software.

Measurement of atrophy area and foveal sparing area were performed using the RegionFinder software (Heidelberg Engineering).[21] The applied version (2.5.5.0) includes a newly implemented feature that automatically registers FAF to corresponding NIR reflectance images and allows easily toggling from one to the other modality (Fig 2).

The size of the residual foveal island was determined semiautomatically in the NIR reflectance image. The reader manually sets a seeding point inside the foveal island to start the automatic region identification algorithm that also is used for atrophic area segmentation in FAF images. This algorithm is based on the