Symmetry of Bilateral Lesions in Geographic Atrophy in Patients With Age-Related Macular Degeneration

Caren Bellmann, MD; Jork Jorzik, MD; Georg Spital, MD; Kristina Unnebrink, PhD; Daniel Pauleikhoff, MD; Frank G. Holz, MD

Background: As a cause for severe visual loss, geographic atrophy of the retinal pigment epithelium is about half as common as choroidal neovascularization in patients with advanced age-related macular degeneration. To assess symmetry, we determined intraindividual variations of various features of bilateral geographic atrophy in patients with atrophic age-related macular degeneration in a cross-sectional study.

Methods: Patients were examined with the use of a confocal scanning laser ophthalmoscope (Heidelberg Retina Angiograph; Heidelberg Engineering, Heidelberg, Germany). Digital infrared reflection images (excitation, 830 nm) and fundus autofluorescence images (excitation, 488 nm) were recorded. The eyes of each patient were compared regarding number, size, and convex hull of the atrophic areas with the use of image analysis software and with respect to fundus autofluorescence changes in the junctional zone.

Results: Seventy-two patients (mean±SD age, 76.3±7.9 years) were examined. The number of atrophic areas ranged from 1 to 23 (mean±SD, 4.9±4.6); the size of geographic atrophy, from 0.18 to 30.20 (mean±SD, 7.0±6.6) mm²; and the size of the convex hull, from 0.18 to 39.20 (mean±SD, 11.7±8.4) mm². No statistically significant difference was found when comparing these variables between each left and right eye: number, \( P = .62 \); size, \( P = .81 \); and convex hull, \( P = .78 \). Identical patterns of fundus autofluorescence were observed in 43 (80%) of 54 patients.

Conclusions: There is intraindividual symmetry in eyes with bilateral geographic atrophy in the presence of a wide range of interindividual variability. The findings are in accordance with the view that age-related macular degeneration is not merely the result of a nonspecific aging process. Symmetric manifestations, rather, reflect specific individual determinants in the pathogenesis and manifestation of the disease.

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A ge-related macular degeneration (ARMD) is the most common cause for legal blindness in Western countries.1-6 Severe visual loss results from choroidal neovascularization (CNV), pigment epithelial detachment, or geographic atrophy (GA) of the retinal pigment epithelium (RPE).2-4,7-11 Geographic atrophy is less common than the neovascular form of ARMD. In about 12% to 21% of patients with advanced ARMD, severe loss of visual acuity results from foveal involvement of GA.4,10,11 The severity of visual loss from GA may be just as great as from CNV, but the process is much slower than with CNV. In contrast to CNV, GA tends to spare the fovea until late in the course of the disease. While GA usually develops in eyes with drusen and pigmentary alterations, it may also follow flattening of RPE detachments.17-20 Histopathologic examinations have shown that the atrophy is not confined to the RPE layer but also involves the corresponding choriocapillaris and outer neurosensory retina.21-23

Evidence indicates that genetic factors play a role in the pathogenesis of ARMD.24-34 Genetic influences are also thought to account for intraindividual symmetry in the manifestation of the disease. Recently, symmetry has been evaluated for drusen, CNV, disciform scars, and RPE tears.35-38 Geographic atrophy occurs bilaterally in 48% to 65% of the cases.9,14,21 Sunness and coworkers13 described a high correlation in the size and progression of GA between both eyes. However, further characteristics of bilaterality have not been assessed for advanced atrophic ARMD. With the advent of scanning laser ophthalmoscopic imaging, topographic quantitative analysis and recording of fundus autofluorescence (FA) are possible.39-41 We used a confocal scan-
PATIENTS AND METHODS

Patients with bilateral GA secondary to ARMD were recruited at 2 tertiary ophthalmological referral centers in Germany (Department of Ophthalmology, University of Heidelberg; and St Franziskus Hospital, Munster). An appropriate institutional review board approved the project, and informed consent was given by all participants before recruitment into the study.

Digital infrared reflection images (830 nm) produced by a confocal scanning laser ophthalmoscope were recorded in both eyes of each patient. In addition, in patients with clear media for sufficient image quality to allow a meaningful analysis, FA images were obtained with the use of the confocal scanning laser ophthalmoscope. For FA imaging, an argon blue laser (488 nm) was used for excitation. The emitted light was detected above 500 nm (barrier filter). For infrared reflection images and FA images, an image size of 30° × 30° was chosen. The optical and technical principles of the confocal scanning laser ophthalmoscope have been described previously.39-42

To amplify the autofluorescence signal, a flash mode was introduced, ie, the laser power was increased 2-fold for 32 milliseconds. Alternatively, several images were aligned and a mean image was calculated from several images after detection and correction of eye movements with the use of image analysis software, as described previously.39-42 Before examination, the pupil was dilated with tropicamide and phenylephrine hydrochloride eyedrops.

Planimetric measurements in the digital images obtained were performed by encircling the area of interest with a mouse-driven arrow and by calculating the area with the use of image analysis software (Heidelberg Eye Explorer Software; Heidelberg Engineering).

Areas of atrophy are readily delineated on autofluorescence images because they appear dark in the absence of RPE fluorophores (Figure 1 and Figure 2).41 Therefore, autofluorescence images were used for quantitative analysis. In a few cases with poor autofluorescence image quality, infrared reflection images were used for evaluation.

A total of 72 consecutive patients (48 women and 24 men; mean±SD age, 76.3±7.7 years) with bilateral GA were recruited. The median visual acuity in all patients was 20/80, ranging from perception of hand movements to 20/20.

Of 144 eyes, 103 (71.5%) had multifocal patches of GA and 41 (28.5%) had unifocal GA. Foveal involvement was present in 78 (54.2%) of the 144 eyes, and 47 (32.6%) of the 144 eyes had 2 to 4 atrophic areas in 1 eye. In 3 eyes, more than 16 atrophic lesions were observed (maximum of all eyes, 23 lesions; mean±SD, 4.9±4.6 lesions; median, 3 lesions; and interquartile range, 6 lesions) (Figure 4). The size of atrophy ranged from 0.18 to 30.20 (mean±SD, 7.0±6.6; median, 6.4; and interquartile range, 7.8) mm² (Figure 5). The extent of the convex hull ranged from 0.18 to 39.20 (mean±SD, 11.7±8.4; median, 12.5; and interquartile range, 11.4) mm² (Figure 6).

We found a smaller area of atrophy in patients without foveal involvement: for those with multifocal GA, the mean±SD area was 4.3±3.6 mm² (median, 3.2 mm²); and for those with unifocal GA, the mean±SD area was 4.4±5.3 mm² (median, 2.4 mm²). In comparison, we measured the area of atrophy in patients with foveal involvement: for those with multifocal GA, the mean±SD area was 10.3±6.8 mm² (median, 8.7 mm²); and for those with unifocal GA, the mean±SD area was 8.0±8.2 mm² (median, 6.1 mm²). Foveal involvement occurred more often in eyes with unifocal GA (27 [65.9%] of 41 eyes) than in eyes with multifocal GA (51 [49.5%] of 103 eyes).

No statistically significant difference was observed in measured characteristics between each left and right eye of those with unifocal GA and those with multifocal GA, the mean±SD area was 4.4±5.3 mm² (median, 2.4 mm²). In comparison, we measured the area of atrophy in patients with foveal involvement: for those with multifocal GA, the mean±SD area was 10.3±6.8 mm² (median, 8.7 mm²); and for those with unifocal GA, the mean±SD area was 8.0±8.2 mm² (median, 6.1 mm²). Foveal involvement occurred more often in eyes with unifocal GA (27 [65.9%] of 41 eyes) than in eyes with multifocal GA (51 [49.5%] of 103 eyes).

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eye: number of lesions, \( P = .62 \); size of atrophy, \( P = .81 \); and convex hull of atrophy, \( P = .78 \) (Wilcoxon signed rank test) (Figures 4, 5, and 6, respectively). The 95% confidence intervals for the mean difference between right and left eyes were as follows: number of lesions, \(-1.3 \) to \(0.8\); size of atrophy, \(-1.6 \) to \(1.4\); and convex hull of atrophy, \(-1.3 \) to \(1.6\). The lengths of these confidence intervals give an impression of the power this study had to detect differences between right and left eyes. For the calculation of \( \kappa \) coefficients, we grouped the number of atrophic lesions as follows: 1, 2, 3 to 5, 6 to 10, and more than 10 lesions. For the number of lesions, the \( \kappa \) coefficient was 0.30 (95% confidence interval, 0.15-0.46) (Table 1). Correlation coefficients between both eyes were as follows: \( r = 0.58 \) for the area of atrophy, \( r = 0.67 \) for the convex hull, and \( r = 0.56 \) for the number of atrophic areas.

Fundus autofluorescence images with sufficient quality to allow a meaningful analysis were available in 54 of the 72 patients (108 eyes). Three different patterns of increased FA were observed, as previously described\(^4\): a continuous band of increased autofluorescence in the junctional zone was noted in 46 eyes (42.6%), a diffusely increased autofluorescence at the posterior pole was observed in 18 eyes (16.7%), and a focal increased autofluorescence in the junctional zone was present in 23 eyes (21.3%). Normal autofluorescence outside to the atrophic area was noted in 21 eyes (19.4%). Identical patterns of autofluorescence in both eyes of each patient were observed in 43 (80%) of 54 patients. For calculating the \( \kappa \) coefficient, the areas of GA were grouped in the 4 described autofluorescence patterns. The \( \kappa \) coefficient was 0.74 (95% confidence interval, 0.59-0.88) between both eyes and shows high concordance between both eyes (Table 2).

**Table 1. Number of Atrophic Lesions in the Left and Right Eyes of 72 Patients***

<table>
<thead>
<tr>
<th>Left Eye, No. of Lesions</th>
<th>Right Eye, No. of Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>3-5</td>
<td>4</td>
</tr>
<tr>
<td>6-10</td>
<td>4</td>
</tr>
<tr>
<td>&gt;10</td>
<td>0</td>
</tr>
</tbody>
</table>

*Data are given as number of patients.

**Table 2. Fundus Autofluorescence Pattern Comparing Left and Right Eyes of 54 Patients***

<table>
<thead>
<tr>
<th>Left Eye, AF Pattern</th>
<th>Right Eye, AF Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>8</td>
</tr>
<tr>
<td>B</td>
<td>0</td>
</tr>
<tr>
<td>C</td>
<td>0</td>
</tr>
<tr>
<td>D</td>
<td>1</td>
</tr>
</tbody>
</table>

*Data are given as number of patients. A indicates normal autofluorescence; B, a continuous band of increased autofluorescence surrounding the atrophic area; C, focal increased autofluorescence at the junctional zone; and D, diffusely increased autofluorescence at the posterior pole.

To evaluate symmetric bilateral manifestations of GA associated with ARMD, we compared number and size of atrophic patches, area of convex hulls in the presence of multifocal atrophic areas, and FA patterns between the eyes of each patient with the use of scanning laser ophthalmoscopy. No significant differences between both eyes of each patient were observed for area, number, and convex hull of the atrophic patches. Furthermore, FA patterns also showed a high degree of symmetry. Although the \( \kappa \) coefficient for the number of atrophic areas be-
tween both eyes indicates only moderate values for symmetry, the results from the Wilcoxon signed rank test show a tendency for intraindividual symmetry for GA associated with ARMD in the presence of a wide spectrum of interindividual manifestations.

High rates of symmetric manifestations of ARMD have recently been shown in patients with bilateral drusen, disciform scars, and RPE tears. From these observations and the results described herein, it seems that individual determinants play a role in the pathogenesis of the disease. This is not only the case for the specific type of manifestation (eg, atrophic vs neovascular ARMD) but also for a distinct topographic pattern of each particular manifestation. The evolution of GA at the posterior pole seems to be predetermined for each affected individual.

Environmental factors and nonspecific age processes have been implicated in the pathogenesis of ARMD. Also, a familial effect on the presence of ARMD has been shown in case-control series and in comparisons between spouses, siblings, and twins. Age-related macular degeneration is considered to represent a complex multifactorial disease, the pathogenesis of which is incompletely understood. Likewise, it is unclear by what mechanisms a distinct topographic individual evolution of lesions such as areas of atrophy might be genetically determined.

Several previous studies have described the progression of GA over time. In a retrospective study, Schatz...

Figure 3. Mean differences between recordings by 2 independent marked readers (C.B. and J.J.). A, Size of the atrophic areas. Uppermost and bottommost lines indicate 95% limits of agreement (−7.0 to 8.1 mm²); central lines, 95% confidence interval (−0.38 to 1.44 mm²). B, Area of the convex hull. Uppermost and bottommost lines indicate 95% limits of agreement (−8.0 to 8.0 mm²); central lines, 95% confidence interval (−0.91 to 0.98 mm²).

Figure 4. Number of atrophic areas in the left and right eye of each patient.

Figure 5. Areas of atrophy in the left and right eye of each patient. There are obviously some patients with marked asymmetry (P=.81).

Figure 6. Areas of the convex hull of atrophic areas in the left and right eye of each patient.
and McDonald\textsuperscript{43} found a rate of spread of GA growth of 15 to 375 nm/\( \text{µm} \) (average, 139 nm/\( \text{µm} \)), whereby smaller areas tended to grow slower than larger atrophic areas. A prospective study on the natural history of the progression of GA by Sunness and coworkers\textsuperscript{41} recently demonstrated a mean enlargement of the total area of GA of 2.2 disc areas by 2 years. They reported that the amount of enlargement increased with increasing baseline total atrophy up to 5 disc areas of baseline atrophy and, interestingly, leveled off above 5 disc areas. From the results of our cross-sectional study, it may be speculated that the rate of spread observed during a longer period would also show symmetric features when examined in a longitudinal fashion. In addition, relative asymmetry in both eyes with early GA at a certain point may evolve into symmetric manifestation later during the natural course.

The confocal scanning laser ophthalmoscope used in this study, with an excitation wavelength of 488 nm and a barrier filter above 500 nm, allows for topographic detection of FA in vivo. Several findings of in vitro fluorescence microscopic examinations and in vivo fundus spectrophotometric studies suggest that the increased autofluorescence signal originates from lipofuscin accumulation in the lysosomal compartment of postmitotic RPE cells.\textsuperscript{36-34} In eyes with GA, various patterns of increased autofluorescence in the junctional zone, which phenotypically cannot be distinguished by conventional ophthalmoscopy, were recently described.\textsuperscript{41} A high degree of symmetry has been detected in these autofluorescence patterns. Therefore, symmetry seems not to be confined to visible lesions at the posterior pole but also involves metabolic changes in the surrounding RPE in the presence of GA. The accumulation of autofluorescent material may affect normal cellular function and may, therefore, be of pathophysiologic relevance.\textsuperscript{4,9,52,53} Further studies are needed regardless of whether different patterns of increased autofluorescence have an impact on the progression of the atrophy and the spread of corresponding scotoma and, therefore, whether they are of prognostic value.

Limitations of the present study include its retrospective design and the lack of longitudinal observations. Based on this cross-sectional study, we initiated an expanded natural history study for further evaluation of the progression over time, the functional impact, and the role of baseline autofluorescence patterns for the subsequent course.

Our results indicate intraindividual symmetry between both eyes in patients with GA associated with ARMD for number of lesions, size of atrophic areas, and convex hulls in the presence of a wide spectrum of intraindividual manifestations. The findings support the view that genetics may play an important role in the phenotypic appearance of ARMD and, therefore, that ARMD is not solely a result of a nonspecific aging process. Intraindividual symmetric manifestations, rather, reflect specific individual determinants, including genetic factors, in the pathogenesis of the disease. However, it is difficult to exclude the possibility that the similar phenotypic appearance in late stages of ARMD could be the result of a similar long-term exposure.

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\textbf{REFERENCES}
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