Ophthalmic Research

Ophthalmic Res , DOI: 10.1159/000530276
Received: January 10, 2023
Accepted: March 10, 2023
Published online: March 24, 2023

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Jeon GS, Chang IB, Ma DJ, Cho IH, Hong IH

ISSN: 0030-3747 (Print), eISSN: 1423-0259 (Online)
https://www.karger.com/ORE
Ophthalmic Research

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*Research Article*

***Multifocal electroretinography changes over 12 months after resolution of central serous chorioretinopathy: prospective observational study***

Gang Seok Jeon[a], In Boem Chang[b], Dae Joong Ma[c], In Hwan Cho[d], In Hwan Hong[e]

[a] Dasan Samsung Bright Eye Clinic, Gyeonggi-do, Korea
[b] Seoul On Eye Clinic, Seoul, Korea
[c] Department of Ophthalmology, Gangnam Sacred Heart Hospital, Hallym University Medical Center, Seoul, Korea
[d] Department of Ophthalmology, College of Medicine, Soonchunhyang University, Cheonan-si, Chungcheongnam-do, South Korea
[e] Department of Ophthalmology, Dongtan Sacred Heart Hospital, Hallym University Medical Center, Hwaseong-si, Gyeonggi-do, Korea

Short title: mfERG changes after resolution of CSC

Corresponding Author:
In Hwan Hong, MD
Department of Ophthalmology
Dongtan Sacred Heart Hospital, Hallym University Medical Center
Hwaseong-si, Gyeonggi-do, South Korea
Tel: 82-31-8086-2660
Fax: 82-31-8086-2774
Email: loperter@hanmail.net

Number of Tables: 3
Number of Figures: 2
Word count: 3282

Key words: central serous chorioretinopathy; multifocal electroretinography; residual functional deficit

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**Abstract**

**Introduction:** This prospective observational study aimed to evaluate the changes in retinal function after the anatomical resolution of central serous chorioretinopathy by multifocal electroretinography.

**Methods:** Thirty-two eyes of 32 patients with unilaterally resolved central serous chorioretinopathy were prospectively studied. Serial multifocal electroretinography examinations were performed at the initial visit for active central serous chorioretinopathy, the time of anatomical resolution (resolved central serous chorioretinopathy), and

3, 6, and 12 months after resolution. The peak amplitudes of the first kernel responses were analysed and compared with those in 27 age-matched normal controls.
**Results:** Compared with controls, the N1 amplitudes of rings 1–4 and P1 amplitudes of rings 1–3 showed statistically significant reductions at 12 months after the resolution of central serous chorioretinopathy ($p$<0.05). The multifocal electroretinography amplitude substantially increased at the time of resolution and gradually improved until three months after the resolution of central serous chorioretinopathy.
**Conclusion:** Serial examinations with multifocal electroretinography showed that retinal responses increased mostly after the resolution of central serous chorioretinopathy, and this improvement slowly progressed until three months; however, the multifocal electroretinography amplitudes remained statistically reduced 12 months after the anatomical resolution of central serous chorioretinopathy, indicating the residual functional deficits detected by multifocal electroretinography.

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**Introduction**

Central serous chorioretinopathy (CSC) is an idiopathic chorioretinal disease that affects the central vision due to the serous detachment of the neurosensory retina and/or retinal pigment epithelial (RPE) layer at the posterior pole.[1] The underlying pathogenesis of CSC is not completely understood; however, it is known to be more predominant in middle-aged men and is associated with psychological stress.[2, 3] Patients with CSC often experience a sudden onset of moderate central visual disturbance and other visual symptoms associated with the disorder, such as metamorphopsia, micropsia, central scotoma, and chromatopsia. [3] The initial episode of CSC is usually a self-limiting process with resolution of retinal detachment and recovery of vision occurring within 1–4 months. [4] Visual acuity (VA) reflects the resolution of any disease that affects the macula, and its measurement is the primary method for the evaluation of macular function.[5] However, its usefulness is limited if the changes in VA are minimal or if the patient complains of visual disturbance with 6/6 vision. Even if patients achieve 6/6 vision after the resolution of macular detachment in CSC, they may still present with visual symptoms, such as decreased contrast sensitivity and metamorphopsia.[1] Thus, alternative methods are required for the functional assessment of CSC. Multifocal electroretinography (mfERG) is an objective modality that allows functional assessment of the retina by simultaneous measurement of the focal electroretinographic responses at different retinal locations. [6, 7] The topographic visual function can be objectively assessed through the mfERG examination. Localized retinal dysfunction has been demonstrated using mfERG in various retinal diseases, including CSC. The use of mfERG in patients with CSC can demonstrate abnormal retinal function in active cases, document the disease course, and evaluate the effect of treatment. [8, 9] However, most previous studies on mfERG in patients with CSC have primarily focused on the acute phase of CSC. Notably, only a few comparable studies investigating the serial changes in the mfERG results after the complete resolution of CSC exist.

This study was designed to prospectively evaluate patients with CSC using mfERG to document the changes in localized retinal response after disease resolution. This study aimed to investigate the pattern of the localized retinal response recovery after the resolution of CSC and whether retinal dysfunction is restored to the normal range in patients with resolved CSC.

**Materials and Methods**

This prospective observational study was approved by the Institutional Review Board of Dongtan Sacred Heart Hospital. Informed consent was obtained from all participants and the study was conducted in accordance with the tenets of the Declaration of Helsinki.

The study included cases of anatomically resolved CSC from the Retina Department of Dongtan Sacred Heart Hospital between December 2018 and January 2022. Each patient had a documented acute episode of CSC, and the patient was enrolled in the study if there was resolution of CSC at the follow-up examination. Anatomical resolution of CSC was defined as the absence of subretinal fluid (SRF) in the macular area on the optical coherence tomography (OCT) image. Only patients with unilateral CSC were included, whereas those diagnosed with recurrent CSC were excluded. Patients who were >55 years or <19 years, those with an underlying disease, and those with a history of ocular surgery were excluded from the study. Eyes with other retinal disorders associated with serous retinal fluid, media opacity, extra or juxtafoveal CSC not involving fovea, or high myopia (> 6 diopters) were also excluded. Twenty-seven eyes of 27 age-matched individuals were used as controls.

A complete ophthalmic examination of all patients with CSC who visited the outpatient clinic for the first time was performed in this study. Complete ophthalmic examinations included best-corrected visual acuity (BCVA) measured using the Snellen chart, intraocular pressure (IOP) measurement, slit-lamp examination, fundus photography, fluorescein angiography (FAG), OCT, and mfERG. All patients underwent ophthalmic examinations at each follow-up visit, except for FAG and mfERG recording. A spectral-domain (SD) OCT image was obtained using Spectralis OCT (Spectralis; Heidelberg Engineering, Heidelberg, Germany), with a 25-line horizontal raster scan covering 20° x 20° centred on the fovea. The automatic real-time function with the eye tracking system in this instrument was used to obtain multiple frames of the same scanning location, and these data were averaged to improve the signal-to-noise ratio. Patients with a serous retinal detachment (SRD) of > 20° × 20° through the centre of the fovea on the OCT image were excluded.

The patients were evaluated at the initial visit and monthly until the resolution of SRF. The patients were enrolled in this study after achieving complete anatomical resolution. Treatment, including intravitreal anti-vascular endothelial growth factor (VEGF), focal laser photocoagulation, and photodynamic treatment (PDT), was attempted if SRF persisted for 3 months after the initial visit.[10] Focal laser treatment was attempted first if the leaking point was located at least 300 microns from the fovea;[11] otherwise, intravitreal anti-VEGF treatment was attempted first. If SRF persisted for a month after focal laser treatment, intravitreal anti-VEGF injection was administered; if SRF persisted for two months after intravitreal injection, PDT was attempted. Serial mfERG examination was performed at the time of anatomical resolution (baseline) and at 3, 6, and 12 months after anatomical resolution. Patients with recurrence during the study period in either diseased or normal fellow eyes were excluded from the study.

The mfERG recordings were obtained using Metrovision Monpack One mfERG (Pérenchies, France). The filter and gain settings were uniformly applied for all patients tested in a given laboratory study. The guidelines of the International Society of Clinical Electrophysiology of Vision (ISCEV) were used for comparison.[12, 13] Multiple retinal areas were stimulated using a stimulus array consisting of 61 hexagons made of a black and white pattern within a field diameter of 40°–50°, at a viewing distance of 33 cm. The gain of the amplifier should produce recognisable signals without saturation. A gain of 100,000 was used in the present study. Filter settings, even within these ranges, can markedly influence the response waveform. Thus, the same filter settings must be used for all patients. A filter range of 10–300 Hz was used in the present study. The stimulus consisted of an array of 61-scaled hexagon-based patterns presented on a liquid crystal display (LCD) monitor with a frame frequency of 75 Hz. The luminance of the stimulus for white was 200 cd/$m^2$, and the contrast was 99.3%. The room was illuminated with dim room lights that ideally produce illumination close to that of the stimulus screen. Before mfERG testing, the pupils were fully dilated using eye drops containing 1% tropicamide and 2.5% phenylephrine hydrochloride, and all patients adapted to ordinary room illumination for 15 min. After instilling proparacaine hydrochloride 0.5% drops for topical anaesthesia, the contact lens electrode (ERG jet, Fabrinal SA) was placed on the cornea. The reference electrodes were placed near each ipsilateral orbital rim, with the ground electrode placed on the vertex. During mfERG testing, an experienced technician monitored the fixation through careful direct observation to assess the stability of fixation. The inspector observed the amount of noise during the recording. The examiner also confirmed the proper visualization of the fixation target by the patient. The responses of the first negative peak (N1) and the first positive peak (P1) for each individual ring were automatically measured in real-time using a group of up to five rings. This study analysed the amplitudes of N1 and P1 in five rings grouped from zones 1 to 5.

This study analysed the amplitudes of N1 and P1 in five rings grouped from zones 1 to 5. The BCVA, OCT value, and N1 and P1 amplitudes at the time of anatomical resolution (resolved CSC) were compared with those at the first visit for acute CSC using the paired t-test. Serial statistical analysis of the mfERG response from baseline to 12 months was performed using a paired t-test. The mfERG results at 12 months after the resolution of CSC were compared with the mfERG results from controls using the Mann–Whitney *U test*. A post hoc analysis using Mann–Whitney *U test* was also conducted to identify the differences between patients who did and did not receive treatment. SPSS 19.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses, and statistical significance was set at p-value <0.05.

**RESULTS**

Thirty-two eyes of 32 patients with unilaterally resolved CSC were included and serially recorded using mfERG in this study (Table 1). There were 28 men and four women with ages ranging from 36 to 55 years (mean age, 47 ± 6.24 years). The same number of right and left eyes were examined. The mean age of the control subjects was 44.80 ± 4.43 (range, 35–51) years, and 24/27 control subjects were men, and three were women. The average time for the anatomical resolution of CSC was 3.75 months. Twelve patients received one treatment option, including intravitreal anti-VEGF antibody injection (three patients) and focal laser treatment (nine patients). One patient received both treatments; no patient received photodynamic therapy (PDT). As the central macular thickness (CMT) decreased from 512.09 ± 121.22 $\mu$m to 272.19 ± 27.44 $\mu$m ($p$<0.001), the average BCVA of the patient improved from 0.16 ± 0.17 logMAR to 0.08 ± 0.10 logMAR ($p$<0.001).

Figure 1 shows the mean mfERG N1 (shown in Fig. 1A) and P1 (shown in Fig. 1B) amplitudes of patients with CSC at 12 months compared with that of controls. Compared with that of controls, the N1 amplitudes of rings 1–4 and P1 amplitudes of rings 1–3 showed statistically significant reductions ($p$<0.05). The changes in VA and mfERG response amplitudes are shown in Figure 2. The N1 response is shown in Figure 2A and the P1 response is shown in Figure 2B. During the active state, the VA and mfERG amplitudes were low; however, these values increased significantly after the resolution of SRF. Significant improvement in VA was observed from the acute stage of CSC to the resolution phase. The amplitude of mfERG also increased significantly after the resolution of CSC in rings 1–3 and 4 of N1 response and rings 1–4 of P1 response. The amplitude of ring 1 was significantly improved in both N1 and P1 response from the time of resolution to 3 months after the resolution of CSC. There was no significant change in any of the eccentric rings after three months.

The comparison of the non-treatment and treatment groups showed no significant difference in age; however, the duration of SRF was significantly longer in the treatment group (Table 2). There was no significant difference between the two groups in terms of VA and CMT at any time point; however, during the active phase of the disease, the visual acuity of the non-treatment group was slightly better than that of the treatment group, and the CMT of the non-treatment group was slightly lower than that of the treated group. Table 3 shows the comparison between the two groups in terms of mfERG amplitude. The N1 responses of ring 1 and ring 4 were significantly lower in the treated group than that in the non-treatment group in the active phase, and the N1 response of rings 1, 2, and 4 and P1 response of rings 1–3 were significantly reduced in the treatment group than that in the non-treatment group at 12 months after the resolution of CSC.

**DISCUSSION**

Even with total recovery of visual acuity after the anatomical resolution of CSC, patients experienced residual disturbances in their vision [3]. Based on this, several researchers postulated that there may be a subtle or localized macular dysfunction. Thus, they investigated the function of the macula using microperimetry (MP), pattern electroretinogram (PERG), and mfERG, which can analyse the macula by dividing the location. [14, 2, 3, 15, 16] Numerous studies using MP reported lower retinal sensitivity in the central macular area in cases with resolved CSC even with good vision compared with normal eyes. However, no mfERG studies have been conducted over a 12-month observation period. This study prospectively evaluated patients with unilateral resolved CSC using mfERG and found that the mfERG amplitude substantially increased at the time of resolution and gradually improved until three

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months. Although there was a significant improvement in the mfERG amplitude after the anatomical resolution of CSC, the mfERG response did not improve to the normal range even 12 months after the resolution of CSC. Chappelow et al. conducted the first study that evaluated retinal function using mfERG in five patients with resolved CSC. [14] The macular ERG amplitudes of the five patients improved after the resolution of the disease but remained borderline or subnormal. Residual macular dysfunctions were also found beyond the detachment area of the affected eyes and fellow normal eyes. The mfERG amplitude of rings 1–4 showed results similar to that of a previous study. However, inconsistent with the results of a previous study, mfERG dysfunction of the most peripheral areas (ring 5) recovered to the normal range with the resolution of CSC, and there was no statistically significant difference with control eyes at 12 months after resolution. Although this study did not measure the size of the CSC, rings 1–3 were the main location for SRD, as this study excluded the patient whose SRF extended beyond 20° x 20° through the centre of the fovea on the OCT image; however, field diameter of the mfERG examination used in this study was 40° to 50°. Thus, there was no SRF in the most peripheral area of the 61 hexagons (ring 5) and the amplitude of this non-detachment area was reduced in the acute phase of CSC but recovered to the normal range as soon as CSC was resolved and maintained until 12 months of the follow-up period.

Previously, we evaluated patients with acute phase CSC using enhanced depth imaging (EDI) – OCT and mfERG. [17] In this study, we found that the retinal response from mfERG was impaired in the area beyond the serous retinal detachment, and the degree of SRF was not associated with mfERG dysfunction, only subfoveal choroidal thickness was associated with mfERG dysfunction. Thus, the impaired mfERG amplitude of ring 5 in the acute phase and its recovery in the resolution phase may not be associated with SRF; however, it is presumed to be associated with a broad range of choroidal dysfunction and its restoration.

In this study, the retinal response was sequentially recorded by mfERG after the resolution of SRF. The results from this study showed that the mfERG amplitude increased mostly during reattachment, which slowly progressed until three months after the complete resolution of SRF. Since mfERG reflects the bioelectric response derived largely from cone-related preganglionic elements, including photoreceptors and bipolar cells. [18] The mfERG results from this research suggest that the physiology of these preganglionic components improves after the regulation of cellular connections of the remaining photoreceptors and retinal pigment epithelium (RPE). However, this recovery was not observed three months after the resolution of CSC, and the mfERG amplitudes in the previous detachment area did not regain their normal range. Persistent functional deficits after the resolution of CSC were observed in mfERG as well as other functional tests, including MP, optical quality analysis system, and different types of ERGs, [2, 3, 19, 15] suggesting remaining damage in the retinal tissue. Anatomically, Ooto et al. examined eyes with CSC showing spontaneous resolution of SRF using an adaptive optics scanning laser ophthalmoscopy and reported loss of cone photoreceptors in patients whose visual acuity was 6/6 or better.[20] These findings explain the complaints of visual disturbance even after recovering normal visual acuity in the quiescent phase of CSC.

On comparing the amplitude of mfERG between the treatment and non-treatment groups, despite no difference in VA and CMT between the two groups 12 months after the resolution of CSC, the N1 and P1 response of the treatment group was impaired compared with that of the non-treatment group. The amplitudes of rings 1 and 2 in the treatment group were significantly decreased than that of the non-treatment group in the N1 and P1 responses. Although not statistically significant, the non-treatment group had lower VA and higher CMT than the non-treatment group in the active phase of the disease. Moreover, the mfERG amplitude of the treatment group in the active phase was also lower than that of the non-treatment group. The mfERG results at 12 months after the resolution showed that the overall response of the treatment group was lower than that of the non-treatment group, which appears to reflect the states during the active phase of the disease; however, compared with the active phase, the differences between the amplitudes of rings 1 and 2 in the two groups were significantly increased at 12 months after the resolution. As this study included patients with foveal CSC, rings 1 and 2 can be considered as the area of previous SRD and the macula of the patients in the treatment group was detached significantly longer than that of those in the non-treatment group, which may have caused more damage to the photoreceptor layer from SRF accumulation. Therefore, a recent study suggested early treatment to minimize irreversible damage, resulting in better vision and

contrast sensitivity. [21] Interestingly, photoreceptor damage, detected only by mfERG, did not make a significant difference in visual acuity.

This study has some limitations. First, the observational prospective study design made it inherently difficult to rule out bias and control confounding factors. Second, this study did not analyse the implicit time. In previous studies with five cases of resolved CSC,[14, 22] the implicit time of mfERG was found to have recovered to within the normal range as soon as CSC resolved, but the amplitude of mfERG did not reach the normal range. According to preliminary studies, this study was designed to analyse the amplitude of mfERG, which can reach the normal range 12 months after the resolution of CSC. However, a previous study that used focal macular ERG in patients with CSC reported that implicit time recovery precedes amplitude recovery. [23] Thus, further serial analysis of the implicit time is needed to understand the change in macular dysfunction in patients with resolved CSC. Another limitation of this study is the relatively small number of patients receiving treatment as well as the limited number of treatments received. Previous studies have reported that different types of treatment rendered different results in the functional examination,[23-25] which means that different types of treatment can lead to different mfERG outcomes. However, there are limitations to revealing the difference in the results of mfERG according to the type of treatment due to the insufficient number of patients and types of treatment. Nonetheless, this is the first study to sequentially analyse the results of mfERG in a relatively large number of patients with resolved CSC. Several previous studies have investigated the functional and anatomical changes in patients with resolved CSC and suspected damage in the photoreceptor layer. The authors hope to use various technologies to learn more regarding photoceptor cell damage and reveal that the damaged photoceptor cell is associated with the persistent deficit in the mfERG amplitude in the future.

In conclusion, this study showed that mfERG is an important tool for the functional and electrophysiological assessment of CSC, as it reveals the presence of residual deficits 12 months after the anatomical resolution of CSC. From serial evaluation with mfERG, it was also found that functional recovery continued for up to three months after achieving complete resolution, and the degree of residual deficit may be dependent on the duration of SRD. Persistent abnormalities in mfERG explain why patients have qualitative visual complications even after the complete resolution of SRF.

## Statements


### Acknowledgments

The authors have no acknowledgment to declare.


### Statement of Ethics

The study was approved by the institutional review board/ethics committee of Dongtan Sacred Heart Hospital (IRB no.HDT 2018-12-006). All procedures performed involving human participants were conducted in accordance with the ethical standards of the institutional and/or national research committee, as well as the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all individual participants included in the study.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.


### Funding Sources

The authors have no funding source to declare.


### Author contributions

In Hwan Hong and In Boem Chang designed and conducted the study.

Gang Seok Jeon collected the data.

In Hwan Cho analysed and interpreted the data.

Dae Joong Ma revised the paper.

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In Boem Chang, Gang Seok Jeon, Dae Joong Ma, In Hwan Cho and In Hwan Hong prepared, reviewed, revised and approved the manuscript.

**Data Availability Statement**

Data is not publicly available due to ethical reasons. Further enquiries can be directed to the corresponding author.

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**FIGURE LEGENDS**

Fig. 1. Box and whisker plots with individual values of the mfERG amplitudes. A. The first-order mfERG N1 response amplitudes of five concentric rings. B. The first-order mfERG P1 response amplitudes of five concentric rings.

Fig. 2. The mean changes in visual acuity (VA, logMAR) and changes in mfERG amplitude over the 12-month follow-up period. A. VA and N1 response of five concentric rings. B. VA and P1 response of five concentric rings.

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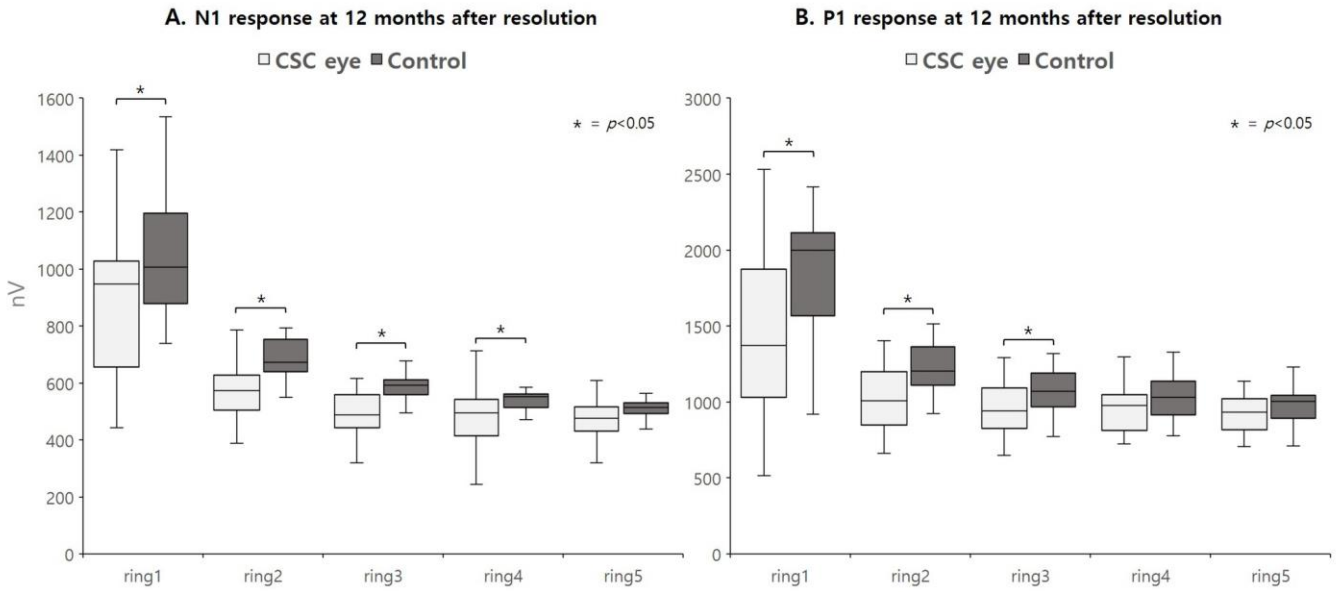


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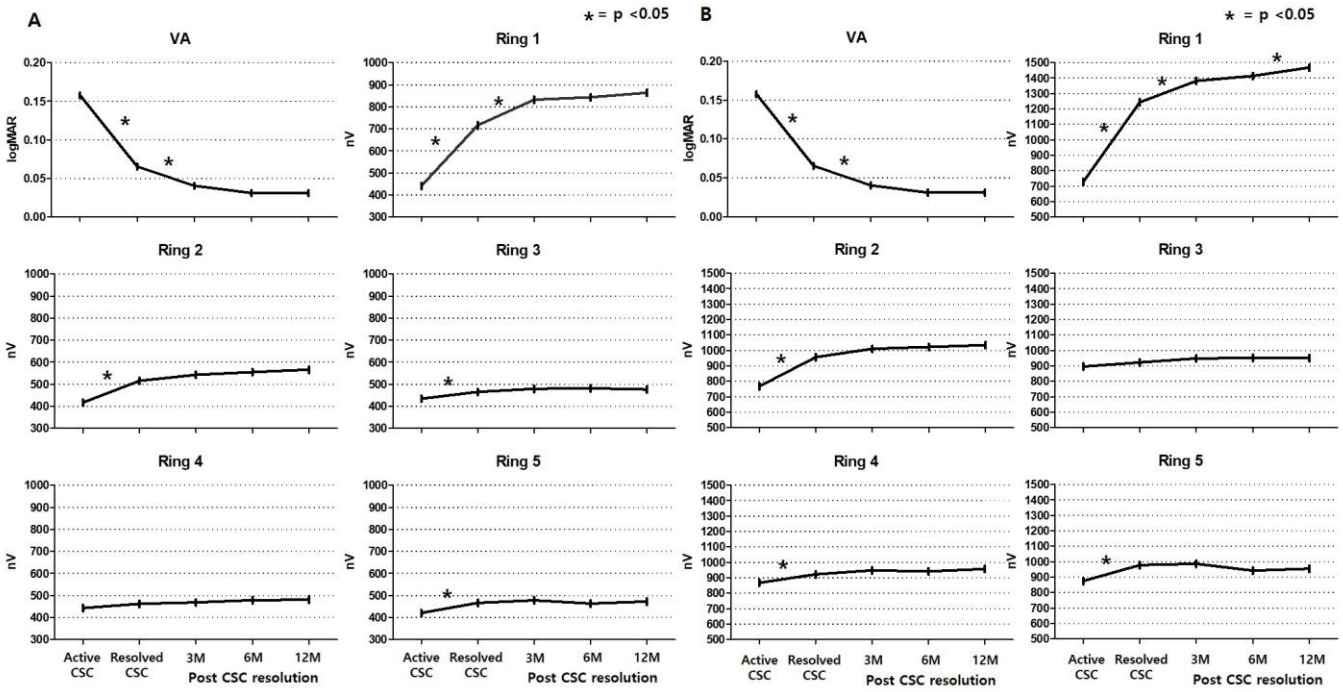


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TABLE 1. Clinical characteristics of patients in the study

| Characteristics | | | |
|---|---|---|---|
| Number of eyes/patients | 32 eyes/32 patients | | |
| Sex (male/female) | 29/4 | | |
| Age (years) | 47.16 ± 6.24 | | |
| Laterality (Right/Left) | 11/11 | | |
| Period to disease resolution (months) | 3.75 ± 1.87 | | |
| | Acute CSC | Resolved CSC | *P* value* |
| Visual acuity (logMAR) | 0.16 ± 0.17 | 0.08 ± 0.10 | <0.0001 |
| Central macular thickness (㎛) | 512.09 ± 121.22 | 272.19 ± 27.44 | <0.0001 |

*Paired t-test

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Table 2. Comparison of clinical characteristics between the group with non-treatment and the group with treatment.

| Characteristics | Non-treatment (19 patients) | Treatment (13 patients) | *P* value* |
|---|---|---|---|
| Age (years) | 46.16 ± 6.32 | 49.38 ± 7.42 | 0.254 |
| BCVA (logMAR) at active CSC | 0.13 ± 0.15 | 0.19 ± 0.18 | 0.343 |
| CMT (㎛) at active CSC | 505.0 ± 115.82 | 522.46 ± 132.82 | 0.65 |
| Time to resolution (months) | 2.58 ± 0.9 | 5.46 ± 1.56 | <0.001 |
| BCVA (logMAR) at resolved CSC | 0.06 ± 0.07 | 0.07 ± 0.07 | 0.623 |
| CMT (㎛) at resolved CSC | 267.84 ± 29.69 | 278.54 ± 23.45 | 0.209 |
| BCVA (logMAR) at 12 months post CSC resolution | 0.03 ± 0.04 | 0.03 ± 0.05 | 0.677 |
| CMT (㎛) at 12 months post CSC resolution | 264.56 ± 22.47 | 268.47 ± 23.34 | 0.662 |

BCVA = best corrected visual acuity; CSC = central serous chorioretinopathy; CMT=central macular thickness,

*Mann–Whitney U-test

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Table 3. Comparison of multifocal electroretinogram parameters between the group with non-treatment and the group with treatment.

| mfERG parameters at active CSC | Non-treatment (19 patients) | Treatment (13 patients) | *P* value* | mfERG parameters at 12 months post resolution | Non-treatment (19 patients) | Treatment (13 patients) | *P* value* |
|---|---|---|---|---|---|---|---|
| N1 amplitude | | | | N1 amplitude | | | |
| Ring 1 | 509.00 ± 343.02 | 343.02 ± 130.27 | 0.014 | Ring 1 | 989.26 ± 172.65 | 679.92 ± 162.29 | <0.001 |
| Ring 2 | 436.58 ± 147.93 | 388.69 ± 88.40 | 0.570 | Ring 2 | 606.84 ± 93.05 | 507.62 ± 78.38 | 0.006 |
| Ring 3 | 462.47 ± 125.51 | 393.69 ± 86.13 | 0.147 | Ring 3 | 493.47 ± 124.85 | 451.38 ± 84.50 | 0.054 |
| Ring 4 | 474.16 ± 64.70 | 398.08 ± 57.60 | 0.003 | Ring 4 | 521.47 ± 83.93 | 422.08 ± 77.79 | 0.001 |
| Ring 5 | 433.32 ± 68.91 | 402.92 ± 77.19 | 0.254 | Ring 5 | 483.68 ± 68.07 | 457.08 ± 75.01 | 0.383 |
| P1 amplitude | | | | P1 amplitude | | | |
| Ring 1 | 796.26 ± 258.10 | 629.54 ± 163.19 | 0.084 | Ring 1 | 1695.11 ± 507.80 | 1137.77 ± 310.96 | 0.001 |
| Ring 2 | 809.05 ± 159.94 | 708.60 ± 132.27 | 0.092 | Ring 2 | 1129.63 ±176.41 | 898.08 ± 169.51 | 0.001 |
| Ring 3 | 917.90 ± 177.08 | 863.85 ± 111.02 | 0.287 | Ring 3 | 1007.21 ± 157.50 | 870.08 ± 135.17 | 0.011 |
| Ring 4 | 881.16 ± 156.21 | 849.23 ± 120.02 | 0.495 | Ring 4 | 991.58 ± 131.71 | 893.54 ± 132.15 | 0.059 |
| Ring 5 | 874.00 ± 148.50 | 877.31 ± 141.08 | 0.448 | Ring 5 | 961.11 ± 108.79 | 891.31 ± 136.13 | 0.092 |

mfERG = multifocal electroretinography, *Mann-Whitney U test

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