Fundus autofluorescence (FAF) is a diagnostic imaging technique used to detect and document the presence of fluorophores in the retina. Fluorophores are chemical compounds that can re-emit light upon being exposed to light at a specific wavelength. In FAF, the fundus is illuminated with a specific wavelength, the natural fluorophores present in the fundus emit fluorescence when excited by this light, and the emitted fluorescence is captured and then processed into images.

There are several ways to detect FAF. Conventional fundus cameras are not very helpful in this regard; there is a low visual signal from intrinsic retinal fluorescence, high background noise, and a further drop in quality in the elderly mostly due to the crystalline lens. Therefore, either modifications of conventional cameras are needed, or more sophisticated imaging devices can be used. Delori and colleagues in 1995 used a fundus spectrophotometer to characterize FAF, mainly in a research setting. Also in 1995, von Ruckmann et al described use of scanning laser ophthalmoscopy (SLO) for this purpose.

Confocal scanning laser ophthalmoscopy (cSLO) offers the advantages of high image contrast and sensitivity, low light exposure, and reliable analysis of the relative distribution of FAF intensities. The quality of the images is much better with cSLO than with a modified fundus camera (Figure 1).

An individual FAF image provides only a low signal. During processing by cSLO devices such as the Spectralis (Heidelberg Engineering), therefore, several FAF images are averaged, a mean image is calculated, and the distribution of pixels is normalized, resulting in a better quality image.

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FAF in vivo shows the characteristics of lipofuscin in the fundus. Lipofuscin is a metabolic waste product found in many organs. In the eye, it is a product of retinoid and lipid oxidation during the visual cycle, as photoreceptor outer segments are recycled and incompletely digested. The concentration of lipofuscin in the fundus increases with age and in certain pathologic entities, including age-related macular degeneration (AMD).

**GEOGRAPHIC ATROPHY**

Using FAF, we can see the distribution of lipofuscin at the posterior pole. In healthy eyes, there is a relative

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**Figure 1.** Spectralis cSLO BluePeak FAF of geographic atrophy (A). Notice the much better quality of the image obtained with the Spectralis compared with a modified fundus camera (B).
decrease in signal at the center of the macula. This is due to absorption of light by the luteal pigment, an increase of melanin concentration in the retinal pigment epithelium (RPE), and a decrease in lipofuscin density.

In AMD, FAF is a marker that reflects the health of the RPE. It is particularly useful in the study of geographic atrophy (GA) in dry AMD (Figures 1-5). GA, for which no treatment is currently available, is the most common cause of visual dysfunction in patients with AMD.

In a prospective study in patients with high-risk drusen, members of the Fundus Autofluorescence in Age-related Macular Degeneration (FAM) Study Group showed that FAF patterns can predict progression from drusen to choroidal neovascular membrane and visual loss. These researchers examined 125 patients with multiple drusen using FAF with cSLO and described several baseline FAF patterns. The highest risk of developing neovascular membrane was associated with a patchy FAF pattern.

The FAM Study Group explored the significance of FAF patterns further in a larger study including 195 eyes of 129 patients with GA. Distinct phenotypic FAF patterns that have an impact on risk of disease progression were identified. The researchers determined that zones of hyper-autofluorescence at the borders of GA lesions can be important prognostic indicators.

This work suggested that increases in FAF seen in GA are caused by an increase in lipofuscin in the RPE. The increase in lipofuscin generally precedes cellular death; therefore, an increase in FAF represents an incipient area of atrophy.

The FAM researchers described several patterns and their associated rates of GA progression, which are listed in Table 1. In eyes with no anomalies in FAF, the rate of lesion enlargement was 0.02 mm²/yr. The progression rates in eyes with banded and diffuse patterns were significantly higher than in those without abnormalities or with focal FAF patterns.

**Table 1. Rates of GA lesion growth with different patterns of increased FAF**

<table>
<thead>
<tr>
<th>Pattern of Increased FAF</th>
<th>Lesion growth (mm²/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patterns</td>
<td>1.52</td>
</tr>
<tr>
<td>No abnormalities</td>
<td>0.38</td>
</tr>
<tr>
<td>Focal pattern</td>
<td>0.81</td>
</tr>
<tr>
<td>Diffuse (granular)</td>
<td>1.77</td>
</tr>
<tr>
<td>Band</td>
<td>2.52</td>
</tr>
<tr>
<td>Diffuse</td>
<td>3.78</td>
</tr>
</tbody>
</table>
Buildup of lipofuscin in the RPE is a normal function of age, but it can also occur in disease states including AMD, and increased FAF serves as a marker of RPE health.

These findings can help the clinician estimate how fast a given patient with GA will lose vision. FAF can identify patients at risk of rapid progression, and, once efficacious therapeutic interventions for GA become available, these patients can be treated expeditiously. Software now available for the Spectralis, called Region Finder, allows the clinician to measure FAF zones in a semiautomated way, and to follow them over time. (Figure 2).

CHOROIDAL NEOVASCULARIZATION

FAF has also been suggested to have predictive value in choroidal neovascularization (CNV) in wet AMD. Dandekar and colleagues observed used FAF to describe the characteristics of CNV in patients with AMD. In 65 eyes classified into 3 groups depending on the duration of CNV, FAF demonstrated that the RPE was preserved in eyes with early CNV, and visual acuity was better in eyes in which the RPE was preserved. They concluded that decreased FAF in eyes with longer duration of CNV indicated loss of RPE and photoreceptors.

Performing FAF in 43 eyes of 40 patients with exudative AMD, McBain and coworkers observed distinct patterns of FAF in eyes with pure classic vs occult CNV lesions. Notably, these authors did not detect hyper-FAF in eyes with CNV, suggesting that RPE lipofuscin does not play an important role in the pathogenesis of CNV membranes.

Using a combined grading system, Vujosevic and colleagues found that certain patterns of FAF are correlated with poor visual acuity outcomes. In general, hypo-FAF was correlated with poor visual acuity, and reticular and diffuse FAF patterns had worse prognoses. In addition, a reticular hyper-FAF pattern was correlated with worse visual acuity.

In another study from the same group, intact FAF at the macula in early CNV membranes correlated with visual acuity, symptom length, and lesion size. Notably in this study, it was posited that the RPE-photoreceptor complex remains intact for several months, even in the presence of CNV. This suggests that visual acuity might be rescued if an effective treatment was capable of suppressing neovascularization without damaging the RPE-photoreceptor complex.

Finally, a study by Heimes et al in 128 patients with exudative AMD found that eyes with normal FAF at baseline had better visual acuity outcomes. This may indicate that preexisting changes and irreversible damage in the outer retina or RPE are responsible for visual results after therapy.

Taken together, these studies suggest that, in eyes with exudative AMD, FAF can provide information about the health of the RPE and, indirectly, the photoreceptors. This could have value in predicting the natural history of exudative AMD and could help us to predict the visual response to treatment.

SUMMARY

FAF is a noninvasive method for imaging the fundus. Lipofuscin, the metabolic byproduct found in the RPE, is the fluorophore primarily responsible for FAF. Buildup of lipofuscin in the RPE is a normal function of age, but it can also occur in disease states including AMD, and increased FAF serves as a marker of RPE health.

In eyes with drusen, a patchy FAF pattern represents a high risk of developing CNV. The pattern of FAF seen in eyes with GA may be predictive of the velocity of progression of disease. And in eyes with CNV, FAF may have a predictive value for the natural history of the disease and may help predict the response to treatment.

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