Table 3. Electrophysiological Findings of Four Japanese Patients with KCNV2-retionpathy

Pt	DA 0.01		DA 30.0				Square shaped a-wave	Excessive enlargement of b-wave in the extended protocol	LA 3.0			LA 3.0 30Hz		
			A-wave		B-wave				A-wave	B-wave		B-wave		
	Amp (μv)	PT (ms)	Amp	PT	Amp	PT			Amp	PT	Amp	PT	Amp	PT
1	N	Del	N	Del	Super N	NA	(+)	(+)	Sub N	Del	Sub N	UD	UD	UD
2	UD	UD	N	Del	Super N	NA	(+)	NA	Sub N	Del	Sub N	Del	Sub N	Del
3	Sub N	Del	N	Del	Super N	N	(+)	NA	Sub N	Del	Sub N	Del	Sub N	N
4	Sub N	Del	N	Del	Super N	NA	(+)	(+)	Sub N	Del	Sub N	Del	Sub N	Del

Pt = patient; Amp = amplitude; PT = peak time; N = normal; UD = undetectable response; Sub N = subnormal; Del = delayed response; Super N=supernormal response; NA = not available. Full-field electroretinography (ERG) incorporating the standards of the International Society for Clinical Electrophysiology of Vision (ISCEV) included: (i) dark adapted dim flash 0.01 cd•s•m^{-2} (DA0.01), (ii) dark adapted bright flash 30.0 cd•s•m^{-2} (DA30.0), (iii) light adapted 3.0 cd•s•m^{-2} at 2 Hz (LA 3.0), and (iv) light adapted 3.0 cd•s•m^{-2} 30 Hz flicker (LA 3.0 30 Hz). The extended protocol also included the recording of dark adapted responses to an intensity series of flashes in order to detect an excessive enlargement of dark adapted b-wave (patients 1 and 4).

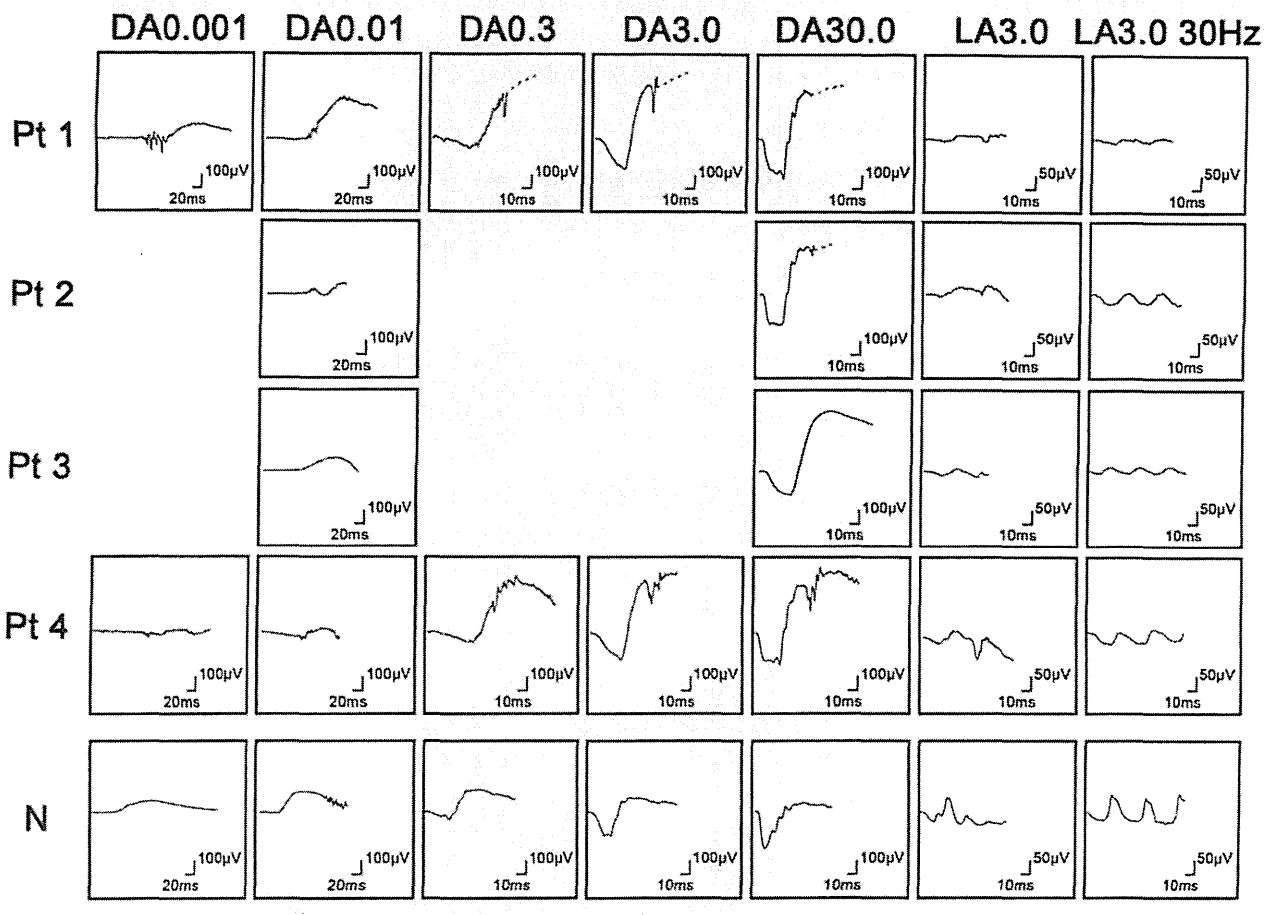

Figure 2. Electrophysiological findings of each patient with potassium channel, subfamily V, member 2 (*KCNV2*) retinopathy. Full-field electroretinograms (ERGs) of patient 1 (top row), patient 2 (second row), patient 3 (third row), and patient 4 (forth row) are shown. The ERGs from a normal control (bottom row) are also shown for comparison. All four patients underwent full-field ERG testing with the minimum standards of the International Society for Clinical Electrophysiology of Vision (ISCEV): (i) dark adapted dim flash 0.01 cd•s•m^{-2} (DA 0.01), (ii) dark adapted bright flash 30.0 cd•s•m^{-2} (DA 30.0), (iii) light adapted 3.0 cd•s•m^{-2} at 2 Hz (LA 3.0), and (iv) light adapted 3.0 cd•s•m^{-2} 30 Hz flicker ERG (LA 3.0 30Hz). The extended protocol was applied to two subjects (patients 1 and 4), including the recording of dark-adapted ERGs to an intensity series of flashes; 0.001 cd•s•m-^{2}, 0.01 cd•s•m^{-2}, 0.3 cd•s•m^{-2}, 3.0 cd•s•m^{-2}, and 30.0 cd•s•m^{-2}.

p.Arg206Pro, were not identified. Three missense variants, p.Arg27His, p.Cys177Arg, and p.Arg206Pro, were highly conserved among the orthologs, and one missense variant, p.Gly461Arg, was completely conserved (Figure 3).

A model of the *KCNV2* protein structure showing the approximate position of the missense disease-causing variants identified is presented in Figure 4. The KCNV2 protein comprises 545 amino acids and contains an N-terminal A and B box (NAB) and six transmembrane domains, (S1–S6), with a K selective motif, GlyTyrGly, in the pore-forming loop (P loop) between S5 and S6 [18]. One variant is located within the N-terminus (p.Arg27His), two variants, p.Cys177Arg and p.Arg206Pro, within the NAB, and one variant, p.Gly461Arg, within the P-loop.

Detailed molecular results of two non-disease-causing variants (polymorphisms) including the in silico analyses are summarized in Appendix 2. These two homozygous variants, p.Gly61Gly and p.Ala265Ala, were synonymous changes in the cording region and were predicted to be benign or have no effect on splicing (Polyphen2 and Human Splicing finder program analysis). Both were present in a high number of chromosomes in the Exome Variant Server database (7647/13006 for p.Gly61Gly and 5636/13006 for p.Ala265Ala, respectively).

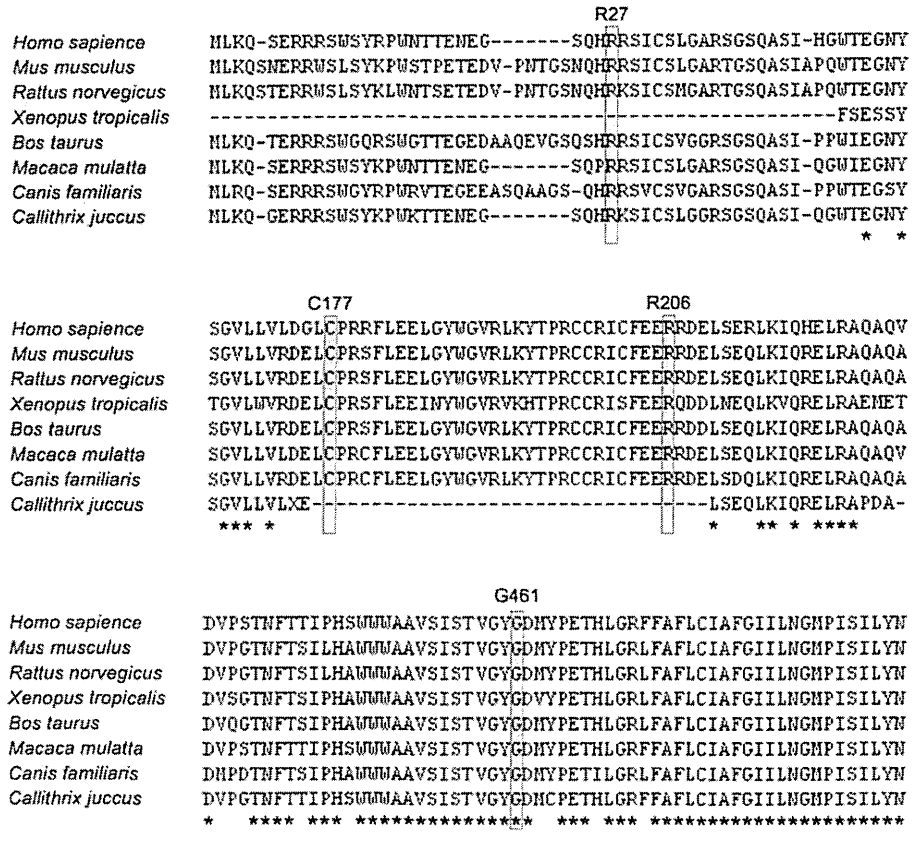

Figure 3. Multiple alignment of eight species of potassium channel, subfamily V, member 2 orthologs. The amino acid-sequence alignment is numbered in accordance with the *Homo sapiens* potassium channel, subfamily V, member 2 (*KCNV2*) sequence (ENSP00000371514). The positions of mutated residues, Arg27 (c.80 G>A, p.Arg27His), Arg177 (c.529 T>C, p.Cys177Arg), Arg206 (c.617 G>C, p.Arg206Pro), and Gly461 (c.1381 G>A, p.Gly461Arg), are highlighted. The alignment was performed with the Clustal Omega program, and the asterisk indicates a completely conserved residue.

DISCUSSION

Our results showed the molecular genetic characteristics of four Japanese patients with CDSRR, which, to the best of our knowledge, is the first report of these characteristics of *KCNV2* retinopathy in an East Asian population. Our four patients harbored the likely disease-causing variants in *KCNV2*. Compound heterozygosity for two alleles, p.Cys177Arg and p.Gly461Arg, in three patients and homozygosity for two complex alleles, p.Arg27His and p.Arg206Pro, in one subject were confirmed. Three of the four variants, p.Arg27His, p.Cys177Arg, and p.Arg206Pro, were novel, which indicates all genotypes identified in our series have never been described before.

The clinical and electrophysiological characteristics of our four patients were similar to those of reported patients [8-11,13,14,17,18]. Additionally, all four patients presented with a decrease in central vision whose onset was in the first decade of life with minimal fundus changes and a characteristic ring enhancement of the AF signal (Table 2 and Figure 1). These findings are also in accordance with earlier reports [9-12,14]. SD-OCT demonstrated a discontinuous or absent inner and outer segment junction line in two patients

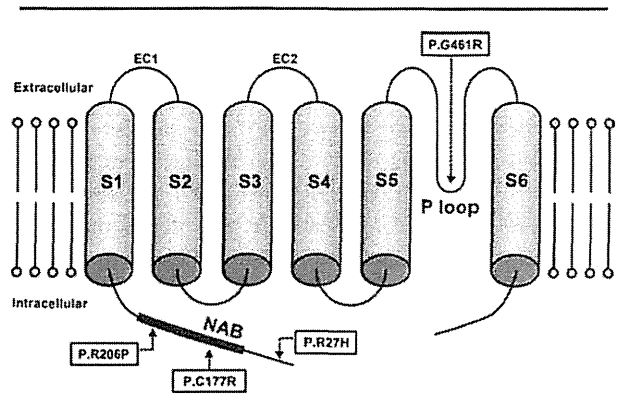

Figure 4. Model of the potassium channel, subfamily V, member 2 protein structure. A schematic representation of the potassium channel, subfamily V, member 2 (*KCNV2*) subunit of the K channel is drawn showing the approximate position of missense disease-causing variants identified in this study. The *KCNV2* protein consists of an N-terminus, an N-terminal A and B box (NAB), and six transmembrane domains (S1–S6), with two extracellular loops (EC 1, 2) and a K selective motif, GlyTyrGly, in the pore-forming loop (P loop) between S5 and S6.

as previously reported [10]. In addition, the absence of the cone outer segment tip line at the macular region was also confirmed in all four patients.

The pathognomonic electrophysiological features were demonstrated in all four patients, viz., delayed and reduced photopic ERGs, delayed ERGs for DA 0.01, and a square-shaped a-wave with a supernormal b-wave for DA 30.0 (Table 3 and Figure 2). An excessive increase in the b-wave for the DA ERGs to an intensity series of flashes was also confirmed in patients 2 and 3. Therefore, the unique rod system abnormalities were identical to those reported for *KCNV2* retinopathy [9,14].

Compound heterozygosity for two alleles, p.Cys177Arg and p.Gly461Arg, was found in patients 1, 2, and 3. The p.Gly461Arg with relatively higher allele frequency affects the third residue of the ultraconserved-GYG-tripeptide motif that acts as an ion selectivity filter in the K channel's pore-forming loop, P loop, between S5 and S6 (Figure 4) [30]. The clinical effect of p.Gly461Arg was well characterized earlier [10,16,17]. Friedburg et al. reported that three siblings with homozygous p.Gly461Arg had a relatively severe phenotype with an early onset and nystagmus at <5 years of age, visual acuity decrease (0.1–0.25, constantly), minimal fundus changes, ring enhancement at the foveal AF image, and an excessive increase in the b-wave for scotopic ERGs to an intensity series [17]. In contrast to the previous reports on homozygous patients, the three patients with heterozygous p.Gly461Arg in our series did not have nystagmus, and two of our patients had less severe BCVA decrease (0.7–0.8). These findings imply that the phenotype of the compound heterozygous for p.Gly461Arg and p Cys177Arg could have a less severe phenotype than those homozygous for p.Gly461Arg. It is of interest that the phenotypic spectrum, compound heterozygous for p.Gly461Arg and p Cys177Arg, was also observed in our series. Two relatively mild phenotypes were observed in the two siblings in our series (patients 1 and 2). In addition, one relatively severe phenotype, with more severe visual acuity decrease (0.1) and photoreceptor/RPE abnormalities at the macula, was detected in patient 3.

Three of the new disease-causing missense variants were located within the N-terminal region of the protein (Figure 4): p.Arg27His within the N-terminus and p.Cys177Arg and p.Arg206Pro within NAB. p.Cys177Arg was completely segregated, and the predicted pathogenesis and evolutionary conservation were confirmed. The coexistence of two likely disease-causing variants, p.Arg27His and p.Arg206Pro, on the same chromosome was also identified in our series with segregation analyses. The patient who was homozygous for these two complex variants had a severe phenotype, with an early onset (2 years), nystagmus, and severe visual acuity decrease (0.1 to 0.08). Both variants were predicted to be pathogenic with evolutionary high conservation (Appendix 1and Figure 3). Whether one of these variants is a neutral polymorphisms in cis with disease-causing one, or whether family 4's alleles are complex with two independently damaging missense variants remains to be determined.

To conclude, this study further delineates the molecular genetic findings of *KCNV2* retinopathy. Three putative novel variants were identified in our four Japanese patients with CDSRR, and our findings suggest there may be a distinct spectrum of *KCNV2* alleles in the Japanese population. However, the clinical findings were similar to that of the reported other population. Electrophysiology was fundamental to the diagnosis with pathognomonic findings due to channelopathy. The pathognomonic characteristics may be a useful method of determining the success of clinical therapeutic trials with gene replacement or pharmacological treatments for channelopathy.

APPENDIX 1. RESULTS OF IN SILICO MOLECULAR GENETIC ANALYSIS OF *KCNV2* MUTATIONS IDENTIFIED.

To access the data, click or select the words "Appendix 1." Pt = patient; Hom = homozygous; Het = heterozygous; SIFT = sorting Intolerant from Tolerance; HSF = human splicing finder program; CV = consensus values; EVS = exome variant server; POD = possibly damaging; PRD = probably damaging; ND = not detected. SIFT (version 4.0.4) results are reported to be tolerant if tolerance index ≥ 0.05 or intolerant if tolerance index < 0.05. Polyphen-2 (vision 2.1) appraises mutations qualitatively as Benign, Possibly Damaging or Probably Damaging based on the model's false positive rate. The cDNA is numbered according to Ensemble transcript ID ENST00000382082, in which +1 is the A of the translation start codon. Human splicing finder version 2.4.1 was applied to predict the effect of each variant on splicing. The results from HSF matrix indicate the values for the wild type and mutant sequences. The larger difference of values between the wild type and the mutant sequences indicates the greater change that the variant can affect on the splice site. EVS denotes variants in the Exome Variant Server, NHLBI Exome Sequencing Project, Seattle, WA.

APPENDIX 2. MOLECULAR ANALYSIS OF *KCNV2* POLYMORPHISMS.

To access the data, click or select the words "Appendix 2." Pt = patient; Hom = homozygous; Het = heterozygous; SIFT = sorting Intolerant from Tolerance; HSF = human splicing

finder program; CV = consensus values; EVS = exome variant server.

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Comparisons of Pattern Visually Evoked Potentials Elicited by Different Response Time Liquid Crystal Display Screens

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Key Words
Liquid crystal display monitor · Visually evoked potentials · Cathode ray tube · Flash visually evoked potentials · Pattern reversal visually evoked potentials · Contrast · Response time

Abstract
Purpose: To evaluate the usefulness of a liquid crystal display (LCD) with higher driving frequency and shorter response time (2 ms) as a visual stimulator to elicit pattern reversal visually evoked potentials (p-VEPs). ***Method:*** p-VEPs were recorded from 12 eyes of 12 healthy volunteers (28.3 ± 9 years). The p-VEPs elicited by a conventional cathode ray tube (CRT) screen were compared to those elicited by a high-speed LCD screen (2-ms LCD, GD245HQbid, Acer, Taipei, Taiwan). The luminance changes of each monitor were measured with a photodiode. ***Results:*** During the reversal phase the luminance of the 2-ms LCD screen with 97% contrast was transiently reduced, which can elicit an electroretinogram (ERG) and therefore a flash VEP. The 2-ms LCD with 81% contrast checkerboard had a minimal luminance reduction during the reversal phase, and therefore no ERGs were elicited. No significant differences in the amplitude of P100 and the implicit times of N75 and P100 were observed in the p-VEPs elicited by a CRT or the 2-ms LCD screens as stimulators. ***Conclusion:*** The luminance change can elicit flash VEPs, and this artifact can be minimized by using a 2-ms LCD screen with reduced contrast of the checkerboard stimulus.

Introduction

Cathode ray tube (CRT) monitors have been replaced by liquid crystal display (LCD) screens as visual stimulators to elicit pattern reversal visually evoked potentials (p-VEPs). However, LCDs have an inherent problem as visual stimulators because they take several milliseconds for the crystal molecules to change their alignment to permit the light to pass through the polarizing filter of the LCD (http://www.sharp.co.jp/products/lcd/tech/s2_1.html) [1, 2].

The results of earlier investigators [3–5] and our studies [6] showed that the p-VEPs elicited by LCD screens had longer implicit times than those elicited by CRT screens. This was partly due to a transient reduction of the mean luminance of the entire LCD screen at the time of the reversal. This reduction in the luminance was significant because it could elicit electroretinograms (ERGs) and flash VEPs. We named this phenomenon the flash effect. Our earlier study [6] showed that the luminance changes of the LCD were not symmetrical when going

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from black to white or from white to black. We suggested that one solution to the flash effect might be to optimize the contrast of the checkerboard luminance of the LCD screens [6]. However, it would be necessary to reduce the contrast to 65% for some of the commercial monitors to completely eliminate the flash effect. Unfortunately, this exceeds the limit of the International Society for Clinical Electrophysiology of Vision (ISCEV) standard which recommends that the contrast be not less than 80%.

Because the time delay in the luminance change depends on the driving frequency of the LCD, we assumed that a high-speed LCD with a 2-ms response time would have less reduction in the luminance and thereby achieve better performance as a stimulator to elicit p-VEPs.

Thus, the purpose of this study was to compare the luminance profile of LCDs with a 2-ms response time to the more widely used LCD displays with a 5-ms response time. We also compared the p-VEPs elicited by these two types of monitors.

Subjects and Methods

Subjects

Twelve eyes of 12 healthy volunteers, who did not have any ocular diseases except for refractive errors, were studied. There were 4 men and 8 women whose mean age was 28.3 ± 9 years (±standard deviation) with a range of 22–46 years. The guidelines of the Declaration of Helsinki were followed, and this study was approved by the Institutional Review Board of Teikyo University. An informed consent was obtained from all of the subjects after an explanation of the purpose of the study, procedures to be used and possible complications.

Methods

Measurement on Luminance of Single Check

To determine the time delay of each monitor, the luminance change of a single check was measured with a photodiode (S1133, Hamamatsu Photonics Co. Ltd., Hamamatsu, Japan). The photodiode was attached in the upper left corner of the single check.

In addition, the luminances at the 4 corners and 1 point at the center of the entire checkerboard screen were measured with a luminance meter (CA-100S, Konica Minolta Inc., Osaka, Japan). We confirmed that the variation from the center to the periphery was within 20% for each of the monitors, which complies with the standards of the ISCEV guidelines [7].

The luminance and contrast of both the CRT and LCD screens were matched. The contrast between the black and white checks was calculated with the Michaelson contrast formula [8].

Pattern Reversal Stimuli

The visual stimulus was a black-and-white checkerboard generated either on a CRT screen (17 inches, 320 × 230 mm, S710, Compaq Computer Co., USA), an LCD screen (17 inches, 340 × 270 mm, E170Sc, Dell, Tex., USA) or another LCD screen (23.6 inches, 521 × 293 mm, GD245HQbid, Acer, Taipei, Taiwan). Because the aspect ratio of the 2-ms response LCD screen did not match the checkerboard stimulus pattern, the checkerboard pattern of 370 × 275 mm in size was displayed at the center of the 2-ms LCD display by an analog-digital converter (CP-293 Cypress Technology Enterprises Inc., Calif., USA). The overall size of the CRT screen was 19 × 28°, that for the 5-ms response LCD was 21 × 26.2° and that for the 2-ms response LCD screen was 22 × 29°. Both LCD screens are commercially available. The response time was 5 ms for one LCD screen (5-ms response LCD) and 2 ms for the other (2-ms response LCD) according to the specifications of the manufacturers. The response time was defined as the time it takes 1 pixel to turn from white to black or from black to white. Others consider the response time as the time required to change from gray to gray [1, 2].

The maximum contrast was 97% for the experiments. The check size was 0.25° at an observation distance of 70 cm, and the reversal rate was 3.0 reversals/s. The resolution of each monitor was 800 × 600 pixels, and the vertical frequency was 59.8 Hz.

We found that the time delay for the luminance change in the 5-ms response LCD screen led to a transient reduction in the average luminance which we named the flash effect. In our earlier study, we showed that the flash effect was important because it could elicit ERGs and flash VEPs when the stimuli were presented through a diffuser (Kuraray, DFA2-P, Tokyo, Japan) [6]. We compared the flash effect for the 5-ms and 2-ms response LCD screens. Because we found a weak flash effect even with the 2-ms response LCD screen, the contrast of the checkerboard pattern was reduced from 97 to 80% to minimize the flash effect.

p-VEP Recordings

All recordings were performed under dim room lights with an illumination of about 104 lx. The subjects were preadapted to the room lighting before beginning the recordings. A small black fixation point was positioned at the corners of the 4 central checks of the stimulus screen, and the subjects were instructed to fixate the point or the center of the screen and to try not to blink. The subjects wore their best refractive correction, and all recordings were monocular.

The recording electrode was placed on the inion (Oz), and the reference electrode was placed at Fz. The ground electrode was placed on the right earlobe. Signals were amplified 4,000 times (LE-4000, Tomey Corporation, Nagoya, Japan) and bandpass filtered from 1.0 to 100 Hz. The sampling rate was 1.0 kHz, and 128 responses were averaged. The recordings were performed at least twice to determine the repeatability. In addition, the measurements for each subject were performed twice with a 1-week interval to determine the intermeasurement variability.

Data Analyses

The P2 amplitude was measured between N75 and P100, and the implicit times of N75 (N1 implicit time) and P100 (P2 implicit time) were also measured. Student's t tests were used to determine the significance of differences of each parameter. A $p < 0.05$ was taken to be significant.

Results

Luminance Changes of Checkerboard for Each Monitor

The changes in the luminance are plotted against time in figure 1. The input lag, the time between the signal input

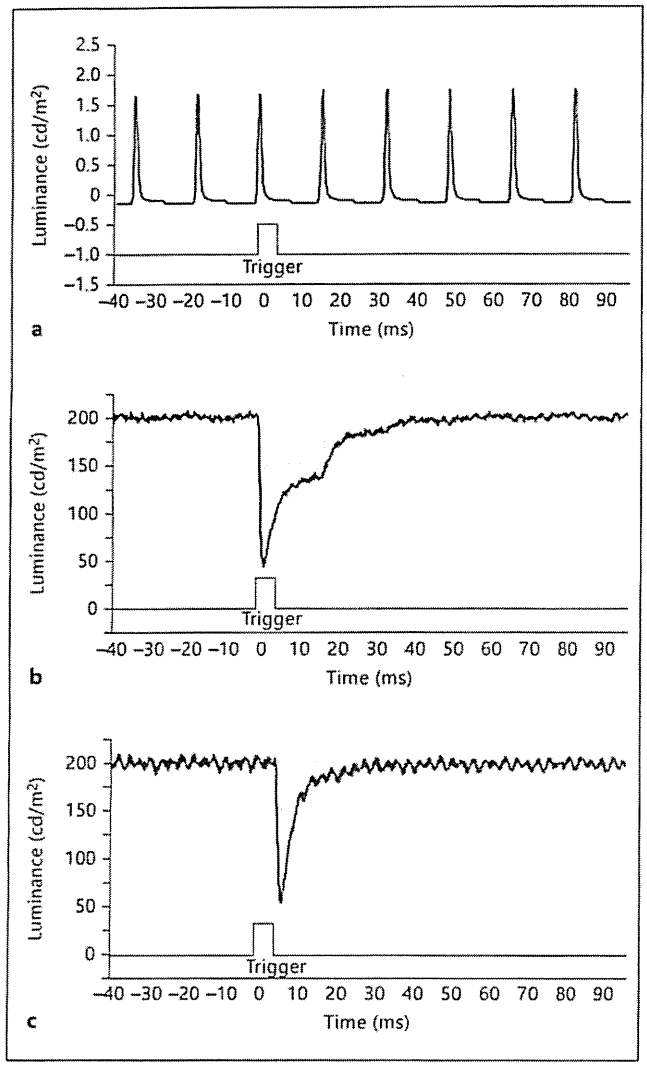

Fig. 1. Changes in the average luminance of a single check of each monitor during a pattern reversal. There is no real luminance change in a single check because half of the checks are changing in the opposite direction. The figure represents luminance changes of the entire screen. **a** Luminance changes of the CRT screen. There is no change in the total luminance (y-axis) during time (x-axis). **b** Luminance changes of a conventional 60-Hz LCD display which we refer to as 5-ms response LCD. There is an abrupt change of the luminance (y-axis) at the time of reversal of the checkerboard (x-axis). The descending point of the luminance reduction begins with a 1.2-ms delay after the trigger signal which is called the input lag. **c** Luminance changes of a conventional 120-Hz LCD screen which we call the 2-ms response LCD screen. An abrupt change of the luminance can be seen. The reduced luminance recovered to the baseline faster than that with the 5-ms response LCD. This may result in a weaker flash effect compared to the 5-ms response LCD. The input lag was 13.7 ms.

to the display to the time a change in luminance is detected, was the longest for the 2-ms response LCD. A burst of pulses at 60 Hz was delivered to the CRT monitor to change the luminance of the white checks, and a square wave pulse was delivered to the LCD screens. No significant delay was detected during the check reversal in the CRT monitor.

During the reversal phase, the luminance change was delayed in the 5-ms response LCD screen especially from black to white. The delay was caused by the time for the crystal liquid molecules to line up to permit light transmission through the polarizing layers. The change in the luminance on the ascending slope was unique to a specific LCD screen. The delay was asymmetrical between black to white and white to black which led to a transient reduction in the mean luminance of the entire screen. However, because the recovery period was rapid in the 2-ms response LCD, the transient reduction was minimal compared with that of the 5-ms response LCD screen.

Nagy et al. [5] reported that the p-VEPs elicited by LCD displays had longer implicit times. The delay was attributed to the total temporal differences between the LCD's electronic input and radiometric output signals, caused by the response time and the input lag. When referred to the trigger, the input lag was measured to be approximately 1.2 ms for the 5-ms response LCD and 13.7 ms for the 2-ms response LCD screens used in this study. The input lag is the time between the input signal leaving the video card and the image appearing on the screen [5, 9]. The reason for this is that the input signal is usually further processed at the display level before it appears on the screen. The image-processing technologies and processing times can vary with the manufacturer, display type and setup parameters, such as the resolution, color settings and internal processes [10]. Because the input lag was constant for the monitors used, it was subtracted from the implicit time in the analyses of the p-VEPs (see 'Comparison of p-VEP components' below).

Pattern Reversal Stimuli to Minimize the Flash Effect

The changes in the luminance of the checks on the LCD screen with contrasts of 97 and 81% are shown in figure 2. The transient changes in the luminance were significantly smaller with 81% contrast.

When a contact lens electrode was placed on the cornea and the stimulus pattern on the monitor was screened by a diffuser, ERGs could be recorded but when the diffuser was placed in front of the CRT monitor, no ERGs were elicited. When the diffuser was placed before the LCD screen with 97% contrast, an ERG was elicited with a positive peak at about 100–120 ms (fig. 3). When the

Fig. 2. Luminance changes of the 2-ms response LCD screen with a maximal contrast of 97% (**a**) and 81% (**b**). The LCD with 81% contrast showed a significant reduction in the change of total luminance during time (x-axis) compared with that with 97% contrast.

contrast was reduced to 81% on the LCD screen, ERGs were not elicited. This indicated that a flash VEP can be elicited with the contrast of the LCD monitor set at 97% but will not when the LCD monitor is set at 81% contrast.

Comparison of p-VEP Components between 5-ms and 2-ms Response LCD Screens

Reproducible VEPs were recorded using each monitor. The P100 amplitude and the N75 and P100 implicit times are plotted in figures 4a–c, respectively. When measuring the implicit time, the input lag of 1.2 ms for the

Fig. 3. ERGs elicited by placing a diffuser before each monitor screen. The ERGs elicited with the diffuser on the CRT monitor (**a**) were below the noise level whereas those with the 2-ms response LCD screen with 97% contrast for checkerboard stimulus (**b**) had a slow negative response. No ERG was recorded (**c**) when the 2-ms response LCD screen with 81% contrast checkerboard was covered by a diffuser.

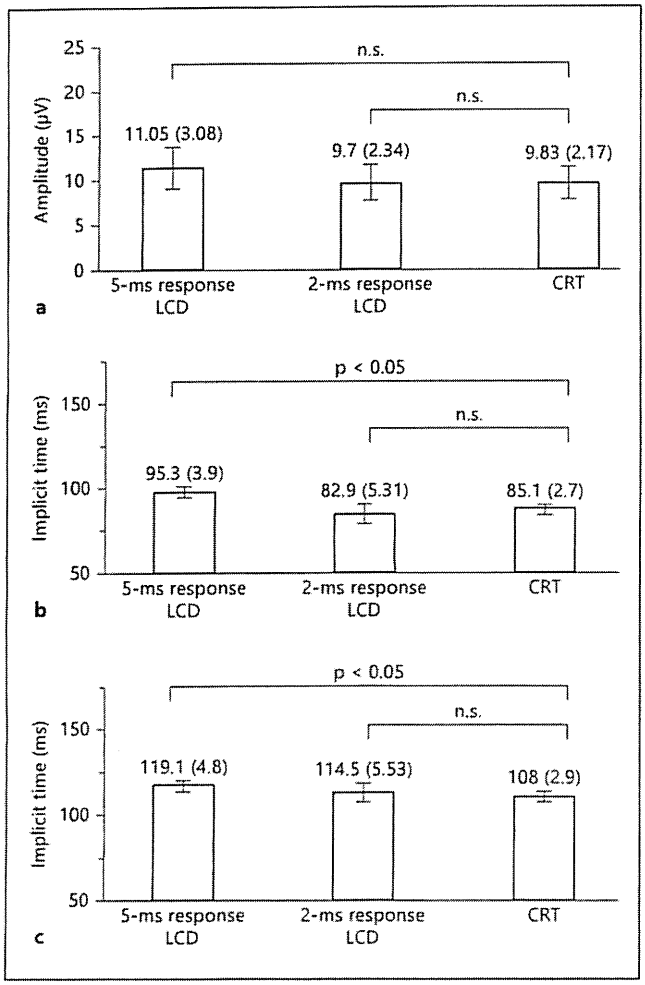

Fig. 4. Comparisons of each parameter between the p-VEPs elicited by CRT and by 5- and 2-ms response LCD screens. **a** No significant difference was found in the VEP P100 amplitude elicited either by the 5- or 2-ms response LCD screen to that elicited by the CRT screen. **b** The implicit time of N75 elicited by the 5-ms response LCD screen was significantly longer than that elicited by the CRT screen. No significant difference was observed in the implicit times of N75 between the p-VEPs elicited by the 2-ms response LCD screen and the CRT screen as a stimulator. **c** The implicit time of P100 elicited by the 5-ms response LCD screen was significantly longer than that elicited by the CRT screen, whereas no significant difference was observed between the implicit times of P100 between the p-VEPs elicited by the 2-ms response LCD screen and CRT screen. n.s. = Not significant.

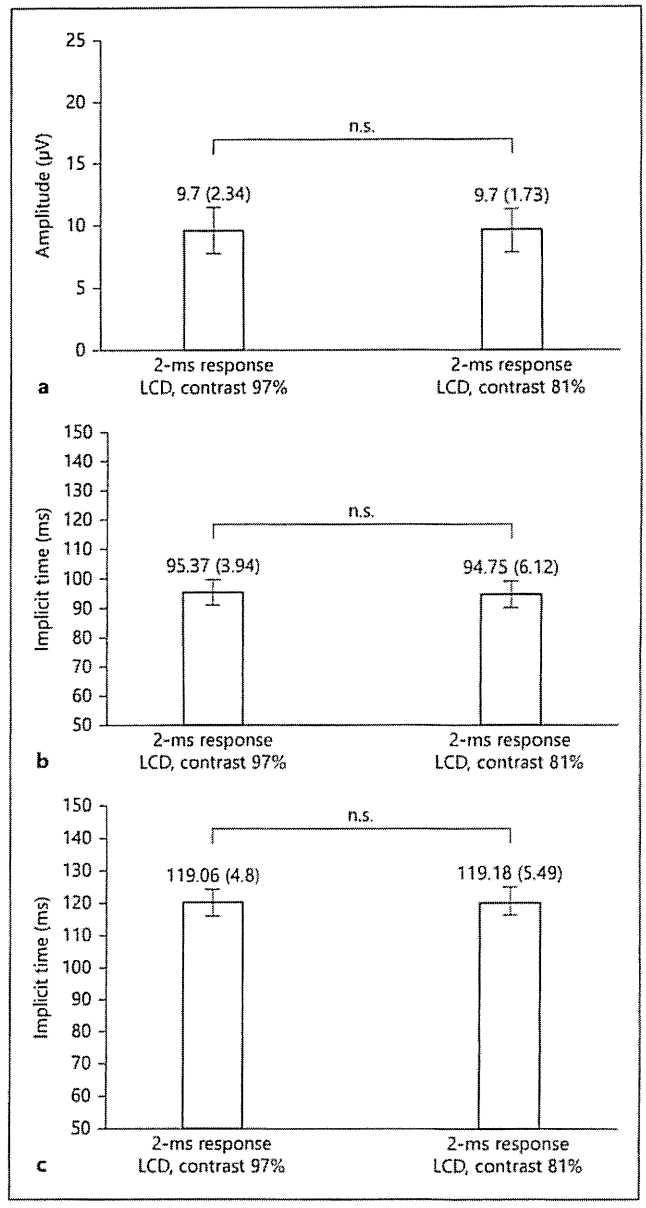

Fig. 5. Comparisons of each parameter of the p-VEPs elicited by a 2-ms response LCD screen with different contrasts of the checkerboard pattern. No significant difference was found in the VEP P100 amplitude (**a**), N75 implicit time (**b**) and P100 implicit time (**c**) elicited either by the 2-ms response LCD screen for contrasts of 97% (left) and 81% (right) of the checkerboard stimulus. n.s. = Not significant.

5-ms LCD display and 13.7 ms was subtracted from the measured times (see 'Luminance changes' above). The difference in the P100 amplitude between the responses was not significant. When compared to the VEPs recorded using the CRT display, the N75 and P100 implicit times were delayed in the VEPs elicited by the 5-ms response LCD screen. However, the N75 and P100 implicit times were not delayed with the 2-ms response LCD screens compared to those elicited by the CRT display.

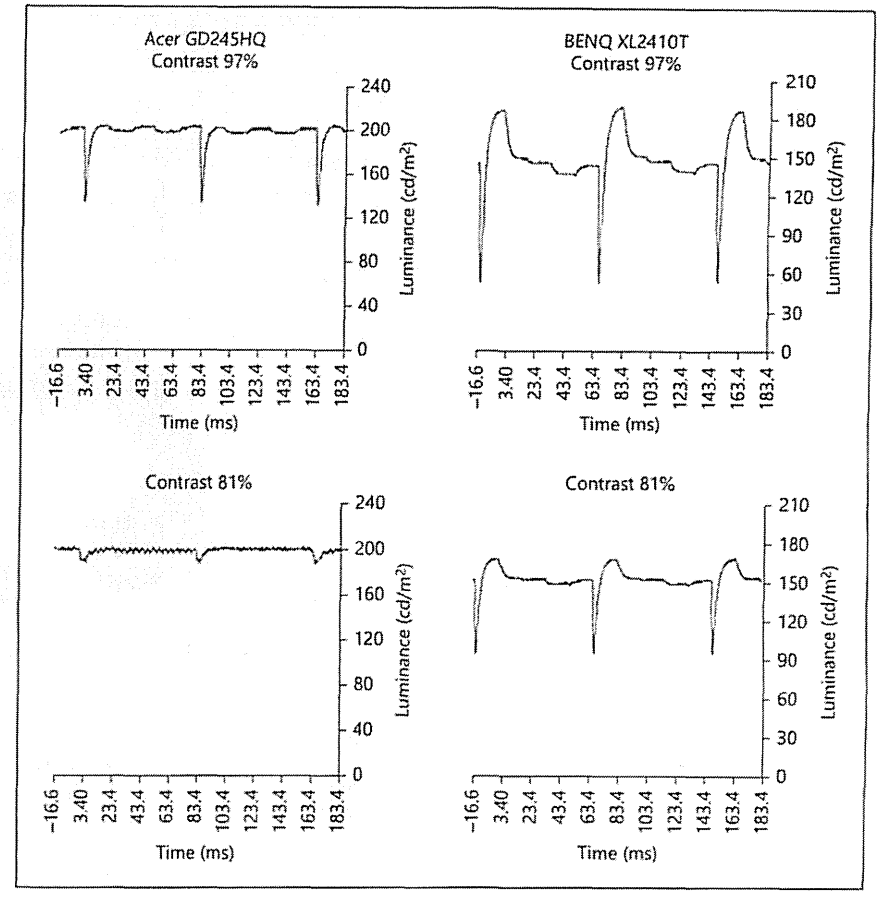

Fig. 6. Transient changes in the luminance in another 2-ms response LCD screen. The left column shows the luminance change of the 2-ms response LCD monitor used in this study (GD245HQbid, Acer) and the right column shows that in another 2-ms response LCD monitor (XL2410T, BENQ, Taipei, Taiwan). Note that the transient change was almost extinguished with the contrast of 81% in the left column whereas it was still marked even with the contrast of 81% in the right column.

Comparison of the p-VEP Waveforms Elicited by 2-ms Response LCD Screen with 97 and 81% Contrast

The P100 amplitude and the N75 and P100 implicit times of the p-VEPs elicited by the 2-ms response LCD display with 97 and 81% contrast are shown in figures 5a–c, respectively. No significant differences in the P100 amplitude, and the N75 and P100 implicit times between the responses with the different contrasts were found.

Discussion

The ISCEV standard for p-VEPs (2009 update) [7] states that the reversal of the black and white checks changes abruptly and repeatedly at a specified number of reversals per second. It also states that there must be no overall change in the luminance of the screen which requires that there be an equal number of light and dark elements in the display, and no transient luminance changes during the pattern reversal. At present, only CRT displays can meet these standards because LCD screens have an inherent time delay when the luminance reverses. For our experiments, we used a 5-ms and a 2-ms response LCD screen.

The effect of the response time on the implicit time has not been fully determined. The input lag and response time are specific to LCD screens, and it is important to compare the p-VEPs elicited by LCD displays to that elicited by CRT displays to normative data obtained from a control group.

Our earlier results showed that when the VEPs were elicited by a 5-ms response LCD screen, the implicit times of N75 and P100 were longer than that for VEPs elicited by a CRT screen. The delay is partly attributed to a transient change in the average luminance of the LCD monitor or the flash effect [6]. The flash effect can be minimized by decreasing the contrast of the checks, but the contrast must be reduced to 65% to completely remove the luminance artifact when using the 5-ms response LCD screen (17 inches, 340 × 270 mm, RDT233WX, Mit-

subishi, Tokyo, Japan). This lower contrast does not meet the ISCEV standard [6].

We hypothesized that using an LCD screen with shorter response time would minimize the flash effect. To test this hypothesis, we compared the p-VEPs elicited by a 2-ms response LCD screen to those elicited by a 5-ms response LCD. Our results showed that the implicit times of the p-VEPs elicited by the 2-ms response LCD screen were significantly shorter than that by the 5-ms response LCD screen (fig. 1), but ERGs could still be elicited when the 2-ms response LCD screen was covered with a diffuser (fig. 3).

Thus, we reduced the contrast of the checkerboard pattern to decrease the flash effect as we did for the 5-ms LCD display [6]. Our results showed that the flash effect was greatly reduced, and ERGs were not elicited with 81% contrast (fig. 2, 3). From these results, we conclude that a flash VEP can be eliminated by using a 2-ms response LCD screen with 81% contrast.

When comparing the p-VEPs elicited by the 2-ms response LCD screen to those elicited by the CRT, no significant difference was found in the amplitude of the P100 and the implicit times of N75 and P100 when the contrast of the 2-ms response LCD screen was set at 97 or 81% (fig. 5). These findings suggest that the 2-ms response LCD screen is a better substitute for the CRT screen as a stimulator for eliciting p-VEPs especially when the contrast was set at 81%.

However, the luminance change during the pattern reversal is different depending on the specifications of the LCD screen (fig. 6) as was the case for the LCD screens used in this study [6]. Thus, a reduction of the contrast may not eliminate the flash effect in all the commercial 2-ms response LCD displays. Further investigations on how to eliminate the flash effect are needed. Alternative ways might be using an organic electric-luminescence display to eliminate the flash effect.

In conclusion, the p-VEPs are affected by the flash effect and the input lag during the reversal phase when the checkerboard stimulus is generated on LCD screens. The flash effect can be reduced by using 2-ms response LCD screens and by reducing the contrast of the checkerboard pattern to approximately 81%. The p-VEPs elicited by such LCD displays are comparable to those elicited by conventional CRT screens.

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Disclosure Statement

No author has any financial or proprietary interest in any material or method mentioned.

H. Funada is an employee of Tomey Corp., Japan. Tomey Corp. had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. All commercial identities mentioned in the manuscript were purchased by Teikyo University School of Medicine without receiving any financial gain. All authors have no additional competing interest that potentially influences the study, including financial relation.

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RESEARCH PAPER

Low luminance visual acuity in patients with central serous chorioretinopathy

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Background: The aim was to determine the low luminance visual acuity in eyes with central serous chorioretinopathy.

Methods: Seven eyes of seven patients with central serous chorioretinopathy and six eyes of six age-matched normal volunteers were examined. Low luminance visual acuity charts were created by an Apple Power Mac G5 computer and displayed on a cathode ray tube monitor (SONY GDM-F500). The background luminance was set at six different levels from 78.20 cd/m^2 to 0.37 cd/m^2. The visual acuities of the eyes with central serous chorioretinopathy at each of the six luminance levels were compared to those from their fellow eyes and to normal eyes.

Results: The mean visual acuities varied from 0.13, 0.23, 0.29, 0.42, 0.62 to 0.70 logMAR units as luminance varied from high to low. At the lowest luminance (0.37 cd/m^2), five of the seven eyes could not read any character. The mean visual acuities of the fellow eyes at the same luminance levels were 0.03, 0.06, 0.11, 0.20, 0.27 and 0.45 logMAR units and those of the normal volunteers were 0, 0.03, 0.08, 0.14, 0.23 and 0.38 logMAR units, respectively. The visual acuities of the eyes with central serous chorioretinopathy were significantly poorer than those of the normal eyes at all luminance levels except 0.37 cd/m^2 ($p < 0.05$ for all).

Conclusions: Although the eyes from all three groups had 0 logMAR units visual acuity under standard testing condition, the visual acuity of the eyes with central serous chorioretinopathy were significantly worse at low luminance levels. The low luminance visual acuity may provide information on the visual disturbances reported by central serous chorioretinopathy patients with 0 logMAR units visual acuity.

Key words: central serous chorioretinopathy, contrast sensitivity, low luminance visual acuity, optical coherence tomography, serous retinal detachment

Central serous chorioretinopathy (CSC) is characterised by a serous retinal detachment in the macular area. Central serous chorioretinopathy patients range in age from 20 to 50 years but most are middle-aged men. The central serous chorioretinopathy causes a central and paracentral relative scotoma in the visual field.[1–3] Although the visual acuity (VA) is relatively good, patients often complain of difficulty with visual activities performed in the evening and at night under low ambient illumination. In conventional VA tests, such visual disturbances are usually not detected because the backgrounds of VA testing charts have high luminance.

To evaluate patients with central serous chorioretinopathy and visual disturbances

under low luminance conditions, we need to measure the VA using test charts with low background luminance. It is well known that VA is affected by the degree of ambient luminance and Shaler[4] reported that the VA of normal eyes decreased under low luminance conditions. Because patients with good VA can have depressed visual function, for example, decreased contrast sensitivity, poorer colour discrimination, reduced focal macular electroretinogram (ERG), reduced focal retinal sensitivity and visual field defects,[5–12] it might be expected that patients with central serous chorioretinopathy would also have decreased VA under low luminance. There have been no studies focusing on low luminance VA in patients with central serous chorioretinopathy.

The purpose of this study was to determine the VA of patients with central serous chorioretinopathy under low luminance conditions. To accomplish this, we made a computer program to create low luminance visual acuity charts and determined the VA under six different background luminance levels in seven patients with central serous chorioretinopathy.

METHODS

Seven eyes of seven patients with central serous chorioretinopathy and six eyes of six age-matched healthy control subjects were tested. The inclusion criteria were:

1. presence of subretinal fluid (serous retinal detachment: SRD) involving the fovea in the optical coherence tomographic (OCT) images
2. unilateral central serous chorioretinopathy with the fellow eye normal and
3. visual acuity of 0 logMAR or better in both eyes.

The exclusion criteria were:

1. evidence of choroidal neovascularisation in the fluorescein angiographic (FA) and indocyanine green angiographic images and
2. the presence of other ocular or macular diseases.

Patients with central serous chorioretinopathy, who had received laser photocoagulation were also excluded.

The diagnosis of central serous chorioretinopathy was based on the presence of a serous retinal detachment documented by leakage from the retinal pigment epithelium in the fluorescein angiographic images. The VA was measured with a Landolt C chart using standard retroillumination with a luminance of 220 cd/m^2. We also examined six eyes of six normal volunteers with the same testing protocol. The OCT examination was carried out with either a Heidelberg Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany) or with a Stratus OCT 3000 (Carl Zeiss Meditec, Inc, Dublin, CA, USA). The height of the serous retinal detachment (SRDH), the width of the serous retinal detachment (SRDW) and the thickness of sensory retina (foveal thickness: FT) were manually measured in the horizontal cross-sectional OCT images, which included the fovea (Figure 1). These measurements were made by one of the authors (KS), who had no information about the patients. The values of these parameters were used for statistical analyses.

The procedures used in this study conformed to the tenets of the Declaration of Helsinki. An informed consent was obtained from all subjects. Approval to conduct this study was obtained from the Institutional Review Board of Surugadai Nihon University Hospital, Tokyo, Japan.

Low luminance visual acuity charts and procedures

Low luminance VA charts were created with an Apple PowerMac G5 computer and displayed on a monitor (SONY GDM-F500). Landolt Cs were used for the characters and they followed the design rule of the Early Treatment Diabetic Retinopathy Study charts (Figure 2). Six levels of background luminance were used, namely, 78.20 cd/m^2, 31.87 cd/m^2, 11.37 cd/m^2, 4.14 cd/m^2, 1.30 cd/m^2 and 0.37 cd/m^2. The luminance of the Landolt C rings was kept as close to zero cd/m^2 as possible and the contrast for all conditions approached 100 per cent.

Identification of the largest Landolt C at the distance of 308 cm represented a VA of 0.7 logMAR units. The ring size was reduced in steps of 0.1 to -0.4 logMAR units. The tests were conducted from the lowest luminance level in a dark room after waiting seven minutes for dark adaptation.

Analyses

We compared the VA of the eyes with central serous chorioretinopathy with that of the fellow eyes and that of normal eyes at each luminance level. To determine the statistical significance of any differences, Student's t-tests were used. The VA in logMAR units was plotted on the ordinate for the different luminance levels on the abscissa. The data were fit to a linear equation as:

$$y = a \times x + b,$$

where 'y' is the logMAR VA and 'x' is the luminance expressed in logarithmic units. 'a' is the steepness of the best-fitted line and represents how much the VA is altered by a step change in the background luminance.

Thus, a large 'a' value means that the VA would be greatly changed by a step change in the background luminance. 'b' is the logMAR VA at very low or no background luminance, that is, when 'x' is zero. This is the point where the regression line intersects the ordinate of the logMAR VA line (Figure 1). The difference in the slopes for central serous chorioretinopathy, fellow and normal eyes were tested for significance by assessing the interaction term between background luminance and eye type using an analysis of covariance (ANCOVA) technique.

The correlations between the parameters of the OCT images and the constants 'a' and 'b' were determined by the Spearmann coefficients of correlation. The Bonferroni correlation was used to avoid type I error. The statistical significance was set at 0.01 for the t-tests because there were five comparisons and at 0.17 for the ANCOVA because there were three comparisons.

RESULTS

The patients with central serous chorioretinopathy included five men and two women and the mean and standard deviation of their ages was 41.3 ± 3.9 years (range 39–50 years). The duration of the

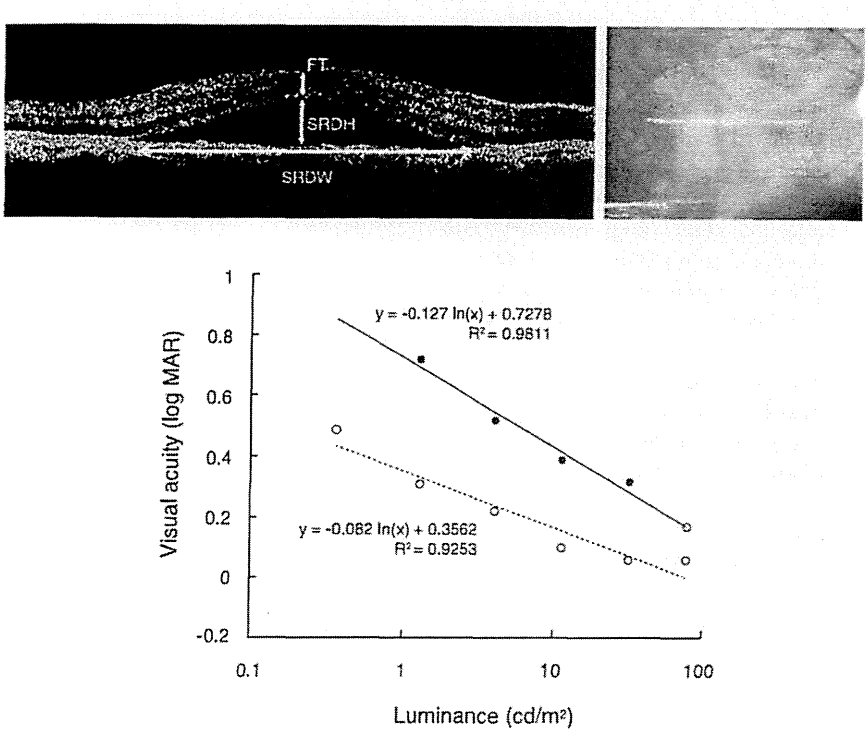

Figure 1. Optical coherence tomographic (OCT) image and infrared fundus photograph; also shown in a graph relating the visual acuity in logMAR units to the background luminance in eyes with central serous chorioretinopathy (CSC). The serous retinal detachment height (SRDH) was taken to be the distance between the outer segment/inner segment (IS/OS) line of the photoreceptors and the anterior surface of the retinal pigment epithelium/Bruch membrane. The width of the serous retinal detachment (SRDW) was taken to be the width of the serous retinal detachment in the OCT images and the foveal thickness was the distance between the internal limiting membrane (ILM) and IS/OS line. In cases where the IS/OS line was not clear, the basal edge of the hyper-reflective band representing the detached sensory retina was used.
Top left: Horizontal cross-sectional optical coherence tomographic (OCT) image including the fovea in an eye with central serous chorioretinopathy (Case 5). The cross-section corresponds to the horizontal line indicated in the right side of the fundus photograph. The serous retinal detachment height (SRDH), width of the serous retinal detachment (SRDW) and the foveal thickness (FT) are shown.
Top right: Infrared fundus photograph indicating the cross line of the left-side OCT image.
Bottom: Relationship between logMAR visual acuity (VA) and background luminance in Case 5. The logMAR VA was linearly correlated with the luminance. The logMAR VA of the central serous chorioretinopathy-affected eye was higher than that of the healthy fellow eye at each luminance level. ●: affected eye, ○: healthy fellow eye. The fitted line and the formula are shown as well.

symptoms was 1.0–1.5 months (Table 1). The mean ages of the normal volunteers was 38 ± 9 years (range 22–47 years). The mean VAs of the central serous chorioretinopathy and fellow eyes at each luminance are shown in Table 1. At the lowest luminance level of 0.37 cd/m^2, five of seven patients could not correctly identify any of the targets using the eye with central serous chorioretinopathy. The mean VAs of the normal volunteers were 0 ± 0.05, 0.03 ± 0.04, 0.07 ± 0.06, 0.14 ± 0.06, 0.23 ± 0.11 and 0.38 ± 0.11 logMAR units, respectively.

The VA in logMAR units is plotted against the background log luminance in Figure 3. The VA of the eyes with central serous chorioretinopathy was significantly poorer than that of normal eyes at all luminances except 0.37 cd/m^2 and 78.20 cd/m^2 ($p < 0.01$ for all). The VA of the eyes with central serous chorioretinopathy was significantly poorer than that of fellow eyes at all luminances except 0.37 cd/m^2 and 78.20 cd/m^2 ($p < 0.01$ for all). No significant differences were found among the central serous chorioretinopathy, fellow and volunteer eyes in the slopes of the fitted linear function by ANCOVA.

The constants, 'a' and 'b' and the coefficient of regression (R^2) are shown in Table 2. There was no significant correlation between any OCT parameters and 'a' (slope) or 'b' (intercept).

DISCUSSION

Patients with central serous chorioretinopathy have a relatively central scotoma, metamorphopsia, micropsia, colour vision abnormalities and visual disturbances under low luminance despite the relatively good standard VA. Studies on the relationship between the luminance of the VA charts and VA in eyes with central serous chorioretinopathy have not been reported. Patients with central serous chorioretinopathy often complain of difficulty in reading during the evening and night, that is, at low luminance levels. The VA obtained by conventional acuity charts is not a good measure for predicting how these patients will perform in low luminance environments.

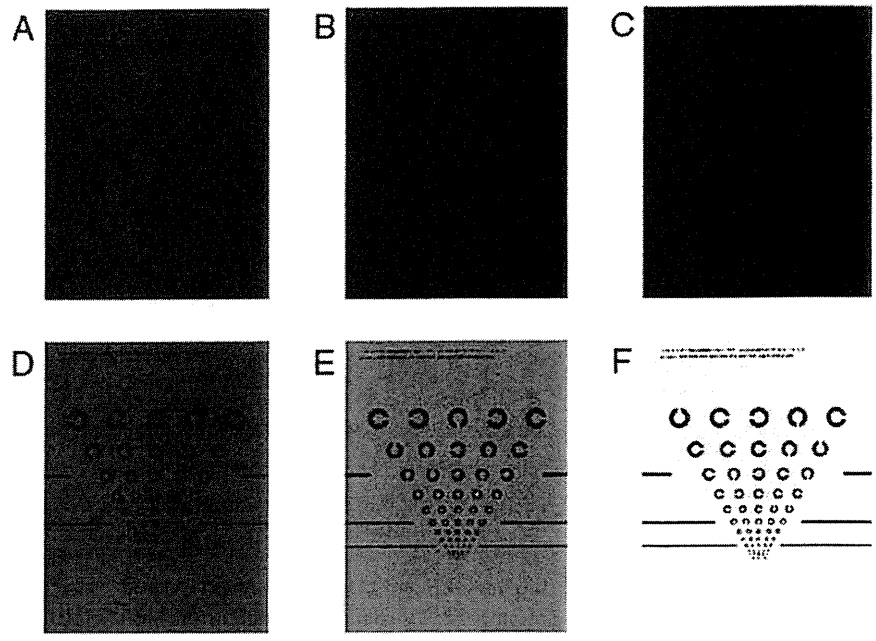

Figure 2. Low luminance visual acuity charts. The background luminance values were (A) 0.37 cd/m², (B) 1.30 cd/m², (C) 4.14 cd/m², (D) 11.37 cd/m², (E) 31.87 cd/m² and (F) 78.20 cd/m². Low luminance charts are difficult to reproduce in print.

Table 1. Visual acuities under different background luminances in patients with central serous chorioretinopaty

Patient no.	Age (years)	Gender	Affected eye						Fellow eye					
			78.20 cd/m²	31.87 cd/m²	11.37 cd/m²	4.14 cd/m²	1.30 cd/m²	0.37 cd/m²	78.20 cd/m²	31.87 cd/m²	11.37 cd/m²	4.14 cd/m²	1.30 cd/m²	0.37 cd/m²
1	39	M	0.01	0.12	0.15	0.27	0.55	N.R.	-0.04	0	0	0.03	0.13	0.35
2	41	F	0.16	0.16	0.24	0.3	0.46	0.64	0.03	0.06	0.12	0.17	0.34	0.45
3	50	F	0.16	0.28	0.31	0.5	0.65	N.R.	0.1	0.22	0.31	0.4	0.42	0.55
4	41	M	0.13	0.29	0.3	0.41	0.58	0.76	0.03	0.02	0.07	0.17	0.18	0.45
5	40	M	0.17	0.32	0.39	0.52	0.72	N.R.	0.06	0.06	0.1	0.22	0.31	0.49
6	39	M	0.15	0.23	0.26	0.37	0.59	N.R.	0.04	0.07	0.1	0.24	0.35	0.5
7	39	M	0.1	0.22	0.36	0.6	0.76	N.R.	0.01	0	0.1	0.2	0.29	0.36

Visual acuities are shown as logMAR. M: male, F: female, N.R.: not recordable

Table 2. Parameters of the optical coherence tomographic image and fitting of low luminance visual acuity in eyes with central serous chorioretinopathy

Case	Age	Gender	OCT parameter (μm)			Low luminance visual acuity			
			FT	SRDH	SRDW	a	b	R^2	p
1	39	M	183.3	275.0	2703.1	-0.121	0.5098	0.9079	0.0122
2	41	F	216.7	141.7	1171.9	-0.091	0.4932	0.9292	0.0193
3	50	F	244.1	141.1	2458.2	-0.118	0.6607	0.9636	0.0030
4	41	M	180.7	231.4	3004.7	-0.111	0.6143	0.9648	0.0005
5	40	M	191.7	308.3	2745.0	-0.127	0.7278	0.9811	0.0011
6	39	M	183.1	404.3	4086.0	-0.101	0.5603	0.9171	0.0104
7	39	M	181.2	322.1	3239.9	-0.166	0.8049	0.9894	0.0005

M: male, F: female, OCT: optical coherence tomography, these parameters are indicated in Figure 1.
FT: foveal thickness, SRDH: height of the serous retinal detachment, SRDW: width of serous retinal detachment. When low luminance visual acuity was plotted against background luminance as shown in Figure 1, the following formula was fitted: $y = a \times x + b$, when y indicates logMAR and x indicates log(luminance), R^2: coefficient of regression

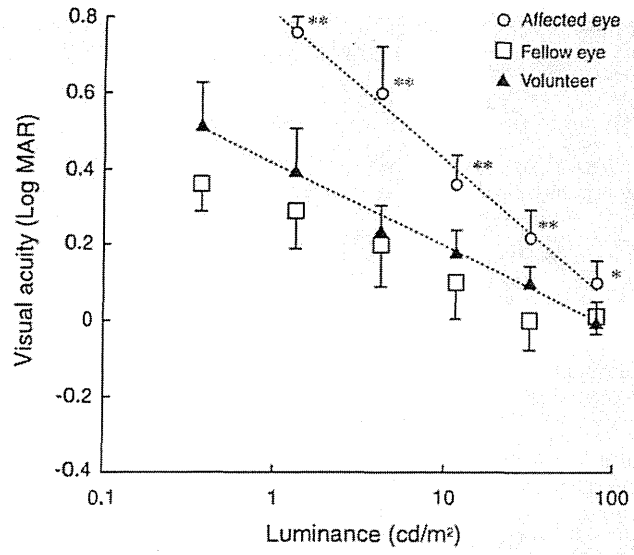

Figure 3. Relationship between logMAR visual acuity (VA) and the log background luminance. The data were fitted by the least square method and a linear equation between the logMAR VA and log luminance for the three groups. The logMAR VA is linearly correlated with the luminance. The logMAR VA of the eye with central serous chorioretinopathy is significantly higher than that of the fellow eye at each luminance level. Visual acuities at all levels of luminance except 0.37cd/m² are significantly different between central serous chorioretinopathy and the eyes of normal volunteers (*p < 0.05, **p < 0.01). ○: affected eye, □: fellow eye, ▲: normal eye of control participants, error bars indicate standard deviation.

Thus, we developed a computer program which allowed us to create Landolt Cs on a computer monitor screen with different background luminances. With these targets and background luminances, we were able to evaluate how luminance levels affected the VA in central serous chorioretinopathy patients.

Shlaer[4] reported that lower background luminances led to lower VA in normal eyes and we obtained similar results in our normal eyes. The VA of eyes with central serous chorioretinopathy also decreased according to the decrease in background luminance but the deterioration was more severe than that of normal eyes at all background luminance levels. We found that VA in logMAR units was linearly correlated with the logarithm of the background luminance. The logMAR VA in eyes with central serous chorioretinopathy was significantly higher, that is, poorer VA, than that in normal control eyes.

Hypotheses have been presented to explain the decreased VA under low luminance in normal eyes.[13,14] Thus, Hecht[13] suggested that the number of cone photoreceptors activated is decreased at low luminances. Our subjects were dark-adapted for seven minutes before testing and the cone system was expected to be functioning during this period in a healthy retina, and all of the normal fellow eyes could see at the lowest background luminance. Five of seven eyes with central serous chorioretinopathy could not identify even one Landolt C at the lowest luminance level, although the VA measured under standard conditions was at least 0 logMAR units in all eyes. These findings suggest that the foveal cones are not functioning normally in low light conditions in eyes with central serous chorioretinopathy.

Chuang and colleagues[15] reported that the rods were more affected than cones in eyes with central serous chorioretinopathy; however, they did not evaluate the rods selectively to determine whether the cones were indeed normal. The decreased VA measured under mesopic conditions in our study is probably due to impairments of both cone and rod function. This is consistent with the results of the Humphrey perimetric retinal sensitivity decrease in the detached area in eyes with central serous chorioretinopathy.[9]

Recent advances in OCT have provided some correlations of the foveal microstructure with visual function in several retinal diseases.[9,16–19] Sekine, Imasawa and Iijima[9] reported that the thickness of the serous retinal detachment and not neurosensory retinal thickness, was significantly correlated with visual sensitivity measured by automated static perimetry in eyes with central serous chorioretinopathy. It was also reported that the initial VA was significantly worse in eyes with a higher serous retinal detachment in Vogt-Koyanagi-Harada disease but it was not significantly correlated with foveal thickness.[17] Therefore, we anticipated the possibility that some morphological parameters might be correlated with low luminance VA but this was not the case. Many factors such as the patient's age, duration of central serous chorioretinopathy, size of the detached area, central cone function and arrangement of cone and rod cells, may have influenced the low luminance VA.

There are some limitations of this study. The small sample might have limited the statistical power of our anlayses. Further investigation on the relationship between microstructural changes and low luminance VA would be helpful for understanding the pathologic mechanism of patients' complaints under reduced luminance conditions.

Studies of cases of unilateral central serous chorioretinopathy have shown that

the fellow eyes can have subclinical central serous chorioretinopathy. The studies of Maaranen, Tuppurainan and Mäntyjärvi[20] and Baran, Gürlü and Esgin[21] support this suggestion because they found a high percentage of colour deficiency in the fellow eyes of patients with central serous chorioretinopathy. Baran, Gürlü and Esgin[21] also observed that contrast sensitivity was reduced in the fellow eyes of patients with unilateral central serous chorioretinopathy. Iida and colleagues[22] reported choroidal vascular abnormalities in indocyanine green angiographic images in the unaffected fellow eye. In our study, the VA of fellow eyes was not significantly different from that of age-matched normal eyes. Further studies are needed to assess the visual status of fellow eyes.

In conclusion, the VA of eyes with central serous chorioretinopathy was significantly more depressed at low background luminances than normal eyes. Low background luminance VA testing is useful for evaluating visual disturbances at low ambient luminance experienced by patients with central serous chorioretinopathy. There is a potential use here as one of the functional parameters in evaluating and flagging of central serous chorioretinopathy or therapeutic effect of new therapies such as photodynamic therapy.

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ORIGINAL RESEARCH ARTICLE

Liquid crystal display screens as stimulators for visually evoked potentials: flash effect due to delay in luminance changes

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Abstract
Purpose The cathode-ray tube (CRT) screen has recently been replaced by liquid crystal display (LCD) screens as visual stimulators for pattern-reversal visually evoked potentials (p-VEPs). The aim of the study was to evaluate the usefulness of LCD screen to elicit p-VEPs.
Methods The waveforms of the p-VEPs elicited by a LCD panel were compared with those elicited by a conventional CRT screen. The changes in the luminance of each screen were measured with a photodiode, and the mean luminance change was measured with a luminance meter. VEPs and electroretinograms (ERGs) were also recorded when the monitor was covered by a diffuser.
Results The p-VEPs elicited by the LCD consisted of the N75 and P100 components of the conventional VEPs and had good reproducibility. The average latency of these components was significantly delayed by 9.8 ms for N75 and 10.2 ms for P100, and the N75-P100 amplitude was significantly larger than the conventional p-VEP elicited by the CRT screen. During the reversal phase, especially from black-to-white, the luminance of the LCD screen was transiently reduced, and it elicited a flash VEP and ERG. A reduction in the contrast of the checks minimized the transient change in the luminance, and the VEP waveform was more similar to that elicited by the CRT screen.
Conclusions The results suggest that when an LCD monitor is used as an alternative visual stimulator to elicit p-VEPs, the delay in the luminance change and the flash effect needs to be taken into account.

Keywords Liquid crystal display monitor · Visually evoked potentials · Cathode-ray tube · Flash visually evoked potentials · Pattern-reversal visually evoked potentials · Contrast

Introduction

Most electrophysiological laboratories use cathode-ray tubes (CRTs) on which various types of stimuli can be generated, for example, checkerboard patterns to elicit pattern-reversal visual evoked potentials (p-VEPs). However, the CRT has recently been replaced by liquid crystal display (LCD) screens, and more and more manufacturers of VEP instruments have been selected to use LCD screens as visual stimulators. In the International Society for Clinical Electrophysiology of Vision (ISCEV) standard for clinical visual evoked potentials (2009 update) [1], the type of optimal stimulator was not mentioned.

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