Differential Disease Progression in Atrophic Age-Related Macular Degeneration and Late-Onset Stargardt Disease

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PURPOSE. To compare the disease course of retinal pigment epithelium (RPE) atrophy secondary to age-related macula degeneration (AMD) and late-onset Stargardt disease (STGD1).

METHODS. Patients were examined longitudinally by fundus autofluorescence, near-infrared reflectance imaging, and best-corrected visual acuity (BCVA). Areas of RPE atrophy were quantified using semi-automated software, and the status of the fovea was evaluated based on autofluorescence and near-infrared reflectance images. Mixed-effects models were used to compare atrophy progression rates. BCVA loss and loss of foveal integrity were analyzed using Turnbull’s estimator.

RESULTS. A total of 151 patients (226 eyes) with RPE atrophy secondary to AMD and 38 patients (66 eyes) with RPE atrophy secondary to late-onset STGD1 were examined for a median time of 2.3 years (interquartile range, 2.7). Mean baseline age was 74.2 years (SD, 7.6) in AMD and 65.4 (SD, 9.9) in late-onset STGD1 (P = 1.1 × 10⁻⁷). Square root atrophy progression was significantly faster in AMD when compared with late-onset STGD1 (0.28 mm/year [SE, 0.01] vs. 0.23 [SE, 0.03]; P = 0.030). In late-onset STGD1, the median survival of the fovea was significantly longer when compared with eyes with AMD (8.60 vs. 3.55 years; P = 0.005) with a trend to a later BCVA loss of ≥3 lines (5.97 vs. 4.37 years; P = 0.382).

CONCLUSIONS. These natural history data indicate differential disease progression in AMD versus late-onset STGD1. The results underline the relevance of refined phenotyping in elderly patients presenting with RPE atrophy in regard to prognosis and design of interventional trials.

Keywords: Stargard disease, age-related macular degeneration, fundus autofluorescence, retinal pigment epithelium, geographic atrophy

Atrophy of the RPE represents a common late-stage manifestation of various retinal diseases, including late-stage dry age-related macula degeneration (AMD) and Stargardt disease (STGD1). In industrialized countries, late-stage neovascular or advanced dry AMD is the leading cause of legal blindness in the elderly. Although the exact pathogenetic mechanisms leading to geographic atrophy are still poorly understood, chronic inflammatory processes, excessive lipofuscin accumulation in the RPE lysosomal compartment, complement system dysregulation, and vascular factors have been implicated in the development of AMD.

In contrast to the multifactorial etiology of AMD, STGD1 is an autosomal recessive retinal dystrophy caused by pathogenic sequence variants in the adenosine triphosphate-binding cassette, subfamily A, member 4 (ABCA4, MIM 601691) gene. ABCA4 encodes an integral transmembrane protein, expressed in retinal photoreceptors. It is involved in the clearance of all-trans-retinal aldehyde, a byproduct of the retinoid cycle of vision. ABCA4 dysfunction leads to the accumulation of lipofuscin and its constituent, di-retinoid-pyridinium-ethanolamine, finally resulting in RPE atrophy development. Comparable ages of onset as well as funduscopic parallels result in a certain risk in confounding AMD and late-onset STGD1. It is well understood that distinction between both conditions is of practical relevance to an individual patient with regard to genetic counseling. Yet to what extent differentiation between both conditions also influences individual prognosis in terms of visual acuity loss and RPE atrophy progression has not been assessed. Extending our analysis on two recently described cohorts, in the present work we identify significant differences in the course of AMD and late-onset STGD1. These results underline the relevance of refined phenotyping in patients presenting with RPE atrophy. Furthermore, the improved understanding of the distinct kinetic of disease progression will be relevant for emerging therapeutic approaches.

METHODS

Patient Identification

The present study consists of the following two distinct cohorts: patients with RPE atrophy secondary to AMD and...
patients with RPE atrophy associated with late-onset STGD1. Inclusion criteria for the current analysis for both cohorts were the following: (1) at least one well-defined contiguous area of RPE atrophy corresponding to areas of reduced fundus autofluorescence (FAF) to an extent of ≥0.05 mm² (the size of the smallest atrophic area in cases of multifocality) in one or both eyes and (2) clear ocular media allowing for acquisition of high-quality FAF images. For inclusion into the AMD cohort, soft drusen and/or retinal pigment abnormalities consistent with the diagnosis of AMD had to be present. For inclusion into the late-onset STGD1 cohort, patients had to exhibit typical yellow-white flecks or dots correlating with hyperautofluorescent flecks on 488-nm FAF imaging. This FAF pattern had previously been termed “fine granular pattern with peripheral punctate spots (GPS+).” The clinical phenotype of late-onset STGD1 was supported by at least one (likely) pathogenic variant in the ABCA4 (NM_000350.2) gene. The peripherin-2 gene (PRPH2, NM_000322.4) was additionally sequenced in patients with fewer than two ABCA4 (likely) pathogenic variants to exclude autosomal-dominant multifocal pattern dystrophy or central areolar choroidal dystrophy. Patients had to be at least 45 years of age at self-reported symptom onset. Both eyes of a patient were included in the analysis if the inclusion criteria were met. General exclusion criteria for both cohorts were the presence of retinal disease that could possibly confound observations (e.g., diabetic retinopathy, present or past exudative events, idiopathic serous chorioretinopathy).

All of the patients were recruited in the context of the Fundus Autofluorescence in Age-Related Macular Degeneration (FAM) Study or at the outpatient department of Radboud University Medical Center. The study followed the tenets of the Declaration of Helsinki. Approval by the institutional review boards was obtained by each of the participating centers. Informed consent was obtained from each participant after an explanation of the study’s nature and possible consequences of participation. Both cohorts have previously been reported elsewhere.

Assessment of Visual Acuity

At each visit, best-corrected visual acuity (BCVA) was determined using a Snellen or Early Treatment Diabetic Retinopathy Study chart. Visual acuity is reported in logarithm of the minimum angle of resolution (logMAR) notation. Visual acuity of counting fingers was set to 1.8 logMAR and hand motions to 2.2 logMAR.

Image Acquisition and Grading

FAF images were acquired using HRA2 or Spectralis HRA+OCT (Heidelberg Engineering, Heidelberg, Germany) with an excitation wavelength of 488 nm and an emission spectrum of 500 to 700 nm using the high-speed mode. Near-infrared (NIR) reflectance images were obtained with an excitation wavelength of 820 nm. The field of view was centered on the fovea and set to 30° × 30° or 55° × 55° to fit the entire area of atrophy. Images were acquired with a minimum resolution of 512 × 512 pixels and single FAF images were automatically aligned and averaged to maximize the signal-to-noise ratio using the manufacturer’s software.

Areas of RPE atrophy were measured on FAF images applying image processing software based on gray value detection for semi-automated identification of atrophic RPE areas. Only areas of decreased autofluorescence > 0.05 mm² were considered to represent RPE atrophy. The involvement of the fovea by the atrophic process was determined based on FAF and NIR reflectance images and was graded as present or past exudative events, idiopathic serous chorioretinopathy.

The total atrophy size measured for each visit was square-root transformed to reduce the dependency of enlargement rates on baseline lesion size (√area [mm²]) as previously suggested. To quantify atrophy progression rates within the patient collective, a linear mixed-effects model was used as described earlier. The two-level, random-effects model used here separates eye-specific and patient-specific effects and accounts for dependencies between measurements that were obtained from the same patient and/or eye.

The factor “AMD” versus “LO-STGD1” was included as a fixed effect in the model. Backward selection of the other covariates, including higher order interactions, was used to build the final linear-mixed-effects model.

Turnbull’s estimator was used to estimate the percentages of eyes with BCVA loss ≥ 0.6 logMAR (≥ 6

FIGURE 1. Multimodal imaging as performed in this study of representative left eyes of a patient with retinal pigment epithelium atrophy secondary to AMD and a patient with retinal pigment epithelium atrophy secondary to late-onset STGD1.

follows: definitely involved, probably involved, probably not involved, and definitely not involved. For further analysis, these gradings were summarized to “involved” and “not involved.” A representative example of an eye with RPE atrophy secondary to AMD and RPE atrophy secondary to late-onset STGD1 is provided in Figure 1.

Statistical Analysis

The total atrophy size measured for each visit was square-root transformed to reduce the dependency of enlargement rates on baseline lesion size (√area [mm²]) as previously suggested. To quantify atrophy progression rates within the patient collective, a linear mixed-effects model was used as described earlier. The two-level, random-effects model used here separates eye-specific and patient-specific effects and accounts for dependencies between measurements that were obtained from the same patient and/or eye.

The factor “AMD” versus “LO-STGD1” was included as a fixed effect in the model. Backward selection of the other covariates, including higher order interactions, was used to build the final linear-mixed-effects model.

Turnbull’s estimator was used to estimate the percentages of eyes with BCVA loss ≥ 0.3 logMAR (≥ 3 Early Treatment Diabetic Retinopathy Study chart lines) and ≥ 0.6 logMAR (≥ 6
Disease Progression in AMD and Late-Onset STGD1

| TABLE 1. Baseline Characteristics of Patients With AMD and Late-Onset STGD1 |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Characteristic  | AMD Patients, n | Mean ± SD, %    | Late-Onset STGD1 Patients, n | Mean ± SD, %    |
| Gender          | 55              | 36.4            | 17              | 44.7            | 0.449*          |
| Male            | 96              | 65.6            | 21              | 55.3            |
| Disease status  |                 |                 |                 |                 |
| Bilateral RPE atrophy | 86          | 61.4            | 27              | 71.1            | 0.006*          |
| RPE atrophy + NV in fellow eye | 39        | 27.9            | 2               | 5.2             |
| RPE atrophy + “early” changes in fellow eye | 15    | 10.7            | 9               | 23.7            | 0.117*          |
| Follow-up time, y | 151         | 2.2† (IQR: 2.6) | 38              | 2.5† (IQR: 3.6) | 0.774‡         |
| Age, y          | 151            | 74.2 ± 7.6      | 38              | 63.4 ± 9.9      | <0.001§        |
| Status of the fovea at baseline | 226 | 6.3 ± 5.0        | 66              | 6.2 ± 7.3       | 0.914§          |
| Atrophy size, mm² | 226          | 6.3 ± 5.0        | 66              | 6.2 ± 7.3       | 0.914§          |
| Not involved    | 122            | 54.0            | 57              | 86.4            | <0.001*         |
| Involved        | 104            | 46.0            | 9               | 13.6            |
| Visual acuity, logMAR | 226 | 0.6 ± 0.4        | 66              | 0.4 ± 0.4       | 0.001§          |

SD, standard deviation; IQR, interquartile range.
*χ² test.
†Mean.
‡ Mann-Whitney.
§ t-test.

Early Treatment Diabetic Retinopathy Study chart lines) from baseline, as previously reported. A similar approach was used to estimate the percentage of eyes with loss of foveal integrity over time (status transition of the fovea from “not involved” to “involved”). A comparison of the course of BCVA and of the foveal status between AMD versus late-onset STGD1 was performed using the log-rank test.

RESULTS

Patients

A total of 226 eyes (151 patients; 55 males, 96 females) with RPE atrophy secondary to AMD and 66 eyes (38 patients; 17 males, 21 females) with RPE atrophy secondary to late-onset STGD1 were examined over time. At baseline, 113 patients exhibited bilateral RPE atrophy (86 patients with AMD and 27 patients with late-onset STGD1). In 24 patients, the fellow eye had early changes, that is, disease-related alterations without atrophy or neovascularization (15 patients with AMD and nine patients with late-onset STGD1; $P = 0.117$), and 41 patients exhibited neovascularization in the fellow eye (39 patients with AMD and two patients with late-onset STGD1; $P = 0.006$). In 11 patients, only one eye was included because the fellow eyes fulfilled any of the exclusion criteria (e.g., insufficient imaging quality). One eye did not contribute to the analysis because neovascularization developed right after the first visit.

Baseline Characteristics

Mean age at baseline was 74.2 years (SD, 7.6) in the AMD and 63.4 years (SD, 9.9) in the late-onset STGD1 patient cohort. At first presentation, RPE atrophy size in AMD patients was 6.5 mm² (SD, 5.0) and 6.2 mm² (SD, 7.5) in late-onset STGD1 ($P = 0.914$). At baseline, the fovea was graded as “not involved” in 54.0% of eyes (122 of 226 eyes) with AMD and in 86.4% of eyes (57 of 66 eyes) with late-onset STGD1 ($P = 4.1 \times 10^{-6}$). BCVA at baseline was significantly different between both cohorts with 0.6 logMAR (SD, 0.4) in AMD and 0.4 logMAR (SD, 0.5) in late-onset STGD1 ($P = 1.3 \times 10^{-3}$). An overview on baseline characteristics is given in Table 1.

Disease Progression

Data of a total of 897 eye visits were included in the analysis. The median follow-up time was 2.2 years (interquartile range [IQR], 2.6) in AMD and 2.5 years (IQR, 3.6) in late-onset STGD1 ($P = 0.774$). To compare atrophy progression kinetics between AMD and late-onset STGD1, a linear mixed-effects model was used. Average square-root transformed atrophy progression was 0.28 mm/year (SE, 0.01) in AMD, and 0.23 mm/year (SE, 0.03) in late-onset STGD1 ($P = 0.011$). Model results were corrected for distinct age structures between the cohorts by including age as a fixed effect (coefficient estimate: 0.02 ± 0.00; $P = 0.011$).

Transition of the status of the fovea from “not involved” to “involved” during the observational period was observed in 48 eyes with AMD (39.3% of eyes with “not involved” fovea at baseline) and in only 5 eyes with late-onset STGD1 (8.8% of eyes with “not involved” fovea at baseline). Notably, the follow-up period in late-onset STGD1 patients was longer than in AMD patients (see earlier). Time-to-event analyses revealed a median time from noninvolvement of the fovea at baseline to foveal involvement of 3.55 years (95% confidence interval [CI], 2.50–4.15) in AMD and 8.60 years (CI, not available) in late-onset STGD1 (Table 2). In parallel, a visual acuity loss of ≥5 and ≥6 lines, respectively, occurred consistently, although not significantly, later in late-onset STGD1 when compared with AMD (Table 2). Figure 2 shows two representative disease courses in an eye with late-onset STGD1 and an eye with AMD.

DISCUSSION

This study reveals differences between AMD and late-onset STGD1 with respect to both atrophy progression and changes in visual acuity. We found a significantly faster atrophy
progression in eyes with AMD along with significantly lower BCVA scores at baseline and faster, albeit not significant, loss of BCVA.

Atrophy progression and visual acuity courses have been previously assessed independently in both AMD and STGD1. Although distinct analytic strategies preclude direct comparisons, our data are overall compatible with previously published values.10,25–28 Despite similar lesion size at baseline, patients with late-onset STGD1 had a better BCVA, presumably because their fovea was more frequently intact (86.4% vs. 54% of eyes with AMD). Moreover, they had both atrophy progression kinetics and survival times of the fovea in favor, but the difference in decline in BCVA when compared with AMD was less pronounced. We have recently reported that the parameters “status of the fovea,” “total lesion size,” and the “age at baseline” in eyes with atrophy as a result of AMD have a significant impact on BCVA and that these factors together explain 65% of BCVA variability.9 The remaining 35% of BCVA variability may be explained by other factors, such as media opacities and the general mental status. In addition, it may be explained by BCVA test variability itself.

Foveal sparing is observed in several retinal diseases,8,10,15,20,29–33 exhibiting a specific pattern of RPE atrophy surrounding an intact foveal island. Although the present study did not differentiate between this typical pattern of foveal sparing and general foveal noninvolvement, patients with a long-term preservation of foveal integrity may develop eventual foveal sparing. Interestingly, eyes with an uninvolved fovea at baseline progressed to foveal atrophy during the review period in almost 40% of eyes with AMD, but only 8.8% of eyes with late-onset STGD1, despite their slightly longer follow-up. Atrophy being more closely to the fovea at first presentation may be a reason for requiring less time to involve the fovea into the atrophic process in AMD. Another explanation may be a longer foveal survival because of the protecting mechanisms in late-onset STGD1. Yet foveal sparing can be present in phenotypes that are independent of ABCA4 sequence variants, including AMD.8,15,20,29–35 and is infrequent in a general STGD1 population.15 Therefore, other genetic factors and distinct anatomical, metabolic, and/or biochemical aspects are likely involved.

A further hallmark contrast between both cohorts was the frequency of neovascularization observed in fellow eyes, which was less frequent in late-onset STGD1. For AMD, it has been described that atrophy progression is slower in eyes with a fellow eye exhibiting neovascularization.34 We did not correct for this factor in the linear mixed-effects model. Yet from the available data on AMD,34 we would expect the difference between AMD and late-onset STGD1 to become even larger when correcting for this factor.

Our patients with biallelic—but also with mono-allelic—ABCA4 variants share an identical phenotype that exhibits typical flecks of increased FAF surrounding the atrophic lesion; it resembles the FAF pattern in patients with typical STGD1. Given the high carrier frequency up to 1:25,35 it is highly unlikely that a single pathogenic ABCA4 variant can cause this phenotype on its own. In analog, several cases with typical STGD1 are to date also genetically still unsolved by failing to detect a second pathogenic ABCA4 variant. However, these second “missing” pathogenic variants are now increasingly being found with recent genetic techniques.36 We postulate that either a second sequence variant affecting ABCA4 function or other genetic factors that lower the total ABCA4 function are still to be found in our patients with mono-allelic

### Table 2. Median Times to Event for Foveal Involvement and Vision Loss in AMD and Late-Onset STGD1

<table>
<thead>
<tr>
<th>Event</th>
<th>AMD</th>
<th>Late-Onset STGD1</th>
<th>Log-Rank</th>
<th>P Value, Log-Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fovea becomes involved</td>
<td>3.35 y, 2.50–4.15</td>
<td>8.60 y, n.a.</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>Visual acuity loss ≥3 lines</td>
<td>4.37 y, 2.96–4.37</td>
<td>5.97 y, 4.01–5.97</td>
<td>0.382</td>
<td></td>
</tr>
<tr>
<td>Visual acuity loss ≥6 lines</td>
<td>7.52 y, 7.52–∞</td>
<td>33.2% had event after 7.50 years</td>
<td>0.320</td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; n.a., not available.
ABCA4 variants. They may be sufficient to cause this distinct phenotype at the mild end of STGD1 and in the disease spectrum of AMD. With regard to these hypotheses, recent studies are of particular interest quantifying normal levels of lipofuscin in parents of patients with STGD1.57,58 Furthermore, it has also been reported that abca4+/− mice show increased levels of some bis-retinoids.39 Overall, the pathogenesis of cases with a typical STGD1 phenotype and only one identified pathogenic ABCA4 variant remains controversial. Nonetheless, it appears reasonable to require detection of at least one pathogenic ABCA4 variant in patients with this distinct late-onset phenotype to assign the clinical diagnosis late-onset STGD1.

One may argue about how this distinct late-onset atrophy phenotype associated with ABCA4 should be entitled. In the FAM Study, this phenotype was originally termed “fine granular pattern with peripheral punctate spots” (GPS[+]i) and was classified as a subtype of AMD.11,12 In two independent approaches, we found an association of this late-onset phenotype with mono- and biallelic ABCA4 variants.8,11 Here, we postulate that late-onset STGD1 and GPS[+]i describe the same entity. Analyses of ABCA4 gene variants in AMD were not performed in this study. Several earlier works have addressed the issue of ABCA4 in large cohorts from a genetic point of view, giving controversial results.40-42 A recent study in AMD did not detect increased lipofuscin levels, which should be expected in retinal disease associated with ABCA4.43 However, further contributing to this controversy will require (1) a clinically well-phenotyped AMD cohort where late-onset STGD1/GPS[+]i patients are excluded, (2) a well-matched control cohort, and (3) state-of-the-art genetic approaches to identify relevant variants, which was beyond the scope of this work.

Optical coherence tomography was not included in this study, which may have caused uncertainty to the grading of foveal involvement. In particular, only the definite gradings “involved” versus “not involved” were compared in contrast to other works.9,44 Another limitation included the two cohorts being unequal in number of patients: because of the smaller late-onset STGD1 cohort, time-to-event curves were affected more strongly by the potential loss of follow-up here when compared with a dropout of an AMD patient. Yet time-to-event analyses are robust against such dropouts as long as patients who are more likely to suffer the event early during follow-up are not more (or less) likely to drop out. These limitations are balanced by the large cohorts of both AMD and late-onset STGD1 patients who were included into this study and followed during a long period of time.

Differential disease progression between AMD and late-onset STGD1 are particularly important to emerging therapeutic trials. Strategies in multifactorial AMD range from choroidal perfusion enhancers over neuroprotective agents to complement inhibitors.4 Preclinical data suggest that complement activation is a final common pathway leading to RPE cell death in both conditions45,46; for AMD, the MAHALO trial also shows therapeutic effects in human.47 Yet patients with ABCA4-related late-onset STGD1 will rather benefit if earlier and more specific disease processes are targeted, for example, by focusing on the visual cycle or retinal ABCA4-gene delivery (e.g., NCT01367444, clinicaltrials.gov and Ref. 48). Therefore, it appears prudent to carefully distinguish between late-onset STGD1 and AMD. Inclusion of late-onset STGD1 patients into interventional AMD trials, and vice versa, would blur the therapeutic effect under observation and potentially lead to a fail in proving efficacy.

Furthermore, although the clinical diagnosis of late-onset STGD1 can be supported by the detection of one disease-causing ABCA4 variant, it would be prudent to require the identification of two disease-causing variants before enrollment in early therapeutic trials involving late-onset STGD1 patients.

In summary, the present analysis reveals distinct progression characteristics in eyes with RPE atrophy associated with AMD and late-onset STGD1. These results underscore the relevance of refined phenotyping to predict the course of disease in a patient presenting with RPE atrophy. The results enable more sophisticated prognosis for the individual patient and should be considered when designing future intervention trials for both.

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References


APPENDIX

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