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Dark Atrophy: An Optical Coherence Tomography Angiography Study

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Purpose: To assess the status of choriocapillaris in eyes with macular atrophy secondary to age-related macular degeneration (AMD) (geographic atrophy [GA]) and Stargardt disease (STGD) using optical coherence tomography angiography (OCTA).

Design: Prospective, observational case series.

Participants: A total of 14 patients (20 eyes) affected by GA and 10 patients (20 eyes) affected by STGD.

Methods: Each patient underwent a complete ophthalmological examination including fundus autofluorescence (FAF), dynamic simultaneous fluorescein angiography (FA) and indocyanine green angiography (ICGA), enhanced-depth imaging optical coherence tomography (EDI-OCT) (HRA+OCT Spectralis, Heidelberg Engineering, Heidelberg, Germany), and OCTA using AngioVue technologies (Optovue Inc, Freemont, CA).

Main Outcome Measures: An evaluation of the status of choriocapillaris in the 2 groups was performed.

Results: Patients' mean age was 75 years for subjects with GA (median, 76 years; range, 63−88 years) and 61 years for STGD (median, 62 years; range, 40−74 years). Atrophy was bilateral in 42% (n = 6) of subjects with GA and 100% (n = 10) of subjects with STGD. In the early frames, FA displayed hyperfluorescence in the atrophic area in 100% (n = 20) of eyes affected by GA and 20% (n = 4) of eyes affected by STGD; dark choroid was present in 0% of GA eyes and 65% of STGD eyes (n = 13). Atrophy in ICGA late frames was hypofluorescent in 20% (n = 4) of GA eyes and 100% (n = 20) of STGD eyes. A ring at atrophy margins was detected in both FA (90%, n = 18) and ICGA (100%, n = 20) in STGD eyes. Mean subfoveal choroidal thickness was 156 μm (147, 42−362 μm) for GA eyes and 168 μm (167, 55−320 μm) for STGD eyes ($P = 0.59$). At OCTA evaluation, GA eyes showed persisting, rarefied choriocapillaris in correspondence of retinal pigment epithelium (RPE) atrophy in 80% (n = 16) of cases, whereas eyes affected by STGD had disappearance of this tissue in 100% (n = 20; $P < 0.0001$).

Conclusions: Analysis of macular atrophy by OCTA in patients with STGD revealed an extensive loss of choriocapillaris in the central area with persisting tissue at its margins, whereas in those with GA the area of RPE loss showed persistent but rarefied choriocapillaris. *Ophthalmology 2016;■:1−8 © 2016 by the American Academy of Ophthalmology.*

Fundus autofluorescence (FAF) represents a useful, noninvasive imaging technique capable of providing information related to the metabolic status of retinal pigment epithelium (RPE).[1,2] For this peculiarity, FAF gradually has become the gold standard for identifying areas of RPE atrophy occurring in several retinal and choroidal disorders and monitoring their progression over time.[3−6] Previous studies based on FAF imaging also have described the possibility of recognizing peculiar autofluorescence patterns in eyes affected by geographic atrophy (GA) and predicting their rate of progression.[7,8] Despite the possibility of providing evidence of signs of disease activity, FAF features inside the area of RPE atrophy do not provide information on the pathogenesis, and a multi-imaging approach is often crucial.

In 2012, we observed that indocyanine green angiography (ICGA) could play a role in characterizing areas of RPE atrophy.[9] In particular, the authors described ICGA findings in eyes affected by GA and Stargardt disease (STGD) and defined the so-called dark atrophy consisting of hypofluorescence by ICGA late phases. This sign possibly was correlated to an early damage to the choriocapillaris and was described in 92% of eyes affected by STGD and only 13% of eyes affected by GA. For this reason, the identification of this sign represents a possible diagnostic tool, especially for those patients with late onset of the disease.

More recently, new imaging techniques have been described: optical coherence tomography angiography (OCTA), and, in particular, the split-spectrum amplitude decorrelation angiography (SSADA) algorithm provides a noninvasive, safe, and rapid assessment of both retinal and choroidal vascular structures.[10−12] In this series, we evaluated OCTA features in subjects affected by atrophic age-related macular degeneration (AMD) and STGD with particular attention to the choriocapillaris and ICGA pattern.

Methods

This prospective, observational case series was conducted on 20 eyes from 14 subjects diagnosed with GA and 20 eyes from 10 patients affected by STGD. All eyes were evaluated by OCTA at the Eye Clinic, Department of Biomedical and Clinical Sciences

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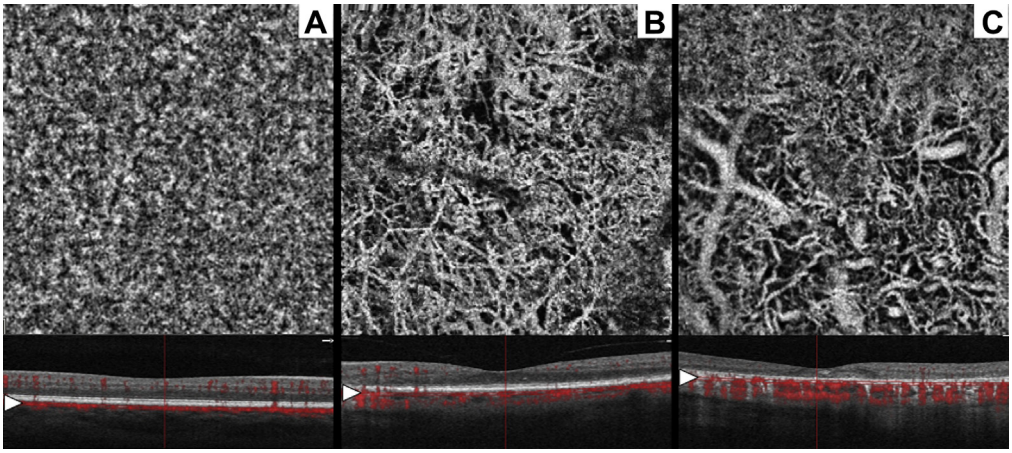

Figure 1. Optical coherence tomography angiography (OCTA) of 3 eyes showing different degrees of choriocapillaris impairment and used as reference images by reviewers: normal (**A**), rarefied (**B**), and absent (**C**); the corresponding cross-sectional images and slab position are shown (*bottom*).

"Luigi Sacco," Luigi Sacco Hospital, University of Milan between September 2014 and April 2015. Institutional review board approval was obtained. A literature review on the Medline website (http://www.ncbi.nlm.nih.gov/pubmed) was conducted using the key words "optical coherence tomography angiography," "split-spectrum amplitude decorrelation angiography," and "Stargardt" "atrophic age-related macular degeneration" to find previous studies on this topic with no significant reports available. Criteria for STGD diagnosis were a history of decreased best-corrected visual acuity (BCVA) before 40 years of age in association with the presence of flecks at slit-lamp biomicroscopic fundus examination and RPE atrophy at the posterior pole; details of ABCA4 genotyping were recorded for diagnosis confirmation. Subjects with a history of surgical or laser procedures on the retina and local or systemic disorders possibly affecting the choroid or the RPE were excluded from the study, as well as eyes with poor fixation.

Demographic and clinical data recorded included age, race, gender and laterality (unilateral, bilateral, and eye affected), and BCVA using Early Treatment Diabetic Retinopathy Study (ETDRS) charts. All patients underwent a complete ophthalmologic and imaging assessment; informed consent was obtained for each subject. Fundus photography was obtained with the Canon CX-1 camera (Canon, Tokyo, Japan). Near-infrared, 488 nm FAF, fluorescein angiography (FA), ICGA, and enhanced-depth imaging optical coherence tomography (EDI-OCT) were captured using a confocal scanning laser ophthalmoscope (Spectralis HRA+OCT, Heidelberg Engineering, Heidelberg, Germany). Fluorescein angiography and ICGA pattern of both the center and margins of the atrophic area (hypofluorescence or hyperfluorescence during FA early phases and evidence of dark atrophy at ICGA) were recorded. The EDI-OCT examination included volume scans of the macula with rasters varying according to the extension of the atrophic area and ART image averaging equal 25 frames and a cross-line through the foveola with automatic real time (ART) image averaging equal 100 frames. Mean subfoveal choroidal thickness was manually assessed using the software-based caliper function by tracing a straight line from Bruch's membrane (or outer RPE surface if Bruch's membrane was not directly detectable) to the sclero-choroidal interface. The OCTA examination was performed using the SSADA algorithm included in the AngioVue imaging system based on the RTVue XR Avanti (Optovue Inc, Freemont, CA). At OCTA imaging, the choriocapillaris typically appeared as a dense, fine, vascular network immediately below the RPE as described by previous OCTA reports and was identified by setting 2 reference lines (choriocapillaris slab) separated by 10 μm immediately below the RPE level and eventually manually adjusting only their position in case of projection artifacts and consequently finding the first plane with no projection artifacts.[13–15] The status of choriocapillaris inside the atrophic area, at its margins, and outside the area of RPE loss was recorded for both GA and STGD. Analysis of the imaging was conducted by 2 independent physicians (M.P. and A.A.) with a further evaluation by a senior consultant (G.S.) in case of disagreement using reference pictures showing a different amount of choriocapillaris impairment (Fig 1). The significance of the difference between the 2 groups was analyzed using the Fisher exact test for qualitative features and the *t* test for quantitative data.

Results

A total of 20 eyes from 14 subjects (7 men and 7 women) affected by GA and 20 eyes from 10 patients (6 men and 4 women) affected by STGD were included in this series. The demographic features and symptoms are listed in Table 1. All subjects were white; mean age was 75 years (median, 76 years; range, 63–88 years) for those with GA and 61 years (median, 62 years; range, 40–74 years) for those with STGD. Macular atrophy defined as areas of RPE loss was bilateral in 42% (n = 6) of GA eyes and 100% (n = 10) of STGD eyes. Mean BCVA was 20/50 (median, 20/50; range, 20/400–20/20) in eyes affected by GA and 20/63 (median, 20/80; range, 20/400–20/25) for eyes affected by STGD.

Imaging features (FAF, FA, ICGA, EDI-OCT, and OCTA) are summarized in Table 2. The atrophic area at FAF examination was hypoautofluorescent in all cases. Fluorescein angiography examination displayed increasing fluorescence by early frames in the atrophic area in 100% (n = 20) of eyes affected by GA and 20% (n = 4) of eyes affected by STGD; in 80% of eyes affected by STGD (n = 16), hypofluorescence was noticed in the atrophic area with residual well-demarcated hyperfluorescent choroidal vessels. Dark choroid evaluated by FA was present in 0% of subjects diagnosed with GA and 65% (n = 13) of subjects diagnosed with STGD. In ICGA, dark atrophy (late hypofluorescence) was observed in 20% (n = 4) of GA eyes and 100% (n = 20) of STGD eyes. A ring of mild hyperfluorescence at FA imaging and hyperfluorescence on ICGA at atrophy margins could be evidenced at both FA (90%, n = 18) and ICGA (100%, n = 20) examination in STGD eyes, whereas this finding did not occur in the GA group. Mean subfoveal choroidal thickness evaluated by EDI-OCT was 156 μm (median, 147 μm; range, 42–362 μm) in