

# Relation between Visual Acuity, Macular Retinal Thickness, Visual Field and Multifocal Electroretinography in Patients with Retinitis Pigmentosa

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## ABSTRACT

**Purpose:** To investigate the correlation between corrected visual acuity (CVA), macular retinal thickness, visual field and multifocal electroretinography (mfERG) responses in patients with retinitis pigmentosa (RP).

**Materials and Methods:** The study included RP patients who were admitted to our clinic between January 2014 and December 2018 and had CVA at least  $\geq 0.05$ . All patients underwent thorough ophthalmologic examination. Spectral domain (SD) optical coherence tomography (OCT) was performed to assess macular retinal thickness and standard central 30-2 threshold test was used as visual field test. The visual field responses, matching to mfERG, were estimated by calculating average value for 5 concentric rings. Correlation analysis was performed among CVA, macular retinal thickness, visual field and mfERG responses.

**Results:** Forty-four eyes of 22 patients were included in the study. The mean age was  $30.6 \pm 13.0$  (range 17 to 52) years in the study population. The CVA ranged from 0.05 to 1. In our study, there was a positive correlation between CVA, macular retinal thickness ( $r=0.668$ ,  $p<0.01$ ), visual field ( $r=0.578$ ,  $p<0.01$ ) and mfERG responses for ring 1 ( $r=0.511$ ,  $p<0.01$ ).

**Conclusion:** In addition to ophthalmologic examination, visual field, SD-OCT and mfERG are important tests in the follow-up of patients with RP. We think that ophthalmologic examination together with anatomical and functional tests will be useful in the clinical follow-up of these patients.

**Key words:** Retinitis pigmentosa, Multifocal electroretinography, Macular retinal thickness, Visual field, Visual acuity, Visual loss.

## INTRODUCTION

The retinitis pigmentosa (RP) is a term that defines a group of heterogeneous, inherited, degenerative diseases mainly characterized by progressive loss of function in retinal rod photoreceptors and involvement of cone photoreceptors later in the course of disorder. The estimated prevalence for typical RP or RP without associated systemic disease is 1: 4,000 worldwide.<sup>1</sup> In Turkey, it is thought to affect 15,000-20,000 individuals.<sup>2</sup> Clinically, night blindness emerges within first or second decades of life in patients with typical RP. Progression to full blindness is seen as a result of progressive narrowing in visual field in both eyes and eventual loss of central vision. Classical fundus image for typical RP includes faded optic disc, thinner retinal vascularity, spotted retinal pigment epithelium and peripheral bone spicule-like pigmentation.<sup>1</sup>

In the RP, primary pathology is cell death as a result

of genetic mutation in rod photoreceptors; however, interestingly, apoptosis also develops in cone cell playing role in the central vision without any genetic defect over time.<sup>3</sup> Although it hasn't been fully elucidated, it is thought that free radicals released from rod photoreceptors undergoing apoptosis, toxic substances and pro-apoptotic macro-molecules are involved in this cascade.<sup>4,5</sup>

In the RP, inheritance pattern is variable, including autosomal recessive, autosomal dominant and X-linked inheritance. It has been reported that at least 50 distinct genes are associated with RP.<sup>6</sup> The autosomal dominant form is the most common form of RP (20-40%) and has best prognosis. The X-linked form is the rarest form (10%) with worst prognosis; the symptoms occur at earlier ages in this group of patients and the disease generally results in legal blindness at fourth decade of life.

Clinical findings are generally sufficient for diagnosis in RP

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patients. However, spectral domain (SD) optic coherence tomography (OCT), visual field test and electroretinography (ERG) are supportive in the diagnosis.<sup>7,8</sup> In ERG, scotopic injury is typically predominant.<sup>7</sup>

In all forms, thinning at photoreceptor outer segment is the earliest histopathological change.<sup>9</sup> These changes manifest as impairment, shortening or loss of IS/OS band on SD-OCT.<sup>3</sup> The cone cell loss at terminal stage of disease results in disrupted central vision.<sup>9,10</sup> Thus, it is important to assess macular photoreceptor morphology and functions in order to detect remaining potential for residual central vision.<sup>1</sup> Clinical, anatomic and electrophysiological measurements should be used to gather objective data regarding changes in retinal functions. Examinations such as visual acuity measurement and perimeter rely on subjective responses; thus, electrophysiological methods should be used to assess retinal function in a more objective manner.<sup>11</sup>

The multifocal ERG (mfERG) allows mapping of retinal electrical activity based on a technique first introduced by Sutter and Tran in 1992.<sup>12</sup> The mfERG is used to assess central and regional differences of retinal function loss in RP patients. It helps to distinguish involved and intact retinal regions. In mfERG, it was shown that both amplitude and implicit time abnormalities are associated to retinal changes. In RP patients, it was shown that mfERG response amplitudes are significantly decreased and implicit time is generally normal in central areas but markedly delayed when moving peripheral retina. In patients with advanced RP, it is generally difficult to identify full-field ERG waveform. The mfERG is highly helpful to demonstrate residual central retinal functions preserved in RP patients.<sup>13</sup> In RP patients, the follow-up using anatomic and functional parameters together is very important for effective clinical follow-up and determining optimal treatment modality in the patient. Thus, in addition to visual acuity assessment, macular thickness analysis by SD-OCT for anatomic monitoring and visual field assessment and mfERG for functional monitoring are valuable tests. Periodical evaluations using these tests simultaneously will allow better understanding of visual loss in these patients.

The aim of our study was to determine whether there is a correlation among corrected visual acuity (CVA), macular retinal thickness, visual field and mfERG responses and the direction and magnitude of correlations if present.

## MATERIALS AND METHODS

### *Patient selection*

We retrospectively reviewed files of 82 RP patients who presented our clinic between January, 2014 and December, 2018. The study included 44 eyes of 22 patients who had all diagnostic tests and fulfilled inclusion criteria. In the

patients, RP diagnosis was made based on family history and funduscopy, SD-OCT, visual field test and mfERG findings. The exclusion criteria included: presence of any systemic or neurological disease; clinically relevant opacity (cataract, corneal scarring etc.); previous retinal surgery; RP in conjunction with a systemic disease; atypical RP-like central RP, sector RP or bilateral RP, amblyopia; strabismus, nystagmus, myopia > -6.00 diopter, cystoid macular edema and glaucoma. All patients underwent thorough ophthalmological examination including corrected visual acuity measurement by Snellen charts (in decimals), visual field test and macular retinal thickness analysis as assessed by SD-OCT and mfERG.

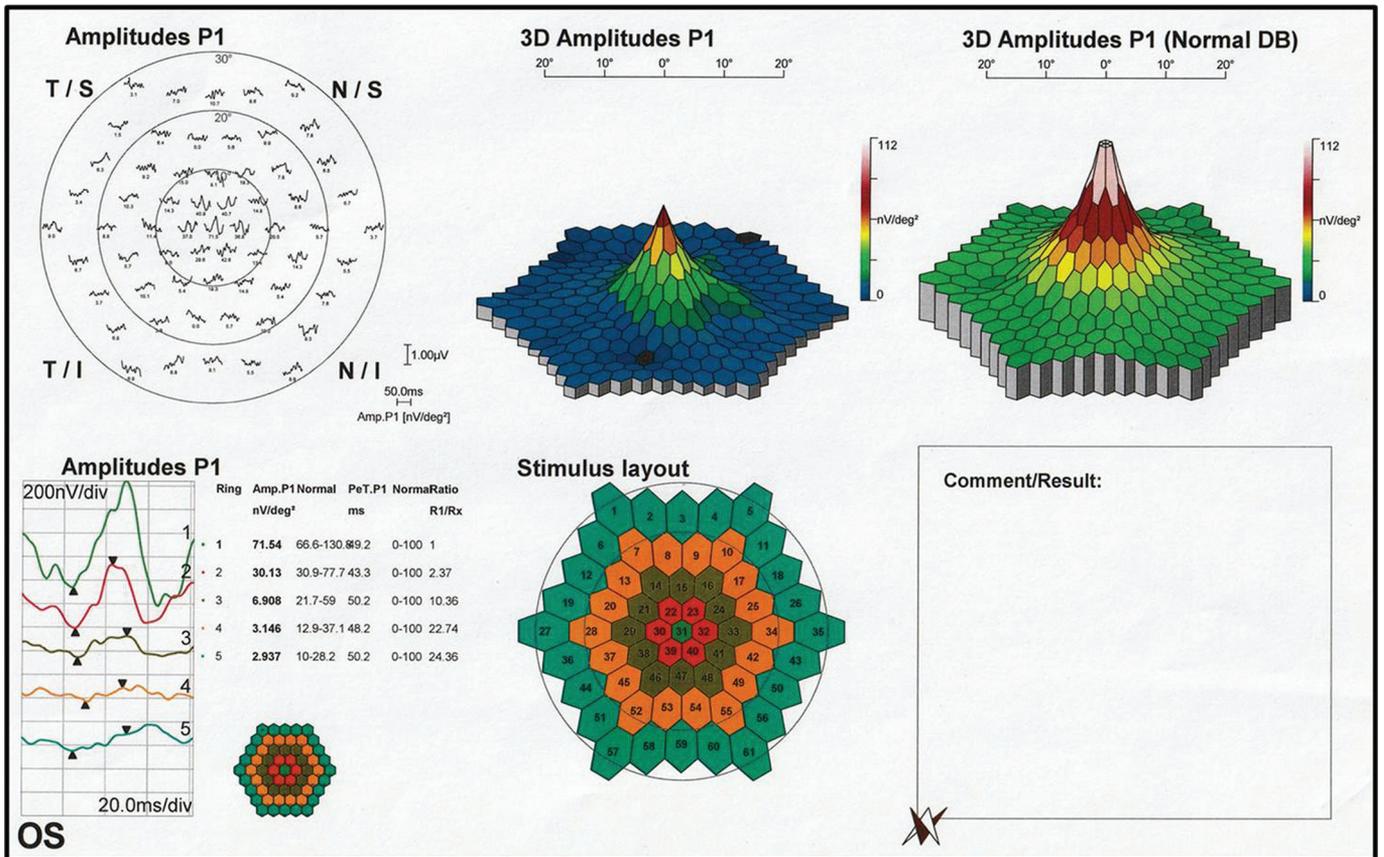
The correlation analyses were performed among CVA measurements by Snellen charts (in decimals), macular retinal thickness measurements, mfERG amplitudes and visual field responses. mfERG and visual field stimulus locations on retina and the relationship corresponding anatomic areas were as follows: first ring to fovea (0°–2°); second ring to parafovea (2°–7°); third ring to perifovea (7°–13°); fourth ring to peripheral area (13°–22°); and fifth ring to central to mid-peripheral area (22°–30°). This study was conducted in accordance to Helsinki Declaration. The study was approved by Ethics Committee of Istanbul Medipol University (approval date: 15.01.2019; approval#10840098-604.01.01-E1590).

### *Multifocal electroretinography*

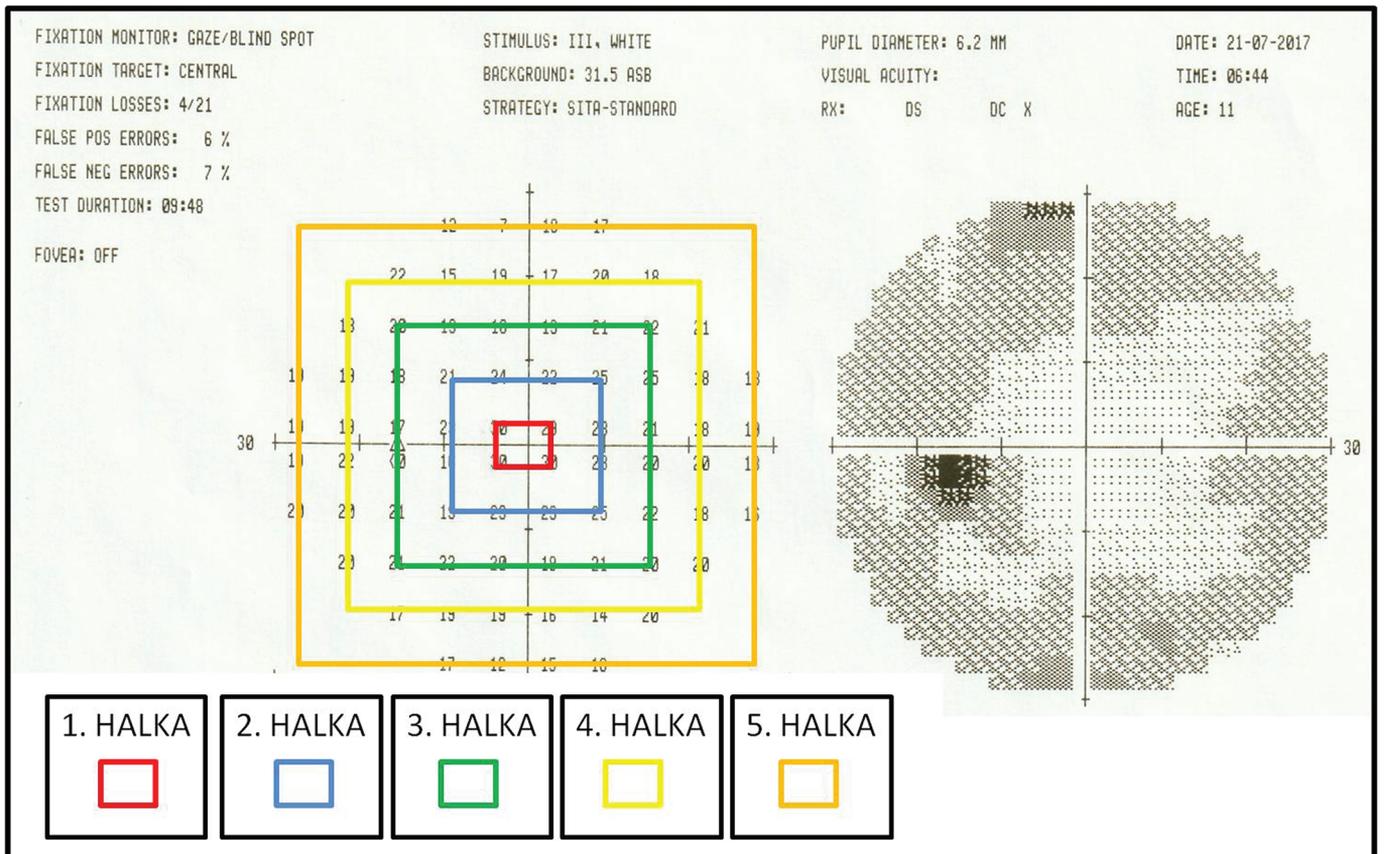
As - primary protocol for mfERG, we employed guidelines recommended by The International Society of Electrophysiology of Vision For light adaptation, all patients were awaited in the test room over 15 minutes before test. In all patients, full pupil dilatation was achieved using 1% tropicamide (Tropamid<sup>®</sup>, Bilim, Beyoglu, Istanbul, Turkey) and 1% cyclopentolate hydrochloride (Sikloplejin<sup>®</sup>, Abdi Ibrahim, Maslak, Istanbul, Turkey). The multifocal electroretinography (Retiscan, Roland Consult, Weisbaden, Germany) recordings were made using scleral gold leaf active electrode. P1 amplitudes and latencies were measured in 61 hexagons and 5 ring analysis at central 30 degrees of retina (Picture 1). Mean P1 amplitude was calculated for each ring starting from central ring. Stimulus brightness was 120 cd/m<sup>2</sup> as bright flash and 1 cd/m<sup>2</sup> as dark flashes.

### *Visual field test*

In all patients, 30° static automated perimetry ([Central 30-2, Swedish Interactive Threshold Algorithm (SITA) standard], Humphrey Visual Field Analyzer, Carl Zeiss Meditec AG, Jena, Germany) was performed as visual field test. In the assessment, first 4 central measurements were considered as first ring and values in each ring were estimated as mean value of 5 rings as similar to mfERG (Picture 2). In visual field test, measurements with low



Picture 1. Multifocal electroretinography test by analysis of 5 rings at 30 degrees of central retina in a representative patient with retinitis pigmentosa.



Picture 2. Calculation of Central 30-2 threshold test of visual field in 5 rings as similar to multifocal electroretinography in a representative patient with retinitis pigmentosa.

reliability (20% false-positive or false-negative responses or loss of fixation) were excluded from analysis.

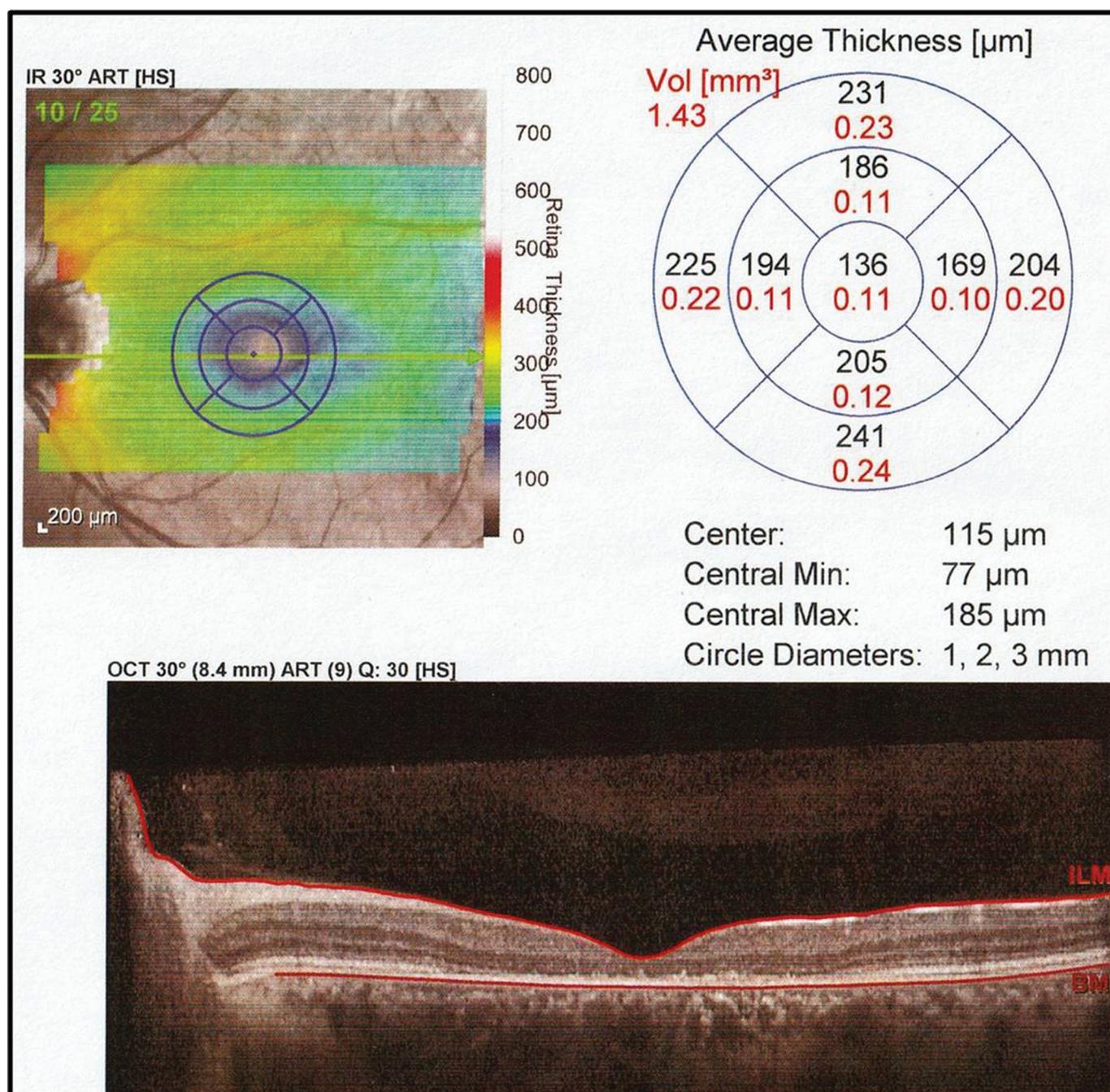
**Optic coherence tomography**

For optic coherence tomography, macular analysis was performed to measure retinal thickness after pupil dilatation using SD-OCT (Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany). The SD-OCT measurements were conducted in accordance to Early Treatment Diabetic Retinopathy Study (ETDRS) guideline. The mean retinal thickness at a field of 1.0 mm at central macula was

considered as first ring whereas mean retinal thickness a field from 1.0 to 2.0 mm and from 2.0 to 3.0 mm was considered as second and third rings respectively (Picture 3).

**Statistical analysis**

All statistical analyses were performed using SPSS for Windows version 22.0 (SPSS Inc., Chicago, IL, USA). The Pearson's and Spearman's correlation analyses were used to assess correlations among CVA level and macular retinal thickness, visual field and mfERG responses and direction



**Picture 3.** Determining 3 rings from central in the macular analysis of spectral domain optic coherence tomography in a representative patient with retinitis pigmentosa.

and extent of correlations if present. A  $p$  value  $<0.05$  was considered as statistically significant.

## RESULTS

There were 12 women (54.5%) and 10 men (45.5%) in the study. The mean age was  $30.6 \pm 13.0$  (range 17 to 52) years in the study population. The CVA ranged from 0.05 to 1. There was visual field defect with varying degrees in all patients. On macular SD-OCT scans, thinning at outer retinal layers and impairment in IS/OS band were striking (Picture 3). Macular retinal thickness, mfERG, and visual field responses in patients with RP are shown in table 1. In our study, there was a positive correlation between CVA, macular retinal thickness ( $r=0.668$ ,  $p<0.01$ ), visual field ( $r=0.578$ ,  $p<0.01$ ) and mfERG responses for first ring ( $r=0.511$ ,  $p<0.01$ ) (Table 2). In addition, correlation analysis was performed for macular retinal thickness, visual field and mfERG responses in corresponding to rings. In the analysis, it was seen that there was a positive correlation between macular retinal thickness and mfERG responses in first two rings ( $r=0.689$ ,  $p<0.01$ ;  $r=0.394$ ,  $p<0.01$ , respectively) while no correlation was detected in third ring ( $r=0.292$ ;  $p=0.054$ ). It was also found that there was no correlation between macular retinal thickness and visual field in all 3 rings ( $r=0.184$ ,  $p=0.231$  /  $r=0.095$ ,  $p=0.538$  /  $r=0.049$ ,  $p=0.753$ , respectively). A weak correlation was detected between visual field and mfERG responses in first, second and fifth rings ( $r=0.359$ ,  $p=0.017$  /  $r=0.353$ ,  $p=0.019$  /  $r=0.341$ ,  $p=0.023$ , respectively) while no such correlation was detected in third and fourth rings ( $r=0.199$ ,  $p=0.195$  /  $r=0.232$ ,  $p=0.130$ ). Table 2 presents correlation analyses.

## DISCUSSION

The retinitis pigmentosa is the most prevalent, inherited retinopathy in the population. It is one of the major causes of early blindness.<sup>14</sup> Despite major scientific advances regarding retinitis pigmentosa, there is no treatment modality that can recover visual functions or halt disease progression. However, novel therapies including gene replacement,<sup>15</sup> optogenetics,<sup>16</sup> stem cell therapy,<sup>17</sup> retinal transplantation<sup>18</sup> and retinal prosthesis are

being investigated.<sup>19</sup> Thus, it is very important to assess individual retinal morphology and function thoroughly for selecting patients eligible for treatment and planning treatment strategy as well as monitoring visual prognosis. In the typical form of RP, diagnosis can be readily made by clinical findings; however, it may not be appropriate to assess residual functional retinal area by clinical examination. The visual field test is a first-line, simple, non-invasive diagnostic method that can be used to assess retinal function in this group of patients. However, it may misinterpretation in clinical practice due to subjectivity, need for patient compliance and scan errors. Given that some patients fail in visual field test, mfERG should be kept in mind as a valuable tool to assess functional retina in these patients. In support for mfERG, it was shown that mfERG responses are associated to subjective visual field in some studies.<sup>20,21</sup> In agreement with literature, we found a correlation, albeit weak, between mfERG and visual field in ring 1, 2 and 5 (Table 2).

In a study on mERG in RP patients, Moschos et al. showed that there was a correlation between mfERG amplitudes in first ring and visual acuity.<sup>22</sup> In a study by Janaky et al., it was reported that mfERG responses from central ring is highly variable among RP patients.<sup>23</sup> Authors proposed that the variable response may be due to several factors such as inheritance pattern, central cone density and disease duration. Moon et al. published their work investigating relationship among foveal retinal thickness, visual field and mfERG in patients with advanced RP.<sup>24</sup> In the study, authors showed a positive correlation between foveal retinal thickness and central visual field and mfERG amplitudes. On contrary to our study, Gerth et al. reported that visual field was more sensitive to detect central visual function when compared to mfERG in patients with advanced RP.<sup>25</sup> In a study by Granse et al., it was reported that mfERG and multifocal visual evoked potential (mfVEP) are highly useful in the assessment of residual visual functions in patients with advanced RP.<sup>26</sup> Nagy et al. reported that mfERG could be used in the long-term follow-up of RP.<sup>11</sup> Wen et al. showed that there was a significant correlation among mfERG, visual field and retinal photoreceptor layer thickness in RP patients.<sup>27</sup> In a study by Hazirolan et al., a significant

**Table 1.** Macular retinal thickness, multifocal electroretinography and visual field responses in patients with retinitis pigmentos.

	First Ring	Second Ring	Third Ring	Fourth Ring	Fifth Ring
<b>SD-OCT macular retinal thickness (mm)</b>	196.5 ± 39.9	245.0 ± 40.8	271.0 ± 33.6		
<b>mfERG responses (mv)</b>	47.7 ± 21.4	31.1 ± 11.8	22.6 ± 8.9	16.5 ± 5.9	12.9 ± 4.6
<b>VF responses (dB)</b>	22.0 ± 7.3	20.4 ± 7.7	17.8 ± 7.2	15.9 ± 7.9	13.4 ± 8.4

SD-OCT; Spectral domain optic coherence tomography, mfERG; Multifocal electroretinography, VF: Visual field

**Table 2.** Correlation analyses for corrected visual acuity, macular retinal thickness on SD-OCT, visual field responses and mfERG responses in patients with retinitis pigmentosa.

	CVA	SD-OCT R1	SD-OCT R2	SD-OCT R3	mfERG R1	mfERG R2	mfERG R3	mfERG R4	mfERG R5
CVA		R=0.668 P<0.01**			R=0.511 P<0.01**				
SD-OCT R1	R=0.668 P<0.01**				R=0.689 P<0.01**				
SD-OCT R2						R=0.394 P<0.01**			
SD-OCT R3							R=0.292 P=0.054		
VF R1	R=0.578 P<0.01**	R=0.184 P=0.231			R=0.359 P=0.017*				
VF R2			R=0.095 P=0.538			R=0.353 P=0.019*			
VF R3				R=0.049 P=0.753			R=0.199 P=0.195		
VF R4								R=0.232 P=0.130	
VF R5									R=0.341 P=0.023*

CVA; Corrected visual acuity, SD-OCT Rx; Spectral domain optik coherence tomography ring, mfERG Rx: Multifocal electroretinography ring, VF Rx; Visual field ring \* Weak positive correlation \*\* Strong positive correlation

correlation was reported between visual function and IS/OS band integrity on OCT.<sup>8</sup> Our results are supportive for those in the literature; in addition, we observed that there is no correlation between macular retinal thickness and visual field values. We think that this may be due to need for patient compliance in visual field test.

In our study, we observed that CVA was correlated with macular retinal thickness, visual field results and mfERG responses. In addition, it was also found that there was a correlation between macular retinal thickness and mfERG responses in first 2 rings while there was no correlation between macular retinal thickness and visual field in any ring. These findings suggest that objective test can be more valuable in the assessment of patients. As a result, visual field test is a subjective method which is affected by patients' responses. On the other hand, SD-OCT and mfERG are not affected by patients' responses. These tests provide information independent from patient responses and more objective data regarding disease process. Thus, we think that it will be beneficial to perform SD-OCT and mfERG in disease threatening vision such as RP. However, we think that lack of correlation between macular retinal thickness and visual field responses in our study may be due to likelihood test that performance had a margin of error in this group of patients experiencing vision loss although the tests with scan error  $\geq 20\%$  were excluded. In addition,

it may be also due to fact that tests were retrospectively reviewed, which did not allow re-scan.

This study has some limitations including small sample size, accepted margin of error in visual field and mfERG recordings due to retrospective nature, lacking of a control group, wide age range of patients, presence of refractive errors at varying degrees (From +1.25 to -4.50 diopters) in the patients despite exclusion of high myopia and lack of stratification according to gene analysis. Finally, we did not measure retinal photoreceptor layer thickness selectively on SD-OCT, rather, we used macular retinal thickness values provided by device in an automated manner. In the future, prospective studies with larger sample size using gene analysis will provide more objective results.

The retinitis pigmentosa is defined is a disease causing blindness in all sources. This leads increased anxiety and curiosity of current clinical stages in the patient. In conclusion, this forces clinicians to performed more detailed evaluations. We think that optimal way to provide most accurate data to patients regarding functional retina is to employ SD-OCT, visual field test and mfERG in addition to detailed clinical examination.

In conclusion, CVA levels vary according to macular anatomic and physiological conditions in RP. Thus, we think that support by anatomic and functional diagnostic

test will be helpful when planning treatment and follow-up in RP patients.

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