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 mm² in eyes with VRT and 5.73±4.72 mm² in eyes with no VRT. The annual rate of progression of GA area progression was 2.99±0.66 mm² in eyes with VRT and 1.45±0.67 mm² 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; F9.93 = 72.542, P<0.001; adjusted R² = 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;121:1734-1739 © 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.2,3 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.6,7 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.11-13

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.9

Risk factors affecting the progression rate of GA are little known. Holz et al15 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.
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.10 The process of separating the posterior vitreous from the retina, eventually resulting in a posterior vitreous detachment (PVD), has been documented using SD-OCT.10 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 ophthamoscopy and spectral-domain OCT images were obtained using Spectrals 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 protocol17–24 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.23 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.23 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
Detection of Vitreoretinal Traction, Epiretinal Membrane, and Posterior Vitreous Detachment

All individual OCT B-scans within the acquired volumes were analyzed by a third independent grader (H.A.) for signs of VRT, epiretinal membrane (ERM), and partial or full PVD to in a random sequence using the Heidelberg Eye Explorer software without access to the FAF images or data. Vitreoretinal traction was considered to be present when at least an apparent distortion of the retinal surface contour was detectable. Epiretinal membrane was graded as present if a highly reflective band internal to the nerve fiber layer was clearly seen. Eyes were grouped according to the presence or absence of signs of VRT.

Classification of Geographic Atrophy According to Fundus Autofluorescence Pattern

The classification of GA in this study was based on the system devised by Bindewald et al. According to hyperfluorescence patterns in the junctional zone of GA, Bindewald et al identified 9 different FAF patterns in GA: none, focal, banded, patchy, and diffuse, with diffuse being further subdivided into 5 subcategories. The present study adhered to this system with the exception of the subdivisions of the diffuse pattern, using 5 possible categories only.

Statistical Analysis

Prism version 5.00 (GraphPad Software, San Diego, CA) and SPSS version 17 (SPSS/IBM Corporation, Armonk, NY) were used for statistical analyses. Demographic characteristics of the patients are summarized using descriptive statistics. Data are expressed as the mean ± standard deviation (SD) and percentages. Lin’s concordance correlation coefficient was used to establish the statistical significance of differences in GA area between the groups with or without VRT. Given the exploratory nature of this study, P ≤ 0.05 was accepted as statistically significant.

Results

Ninety-seven eyes of 97 patients were examined; patients’ age ranged from 61 to 90 years (mean, 78.4 years; SD, 7.3 years); and 36 (37%) were male, 61 (63%) were female. The mean age of patients with VRT was 79.5 ± 7.3 years and 77.7 ± 7.3 years for those without signs of traction.

Visual Function

Best-corrected visual acuities ranged from 0 to 95 letters (mean, 57 letters; SD, 19 letters) Snellen equivalent counting fingers to 20/13 (mean, 20/80; SD, 20/400). Eyes with VRT had a mean letter score of 57.6 letters (range, 15–85; SD, 20.5; range, 20/500–20/20; SD, 20/400 Snellen equivalent), and eyes with no detectable lesion had

<table>
<thead>
<tr>
<th>Table 1. Geographic Atrophy Area at Baseline and Annual Rate of Area Progression in Eyes with and without Vitreoretinal Traction</th>
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</thead>
<tbody>
<tr>
<td><strong>GA Area at Baseline</strong> (mm²)</td>
</tr>
<tr>
<td>Mean ± SD</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>VRT</td>
</tr>
<tr>
<td>No VRT</td>
</tr>
<tr>
<td>All eyes</td>
</tr>
</tbody>
</table>

GA = geographic atrophy; SD = standard deviation; VRT = vitreoretinal traction.
Data represent annual rate of progression.
Table 2. Distribution of Geographic Atrophy Patterns in Eyes with and without Vitreoretinal Traction

<table>
<thead>
<tr>
<th></th>
<th>None n</th>
<th>None %</th>
<th>Focal n</th>
<th>Focal %</th>
<th>Banded n</th>
<th>Banded %</th>
<th>Patchy n</th>
<th>Patchy %</th>
<th>Diffuse n</th>
<th>Diffuse %</th>
</tr>
</thead>
<tbody>
<tr>
<td>VRT</td>
<td>10</td>
<td>10.3</td>
<td>6</td>
<td>6.2</td>
<td>1</td>
<td>1.0</td>
<td>18</td>
<td>18.6</td>
<td>18</td>
<td>18.6</td>
</tr>
<tr>
<td>No VRT</td>
<td>6</td>
<td>6.2</td>
<td>13</td>
<td>13.4</td>
<td>7</td>
<td>7.2</td>
<td>3</td>
<td>3.1</td>
<td>29</td>
<td>29.9</td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
<td>16.5</td>
<td>17</td>
<td>17.5</td>
<td>13</td>
<td>13.4</td>
<td>4</td>
<td>4.1</td>
<td>47</td>
<td>48.5</td>
</tr>
</tbody>
</table>

VRT = vitreoretinal traction.
*The focal pattern showed a statistically significant difference between the eyes with and without VRT. Student t test was performed for this analysis.

a mean letter score of 56.4 letters (range, 0−95; SD, 19.8; Snellen counting fingers to 20/13; SD, 20/400), but the differences were not statistically significant (P = 0.786, Student t test).

Vitreoretinal Traction

Signs of VRT were detected in 39 eyes (40%), of which 30 (77%) had an ERM. Twenty-three of 57 eyes (40%) with no demonstrable traction showed signs of ERM. Partial or full PVD also was examined. Twelve eyes with traction (31%) had partial PVD, and 1 eye (3%) had full PVD. Without traction, 3 eyes (5%) had partial PVD and 4 eyes (7%) had full PVD.

Geographic Atrophy

The GA areas at baseline and progression rates are presented in Table 1. Differences in both parameters between groups were statistically significant (n = 97; P<0.001). The distribution of eyes by GA pattern according to the modified classification by Holz et al12 is presented in Table 2. Differences between eyes with or without VRT reached statistical significance in case of the focal pattern (P<0.03, chi-square test; n = 17). To investigate the relative impact of clinical parameters on the GA progression rate, we performed a multiple linear regression analysis. In an initial model, we included GA area at baseline, presence of VRT or ERM, partial PVD, full PVD, the 5 GA patterns, and patient age as independent variables (Table 3). By narrowing down the model to the predictors that proved significant, a second calculation yielded a significant model (F3,93 = 72.542; P<0.001; adjusted R² = 0.691) with the predictors as follows: presence of VRT (B = 0.714; P<0.001), diffuse GA pattern (B = 0.208; P = 0.002), and focal GA pattern (B = −0.243; P<0.001).

Discussion

Several studies have found an association between traction caused by the separation of the posterior vitreous from the retina and the development of neovascular (wet) AMD.17,18,21,28,29 The literature on the relationship of VRT and dry AMD is limited. One study by Schulze et al30 found a higher frequency of AMD-like changes in non-vitreomized eyes relative to vitrectomized eyes. All AMD cases in that study were nonneovascular. The authors concluded that a persistent attachment of the vitreous to the macula may be a risk factor of AMD and that the role of VRT in the development of dry AMD might be similar to that of wet AMD.31 The aim of our study was to investigate the relationship of traction caused by VRT changes and GA parameters in dry AMD eyes.

We observed signs of traction within the VRI in 39 of 97 eyes (40%). Mojana et al11 reported VRT in 59% of neovascular and 13% of nonneovascular AMD cases studied. However, the nonneovascular group also included less severe cases of AMD, without the presence of GA. On the basis of a meta-analysis of 16 previous publications, Jackson et al31 reported for vitreomacular adhesion a prevalence of 23% in wet and 9.5% in dry AMD cases. Differences in prevalence data may be, at least to some extent, due to variation in sample size, definitions of vitreoretinal abnormality, and disease severity within disease categories.

The GA area at baseline and mean annual progression rate in GA area in these eyes were significantly higher than in eyes with no observable traction (B = 0.714; P<0.001). Our data support the hypothesis that in dry AMD, just as in wet AMD, mechanical stress may affect the natural history of the disease. Although the pathogenetic pathways of VRT-induced retinal changes are unknown (and it needs to be acknowledged that the causality may indeed be the reverse), several possible mechanisms have been proposed. Vitreoretinal traction can lead to a structural distortion of the RPE cell layer,32 and RPE cells respond to pulsatile stretching with increased secretion of growth factors, including vascular endothelial growth factor.33 Disruption of choroidal blood supply to the macula caused by VRT may lead to hypoxia and consequently increased vascular endothelial growth factor levels.34 However, considering the interdependence of choroid and RPE, this effect also may influence GA. Persistent vitreomacular adhesion might confine cytokines to the macula. Growth factors and proinflammatory cytokines are less able to diffuse into the vitreous. With their concentrations remaining high in the retina, they are able to promote neovascularization and inflammation.18,35 Low-grade retinal inflammation has been implicated in the pathogenesis of AMD.30−35 Major components of human drusen include albumin, apolipoprotein E, complement factors and related proteins (including complement components C1q, C3, C5, and C5b-9 and vitronectin), immunoglobulins,
and amyloid-β. Furthermore, drusen also contain components of dendritic cell processes, which support a role for humoral and local immunity in their biogenesis. Vitreoretinal traction itself may promote inflammation and contribute to AMD pathogenesis. Although the inflammatory response is more pronounced in neovascular AMD, emerging evidence indicates RPE-specific inflammasome-mediated degeneration as a driving force for RPE atrophy, suggesting that immune-mediated tissue damage may play a role in GA.

On the basis of the pattern of abnormal hyperfluorescence and hypofluorescence in FAF images, GA may be divided into subtypes (focal, banded, patchy, and diffuse, with further subdivision of the latter). Holz et al reported significant differences in the progression rate between subtypes. The highest progression rate was associated with the diffuse pattern. In our sample, the diffuse pattern was observed with the highest frequency, and a clear although weak correlation with a higher progression rate could be demonstrated (B = 0.208; P = 0.002), supporting previous reports. The focal pattern showed a statistically significant association with the lack of VRT and an inverse correlation with the progression rate. However, in view of the relatively small sample size, we treat this result with caution, and confirmation using a larger sample is warranted.

In conclusion, our results indicate an association of VRT with an increased rate of progression of GA area in dry AMD. Risk factors affecting the progression rate of GA are little known. Monitoring VRT ultimately may contribute to an improved estimate of the prospective time of visual loss and to the correct timing of emerging therapies.

Acknowledgments. The authors thank Anita Zenger for help with image acquisition and Martin Niederhaeuser for image analysis.

References

Footnotes and Financial Disclosures

Originally received: August 14, 2013.
Final revision: March 25, 2014.
Accepted: March 28, 2014.

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Financial Disclosure(s):
The author(s) have made the following disclosure(s): S.W. received support from Novartis, Alcon, Roche, Bayer, Optos Inc., and Heidelberg Engineering. U.E.K.W.-S. received an unrestricted grant from Novartis and sponsorship of other studies from Alcon, Allergan, Novartis, Heidelberg, and Velux. These sponsors had no role in the design or conduct of this research.

Abbreviations and Acronyms:
AMD = age-related macular degeneration; CNV = choroidal neovascularization; ERM = epiretinal membrane; FAF = fundus autofluorescence; GA = geographic atrophy; PVD = posterior vitreous detachment; RPE = retinal pigment epithelium; SD = standard deviation; SD-OCT = spectral-domain optical coherence tomography; VRI = vitreoretinal interface; VRT = vitreoretinal traction.

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