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Ocular Findings and Multimodal Imaging Characteristics of Retinitis Pigmentosa Patients

Retinitis Pigmentosa Hastalarının Oküler Bulguları ve Multimodal Görüntüleme Özellikleri

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ABSTRACT

Background: To investigate the ocular findings and multimodal imaging characteristics of retinitis pigmentosa (RP) patients.

Materials and Methods: Patients who were followed up in our clinic for RP were evaluated retrospectively between June 2014 and July 2017. Ophthalmological examination included best corrected visual acuity (BCVA), biomicroscopy, fundoscopy, and axial length (AL) measurements. Optical coherence tomography (OCT) and fundus autofluorescence (FAF) imaging properties of macular region were examined in detail.

Results: In the study, 865 eyes of 446 RP patients were evaluated. In biomicroscopic examination, cataract surgery was performed in 23.6% of the eyes, and 29.1% of the eyes had posterior subcapsular cataract. In fundus examination, end-stage RP was detected in 67.4% of the eyes and severe macular atrophy in 9.8% of the eyes. The mean AL was 23±1.8 mm, the mean central macular thickness (CMT) was 136.6±87.1 um, and the mean subfoveal choroidal thickness (SCT) was 178.3±89.1 um. There was a positive correlation between BCVA and CMT, SCT, external limiting membrane and ellipsoid zone line integrity ($p<0.001$). Inner limiting membrane thickening and/or epiretinal membrane 47.7%, intraretinal hyperreflective foci 43.1%, micropseudocyst 15.8% and cystoid macular edema 6.5% were among the most commonly seen macular abnormalities detected in OCT. There was presence of a hyper-autofluorescent (AF) ring in 28.4%, abnormal hyper-AF patterns at the macula in 45.3%. There was a positive correlation between external limiting membrane-ellipsoid zone line integrity and the hyper-AF ring ($p<0.001$).

Conclusion: Screening RP patients using OCT, FAF and biometry findings may be useful both for documenting of the disease and for selecting candidates for innovative treatment modalities like retinal prosthesis, stem cell therapy.

Keywords: Fundus autofluorescence, optical biometry, optical coherence tomography, retinal dystrophy

ÖZ

Amaç: Retinitis pigmentosa (RP) hastalarının oküler bulgularını ve multimodal görüntüleme özelliklerini araştırmak.

Gereç ve Yöntemler: Kliniğimizde RP nedeniyle takip edilen hastalar Haziran 2014 ve Temmuz 2017 tarihleri arasında retrospektif olarak değerlendirildi. Oftalmolojik muayenede en iyi düzeltilmiş görme keskinliği (EİDGK), biyomikroskopi, fundoskopi, aksiyel uzunluk (AL) ölçümleri yapıldı. Maküla bölgesinin optik koherens tomografi (OKT) ve fundus otofloresans (FOF) görüntüleme özellikleri ayrıntılı olarak incelendi.

Bulgular: Çalışmada 446 RP hastasının 865 gözü değerlendirildi. Biyomikroskopik muayenede; gözlerin %23,6'sına katarakt ameliyatı yapılmıştı, %29,1'inde arka subkapsüler katarakt mevcuttu. Fundus muayenesinde; gözlerin %67,4'ünde son dönem RP ve % 9,8'inde ciddi maküler atrofi saptandı. Ortalama AL değeri 23±1,8 mm, ortalama merkezi maküla kalınlığı (MMK) 136,6±87,1 um, ortalama subfoveal koroid kalınlığı (SKK) 178,3±89,1 um idi. EİDGK ile MMK, SKK, external limitan membran ve elipsoid zon hattı

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bütünlüğü arasında anlamlı pozitif korelasyon mevcuttu (p<0,001). OKT'de saptanan en sık görülen makula patolojileri sırasıyla; iç limitan membran kalınlaşması ve/veya epiretinal membran %47,7, retina içinde hiperreflektif odaklar, %43,1, mikropseudokist %15,8 ve kistoid maküla ödemi %6,5 idi. FOF görüntülemede; gözlerin %28,4'ünde hiper-otofloresan halka, %45,3'ünde makulada anormal hiper otofloresans paternler mevcuttu. External limitan membran ve elipsoid zon hattı bütünlüğü ile hiper-otofloresan halka varlığı arasında pozitif korelasyon saptandı (p<0,001).

Sonuç: RP hastalarının OKT, FOF ve biyometri bulguları kullanılarak taranması, hem hastalığın belgelenmesi hem de retina protezi, kök hücre tedavisi gibi yenilikçi tedavi modaliteleri için adayların belirlenmesinde faydalı olabilir.

Anahtar Kelimeler: Fundus otofloresans, optik biyometri, optik koherens tomografi, retina distrofisi

Introduction

Retinitis pigmentosa (RP) encompasses a group of inherited retinal dystrophies characterized by primary degeneration of rod and cone photoreceptors and is a leading cause of visual disability, affecting more than 1.5 million patients worldwide (1).

Morphological and functional assessment of photoreceptors in the macula can be useful in estimating residual retinal function in RP patients. Optical coherence tomography (OCT) is a well-established method of examining retinal and choroidal architecture in situ. It allows the evaluation of retinal and choroidal changes of RP at presentation and during the follow-up period (2,3,4). Fundus autofluorescence (FAF) results from the accumulation of lipofuscin in retinal pigment epithelium (RPE) cells and has been used to investigate RPE and retinal function. Several FAF patterns have been observed in patients with RP (2).

In this study, the clinical and multimodal imaging findings of 446 RP patients were evaluated by using biometry, OCT and FAF. Therefore, we aimed to report our findings to contribute to the literature in terms of presenting quantitative data in Turkey.

Material and Methods

Patient charts and medical records were reviewed retrospectively between June 2014 and July 2017. Non-syndromic RP cases were evaluated. This study was approved by the local human research ethics committee, in accordance with the Declaration of Helsinki, and written informed consent was obtained from all participants.

Age, gender, past cataract or other ophthalmic surgeries and presence of additional eye disease were recorded in the patients' personal histories. Parental consanguinity was recorded in the family history. Genetic analysis was not performed in terms of hereditary transmission.

Eye position in primary gaze, presence of strabismus and nystagmus, best corrected visual acuity (BCVA), biomicroscopy and fundus were evaluated. The BCVA was recorded using the Snellen chart. Tropicamide 1% eye drops were used for pupil dilatation and lens clarity was assessed by biomicroscopy. The state of the lens was grouped as clear lens, pseudophakia, posterior subcapsular cataract (PSC), nuclear-nucleocortical cataract and aphakic.

The degree of retinopathy was assessed with fundoscopy and classified as early stage (bone spicule-like pigment changes in the equatorial region, macula and optical disc unaffected), late stage (widespread chorioretinal atrophy, loss of foveal reflex in the macula, waxy pallor of the disc), severe macular atrophy, sectorial RP and RP sine pigmento. Optical biometry (AL-Scan, Nidek Co., Aichi, Japan) was used for measuring axial length (AL).

A high resolution spectral-domain OCT (3D-OCT 2.000, Topcon Corp., Tokyo, Japan) device was used for detailed evaluation of the macula area and FAF imaging. The "6 mm 3D mode and 9 mm line mode" technique was used for macula imaging, the "9 mm line mode" enhanced depth imaging technique was used for subfoveal choroid imaging. The values of central macula thickness (CMT) and subfoveal choroidal thickness (SCT) were recorded between 12.00 and 14.00 o'clock in the afternoon. The CMT was measured from the foveola, so that the inner border would be the inner limiting membrane (ILM) and the outer border would be the RPE. The SCT was measured manually at 500 microns interval from the fovea, so that the inner border would be the RPE and the outer border would be the sclera (5). SCT less than 250 microns was evaluated as choroidal thinning. The presence of choroidal symmetry between both eyes was also recorded.

The macular area was examined in 3 groups with OCT as outer retinal, intraretinal and vitreomacular interface abnormalities. Outer retina abnormalities were evaluated in detail as loss of external limiting membrane (ELM) line integrity and loss of ellipsoid zone (EZ) line integrity. The loss of EZ and ELM line integrity was classified as total loss and partial loss (partially preserved in subfoveal area). Intraretinal abnormalities were evaluated in detail as micropseudocyst (MPC), cystoid macular edema (CME), subretinal fluid and presence of intraretinal hyperreflective foci (HF). Vitreomacular interface abnormalities were evaluated in

detail as ILM thickening (ILMT), epiretinal membrane (ERM), combination of ILMT and ERM, presence of vitreous bands, full thickness macular hole (FTMH) and lamellar macular hole (LMH).

FAF imaging was evaluated under the headings of FAF symmetry between both eyes, presence of hyper-AF ring, abnormal hyper-AF patterns at the macula with irregular distribution, absence of AF and decreased AF at the periphery (5). In case of media opacities, nystagmus, low patient cooperation FAF, OCT or biometry were not evaluated.

Statistical Analysis

SPSS 22.0 for Windows software was used for statistical analysis. Descriptive statistics were given as number and percentage for categorical variables and as mean, standard deviation, minimum, maximum, and median for numerical variables. When the numerical variables met the conditions of the normal distribution, the Student's t-test was used to compare the two independent groups and the Mann-Whitney U test was used when the normal distribution conditions were not met. Since the relationships between numerical variables did not meet the condition of a parametric test, they were analyzed using the Spearman Correlation Analysis. Statistical significance level of alpha was accepted as $p<0.05$.

Results

Demographic Findings: Eight hundred seventy-five eyes of 446 RP patients were evaluated. The mean age was 43.5±14.9 (6.5-82) years, 173 patients were (38.8%) female, 273 patients (61.2%) were male. The parental consanguinity rate was 56.4%. According to the expression of the patients, the mean age of nyctalopia was 15.8±12.3 years, the mean age of onset of central vision loss was 22.8±12.6 years, and the mean age of severe central blindness was 34.6±15 years.

Additional Eye Diseases: There was no additional ocular pathology in 639 eyes (71.6%). The most common additional eye diseases were myopia in 134 eyes (15%), glaucoma in 45 eyes (5%), hypermetropia in 26 eyes (2.9%) and corneal opacity in 15 eyes (1.6%). Nystagmus was seen in 88 (23.4%), orthophoria in 212 (57%), exotropia in 148 (39.8%), esotropia in 7 (1.9%) and vertical strabismus in 5 (1.3%) of the patients. As the BCVA decreased, the frequency of strabismus and nystagmus was found to be significantly higher ($p<0.001$).

Best Corrected Visual Acuity: Categories and corresponding percentages were: no light perception in 56 (6.4%), only light perception in 257 (29.4%), seeing hand movements in 254 (29%), counting fingers at 1 meter at 10/100 in 127 (14.5%) and ≥10/100 in 181 (20.7%) of the eyes.

Fundus Findings: Fundus examination revealed early-stage RP in 139 (16.4%), end-stage RP in 570 (67.4%), severe macular atrophy in 83 (9.8%), RP sine pigmento in 13 (1.5%) and sectorial RP in 2 (0.2%) of the eyes.

Lens Findings: Two hundred eleven (23.6%) eyes were pseudophakic and 14 eyes (1.6%) were aphakic. Biomicroscopic examination revealed clear lens in 326 (37.7%), PSC in 252 (29.1%) and senile nuclear-nucleocortical cataract in 69 (8%) of the eyes. The BCVA of the eyes with PSC and nuclear cataract were less than eyes with clear lens and pseudophakic ($p<0.001$). The mean CMT was 134.2±92 um in eyes that had undergone cataract surgery and 136.4±76 um in the others ($p=0.194$).

Axial Length: The mean AL was 23±1.8 (17-42.2) mm. There was no difference in AL between right and left eyes ($p=0.082$). There was no correlation between AL and age, CMT and SCT (p values of 0.085, 0.669, 0.073, respectively).

Macula OCT Imaging Findings: The macular area could be evaluated in 633 of the eyes (79.4%) with OCT. The distribution of OCT imaging findings of patients with RP is shown in Table 1. Macula OCT images of some of our cases are shown in Figure 1. The mean CMT was 136.6±87.1 (2-839) um. There was no significant difference in CMT between right and left eyes ($p=0.626$). There was a significant negative correlation between age and CMT ($p<0.001$), and no difference between gender and CMT ($p=0.559$).

Table 1. Distribution of optical coherence tomography imaging findings of patients with retinitis pigmentosa

	Optical coherence tomography imaging findings	Eyes (n) %
ILMT	186	28.2
ERM	108	16.3
ILMT and ERM	21	3.2
Vitreous bands	16	2.4
MPC	100	15.8
CME	41	6.5
Subretinal fluid	11	1.7
LMH	10	1.5
FTMH	6	0.9
Intraretinal HF	290	43.1
Total loss of ELM line integrity	402	60.4
Partial loss of ELM line integrity	224	33.7
Total loss of EZ line integrity	396	58.2
Partial loss of EZ line integrity	235	34.4

ILMT: Inner limiting membrane thickening, ERM: Epiretinal membrane, MPC: Micropseudocyst, CME: Cystoid macular edema, LMH: Lamellar macular hole, FTMH: Full thickness macular hole, HF: Hyperreflective foci, ELM: External limiting membrane, EZ: Ellipsoid zone

There was a positive correlation between BCVA and CMT, ELM and EZ line integrity (p<0.001). Vitreomacular interface anomalies were seen more often in patients who underwent cataract surgeries, had less BCVA and were elderly (p values of <0.001, 0.006, <0.001, respectively). A significant positive correlation was found between CMT and subretinal fluid, vitreomacular interface anomalies, and CME (p values of 0.012, <0.001, <0.001, respectively). There was a significant positive correlation between CMT and ELM and EZ line integrity (p<0.001) and a significant negative correlation between the CMT and intraretinal HF (p<0.001).

Choroidal OCT Imaging Findings: The mean SCT was 178.3±89.1 (2-441) µm. SCT thinning was observed in 521 (77.4%) of the eyes. Choroid findings were asymmetry between two eyes in 39 (12.3%) of patients. As patients were older, SCT thinning was greater (p<0.001). There was a significant positive correlation between BCVA and SCT (p<0.001). The mean SCT was 132.5±93 µm in eyes with no light perception, 157±88 µm in eyes with only light perception, 169.3±95 µm in eyes with seeing hand movements, 191.2±85 µm in eyes with counting fingers at 1 meter at 10/100 and 214.0±71 um in eyes with ⩾10/100. There was a significant positive correlation between SCT and CMT (p<0.001).

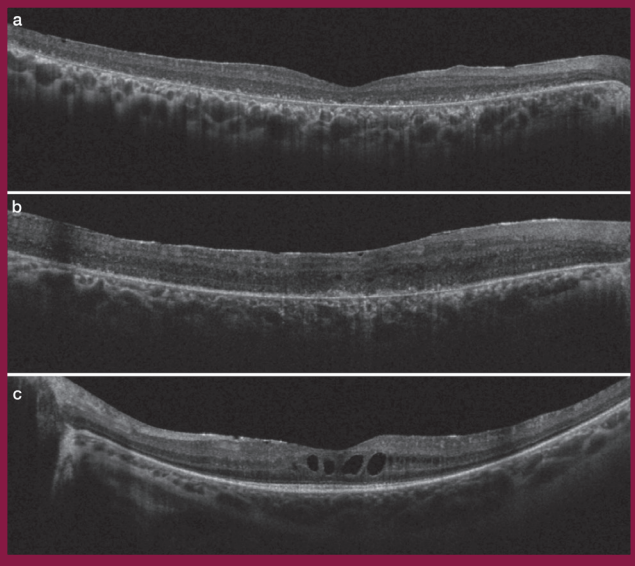

Figure 1. a-c. Macula OCT image patterns of our patients with retinitis pigmentosa. The OCT image shows intraretinal hyperreflective foci, epiretinal membrane and total loss of ellipsoid zone (EZ) and external limiting membrane (ELM) line integrity (a). The OCT image shows intraretinal hyperreflective foci, micropseudocyst, epiretinal membrane and total loss of EZ and ELM line integrity (b). The OCT image shows cystoid macular edema, inner limiting membrane thickening and partial loss of EZ and ELM line integrity (c)

Fundus Autofluorescence Imaging Findings: The distribution of FAF imaging findings of patients with RP is shown in Table 2. FAF images of some of our cases are shown in Figure 2. FAF findings of asymmetry between the two eyes were detected in 44 (15%) of the patients. There was a significant negative correlation between BCVA and loss of AF (p<0.001).

The CMT was 148.7±62 µm in eyes with hyper-AF ring and 129.1±92 µm in eyes without hyper-AF ring (p<0.001). The CMT was 115.4±87 µm in eyes with the absence of AF, 150.9±83 µm in the others (p<0.001). The CMT was 130.5±74 um in eyes with abnormal hyper-AF patterns at the macula and 139.7±97 µm in the others (p=0.254). The SCT was 209±81 µm in eyes with hyper-AF ring and 170.2±88 µm in eyes without hyper-AF ring (p<0.001). The SCT was 166±90 µm in eyes with the absence of AF and 189.9±87 µm in the

Table 2. Distribution of fundus autofluorescence imaging findings of retinitis pigmentosa patients

Fundus autofluorescence imaging findings	Eyes (n) %
Presence of hyper-AF ring	169 28.4
Abnormal hyper-AF patterns at the macula	271 45.3
Absence of AF	268 44.4
Decreased AF at the periphery	486 81.2

AF: Autofluorescence

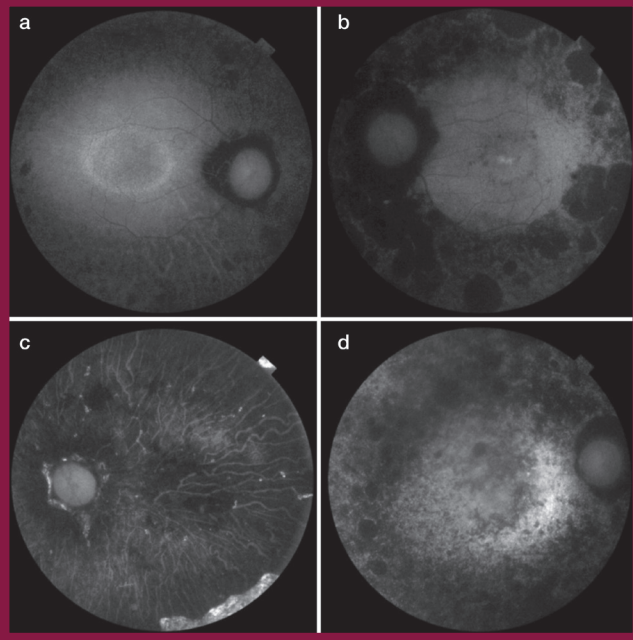

Figure 2. a-d. Fundus autofluorescence image patterns of our patients with retinitis pigmentosa. Hyper-autofluorescence (AF) ring (a). Decreased AF at the periphery (b). Absence of AF (c). Abnormal hyper-AF pattern at the macula (d)

others (p=0.002). The SCT was 187.6±85 um in eyes with abnormal hyper-AF patterns at the macula and 176.1±90 um in the others (p=0.079). We found a strong correlation between ELM-EZ line integrity and hyper-AF ring or the absence of AF (p<0.001).

Discussion

To the best of our knowledge, our study includes the ocular findings and multimodal imaging characteristics of the largest number of patients with RP were examined in Turkey. OCT and FAF imaging features of the macula region and the presence of cataract were examined in detail.

The incidence of cataracts (especially PSC) in RP is higher than in the normal population. This condition is thought to develop secondary to inflammation (6). In the study of Lee et al. (7) the incidence of PSC was 25.8%. In our study, 23.6% of the eyes had cataract surgery and 29.1% of the eyes had PSC, although the mean age was 43 years. The VA of the eyes with clear lens and pseudophakic was higher than eyes with PSC and nuclear cataract. Therefore, we think that cataract surgery should be performed in patients with RP who have decreased visual acuity due to cataracts.

It has been shown that histopathologic changes in the macula area in RP can be visualized by OCT. These changes revealed by OCT have provided insights into the pathology of RP as well as for predicting the prognosis of RP (8). Several OCT studies have been published on RP patients to determine whether there is a significant correlation between retinal microstructure and visual function (9,10,11). In our study, the CMT (136.6±87) was significantly thinner because most of our patients were end-stage RP. As the VA decreased, thinning of the CMT was greater. The EZ line integrity in patients with RP disappeared partially in the early stage and completely in the advanced stage (12). Tamaki et al. (11) reported that CMT and the presence of the EZ line could serve as objective signs for better VA in RP. In our study, deterioration in ELM line integrity was seen in 94.1% and deterioration of EZ line integrity in 92.6% of the eyes. Like other studies, we found a strong correlation between ELM-EZ line integrity and VA or CMT. We think that the presence of the ELM-EZ line integrity is associated with better VA and CMT in RP patients.

Patients with RP may develop CME due to breakdown of the blood-retinal barrier, failure (or dysfunction) of the pumping mechanism in the RPE, Müller cell oedema and dysfunction, antiretinal antibodies or vitreous traction (13). Previous studies have reported CME at the rates from 5.5% to 38% in RP patients (14,15,16,17). In our study, we detected CME in 6.5% and MPC in 15.8% of eyes. No correlation was found between VA and CME or MPC.

Kuroda et al. (12) evaluated intraretinal HF in the OCT of patients with RP. They reported that HF represented macrophages, migrating RPE cells or extracellular lipoproteins. In our study, HF was detected in 43.1% of the eyes. We found that as the CMT decreased, the ratio of HF presence increased. Therefore, we think that the presence of HF is a very important OCT finding in patients with RP during the progress of the disease.

It was reported that RP patients have a degenerative vitreous, including collapse of vitreous gel, and posterior vitreous detachment may cause macular complications related to the vitreoretinal interface (18). In the study of Testa et al. (15), ERM in 15.6%, LMH in 1% and FTMH in 0.6% were detected in patients with RP. Triolo et al. (19) found ILMT in 67%, ERM in 27.3%, ILMT and/or ERM in 94.3% and FTMH in 4.5% of 176 eyes. In our study, we detected ILMT in 28.2%, ERM in 16.3%, a combination of ILMT and ERM in 3.2%, vitreous bands in 2.4%, LMH in 1.5% and FTMH in 0.9% of 875 eyes. The incidence of vitreomacular interface abnormalities varies among studies. We think that this is due to reasons such as ethnic origin, environmental risk factors, age and having undergone ocular surgery. We also found that vitreomacular interface abnormalities were seen more often in patients who had lower VA, in the elderly and in eyes that underwent cataract surgeries.

Recent studies have evaluated changes in choroidal thickness in patients with RP (4,20,21). Dhoot et al. (4) reported that SCT was significantly reduced in patients with RP, but this did not correlate with VA or CMT. Egawa et al. (20) detected significant correlations between choroidal structures and VA and retinal structures. In our study, thinning of the SCT was found in 77.4% of the eyes. When patients were older, thinning of the SCT was greater. We found significant correlations between SCT and VA or CMT, but this did not correlate with AL.

FAF results from the accumulation of lipofuscin in RPE cells. Lipofuscin is a by-product of the degradation of photoreceptor outer segments. Hyper-AF indicates abnormal metabolism in RPE cells, a high turnover of photoreceptor outer segments, disrupted phagocytosis, or an intrinsic defect in the ability of the RPE to recycle phagosomes. Hypo-AF indicates RPE atrophy and loss of photoreceptors (22). Murakami et al. (5) reported hyper-AF ring in 59%, and abnormal central AF in 18%, and the absence of both patterns was detected in 24% of patients with RP. The hyper-AF ring is considered to represent the border between functional and dysfunctional retina (22). Lima et al. (23) reported that the diameter of the hyper-AF ring was significantly correlated with the length of the EZ line in patients with RP. In our study, we found hyper-AF ring in 28.4%, abnormal hyper-AF patterns at the macula in 45.3%, the absence of AF in 44.4% and decreased AF at the periphery in 81.2% of the eyes. We think that the rate of the presence of hyper-AF ring is less

in our study than in the other studies because the majority of our cases were end-stage RP patients (77.2%). We think that hyper-AF ring disappears as the disease progresses, and also remaining macular RPE cells filled with lipofuscin pigment are developing abnormal hyper-AF patterns at the macula. We also found a strong positive correlation between ELM-EZ line integrity and hyper-AF ring, but a strong positive correlation between ELM-EZ line integrity and the absence of AF. While the CMT and SCT were thicker in eyes with the presence of hyper-AF ring, CMT and SCT were thinner in eyes with the absence of AF. VA is significantly lower in eyes with the absence of AF. Therefore, we think that FAF images should be evaluated together with OCT at presentation and during the follow-up period in patients with RP.

Sujirakul et al. (24) followed patients with RP by multimodal imaging for 2 years. They demonstrated an asymmetric structural progression rate between the two eyes. In our study, asymmetry was also observed between the two eyes of the same patient in terms of choroidal and FAF findings. For this reason, we have evaluated both eyes of our patients separately. We think that this should be taken into consideration in subsequent studies.

Study Limitations

The limitation of this study was the lack of genetic testing for a hereditary transition pattern and electrophysiologic testing. The different patterns we detected in OCT and FAF imaging may be specific to some particular gene defects.

Conclusion

This is the largest report on clinical and multimodal imaging characteristics of RP in Turkey. In countries with high consanguineous marriages, like Turkey, it is thought that the frequency of seeing issues with time will increase. OCT, FAF and biometry should be used in the examination and follow-up of patients with RP. We believe that this study will provide a database for describing the patients who can benefit from innovative treatment strategies such as retinal prosthesis and stem cell therapy.

Ethics

Ethics Committee Approval: This study was approved by the local human research ethics committee, in accordance with the Declaration of Helsinki (number: 1129, date: 24/11/2015).

Informed Consent: Written informed consent was obtained from all participants.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.G., S.T.D., H.K., M.K., S.Ü.U., Concept: D.G., S.T.D., Design: D.G., S.T.D., H.K., S.Ü.U., M.K., Data Collection or Processing: H.K., M.K., S.Ü.U., Analysis or Interpretation: D.G., S.T.D., Literature Search: H.K., M.K., S.Ü.U., Writing: S.T.D., D.G.

Conflict of Interest: No conflict of interest was declared by the authors.

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