Correlation between Optical Coherence Tomography and Multifocal Electroretinogram Findings in Patients with Central Serous Chorioretinopathy

Santral Seröz Koryoretinopati Hastalarında Optik Koherens Tomografi Ve Multifokal Elektroretinografi Bulgularının Korelasyonu

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ABSTRACT

Purpose: To evaluate optical coherence tomography (OCT) and multifocal electroretinogram (mfERG) findings in patients with central serous chorioretinopathy (CSC)

Methods: Sixty-two eyes of 31 patients with unilateral treatment naive CSC were included to the study. All subjects underwent complete ophthalmologic examination including best-corrected visual acuity (BCVA), subfoveal and parafoveal choroidal thickness (CT), central foveal thickness (CFT), macular volumes with OCT, and also mfERG responses. Correlation analyses were performed between BCVA, OCT parameters, and mfERG responses.

Results: There was significant increase in subfoveal and parafoveal CT in both affected and fellow eyes of CSC compared to healthy subjects. There was significant decrease in the N1, P1, and N2 amplitudes and increase in N1 implicit times for all rings in both affected and fellow eyes of CSC patients compared to control subjects. Correlation analysis revealed that BCVA was significantly correlated with N1, P1, and N2 amplitudes for Ring 1 ($p<0.05$). No significant correlation was found between BCVA and various OCT parameters.

Conclusion: Our study showed significant correlations between BCVA (logMAR) and mfERG amplitudes in CSC patients. Furthermore, no significant correlation was found between BCVA and various OCT parameters. Our findings indicate that mfERG and OCT could both serve as noninvasive tools for functional and anatomical assessments of CSC patients.

Key words: central serous chorioretinopathy, multifocal electroretinogram, optical coherence tomography.

ÖZ

Amaç: Santral seröz koryoretinopati (SSKR) hastalarının optik koherens tomografi (OKT) ve multifokal elektroretinografi (mfERG) bulgularını değerlendirmek.

Yöntem: Tek taraflı daha önce tedavi almamış 31 SSKR hastasının 62 gözü çalışmaya dahil edildi. Hastaların tamamına ayrıntılı oftalmoojik muayene ile birlikte en iyi düzeltilmiş görme keskinliği (EİDGK), OKT ile subfoveal ve parafoveal koroid kalınlığı (KK), santral fovea kalınlığı (SFK), makula volümü ölçümleri yapıldı ve ayrıca mfERG cevapları analiz edildi. Korelasyon analizi ile EİDGK, OKT parametreleri ve mfERG cevapları değerlendirildi.

Bulgular: Sağlıklı bireyler ile karşılaştırıldığında SSKR hastalarının hem etkilenen gözleri hem de diğer gözlerinde subfoveal ve parafoveal KK değerlerinde anlamlı artış vardı. Sağlıklı bireyler ile karşılaştırıldığında SSKR hastalarının hem etkilenen gözleri hem de diğer gözlerinde tüm halkalarda N1, P1 ve N2 amplitüdlerinde azalma ve N1 iletim zamanında uzama görüldü. Korelasyon analizinde EİDGK değerleri ile mfERG 1. halka N1 dalga amplitüdleri ($p<0,05$) arasında anlamlı korelasyon bulundu**.** EİDGK ile OKT parametreleri arasında anlamlı korelasyon bulunmadı**.**

Sonuç: Çalışmamızda SSKR hastalarında EİDGK değerleri ile mfERG amplitüdleri arasında anlamlı korelasyon bulundu. Ayrıca EİDGK ile farklı OKT parametreleri arasında anlamlı korelasyon bulunmadı**.** SSKR hastalarının anatomik ve fonksiyonel değerlendirilmesinde mfERG ve OCT birbirlerini tamamlayıcı invaziv olmayan tetkikler olarak kullanılabilir.

Anahtar Kelimeler: Santral seröz koryoretinopati, multifokal elektroretinografi, optik koherens tomografi.

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INTRODUCTION

Central serous chorioretinopathy (CSC) is characterized by serous retinal detachment and/or pigment epithelial detachment (PED), predominantly affecting the macular area, and usually associated with choroidal hyper-permeability, and increased choroidal thickness. Central serous chorioretinopathy generally resolves spontaneously within 2 to 3 months with minimal sequel; thus, observation without treatment is generally recommended as initial management.[1, 2] Recurrent or persistent disease can lead to widespread RPE damage, photoreceptor death, and deterioration in vision permanently.[2]

Several reports have investigated the relationship between retinal outer structures and visual acuity in eyes with CSC. A decrease in outer nuclear thickness[3-5] or disruption of the external limiting membrane (ELM) and the photoreceptor inner and outer segment (IS/OS) junction,[6, 7] recently called an ellipsoid zone,[8] have been shown to correlate with visual acuity loss. Intra-retinal hyper-reflective foci or hyper-reflective dots have been described in patients with active CSC. The hyper-reflective foci were thought to possibly serve as accumulations of proteins or activated microglia or macrophages.[9]

Previous studies have reported that functional evaluation of CSC can be achieved with mfERG. Recent studies have shown decreased mfERG response amplitudes with delayed latencies in corresponding areas of the neurosensory retinal detachment.[10-17] However there are only few studies which attempted to evaluate the correlation between functional and structural changes in CSC patients.[16,18]

In this study we aim to assess the correlation between the functional mfERG responses, structural choroidal and retinal OCT findings in eyes with chronic CSC.

METHODS

This cross-sectional, non-randomized, comparative study was carried out at the Department of Ophthalmology, University Hospital of Erciyes, from January to March 2016. The study was approved by Institutional Review Board of the University Hospital. All participants gave written informed consent.

The study included patients with unilateral, treatment-naive CSC of less than 6 months duration and age- and sex- matched healthy controls.

Exclusion criteria were history of previous eye surgery or trauma, retinal pathology other than CSC (macular edema, epiretinal membrane, diabetic retinopathy, wet or dry age-related macular degeneration), and media opacity. All patients and healthy controls with a refractive error of greater than ±6.00 diopters were excluded because pathologic myopia/hypermetropia may affect the analysis of the choroid. There was no significant difference between CSC patients and healthy controls regarding axial length and refraction.

All measurements were made between 10 AM and 2 PM to limit the potential confounding influence of diurnal variations on OCT. Patients and healthy controls were asked to not use topical drops (mydriatic agent) and alcoholic or not to consume caffeinated drinks for at least 12 hours before measurements.

Charts of the participants who had a complete ophthalmologic examination including BCVA, central foveal thickness (CFT), and choroidal thickness (CT) measurements (Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany) and mf-ERG recordings (Vision Monitor, Monpack 3, Metrovision, France) were used in the study.

Best-corrected visual acuity recorded in Snellen equivalents was converted into the logarithm of the minimum angle of resolution (logMAR) for the statistical analysis.

OCT imaging

Imaging was performed after standard pupillary dilation using tropicamide 0.5% drops with the Spectralis (Heidelberg Engineering, Heidelberg, Germany). A 30°x20° 97-sections SD-OCT macular volume, a 30° enhanced- depth imaging (EDI) SD-OCT horizontal scan through the fovea the “automatic real time” averaging set at the maximal value of 100 images, a 30°x30° fundus infrared reflectance were acquired.

All scans were performed with support of the eye tracking system. Average thicknesses were calculated for macular retinal nerve fiber layer (mRNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL), outer nuclear layer (ONL), inner and outer segments of the photoreceptors (PR) and retinal pigment epithelium (RPE).

Macular volumes were quantified using manufacturer's software based on the ETDRS protocol. Three retinal volumes were centered on the foveola with radii of 0.5, 1.0 mm, and 1.5 mm. Macular volumes were divided into two regions as inner macular and outer macular. Inner macular volume was defined as the average of five measurements at foveal center and 500 µm away from the nasal, temporal, superior, and inferior to foveal center. Outer macular volume was defined as the average of four measurements at 1.500 µm away from the nasal, temporal, superior, and inferior to foveal center.

Choroidal thickness (CT) was measured manually by the same observer on enhanced-depth imaging scans as the axial distance from the RPE to the outer choroid/sclera

interface at 7 different points (from the central subfoveal point, and 500, 1.000, and 1.500 µm away from the foveal center at nasal and temporal quadrants).[19] Submacular CT measurements were divided into two regions as subfoveal and parafoveal. Subfoveal CT was defined as the average of 3 CT measurements at foveal center and 500 µm away from the nasal and temporal to foveal center. Parafoveal CT was defined as the average of 4 CT measurements at 1.000 µm and 1.500 µm away from the nasal and temporal to foveal center.

The central subretinal fluid (SRF) thickness was defined as the axial distance between the RPE and the outer aspect of photoreceptor outer segments. The vertical and horizontal SRF diameters were measured at the maximum width of the SRF in the vertical and horizontal OCT scans.

Multifocal electroretinography

Multifocal ERG (Vision Monitor, Monpack 3, Metrovision, France) was recorded according to the ISCEV guidelines.[20] Patients were light adapted for at least 15 minutes in room light, with fully dilated pupils. A liquid crystal display screen was used to produce 61 scaled hexagonal stimulus patterns (30-degree horizontal and 24-degree vertical field) with central fixation point. Luminance of bright and dark hexagons was kept at 100 cd/m^2 and <1 cd/m^2, respectively. The recording was performed in a mono-ocular manner using contact lens electrodes after anaesthetizing the cornea with topical 1% proparacaine drops, with refractive correction prescribed for near vision. The right eye was tested first, followed by the left eye each with fresh disposable corneal electrodes. The stimulus frequency was set at 17 Hz and overall duration of pseudo-random stimulation was 5 minutes.

Analysis of mfERG

The first-order mfERG responses were analyzed using color maps of amplitudes given as density and implicit times of N1, P1 and N2 wave peaks. The typical waveform of the mfERG response is a biphasic wave with an initial negative deflection followed by a positive peak. Usually, there is a second negative deflection after the positive peak. These three peaks are called N1, P1, and N2, respectively. The average responses were over a group of up to five rings from zero to 25 degrees of eccentricity relative to fixation. The analysis develops a histogram for each of the extended zones indicating the average amplitude of the N1, P1, N2 peaks.

Statistical Analysis

Data were analyzed using SPSS software (SPSS 18.0, SPSS Inc., Chicago, IL). Descriptive statistics were used for all parameters. Data were tested for normal distribution using the Kolmogorov-Smirnov test. Spearman's correlation was used to evaluate the correlations between BCVA, OCT parameters, and mfERG findings. A p value <0.05 was considered as statistically significant.

RESULTS

Overall, 31 CSC (62 eyes) patients were compared to 30 healthy (30 eyes) controls. Demographic and clinical characteristics of the CSC patients and healthy controls are shown in Table 1. There were no differences between participants in the CSC patients and control groups with regarding age or gender. Best-corrected visual acuity (logMAR) scores were significantly poorer in affected eyes of CSC patients compared to controls (p=0.01). The mean duration of symptoms in CSC subjects was 4.4±1.1 months. The mean vertical and horizontal SRF thicknesses were

Table 1. *Clinical characteristics and OCT parameters of study subject and healthy control.*

	CSC group Affected eye (n=31)	**CSC group Fellow eye (n=31)**	**Control group (n=30)**	**P value**
Age (y. mean ±SD)	48.78±8.79	48.78±8.79	49.12±9.23	0.4
Duration of symptoms. months	5.4±2.1	-	-	-
BCVA (logMAR)	0.49±0.39	0.15±0.28	0.10**±0.14**	*0.01
Central foveal thickness (CFT). µm	338.40±119.34	229.82**±38.60**	225.42**±42.30**	*< 0.0001
Subfoveal CT. µm	343.80±94.44	346.81±144.58	331.42±96.12	*0.02
Parafoveal CT. µm	237.93±137.25	242.25±175.69	228.83±85.76	*0.02
Inner macular volume. mm^3	2.44±0.39	2.36±0.14	2.34±0.34	0.4
Outer Macular volume. mm^3	6.58±1.09	6.73±1.12	6.68±1.06	0.3
Vertical diameter of SRF. µm	156.18±113.76	19.00±7.37	-	*< 0.0001
Horizontal diameter of SRF. µm	1998±1082	179.39**±65.02**	-	*< 0.0001

SD: standard deviation. BCVA: Best corrected visual acuity. IRL: Inner retinal layer. ORL: Outer retinal layer. CT: Choroid thickness. SRF: Subretinal fluid. *P value < 0.05 was considered statistically significant.

significantly higher in CSC patients compared to healthy subjects. The central foveal thickness was significantly higher in affected eyes of CSC (338.40 µm) compared to fellow eyes of CSC (229.82 µm) and healthy control (225.42 µm) ($p < 0.001$).

There was significant increase in subfoveal and parafoveal CT in both affected and fellow eyes of CSC compared to healthy subjects ($p < 0.05$) (Table 1). There was no significant difference in inner and outer macular volumes between CSC patients and healthy controls.

The mean mfERG N1, P1, and N2 amplitudes are presented in Table 2. There was significant decrease in the N1, P1, and N2 amplitudes for all rings in both affected and fellow eyes of CSC patients compared to control subjects ($p <$

Table 2. *Comparison of mfERG parameters between central serous chorioretinopathy and control subjects.*

mfERG parameters	**CSC group Affected eye (n=31)**	**CSC group Fellow eye eye (n=31)**	**Control group (n=30)**	**P value**
Amplitude N1 (Nv/deg²)				
Ring 1 (<2°)	-583.12±337.5	-891.40± 415.98	-1521.74±315.78	*<0.0001
Ring 2 (2-5°)	-503.26±226.20	-558.03±207.64	-801.97±145.97	*<0.0001
Ring 3 (5-10°)	-436.62±342.01	-458.92±274.27	-706.88±103.66	*<0.0001
Ring 4 (10-15°)	-518.03±202.79	-546.28±138.73	-677.42±104.97	*<0.0001
Ring 5 (>15°)	-554.25±148.91	-561.00±137.88	-610.45±529.78	*<0.0001
Amplitude P1 (Nv/deg²)				
Ring 1 (<2°)	999.90±527.32	1545.35±684.25	2516.57±546.64	*<0.0001
Ring 2 (2-5°)	965.50±362.78	1122.21±340.48	1542.60±327.30	*<0.0001
Ring 3 (5-10°)	1047.31±310.09	1063.96±284.11	1448.25±193.67	*<0.0001
Ring 4 (10-15°)	1111.15±280.03	1133.00±298.64	1436.22±208.51	*<0.0001
Ring 5 (>15°)	1261.46±312.61	1262.28±349.68	1458.68±686.02	*<0.0001
Amplitude N2 (Nv/deg²)				
Ring 1 (<2°)	-799.31±482.28	-1374.25±838.30	-2327.14±575.09	*<0.0001
Ring 2 (2-5°)	-749.21±366.60	-942.25±336.87	-1220.14±674.08	*<0.0001
Ring 3 (5-10°)	-861.65±297.36	-931.46±284.88	-1159.37±482.14	*<0.0001
Ring 4 (10-15°)	-1024.93±274.92	-1037.46±294.39	-1306.25±225.24	*<0.0001
Ring 5 (>15°)	-1029.93±278.46	-1173.85±374.14	-1449.37±252.81	*<0.0001
Implicit Time N1 (ms)				
Ring 1 (<2°)	27.63±5.77	27.38±2.58	26.88±1.66	*0.004
Ring 2 (2-5°)	27.32±1.34	26.74±1.63	26.28±1.30	*0.012
Ring 3 (5-10°)	26.52±1.15	25.93±1.49	25.41±1.57	*0.008
Ring 4 (10-15°)	26.12±1.11	25.97±1.15	25.31±1.19	*0.009
Ring 5 (>15°)	26.13±1.20	25.81±1.05	25.90±3.87	*0.04
Implicit Time P1 (ms)				
Ring 1 (<2°)	49.50±8.94	48.70±3.39	46.56±2.61	0.09
Ring 2 (2-5°)	46.16±1.58	45.74±1.86	45.56±1.46	0.2
Ring 3 (5-10°)	44.66±1.33	44.15±1.32	43.83±1.37	*0.02
Ring 4 (10-15°)	43.97±1.24	43.52±1.37	43.22±1.31	0.05
Ring 5 (>15°)	43.86±1.37	43.78±1.21	43.45±4.02	0.3
Implicit Time N2 (ms)				
Ring 1 (<2°)	71.23±21.76	70.32±19.33	66.12±3.56	0.05
Ring 2 (2-5°)	65.31±13.67	63.25±13.07	64.57±1.98	0.3
Ring 3 (5-10°)	62.24±12.03	61.92±1.59	61.26±1.51	0.2
Ring 4 (10-15°)	61.73±1.35	61.15±1.64	61.05±1.58	0.1
Ring 5 (>15°)	61.29±1.55	60.88±1.46	60.78±1.54	0.4

mfERG = multifocal electroretinography. *P value < 0.05 was considered statistically significant.

0.001) (Figure 1-3). There was significant decrease in N1, P1, and N2 amplitudes only for Ring 1 in affected eyes of CSC patients compared to fellow eyes. There was also significant increase in N1 implicit times for all of five rings in both affected and fellow eyes of CSC patients compared to healthy controls ($p < 0.05$). There was no difference in the mean N2 implicit times for all rings between CSC and control subjects. The mean mfERG N1, P1, and N2 implicit

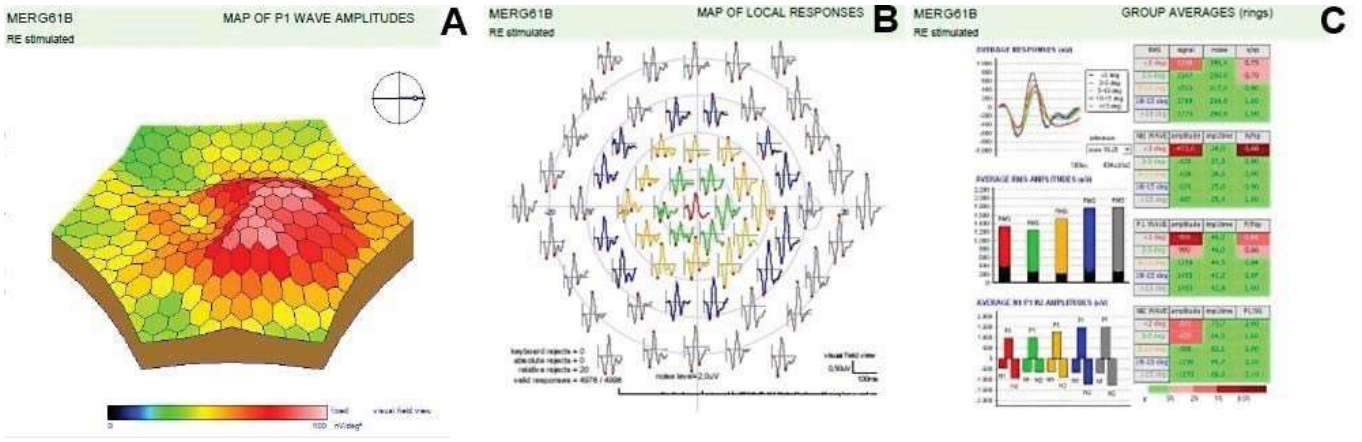

Figure 1: *Example of mfERG recordingsand macular OCT scan of a CSC patient's affected eye. (A) Response density three-dimensional plot at the central macula. (B) first-order trace array. (C) average reduced amplitudes and increased implicit times of rings.*

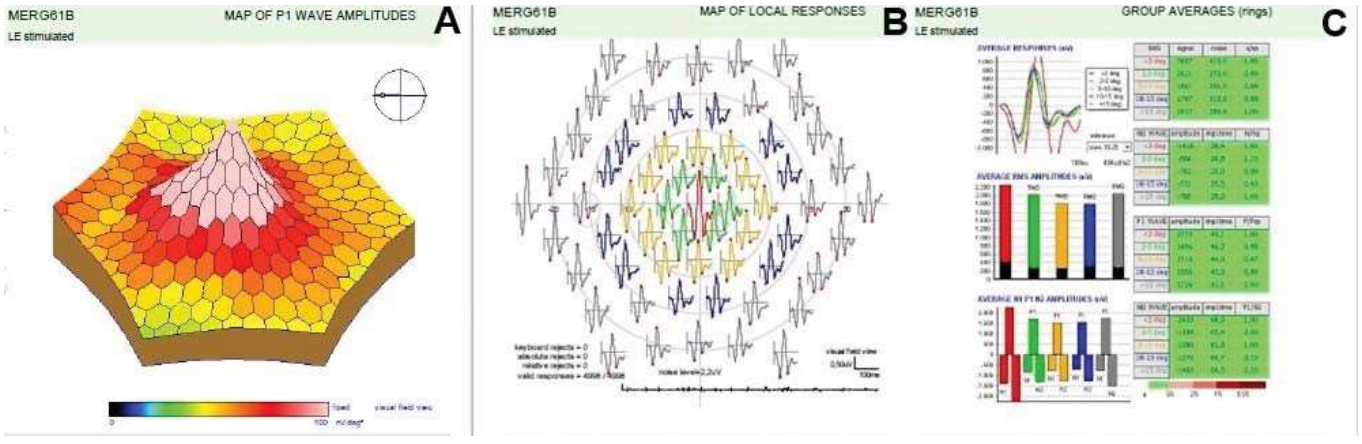

Figure 2: *Example of mfERG recordings and macular OCT scan of a CSC patient's fellow eye. (A) Response density three-dimensional plot at the central macula. (B) first-order trace array. (C) average reduced amplitudes and increased implicit times of rings.*

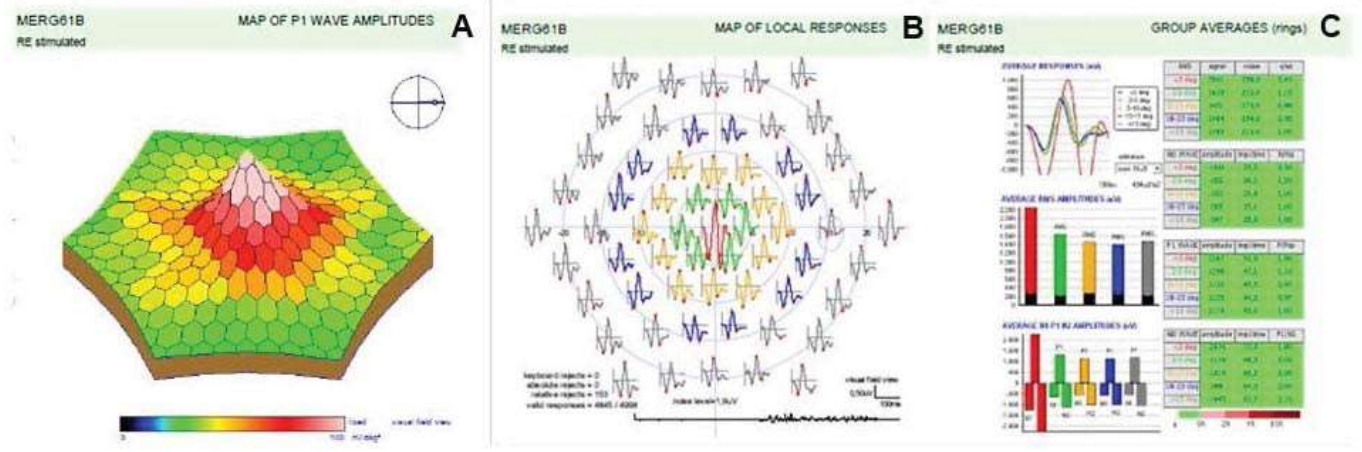

Figure 3. *Example of mfERG recordings and macular OCT scan of a normal subject. (A) Response density three-dimensional plot at the central macula. (B) first-order trace array. (C) average amplitudes and implicit times of rings.*

times for all rings were the same for affected and fellow eyes of CSC patients.

Spearman's correlation analyses were performed to evaluate the association between BCVA, OCT parameters and mfERG findings. The BCVA was significantly correlated with N1, P1, and N2 amplitudes for Ring 1 (r = 0.808; p = 0.003, r= -0.545; p = 0.03, r = -0.551; p = 0.03, respectively). No significant correlation was found between BCVA and OCT parameters (CFT, subfoveal and parafoveal CT, vertical and horizontal diameters of SRF, inner and outer macular volumes). In addition, we found moderate correlations between inner macular volumes and N1, P1, and N2 implicit times of Rings 4 and 5. The horizontal diameter of SRF was moderately correlated with P1 implicit times of Ring 5 and N2 implicit times of Ring 2.

DISCUSSION

Our study revealed significant correlations between BCVA (logMAR) and mfERG amplitudes in CSC patients. Furthermore, no significant correlations were found between BCVA and OCT parameters (CFT, subfoveal and parafoveal CT, vertical and horizontal diameters of SRF, inner and outer macular volumes).

The multifocal ERG (mfERG) was established to contribute a topographical assessment of retinal electrophysiological response.[20] The principal scientific use of the mfERG is to recognize spatial variations in mfERG activities that pinpoint retinal damage to distinct zones of retina: the macula, paramacula, or distinct peripheral regions[20]. Decreased mfERG response amplitudes with delayed latencies in CSC patients has been demonstrated but only few attempted to assess the correlation between functional and structural changes.[16,18] Moschos et al. evaluated mfERG and OCT findings in unilateral CSC patients at presentation and after resolution of disease. They performed automatic central retinal thickness measurement using the OCT software and did not evaluate correlation between the OCT and mfERG parameters. In another OCT study, manual measurements were performed for various OCT parameters, including central retinal thickness, central SRF thickness and diameter of SRF, in CSC patients.[18] They concluded that they could perform more accurate thickness measurements, enabling to correlate mfERG and the OCT parameters by manual OCT measurement method. We also performed manual OCT measurements according to their suggestions.

Choroidal hyper-permeability and choroidal thickening play crucial role in the pathogenesis of CSC, but their relationship is still controversy. We found the statistically significant increase in subfoveal and parafoveal CT in both affected and fellow eyes of CSC compared to healthy subjects. Choroidal hyper-permeability has been reported in >90% of affected eyes of patients with CSC and 62–73% of unaffected fellow eyes in the literature.[21-23] Maruko *et al.* reported that the choroid was thicker in fellow eyes of patients with CSC with choroidal hyperper-meability than those without choroidal hyper-permeability.[22] Kim *et al.* found that choroidal vascular dilatation was present in 70% of CSC eyes and 60% of unaffected fellow eyes.[21] They suggested that choroidal dilatation and hyper-permeability may be different phases of the disease.[21] There was significant decrease in the N1, P1, and N2 amplitudes for all rings in both affected and fellow eyes of CSC patients compared to control subjects. Although patients did not suffer decreased vision from their fellow eyes, both eyes had decreased mfERG amplitudes.

In our study, we found significant correlations between BCVA (logMAR) and mfERG amplitudes in CSC patients. However, our results revealed that BCVA had no correlation with any of the OCT parameters. These results are compatible with previous study of Yip et al. that evaluated the correlation between functional and anatomical findings in CSC patients.[18]

We also found that there was no significant correlation between mfERG amplitudes and OCT parameters. The lack of correlation between mfERG amplitudes and OCT parameters proposed that the amount of SRF did not appear to have remarkable impact on the mfERG amplitudes. This might be due to other factors which can influence macular function including chronicity of CSC, the content of SRF, and any preceding photoreceptor loss.[18]

Furthermore, our study revealed significant correlations between N1, P1, and N2 implicit times of the paracentral rings (Rings 4 and 5) with the inner macular volumes. In addition, the horizontal diameter of SRF was also found moderately significantly correlated with P1 latencies of Ring 5 and N2 latencies of Ring 2. Yip et al found significant correlation between mfERG N1 and P1 latencies of the paracentral rings and the central SRF thickness, diameters of the SRF, and macular volume. Their findings suggested that delayed electrical responses from the photoreceptors and the inner retinal layers are proportional to the amount of SRF in CSC.[18]

Our study has several limitations, particularly due to the small number of CSC patients and cross-sectional assessment of OCT and mfERG findings. A longitudinal study should be more proper for evaluating the correlations with disease severity and duration.

In conclusion, our study showed significant correlations between BCVA (logMAR) and mfERG amplitudes in CSC patients. Furthermore, no significant correlations were found between BCVA and various OCT parameters. Therefore, mfERG findings seem a more sensitive prognostic factor for visual acuity compared with OCT. Our findings indicate that mfERG and OCT could both serve as noninvasive tools for functional and anatomical assessments of CSC patients.

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