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Retinal and Choroidal Imaging Update

Fundus autofluorescence imaging Fundamentals and clinical relevance

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Abstract

Fundus autofluorescence (FAF), a relatively new imaging modality, focuses on the fluorescent properties of pigments in the retina to generate images that help us view various disease processes from a different perspective. It aids us in the understanding of the pathophysiology of different retinal disorders. Recently, FAF imaging is being used commonly to help us in the diagnosis, prognosis as well as in determining the treatment response of various retinal disorders. It generates an image based on the distribution pattern of a fluorescent pigment called lipofuscin. Knowing the distribution pattern of lipofuscin in the normal retina is key to understanding an FAF image representing a retinal pathology. Like most other imaging modalities, FAF comes with its own limitations, taking steps to overcome these limitations will be of utmost importance in using this imaging modality to its fullest potential.

Keywords: Fundus autofluorescence, Retina, Imaging

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Introduction

Fundus autofluorescence (FAF) is a relatively new, non-invasive imaging modality that has been developed over the past decade. The FAF images are obtained through the use of confocal laser scanning ophthalmoscopy (cSLO). It uses the fluorescent properties of lipofuscin to generate images that provide information beyond that is acquired by utilizing more conventional imaging methods such as fluorescein angiography, fundus photography, and regular optical coherence tomography (OCT). FAF has been an area of interest in ophthalmic research for over 40 years. However, it has only recently become clinically relevant because of various important technological advances. FAF has proved to be helpful in understanding the pathophysiological mechanisms, diagnostics and identification of predictive markers for disease progression, and for monitoring of novel therapies.

Principle of auto-fluorescence imaging and interpretation of FAF Images

Retinal pigment epithelium (RPE) and lipofuscin

RPE is a single layer of polygonal shaped cells, which separates the choroid from the neurosensory retina. This epithelial layer plays a critical role in the normal functioning of the retina. It is responsible for phagocytosis and lysosomal

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breakdown of pigmented outer segments of photoreceptors, which allows the renewal process necessary to maintain photoreceptor excitability. Over the course of a lifetime, each RPE cell will phagocytose 3 billion outer segments.[1] With aging, incomplete or partial breakdown of these segments in the post-mitotic RPE cells causes the accumulation of lipofuscin (LP). Lipofuscin is composed of several different molecules, most important of which is A2E (*N*-retinyl-*N*-retinylidene ethanolamine) (Fig. 1). A2E is not recognized by lysosomal enzymes and therefore is incompletely broken down and accumulates in the lysosomes. An increased accumulation of this degraded material in the lysosomal compartment of the RPE cells is considered a hallmark of the aging process in the eye. In fact, a quarter of the RPE cytoplasm is composed of lipofuscin and melano-lipofuscin in persons over the age of seventy. Excessive lipofuscin deposition is considered pathologic and is associated with visual loss. There are significant clinical and experimental lines of evidence demonstrating that accumulation of lipofuscin above a certain threshold can cause functional loss of cells and lead to apoptosis.

Another component of lipofuscin, a toxic aldehyde known as all-trans retinal, is produced in the outer segments of the photoreceptor when exposed to light. Photoreceptors lack cis–trans isomerase function for retinal and are unable to regenerate all-trans-retinal into 11-cis-retinal after transduction of light energy (Fig. 2) into electrical impulses.[21] The excess all-trans-retinal accumulates within the photoreceptor, forming bisretinoids which upon oxidation contribute to lipofuscin production.[20]

Typical findings in the retina using fundus autofluorescence

FAF images demonstrate a spatial distribution corresponding to the intensity of the signal emitted, where dark pixel values correspond to low intensities of emission and bright pixel values correspond to high intensities of emission.[1] The naturally occurring autofluorescence of the ocular fundus is known to be of low intensity such that the distribution of FAF in normal eyes demonstrates a consistent pattern in which the optic nerve head typically appears dark due to the absence of lipofuscin in this area.[1] Retinal vessels are characterized by a reduced FAF signal due to the absorption by blood.[1] FAF signal is also reduced in the macular area, particularly around the fovea due to the absorption of the luteal pigment.[1] It can be noted that even though the signal in the parafoveal area tends to be higher, it presents with a relatively reduced intensity when compared to the background signal in the more peripheral areas of the retina. This observation is thought to be caused by an increased concentration of melanin, and decreased concentration of lipofuscin granules in central RPE cells.[1]

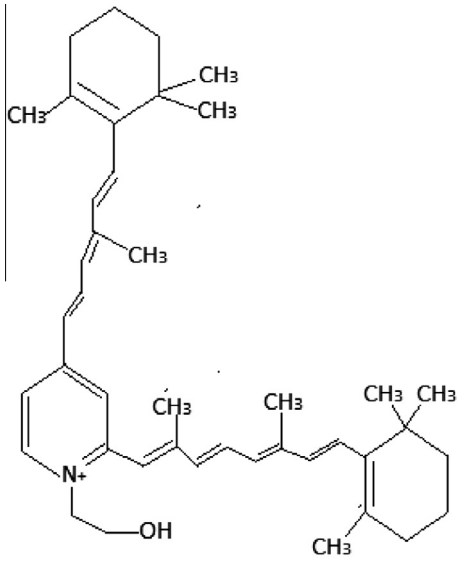

Figure 1. Chemical structure of A2E. (*N*-retinyl-*N*-retinylidene ethanolamine).

However, the distinction between the optic disk and the macula is reversed if the wavelength of the excitation source is changed (e.g. devices using blue light will give you the former pattern on the FAF images while devices using the green light will give you the latter) (Fig. 3). Green light FAF is relatively new and has not been available commercially until recently. Hence there is a lack of information as to how various diseased retinas would appear when scanned with a device utilizing a green light as the fluorophore excitation source.

Interpretations of the fundus autofluorescence images

Fundus autofluorescence imaging is used to record fluorescence that may occur naturally in ocular structures or as a byproduct of a disease process. This technique allows the topographic mapping of lipofuscin distribution in the RPE.[1] The intensity portrayed by FAF corresponds to the accumulation of lipofuscin, which increases with aging, RPE cell dysfunction or an abnormal metabolic load on the RPE.

When evaluating an FAF image, any deviation from the normal should be thoroughly investigated to identify a possible cause. Reasons for a reduced FAF signal may include but are not limited to: RPE loss or atrophy, intraretinal fluid, reduction in RPE lipofuscin density, fibrosis or presence of luteal pigment.[1] Causes for increased FAF signal may include but are also not limited to: drusen in the sub-pigmented epithelial space, excessive RPE lipofuscin accumulation, age-related macular degeneration or the occurrence of fluorophores anterior or posterior to the RPE cell monolayer.[1] However, it is to be noted that the quality of the image may be affected by the opacity of the vitreous, lens, cornea or anterior chamber and thus influence the identification of abnormalities. Thinner areas of retina adhere to the ''window effect'' meaning that they exhibit increased autofluorescence otherwise known as hyperautofluorescence.[2]

Clinical applications of fundus autofluorescence imaging

Various histopathological studies have demonstrated the accretion of autofluorescent material and deposits in the RPE in various retinal dystrophies. Since FAF imaging enables the visualization of changes in lipofuscin distribution in the RPE,[3] it can be useful in providing information about retinal dystrophies in which the health of the RPE is an important factor. FAF imaging has proven to be useful in regard to understanding and providing new perspectives concerning