Progression of Geographic Atrophy and Impact of Fundus Autofluorescence Patterns in Age-Related Macular Degeneration

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Holz et al. tested whether fundus autofluorescence (FAF) patterns around geographic atrophy have an impact on geographic atrophy progression rates in atrophic age-related macular degeneration. Using confocal scanning laser ophthalmoscopy, the researchers obtained standardized digital FAF images from 195 eyes of 129 patients with geographic atrophy. They quantified areas of geographic atrophy and classified patterns of abnormal FAF in the perilesional zone. Conducting repeat FAF images over a median follow-up period of 1.8 years, the researchers identified distinct phenotypic FAF patterns with an impact on atrophic AMD disease progression. Progression rates were greater in eyes with the banded and diffuse FAF patterns and significantly higher than in eyes without FAF abnormalities or with focal FAF patterns. A new phenotype—diffuse trickling pattern—exhibited the highest spread rate (median 3.02 mm^2/year). This was nearly double the rate of other diffuse types (1.67 mm^2/year, $P = 0.001$). Underscoring the relevance of FAF imaging and the pathogenetic role of excessive lipofuscin accumulation in geographic atrophy, the study's findings indicate the prognostic power of phenotypic FAF patterns in the progression of atrophic AMD.

Thought to be the end stage of atrophic age-related macular degeneration, geographic atrophy is responsible for about 20 percent of legal blindness related to the disease.[1] However, until recently, geographic atrophy has garnered relatively little attention compared with wet macular degeneration.

"There is now a very efficient pharmacological treatment for neovascular AMD," said Frank G. Holz, MD. "But for late dry AMD, there is no treatment available yet. Therefore, better insight into its pathophysiology is needed to come forward with treatments for this disease."

Changes in cells during pathological processes such as geographic atrophy produce modifications in the amount and distribution of endogenous fluorophores. In this study, FAF was recorded using confocal scanning laser ophthalmoscopy. Generating an image with high resolution, it can "visualize a metabolic process in the retinal pigment epithelium," said Dr. Holz.

A laser source induces autofluorescence signals in lipofuscin granules, which are located in the RPE cell monolayer and composed of many fluorophores and molecular species. Based on observation using FAF imaging, lipofuscin is implicated in the AMD disease process, said Dr. Holz.

"Areas of the retina with the highest FAF signal—indicative of a high level of toxic lipofuscin compounds—undergo cell death over time. When we looked at a multicenter natural history study, there were distinct phenotypes with regard to the alterations in the fundus autofluorescence of the retinal area outside the atrophic patches," said Dr. Holz, who identified a new diffuse pattern with the fastest progression rate.

By contrast, no significant correlation to progression was found with risk factors such as smoking, hypertension or diabetes. Although not proven, said Mark W. Johnson, MD, this suggests that the amount or pattern of lipofuscin in eyes with geographic atrophy is genetically determined.

Nelson R. Sabates, MD, called this the "first significant study that shows us some objective parameters for measuring geographic atrophy over time. To really definitively stamp this classification system as appropriate, we need obviously to look at hundreds more."

This predictor of progression allows us to do several things, said Dr. Johnson. "For one, it gives the clinician a simple, noninvasive, photographic test that provides patients with information about their own prognosis." Dr. Johnson admitted that this "raises the conundrum of any test that tries to predict a patient's future," particularly when treatment is unavailable. However, said Dr. Holz, it is encouraging that "promising targets, including accumulation of toxic lipofuscin compounds such as A2-E, have been identified and clinical trials have been initiated that incorporate fundus autofluorescence."

Dr. Holz identified two questions his study could not answer: One concerns whether the fundus camera—more readily available in general ophthalmologists' offices—might be suitable for identifying FAF patterns. The other question concerns the precise morphologic substrate of the phenotypes. For instance, is the increased lipofuscin due to proliferation of RPE cells sitting on top of each other? Or, have individual cells become enlarged with more lipofuscin? These are questions for ongoing studies applying simultaneous spectral-domain, high-resolution optical coherence tomography.

—*Annie Stuart*

Dr. Holz has consulted for Heidelberg Engineering, the manufacturer of the cSLO Heidelberg Retina Angiograph, which was used for this study.

1 Friedman, D. S. et al. *Arch Ophthalmol* 2004;122:564–572.

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