Original Article

Evaluation of Full-Field Stimulus Threshold Test Results in Retinitis Pigmentosa: Relationship with Full-Field Electroretinography, Multifocal Electroretinography, Optical Coherence Tomography, and Visual Field

Ayşe Öner*, Neslihan Sinim Kahraman**

*Acıbadem Health Group, Taksim Hospital, Clinic of Ophthalmology, İstanbul, Türkiye
**Acıbadem University, Vocational School of Health Services, Division of Opticianry, İstanbul, Türkiye

Abstract

Objectives: The full-field stimulus threshold (FST) test was developed to evaluate the efficacy and safety of treatments of hereditary retinal diseases. In this study we performed the FST test in patients with retinitis pigmentosa (RP) and compared the results with findings from other ophthalmological tests.

Materials and Methods: The study included 51 intermediate and advanced RP patients and 21 normal subjects. All patients and controls underwent routine examination and ophthalmological tests including visual field, optical coherence tomography, full-field and multifocal electroretinography (mfERG), and FST tests. During FST testing, the perception thresholds of retina to the white, blue, and red FST were determined in decibels.

Results: The mean age of the patients and the controls were 35.2 and 33.5 years, respectively. For all RP patients, no response was obtained on full-field ERG. All subjects were able to perform reliable FST tests. The mean values of visual acuity and central macular thickness were significantly lower and visual field mean deviation values were significantly higher in the RP group than the controls. When we evaluated the mfERG findings, the mean P1 wave amplitudes in all rings were significantly lower and the mean peak times were significantly longer in RP patients than controls. In comparisons of FST test results, the mean values for white, blue, red and the difference between blue-red thresholds were significantly lower in the RP group than the control group.

Conclusion: The FST test is a fast and a reliable exam which can be done in subjects with poor visual acuity and reduced visual field. The results of this study confirm that the FST test can measure retinal sensitivity in severely affected RP subjects with flat flash ERG.

Keywords: Full-field electroretinography, full-field stimulus threshold test, visual field, multifocal electroretinography, optical coherence tomography, retinitis pigmentosa

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Address for Correspondence: Ayşe Öner, Acıbadem Health Group, Taksim Hospital, Clinic of Ophthalmology, İstanbul, Türkiye
E-mail: ayseozoner@gmail.com **ORCID-ID:** orcid.org/0000-0002-8583-1836
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Introduction

Retinitis pigmentosa (RP) is a progressive, hereditary retinal disease that causes damage to the retinal photoreceptors. The condition first manifests with impaired night vision, followed by visual impairment during the day, narrowing of the visual field, and total vision loss in the end stage.[1] Although there is not yet an accepted effective treatment option, successful results have been reported in recent years with gene and stem cell therapies and electrical stimulation interventions aiming to halt disease progression and regenerate the retinal cells.[2,3,4,5,6,7,8,9] Many of these clinical studies have included patients with advanced RP, and reliable results cannot be obtained with standard tests of visual function in such cases.

Standard full-field electroretinography (ERG) testing is often used in the clinic to evaluate photoreceptor function in patients with RP. Full-field ERG demonstrates total rod and cone responses from the entire retina. As there is more retinal damage in advanced RP, amplitudes may be very low and reliable data may not be attainable. In addition, full-field ERG cannot aid in regional assessment of the retina and is therefore insufficient for evaluation of the central retina, which is spared until the final stages of RP.[10] Previous studies have indicated that multifocal

ERG (mfERG), which is a cone-derived electrophysiological test, can be used to monitor disease progression in cases where full-field ERG readings cannot be obtained, there is advanced damage to the rod cells, and the cone cells have also begun to be affected. These publications have shown that reliable mfERG responses can be obtained in a large majority of advanced RP cases.[11,12,13] Therefore, performing mfERG in addition to full-field ERG in advanced RP cases will aid in evaluating the condition of the retina. However, it should be kept in mind that the visual field and mfERG tests used in the follow-up of RP are dependent on patient cooperation and fixation.[10,11]

The full-field stimulus threshold (FST) test is an electrophysiological test developed to evaluate the level of light perception after dark adaptation, especially in cases of advanced retinal dystrophy. This easy and rapid test is based on whether the patient perceives a light shown using a full-field stimulation system, with no need for fixation. At the end of the test, the level of light sensitivity of the retina is determined in decibels (dB). The biggest advantage is that it can be performed easily even in cases with very low vision or nystagmus. The FST test allows the determination of dark-adapted light and color perception levels as dB. Chromatic tests give us information about the condition of the rods and cones affected by the disease. Rods are more sensitive to blue light than red light, whereas cones are equally sensitive to blue and red light. A difference in sensitivity between the two color tests indicates that the rods are affected, while a similar decrease in sensitivity indicates that the cones are affected. In exclusively rod-derived responses, blue light sensitivity is approximately 25 dB higher than red. In cone-derived responses, blue and red light sensitivities are very similar. In previous studies, the blue-red sensitivity threshold difference has been calculated to determine from which cells the responses originate. It was reported that in cases where this difference is less than 10 dB, the rod cells made no contribution to the FST test.[14,15]

The present study aimed to use the FST test to evaluate white and color light sensitivity levels of the retina in RP patients. In addition, we planned to compare FST test results with optical coherence tomography (OCT) findings and visual field results to evaluate their relationship with anatomical and functional damage to the retina. As the study would include intermediate and advanced cases, we considered that it may not be possible to obtain rod-based electrophysiological responses. Therefore, we also planned to compare the results of the FST test and mfERG, which is a cone-based test.

Materials and Methods

Patient Selection and Evaluation

Patients over 18 years of age who presented to our clinic, were diagnosed with RP clinically and electrophysiologically, and whose disease was in the intermediate to advanced stage were included in this study. Approval for the study was received from Acıbadem University Medical Research Ethics Committee (ethics committee no: 2023-05/160, date: 24.03.2023) and adhered to the tenets of the Declaration of Helsinki. All patients were informed about the study and signed an informed consent form.

Criteria for inclusion in the study were:

1. Being over 18 years of age,
2. Having a clinical diagnosis of RP, confirmed with the tests performed,
3. Having the mental capacity to perform the tests,
4. Having undergone any ocular surgery other than cataract surgery.

Exclusion criteria were:

1. Having any retinal diseases other than RP (e.g., cataract, glaucoma, diabetic retinopathy) or vitreous opacity that may affect the test results,
2. Having any systemic or neurological disease that may affect the test results,
3. Having RP associated with a diagnosed syndrome such as Usher or Bardet-Biedl (due to the coexisting problems).

In addition to routine ophthalmological examinations of the patients, visual field results were recorded with the Humphrey 30-2 program (Carl Zeiss Meditec AG, Germany), and central macular thickness (CMT) and ellipsoid zone (EZ) band width were evaluated with OCT (Figure 1). CMT and EZ band width were measured independently by two separate evaluators and the values were averaged. Measurements were made using a horizontal OCT section passing through the foveal center. CMT was manually measured as the distance between the inner limiting membrane in the center of the fovea and the retinal pigment epithelium. EZ band width was determined by manually measuring the EZ band line between the nasal and temporal ends in the same horizontal OCT section (Figure 1C).

All patients in the study underwent electrophysiological testing with full-field ERG, mfERG, and FST test (Metrovision, France) performed in accordance with international standards. Full-field ERG aimed to assess rod and cone responses in the whole retina, while mfERG aimed to locally assess cone responses in the central retina. In the mfERG test, a stimulus consisting of 61 hexagons and 5 concentric rings (<2°, 2-5°, 5-10°, 10-15°, and >15°) was used, and the mean amplitude and latency of the P1 wave were recorded for all rings.

Patient evaluations started with routine examination, OCT, and visual field tests. The pupil was then dilated by instilling 1% tropicamide 3 times at intervals of 5 minutes, after which the electrophysiological tests were started. After completing the full-field ERG and mfERG tests in accordance with International Society for Clinical Electrophysiology of Vision (ISCEV) standards, the patient was taken for dark adaptation for the FST test.[16,17] As the FST test is relatively new, the procedure is explained in detail below.

FST Test Procedure

The patients with dilated pupils were taken into a dark room where their eyes were covered with a bandage for 40 minutes to allow dark adaptation. During the test, recordings were obtained from each eye separately while the other eye remained covered.

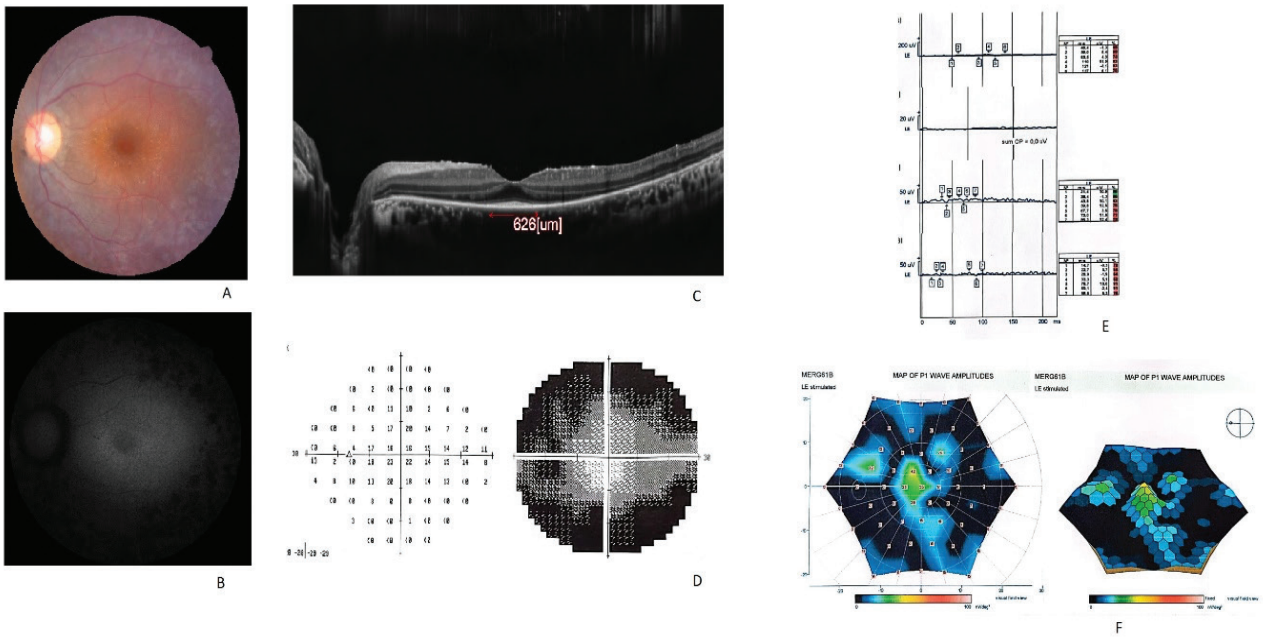

Figure 1. Fundus photograph (A), fundus autofluorescence (FAF) (B), optical coherence tomography (OCT) (C), visual field (D), full-field electroretinogram (ERG) (E), and multifocal ERG (F) images from the left eye of a patient with retinitis pigmentosa and visual acuity of 0.8 Snellen decimal. The fundus photograph shows peripheral pigmentary changes, FAF shows a central hyperautofluorescent ring, and OCT shows a decrease in retinal thickness, narrowing of EZ band, and the measurement of the EZ band. The visual field test indicates peripheral field loss. Full-field ERG responses are completely flat, while multifocal ERG shows depressed peripheral responses and attenuated central responses

The FST test was performed with the MonCvONE-CR system produced by Metrovision using full-field light as the stimulus. The device uses an LED light source for white light, a 500 nm filter for blue, and a 647 nm filter for red. During the test, patients were shown light stimuli of different colors every 3 seconds, and the patient was asked to press a button held in their hand when they saw the light. Sensitivity thresholds were determined using the 8-4-2-1 step method, in which the luminance (light value) is first increased by intervals of 8 dB. When the patient saw the light, the luminance was decreased and increased by 4 dB, then 2 dB, and finally by 1 dB to determine the threshold value. To ensure the reliability of the test, checks were made at regular intervals to ensure the patient was not responding without presenting the stimulus.[18]

The control group included patients in the same age group who presented to our outpatient clinic for examination and had no pathology detected in the ophthalmological examination. After obtaining consent, the control subjects underwent visual field, OCT, mfERG, and FST tests in addition to routine examination.

Due to the very low amplitudes in the full-field ERG test in the RP group and the inability to obtain reliable records, full-field ERG was not performed in the control group.

Statistical Analysis

The study data were statistically analyzed using SPSS for Windows version 21.0 (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was used to test for normal distribution, descriptive statistics (mean, standard deviation) were used to evaluate the data, analysis of variance (ANOVA) was used for comparisons of paired groups, and Pearson correlation analysis was used for correlation analysis. The results were considered statistically significant at p values less than 0.05.

Results

A total of 101 eyes of 51 RP patients and 42 eyes of 21 control subjects were included in the study. Both groups conformed to normal distribution. The mean age was 35.2 years (range: 18-70 years) in the RP group and 33.5 years (range: 18-50 years) in the control group. The mean disease duration in RP patients was 16.9 years (range: 4-49 years). The mean visual acuity in the eyes with RP was 0.19 (range: 0.03-0.7) Snellen decimal, compared 1.0 in the control group. To examine the findings in more detail, the RP group was divided into two subgroups based on visual acuity: ≤0.05 and >0.05 Snellen decimal. The demographic data of the patients are given in Table 1. As patient age and disease duration increase, vision level decreases. Due to the very low full-field ERG amplitudes in all of the RP patients included in the study, no measurable response could be obtained. Of the 101 eyes, 91 had visual field and 89 had mfERG data. The visual acuity of eyes that could not be assessed with these tests was found to be lower than 0.05 Snellen decimal. All patients were able to perform the FST test easily. Meaningful FST test results could be obtained in 46 eyes of 23 patients with a vision level of 0.05 Snellen decimal or lower.

The patients' visual acuity, visual field, and OCT findings are shown in Table 2. When OCT findings were evaluated, the mean CMT was 132.2 µm in the RP group and 221.5 µm in the control group, which was a statistically significant difference ($p<0.05$). When the RP subgroups were examined, we observed that mean CMT value was significantly lower (121.5 µm) in the group with low visual acuity ($p<0.05$). The mean EZ band width was 1018.8 µm in the RP group. According to the RP subgroups, the EZ bands were significantly narrower (629.3 µm) in the group with low visual acuity ($p<0.05$). The control group exhibited no deterioration in EZ band integrity. These findings show that as the disease progresses, vision level decreases and the anatomical findings on OCT also worsen due to cell loss.

When the visual field results were evaluated, we observed that the mean MD value was -4.38 dB in the control group versus -30.91 dB in the RP group, and this difference is statistically significant ($p<0.05$). When evaluated by RP subgroup, we determined that visual field defects were more severe in the group with lower visual acuity (mean deviation: -32.53). These findings indicate that functional loss in the visual field increases as the disease progresses.

On mfERG, mean P1 wave amplitudes were significantly lower and mean P1 wave latency was significantly longer in all rings in eyes with RP compared to the control group, with a more prominent difference in the peripheral rings ($p<0.05$) (Tables 3, 4). These data demonstrate that mfERG recordings can be obtained even in advanced cases of RP, and the cone cell damage detected in mfERG progressed from the periphery toward the center.

When the FST test results were evaluated, the white, blue, and red light thresholds and the blue-red threshold difference were found to be significantly lower in the RP group than in the control group ($p<0.05$) (Table 5). The mean blue-red FST difference was 11.1 dB, and this difference was below 10 dB in 51 eyes. In these cases, the rod response was minimal or absent. In 13 eyes, this difference was found to be 0 dB, indicating that there is no rod response. When the RP subgroups were evaluated, all FST test values were found to be significantly lower in the group with low visual acuity. In addition, the mean blue-red threshold difference in this group was 9.2 dB, which is below 10 dB. Therefore, it can be said that there is very little to no

Table 1. Demographic characteristics of all subjects

Characteristic	RP group total (n=51)	RP group VA ≤0.05 (n=23)	RP group VA >0.05 (n=28)	Control (n=21)	p value
Age (years), mean	35.2	39.2	32.5	33.5	0.08
Sex (male), n (%)	27 (53)	11 (47)	16 (57)	11 (52)	0.31
Disease duration (years), mean	16.9	19.8	12.5		0.001*

*Mean disease duration was statistically longer in the group with VA ≤0.05 Snellen decimal. RP: Retinitis pigmentosa, VA: Visual acuity (in Snellen decimal), n: Number of patients

Table 2. Comparison of visual acuity, visual field, and OCT data of RP patients and the control group

	RP group total (n=101 eyes)	RP group VA ≤0.05 (n=46 eyes)	RP group VA >0.05 (n=55 eyes)	Control (n=42 eyes)	p value
VA (Snellen decimal)	0.19±4.4	0.04±0.03	0.31±5.2	1.0	0.008*
Visual field MD (dB)	-30.91±9.52	-32.53±5.52	-28.05±7.52	-4.38±2.63	0.020*
OCT CMT (µm)	132.2±47.4	121.5±37.4	145.7±42.6	221.5±19.3	0.023*
OCT EZ band width (µm)	1018.8±761.8	629.3±642.6	1363.6±833.6		0.010**

*There was a statistically significant difference between all groups. **There was a statistically significant difference between all groups, with lowest EZ band width on OCT in the RP group with visual acuity of 0.05 Snellen decimal. RP: Retinitis pigmentosa, OCT: Optical coherence tomography, VA: Visual acuity (in Snellen decimal), dB: Decibel, MD: Mean deviation, CMT: Central macular thickness, EZ: Ellipsoid zone

Table 3. Comparison of P1 wave amplitudes on multifocal electroretinography

Ring	RP group Mean ± SD (nV)	Control group Mean ± SD (nV)	p value
<2°	349.3±86.0	1412.3±162.2*	0.001*
2-5°	192.2±96.9	1192.5±163.4*	0.001*
5-10°	141.5±63.5	1112.5±141.3*	0.001*
10-15°	137.8±65.6	1054.5±132.4*	0.001*
>15°	95.1±58.1	1008.2±144.6*	0.001*

*P1 wave amplitudes were significantly lower in all rings in the RP group than in the control group. RP: Retinitis pigmentosa, SD: Standard deviation, nV: Nanovolt

rod response in eyes with a vision level of 0.05 Snellen decimal or lower. The blue-red threshold difference was greater than 20 dB in 17 eyes, all of which had visual acuity higher than 0.05 Snellen decimal. In our study, the mean test duration was 199 seconds (3.3 minutes) after dark adaptation.

Correlation analyses showed that older age, longer disease duration, and lower CMT and EZ band width were associated with lower visual acuity and increased visual field loss. All FST test results were negatively correlated with age, disease duration, and visual field MD values ($p<0.05$), indicating that FST test values decreased as age, disease duration, and visual field defects increased. All FST test results were positively correlated with mfERG amplitudes in all rings, with stronger correlation in the peripheral fourth and fifth rings. In addition, all FST test results showed a strong positive correlation with CMT and EZ band width ($p<0.05$).

Figure 1 shows the full-field ERG, mfERG, visual field, and OCT results of a patient with a visual acuity of 0.8 Snellen decimal, and Figure 2 shows the FST test results of the same patient and a subject in the control group.

Discussion

Developments in gene and stem cell therapies in recent years have required the inclusion of patients with low vision in clinical trials. Unfortunately, available tests were not sufficient to understand whether patients with low vision, especially the legally blind, benefitted from any of the treatment options applied. Visual field testing cannot always be performed reliably in this patient group, and existing electrophysiological tests do not yield meaningful responses due to the severe retinal damage. This demonstrated the need for a new test for use in the low vision patient group. As a result, the FST test was developed to be used in clinical trials for hereditary retinal diseases. As the FST test enables the light sensitivity threshold of the retina to be determined in dB even in patients with only light perception, it is expected to enable the collection of objective data in studies conducted in patients with low vision.[19,20]

Since FST is a new test, there are few studies on this subject in the literature. To date, this test has been used in studies involving low vision patient groups such as Leber congenital amaurosis (LCA), RP, Usher syndrome, and Stargardt's macular dystrophy.[21,22,23]

Klein and Birch[24] evaluated the accuracy, sensitivity, and repeatability of the FST test in 53 eyes of 42 advanced RP patients. The patients included in the study could not perform static perimetry and had no response on full-field ERG. Seven control subjects were also included in the study. In 51 of the 53 eyes, a light sensitivity threshold could be determined in the FST test. Of the 2 eyes with no result, one had no light perception and the other had only slight light perception. A threshold value could be obtained in the FST test in 14 eyes of 13 patients with light perception only. All patients who could count fingers were able to perform the test easily. The test was repeated at different times in 24 patients and yielded similar results. The authors concluded that the FST test is an easily reproducible and useful test that can be used to evaluate retinal light sensitivity and light perception level in patients with low vision.[24] In our study, none of the patients had a measurable response in the full-field ERG but all were able to perform the FST test easily. Our study group did not include any patients whose vision was at the level of light perception. The lowest level of visual acuity was hand

Table 4. Comparison of P1 wave latencies on multifocal electroretinography

Ring	RP group Mean ± SD (ms)	Control group Mean ± SD (ms)	p value
<2°	51.8±6.4	47.5±6.4*	0.020*
2-5°	52.9±8.0	46.3±5.4*	0.023*
5-10°	56.2±8.3	46.3±6.5*	0.010*
10-15°	54.5±8.4	49.4±5.7*	0.030*
>15°	55.7±12.4	48.4±6.3*	0.026*

*P1 wave latencies were significantly longer in all rings in the RP group than in the control group. RP: Retinitis pigmentosa, SD: Standard deviation, ms: Millisecond

Table 5. Comparison of full-field stimulus threshold test values

FST	RP group	RP group VA ≤0.05	RP group VA >0.05	Control group	p value
White FST	43.9±13.9	36.8±11.6	48.2±14.6	81.8±18.4	0.001*
Red FST	41.5±12.5	34.7±9.8	45.7±12.9	67.3±17.6	0.001*
Blue FST	52.6±16.2	43.2±10.6	58.3±15.7	92.8±18.3	0.001*
Blue-red FST	11.1±10.3	9.2±7.8	12.6±11.9	27.4±11.8	0.001*

*All FST test results and the blue-red threshold difference were significantly lower in the RP group than in the control group. All test results were significantly lower in the group with visual acuity of ≤0.05 Snellen decimal than in the other groups. FST: Full-field Stimulus Threshold, RP: Retinitis pigmentosa, VA: Visual acuity (in Snellen decimal), SD: Standard deviation

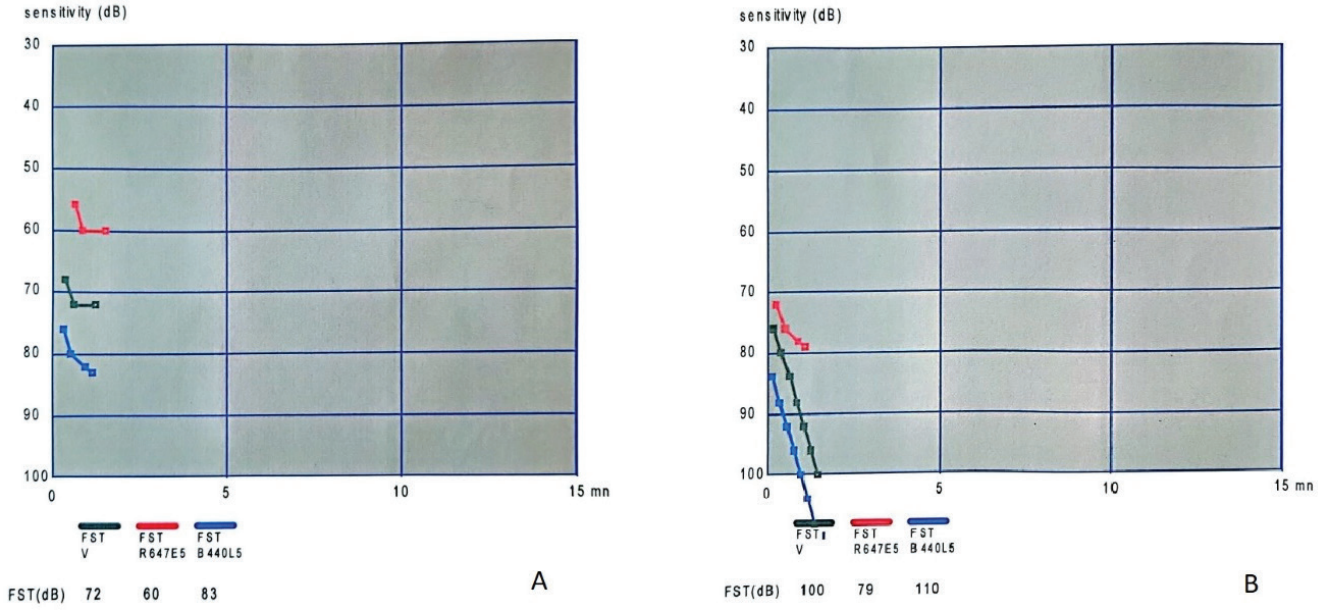

Figure 2. The full-field stimulus threshold (FST) test results of the patient shown in Figure 1 (A) and a control subject (B). White, blue, and red FST values were 72, 60, and 83 decibels (dB) in the patient with retinitis pigmentosa compared to 100, 79, and 110 dB in the control subject, respectively

movements at a distance of 1 meter. Significant FST test results could be obtained in all 46 eyes of the 23 patients with visual acuity lower than 0.05 Snellen decimal. Therefore, it can be said that the FST test is reliable in all patients whose vision level is better than light perception. However, all FST test results also decreased in correlation with the decrease in visual acuity.

Another clinical trial including 42 eyes of 21 RP patients compared FST results with flicker ERG, fundus autofluorescence (FAF), and OCT findings. White, blue, and red FST results were found to correlate with 3.0 flicker ERG amplitude, EZ band length on OCT, and the vertical and horizontal diameter of the hyperautofluorescent ring detected on FAF.[25] In two similar studies examining the relationship between the central retinal cell layers and visual field in RP patients, retinal sensitivity detected within the visual field decreased linearly as the outer nuclear layer thinned. It was also noted in these studies that the outer segment length (EZ band width) was proportional to photoreceptor cell density and correlated with visual field.[26,27] In our study, the retinal layers were not evaluated separately on OCT, but CMT and EZ band width (which indicates photoreceptor cell integrity) were examined. Similar to previous studies, we observed that as the retina thins and the EZ band narrows, visual field loss increases and the level of vision decreases. Our correlation analyses demonstrated that anatomical losses detected on OCT were strongly correlated with visual field and visual acuity loss. When other correlation data obtained from our study were evaluated, both white FST and chromatic (blue and red) FST values were positively correlated with the wave amplitudes in all rings on mfERG and with EZ band width and CMT values on OCT. This indicates that FST values decreased with increased retinal cell damage, narrowing of the EZ band, and thinning of the macula. Similarly, FST values decreased as mfERG wave amplitudes decreased (i.e., as cone cell function deteriorated). These results show that the FST test reflects functional and anatomical findings and can be used reliably in the clinical evaluation of patients with retinal disease.

The multicenter RUSH2A study published by Birch et al.[28] included 127 patients with Usher syndrome type 2A (*USH2A*)-associated retinal degeneration or biallelic *USH2A* mutation from 16 centers in the United States and Europe. The patients were aged 8 years and older with visual field less than 10° and were assessed with full-field ERG and FST tests during follow-up. As all patients in this study had severe retinal damage, full-field ERG results could not be obtained in 47% of the study group. All patients with unmeasurable ERG responses were able to perform the FST test. Therefore, the authors stated that the FST test complements ERG and may be more useful in follow-up. The results of their study showed that white FST and the blue-red FST difference were correlated with duration of vision loss. In eyes with a blue-red FST difference of less than 10 dB, the responses were assumed to be cone-derived. Rod function was found to be absent in 43% of all patients. In these cases, the white FST was below 30 dB and the blue-red difference was approximately 0 dB, suggesting that the response was entirely from cones. In eyes with a blue-red FST difference greater than 20 dB, the responses were presumed to be mostly rod-derived.

Eyes with rod-driven responses mostly had disease durations of less than 20 years, while most patients with a disease duration longer than 20 years had no rod response and cone-mediated FST. In that study, visual acuity was very weakly correlated with scotopic ERG results and weakly correlated with photopic ERG results, but a strong correlation was found with FST results. The FST test was strongly correlated with disease duration, and thus with disease severity. White FST values were found to be 18 dB higher in eyes with a disease duration of less than 10 years versus more than 20 years.[28]

In our study, all FST test values showed a strong negative correlation with patient age and disease duration. To better evaluate the results, we divided the RP patients into subgroups based on visual acuity. The mean age was 6.7 years older and the mean disease duration was 7.3 years longer in patients with visual acuity of 0.05 Snellen decimal or lower compared to RP patients with higher visual acuity. In cases with low vision, CMT and EZ band widths were found to be more significantly decreased, indicating greater anatomical damage to the retina. Consistent with these findings, visual field defects were more advanced in the subgroup with low visual acuity. Considering the FST results, there was a similar decrease in both white and chromatic FST results in the RP patients in our study. This indicates damage not only to rod cells but also cone cells. The mean blue-red FST difference was 11.1 dB, with values lower than 10 dB in 51 eyes. When visual acuity decreased to below 0.05 Snellen decimal, the mean blue-red FST difference decreased to less than 10 dB (9.2 dB). In 13 eyes, this difference was found to be 0 dB. These findings indicate that rod cells contribute little to the FST results in advanced disease and even make no contribution in some cases. The continued ability to obtain FST responses in patients with very low vision is due to the fact that cone cell function continues until the end stage. This also supports the mfERG results reported in the literature. The blue-red threshold difference on the FST test was greater than 20 dB in 17 eyes, all of which had visual acuity better than 0.05 Snellen decimal. It can be concluded that rod cells contributed to the FST results in these eyes. Based on the FST results, rod responses were absent in approximately half of the eyes in our study and were very low overall, leading to the conclusion that cones contribute more to light perception in advanced RP.

The FST is a fairly quick test. In previous studies, the average test duration per eye was 3.6 minutes, with a range of 2.9 to 4.8 minutes. In addition, it has high repeatability. The average difference between repeat tests in the same patients was reported to be 1.51 dB.[14,22] In our study, the mean duration of the test was 199 seconds (3.3 minutes) after dark adaptation.

As mentioned earlier, the FST test was developed to evaluate the effectiveness of treatment in clinical studies of gene and stem cell therapies in which low vision patients are included. The FST test was first used in clinical studies investigating the active substance in voretigene neparvovec, which received U.S. Food and Drug Administration approval for use in patients with LCA and RP associated with homozygous *RPE65* gene mutation. The open-label randomized controlled phase 3 trial by Russell et al.[29] included patients over 3 years of age with visual acuity 20/60 or worse, visual field less than 20 degrees, and biallelic *RPE65* mutation. All patients were able to perform the FST test and 90% of them exhibited improvements in the FST test at 1-year follow-up.[30] In studies presenting the 4-year results of treated patients, the FST test was repeated during follow-up and the improvements in the FST test achieved at 1 year were found to be maintained at 4 years.[30,31]

In another study, patients with CEP290-associated LCA type 10 were treated with sepofarsen, an RNA antisense oligonucleotide targeting CEP290. In this phase 1b/2 trial, intravitreal sepofarsen was administered to 11 patients, 5 of which were children, up to 4 times and the 12-month follow-up results were examined. FST was the only electrophysiological test used in the study. It was a dose determination study and 5 patients had light perception only. In such a low-vision group, responses could not be obtained with other electrophysiological tests. However, FST could be performed by all patients. Improved light perception was detected in both white and chromatic (blue/red) FST tests in the treated eyes of all patients.[32] It is clear that there is no test other than FST that can be used to evaluate treatment outcomes in patients with light perception only.

Study Limitations

Our patient group consisted of intermediate to advanced cases. There were no patients with early RP in the study. Therefore, it was not possible to evaluate how FST tests would be affected at an early stage. In addition, the RP cases were only subdivided according to visual acuity. In a larger patient group, the interpretation of FST tests will be more informative by grouping according to inheritance patterns, genetic test results, or clinical findings. Finally, there is no database of FST test results in normal individuals in the literature, and we have not yet created a normative database in our own laboratory. It would be more useful to determine normal data by age group and compare them with disease groups.

Conclusion

In summary, FST is an easy, rapid, non-interventional test that can be performed reliably in all patients who have low vision, nystagmus, and unmeasurable ERG responses. Clinical studies conducted in recent years, especially in patients with low vision, have revealed the importance of this test. Therefore, it is necessary to know and evaluate FST test results in different patient groups. This study presents a detailed analysis of FST test results and their relationship with other ophthalmological tests in patients with RP.

Ethics

Ethics Committee Approval: Approval for the study was received from Acıbadem University Medical Research Ethics Committee (ethics committee no: 2023-05/160, date: 24.03.2023).

Informed Consent: Obtained.

Authorship Contributions

Surgical and Medical Practices: A.Ö., N.S.K., Concept: A.Ö., Design: A.Ö., Data Collection or Processing: A.Ö., N.S.K., Analysis or Interpretation: A.Ö., Literature Search: N.S.K., Writing: A.Ö.

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References

1. Öner A. Stem Cell Treatment in Retinal Diseases: Recent Developments. Turk J Ophthalmol. 2018;48:33-38.
2. Prado DA, Acosta-Acero M, Maldonado RS. Gene therapy beyond luxturna: a new horizon of the treatment for inherited retinal disease. Curr Opin Ophthalmol. 2020;31:147-154.
3. Maguire AM, Bennett J, Aleman EM, Leroy BP, Aleman TS. Clinical Perspective: Treating RPE65-Associated Retinal Dystrophy. Mol Ther. 2021;29:442-463.
4. Oner A, Gonen ZB, Sinim N, Cetin M, Ozkul Y. Subretinal adipose tissue-derived mesenchymal stem cell implantation in advanced stage retinitis pigmentosa: a phase I clinical safety study. Stem Cell Res Ther. 2016;7:178.
5. Kahraman NS, Oner A. Umbilical cord derived mesenchymal stem cell implantation in retinitis pigmentosa: a 6-month follow-up results of a phase 3 trial. Int J Ophthalmol. 2020;13:1423-1429.
6. Özmert E, Arslan U. Management of retinitis pigmentosa by Wharton's jelly-derived mesenchymal stem cells: prospective analysis of 1-year results. Stem Cell Res Ther. 2020;11:353.
7. Zhao T, Liang Q, Meng X, Duan P, Wang F, Li S, Liu Y, Yin ZQ. Intravenous Infusion of Umbilical Cord Mesenchymal Stem Cells Maintains and Partially Improves Visual Function in Patients with Advanced Retinitis Pigmentosa. Stem Cells Dev. 2020;29:1029-1037.
8. Sinim Kahraman N, Oner A. Effect of Transcorneal Electrical Stimulation on Patients with Retinitis Pigmentosa. J Ocul Pharmacol Ther. 2020;36:609-617.
9. Dizdar Yigit D, Sevik MO, Şahin Ö. Transcorneal electrical stimulation therapy may have a stabilization effect on multifocal electroretinography for patients with retinitis pigmentosa. Retina. 2022;42:923-933.
10. Gerth C, Wright T, Héon E, Westall CA. Assessment of central retinal function in patients with advanced retinitis pigmentosa. Invest Ophthalmol Vis Sci. 2007;48:1312-1318.
11. Chan HL, Brown B. Investigation of retinitis pigmentosa using the multifocal electroretinogram. Ophthalmic Physiol Opt. 1998;18:335-350.
12. Gränse L, Ponjavic V, Andréasson S. Full-field ERG, multifocal ERG and multifocal VEP in patients with retinitis pigmentosa and residual central visual fields. Acta Ophthalmol Scand. 2004;82:701-706.
13. Nagy D, Schönfisch B, Zrenner E, Jägle H. Long-term follow-up of retinitis pigmentosa patients with multifocal electroretinography. Invest Ophthalmol Vis Sci. 2008;49:4664-4671.
14. Collison FT, Fishman GA, McAnany JJ, Zernant J, Allikmets R. Psychophysical measurement of rod and cone thresholds in stargardt disease with full-field stimuli. Retina. 2014;34:1888-1895.
15. Messias K, Jägle H, Saran R, Ruppert AD, Siqueira R, Jorge R, Messias A. Psychophysically determined full-field stimulus thresholds (FST) in retinitis pigmentosa: relationships with electroretinography and visual field outcomes. Doc Ophthalmol. 2013;127:123-129.
16. Robson AG, Frishman LJ, Grigg J, Hamilton R, Jeffrey BG, Kondo M, Li S, McCulloch DL. ISCEV Standard for full-field clinical electroretinography (2022 update). Doc Ophthalmol. 2022;144:165-177.
17. Hoffmann MB, Bach M, Kondo M, Li S, Walker S, Holopigian K, Viswanathan S, Robson AG. ISCEV standard for clinical multifocal electroretinography (mfERG) (2021 update). Doc Ophthalmol. 2021;142:5-16.
18. Hirji SH. Measure of Visual Function. Methods Mol Biol. 2023;2560:145-151.
19. Roman AJ, Schwartz SB, Aleman TS, Cideciyan AV, Chico JD, Windsor EA, Gardner LM, Ying GS, Smilko EE, Maguire MG, Jacobson SG. Quantifying rod photoreceptor-mediated vision in retinal degenerations: dark-adapted thresholds as outcome measures. Exp Eye Res. 2005;80:259-272.
20. Roman AJ, Cideciyan AV, Aleman TS, Jacobson SG. Full-field stimulus testing (FST) to quantify visual perception in severely blind candidates for treatment trials. Physiol Meas. 2007;28:51-56.
21. Jacobson SG, Aleman TS, Cideciyan AV, Roman AJ, Sumaroka A, Windsor EA, Schwartz SB, Heon E, Stone EM. Defining the residual vision in leber congenital amaurosis caused by RPE65 mutations. Invest Ophthalmol Vis Sci. 2009;50:2368-2375.
22. Messias K, Jägle H, Saran R, Ruppert AD, Siqueira R, Jorge R, Messias A. Psychophysically determined full-field stimulus thresholds (FST) in retinitis pigmentosa: relationships with electroretinography and visual field outcomes. Doc Ophthalmol. 2013;127:123-129.
23. Roman AJ, Cideciyan AV, Wu V, Garafalo AV, Jacobson SG. Full-field stimulus testing: Role in the clinic and as an outcome measure in clinical trials of severe childhood retinal disease. Prog Retin Eye Res. 2022;87:101000.
24. Klein M, Birch DG. Psychophysical assessment of low visual function in patients with retinal degenerative diseases (RDDs) with the Diagnosys full-field stimulus threshold (D-FST). Doc Ophthalmol. 2009;119:217-224.
25. Ngo WK, Jenny LA, Kim AH, Kolesnikova M, Greenstein VC, Tsang SH. Correlations of Full-Field Stimulus Threshold With Functional and Anatomical Outcome Measurements in Advanced Retinitis Pigmentosa. Am J Ophthalmol. 2023;245:155-163.
26. Rangaswamy NV, Patel HM, Locke KG, Hood DC, Birch DG. A comparison of visual field sensitivity to photoreceptor thickness in retinitis pigmentosa. Invest Ophthalmol Vis Sci. 2010;51:4213-4219.
27. Sayo A, Ueno S, Kominami T, Okado S, Inooka D, Komori S, Terasaki H. Significant Relationship of Visual Field Sensitivity in Central 10° to Thickness of Retinal Layers in Retinitis Pigmentosa. Invest Ophthalmol Vis Sci. 2018;59:3469-3475.
28. Birch DG, Cheng P, Duncan JL, Ayala AR, Maguire MG, Audo I, Cheetham JK, Durham TA, Fahim AT, Ferris FL 3rd, Heon E, Huckfeldt RM, Iannaccone A, Khan NW, Lad EM, Michaelides M, Pennesi ME, Stingl K, Vincent A, Weng CY; Foundation Fighting Blindness Consortium Investigator Group. The RUSH2A Study: Best-Corrected Visual Acuity, Full-Field Electroretinography Amplitudes, and Full-Field Stimulus Thresholds at Baseline. Transl Vis Sci Technol. 2020;9:9.
29. Russell S, Bennett J, Wellman JA, Chung DC, Yu ZF, Tillman A, Wittes J, Pappas J, Elci O, McCague S, Cross D, Marshall KA, Walshire J, Kehoe TL, Reichert H, Davis M, Raffini L, George LA, Hudson FP, Dingfield L, Zhu X, Haller JA, Sohn EH, Mahajan VB, Pfeifer W, Weckmann M, Johnson C, Gewaily D, Drack A, Stone E, Wachtel K, Simonelli F, Leroy BP, Wright JF, High KA, Maguire AM. Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial. Lancet. 2017;390:849-860. Erratum in: Lancet. 2017;390:848.
30. Maguire AM, Russell S, Wellman JA, Chung DC, Yu ZF, Tillman A, Wittes J, Pappas J, Elci O, Marshall KA, McCague S, Reichert H, Davis M, Simonelli F, Leroy BP, Wright JF, High KA, Bennett J. Efficacy, Safety, and Durability of

Voretigene Neparvovec-rzyl in RPE65 Mutation-Associated Inherited Retinal Dystrophy: Results of Phase 1 and 3 Trials. Ophthalmology. 2019;126:1273-1285.

31. Maguire AM, Russell S, Chung DC, Yu ZF, Tillman A, Drack AV, Simonelli F, Leroy BP, Reape KZ, High KA, Bennett J. Durability of Voretigene Neparvovec for Biallelic RPE65-Mediated Inherited Retinal Disease: Phase 3 Results at 3 and 4 Years. Ophthalmology. 2021;128:1460-1468.
32. Russell SR, Drack AV, Cideciyan AV, Jacobson SG, Leroy BP, Van Cauwenbergh C, Ho AC, Dumitrescu AV, Han IC, Martin M, Pfeifer WL, Sohn EH, Walshire J, Garafalo AV, Krishnan AK, Powers CA, Sumaroka A, Roman AJ, Vanhonsebrouck E, Jones E, Nerinckx F, De Zaeytijd J, Collin RWJ, Hoyng C, Adamson P, Cheetham ME, Schwartz MR, den Hollander W, Asmus F, Platenburg G, Rodman D, Girach A. Intravitreal antisense oligonucleotide sepofarsen in Leber congenital amaurosis type 10: a phase 1b/2 trial. Nat Med. 2022;28:1014-1021.