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Use of fundus autofluorescence in the diagnosis and management of uveitis

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Fundus autofluorescence (FAF) represents a relatively new imaging modality that has been investigated in a variety of uveitic disease processes. Autofluorescence was first described in the setting of fluorescein angiography (FA) as “pseudofluorescence” prior to injection of fluorescein dye (1). FAF relies on the presence of innate fluorophores within ocular tissues, which can be induced to emit light when stimulated with specific frequencies of light. Using a fundus spectrophotometer, Delori et al showed that the dominant fluorophore in the retina is lipofuscin (2). Initial quantitative assessment of autofluorescence was done using fluorophotometry in the late 1980s (3). Lipofuscin can contain different fluorophores with varying emission characteristics from green to orange-red range. Lipofuscin is thought to represent the breakdown product of various retinal proteins. The accumulation of lipofuscin in tissues has been described in a number of hereditary or degenerative retinal diseases, and likely reflects a common mechanism resulting from cumulative oxidative damage (4, 5). Autofluorescence in the RPE depends on the outer segment renewal and can be affected by the RPE's ability to clear lipofuscin. Accumulation of lipofuscin leads to reduced phagocytic capacity of the RPE which in turn can lead to RPE cell death and photoreceptor loss (6). While lipofuscin accumulates in response to various types of damage, its accumulation in the RPE is shown to decrease in animal models with light-induced loss of photoreceptor cells or when RPE cells fail to phagocytose outer segments (7). Hence, an increased autofluorescence is seen with RPE dysfunction and a decreased autofluorescence is seen with loss of photoreceptors or the RPE. Lipofuscin has also been shown to accumulate in experimental models of autoimmune uveitis (8). Oxidative damage to various ocular tissues is also thought to play a role in uveitic diseases. A primary target of oxidative damage in the setting of uveitis appears to be the retinal pigment epithelium (9). The RPE is also the primary site of accumulation of lipofuscin. As such, the visualization of lipofuscin accumulation in the RPE using fundus autofluorescence may reflect disease activity in the setting of uveitis.

Lipofuscin has a broad excitation and emission range with excitation spectrum ranging from 300 to 600 and emission spectrum ranging from 480 to 800 with maximal emission at 600-640nm. Two common fundus cameras used in autofluorescence imaging utilize differing excitation and barrier filters; 488 nm excitation with a 500nm barrier filter in HRA2 laser scanning ophthalmoscope (Heidelberg Engineering, Heidelberg, Germany), and 550 to 600 nm excitation and 660 nm barrier filter in Topcon fundus camera (Topcon medical systems, Paramus, New Jersey, USA). In addition to HRA 2 and Spectralis, Rodenstock cSLO (RcSLO; Rodenstock, Weco, Dusseldorf, Germany) and the Zeiss prototype SM 30 4024 (ZcSLO; Zeiss, Oberkochen, Germany) are the confocal SLO (cSLO)

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devices capable of producing FAF images whereas Topcon is a fundus camera based system (10).

FAF intensity is generally significantly lower than the background of an FA. A number of structures anterior to the retina also possess autofluorescent properties, most significantly the lens. Confocal optics can help reduce the signal coming from the lens. Longer wavelength of excitation and barrier filters can also decrease the effect contributed by nuclear sclerosis and macular pigment. Each imaging system normalizes the pixel value to allow for better visualization of relative distribution of autofluorescence resulting in “averaged” or “normalized” image. While this makes evaluation of an image easier by accounting for topographic differences within an individual image it can not be used for quantitative calculation or comparison between different images even within the same patient. It is important to remember that lipofuscin is a combination of multiple fluorophores with different excitation characteristics and the different wavelengths in different imaging systems may indeed be recording fluorescence from different components of the lipofuscin.

In normal autofluorescence imaging the optic nerve head appears dark due to the absence of RPE and lipofuscin. Retinal vessels typically block FAF that would otherwise originate from the underlying RPE. The fovea also shows reduced signal due to absorption of light by luteal pigment. In general, the parafoveal region shows a slightly increased FAF signal. The contrast between the vessels and the background is less in fundus camera based FAF images than in images acquired by cSLO mainly owing to the fact that wavelengths used in fundus cameras are absorbed less by blood than wavelengths used in cSLO (11, 12). There are a number of causes for increased or decreased FAF signals as outlined in the table which may be relevant in the context of uveitic diseases (Table). In the clinical setting, it is important to take into account the normalization done by each imaging system, the difference in contrast, brightness and image quality (10, 11, 12).

Fundus autofluorescence findings in specific uveitic diseases

Abnormal autofluorescence patterns have been described in a number of infectious and non-infectious uveitides. Most reports of abnormal FAF in patients with uveitis belong to the spectrum of white-dot-syndromes. Below are examples of utility of FAF in the setting of uveitis.

Serpiginous choroidopathy

In serpiginous choroidopathy, prior areas of activity with chorioretinal atrophy are associated with hypoautofluorescence. Disease exacerbations at the borders of pre-existing atrophy have been associated with hyperautofluorescence (13). New lesions are often hyperautofluorescent initially throughout the area of involved RPE/choroid. These autofluorescence findings can be preceded by changes on spectral domain optical coherence tomography (SD-OCT) testing and with resolution of active lesions hypofluorescence ensues (14) (Figure 1).

Acute posterior multifocal placoid pigment epitheliopathy

Round, placoid, gray-white lesions in APMPE at the level of the retinal pigment epithelium (RPE) show hypoautofluorescence which is attributed to presumably inflamed or swollen retinal cells overlying the RPE. An increase in autofluorescence is typically seen at the borders or as the lesions evolve. Eventually hypoautofluorescence is seen as the lesions are replaced by atrophy and RPE loss (15,16)

Multiple evanescent white dot syndrome and acute zonal occult outer retinopathy

Similar to other white dots syndromes, abnormal autofluorescence is noted in multiple evanescent white dot syndrome (MEWDS) and acute zonal occult outer retinopathy (AZOOR) (17,18). Hyperautofluorescence of lesions in MEWDS correspond to areas of hypofluorescence on indocyanine green angiography (ICG) and decreased sensitivity on visual fields. Peripapillary hypoautofluorescence and granular mixture of hyper- and hypoautofluorescence described in AZOOR are associated with thinning in photoreceptor layer and defects in visual field, and are progressive in most patients (19) (Figure 2).

Multifocal choroiditis and Punctate inner choroidopathy

The predominant autofluorescence finding in multifocal choroiditis is hypoautofluorescence associated with areas of chorioretinal atrophy. Numerous areas of punctate hypoautofluorescence (less than 125 microns) not associated with ophthalmoscopically visible lesions have also been noted (20). Areas of active chorioretinitis are associated with hyperautofluorescent signal which resolve with institution of immunosuppressive therapy (13). However, in PIC hyperautofluorescent halo surrounding active PIC lesions do not always change with therapy (21). Choroidal neovascularization (CNV) associated with multifocal choroiditis or PIC appears to be associated with hyperautofluorescence surrounding the CNV lesion (20, 21). This is consistent with autofluorescence findings in AMD associated with classic CNV lesions (22). Scarring also appears to be associated with hypoautofluorescent signal (20).

Birdshot chorioretinopathy

Discrete areas of hypoautofluorescence have been noted in patients with birdshot chorioretinopathy (BCR), some of which do not correspond to clinically visible birdshot lesions (23, 24). Additionally, larger and more diffuse areas of hypoautofluorescence compared to visible lesions on exam or fundus photography have been shown in BCR patients. The presence of these areas of hypoautofluorescence may reflect a more widespread damage than what is visible in BCR and may explain vision and field loss in these patients (25) (Figure 3). Hyperautofluorescence has also been noted in BCR associated with vessels in regions of vasculitis and in association with CNV, likely a non-specific finding (23).

Vogt-Koyanagi-Harada disease

Autofluorescence findings in Vogt-Koyanagi-Harada disease (VKH) are variable with both increased and decreased levels of autofluorescence (26, 27). Hypoautofluorescent signals in VKH are associated with peripapillary atrophy, atrophic retinal scars and old pigmented scars. Additionally, areas of serous retinal detachment can also show hypoautofluorescence on both blue-light and near-infrared FAF which is likely due to blockage by the serous fluid of the reflectance from the RPE. However, this finding is not consistent in all areas of serous detachment (28). Hyperautofluorescent signals have been noted in association with cystoid macular edema, and areas of normal fundus. Interestingly the sunset glow fundus feature of chronic VKH is not associated with any significant change in autofluorescent signal, perhaps reflecting a loss of choroidal melanocytes instead of RPE pigment loss (26).

Uveitic macular edema

Increased hyperautofluorescence at the fovea has been noted in the setting of uveitic cystoid macular edema (CME). Presence of hyperautofluorescence in eyes with uveitic macular edema is associated with loss of reflective band representing inner-outer segment junction on SD-OCT and poor visual acuity. However, an abnormal autofluorescence was noted only in 50% of eyes with uveitic macular edema and lacked a distinctive pattern, highlighting the

weakness of this technique in detecting macular edema (29). An increase in autofluorescent signal can be found in non-uveitic cases of CME and is thought to be due to the displacement of macular pigment by cystic changes causing the unmasking of underlying lipofuscin signal from the RPE (30) (Figure 4).

Primary intraocular lymphoma (Primary vitreoretinal lymphoma)

Primary intraocular lymphoma (PIOL/PVRL) is an important masquerade syndrome that can present with clinical findings similar to posterior and intermediate uveitis. There are a number of clinically distinctive autofluorescence patterns associated with PIOL. Hypopigmented areas of subretinal infiltration are associated with hypoauflorescent signal whereas the brown clumps overlying the subretinal masses are associated with hyperautofluorescent signal (31). Additionally, an alternating pattern of granular hypo- and hyperautofluorescence has also been described in eyes with PIOL (31,32). This gives rise to a reverse of the characteristic “leopard spot” pattern seen on FA (Figure 5).

Infectious uveitides

Recurrent activity in cytomegalovirus (CMV) retinitis can sometimes be subtle and difficult to detect. Autofluorescence can be helpful in detecting areas of activity in CMV retinitis via demonstration of a hyperautofluorescent signal along the advancing edge of the lesions (33) (Figure 6). Inactive areas of CMV retinitis are often associated with stippled areas of autofluorescence. Progressive outer retinal necrosis demonstrates large areas of hypoauflorescence which progress, reflective of the widespread RPE dysfunction in this disease (34). Hyperautofluorescence is also described in syphilitic chorioretinitis corresponding to yellowish placoid lesions. These lesions showed early hypofluorescence with late staining on FA with corresponding areas of hypofluorescent spots on ICG (35).

Conclusion

In many posterior uveitides, active disease is often reflected by a hyperautofluorescent signal. It is possible that an increase in the size, number, or fluorophore content of the RPE during acute inflammatory phase leads to an increase in autofluorescence. Inactive disease and areas of chorioretinal atrophy are generally associated with a hypoauflorescent signal. Interestingly in some conditions, FAF imaging has also revealed more widespread areas of disease involvement than can be seen ophthalmoscopically, as noted in BCR, AZOOR and MFC (17, 20, 23, 24). In most white dot syndromes areas of increased autofluorescence corresponds to areas of abnormal fluorescence on FA, hypofluorescent spots on ICG and decreased sensitivity on visual fields. While autofluorescence patterns are not particularly distinctive in some cases, it is valuable in the presence of other imaging modalities and can be helpful in following recurrences in a number of uveitic syndromes. Hypoauflorescence at the fovea has been associated with decreased visual acuity in a number of uveitic diseases (13, 28), and may be a valuable prognostic indicator. As the use of fundus autofluorescence becomes more common we may be better able to identify the pathophysiology underlying abnormal autofluorescence in uveitis and understand how the hyperautofluorescent lesions evolve during the course of a particular uveitic syndrome. Overall, FAF imaging, used in concert with clinical exam and other ancillary testing provides a clinically useful and non-invasive modality that plays a role in both diagnosis and management of many uveitides.

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Figure 1. In serpiginous choroiditis areas of activity at the margins of the lesion show hyperautofluorescence (arrows) (A) which correspond to yellowish elevated areas of fundus photography (B) and early blockage (C) followed by late staining on fluorescein angiogram (D).

Figure 2.

Fundus photograph of the left eye of a patient with AZOOR shows zonal loss of RPE in the peripapillary area into the arcades (A, arrow represents line scan for OCT) which corresponds to hypoautofluorescence on FAF imaging (B) and hyperfluorescence caused by window defect on FA (C). These areas also correspond to visual field defects (D) and loss of reflective band representing inner-outer segment junction on SD-OCT (between arrows, E).

Figure 3. Areas of hypoautofluorescence in birdshot chorioretinopathy (A) correspond to the typical lesions in most part but appear more widespread than the ophthalmologically visible area of involvement (B).

Figure 4. Uveitic CME can lead to foveal and perifoveal hyperautofluorescence (B) consistent with area of perifoveal leakage on FA (A) and cystic changes on OCT (C).

Figure 5. The right eye of a patient with PIOL/PVRL shows subtle pattern of leopard skin-like changes (arrows, A). These changes are more readily seen throughout the entire retina on FAF images as granular hyper- and hypoautofluorescence (B).

Figure 6.

Extensive areas of active CMV retinitis seen on fundus photography (A) show hyperautofluorescence, particularly at the advancing borders, as well as staining and leakage on FA (C).

Table**Abnormal fundus autofluorescence signals in uveitic disease processes**

Reduced FAF signal

- Absence of or reduction in RPE lipofuscin density
- Loss of RPE (e.g., AZOOR, VKH)
- Increased RPE melanin content
- Absorption from extracellular material, cells or fluid anterior to RPE
- Intraretinal fluid (e.g., macular edema)
- Intraretinal hemorrhage
- Fibrosis, scar tissue or borders of laser scars
- Media opacities (e.g., cataract)

Increased FAF signal

- Excessive RPE lipofuscin accumulation
 - Fluorophores anterior or posterior to the RPE monolayer
 - Intraretinal fluid (e.g. macular edema)
 - Subretinal fluid (e.g., VKH)
 - Macrophages containing lipofuscin in the subretinal space
 - Older intraretinal and subretinal hemorrhages
 - Choroidal vessel underlying RPE atrophy
 - Displacement of luteal pigment (e.g cystoid macular edema)
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Adapted from Schmitz-Valckenberg S, Holz FG, Bird AC, Spaide RF. Fundus autofluorescence imaging: review and perspectives. *Retina*. 2008 Mar;28(3):385-409. Review. PubMed PMID: 18327131.