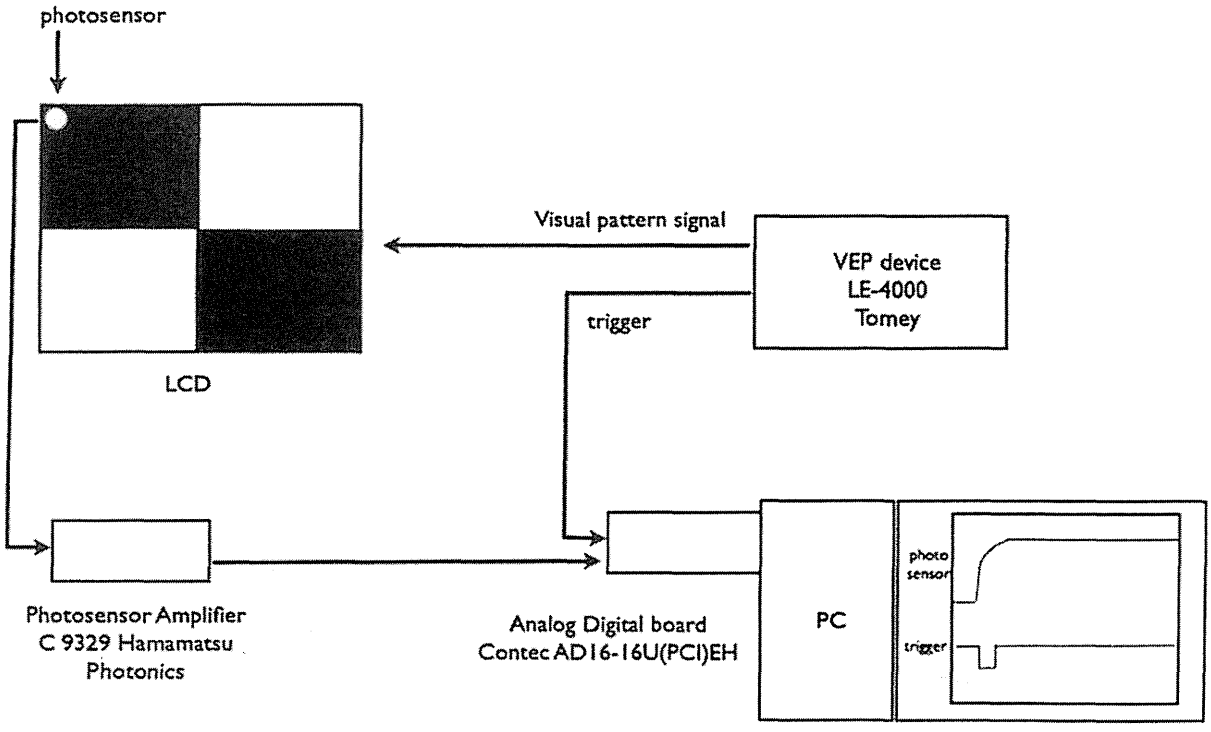

Fig. 1 System used for measuring the luminance changes of a single check

The LCD has an inherent difficulty in increasing the luminance rapidly because it takes several milliseconds for the crystal molecules to become aligned to permit light to pass through the polarizing filter of the LCD screen (http://www.sharp.co.jp/products/lcd/tech/s2_1.html, Fig. 1) [2, 3]. Some investigators [4–6] and our earlier results [7] found that the latency of the VEPs elicited by LCD screens was longer than that with CRT screens. The delay was believed to be related to the total temporal differences between the signal input to the LCD and radiometric output that is caused by both the response time and the input lag. It is well known [7] that the time course of the luminance change of the LCD screen was not symmetrical when switching from black-to-white and from white-to-black. This produced a transient change in the mean luminance of the entire display which could possibly elicit a flash VEP. This prompted us to evaluate this unwanted transient change in luminance and to minimize the flash VEP component by reducing the contrast luminance of the checkerboard pattern.

The purpose of this study was to determine the luminance changes of the LCD as a stimulator for eliciting p-VEPs and to investigate potential artifacts when an LCD screen is used to elicit p-VEPs.

Subjects and methods

Subjects

p-VEPs were recorded from 29 eyes of 29 healthy volunteers who did not have any ocular diseases except for refractive errors. There were 10 men and 19 women, and their mean ± standard deviation age was 24.2 ± 6.5 years with a range from 21 to 46 years. The procedures used conformed to the tenets of the Declaration of Helsinki. The study was a prospective study with approval of the Ethics Committee of the Teikyo University (Study ID Number: 10-075). Informed consent was obtained from all participants to participate in the research.

p-VEP recordings

Subjects were preadapted to the room lighting, and all recordings were performed under room lights with a illuminance of about 104 lux. A small black fixation point was positioned at one corner of four checks in the center of the stimulus display, and the subjects were instructed to fixate the point and to try not to blink. The

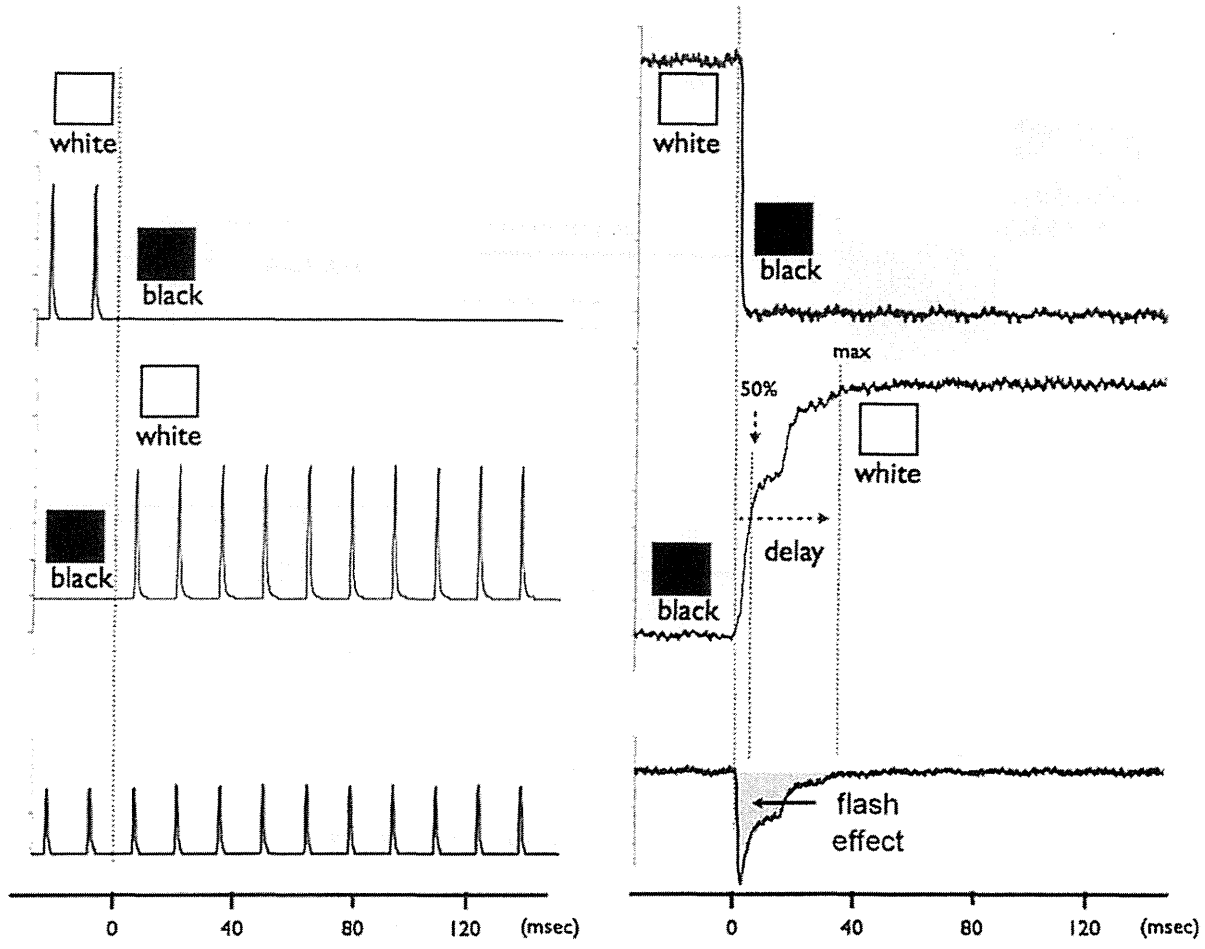

Fig. 2 Luminance changes of cathode-ray tube (CRT) screen in *left column* and conventional 60 Hz liquid crystal display (LCD) screen in the *right column*. In both columns, the *top figure* shows the changes of the checkerboard luminance from white-to-black; the *middle figure* shows the changes in luminance from black-to-white; and the *bottom figure* shows a simulation of the average of the reversal pattern luminance of a single check. It does not show the real luminance change in a single check. Because half of the checks are changing in the opposite direction, the bottom figure represents luminance change of entire screen. Note that, in the CRT screen (*left side*), there is no change in the total luminance (*y* axis) during time (*x* axis). On the other hand, the conventional LCD screen (*right side*) has an abrupt change of the luminance (*y* axis) at the time of reversal change of the checkerboard (*x* axis)

subjects wore their best refractive correction, and all recordings were monocular.

The recording electrode was placed 2.0 cm superior to the inion (Oz), and the reference electrode was placed on Fz. The ground electrode was placed on the earlobe. Signals were amplified 4,000 times with an amplifier (LE-4000, Tomey Corporation, Nagoya, Japan), and the band pass filters were set at 1.0–100 Hz. The sampling rate was 1.0 kHz, and 128 responses were averaged.

The recordings were performed at least two times to confirm the reproducibility. In addition, the measurements for each subject were performed two times with a 1 week interval to determine the inter-measurement variability.

Measurements of luminance of single check

To determine the time course of the luminance changes, the luminance of one check was measured with a photodiode (S1133, Hamamatsu Photonics Co. Ltd, Hamamatsu, Japan) attached to the upper left corner (Fig. 1). The luminance was also measured at the 4 corners and at the center of the screen with a luminance meter (CA-100S, Konica Minolta, Inc.,

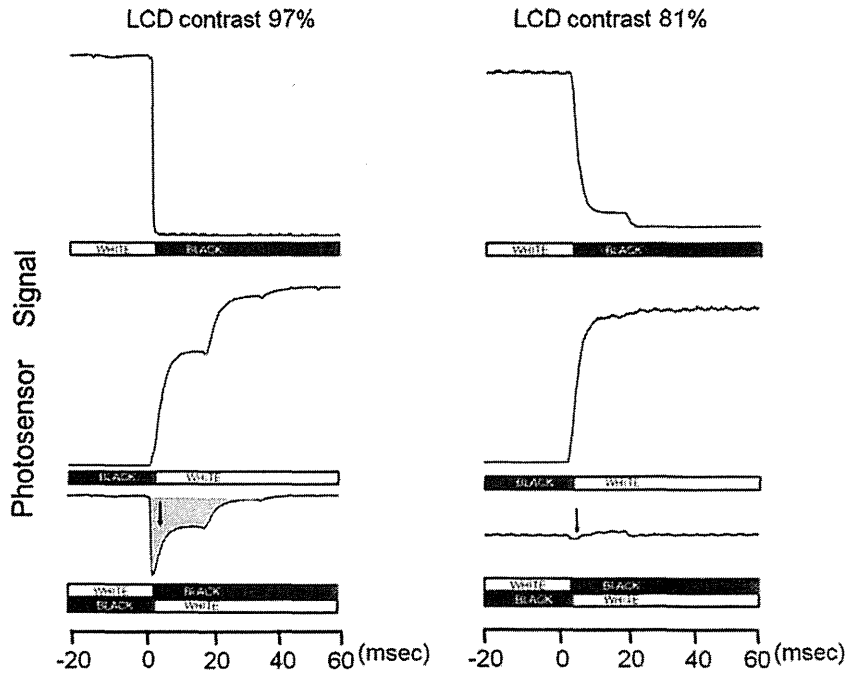

Fig. 3 Luminance changes of liquid crystal display (LCD) screen with a maximal contrast of 97 % in the *left column* and 81 % contrast in the *right column*. In both *columns*; the *top figure* shows the changes of the checkerboard luminance from white-to-black; the *middle figure* shows from black-to-white; and the *bottom* signal shows the averaging of the reversal pattern luminance of a single checkerboard. Note that, for the LCD with 81 % contrast (*bottom right column*), there is a considerable reduction in the change of total luminance (*arrow*) during time (*x* axis) compared with 97 % contrast (*bottom left column*)

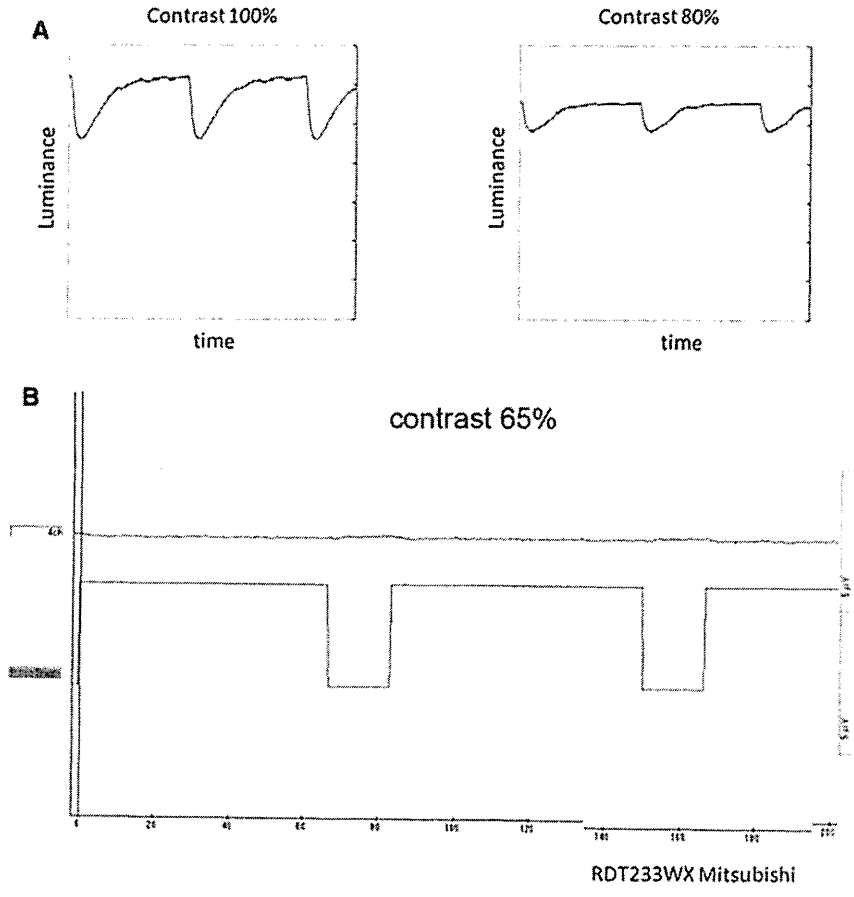

Fig. 4 **a** The transient change in the luminance was decreased in another LCD monitor (17 in., 340 × 270 mm, RDT233WX, Mitsubishi, Tokyo, Japan). **b** When the contrast was reduced to 65 %, the luminance artifact was completely removed

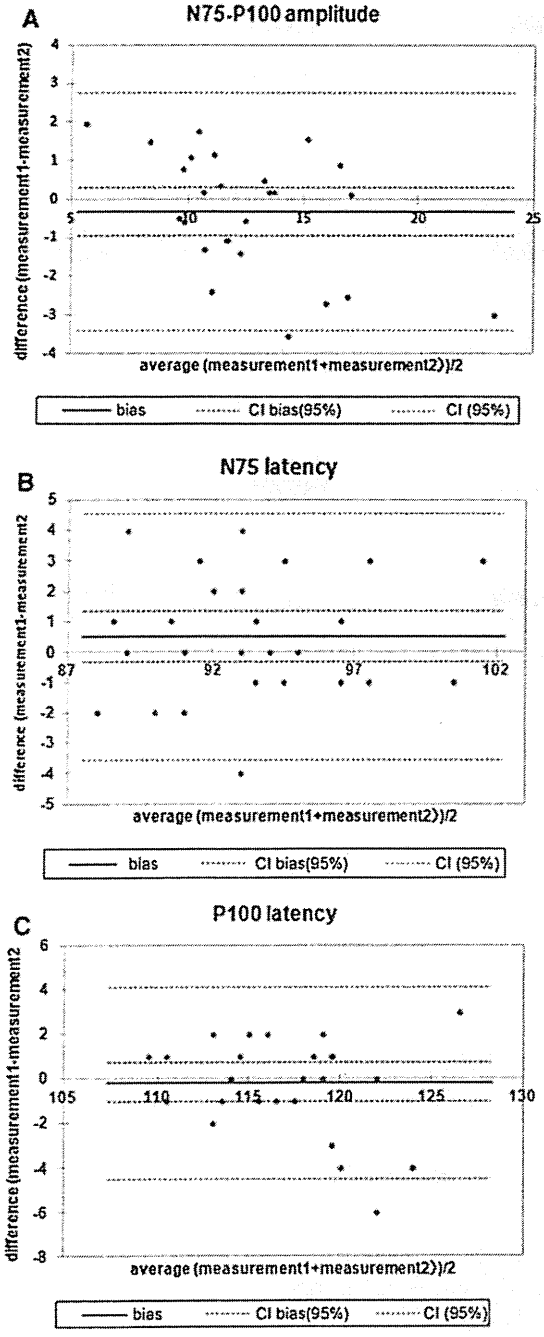

Fig. 5 Bland–Altman *plots* for N75-P100 amplitude (a), N75 latency (b), and P100 latency (c). Bland–Altman analysis to evaluate the agreement between two different measures did not show any systematic or proportional error or any dependency on the magnitude of one of the values. But, the individual deviations are not negligible especially for the amplitude (a) considering that the deviation of 3 μV is approximately 30 % of the mean value (11.3 μV)

Osaka, Japan). We confirmed that the variations in the luminance across the screen were within 20 % which complied with the recommendation of the ISCEV standards [1].

The luminance and contrast of the CRT were matched to that of the LCD screen. The contrasts were calculated with the Michelson contrast formula [8].

Pattern-reversal stimuli

The visual stimulus was a black-and-white checkerboard pattern generated on either a CRT monitor (17 in., 320 × 230 mm, S710, Compaq Computer Co., USA) or a commercial LCD screen (17 in., 340 × 270 mm, E170Sc, DELL, TX, USA).

We here define the response time of an LCD panel as the time it takes one pixel to turn from white-to-black or black-to-white. Other investigators have defined the response time as the time required to change from gray-to-gray [2, 3]. The mean luminance was kept at 81 cd/m^2 with a 97 % maximum contrast, and the reversal rate was 3.0 rev/s. The check size was 0.25° at an observation distance of 70 cm. The overall size of the CRT was 19°× 28°, and that for the LCD was 21° × 26.2°. The resolution of each monitor was 800 × 600 pixels, and the vertical frequency was 59.8 Hz.

We found a time delay in the luminance change of the LCD, and this produced a transient change in the average luminance which we named the "flash effect." We predicted that the flash effect would elicit electroretinograms (ERGs) and VEPs. To determine what influence of the flash effect had on the p-VEPs, the screens of both types of stimuli were covered with a diffuser (Kuraray, DFA2-P, Tokyo, Japan).

To minimize the flash effect, the contrast of the checkerboard pattern of the LCD monitor was reduced from 97 to 81 %, and the resulting p-VEPs elicited by each were compared.

Data analysis

The P100 amplitude was measured from the trough of N-75 to the peak of P-100, and the latency of N-75 and P-100 was measured from the onset of reversal to the peak of each component. Student's *t* tests were used to determine the significance of difference.

Table 1 Bland–Altman analysis of amplitude and latency of measurement 1 and measurement 2

	N75-P100 amplitude (μV)	Latency (ms)	
		N75	P100
Measurement 1	11.1 ± 3.1	95.4 ± 4.0	119.1 ± 4.8
Measurement 2	11.4 ± 3.7	95.9 ± 4.2	118.9 ± 4.7
Difference of measurement 1 and measurement 2 (m1 − m2)	0.3 ± 1.6	−0.5 ± 2.1	0.2 ± 2.2
Average of measurement 1 and measurement 2	11.3 ± 3.5	95.7 ± 4.0	119.0 ± 4.7
Percentage of eyes within 1.96 × SD-range (%)	96.2	96.2	96.2

The Bland–Altman analysis did not reveal any systematic or proportional error nor any dependence on the magnitude of one of the values

Results

Changes in luminance of checks of each type of screen

The luminance of the checks is plotted against time in Fig. 2. The luminance of the white checks was caused by a burst of flashes resulting from the luminance spot from the electron beam sweeps ("flies") across the photodiode at 60 Hz on the CRT screen, and a homogenous square luminance pattern on the LCD screen. There was no delay during the change from both black-to-white and white-to-black for the pattern on the CRT screen. In contrast, the luminance was slow to develop and decays on the LCD screen especially from black-to-white. The slow development was due to the time course for the crystal liquid molecules to be aligned to permit light to pass through the polarizing layers. The exact shape of the ascending limb may be different for different LCD screens from different manufacturers.

The input lag was defined as the time between the trigger pulse and the beginning of the luminance change [6, 9], and it was approximately 1.2 ms for the LCD used in this study. The reason for this lag is that the input signal is usually further processed at the display level before the luminance change appears on the screen. These image processing technologies and processing times can vary with the manufacturer, display type, and setup parameters, for example, resolution, color settings, and internal processing [10].

Luminance changes of checks on LCD screens with contrasts of 97 and 81 %

The changes in the luminance of the checks on the LCD screen with stimuli of contrasts 97 and 81 % are shown in Fig. 3. The transient change in luminance is significantly smaller with 81 % contrast. The transient change in luminance on the LCD with stimulus of 60 % contrast was even lower (data not shown). The changes in the luminance on another LCD screen (17 in., 340 × 270 mm, RDT233WX, Mitsubishi, Japan) are shown in Fig. 4.

Recorded VEPs

Comparison of p-VEP components elicited by stimuli generated on CRT and LCD screens

VEPs were elicited by each type of screen, and the amplitudes and latency of the different components were reproducible. Bland–Altman analysis to evaluate the agreement between two different measures did not show any systematic or proportional error or any dependency on the magnitude of one of the values (Fig. 5; Table 1).

The N75-P100 amplitudes are shown in Fig. 6a, and the N75 latency and P100 latency are shown in Fig. 6b, c, respectively. The P100 amplitudes elicited by the LCD screen were not significantly different from those elicited by the CRT screen. However, the latency of N75 and P100 elicited by the LCD screen was significantly longer than those elicited by the CRT screen (Fig. 6b, c).

Comparisons of p-VEPs elicited with or without diffuser placed before CRT and LCD screens

The VEPs elicited by the CRT and LCD screens with and without a diffuser are shown in Fig. 6a. The VEPs elicited with the diffuser place in front of the CRT

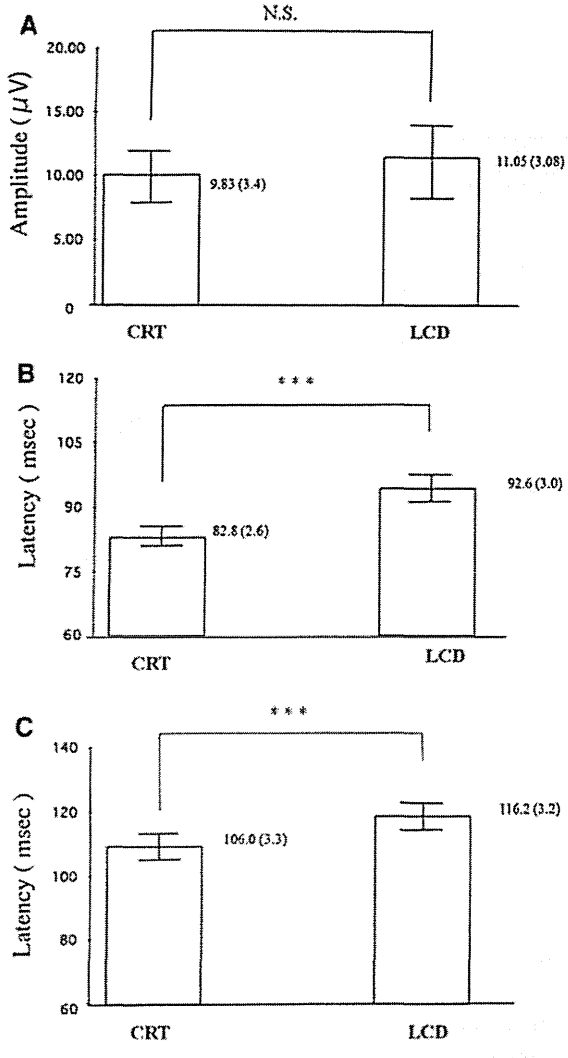

Fig. 6 Comparisons of each parameter between the p-VEP elicited by CRT and by LCD. **a** No significant difference was found in the VEP P100 amplitude elicited by the LCD screen to that elicited by the CRT screen. *NS* not significant. **b** The VEP N75 latency elicited by the CRT and LCD screens. The latency of the VEP N75 elicited by the CRT screen was significantly shorter than that elicited by the LCD screen. **c** The VEP P100 latency elicited by CRT and LCD monitor. There was a statistically significant difference in latency of VEP P100 between those obtained by using CRT and LCD monitor. $***P < 0.05$

monitor were below the noise level, whereas those elicited with the diffuser before the LCD screen had a positive peak at about 100–120 ms. This response was most likely a flash VEP. In addition, when a contact lens electrode was placed on the cornea and the stimulus pattern on the LCD screen was behind a diffuser, a small but distinct ERG was recorded (Fig. 7b).

When the VEPs were elicited with a diffuser before the CRT screen was subtracted from the VEP recorded without the diffuser, the waveform, the N75 and P100 latency, and the N75-P100 amplitude were not changed. When the VEPs elicited with the diffuser before the LCD screen and with 97 % contrast was subtracted from the VEP recorded without the diffuser, the N75 and P100 latencies were not changed but the N75-P100 amplitude was slightly decreased.

Comparison of p-VEP elicited at contrasts of 97 and 81 %

When the VEPs were elicited with the diffuser before the LCD screen with 81 % contrast checks was subtracted from the VEP recorded without the diffuser, no significant change was observed in the N75 and P100 latency and in the N75-P100 amplitude. A comparison of the N75 and P100 latency and the N75-P100 amplitudes of the VEPs elicited by the LCD screen with each contrast are shown in Fig. 8. No significant difference was found in the P100 amplitude between the responses elicited by 81 % contrast stimulus compared to that by using 97 % stimulus (Fig. 8a). No significant difference was observed in the N75 and P100 latency (Fig. 8b, c).

Discussion

The ISCEV standard protocol for clinical visual evoked potentials (2009 update) [1] stated that p-VEPs should be elicited by black-and-white checks that change phase abruptly and repeatedly at a specified number of reversals/s. Further, it stated that there must be no overall change in the mean luminance of the screen, which requires equal numbers of light and dark elements in the display, and no transient luminance changes during the pattern reversal. Thus far, stimuli generated on a CRT screen meet these requirements. But, the LCD screen has an inherent time delay when the luminance changes from black-to-white and also from white-to-black. This delay is the time required for the liquid crystals to align and can cause image blurring during fast-moving scenes [2, 3].

Our results showed that the VEPs elicited by the LCD screen had good reproducibility, but it should be noted that the individual deviations are not negligible especially for the amplitude (Fig. 5a) considering that

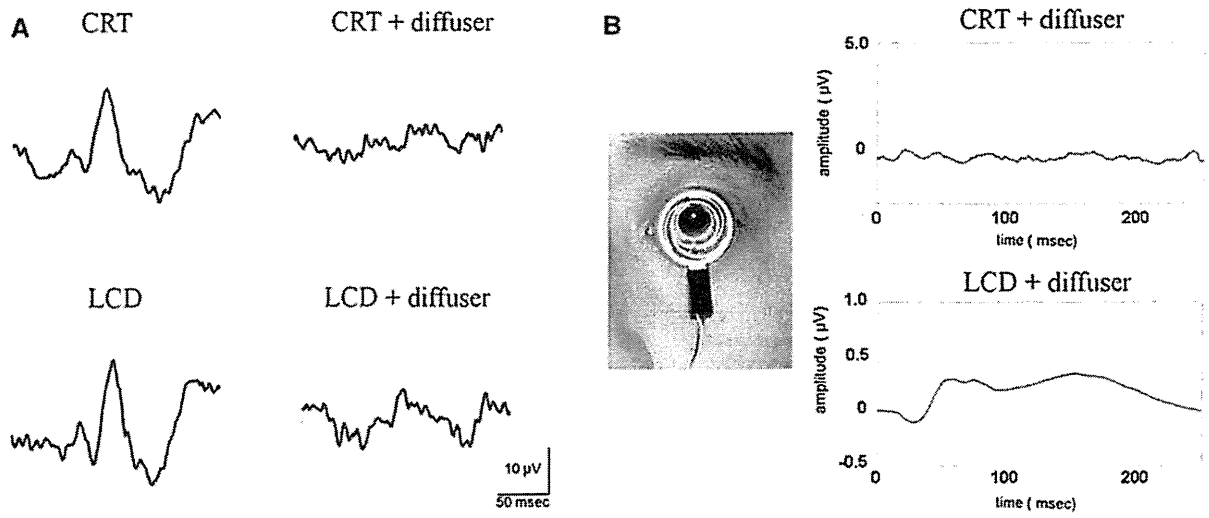

Fig. 7 Pattern visual evoked potentials and electroretinogram elicited by placing a diffuser before each monitor. a VEPs elicited by diffuser on the cathode-ray tube (*CRT*) monitor (*upper*) was below the noise level, whereas those on the liquid crystal display (*LCD*) had a physiological response producing positive peak at around 110 ms (*lower*). b A gold foil contact lens active electrode was placed on the cornea (*left*), and no ERG response was recorded (*upper right*) when the CRT with diffuser was used for stimulation. In contrast, a small but discernible electroretinogram was recorded (lower right) when the LCD with diffuser was used for stimulation

the deviation of 3 μV is approximately 30 % of the mean value (11.3 μV). And when compared to the conventional VEPs elicited by stimuli on a CRT screen, the latency of N75 and P100 was delayed and the N75-P100 amplitude was decreased. These findings are in good agreement with earlier reports [5, 6]. Nagy et al. [6] reported that p-VEP elicited using LCD had longer latency [6]. They attributed the delay to the total temporal differences between the LCD's electronic input and radiometric output signals caused by the response time and the input lag. They showed a model of the relative characteristics of the video and photodiode signals on the oscilloscope. Although it is not known whether this was the case from their figure, the raw value of the luminance change of our monitor was asymmetrical.

Thus, there was a transient change of the mean luminance. Direct monitoring of the luminance changes of our LCD screen showed an input lag of 1.2 ms and a transient change in luminance. The response time according to the specification was 5 ms; therefore, the mean N750 ms of latency delay compared to that when CRT monitor used as stimulator was longer than the sum of the input lag and response time. Because the input lag can be measured easily and is constant, it can be subtracted from delayed latency. But, the influence of the response time on the latency was not fully determined. The input lag and the response time are specific to the LCD monitor, and the information provided by the manufacture as well as measurements by the user is important. In addition, to compare the p-VEPs elicited by stimuli created on the LCD screen to that elicited by the CRT screen, reference to normative data from control group would be recommended.

To determine whether the transient change in the luminance might elicit a flash-evoked physiological response, we recorded VEPs and ERGs with the LCD screen covered by a diffuser. The results indicated that the p-VEPs elicited by the LCD screen were contaminated by f-VEPs. The influence of the flash effect was a prolongation of the latency, but the amplitude was not affected.

The best way to test the luminance changes of LCD screens would be to evaluate the luminance changes by using a photosensor. However, it is time-consuming and expensive, so impractical. Instead, the easiest and least expensive way to check luminance changes during a reversal is to place a diffuser in front of the monitor (Fig. 7) and to let the monitor display a reversal checkerboard pattern of small angle of <0.25°. Our standard way of tuning the luminance of the LCD is first to check the monitor in the default mode. Second, we check the flashing effect with

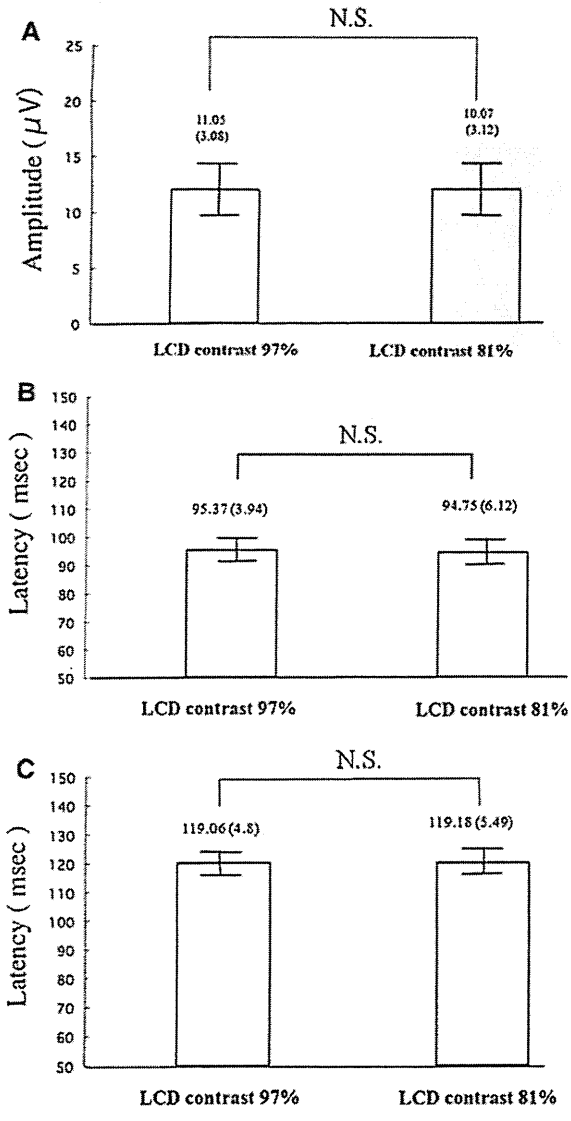

Fig. 8 Comparisons of each parameter between the p-VEP recorded using different checkerboard contrasts of the LCD. **a** No significant difference was found in the P100 amplitude between the responses elicited by 81 % contrast stimulus compared to that by 97 % stimulus. *NS* not significant. **b** and **c** No significant difference was observed in the N75 and P100 latency between the VEPs elicited by 81 and 97 % contrast stimuli. *NS* not significant

diffuser in an above-mentioned way, and third, we check the flashing effect after reducing the contrast of the checkerboard.

However, when using another LCD monitor (17 in., 340 × 270 mm, RDT233WX, Mitsubishi, Tokyo, Japan), the contrast must be reduced to 65 % to completely remove the luminance artifact and such contrast does not match the ISCEV standard.

An alternative way might be to decrease the checksize. For example, if the checksize can be reduced so that one pixel equals one check, then one cannot resolve the pattern when one is sufficiently far away from the screen. In that case, no VEP should be obtained. But, due to the luminance artifact, there should be a sizable VEP, a flash VEP. Given this, the VEP amplitude can be affected depending on the checksize, but it is minimal for standard check sizes.

One of the ways to minimize the flash effect might be to optimize the contrast of the checkerboard luminance. The transient change of the luminance is constant depending on the contrast of the checkerboard and specific to the LCD monitor. The latency delay in the p-VEP is also constant although it did not correspond with the luminance artifact (Fig. 6b, c). A reduction in the contrast of the checkerboard to 81 % still complies with the ISCEV standards (checkerboard pattern contrast $\geqq$80 %) can be considered. However, a reduction in the contrast may not eliminate the flash effect in all LCD monitors in the market. Further investigations on how to eliminate the flash effect are needed.

We did not record pattern ERGs (PERGs). However, when recording PERGs with LCD screens, the responses might be easily contaminated by flash responses. In other words, PERGs might be better suited as an electrophysiological indicator of flash effects. And for those who want to record PERGs with LCD screens, a corresponding validation with PERGs is necessary.

In conclusion, the p-VEP waveforms are affected by a delay in the reversal phase of a checkerboard pattern generated on a LCD screen. The flash effect might be reduced by optimizing the contrast of the checkerboard luminance. The p-VEP recorded using LCD for pattern stimulation is comparable to the conventional p-VEP elicited by checkerboards generated on a CRT screen, when the LCD specific parameters such as input lag and response time are measured and latency delay is corrected.

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Conflict of interest H. Funada is an employee of Tomey Corp., Japan. None of other authors has any commercial relationship.

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Case Report

Pars Plana Vitrectomy Combined with Focal Endolaser Photocoagulation for Idiopathic Macular Telangiectasia

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Background. To report the outcome of pars plana vitrectomy (PPV) combined with intraoperative endolaser focal photocoagulation (PC) on eyes with idiopathic macular telangiectasis (MacTel) type 1. *Methods.* This was a retrospective study of two female patients with MacTel type 1 who were resistant to focal photocoagulation, sub-Tenon triamcinolone injection, and/or antiangiogenic drugs. The best-corrected visual acuity (BCVA) was determined, and fluorescein angiography (FA) and spectral domain optical coherence tomography (SD-OCT) were performed before and after surgery for up to 19 months. *Results.* After surgery, the BCVA gradually improved from 20/100 to 20/20 at 19 months in Case 1 and from 20/50 to 20/13 at 13 months in Case 2. Fluorescein angiography (FA) showed leakage at the late phase, and OCT showed that the cystoid macular edema was resolved and the fovea was considerably thinner postoperatively. *Conclusion.* Patients with MacTel type 1 who are refractory to the other types of treatments can benefit from PPV combined with intraoperative endolaser focal PC with functional and morphological improvements.

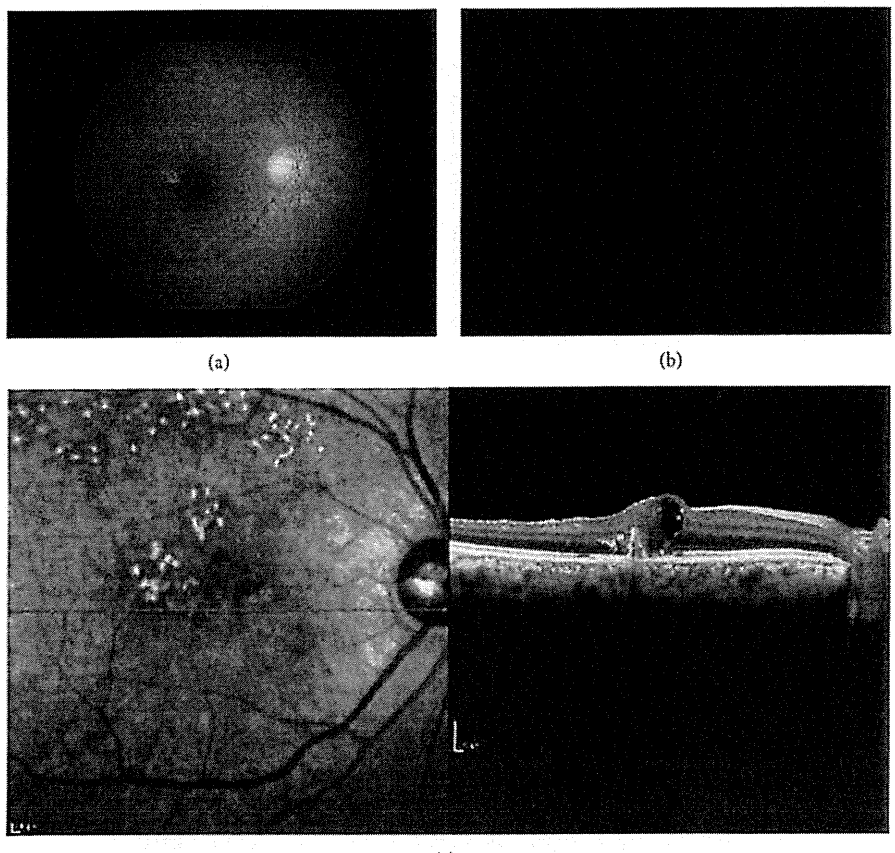
1. Introduction

Idiopathic juxtafoveal macular telangiectasia (MacTel) is characterized by vascular anomalies affecting the macular capillary network. It was first described by Gass and Oyakawa [1] and Gass and Blodi [2] and named idiopathic juxtafoveolar retinal telangiectasis (IJRT). It was recently renamed macular telangiectasis (MacTel) by Yannuzzi et al. [3]. There are two types of MacTel: type 1 with aneurysmal telangiectasia and type 2 with parafoveal telangiectasia. MacTel type 1 or unilateral parafoveal telangiectasis (Group 1B IJRT) typically occurs in one eye of relative young men. The temporal half of the macula is involved by the telangiectasis, and the macular oedema and hard exudates lead to vision reduction. No treatment has been established although some encouraging effects have been obtained by argon laser photocoagulation (PC) [4, 5], intravitreal or sub-Tenon's capsule injection of triamcinolone acetonide (IVTA or STTA) [5–7], or intravitreal bevacizumab (IVR) or ranibizumab (IVB) injections [8–10] in small case series.

We present two patients with MacTel type 1 who were refractory to photocoagulation (PC), STTA, and IVB but responded to pars plana vitrectomy (PPV) combined with intraoperative endolaser focal PC.

2. Materials and Methods

This was a retrospective study of two eyes of two patients with MacTel type 1 who did not respond to focal PC delivered by an integrated slit lamp, to STTA, and/or to IVB. After discussing the possible treatment options including repetition of earlier treatments, an informed consent was obtained for our technique of PPV combined with intraoperative endolaser focal PC. Both patients underwent PPV combined with endolaser focal PC during the surgery. The diagnosis of MacTel type 1 was based on the fundus examination, FA, and OCT after the exclusion of neovascular maculopathy, secondary macular telangiectasia, and diabetes. Both eyes had cystoid macular oedema (CME) and showed a prompt filling of both the superficial and deep capillary networks of the telangiectatic



(a) (b)

(c)

FIGURE 1: Finding of the right eye of Patient 1 with idiopathic macular telangiectasis (MacTel) type 1 on her first visit. Her best-corrected visual acuity (BCVA) was 20/100. (a) Fundus photograph showing hard exudates associated with telangiectasia temporal to the fovea. (b) Fluorescein angiogram showing strong fluorescein leakage in the late phase. (c) Optical coherence tomographic (OCT) image showing cystoid macular edema in the area surrounding the leakage.

vessels. There was also late intraretinal staining by fluorescein. The follow-up period was 19 months for Case 1 and 11 months for Case 2.

The ocular examinations included measurements of the BCVA, ophthalmoscopy, fluorescein angiography (FA), and spectral domain optical coherence tomography (SD-OCT). Serial SD-OCT B-scan images were obtained with the Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA, USA). The foveal thickness (FT) was measured as the distance between the internal limiting membrane and inner border of the retinal pigment epithelium at the foveal centre with the computer-based caliper built into the OCT system. The vertical and horizontal B-scan images across the fovea were used to determine the foveal thickness.

3. Case Reports

3.1. Patient 1. A 79-year-old woman complained of blurred vision in her right eye and came to our clinic. Her BCVA was 20/100 OD and 20/25 OS. FA showed telangiectasia temporal to the fovea with pronounced fluorescein leakage in the late phase in the area of the telangiectasia. OCT showed cystoid macular edema (CME) in the area surrounding the leakage (Figure 1). The right eye was diagnosed with MacTel type 1 and received STTA, IVB twice, and focal PC through a slit lamp. These treatments failed to decrease the leakage on FA and resolve the CME. The BCVA was not improved.

After discussing the treatment options, the patient gave us an informed consent for PPV with a 25-gauge trocar system combined with the endolaser focal PC on the right eye. After core vitrectomy, a posterior vitreous detachment was created by suction through the vitreous cutter. The internal limiting membrane was made more visible with triamcinolone acetonide particle (Maqaid), and it was grasped and peeled with a microforceps. Then, focal PC was performed on the fluorescein leakage points with a 25-gauge endolaser probe and 100 to 120 mW power so that the focal retinal edema was treated.

After that, the CME decreased and the BCVA improved gradually to 20/25 in 3 months. The leakage of fluorescein was not present, the CME could not be detected in the OCT images, and the foveal thickness decreased from 420 to 140 μm (Figure 2). During the 19-month follow-up period, the BCVA and the CME progressively improved (Figure 3).

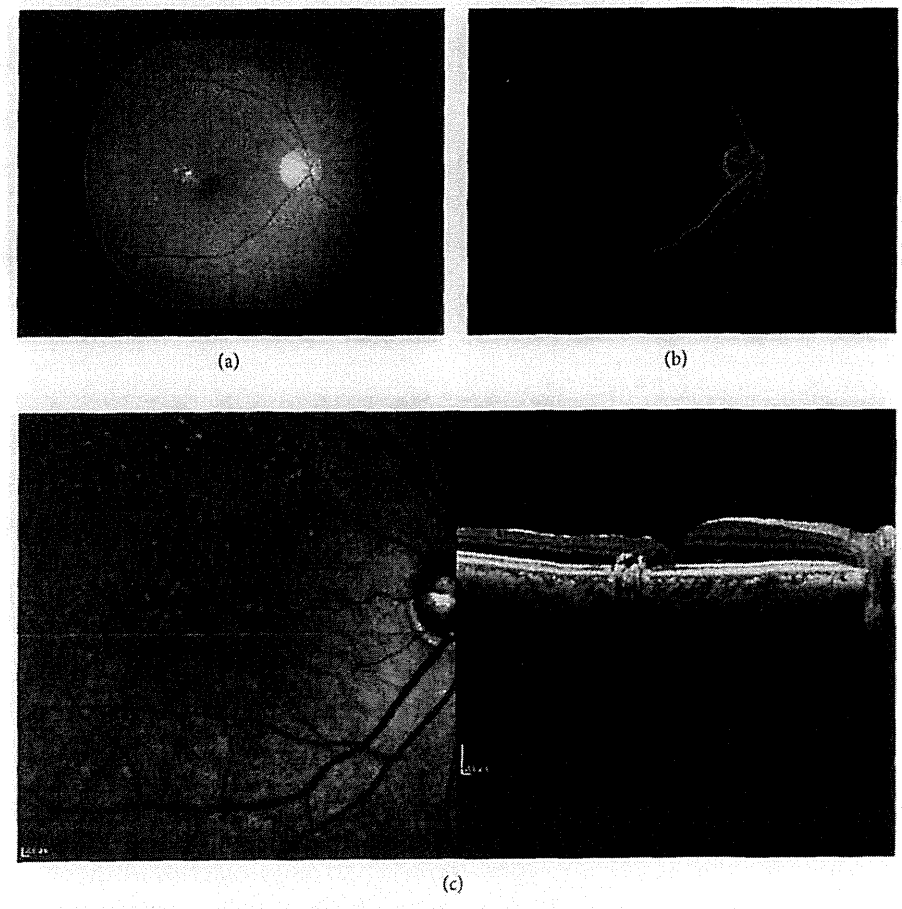


FIGURE 2: Findings of the right eye of Case 1 taken 3 months after surgery. The BCVA has improved to 20/25. (a) Fundus photograph showing localized area of scars from the laser photocoagulation temporal to the fovea. (b) Fluorescein angiogram showing the absence of fluorescein leakage in the late phase. (c) Optical coherence tomographic image showing an absence of cystoid macular edema and regained foveal pit.

3.2. Patient 2. A 69-year-old woman with no relevant medical history presented with decreased vision in her left eye of 1-week duration. She had been diagnosed with macular oedema associated with MacTel type 1 and underwent IVB and focal PC in a private clinic. The treatments were not effective, and she was referred to us two months later.

Our examination showed that her BCVA was 20/20 OD and 20/50 OS. FA revealed ectatic capillaries temporal to the fovea with leakage in the late phase in both eyes but especially in the left eye. SD-OCT showed severe CME in the left eye (Figure 4). She was diagnosed with MacTel type 1 and underwent PPV with intraoperative endolaser focal PC as in Patient 1.

After that, the CME decreased and her BCVA improved gradually to 20/13 in 6 months. The leakage of fluorescein was not present, and the CME in the OCT images was not detected. The FT decreased from 512 μm to 200 μm (Figure 5). The clinical course of the left eye is showed in Figure 3. Nine months later, the right eye developed CME, but the BCVA remained at 20/20.

4. Discussion

Our results showed that PPV with endolaser focal PC can improve the BCVA and reduce the CME in patients with MacTel type 1. Our cases had not responded to focal PC through an integrated slit-lamp system, STTA, and/or antiangiogenic drugs, but after PPV with endolaser focal PC, the vision and CME improved. These findings strongly suggest a causal relationship between the treatment and the improvements.

Several treatments have been reported to be effective for MacTel, especially for type 2 [7, 8, 11], and there are few reports on the treatment of MacTel type 1 [4, 8–10]. IVTA or STTA has been reported to be effective in some cases [3–7] because steroids are anti-inflammatory and might maintain the blood-retina barrier. Recently, antiangiogenic drugs such as bevacizumab or ranibizumab have been reported to be effective in some cases of MacTel type 1 [8–10]. Antiangiogenic drugs are known to reduce neovascularization and oedema; however the follow-up times in those reports were relatively short and some cases had recurrences. Therefore,

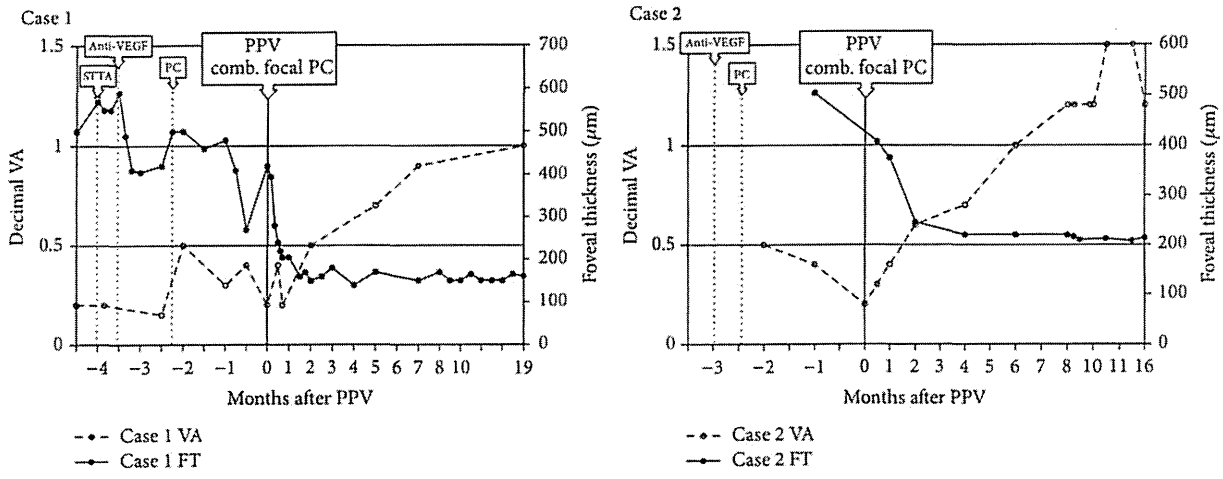


FIGURE 3: Clinical course of the affected eyes in two cases of MacTel type 1. In Case 1, the visual acuity improved to 20/20 and foveal thickness was reduced to 140 μm at 19 months after surgery. In Case 2, the visual acuity improved to 20/13 and foveal thickness to 208 um at 13 months after surgery.

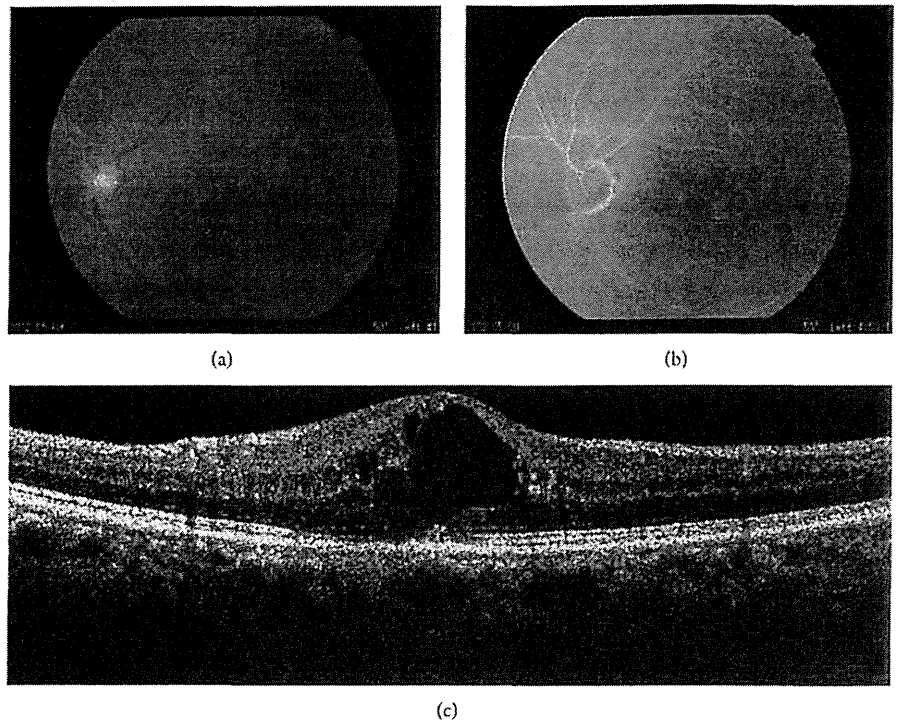


FIGURE 4: Findings of the left eye at the first visit of Case 2. The BCVA was 20/50. (a) Fundus photograph showed hard exudates associated with telangiectasia inferior temporal to the fovea. (b) Fluorescein angiogram showing fluorescein leakage in a circular pattern in the late phase. (c) Optical coherence tomographic image showed cystoid macular edema at the macula surrounded by circularly arranged fluorescein leakages.

the efficacy of those therapies has still not been definitively determined.

At present, there is no consensus regarding the treatment of MacTel. Our two patients had no or only limited improvement clinically and angiographically after PC, STTA, and/or antiangiogenic therapy. Thus, we believed that intraoperative endolaser focal PC may be more effective because it allows for better accuracy in treating the lesions than through an integrated slit-lamp delivery system. Focal PC through a slit lamp has several disadvantages. The site of the lesion can be

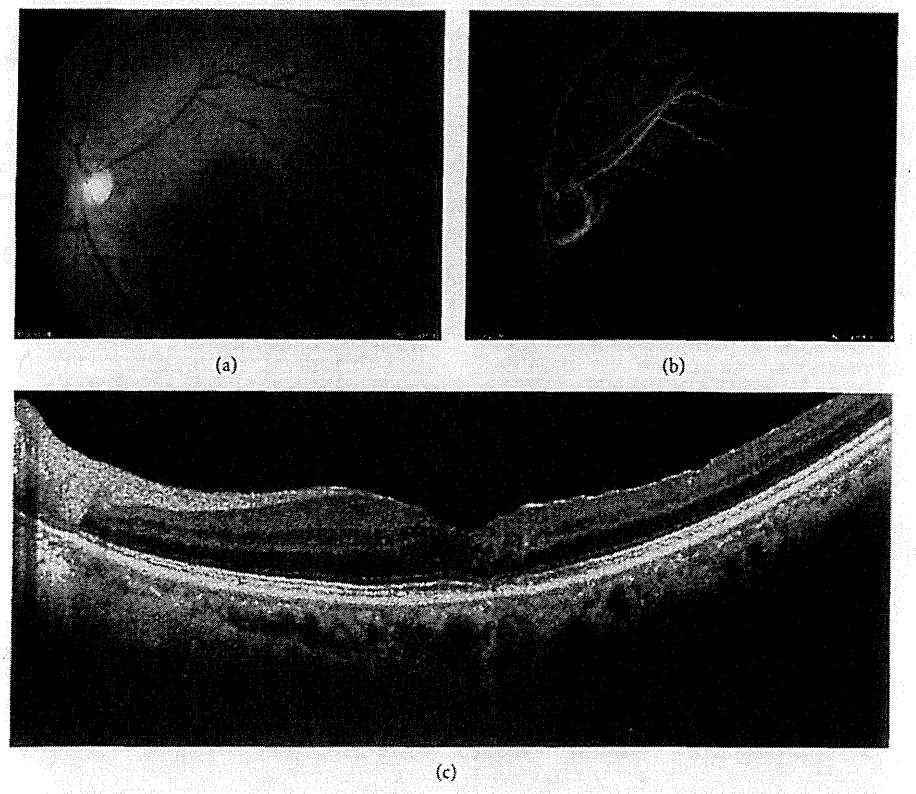


FIGURE 5: Fundus appearance of the left eye of Case 2 six months after surgery. Visual acuity has improved to 20/13. (a) Fundus photograph showed localized area of scarring by laser photocoagulation inferior-temporal to the fovea. (b) Fluorescein angiogram showing the disappearance of fluorescein leakage in the late phase. (c) Optical coherence tomographic image showing the absence of cystoid macular edema and restored foveal contour.

easily affected by micromotions of the eye, the use of a joystick and manipulation of the contact lens require considerable technique and experience, reflected light from the contact lens can reduce the visibility of the macular region, and the endolaser beam can be delivered at different angles which can reduce the energy to the retinal pigment epithelium (RPE) over the fovea. The RPE is located in the outer layer and microaneurysm is in the inner layer, and the laser beam that is delivered obliquely from the inner and central side arrives relatively peripheral to the outer layer. This can prevent damage to the RPE. And finally, the endolaser procedure is not influenced by an opaque media, and the intravitreal laser probe can be brought very close to the retinal surface.

However, there are also drawbacks to the endolaser photocoagulation such as the difficulty for repeated treatments because of the risks associated with intraocular surgery.

There are several factors that may have played a role in improving the macular edema after PPV with endolaser focal PC. The removal of the vitreous and/or ILM may have reduced the level of pathological cytokines or chemical mediators adjacent to the telangiectasia. There are several reports showing that ILM peeling is effective treatment for macular edema secondary to diabetic retinopathy (DME) [12, 13] and retinal vein occlusion (RVO) [14]. Although the mechanism of the ILM peeling has not been fully understood, it might have contributed to the successful outcome. The intraoperative use of TA may have similar effect as STTA or IVTA although its use was only transient. The effectiveness of PPV alone can be assessed if intraoperative PC was not done. But the therapeutic protocol did not allow it. In addition, Sigler et al. reported that PPV was not effective against nonproliferative idiopathic MacTel type 2 [15]. MacTel type 1 is mainly exudative and nonfamilial, while type 2 is primarily nonexudative, obstructive, and occasionally familial. This may explain the differences of our results from the results of Sigler et al. In addition, some cases of MacTel type 1 respond well to antiangiogenic drugs but not type 2.

There are some limitations in our study. This was a retrospective study of only 2 patients. In addition, the follow-up period was short, and there were no controls. However, we believe that PPV with endolaser focal PC is effective and should be considered as an optional treatment for selected cases of MacTel type 1 especially in refractory cases. These treatment protocols should lead to an improvement in both the BCVA and macular edema.

In conclusion, we have experienced two patients with MacTel type 1 who were refractory to photocoagulation (PC), STTA, and IVB but responded to pars plana vitrectomy (PPV) combined with intraoperative endolaser focal PC.

Although further investigations are needed to elucidate the rationale and to establish its indication, we think a stepwise approach to the management of the disease with

the use of surgical management can be considered when conventional treatment fails.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

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CASE REPORT

Improvement of visual acuity after transcorneal electrical stimulation in case of Best vitelliform macular dystrophy

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Abstract
Purpose To report an improvement of the visual acuity after transcorneal electrical stimulation (TES) in a case of Best vitelliform macular dystrophy (BVMD).
Patient and methods A 26-year-old woman diagnosed with BVMD presented with reduced vision. Her best corrected visual acuity (BCVA) was reduced to 20/200 in the right eye, and TES was performed once a month for two sessions. The current of the biphasic pulses (anodic first; duration, 10 msec; frequency, 20 Hz) was delivered using a DTL-electrode, and the duration of the TES was 30 min.
Results The BCVA in the right eye slowly improved after the TES, and 6 months later the BCVA was 20/25. The results of Humphrey visual field tests (VF) and multifocal ERGs (mfERGs) were only slightly changed. Two years later, the BCVA decreased, and it was improved again after another session of TES with the same parameters of the electrical pulses.
Conclusion The improvement of the visual acuity in our case of BVMD indicates that TES should be tried in other cases of retinal dystrophy. Further clinical and laboratory studies on TES are needed.

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Keywords Phosphenes · Transcorneal electrical stimulation · Best vitelliform macular dystrophy

Introduction

Electrical stimulation of the retina can be done with a contact lens electrode with the inactive electrode placed on the skin around the eye. Passing electrical currents between the two electrodes can evoke electrical phosphenes, and this method of stimulating the retina is called transcorneal electrical retinal stimulation (TES) [1, 2].

An improvement of the visual acuity, visual field (VF), and/or electrophysiological functions after TES has been reported in eyes with optic nerve diseases, retinal artery occlusion (RAO), and retinitis pigmentosa (RP) [3–5]. The recent published results of a large case series study showed a recovery of vision after optic nerve lesions by transorbital alternating current stimulation [6].

Best vitelliform macular dystrophy (BVMD) is characterized by an atrophy of the retinal pigment epithelium (RPE) which then affects the photoreceptors and leads to an impairment of central visual function. We present a case of BVMD whose visual acuity improved after TES.

Subjects and methods

Transcorneal electrical stimulation (TES) of retina

The cornea was anesthetized with 0.4 % oxybuprocaine hydrochloride and covered with 3 % hyaluronic acid and 4 % chondroitin sulfate (Viscoat, Alcon Japan, Tokyo, Japan), and a Dawson-Trick-Litzkow (DTL) electrode was placed on the cornea. A skin electrode was placed on the wrist. The electrical current pulses were delivered by a

stimulator (BPG-1,BAK Electronics, Inc., Mount Airy, MD, USA) through a stimulus isolation unit (BSI-2,BAK Electronics, Inc., Mount Airy, MD, USA). The current of the biphasic pulses (anodic first; duration, 10 msec; frequency, 20 Hz) was increased in steps to determine the threshold current necessary to elicit a phosphene. Then the current was increased until a phosphene was elicited that was perceived over the entire VF. This current was selected for the TES, and it was delivered continuously for 30 min for each TES session.

Case report

A 26-year-old woman with BMVD presented with decreased vision OD (Fig. 1). She was diagnosed with BVMD when she was 10-years-old. From the patient's report, her vision was stable, but it was reduced for 1 week when she was 26 years old. She was examined at a private eye clinic, and her best-corrected visual acuity (BCVA) was 20/40 OD and 20/20 OS. The patient was then referred to the Keio University Hospital.

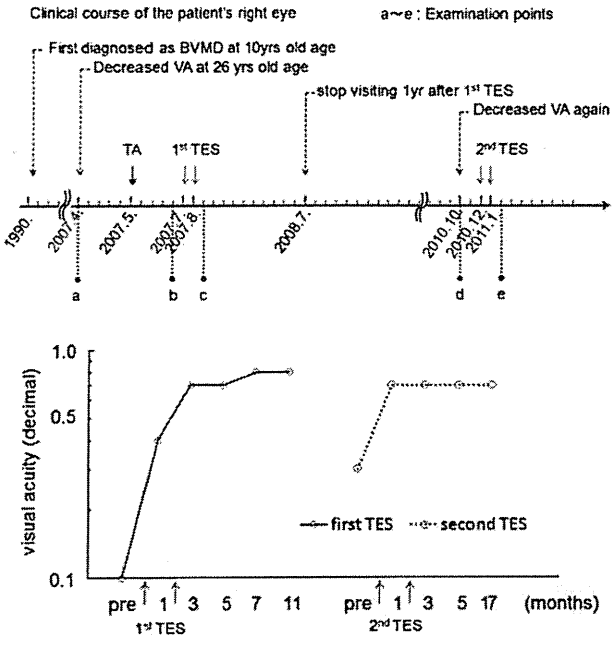

Fig. 1 Results from the right eye of a patient with Best vitelliform macular dystrophy. a Clinical course of the BCVA in the right eye of our patient. Scale shows 1 month intervals unless otherwise indicated. BVMD: Best vitelliform macular dystrophy, TES: transcorneal electrical stimulation, TA: Subtennon injection of triamcinolone acetonide, VA: visual acuity. Point "*a*" is time when the data shown in Fig. 2a, b, c, d, and i were obtained. Point "*b*" is time when the data shown in Fig. 2e was obtained. Point "*c*" is time when the data shown in Fig. 2f and j were obtained. Point "*d*" is time when the data shown in Fig. 2g and k were obtained. Point "*e*" is time when the data shown in Fig. 2h and l were obtained. **b** Effect of transcorneal electrical stimulation (TES) on the best-corrected visual acuity (BCVA) in a patient with Best vitelliform macular dystrophy. After the first and second TES, the BCVA improved and was stable for several months. The *arrow* indicates the point when the TES was performed

Our examination showed that her BCVA was 20/40 OD and 20/20 OS. Ophthalmoscopic examination showed a 1.5-disc-diameter, yellowish macular lesion in both eyes (Fig. 2). Optical coherence tomography (OCT) showed an irregularity of the RPE, and a serous retinal detachment (SRD) in the macula of both eyes (Fig. 2). Her BCVA at this time was reduced to 20/200 OD. Perimetry showed a loss of sensitivity in the central 10° of the VF (Fig. 2). The amplitudes of the mfERGs were reduced and the peak latencies were delayed in the central areas corresponding to the decrease in sensitivity of the VFs (Fig. 2).

A sub-Tennon injection of triamcinolone acetonide failed to improve the BCVA and the SRD. Her visual acuity was measured with a Snellen chart at 5 m by an orthoptist who was masked to the diagnosis and any treatments. The patient had central fixation and her BCVA was measured 1 and 4 weeks after the sub-Tenon injection. The BCVA remained stable at 20/200, and no fundus change was observed.

Two months later, TES (250 μA, 170 μA) was performed twice with an interval of 1 month on the right eye. The procedures used conformed to the tenets of the Declaration of Helsinki, and an informed consent was obtained from the patient after an explanation of the procedures to be used. This study was approved by the Institutional Review Board of Keio University Hospital.

The patient had transient superficial keratitis immediately after each TES session, and otherwise there were no obvious changes by slit-lamp examinations and ophthalmoscopy. OCT showed no changes in the macular region (Fig. 2), but the patient reported an improvement of vision 1 month after the second session. The BCVA had improved to 20/30, and 6 months later, the BCVA in the right eye had improved to 20/25 (Fig. 1). The VFs and mfERGs showed only slight improvements (Fig. 2).

She returned to the Keio University Hospital 2 years later when her BCVA had decreased to 20/70 OD. The macular findings by ophthalmoscopy and OCT showed no changes (Fig. 2). TES was performed again; two sessions at 160 μA with a monthly interval on the right eye. One month later, the BCVA in the right eye improved to 20/30 (Fig. 1). The OCT image (Fig. 2), VFs, and mfERG responses (Fig. 2) were only slight changed. Quantitative analysis on the mfERG parameters failed to show significant changes. At the last examination at 17 months after the second TES session, her BCVA was 20/30. The fundus appearance was stable for more than 5 years in both eyes.

Discussion

Our results showed that TES in a patient with BMVD improved the BCVA significantly for 2 months. Although

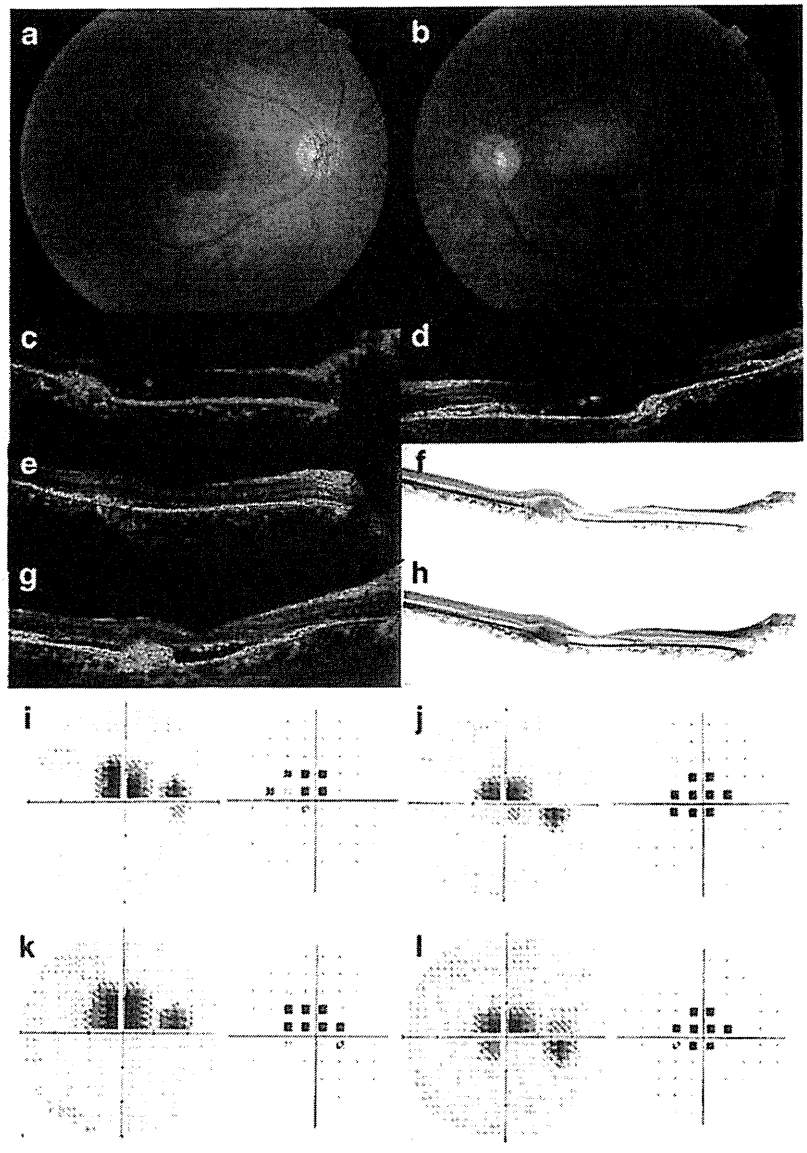

Fig. 2 Fundus appearance and morphological and functional evaluation of the right macula of a patient with Best vitelliform macular dystrophy (BVMD). **a** and **b** Fundus photograph of the right (**a**) and left (**b**) eyes taken when the BCVA was 20/200 at the initial examination at point '*a*' in Fig. 1. **c** and **d** Horizontal crossed sections of time domain optical coherence tomographic (TD-OCT) images of the right (**c**) and left (**d**) eyes obtained on the same day as **a** and **b** at point '*a*' in Fig. 1. **e** Horizontally cross section TD-OCT image of the right eye before the first TES at point '*b*' in Fig. 1. **f** Horizontally cross sectional TD-OCT image of the right eye after the first TES at point '*c*' in Fig. 1. **g** Horizontally cross sectional Fourier domain (FD) OCT image of the right eye before the second TES at point '*d*' in Fig. 1. **h** Horizontally cross section FD-OCT image of the right eye after the second TES at point '*e*' in Fig. 1. After the first and second TES, no significant changes were observed in the OCT images. **i** Humphrey visual field of the right eye before the first TES at point '*b*' in Fig. 1. **j** Humphrey visual field of the right eye 2 months after the first TES at point '*c*' in Fig. 1. **k** Humphrey visual field of the right eye before the second TES at point '*d*' in Fig. 1. **l** Humphrey visual field of the right eye 2 months after the second TES at point '*e*' in Fig. 1

the BCVA was reduced 3 years after the TES, the vision improved again after another TES treatment (Fig. 1). These findings strongly suggest a causal relationship between the treatment and the visual improvement.

It has been reported that the mRNA and protein levels of IGF-1 [7], BDNF, CNTF, and Bcl-2 [8] were time-dependently up-regulated and Bax was down-regulated in the retina of Sprague–Dawley rats after TES. The levels of the mRNA and protein of IGF-1 and neurotrophins in these retinas gradually increased beginning several hours after the TES and reached a peak at around day 7. The levels were still significantly elevated at day 10 after TES [7]. This may explain why only two TES treatments were effective in improving vision for more than 12 months in our case.

Although the duration of the up-regulation of the ICG-1 system by a single TES session is limited, it might have had neuroregenerative effects as well, considering that VA remained improved for more than 12 months. Functional improvements for 3 months of the patient who was already at stationary stage of ION [3], RAO [4], and optic nerve lesions of various origins [6] support this hypothesis.

The optimal parameters of the pulse duration, current intensity, stimulation frequency, stimulation duration, waveform, and repetition times, were not determined. Morimoto et al. [9] reported that the optimal neuroprotective parameters were pulse duration of 1 to 2 ms/phase, current intensity of 100 to 200 μA, and stimulation frequency of 1, 5, and 20 Hz in rats. Inomata et al. reported that in monkeys the strength of the signals increased with longer stimulus durations, and the maximum signals were obtained when the stimulation frequency was between 15 and 20 Hz [10]. In healthy humans, Fujikado et al. studied the amplitude of pupillary reflex (PR) following TES, and reported that biphasic pulse trains (≥10 pulses) with a duration of 0.5 to 1.0 ms and a frequency of 20 to 50 Hz were effective [11]. We used these data to select the stimulation parameters for our patient.

Many investigators use a contact electrode for the stimulation electrode, whereas Fedorov et al. [6] used a skin electrode that was placed on the upper eyelid of patients with optic nerve lesions. This avoided corneal damage and can be considered for retinal diseases as well.

The mechanism for the improvement of the BCVA after TES in our case was not determined. However, we suggest that the reason why the OCT, perimetry, and mfERG findings did not have significant changes over time is because there may have been microstructural changes of the photoreceptors which were too minute to be detected by our OCT. The area of the functional improvement was limited and thus changes in the VFs and mfERGs could not detect it. More precise evaluations with electrophysiological or morphological techniques should help to determine the effect of TES. Further clinical and basic studies on TES are needed to establish TES as an accepted therapeutic modality for retinal dystrophy.

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