Evaluation of Different Phenotypic Features and Progression of Stargardt-Fundus Flavimaculatus Disease with Fundus Autofluorescence Imaging

Fundus Otoflöresans Görüntüleme Yöntemi ile Stargardt-Fundus Flavimakulatus Hastalığı'nın Farklı Fenotipik Özelliklerinin ve Progresyonunun Değerlendirilmesi

Pınar BİNGÖL KIZILTUNÇ[1], Figen ŞERMET[2], Sibel DEMİREL[3], Emin ÖZMERT[2]

ABSTRACT

Purpose: To describe the clinical findings and disease progression of Stargardt–fundus flavimaculatus disease with fundus autofluorescence imaging and to evaluate their correlation with visual acuity.

Materials and Methods: The visual acuity, fundus examination and fundus autofluorescence findings of patients were noted.

Results: Patients with stage 1 showed increased autofluorescence with peripapillary sparing. At stage 2, there were flecks located in the extrafoveal region to the periphery. The active flecks were hyperautofluorescent, and the inactive flecks were hypoautofluorescent. At stage 3, the flecks were accompanied by macular atrophy. Atrophy progression was seen in 6 eyes. The number of flecks were increased in 8 eyes, and the hyperautofluorescent flecks became hypoautofluorescent in 6 eyes. There was no correlation between the stages of the disease and the visual acuity.

Conclusions: The different phenotypic features determined by the FAF imaging in Stargardt–fundus flavimaculatus disease can give information about the progression and prognosis of the disease.

Key Words: Fundus Autofluorescence Imaging, Fundus Flavimaculatus Disease, Stargardt Disease.

ÖZ

Amaç: Fundus otoflöresans görüntüleme yöntemi ile Stargardt-fundus flavimakulatus hastalığının klinik bulgularının ve hastalık progresyonunun tanımlanması ve bu bulguların görme keskinliği ile ilişkisinin değerlendirilmesi.

Gereç ve Yöntem: Hastaların görme keskinliği, fundus muayene bulguları ve fundus otoflöresans bulguları retrospektif olarak kaydedildi.

Bulgular: Evre 1'de artmış otoflöresansa peripapiller korunmuşluk eşlik ediyordu. Evre 2'de ekstrafoveal bölgeden perifere uzanan flekler mevcuttu. Aktif flekler hiperotoflöresan izlenirken, inaktif flekler hipootoflöresandı. Evre 3'te ise fleklere makuler atrofi eşlik ediyordu. Hastaların takipleri sırasında 6 gözde makuler atrofide progresyon, 8 gözde flek sayısında artış, 6 gözde ise fleklerde hiperotoflöresanstan hipootoflöresansa geçiş izlendi. Hastalık evresi ile görme keskinliği arasında ilişki saptanmadı.

Sonuç: Fundus otoflöresans görüntüleme yöntemi ile Stargardt-fundus flavimakulatus hastalığında tespit edilen farklı fenotipik özellikler, hastalık progresyonu ve prognozu hakkında bilgi verebilir.

Anahtar Kelimeler: Fundus Otoflöresans Görüntüleme, Fundus Flavimakulatus Hastalığı, Stargardt Hastalığı.

1- M.D. Kağızman State Hospital, Eye Clinic, Kars/TURKEY
KIZILTUNC BINGOL P., pinarbingol84@gmail.com
KAPTI H.B., burhaneddink@hotmail.com
2- M.D. Professor Ankara University Faculty of Medicine, Eye Clinic, Ankara/TURKEY
SERMET F., fbatioglu@gmail.com
OZMERT E., eozmert56@gmail.com
3- M.D. Associate Professor Ankara University Faculty of Medicine, Eye Clinic, Ankara/TURKEY
DEMIREL S., drsibeldemireltr@yahoo.com

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Yazışma Adresi / Correspondence Adress:
M.D. Pinar BINGOL KIZILTUNC
Kağızman State Hospital, Eye Clinic, Kars/TURKEY

Phone: +90 544 821 41 53
E-mail: pinarbingol84@gmail.com

INTRODUCTION

Stargardt disease is the most common juvenile hereditary macular degeneration with a wide variability in the age of onset, disease severity, and clinical findings.[1,2] Orange-yellow retinal flecks and foveal retinal pigment epithelial (RPE) atrophy with peripapillary sparing characterize the disease. In the early stage, the fundus appearance may be normal, or a foveolar reflex disappearance may be the only fundus examination finding.[3] The flecks, mainly composed of lipofuscin at the level of RPE cells, characteristically have a pisciform appearance. They are located around the macula and the midperipheral retina, but the far peripheral retina is spared.[4] In the late stage of the disease, atrophy of RPE cells causes a "bull's eye" appearance in the macula.

Different classification systems for Stargardt disease have been proposed based on ophthalmoscopic findings and electrophysiological and psychophysical tests,[5-7] but today none of them has been widely accepted. Fundus flavimaculatus, first described by Franceschetti in the 1960s, is generally used to describe a late onset and mild form of Stargardt disease.[3,8-10] In this study, we evaluated Stargardt disease and fundus flavimaculatus (SD/FF) as a similar entity.

Fundus autofluorescence (FAF) imaging is a noninvasive method that enables quantifying the fluorophores, especially lipofuscin, with short-wave autofluorescence (SW-AF) and melanin with near-infrared autofluorescence (NIR-AF). As the main physiopathological mechanism of SD/FF is an accumulation of lipofuscin in the RPE cells, the FAF findings of SD/FF were described in different studies.[11-13] The purpose of this study was to evaluate the FAF findings of SD/FF in different stages and to compare these findings with visual acuity (VA) and disease progression.

MATERIALS AND METHODS

Patients who were diagnosed with SD/FF between April 2004 and October 2013 were included in this study. The records of 44 eyes from 22 patients were retrospectively reviewed. The best-corrected visual acuity (BCVA), fundus examination results, and FAF images were evaluated.

The FAF imaging was performed using a confocal scanning laser ophthalmoscope, the Heidelberg Retinal Angiography 2 (HRA2) (Heidelberg Engineering, Heidelberg, Germany). The SW-AF images were recorded at a 488 nm wavelength via≥500 nm barrier filter, and the NIR-AF images were recorded at 787 nm wavelength via ≥ 800 nm barrier filter.

The patients were classified into three stages according to the FAF findings. The diffuse increased autofluorescence without flecks, and the atrophy was accepted as stage 1. Perifoveal and midperipheral flecks were stage 2, and RPE atrophy accompanied by flecks were stage 3.

All analyses were conducted with the SPSS 15.0 software package (SPSS Inc., Chicago, IL., USA). A p value less than 0.05 was considered statistically significant. Spearman's and Mann–Whitney U tests were used to compare the BCVA, stages, and FAF findings.

RESULTS

The mean age of patients was 37 (10–72) years. Twelve (54.5%) patients were male and 10 (45.5%) were female. Fourteen (63.6%) patients had regular follow-ups. The mean follow-up period of these patients was 32 (4–81) months. All patients had bilateral and symmetric disease involvement. At the initial examination, 6 (13.7%) eyes presented with stage 1, 10 (22.7%) with stage 2, and 28 (63.6%) with stage 3.

At SW-AF imaging, diffuse increased autofluorescence in stage 1 was detected. In stage 2, there were flecks with a location of concentric spread from the fovea to the midperipheral retina. Active flecks had increased autofluorescence with a centrifugal expansion. However, inactive flecks showed a decreased autofluorescent signal. In stage 3, the active/inactive flecks were accompanied by macular atrophy, which had a hypoautofluorescent signal with sharp borders. All eyes showed peripapillary sparing (Figure 1).

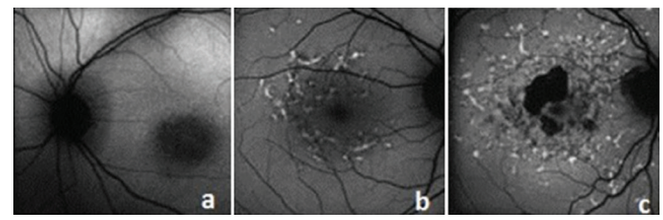

Figure 1a-b: *Stages of SD/FF at FAF imaging a) Stage 1: Diffuse increased autofluorescence with peripapillary sparing b) Stage 2: Perifoveal and midperipheral flecks c) Stage 3: Central atrophy accompanied by flecks.*

At NIR-AF, both the active and inactive flecks had a hypoautofluorescent signal. The atrophic areas were more irregular than the SW-AF images (Figure 2). In addition, the central atrophy involvement was more prominent than the SW-AF images.

The mean visual acuity was 0.3 (0.016–1.0) Snellen. Although eyes with large central atrophy had worse VA, there was no correlation between the stages and VA.

During the follow-up period, the flecks increased in 8 (57%) eyes, the active flecks became inactive with hypoautofluorescent signals in 6 (42%) eyes, and there was atrophy progression in 6 (42%) eyes (Figure 3). There was only 1 (7%) eye with disease progression from stage 1 to stage 3.

DISCUSSION

Different classification systems of SD/FF have been used based on the fundus findings,[2,5,6] but today none of them is widely accepted. Although active flecks can easily be seen by a fundus examination, in the later stages, the resorbed flecks are more difficult to visualize. However, with FAF imaging, both active and resorbed flecks can be detected. Therefore, FAF imaging is the most effective clinical procedure for the diagnosis of the disease and the evaluation of progression. Because of the main pathogenesis of SD/FF is lipofuscin accumulation, the patients were classified according to their FAF findings.

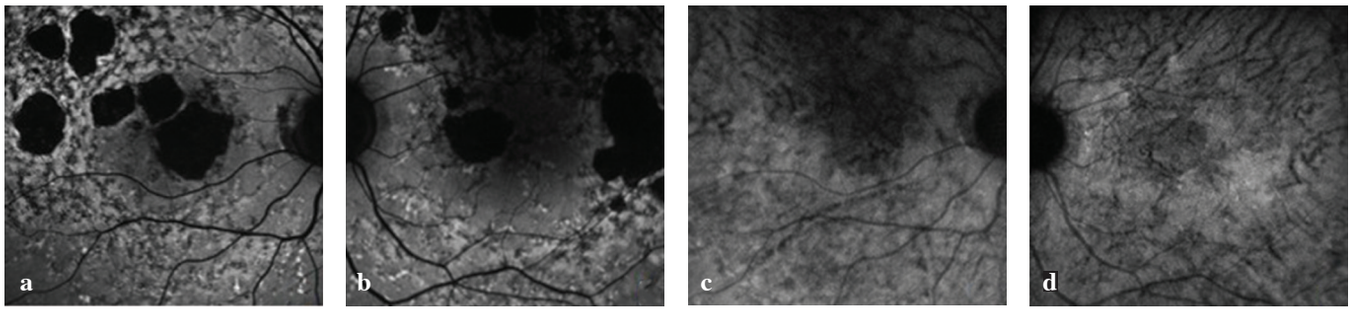

Figure 2a-d: *A 59 year-old woman with stage 3 SD/FF a,b) Hyper-hypoautofluorescent flecks and hypoautofluorescent atrophic areas with sharp borders in her right and left eye at SW-AF c,d) All flecks are hypoautofluorescent and atrophic areas are irregular at NIR-AF and not as clearly visible as SW-AF.*

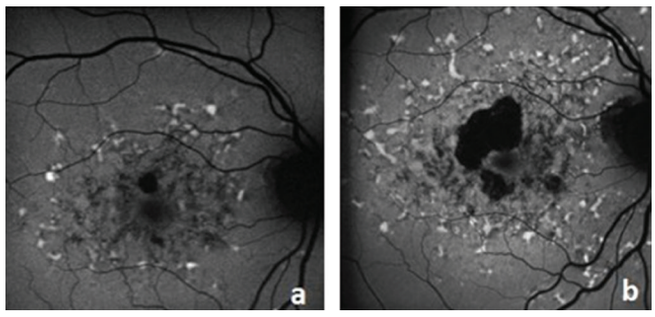

Figure 3a-b: *A 50 year-old man with Stage 3 SD/FF a)Initial SW-AF b) Atrophy progression and centrifugal expansion of flecks at 49th month.*

Lois et al.,[11] claimed that RPE cell damage severity caused by lipofuscin accumulation could be variable in different eyes. Normal levels of lipofuscin accumulation can cause RPE and photoreceptor cell damage in some patients. Therefore, normal lipofuscin levels can indicate early disease. Normal or minimally increased lipofuscin levels may cause diffuse increased autofluorescence without flecks in the early stages. In this study, there were 6 (13.7%) eyes presented with diffuse increased autofluorescence without flecks accepted as stage 1.

SW-AF images of active flecks, a characteristic finding of the disease, appear as focal increased autofluorescence due to the accumulation of lipofuscin. Over time, increased lipofuscin accumulation damages the RPE cells and eventuate with autofluorescent signal decrease. This mechanism may explain why inactive flecks show a hypoautofluorescent signal. In addition, lipofuscin accumulation in the RPE cells can change the distribution of other intracellular components, such as melanin. As the lipofuscin accumulation increases, these granules displace or fuse with melanin granules and cause a loss of melanin granules.[14, 15] Decreased melanin granules cause hypoautofluorescent signal changes in NIR-AF.

The pathologic changes in the neurosensory retina at SD/FF were described in different studies.[14-17] Birnbach et al.,[15] showed lipofuscin accumulation, loss of photoreceptors, and reactive Müller cell hypertrophy with a decreased concentration from macula to the peripheral retina. This distribution also correlates with the expansion of the fundus and the FAF findings. Cukras et al. used FAF imaging to evaluate the progression of flecks and central macular atrophy; they demonstrated the flecks as hyperautofluorescent lesions extending in a centrifugal direction from the fovea with a nonrandom radial path.[13] They also showed that the autofluorescence signal of flecks turned from hyperautofluorescence to hypoautofluorescence over time. The earliest fleck location is similar to the normal distribution of cone photoreceptors, RPE cells, macular pigment, and melanin concentration. Centrifugal expansion of flecks from the fovea to the midperipheral retina may be explained by the location of the photoreceptor and RPE cells. The ATP-binding cassette transporter (ABCA4) gene mutation, the main pathogenesis of SD/FF, causes RPE cell death and loss of photoreceptor cells. Due to the dense location of these cells from the fovea to the peripheral retina, lipofuscin accumulation starts from the fovea. Cukras et al.,[13] suggested another mechanism for the radial expansion pattern of flecks. Intercellular communications between RPE and photoreceptor cells may mediate to the cellular damage; in this way, the disease progression is expanded from the central to peripheral retina. It can be accepted that the earliest flecks with hyperautofluorescent signal changes are seen close to the fovea. After, as the newer flecks occur, they locate step-by-step around the earliest flecks toward the midperipheral retina. In another study, Cideciyan et al.,[18] evaluated the FAF findings; they showed diffusely increased FAF in the posterior pole in the early stages and the appearance of focally hyperautofluorescent flecks in the perifoveal region. In the later stage, decreased signals due to the dysfunction and loss of RPE cells occur. In this study, centrifugal expansion of flecks from fovea to the midperipheral retina was shown. Active flecks were hyperautofluorescent on SW-AF, while inactive flecks were hypoautofluorescent. All types of the flecks were hypoautofluorescent on NIR-AF.

As the disease progresses, the degeneration of photoreceptor cells and underlying retinal pigment epithelium due to lipofuscin accumulation causes atrophic changes.[19] Although atrophic areas were sharply demarcated at SW-AF, the borders were indistinct. The atrophic areas were larger at NIR-AF, as reported by Cukras et al.[13]

Peripapillary sparing is an important finding, especially for the diagnosis of an advanced disease with resorbed flecks.

Many studies showed peripapillary sparing in SD/FF.20-22 Although the mechanism of peripapillary sparing is unclear, the ratio of RPE and photoreceptor cells in the peripapillary area may explain this finding. Cideciyan et al. reported that the presence of a thicker peripapillary retinal nerve fiber layer is one reason.[18] This thicker layer may reduce the photo-oxidative damage on the photoreceptor-RPE complex that eventuate with peripapillary sparing. In addition, they claimed that there could be a clearance mechanism of lipofuscin in the peripapillary area. All of the eyes had peripapillary sparing in our study.

Patients with SD/FF have a decreased VA due to central involvement. It has been shown that VA in Stargardt disease is correlated with the extent of foveal macular pigment that determines the structural integrity of the foveal cones.[23] In addition, patients with less central foveal thickness have worse VA.[24] Today, the presence of foveal sparing is an important factor in determining the VA prognosis. Although Rotenstreich et al. evaluated the presence of foveal sparing ophthalmoscopically and showed a better VA in these eyes, a fundus examination may not be adequate to show foveal involvement.[2] By using FAF imaging, it can be determined easily, especially with NIR-AF. In healthy eyes, due to the absorption of light by melanin and macular pigments, the central macula seems hypoautofluorescent at SW-AF imaging, and the central atrophy involvement cannot be evaluated easily. A hyperautofluorescent signal of a healthy central macula at NIR-AF enables detection of central involvement. In this study, better VA measurements in eyes with foveal sparing was found.

In conclusion, FAF imaging is a valuable imaging method to evaluate the prognosis and progression of SD/FF. Larger scale prospective studies with longer follow-up periods are needed on this subject.

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