Fundus Autofluorescence: From Basic Principles to Clinical Applications

Autofluorescência do Fundo Ocular: dos Princípios Básicos às Aplicações Clínicas

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ABSTRACT

Autofluorescence (FAF) is a valuable imaging technique in numerous retinal diseases, that may be underutilized in day-to-day practice. We aim to review the basic principles of blue-light autofluorescence and to highlight its clinical utility.

FAF is a rapid and noninvasive imaging technique of the ocular fundus. FAF images reflect the distribution of lipofuscin in the retinal pigment epithelium (RPE), allowing an assessment of RPE function and the detection of atrophic areas. There are various systems for image acquisition, resulting in qualitative and quantitative differences that should be considered upon image interpretation. Changes in FAF signal are observed in numerous diseases. Some present typical autofluorescence patterns that assist in the diagnosis, including age-related macular degeneration (AMD), retinal inherited diseases, inflammatory chorioretinopathies and antimalarials retinopathy. In the last years, studies have demonstrated a role for FAF in monitoring and predicting disease progression, especially in patients with AMD.

FAF is a useful modality both for diagnostic and disease monitoring purposes. Incorporation into the routine assessment of diseases such as AMD should be considered.

KEYWORDS: Fluorescein Angiography; Fundus Oculi; Macular Degeneration; Retinal Diseases.

RESUMO

A autofluorescência do fundo ocular (FAF) é um exame de imagem valioso em várias doenças da retina, que poderá ser subutilizado na prática clínica diária. O objectivo deste artigo é rever os princípios básicos da autofluorescência azul e realçar sua utilidade clínica.

A FAF é um exame de imagem não invasivo e rápido do fundo ocular. As imagens de FAF reflectem a distribuição da lipofuscina no epitélio pigmentar da retina (RPE), permitindo uma avaliação da sua função e a detecção de zonas de atrofia. Existem vários sistemas de aquisição de FAF, resultando em diferenças qualitativas e quantitativas que devem ser consideradas aquando da interpretação das imagens. Numerosas doenças do fundo ocular apresentam alterações no sinal de autofluorescência. Algumas apresentam padrões típicos de autofluorescência que auxi-

liam no seu diagnóstico, nomeadamente a degeneração macular ligada à idade (AMD), doenças hereditárias da retina, coriorretinopatias inflamatórias e retinopatia pelos antimaláricos. Nos últimos anos, vários estudos têm demonstrado o papel da FAF na monitorização e no prognóstico de várias doenças, sobretudo na área da AMD.

A FAF é uma modalidade de imagem útil para fins de diagnóstico, mas também para a monitorização de várias doenças retinianas. Deve-se considerar a sua incorporação na avaliação de rotina de doentes com AMD, entre outros.

PALAVRAS-CHAVE: Angiofluoresceinografia; Degenerescência Macular; Doenças Retinianas; Fundo de Olho.

INTRODUCTION

Fundus autofluorescence (FAF) is a noninvasive imaging technique that allows an in vivo mapping of the distribution of fluorophores present in the ocular fundus, mainly lipofuscin granules located in the retinal pigment epithelium (RPE). Lipofuscin naturally accumulates with age but its excessive accumulation with RPE dysfunction is recognized as a common pathogenic pathway in various retinal diseases, such as age-related macular degeneration (AMD).

Thus, FAF imaging not only presents an anatomic description of the ocular fundus but also provides a metabolic mapping of the RPE and a detailed insight into its health.[1] This exam may sometimes be underutilized in everyday practice but is useful in the evaluation of a diverse spectrum of diseases involving the retina and RPE, including AMD, macular dystrophies, retinitis pigmentosa, white dot syndromes, retinal drug toxicities, and various other retinal disorders. This review presents the basic principles and clinical applications of FAF, with special emphasis on the most widely used blue-light autofluorescence.

BASIC PRINCIPLES

Autofluorescence is the characteristic of some materials that have naturally autofluorescent components called fluorophores. Fluorophores are molecules that, when stimulated by a monochromatic light with an appropriate wavelength (excitation light), emit a monochromatic light of greater wavelength (emission light).

Classically, FAF uses blue-light excitation, known as blue-wave autofluorescence (BAF). Lipofuscin granules of the RPE absorb blue-light with an excitation peak at a wavelength of 470 nm and emit a yellow-green fluorescence at a wavelength of 600-610 nm.[2] The terms fundus autofluorescence (FAF), blue-light autofluorescence (BAF) and short-wave autofluorescence (SWAF) all refer to the classical lipofuscin-based autofluorescence and are often used interchangeably, as in this paper.

LIPOFUSCIN AND OTHER OCULAR FLUOROPHORES

Lipofuscin derives its autofluorescent properties from bisretinoid compounds, which are byproducts of the visual cycle.[3] These compounds are initially formed in photoreceptor outer segments and then deposited in the RPE cells as lipofuscin. *N-Retinyl-N*-retinylidene ethanolamine (A2E) is the first and best characterized component of lipofuscin. A2E is not recognized by lysosomal enzymes and therefore is incompletely broken down and accumulates in RPE lysosomes with aging. However, the excessive accumulation of lipofuscin is pathological and takes part in the pathogenesis of several retinal diseases, since its accumulation above a certain threshold may lead to loss of RPE cells due to apoptosis.

Melanin is an ocular pigment located in uveal melanocytes but also in RPE cells (predominantly located in the apical and midportion of these cells). In BAF, this pigment absorbs the excitation beam and decreases overall FAF signal. Near-infrared autofluorescence (NIR-AF) is a more recently described modality of autofluorescence. It requires a longer wavelength signal (787 nm excitation), easily obtained by using the indocyanine green angiography mode of the scanning laser ophthalmoscope. This type of autofluorescence derives mostly from the melanin of the RPE and to a varying degree from melanin in choroidal layers.[3] The ocular fundus exhibits a faint autofluorescence under NIR-excitation that differs in intensity and distribution when compared to BAF.[4] In normal subjects (Fig. 1), NIR-AF presents a central area of high autofluorescence corresponding to the higher concentration of RPE melanin in the foveal area. This area of higher NIR-AF corresponds to the reduced foveal autofluorescence typical of BAF, as we explain later.

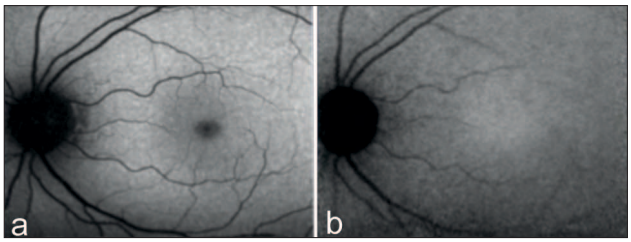

Figure 1. Normal fundus autofluorescence obtained with blue-light autofluorescence imaging (a) and near-infrared autofluorescence (b).

Other clinically significant fundus fluorophores are vitelliform lesions and optic nerve head drusen. Besides, structures anterior to the retina, including the cornea and lens, naturally emit autofluorescence that may interfere with FAF images resolution.[5]

FAF IMAGING SYSTEMS

There are essentially two FAF imaging modalities: confocal scanning laser ophthalmoscopes (cSLO) and modified fundus cameras (mFC). Each system has unique image acquisition and processing techniques, which lead to qualitative and quantitative image differences.

Most commonly, FAF images are obtained clinically with cSLO systems such as Spectralis® Heidelberg Retina Angiograph HRA classic or HRA 2, or Nidek F-10®. They usually use blue excitation wavelengths of 488 and 490 nm, respectively. Confocality ensures that light fluorescence and reflectance are derived from the same plane, avoiding interference from structures outside the retina.[5] cSLO systems record several single images and the final FAF image results from the average of several frames and pixel values normalization. While this method allows better image resolution and contrast compared with the single image of the mFC, patient discomfort by blue-light excitation and poor fixation are possible disadvantages.[6]

Modified fundus cameras (such as Topcon® TRC-50DX or Zeiss® Visucam 224/524) are relatively inexpensive systems that use special filters to detect autofluorescence from lipofuscin. Compared to cSLO, they apply longer wavelength excitation (510 to 580 nm), in the spectrum of green. This wavelength excitation may be less affected by absorption from cataracts and macular pigments (mainly lutein and zeaxanthin located in the neurosensory retina) than the shorter-wavelength excitation utilized in cSLO.[6] Recorded emission is located in the yellow-orange spectrum (675–715 nm).[6] Image acquisition is achieved with a single flash, with better patient comfort but limited image resolution.

Finally, ultra-widefield (UWF) systems such as Optos® 200Tx represent the third example of FAF imaging. This system uses the cSLO technology combined with an ellipsoid mirror to provide images of the retinal periphery achieving up to 200 degrees of view of the ocular fundus in a single capture. This compares to the maximum of 55-60 degrees obtained with conventional cSLO systems.[2] Image acquisition is very brief and does not require pupillary dilation.[2] The most recent Clarus 500 and 700™ from Zeiss also provide ultra-widefield images, automatically synthesized from two images recorded from different horizontal viewing angles (up to 133 degrees each).[7] These devices use a technique called broad line fundus imaging (BLFI) that is capable of capturing a broader range of autofluorescence because it illuminates/excites at two wavelength ranges-green and blue-light excitation.

NORMAL AUTOFLUORESCENCE DISTRIBUTION

Fundus autofluorescence in normal eyes shows a consistent pattern (Fig. 2). The optic nerve head normally appears dark (low FAF signal) due to the absence of lipofuscin. Large retinal vessels also appear dark, because of light absorption by blood vessels. The foveal area typically has a reduced FAF signal, which relates to the absorption of short wavelength light by macular pigments (lutein and zeaxanthin). The parafoveal area maintains relatively low signal intensity, caused by an increased concentration of melanin and a decreased concentration of lipofuscin granules in the central RPE cells. A progressive decline in FAF signal towards the periphery is also typical.

However, FAF images obtained with green light (modified fundus cameras) show noticeable differences in the optic disc and foveal area, appearing with comparably higher intensities of emission (Fig. 3). This should be taken into account when interpreting images obtained with these two different optical systems.

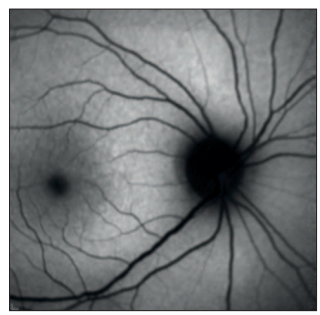

Figure 2. Fundus autofluorescence picture of a healthy eye acquired with Spectralis® (blue-light autofluorescence).

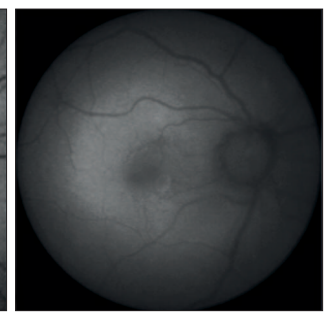

Figure 3. Fundus autofluorescence picture of a healthy eye acquired with Topcon® TRC-50DX fundus camera (green-light autofluorescence).

INTERPRETATION OF FAF IMAGES

The intensity of FAF images is determined by multiple factors, including age, media opacity, pupil diameter and light exposure. Therefore, identification of an abnormal finding basically relies on deviation from the normal distribution or from the signal of intensity of surrounding area.

FAF signal reduction occurs because of two main reasons: RPE loss/atrophy and signal blockage by structures anterior to the RPE. Thus, hypoautofluorescent lesions include but are not limited to: areas of RPE loss or atrophy, reduction in RPE lipofuscin density, presence of intrareti-

nal fluid, fibrosis, media opacities, acute intraretinal or subretinal hemorrhages.

In contrast, hyperautofluorescent lesions are frequently caused by alterations in lipofuscin metabolism and its subsequent accumulation in RPE cells. They can also result from a window defect due to loss of rhodopsin, which normally absorbs the excitation light and decreases autofluorescence. Photoreceptor degeneration and loss of rhodopsin unmasks the autofluorescent signal of the underlying RPE, creating hyperautofluorescent lesions such as those seen in white dot syndromes and other pathologies.[2] Additionally, increased FAF signal can arise from the accumulation of fluorophores other than lipofuscin, including subretinal vitelliform material and optic disc drusen.

CLINICAL APPLICATIONS OF FAF IMAGING

Alterations in FAF signal are observed in numerous diseases. We present some examples in which FAF provides a valuable tool for understanding the pathophysiological mechanisms, for diagnosing or even for monitoring and predicting disease progression.

AMD

FAF imaging is highly valuable in AMD as RPE damage is a hallmark of the disease. The heterogeneity of AMD is consistent with the wide variety of FAF patterns described. Depending on their size, composition and the state of overlying EPR and ellipsoid, drusen have an extremely variable appearance.[8] Large drusen are more likely to result in FAF changes, while small drusen may be isoautofluorescent and remain undetected. Different studies have shown that, in early AMD, FAF imaging has the capacity to reveal RPE alterations in regions that are fundoscopically normal.[9] This is particularly important in the case of reticular drusen, given their prognostic implications. They present a very distinguishing pattern in FAF (multiple rounded hypoautofluorescent dots surrounded by a normal-increased autofluorescence) but are typically hardly noticeable in fundoscopy. In 2005, Bindewald *et al* proposed a classification scheme for eight distinct FAF patterns in early and intermediate AMD, with relatively high intra and inter-observer agreement (normal, minimal change, focal increased, patchy, linear, lace-like, reticular, or speckled).[9] Other descriptions have been reported and some of them even suggest a prognostic value for certain FAF patterns.[10]

Nevertheless, FAF is especially useful in the detection, delimitation, and monitoring of areas of geographic atrophy (GA) and has been used as an endpoint in clinical trials.[11] Manual, semiautomatic, and automatic GA segmentation methods for FAF images have been described.[12] Given the absence of lipofuscin within the RPE, GA appears as a well-demarcated region of marked hypoautofluorescence, usually appearing in the central or parafoveal macula and extending centrifugally (Fig. 4). The normal dark signal of the foveal area in conventional BAF imaging, acquired with

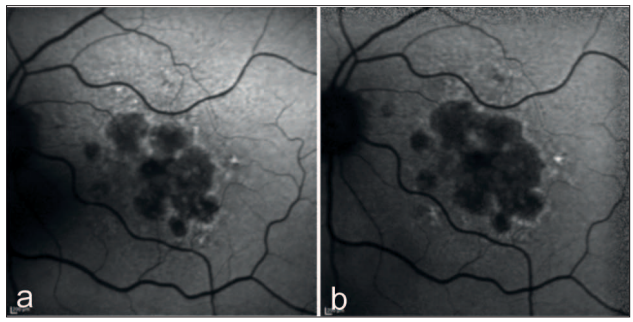

Figure 4. Normal fundus autofluorescence obtained with blue-light autofluorescence imaging (a) and near-infrared autofluorescence (b).

cSLO systems, can make it difficult to appreciate if the fovea is affected in situations of juxtafoveal atrophy. Wolf-Schnurrbusch *et al* demonstrated a possible overinterpretation of the GA size because of this fenomenon.[13] Notably, imaging acquisition with modified fundus cameras may overcome this difficulty,[13] as shown in Fig. 5. Longer wavelengths of excitation such as in the green range overcome light absorption by macular pigments and give the normal fovea a lighter tone when compared to blue-light.

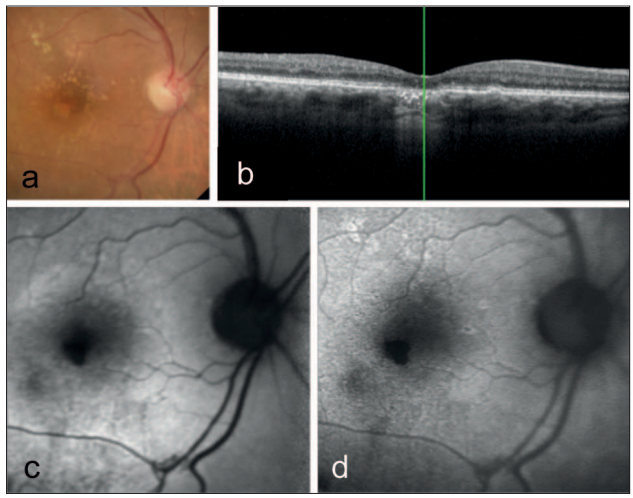

Figure 5. Multimodal imaging of an AMD patient with juxtafoveal atrophy (a- color fundus image; b- B-scan spectral domain-OCT; c- blue-light autofluorescence; d- green-light autofluorescence).

A significant proportion of eyes show increased autofluorescence surrounding areas of GA, varying in appearance from small, isolated spots to large irregularly shaped areas[11] (Fig. 6). Numerous studies have demonstrated that some of these junctional patterns, especially those associated with more diffuse hyperautofluorescence, are associated with an increased rate of disease progression.[14,15]

Regarding neovascular AMD, early choroidal neovascularization (CNV) is not readily detectable on FAF, reflecting intact RPE and photoreceptor layers.[2] Reduced autofluorescence is usually found in most patients with longstanding lesions at the site of the CNV.[16] However, both classic and occult CNV can show enhanced FAF signal next to CNV,

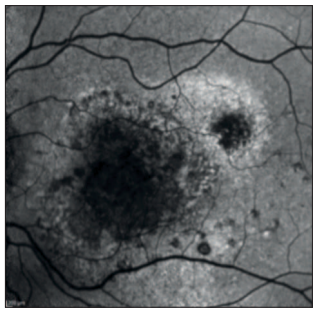

Figure 6. FAF image of a patient with geographic atrophy showing surrounding hyperautofluorescence at the temporal macula.

expressing the presence of phagocytized RPE remnants and chronic accumulation of subretinal fluid.[17] Hemorrhages are initially hypoautofluorescent due to light absorption obscuring the underlying retinal details. They may become hyperautofluorescent after undergoing organization and evolving into an ocher color on fundoscopy.[2] Finally, with clearing of heme, the hyperautofluorescence resolves. RPE scars and areas of atrophy with decreased autofluorescence may also take place.[18]

RPE tears may appear as a complication of neovascular AMD. They present as an area of absent FAF signal where the RPE has been displaced, and hyperautofluorescence in correspondence of retracted RPE at the edge of the tear. Over time, scarring of the tear allows some centripetal recovery of autofluorescence.[2]

CENTRALS EROUS CHORIORETINOPATHY

FAF imaging can complement other imaging techniques in eyes with central serous chorioretinopathy (CSC). CSC can present with various FAF patterns reflecting the metabolic state of the RPE, accumulation of photoreceptor-derived material and masking by serous detachment.[19] Decreased or absent autofluorescence in long-standing lesions may indicate reduced metabolic activity of the RPE due to photoreceptor cell loss.[20] Some chronic cases show a typical hypoautofluorescent atrophic gravitational tract that correlates to prior dependent subretinal fluid.[2]

INHERITED RETINAL DYSTROPHIES

Inherited retinal dystrophies comprise a heterogeneous group of genetically determined diseases that cause death of photoreceptor cells and subsequent vision loss. A broad range of characteristic FAF patterns is observed in these disorders. Increased background autofluorescence is a common feature, usually associated with focally increased FAF, or even areas of decreased or even absent FAF.[21] Late stages with profound RPE cell loss may look similar in various retinal dystrophies, as well as in other retinal disorders.

Autosomal recessive Stargardt disease/fundus flavimaculatus (STGD1) is the most common hereditary juvenile macular dystrophy. FAF patterns are easily explained by the pathogenesis, which include defective outer segment degradation, lipofuscin accumulation, and central degeneration of the RPE and photoreceptors. Early stages may demonstrate a general increase in lipofuscin and thus increased FAF signal, whereas disease progression leads to a pattern of a hypoautofluorescent atrophic macula, surrounded by intensely hyperautofluorescent flecks. The presence of peripapillary sparing is highly characteristic.[21]

Retinitis pigmentosa (RP) is a relatively common group of retinal dystrophies characterized by rod-dominant retinal degeneration. In FAF, RP presents with a ring or arc of increased autofluorescence enclosing a zone of normal signal where photoreceptors are preserved.[22] This finding, known as the Robson-Holder ring, is considered to represent the transition between the degenerating retina and the relatively normal retina.[23] Similar hyperautofluorescent rings are also seen in other retinal diseases, including Leber congenital amaurosis (LCA), X-linked retinoschisis, Best macular dystrophy, cone dystrophy, and cone-rod dystrophy.[23]

FAF imaging of the vitelliform lesions present in Best disease and adult macular vitelliform dystrophy are also very elucidating.[24,25] Shed photoreceptor debris and lipofuscin accumulating in the subretinal space originate the typical bilateral yolk-like lesions seen in Best disease. Querques *et al*[24] described various autofluorescence patterns associated with each of the five stages of progression classically described by fundus examination: the previtelliform lesions caused zero to minimal hyperautofluorescence; the vitelliform stage showed a well-circumscribed, homogenous hyperautofluorescent lesion in the macula; the pseudohypopyon stage showed hyperfluorescent precipitates settling under an isoautofluorescent fluid; the vitelliruptive stage showed a dark lesion bordered by condensations of hyperautofluorescent material; the atrophic stage, characterized by chorioretinal atrophy, presented a diffusely decreased signal. Nevertheless, Parodi *et al*[25] characterized six different FAF phenotypes (normal, hyperautofluorescent, hypoautofluorescent, patchy, multi-focal and spoke-like), with no correlation with the stages of progression of the disease.

HYDROXYCHLOROQUINE RETINOPATHY

Hydroxychloroquine (HCQ) is an anti-malarial medication commonly used as treatment for a variety of autoimmune diseases. Retinal toxicity from HCQ, and its analog, chloroquine, has a relatively low incidence but its irreversible character makes early diagnosis indispensable.[26] In early stages, patients are usually asymptomatic, hence the importance of routine screening with multimodal assessment.

The screening recommendations released by the American Academy of Ophthalmology in 2016[27] suggest a baseline fundus examination to rule out preexisting maculopathy, followed by annual screenings after 5 years, for patients on acceptable doses and without major risk factors. The annual screenings should incorporate an automated perimetry and spectral-domain optical coherence tomography (SD-OCT) of the macula.

FAF is an optional test. It is especially useful in cases of

uncertain visual field changes, in order to provide objective, structural evidence of disease that may correlate with findings on SD-OCT and perimetry. In the early stages of disease, FAF shows a hyperautofluorescent parafoveal ring. As RPE degeneration becomes established in later stages of disease, FAF progresses with a mottled decrease in parafoveal signal. Lastly, FAF shows a characteristic pattern of bilateral parafoveal hypoautofluorescence, known as bull's eye maculopathy.[28]

WHITE DOT SYNDROMES

White dot syndromes (WDS) are a group of inflammatory chorioretinopathies that predominantly affect the outer retinal layers, RPE, and/or choroid.[29] Commonly recognized WDS include multiple evanescent white dot syndrome (MEWDS), acute retinal pigment epitheliopathy (ARPE), acute posterior multifocal placoid pigment epitheliopathy (APMPPE), multifocal choroiditis and panuveitis (MCP), birdshot chorioretinopathy, serpiginous choroidopathy, and punctate inner choroidopathy (PIC). FAF can demonstrate both hyper and hypoautofluorescence changes in these diseases. Overall, increased signal is found in the presence of an active inflammatory response, highlighting areas of disease activity (Fig. 7), whereas quiescent phases and final chorioretinal scarring or atrophy are typically hypoautofluorescent.[30] Specific FAF patterns can help to distinguish among different types of chorioretinitis. Besides, in diseases such as PIC or serpiginous choroidopathy, FAF detects new areas of inflammatory activity and presents as a valuable tool in treatment guidance.[31] Ultra-widefield imaging is particularly relevant for assessing disease activity in the retinal periphery.

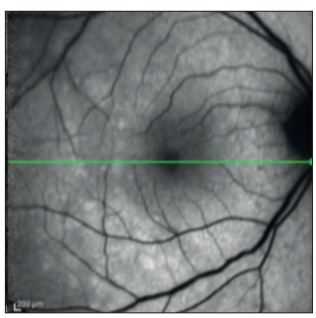

Figure 7. FAF image of a patient with MEWDS showing foveal-sparing hyperautofluorescent active lesions in the posterior pole.

OPTIC NERVE HEAD DRUSEN

Optic nerve head drusen (ONHD) are benign acellular calcium concretions that usually form early in life. ONHD may give a swollen-looking appearance to the optic disc, sometimes difficult to differentiate from true disc edema.

FAF is a convenient method of visualizing more superficial drusen. They produce bright hyperautofluorescent foci in the disc (Fig. 8), thought to represent calcium salts or mitochondrial porphyrins.[32] The diagnosis of buried ONHD usually requires other imaging modalities, such as B-scan ultrasonography, fundus fluorescein angiography or computed tomography.

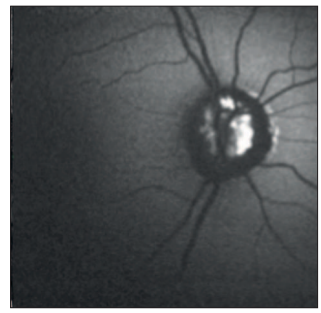

Figure 8. FAF image showing hyperautofluorescent superficial optic nerve head drusen.

CONCLUSION

Overall FAF signal depends on the distribution pattern of lipofuscin in the RPE, which relates to its metabolic activity. For this reason, FAF is considered a measure of RPE health and function and has given valuable insights about pathogenic mechanisms of retinal disorders. The authors highlight that the high-resolution images generated by FAF should be routinely incorporated in the diagnosis and monitoring of numerous diseases, such as AMD, retinal dystrophies and inflammatory chorioretinopathies.

RESPONSABILIDADES ÉTICAS

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Conflicts of Interest: The authors have no conflicts of interest to declare.

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