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Vitreoretinal Interface Changes in Geographic Atrophy

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Purpose: Geographic atrophy (GA) is the end-stage manifestation of atrophic age-related macular degeneration (AMD). The disease progresses slowly over time, eventually causing loss of central vision. Its cause and pathomechanism are not fully known. Previous studies have suggested that vitreoretinal traction (VRT) may contribute to the progression of neovascular AMD. The aim of this study was to examine whether an association between changes at the vitreoretinal interface (VRI), in particular traction (VRT), and the characteristics and progression of GA in eyes with dry AMD can be established.

Design: Clinic-based prospective cohort study.

Participants: A total of 97 patients (age range, 61−90 years; mean, 78.4 years) with GA secondary to dry AMD were enrolled. Patients exhibiting neovascular signs on fluorescein angiography in either eye were excluded.

Methods: The VRI changes were examined using spectral-domain optical coherence tomography (SD-OCT). Characteristics of GA were examined using fundus autofluorescence (FAF) imaging. All imaging was performed using a Spectralis SLO+OCT device (Heidelberg Engineering, Heidelberg, Germany); GA area was measured using the Region Finder (Heidelberg Engineering) software native to the Spectralis platform.

Main Outcome Measures: Area and increase in area of GA.

Results: A total of 97 eyes were examined. Vitreoretinal traction was found in 39 eyes (40%). The GA area at baseline was 6.65±5.64 mm^2 in eyes with VRT and 5.73±4.72 mm^2 in eyes with no VRT. The annual rate of progression of GA area progression was 2.99±0.66 mm^2 in eyes with VRT and 1.45±0.67mm^2 in eyes without VRT. Differences between groups in both parameters were statistically significant (n = 97 total number of eyes; $P<0.001$). Multiple regression analysis confirmed this finding (B = 0.714, $P<0.001$; $F_{3,93} = 72.542$, $P<0.001$; adjusted $R^2 = 0.691$)

Conclusions: Our results indicate an association between VRT and an increased rate of progression of GA area in dry AMD. Monitoring VRT may contribute to an improved estimate of the prospective time of visual loss and to a better timing of emerging therapies in dry AMD. *Ophthalmology 2014;■:1−6 © 2014 by the American Academy of Ophthalmology.*

Age-related macular degeneration (AMD) is a disease of the central retina leading to a severe impairment of central vision. Its precise cause is unknown; however, AMD is multifactorial, driven by both genetic and environmental risk factors.[1−3] Disabling visual impairment may result from exudative (wet) or atrophic (dry) late-stage manifestations of the disease, that is, choroidal neovascularization (CNV) or geographic atrophy (GA). Although progression to legal blindness in purely atrophic AMD is slower, for this form of AMD no effective treatment is currently available, and eyes that underwent successful treatment for CNV also remain at risk of vision loss caused by GA.[4−6]

Geographic atrophy is defined as a sharply demarcated area with atrophy of the retinal pigment epithelium (RPE) and the photoreceptors, which increases in area over time.[4,7] Its exact pathogenesis has yet to be fully explored; however, studies have implicated a number of possible pathways that may contribute. Oxidative damage may cause lipid peroxidation, and toxic components of lipofuscin accumulating within the lysosomal compartments of RPE cells may contribute to the dysfunction and eventual degeneration of the RPE,[7] which in turn may lead to photoreceptor loss.[8−10] There is also mounting evidence that implicates the role of inflammation/immune-mediated processes. Numerous inflammatory components were found in drusen, and several more recent studies have demonstrated an association between AMD and polymorphisms that involve the complement pathway.[11−14]

Recent imaging modalities provide excellent new tools for diagnosing and following disease progression in AMD. Fundus autofluorescence (FAF) recorded using confocal scanning laser ophthalmoscopy at an excitation wavelength of 488 nm is predominantly characteristic of lipofuscin within the RPE and provides a good indicator of its pathologically increased accumulation in the junctional zone of GA or its absence within the GA area because of the loss of RPE cells or cellular content. Spectral-domain optical coherence tomography (OCT) allows a detailed examination of retinal structure and the relationship of the retina and vitreous.[8]

Risk factors affecting the progression rate of GA are little known. Holz et al[15] identified significant differences in progression rate based on the pattern of hyperfluorescence and hypofluorescence in FAF images, although the etiologic and pathogenetic implications are unclear.

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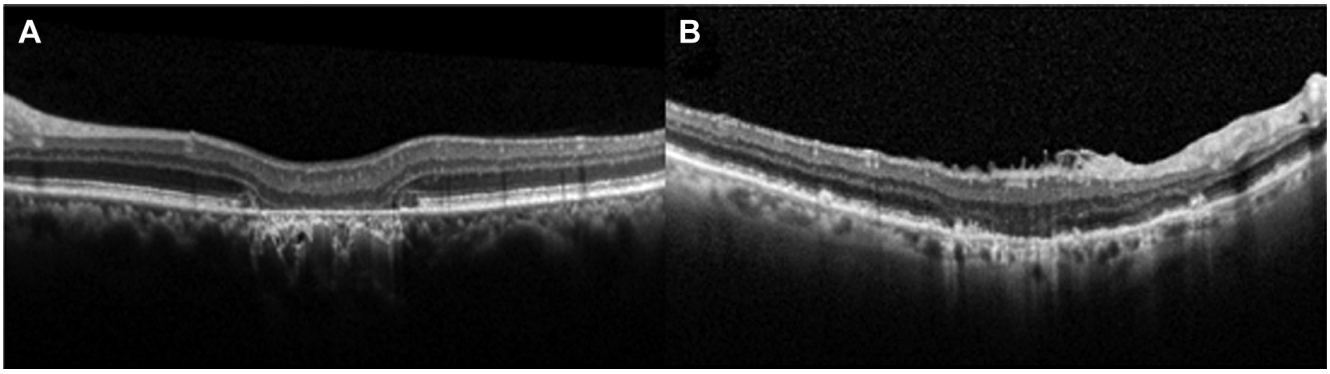

Figure 1. Vitreoretinal traction (VRT) in optical coherence tomography images of eyes with dry age-related macular degeneration **(A)** without VRT and **(B)** with VRT.

Another phenomenon in aging is a weakening of the adhesion in the vitreoretinal interface (VRI) between the posterior cortical vitreous and the inner limiting membrane.[16] The process of separating the posterior vitreous from the retina, eventually resulting in a posterior vitreous detachment (PVD), has been documented using SD-OCT.[16] As the detachment develops, vitreoretinal traction (VRT) may occur (Fig 1A, B), which has been implicated as a risk factor of exudative AMD.[17–21] However, its possible role in atrophic AMD has not been investigated. The objective of this study was to investigate whether an association between the vitreomacular traction and the progression rate of GA and with any specific GA pattern can be identified in atrophic AMD.

Methods

Patients were selected sequentially from the outpatient clinic of a tertiary referral center (Department of Ophthalmology, Inselspital, University of Bern, Bern, Switzerland) between May 2007 and June 2012. Patients older than 50 years with areas of unifocal or multifocal GA secondary to dry AMD were invited to participate. The presence of GA was determined primarily in FAF images, with spectral-domain OCT imaging as an adjunct in questionable cases. All clearly detectable cases of GA were included.

The study was approved by the institutional review board, and the study protocol adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients after an explanation of the nature and possible side effects of the study. If both eyes qualified equally, 1 eye was randomly chosen.

A comprehensive ophthalmic examination was performed. Monocular best-corrected visual acuities were determined according to a standardized protocol using Early Treatment of Diabetic Retinopathy Study logarithm of the minimum angle of resolution visual acuity charts at a distance of 4 m. Scoring of the test was based on the number of letters read correctly. Possible scores ranged from 0 (Snellen equivalent <20/800) to 100 (Snellen equivalent 20/12).

Exclusion criteria were signs or history of exudative AMD or any other vascular, metabolic, or hereditary retinal disease; previous retinal surgery; or laser photocoagulation. To exclude CNV, fluorescein angiography was performed using a Heidelberg Retina Angiograph 2 (Heidelberg Engineering, Heidelberg, Germany).

Image Acquisition

Imaging was performed after dilating the pupil with 0.1% tropicamide. Simultaneous recordings of infrared confocal scanning laser ophthalmoscopy and spectral-domain OCT images were obtained using Spectralis HRA+OCT devices (Heidelberg Engineering). The technical principles have been described elsewhere.[22] The OCT volume scan consisted of 49 B-scans within a 6×6-mm retinal area. The FAF images were acquired at an excitation wavelength of 488 nm according to a standardized operation protocol[23,24] using the same equipment.

Measuring Geographic Atrophy Area Progression

The GA area measurements were performed using the Region Finder software version 1.0.16 (Heidelberg Engineering) (Fig 2A, B) as described previously.[25] Briefly, this software identifies dark areas in FAF images using region-growing algorithms. The software includes algorithms for semiautomated segmentation of atrophic areas and automated identification of interfering vascular structures.[22] By starting from a user-defined seed point placed in a dark area of the image, a so-called region-growing algorithm identifies the border of this dark area and calculates a mean grey value of the pixels. The FAF intensity of every picture element (pixel) is given in grey value. The dramatic decrease in the FAF signal in the GA areas compared with the signal in the nonatrophic retinal areas is used by the software to segment the GA area. After the center of a region is defined by the operator (reader), the region-growing algorithm tends to grow toward the borders of the region, taking into account all pixels with signal intensity below a certain threshold. This threshold is defined by a parameter referred to as "growth power" (the higher the growth power, the larger the enclosed area). The proper adjustment of this parameter allows for the precise measurement of the GA area. For scaling, the individual scaling factor that is registered by the host Heidelberg Eye Explorer software (HEYEX; Heidelberg Engineering) during image acquisition is used. Given the digital image resolution of 768×768 pixels of a 30°×30° frame, 1 pixel edge corresponds to approximately 11 μm.

Total GA size was measured by 2 independent, trained readers (M.N., V.V.W.) in separate sessions at least 1 day apart. To reduce bias, images were presented in a randomized fashion. The readers analyzed the progression rate without access to the OCT images or the GA pattern grading data. For statistical analysis of lesion size, a final copy was created by averaging corresponding data acquired by the 2 graders. Interobserver agreement was assessed and has been reported previously.[4]