Multimodal retinal imaging and electroretinographic findings in fundus albipunctatus

Eyupcan Sensoy[1], *Sibel Doguizi*[2], *Mehmet Ali Sekeroglu*[3]

ABSTRACT

Fundus Albipunctatus (FA) is one of the rare forms of persistent night blindness. Common white or pale yellow spots are present on the fundus. Given its clinical findings; FA is also considered in the group of diseases (retinitis punctata albescens, fundus flavimaculatus, familial drusen, flecked retina of Kandori) termed flecked retina syndromes. In order to ensure an accurate diagnosis of FA, it is important to be aware of the multimodal retinal imaging characteristics and appropriate electroretinographic findings for this disorder. In this manuscript, we aimed to present multimodal retinal images and disease-specific electroretinography findings in two patients diagnosed with FA in our clinic.

Keywords: Fundus Albipunctatus, Electroretinography, Multimodal Imaging, Stationary Night Blindness

INTRODUCTION

Fundus Albipunktatus (FA) is a rare form of stationary night blindness characterized by widespread white or pale yellow spots in the retina. It is distinguished from other types of stationary night blindness by the presence of these spots in the fundus which may or may not involve the macula. It was first described by Mooren in 1882.[1] FA is typically caused by mutations in the retinol dehydrogenase 5 (RDH5) gene, which encodes 11-cis retinol dehydrogenase, an enzyme abundant in the retinal pigment epithelium (RPE).[2] Disruption in the production of 11-cis-retinal leads to impairment in the photoreceptor cycle and photo-transduction along with an imbalance in the production of A2E and lipofuscin.[2] It is known that mutations in retinaldehyde binding protein 1 (RABP1) and RPE-specific protein (RPE65) are also associated with FA.[3] It has both autosomal dominant and autosomal recessive types.[4] In addition, FA is part of a genetically determined heterogeneous group known as flecked retina disorders,[4] which also includes diseases such as retinitis punctata albescens (RPA), fundus flavimaculatus (Stargardt Disease), familial drusen, and Kandori's flecked retina.[5]

The optic nerve head and retinal vessels appear normal in FA cases. Visual field and visual acuity measurements are typically normal unless there is no dark stimulus. Dark stimulation causes a decrease in visual acuity and narrowing of the visual field. Scotopic (DA) electroretinography (ERG) responses are decreased 30-40 minutes after dark adaptation but return to normal after prolonged dark adaptation.[2,6]

Here, it was aimed to present and discuss two cases diagnosed with FA in a tertiary ophthalmology clinic together with multimodal retinal images and typical ERG findings associated with the disease.

Case 1

A 28-year-old male patient presented to our clinic with a complaint of impaired vision in dark. The best-corrected visual acuity (BCVA) was 20/20 in both eyes. Intraocular pressures were 16 mmHg in the right eye and 18 mmHg in the left eye, and anterior segment examination was normal in both eyes. Fundus examination revealed widespread well-defined yellow-white spots without foveal involvement in both eyes. The arterial and venous

1- MD, Etlik City Hospital, Department of Ophthalmology, Ankara, Türkiye

2- MD, Assoc. Prof., Ulucanlar Eye Training and Research Hospital, Ankara, Turkey, Türkiye

3- MD, Prof.,Etlik City Hospital, Department of Ophthalmology, Ankara, Türkiye

Received: 02.08.2023
Accepted: 09.10.2023
J Ret-Vit 2024; 33: 70-77
DOİ:10.37845/ret.vit.2024.33.11

Correspondence Adress:
Eyupcan Sensoy
Etlik City Hospital, Department of Ophthalmology, Ankara, Türkiye
Phone: +90 546 417 7538
E-mail: dreyupcansensoy@yahoo.com

vascular systems appeared normal, and the disc margins were well-defined (Figure 1A and 1B). On horizontal Optical coherence tomography (OCT) (Spectralis OCT, Heidelberg Engineering, Germany) images, there were multiple well-defined, small, dome-shaped lesions which originated from the retinal pigment epithelium (RPE) layer outside the foveal area in both eyes. The lesions projected from RPE to ellipsoid zone, external limiting membrane and outer nuclear layer (Figure 2A and 2B). In infrared images (IR), there were hyper-reflective spots compatible

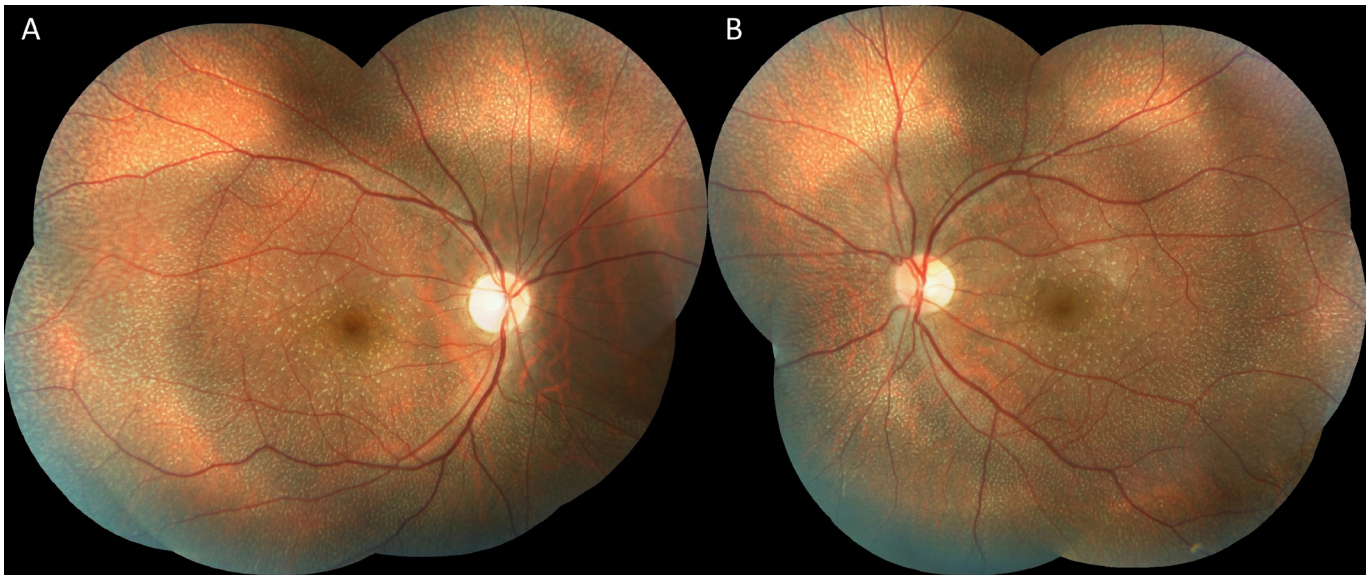

Figure 1: *A and B) Color fundus image of right and left eyes of case 1; in both eyes, widespread, well-defined white-yellow spots at areas other than the foveal area preserved; normal arterial and venous vascularity.*

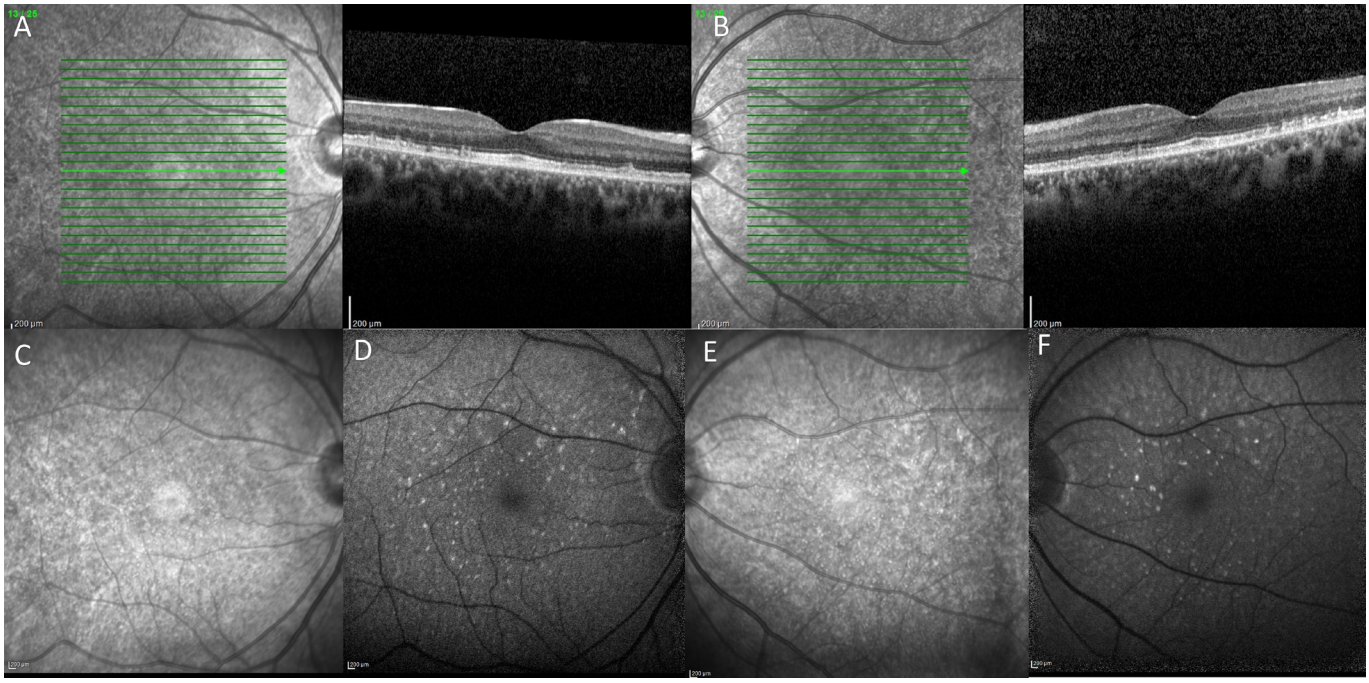

Figure 2: *A and B) Optical coherence tomography (OCT) images of right and left eyes of case 1; in both eyes, multiple, well-defined, dome-shaped lesions originating from retinal pigment epithelium (RPE) layer at areas other than small foveal area; lesion projects from RPE to ellipsoid zone, external limiting membrane and outer nuclear layer. C and E) Infrared (IR) images of right and left eye of case 1; more common than those in FAF images; hyper-reflective dots compatible with white-yellow spots are seen in both eyes. D and F) Fundus autofluorescence (FAF) images of right and left eyes of case 1; hyper-autofluorescent areas compatible with white-yellow spots along with areas showing hypo-autofluorescence in both eyes.*

with yellow-white spots (Figure 2C and 2E). Blue fundus autofluorescence (FAF) imaging showed hyper-autofluorescent spots in areas consistent with yellow-white dots with fewer spots compared to IR images; in addition, there were also hypo-autofluorescent areas (Figure 2D and 2F). In the full-field electroretinography (ERG) performed after 20 minutes of dark adaptation according to the International Society For Clinical Electrophysiology of Vision (ISCEV) standards, there was no a and b waves in the DA 0.01 and 10.0 ERG responses, while the DA 3.0 ERG response was electronegative (b/a<1) (Figure 3). Full-field ERG performed after 10 minutes of light adaptation following ISCEV standards revealed mild impairment in photopic responses (LA 3.0 and LA 3.0 flicker) (Figure 3).[7,8] Based on the patient's history, imaging findings, and ERG responses obtained according to ISCEV standards, the patient was initially diagnosed with FA. Thus, full-field ERG was performed after a prolonged dark adaptation (120 minutes),[7,8] it was found that the impaired scotopic responses (DA 0.01, DA 3.0, and DA 10.0) were normalized while photopic responses (LA 3.0 and LA 3.0 flicker) remained unchanged (Figure 4).

Case 2

A 33-year-old male patient presented with a complaint of impaired vision in the dark. The best-corrected visual acuity (BCVA) was bilateral 20/20 in both eyes. Intraocular pressures were within normal range in both eyes, and anterior segment examination was normal. Fundus examination revealed widespread well-defined yellow-white spots outside foveal area in both eyes (Figure 5A and 5B). The arterial and venous vascularity were normal in both eyes. On horizontal OCT images, there were multiple small, preserved, well-defined dome-shaped lesions originating from the retinal pigment epithelium (RPE) layer outside the limited foveal area in both eyes (Figure 6A and 6B). In FAF, the areas corresponding to the yellow-white spots in fundus photographs showed mild hypo-autofluorescence (Figure 7C and 7D). Full-field electroretinography (ERG) performed after 20 minutes of dark adaptation according to the International Society For Clinical Electrophysiology of Vision (ISCEV) standards showed no a and b waves in the DA 0.01 and 10.0 ERG responses, while the DA 3.0 ERG response was electronegative (b/a<1) (Image 8). Full-field ERG performed after 10 minutes of light adaptation

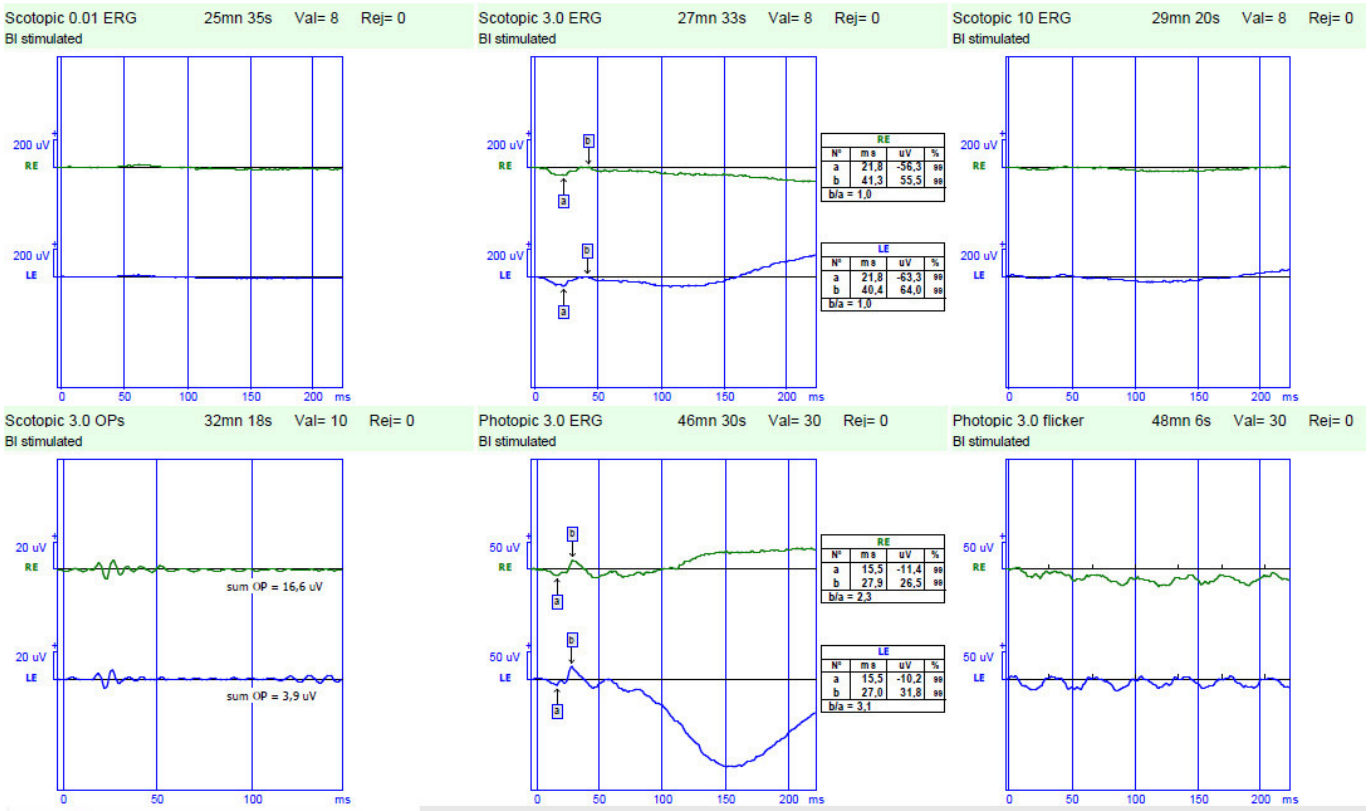

Figure 3: *Full-field electroretinography (ERG) image of case 1 after 20 minutes of dark adaptation, it was seen that there no a and b waves in the DA 0.01 and 10.0 ERG responses, while the DA 3.0 ERG response was electronegative (b/a<1) in both eyes;; phototopic responses were mildly affected (LA 3.0 and LA 3.0 flicker)*

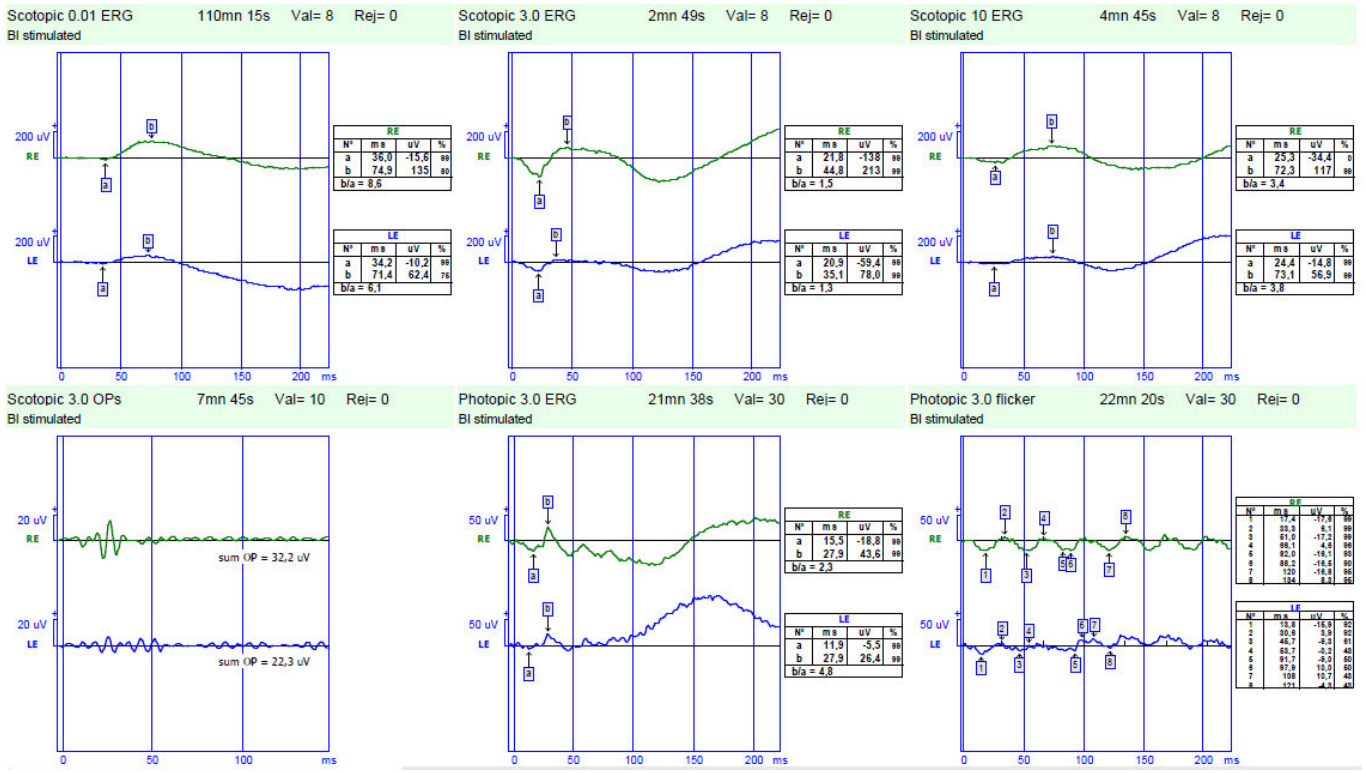

Figure 4: *Full-field electroretinography (ERG) image of case 1 after 120 minutes of dark adaptation, it was found that the impaired scotopic responses (DA 0.01, DA 3.0, and DA 10.0) were normalized while photopic responses (LA 3.0 and LA 3.0 flicker) remained unchanged.*

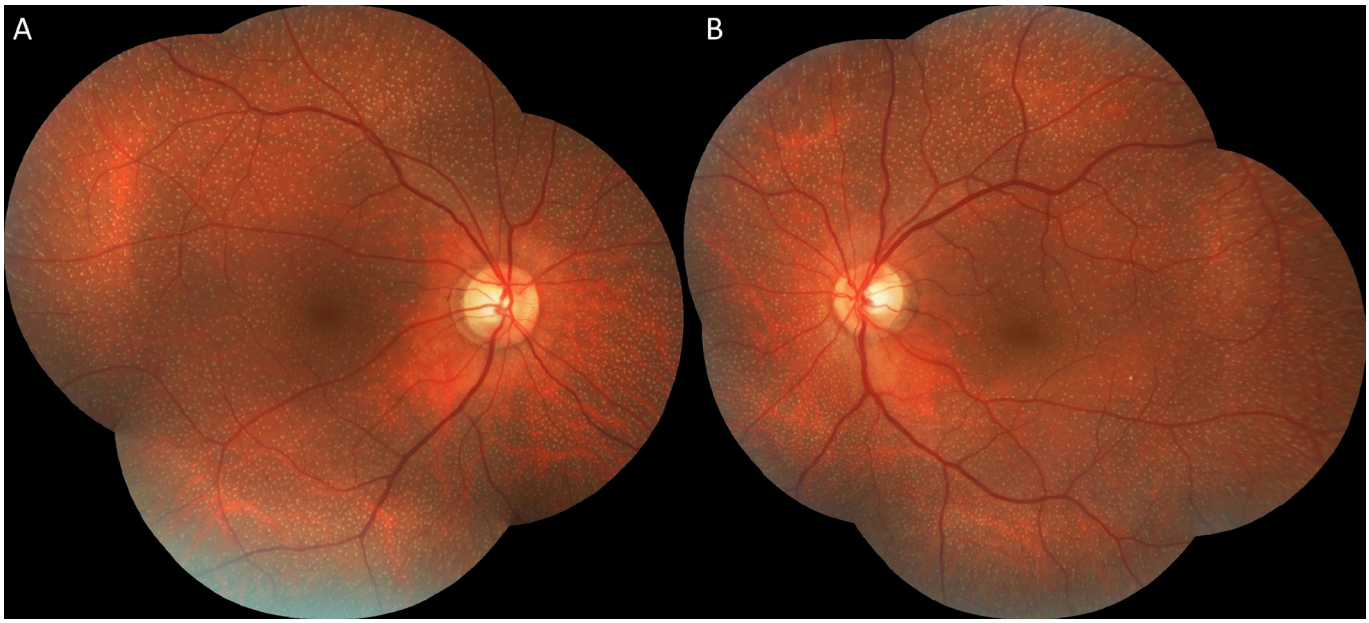

Figure 5: *A and B) Color fundus image of right and left eyes of case 2; in both eyes, widespread, well-defined white-yellow spots at areas other than the foveal area preserved; normal arterial and venous vascularity.*

following ISCEV standards revealed normal photopic responses (LA 3.0 and LA 3.0 flicker) (Image 8). Based on the patient's history, imaging findings, and ERG responses obtained according to ISCEV standards, the patient was initially diagnosed with FA. Thus, full-field ERG with prolonged dark adaptation (120 minutes) was performed and showed that the impaired scotopic responses (DA 0.01 and DA 3.0) were normalized (Figure 9).

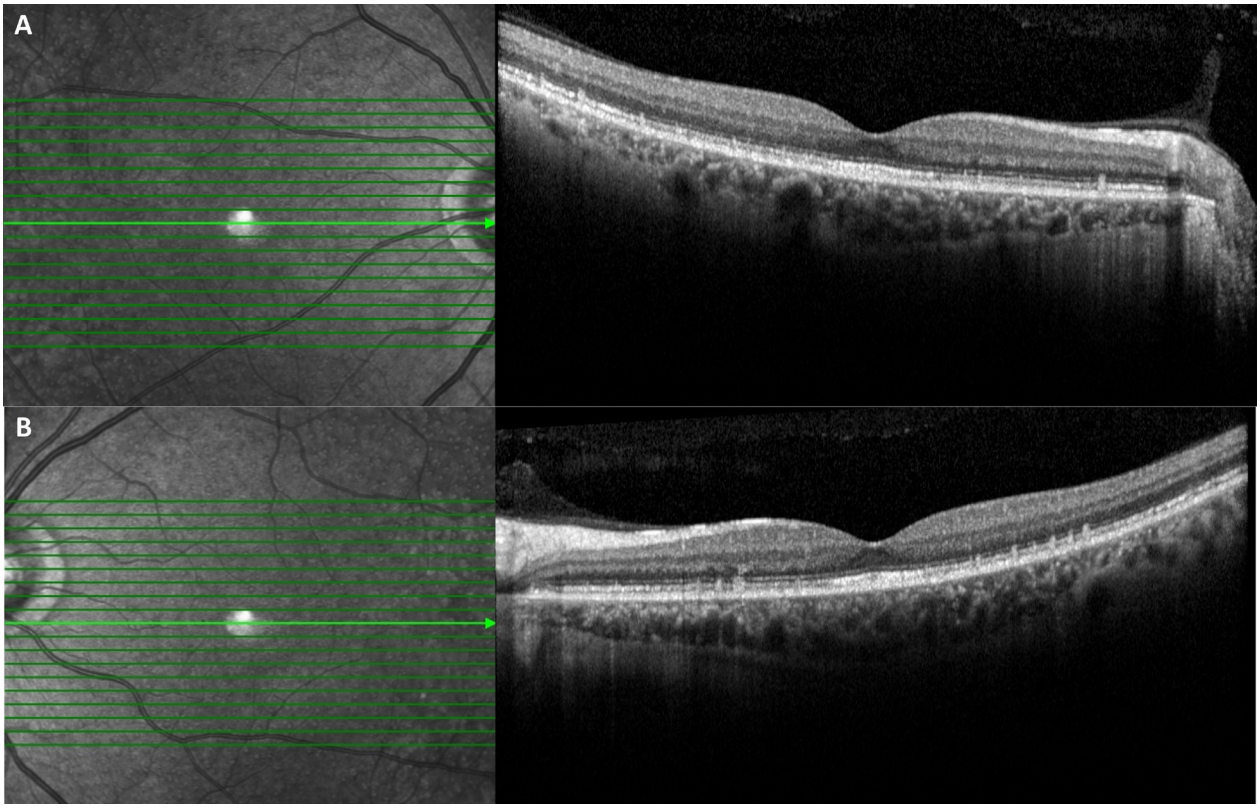

Figure 6: *A and B) Optical coherence tomography (OCT) images of right and left eyes of case 2; in both eyes, multiple, well-defined, dome-shaped lesions originating from retinal pigment epithelium (RPE) layer at areas other than small foveal area; lesion projects from RPE to ellipsoid zone, external limiting membrane and outer nuclear layer.*

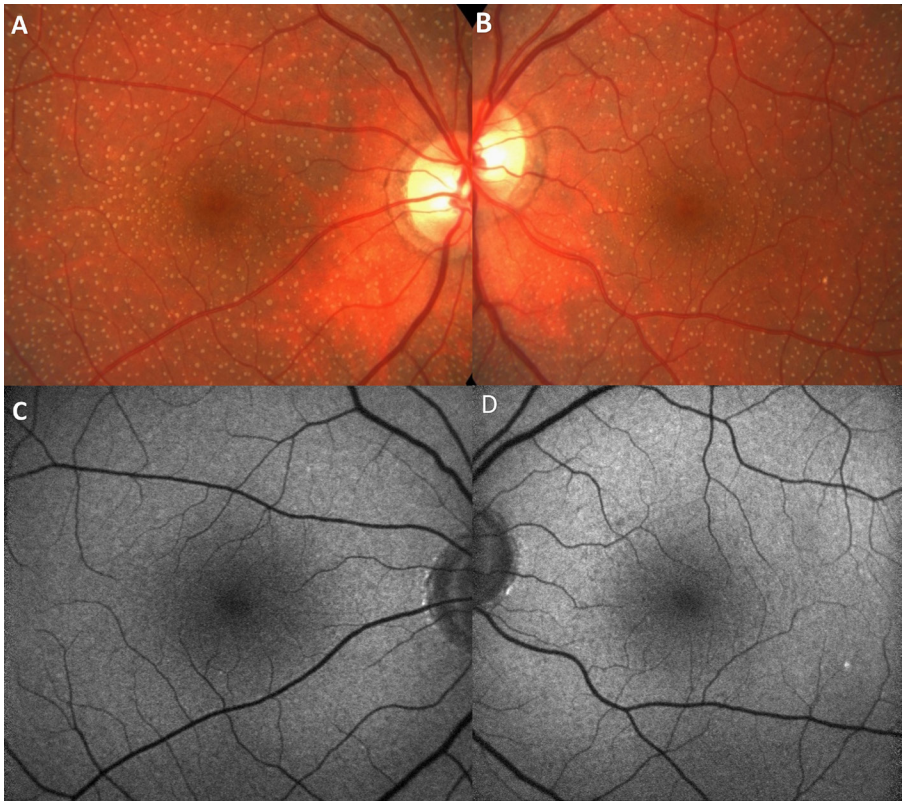

Figure 7: *On fundus autofluorescence (FAF) imaging of case 2, mildly hypofluorescent areas in both eyes on FAF (C and D) corresponding to white-yellow spots on color fundus images (A and B).*

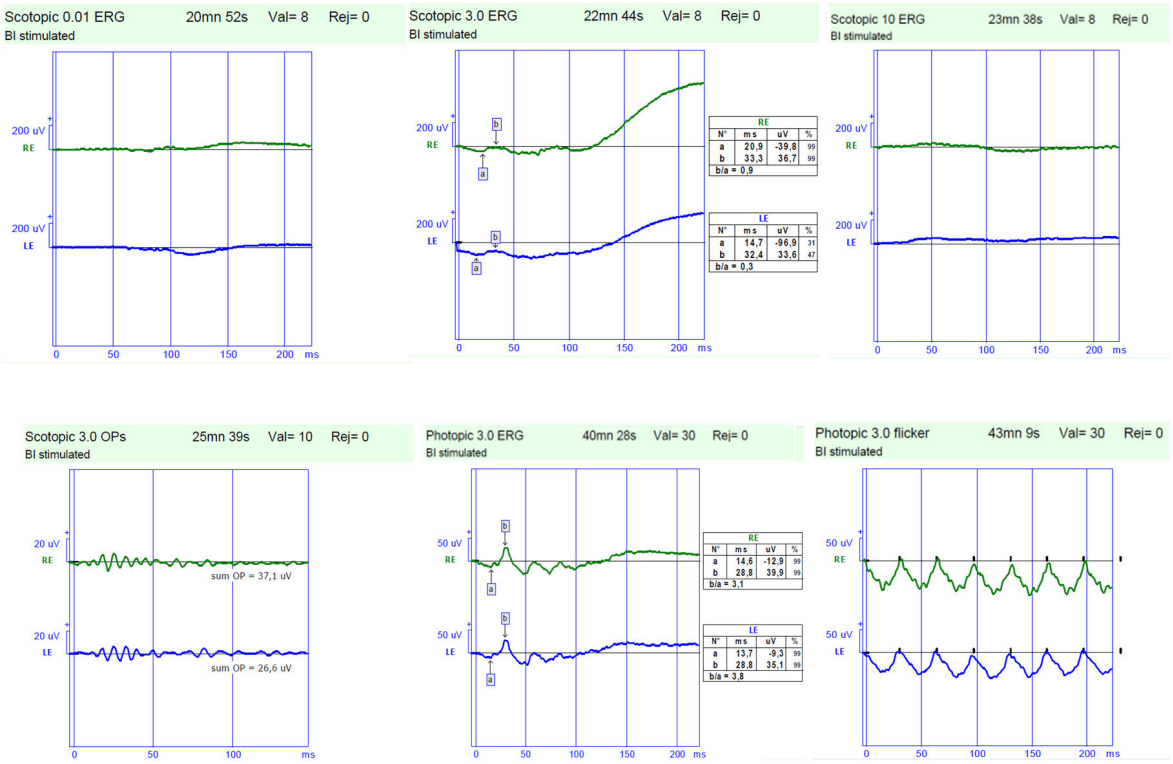

Figure 8: *Full-field electroretinography (ERG) image of case 2 after 20 minutes of dark adaptation, it was seen that there no a and b waves in the DA 0.01 and 10.0 ERG responses, while the DA 3.0 ERG response was electronegative (b/a<1) in both eyes; phototopic responses were normal (LA 3.0 and LA 3.0 flicker).*

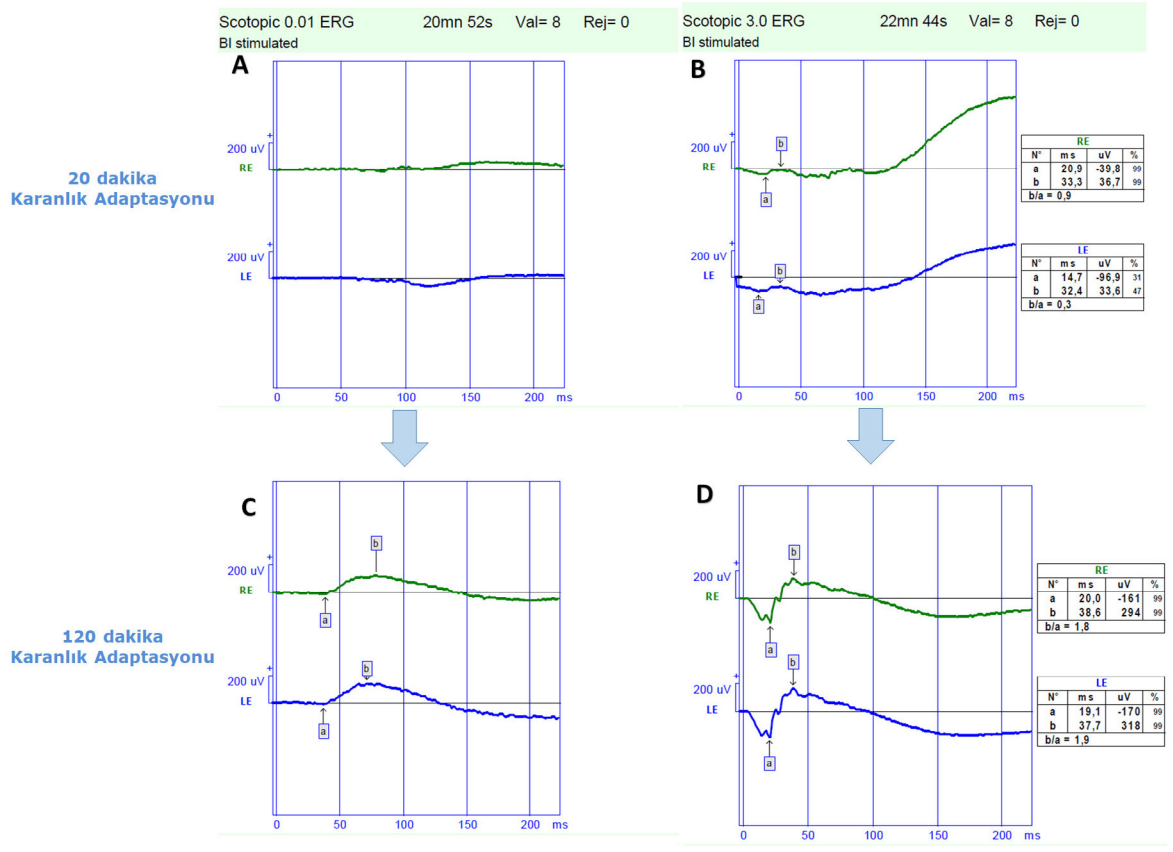

Figure 9: *Full-field electroretinography (ERG) image of case 2 after 120 minutes of dark adaptation, it was found that the impaired scotopic responses (DA 0.01, DA 3.0, and DA 10.0) were normalized.*

DISCUSSION

FA should be differentiated from other diseases within the group of flecked retina disorders, including RPA, fundus flavimaculatus (Stargardt Disease), familial drusen, and Kandori's spotted retina.[5] Thiis can be challenging with routine ophthalmic examination. In this group of diseases with yellow-white spots, OCT alone has limited ability to distinguish between these conditions.[9] Despite the inability to perform genetic analysis in our patients, it is possible to make an accurate diagnosis through multimodal imaging and full-field ERG findings in this disease group.

Fundus autofluorescence is derived from the accumulation of lipofuscin, and A2E is the primary fluorophore derived from the entire trans-retinal accumulation. In FA, impaired all-retinal or deficient visual cycle can restrict photo-pigment conversion and reduce lipofuscin transformation. The impaired lipofuscin formation resulting from RDH5, RPE65 and LRAT mutations can present with decreased autofluorescence in fundus autofluorescence (FAF) images.[10] In addition, studies have shown that there were spots showing hyperfluorescence and even a "bull's eye" pattern of hypofluorescence in the foveal area along with reduced hypo-fluorescence in FA patients, particularly in cases with advanced cone dysfunction.[10] These findings differ from fundus flavimaculatus, where yellow-white spots are spread throughout the whole retina outside the macula and show high-intensity hyperfluorescence. One of our patient(Case-2) showed mild hypo-fluorescence in the macula while the other patient (Case-1) showed hyper-fluorescent small spots together with hypo-fluorescent areas. These FAF findings led us to exclude the diagnosis of fundus flavimaculatus in our patients.

As known, infrared reflectance (IR) imaging can detect light from deeper layers, distinguishing between reflected and scattered light. This provides more insight regarding subretinal lesions.[11] In FA patients, the impairment of the 11-cis RDH enzyme leads to the accumulation of cis-retinol and cis-retinyl esters in the RPE and subretinal accumulations can be observed as hyper-reflective points in IR imaging.[12] In our first patient (Case-1), we observed hyper-reflective areas in IR imaging, corresponding to the yellow-white spots seen in the fundus, and they were more widespread than those observed in fundus autofluorescence (FAF). We believe that IR imaging in FA patients can offer more detailed information compared to FAF imaging.

Full-field electroretinography (ERG) is a crucial test for the diagnosis and differential diagnosis of FA. In our cases, the presence of scotopic electronegative response in the standard 20-minute full-field ERG and the normalization of the electronegative wave pattern in the full-field ERG taken after 120 minutes of dark adaptation together with the normal formation of a and b waves in scotopic responses have a significant role in supporting our diagnosis. The improvement in scotopic ERG responses after 120 minutes of dark adaptation is due to the slow regeneration of photo-pigments in FA patients.[6] This is crucial for distinguishing FA from progressive diseases like retinitis punctata albescens (RPA) where abnormalities observed in ERG waves after 120 minutes of dark adaptation typically do not improve.[10] In addition, ERG responses to light-adapted photopic ERG can vary in FA patients, showing a significant decrease from normal to severe, and these responses may decrease with age.[6] This indicates the potential impact on cone functions in these patients. In our first patient (Case 1), a mild impairment was observed in the full-field ERG photopic responses (LA 3.0 and LA 3.0 flicker), while photopic responses (LA 3.0 and LA 3.0 flicker) were normal in the second patient (Case 2).

In conclusion, FA is a genetically inherited, rare form of stationary night blindness that can be diagnosed by evaluating its clinical presentation, multimodal imaging features, and especially full-field ERG responses (after 20 minutes and 120 minutes of dark adaptation). Although genetic analysis (RDH5, RABP1, and RPE65 gene mutations) is crucial for assessment of etiopathogenesis and confirmation of the diagnosis, knowledge of the clinical, imaging, and ERG findings of this rare disease is critical for an accurate diagnosis.

REFERENCES

1. M1. Mooren A. Fünf lustren ophthalmologischer Wirksamkeit. Bergmann; 1882.
2. Yamamoto H, Simon A, Eriksson U, et al. Mutations in the gene encoding 11-cis retinol dehydrogenase cause delayed dark adaptation and fundus albipunctatus. Nat Genet 1999;22:188-191. https://doi.org/10.1038/9707
3. Naz S, Ali S, Riazuddin SA, et al. Mutations in RLBP1 associated with fundus albipunctatus in consanguineous Pakistani families. Br J Ophthalmol 2011;95:1019-1024. https://doi.org/10.1136/bjo.2010.189076
4. Krill AE. Hereditary retinal and choroidal diseases. Hagerstown: Harper and Row; 1977: 739-824.
5. De Laey JJ. Flecked retina disorders. Bull Soc Belge Ophtalmol 1993;249:11-22.

6. Sergouniotis PI, Sohn EH, Li Z, et al. Phenotypic variability in RDH5 retinopathy (Fundus Albipunctatus). Ophthalmology 2011;118:1661-70. https://doi.org/10.1016/j.ophtha.2010.12.031
7. Constable PA, Bach M, Frishman LJ, et al. International Society for Clinical Electrophysiology of Vision. ISCEV Standard for clinical electro-oculography (2017 update). Doc Ophthalmol 2017;134:1-9. https://doi.org/10.1007/s10633-017-9573-2
8. Robson AG, Frishman LJ, Grigg J, et al. ISCEV Standard for full-field clinical electroretinography (2022 update). Doc Ophthalmol 2022;144:165-77. https://doi.org/10.1007/s10633-022-09872-0
9. Airiani S, Cella W, Chou CL, et al. Benign panretinal uniform radial linear-shaped flecks. Clin Exp Ophthalmol 2008;36:891-4. https://doi.org/10.1111/j.1442-9071.2009.01906.x
10. Wang NK, Chuang LH, Lai CC, et al. Multimodal fundus imaging in fundus albipunctatus with RDH5 mutation: a newly identified compound heterozygous mutation and review of the literature. Doc Ophthalmol 2012;125:51-62. https://doi.org/10.1007/s10633-012-9336-z
11. Elsner AE, Burns SA, Weiter JJ, et al. Infrared imaging of sub-retinal structures in the human ocular fundus. Vision Res 1996;36:191-205. https://doi.org/10.1016/0042-6989(95)00100-e
12. Sparrow JR, Wu Y, Kim CY, et al. Phospholipid meets all-trans-retinal: the making of RPE bisretinoids. J Lipid Res 2010;51:247-61. https://doi.org/10.1194/jlr.R000687