Fundus autofluorescence in retinal disorders

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Background
Fundus autofluorescence (FAF) is a noninvasive, rapid, and potentially useful imaging modality that continues to evolve. It reflects metabolic changes at the level of retinal pigment epithelium/photoreceptor complex and variation of fluorescence derived from lipofuscin and thus provides an assay of retinal and retinal pigment epithelium function.

Aim
Demonstration of the technique, concept, and clinical value of FAF.

Patients and methods
This study was performed on 63 eyes of 41 patients from May 2016 to May 2017 with various retinal diseases (age-related macular degeneration, macular dystrophy, central serous retinopathy) using digital fundus camera TRC-NW8F Plus Topcon with special filter (Spaide filter). Abnormalities in images of FAF were analyzed and correlated with the corresponding alteration in fluorescein angiography and optical coherence tomography findings.

Results
A broad range of characteristic FAF patterns were observed. Distribution and variation with disease imply that the fluorescence is derived from lipofuscin in the pigment epithelium. Autofluorescence is shown to be abnormally high in certain inherited diseases, and low in the presence of retinal atrophy.

Conclusion
FAF imaging constitutes a useful additive tool in the diagnosis and follow-up of various retinal diseases and may detect abnormalities beyond those detected on funduscopic examination.

Keywords:
fundus autofluorescence, lipofuscin, retinal imaging

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Introduction

Fundus autofluorescence (FAF) imaging has recently become broadly used clinically due to its importance and it is believed to provide an assay of the outer retinal and retinal pigment epithelial (RPE) function [1]. Fluorophore plays the main role in autofluorescence (AF). Lipofuscin is an AF storage material that accumulates as a result of cell aging [2]. Lipofuscin derives primarily from phagocytosed photoreceptor outer segment [3]. Failure of the RPE lysosomal system to completely degrade this material results in peroxidative modifications and accumulation of high level of lipofuscin in the RPE which leads to cellular dysfunction, which in turn contributes to photoreceptor dysfunction and degeneration [4].

Elevated lipofuscin levels are associated with a variety of retinal degenerations [5]. It is difficult to determine whether lipofuscin is a cause or consequence of these conditions [6]. But there are many evidences that lipofuscin is cytotoxic and contributes to the pathogenesis of retinal degenerations such as Age related macular degeneration (AMD) and Stargardt disease [7].

FAF helps to give noninvasive maps for lipofuscin distribution in the RPE which is an indirect means of detecting, quantifying, and monitoring outer retinal disease. The currently available FAF imaging modalities include confocal scanning laser ophthalmoscopy and digital fundus camera-based systems [8].

Patients and methods

This is a prospective, observational, cross-sectional study of 63 eyes from 41 patients of Al Forsan Eye Centre from May 2016 to May 2017.

The study was approved and monitored by the Medical Ethics Committee, Assiut Faculty of Medicine.

The investigators explained the steps and value of the research to all eligible participants. Those who agreed to be included in the study signed a fully informed consent.

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Inclusion

Patients with hereditary or acquired macular diseases.

Exclusion

Patients excluded were those with opaque media (e.g. corneal opacity, cataract, and vitreous hemorrhage).

All patients underwent full ophthalmic examination including best-corrected visual acuity, anterior segment evaluation, intraocular pressure, and fundus examination using slit lamp with +90 D lens after dilation of the pupil using tropicamide 1% and phenylephrine 2.5%.

Color fundus photography is done. Fundus fluorescein angiography (FA), optical coherence tomography, and electroretinogram (ERG) and electroocoulogram (EOG) were done in some cases.

Fundus autofluorescence imaging

Using TRC-NW8F Plus Topcon Medical System (Topcon, Tokyo, Japan), which is a fundus camera introducing retinal imaging system by incorporating its Spaide filter that enables this camera to capture FAF, in addition to color and FA imaging.

Spaide filter is an excitation filter centered at 580 nm and a barrier filter centered at 695 nm. These wavelengths are shifted toward the red end of the spectrum to avoid unwanted short-wavelength AF from the crystalline lens.

FAF imaging was done for all patients as follows:

The pupil was dilated with tropicamide 1% and phenylephrine 2.5% before imaging. The patient information including name, birth date, identity, and number are introduced into the computer. The 50 degree field of view mode was used to produce images of the fundus and of the distribution of retinal AF.

FAF images are considered as hyper-AF and hypo-AF according to the intensity of the AF. A relatively decreased intensity compared with the diffuse background is called hypo-AF, whereas increased intensity is called hyper-AF.

Results

A total of 63 eyes of 41 patients from May 2016 to May 2017 were evaluated.

The mean age of the participants was 44.68 years, SD (19.56) with 16 (39%) men and 25 (61%) women.

Four (6.3%) eyes were normal eyes, 18 (28.5%) eyes with age-related macular degeneration, 21 (33.3%) eyes with retinal dystrophies, three (4.7%) eyes were with central serous chorioretinopathy, seven (11.1%) eyes were with macular edema, two (3.1%) eyes were with macular hole, two (3.1%) eyes with choroidal melanocytic lesions, four (6.3%) eyes with macular telangiectasia, and two (3.1%) eyes with Vogt-Koyanagi-Harada disease.

The normal fundus

In normal eyes, there were homogeneous background AF and gradual decrease of AF in the inner macula toward the fovea and reduced AF at the areas of optic dis and blood vessels (Fig. 1).

Age-related macular degeneration

Eighteen eyes had age-related macular degeneration, five eyes had early AMD, two patients showed mixed patchy hyper-AF with focal hypo-AF, while three eyes showed mixed patchy hyper-AF with patchy hypofluorescence.

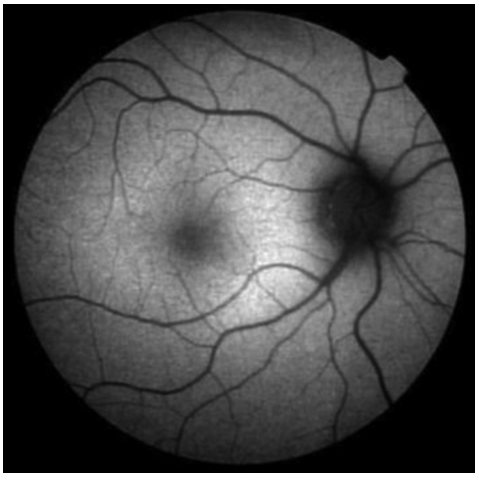
Five eyes had atrophic AMD, four eyes showed diffuse pattern of hyper-AF changes at the margin geographic atrophy while one showed a banded pattern of hyper-AF changes at the margin of geographic atrophy.

Eight had neovascular AMD, three had a heterogeneous pattern, three had central hypo-AF with a hyper-AF rim pattern (Fig. 2) and two with hyper-AF.

Stargardt disease

Four eyes with Stargardt disease showed central macular hypo-AF. Two had mostly hypo-AF flakes and two had alternating hyper-AF and hypo-AF flecks through and

Figure 1



Right eye with normal fundus autofluorescence with dark hypofluorescence of the optic disk and blood vessels as well as hypofluorescence of the fovea.

beyond the posterior pole. Three had peripapillary sparing and one had peripapillary FAF abnormalities (Fig. 3).

Retinitis pigmentosa

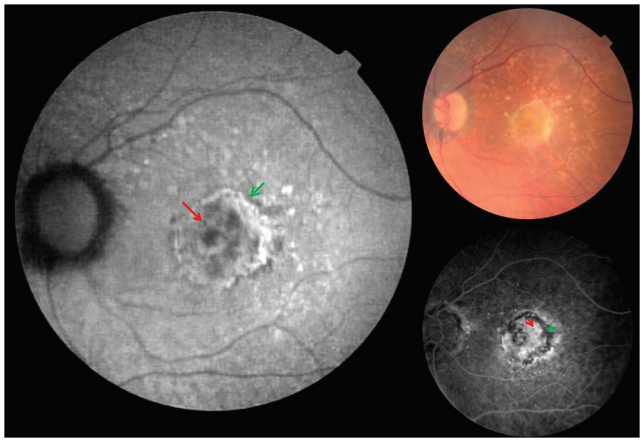
Eight eyes with retinitis pigmentosa, six typical and two of atypical type. The typical cases, four eyes were in early stage and showed hyper-AF perifoveal rings which are not seen in a color photo (Fig. 4). Two eyes were in a late stage showed diffuse hypo-AF in the posterior pole.

Two eyes were with an atypical form which showed central macular hypo-AF and hypo-AF areas superiorly related to bony spicules and inferior foci of hyper- and hypo-AF.

Cone–rod dystrophy

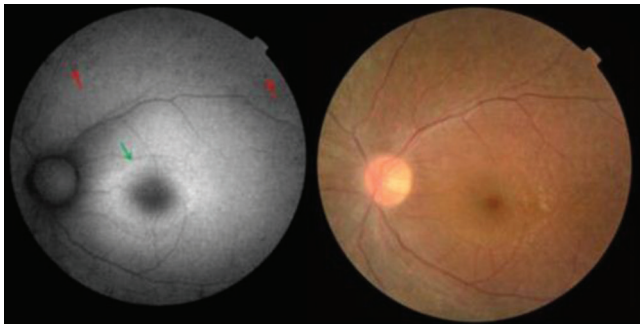
Four eyes with cone dystrophy, FAF showed central macular hypo-AF with outer perifoveal ring of hyper-AF.

Figure 2



Left eye of the patient with neovascular AMD. FAF shows a central area of heterogeneous hyperautofluorescence and hypoautofluorescence (red arrow) corresponding to the area of hyperfluorescence in FA image and ring of hyperautofluorescence (green arrow) corresponding to the ring of hypofluorescence in FA. FA, fluorescein angiography; FAF, fundus autofluorescence.

Figure 4



Left eye of the patient with retinitis pigmentosa. FAF shows perifoveal ring of hyperautofluorescence (green arrow) which is not visible in color fundus image and areas of hypoautofluorescence (red arrows). FAF, fundus autofluorescence.

Best disease

Five eyes were with Best vitelliform macular dystrophy, four eyes were with typical form, and one eye with an atypical form. Three eyes showed macular areas of hyper-AF which are mainly in the inferior part of the lesion (Fig. 5). One eye showed hypo-AF in the central macular area. One eye showed extramacular areas of hyper-AF related to extramacular yellowish lesions in the color photo.

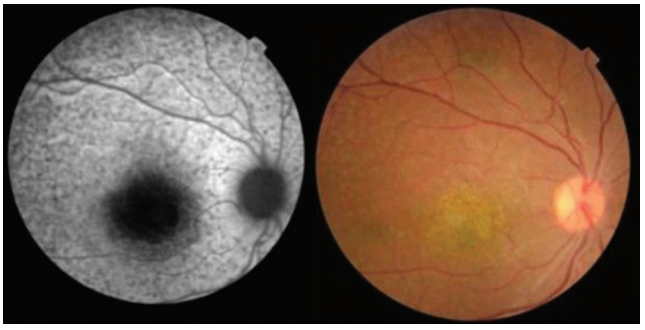
Central serous chorioretinopathy

One eye showed acute central serous chorioretinopathy (CSR) and exhibited central macular hypo-AF. One eye had chronic CSR and showed mottled AF (Fig. 6). The third case was with chronic recurrent CSR with a large macular area with hyper-AF and a central area with hypo-AF.

Macular edema

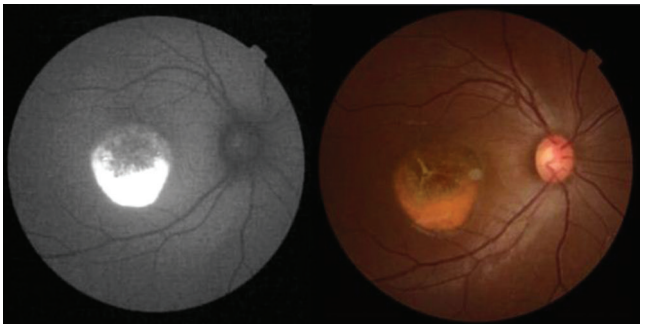
Seven eyes had macular edema, five eyes with diabetic retinopathy, two eyes with branch vein occlusion, two showed no change of FAF in foveal area, four showed

Figure 3



Right eye of the patient with Stargardt disease. FAF shows markedly decreased FAF in the central macula. Outside this area, there are hypoautofluorescent flecks diffusely distributed in the posterior pole with peripapillary sparing. FAF, fundus autofluorescence.

Figure 5



Right eye of the patient with Best disease. FAF showed hyperautofluorescence in the inferior part of vitelliform lesion. The color photograph shows an yellowish material (pseudohypopyon). FAF, fundus autofluorescence.

loss of normal hypo-AF (Fig. 7), and one showed localized area of hyper-AF. All cases showed hypo-AF related to hemorrhage and areas of hyper-AF related to hard exudate.

Melanocytic lesions

Two eyes were with melanocytic lesion. One eye was with choroidal nevus and the FAF showed slight hypo-AF at the site of the nevus. One eye was with choroidal melanoma with heterogeneous pattern of hyper- and hypo-AF (Figs. 8 and 9).

Macular hole

Two eyes had full thickness with a macular hole. FAF shows a well-circumscribed area of hypo-AF related to the macular hole and is surrounded by a ring of hyper-AF.

Macular telangiectasia

Four eyes were with juxtafoveal telangiectasia, one eye showed foveal hyper-AF (Fig. 10) and three eyes showed hypo-AF areas in the macular area.

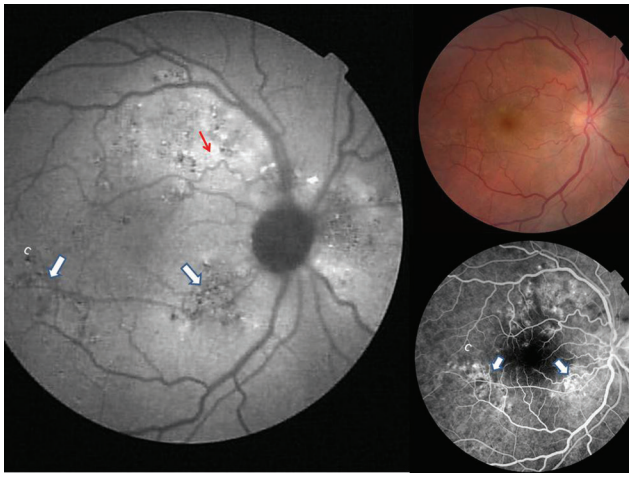
Vogt-Koyanagi-Harada

Two cases were with Vogt-Koyanagi-Harada which showed areas of hyper-AF related to areas of serous detachment.

Discussion

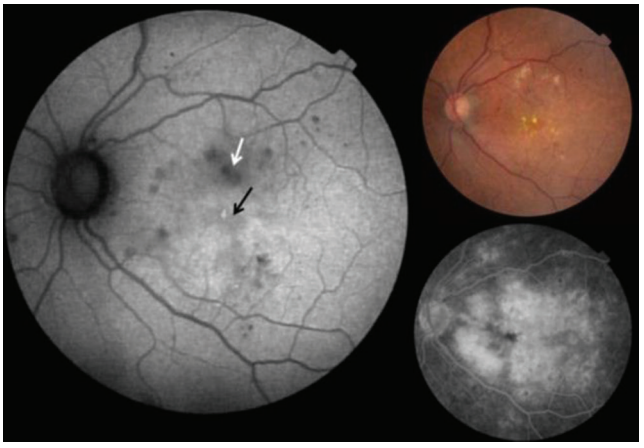
In this study, FAF abnormalities were observed in all examined eyes with an ophthalmoscopically visible retinal disorder accompanied by increased or decreased

Figure 6



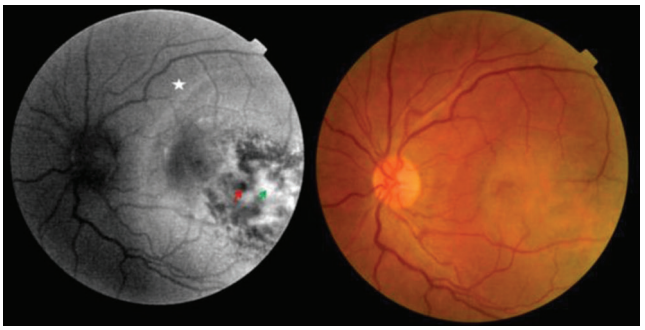
Right eye of chronic CSR. FAF shows areas of mottled autofluorescence as there are foci of hypoautofluorescence corresponding to the area of hyperfluorescence in fluorescein angiography (white arrows) and foci of hyperautofluorescence of residual or former neurosensory detachment. Ares with hypoautofluorescence (white arrows) denoting atrophic retinal pigment epithelium and appear as and areas with hyperautofluorescence (red arrows)denote streesed RPE FAF, fundus autofluorescence.

Figure 7



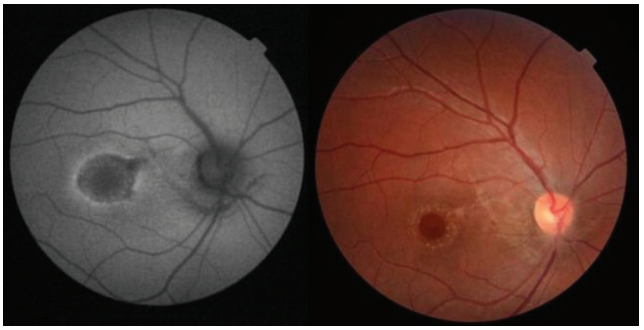
Left eye of the patient with diabetic macular edema and FAF shows loss of normal hypoautofluorescence in the foveal area with area of hypoautofluorescence related to areas of hemorrhage and areas of hyperautofluorescence related to the exudate. FAF, fundus autofluorescence.

Figure 8



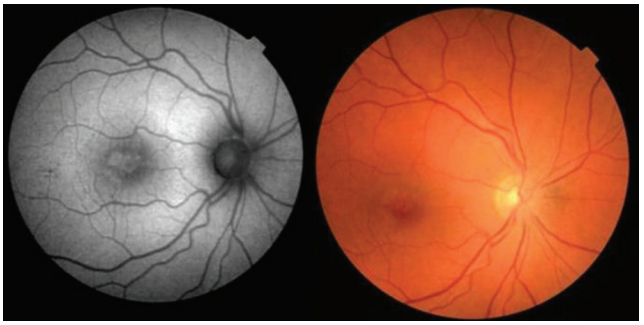
Left eye of the patient with choroidal melanoma FAF shows at the site of melanoma, patches of hyperautofluorescence correspond to orange pigment in color image (green arrow) and shows areas of hypoautofluorescence (red arrow) and there is line of hyperautofluorescence. FAF, fundus autofluorescence.

Figure 9



Right eye of the patient with full thickness traumatic macular hole with choroidal rupture. The FAF shows areas of hypoautofluorescence corresponding to macular hole and is surround by a ring of hyperautofluorescence and hypoautofluorescence line corresponding to an area of choroidal rupture. FAF, fundus autofluorescence.

Figure 10



Right eye of the patient with early macular telangiectasia type 2. FAF showed foveal hyperautofluorescence. FAF, fundus autofluorescence.

FAF. We observed specific FAF abnormalities that were dependent on the examined retinal disorder. It has the potential to show pathologic features may be earlier than on fundoscopy.

Normal fundus: in the healthy eye FAF showed a hypofluorescent area in the foveal region. AF in the macular area is more intense between 5° and 15° from the fovea. Optic disk and retinal vessels appear dark, because of the absence of RPE in the optic disk and the blood blocking AF where vessels lie [9].

Age-related macular degeneration: in early AMD, FAF may show hyper-AF and hypo-AF areas that reveal more widespread disease than appreciated with fundoscopy or color photography. Hyperpigmented lesions may represent melanin granules, which correlate with hypo-AF, or melanolipofuscin granules, which correlate with hyper-AF [10]. Depigmented, hypo-AF areas correspond to RPE atrophy, which may signal early geographic atrophy. In a study by Holz *et al*. [11], patterns of FAF in 100 eyes with early AMD (according to the International Age-related Maculopathy Epidemiological Study Group) were classified into eight patterns: normal, minimal change, focal increased, patchy increased, linear, reticular, lacelike, and speckled.

In our study, five eyes with early AMD showed mixed patterns which were reported by Holz and colleagues, two eyes had a mixed pattern of patchy hyperfluorescence with focal hypofluorescence and the other three eyes had mixed patchy hyperfluorescence with patchy hypofluorescence.

In a study by Bindewald *et al*. [12] AF changes that occur at the margin of geographic atrophy (junctional zone) were classified into five main patterns: none, focal, banded, patchy which localized to the border of geographic atrophy, and diffuse pattern, where changes are not limited to the border of the atrophic area. These phenotypic classification may be helpful to identify prognostic determinants for the spread of atrophy and visual loss [13]. In our study, one eye had a banded pattern and four eyes with diffuse pattern were noticed which implicate excessive RPE lipofuscin accumulation.

In our study, FAF patterns in eight eyes with neovascular AMD were classified into three with heterogeneous, three with central hypo-AF with a hyper-AF rim pattern, and two with a hyper-AF pattern at the site of choroidal neovascularization. In a study by Dandekar *et al*. [14], patients with a choroidal neovascularization (CNV) of recent onset, a normal or minimally abnormal distribution of FAF and in small CNVs, the abnormalities is restricted to the area of the lesion. In a study by McBain *et al*. [15] reduced AF signal at the site of classic in most cases has been which may be due to masking of the RPE-AF signal by the CNV growing in the subretinal space and in cases of occult CNV, multiple foci of low AF signal at the site of the CNV are commonly seen which represent small areas of RPE loss or a more irregular pattern of growth followed by the CNV.

In a study by Peng *et al*. [16] in cases with classic CNV, two patterns were noted: slightly decreased or near-normal FAF pattern which indicates that the RPE function is preserved. Another pattern showed a center of hypo-AF with a hyper-AF edge which may represent macrophages or proliferation of RPE cells. In cases with occult CNV two patterns were noted: normal FAF and heterogeneous fluorescence.

Stargardt disease

In our study, there were four eyes with Stargardt disease with marked macular hypo-AF related to chorioretinal atrophy with mostly hypo-AF flecks and little hyper-AF flecks, which correspond to yellow flecks in the color image, which are diffusely distributed beyond the posterior pole with relative peripapillary sparing similar to a study by Boon and colleagues, which reported that in advanced stages, there is complete degeneration and diffuse atrophy of RPE cells and photoreceptor death and central macular lesions with largely decreased FAF. In most patients, these were surrounded by smaller, well-circumscribed lesions of predominantly increased FAF. Some of the lesions on FAF were not readily seen at ophthalmoscopy. Peripapillary sparing of the hyper-AF flecks is highly suggestive of Stargardt disease [17].

Retinitis pigmentosa

Murakami *et al*. [18] identified three subsets of RP on FAF, where 59% of patients had a hyper-AF perifoveal

ring not visible on funduscopic examination; 18% had abnormal central hyper-AF extending centrifugally from the fovea, and 24% had neither pattern.

The hyper-AF ring, which is known as the Robson–Holder ring, corresponds to the border of the inner/outer segment junction disruption [19]. The ring itself corresponds to outer segment dysgenesis and lipofuscin production, while normal retina lies within the ring [18]. The more encroachment of the ring centrally means more consrtiction of visual field [20].

In our study, four eyes showed a hyper-AF para foveal ring which is not visible in color image. Two eyes were in the late stage of retinitis pigmentosa and shows severe loss of rods and cones and RPE loss which appears as hypo-AF involving macular and extramcular area.

Two eyes with atypical RP showed hypo-AF related to a bony specule-like pigmentation and hyper-AF and hypo-AF foci related to flakes and central macular hypo-AF due to atrophy.

Cone dystrophy

Bull's-eye appearance occurs in the early stages with macular atrophy progressing over time [21].

In a study by Kellner and colleagues, patients with cone dystrophy and cone–rod dystrophy have very striking FAF patterns with areas of central hypofluorescence surrounded by an area of hyper-AF. The areas of decreased AF represent areas of dead or absent RPE, whereas the ring of increased AF is thought to represent the active edge of dysfunctional or injured photoreceptors [22]. But this ring is a nonspecific manifestation as it is seen in different retinal dystrophies. Electrophysiology remains essential for accurate diagnosis [23].

In our study, four eyes showed central hypo-AF with perifoveal rings of hyper-AF.

Central serous choriretinopathy

In our study, one eye with acute CSR showed hypo-AF at the site of leakage and at the area of neurosensory detachment, and this is similar to a study by Eandi *et al.* [24], which reported decreased AF at the site of leakage due to the absence of RPE and hypo-AF at subretinal fluid accumulation due to AF blockage.

One eye with chronic CSR with descending tracts showed a heterogeneous pattern of hyper-AF and hyper-AF which is similar to what Lee and colleagues have observed that most patients with chronic CSC showed more heterogeneous patterns of hyper-FAF in the area of the serous retinal detachment (SRD) than those with acute CSC. This pattern might appear due to uneven distribution of fluorophores within the subretinal fluid by multifocal shedding of the outer photoreceptor layer and phagocytosis by macrophages [25].

One eye with recurrent CSR showed hypo-AF corresponding to RPE atrophy and at an area of source of leakage and showed hyper-AF at an area of neurosensory detachment which is similar to what von Rückmann *et al.* [26] reported that there is increased AF at the site of retinal detachment due to increased metabolic activity of RPE.

Best disease

Best vitelliform macular dystrophy is a hereditary retinal disease characterized by accumulation of lipofuscin in the central macula [27].

In our study, three eyes were in the pseudohypopyon stage, FAF was visible mainly in the inferior portion of the lesion, colocating with the ophthalmoscopically visible pseudohypopyon. One eye showed macular hypo-AF related to an atrophic area in color photo which agrees with the study by Boon *et al.* [28], who reported that early stages lesions showed a predominantly increased FAF, which decreased in later stages.

One eye with atypical presentation of Best disease showed extramacular hyper-AF corresponding to extramacular lesions.

Macular edema

In our study, two eyes showed no change of FAF in the foveal area which may be due to minimal leakage, four eyes showed loss of normal hypo-AF, and one showed localized area of hyper-AF.

Bessho and colleagues documented increased FAF in 488-nm AF in all examined eyes with cystoid macular edema (CME) of different origins corresponding to the petaloid shape on FA and optical coherence tomography cysts. In contrast, in 580 nm AF rarely presented this corresponding petaloid-shaped AF. They hypothesized that AF from CME may be considered as a 'pseudo' or 'relative' AF, due to macular stretching following CME that may result in lateral displacement of macular pigments and subsequent reduction of macular pigment density [29].

Melanocytic lesions

In a study by Pirondini *et al.* [30] choroidal nevus showed hypo-AF in 56%, iso-AF in 19%, and

hyper-AF in 25% according to disruption of the overlying RPE. And here in our study choroidal nevus showed hypo-AF.

In a study by Gündüz *et al*. [31], 90% of the tumors showed at least one focus of increased AF signal corresponding to the locations of the hyperpigmentation over the lesion, which may be due to an accumulation of lipofuscin in areas of hyperpigmentation.

In our study, choroidal melanoma showed confluent patches of hyper-AF over the lesion related to an orange pigment.

Macular hole

In a study by von Rückmann *et al*. [32] it has been demonstrated that in stage 1 macular hole (MH), the distribution of AF was normal and in stages 2, 3, and 4. MH showed an increased AF signal at the site of the hole. These findings can be explained as due to the absence of neurosensory retina at the site of the hole, there is no luteal pigment overlying the defect so intense that the AF signal is subsequently observed at the hole. But in our study, full thickness macular hole in the two cases appeared hypo-AF in spite of the presence of intact RPE by optical coherence tomography examination and the macular hole is surrounded by a ring of hyper-AF.

Juxtafoveal telangiectasia type 2

Disruption of foveal AF could be the earliest finding in macular telangiectasia type 2. The most frequent findings are complete loss of normal foveal hypo-AF or an increase in foveal AF in early stages. Retinal crystals and intraretinal pigment clumping showed hypo-AF corresponding to the blockage of physiological AF of the RPE [33].

In a study Wong *et al*. [34] introduced a severity scale on the basis of AF in macular telangiectasia type 2.

In our study, four eyes with macular telangiectasia type 2, one eye in the early stage showed foveal hyper-AF which is due to the possibility that anatomical changes that result in FAF changes may precede the more typical vascular changes and two had a mixed pattern of hyper-AF and hypo-AF and one had foveal hypo-AF related to pigmentation due to blockage of AF by pigmentation.

Vogt-Koyanagi-Harada

In a study by Malamos and colleagues, FAF images showed poorly defined areas of hyper-AF that were partially surrounded by mixed faint hyper-AF and hypo-AF dots. Hyper-AF was attributable to the impaired metabolism and phagocytosis of photoreceptors' outer segment tips, as a result of the poor apposition between RPE and neurosensory retina [35]. As appeared in our study, FAF showed hyper-AF areas related to areas of serous detachment.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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