unremarkable in both eyes (Fig. 1). Fluorescein fundus angiography, indocyanine-green fundus angiography, and optical coherence tomography were performed, and they were also unremarkable (Figs. 2, 3). Farnsworth panel D-15 test and Farnsworth–Munsell 100-hue test showed tritanopia in both eyes (Fig. 4). Goldmann kinetic perimetry and white-on-white static perimetry showed no abnormality in either

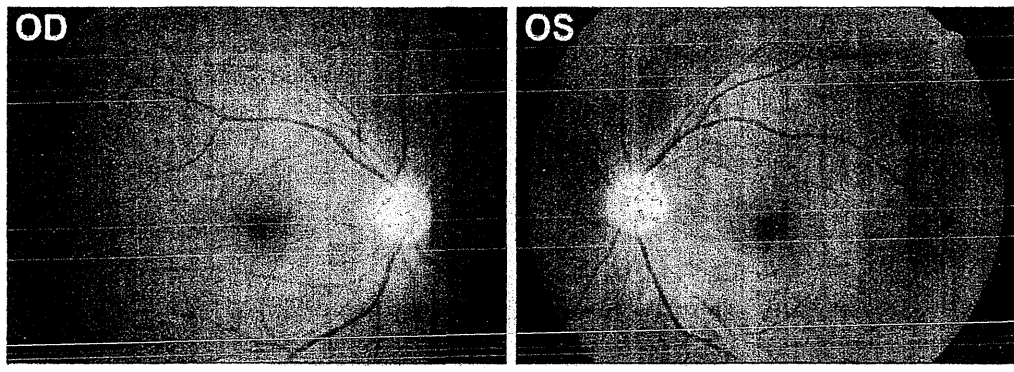


Fig. 1 Fundus photographs. No abnormality was found in both eyes

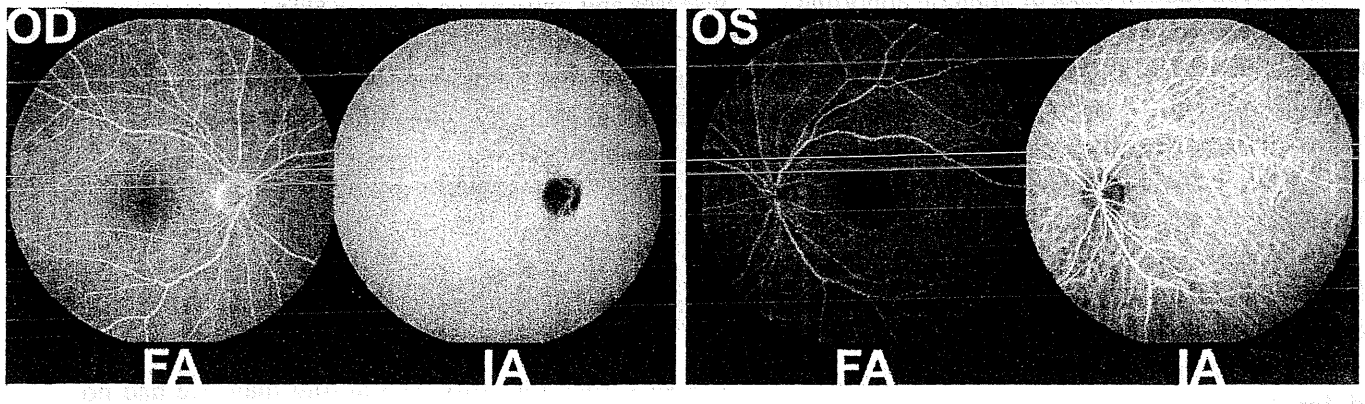


Fig. 2 Results of fluorescein and indocyanine-green fundus angiograms (FA and IA). FA and IA were performed simultaneously using HRA^{TM}2 (Heidelberg Engineering, Heidelberg, Germany)

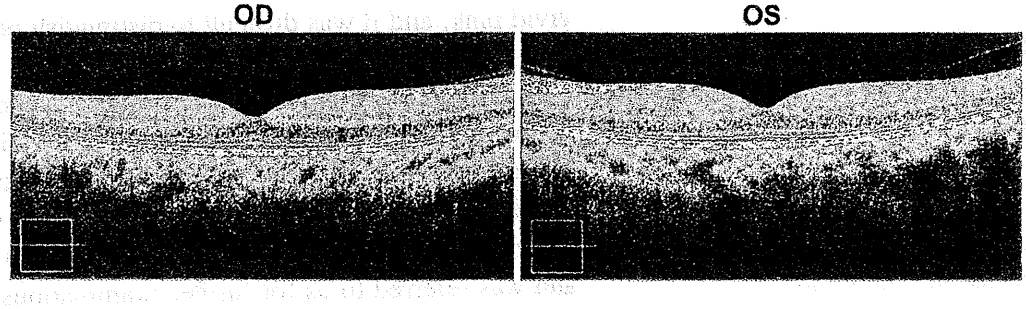


Fig. 3 Results of optical coherence tomography (OCT). Horizontal section of macular area was shown. Retinal structure was normal including photoreceptor layer, middle layer, and nerve fiber layer. OCT was performed using Cirrus^{TM} HD spectral-domain optical coherence tomography (Cirrus^{TM} HD-OCT; Carl Zeiss Meditec, Dublin, CA)

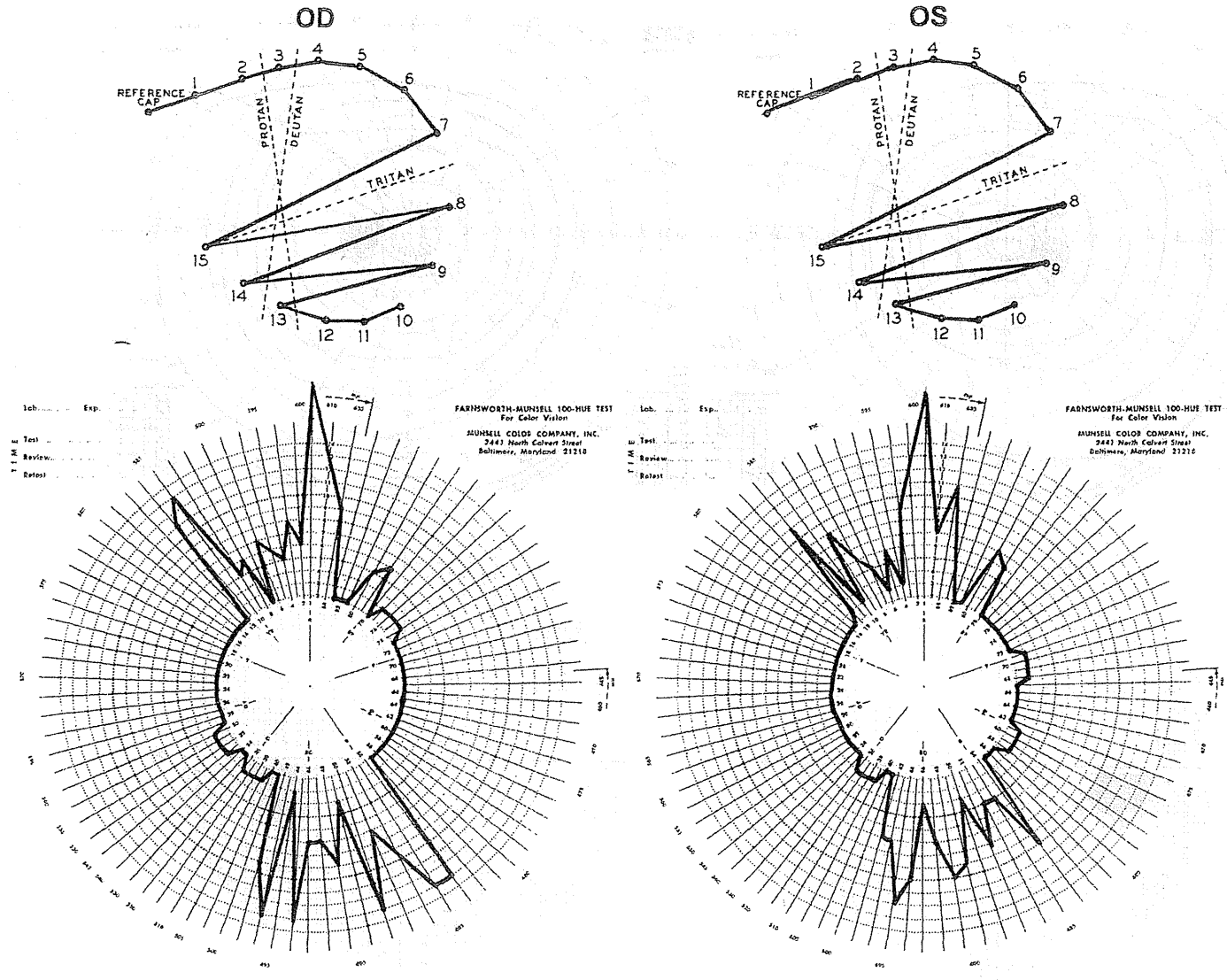


Fig. 4 Results of Farnsworth panel D-15 test (*upper row*) and Farnsworth–Munsell 100-hue test (*lower row*). Tritanopia is suggested clearly in both eyes

eye; however, blue-on-yellow static perimetry detected remarkably reduced sensitivity at the lower visual field in both eyes (Fig. 5).

ISCEV-standard full-field electroretinograms (ERGs) [3] were normal (Fig. 6); however, blue-on-yellow ERGs [4] showed attenuated b-wave that was derived from SWS cone systems in both eyes (Fig. 7).

Optic nerve and central nervous system were investigated using magnetic resonance imaging and recording of visual evoked potentials, and they were unremarkable.

The patient quitted smoking the electronic cigarette after the symptom, and he was observed for 1 year. However, his condition was stationary with no improvement or worsening of color vision, visual acuity, and fundus appearance.

Discussion

The SWS cone system is vulnerable in retinal diseases compared to middle- and long-wavelength-sensitive (MWS and LWS) cone systems [5–8].

The results of color vision test indicated distinct tritanopia (Fig. 4). And the reduction in SWS-cone ERG (Fig. 7) indicated that the tritanopia was caused

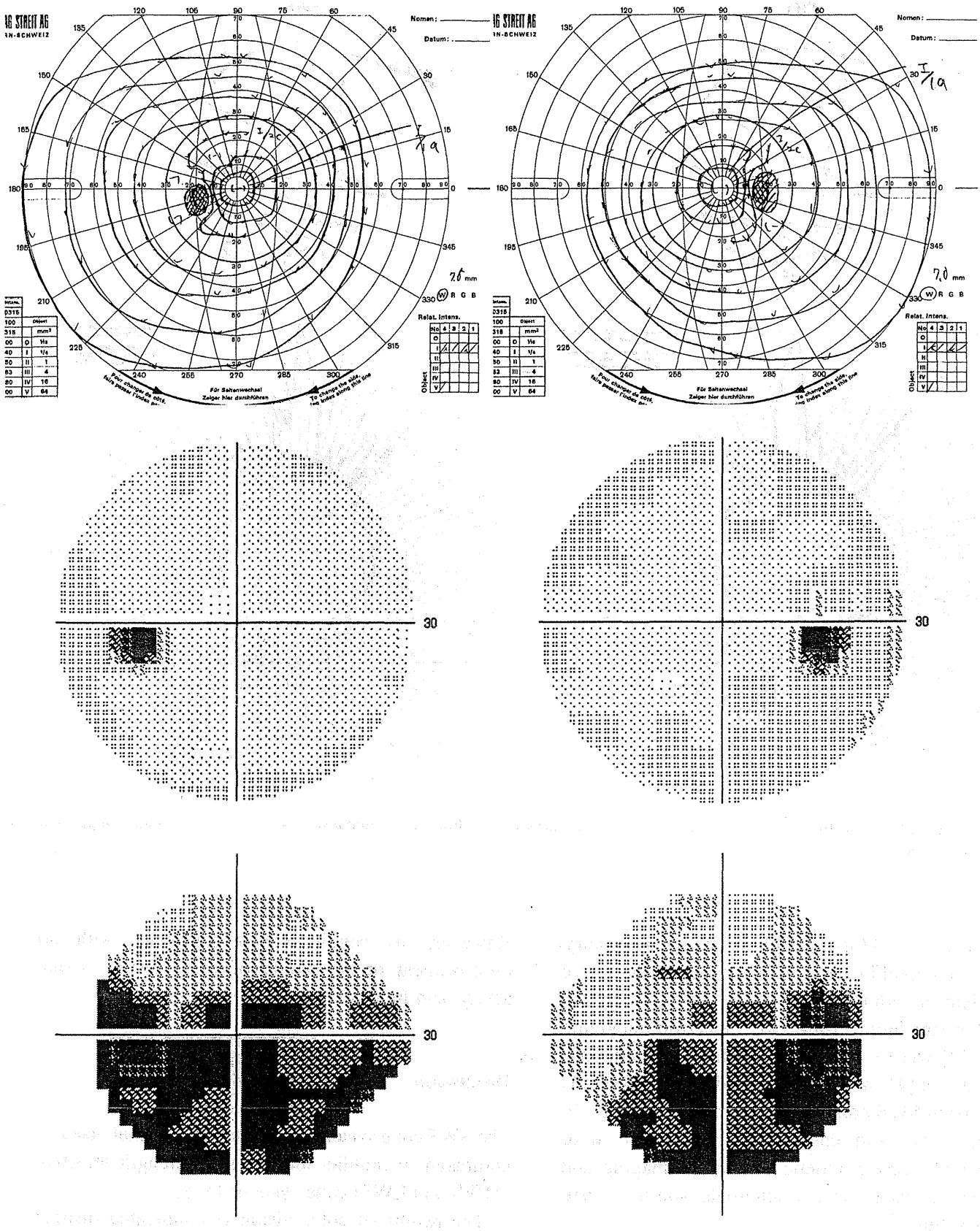


Fig. 5 Results of Goldmann kinetic perimetry (GP *upper row*), Humphrey white-on-white static perimetry (W/W *middle row*), and Humphrey blue-on-yellow static perimetry (B/Y *lower row*). No visual field defects were detected except in blue-on-yellow static perimetry

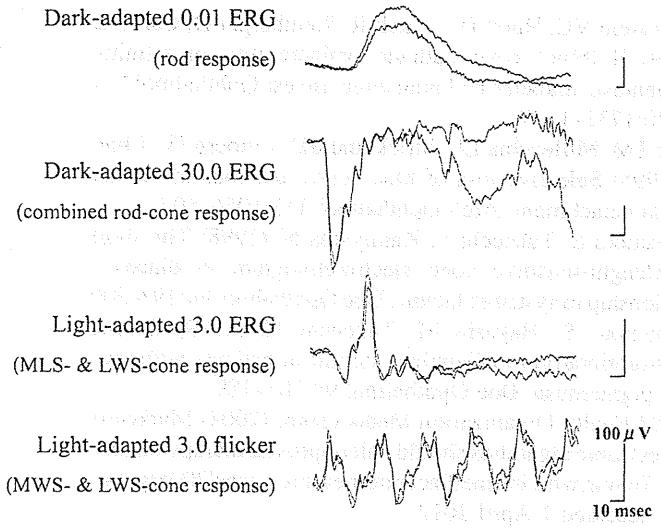


Fig. 6 ISCEV-standard ERGs [3]. Responses from both eyes were superimposed. Photopic and flicker ERG that were derived from middle- and long-wavelength-sensitive (MWS and LWS) cone systems showed normal responses

by dysfunction of SWS cone systems in the retina, in spite of the fact that the fundus appearance was normal. LWS and MWS cone systems seemed to be healthy in this case, because Farnsworth–Munsell 100-hue test showed very few errors in red-green color vision, and full-field photopic and flicker ERG that were derived from MWS and LWS cone systems showed normal responses (Figs. 4, 6). These facts suggest a selective functional disturbance of SWS cone systems in this case.

The patient reported that he had used electronic cigarettes several days before the symptom. Although World Health Organization (WHO) has denied safety of the electronic cigarette [9], relationship between the electronic cigarette and the SWS cone dysfunction was not clear in this case, because authors did not examine the electronic cigarettes he took.

To our knowledge, acquired tritanopia and acute tritanopia due to SWS cone system dysfunction with no ophthalmic diseases have never been reported except by Okuno et al. [10]. They reported a case of sudden-onset tritanopia with no ophthalmic nor general disease. The color vision abnormality in the Okuno's case [10] was unilateral, which is different from our case.

Bilateral and acute dysfunction of SWS cone systems in the case presented here is quite unique. Authors were not able to find any causes of this dysfunction during the 1-year follow-up.

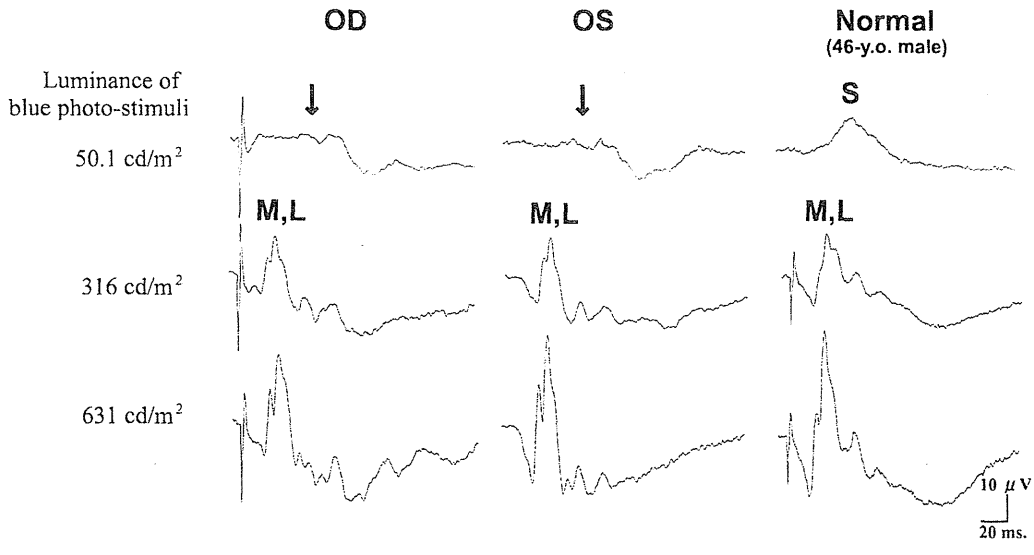


Fig. 7 Blue-on-yellow ERGs [4]. The case showed severely attenuated b-wave (*arrows*) that was derived from short-wavelength-sensitive cones in a normal subject (S), whereas b-waves from middle- and long-wavelength-sensitive cones (M, L) were normal in both eyes. Luminance of the yellow background was 640 cd/m^2, and duration of the blue photo-stimuli was 2 ms

Conflict of interest The authors declared that there is no conflict of interest.

References

1. Krill AE, Fishman GA (1971) Acquired color vision defects. Trans Am Acd Ophthalmol Otolaryn 75:1095–1111
2. Iregren A, Andersson M, Nylén P (2002) Color vision and occupational chemical exposures: I. An overview of tests and effects. Neurotoxicology 23:719–733
3. Marmor MF, Fulton AB, Holder GE, Miyake Y, Brigell M, Bach M (2009) ISECV standard for full-field clinical electroretinography (2008 update). Doc Ophthalmol 118:69–77
4. Kuniyoshi K, Uno N, Irifune M, Shimomura Y (2003) Electroretinography of short-wavelength-sensitive cones with a LED built-in electrode and its normal values. Doc Ophthalmol 106:311–318
5. Greenstein VC, Hood DC, Ritch R, Steinberger D, Carr RE (1989) S (blue) cone pathway vulnerability in retinitis pigmentosa, diabetes and glaucoma. Invest Ophthalmol Vis Sci 30:1732–1737
6. Nork TM, Millecchia LL, Strickland BD, Linberg JV, Chao G (1995) Selective loss of blue cones and rods in human retinal detachment. Arch Ophthalmol 113:1066–1073
7. Yamamoto S, Takeuchi S, Kamiyama M (1998) The short wavelength-sensitive cone electroretinogram in diabetes: relationship to systemic factors. Doc Ophthalmol 94:193–200
8. Yamamoto S, Hayashi M, Takeuchi M (1999) S-cone electroretinogram to Ganzfeld stimuli in patients with retinitis pigmentosa. Doc Ophthalmol 99:183–189
9. World Health Organization Media centre (2008) Marketers of electronic cigarettes should halt unproved therapy claims. http://www.who.int/mediacentre/news/releases/2008/pr34/en/. Accessed 1 April 2012
10. Okuno T, Minami M, Oku H, Sugasawa J, Ikeda T (2010) A case of unilateral impairment of short-wavelength-sensitive cone with sudden onset. J Jpn Ophthalmol Soc 114:527–533

Novel Mutations in Enhanced S-cone Syndrome

Dear Editor:

Enhanced S-cone syndrome (ESCS) is a rare and unique retinal dystrophy with a pattern of autosomal-recessive inheritance.[1-3] Patients with ESCS show night blindness and high sensitivity to short-wavelength light, because of the 2-fold increased number of short-wavelength-sensitive cones (S cones) with absence of rods in the retina. Since the first discovery of mutations in the *NR2E3* gene on chromosome 15q23 in patients with ESCS,[4] >40 mutations have been reported as causes of ESCS and allied diseases (Fig 1, available online at http://aaojournal.org).

In this letter, we report novel mutations in the *NR2E3* gene that were discovered in 2 cases with ESCS.

Cases are 2 Japanese patients who were reported previously.[3] Case 1 was a 31-year-old man whose parents were consanguineous. His vision was 0.7 in the right eye and 0.3 in the left eye. Funduscopy revealed retinal degeneration surrounding the vascular arcade with cystic changes in both maculae (Fig 2, available online at http://aaojournal.org). Perimetry showed ring-shaped scotoma and electrophysiology showed unique responses corresponding to ESCS (Figs 3–6, available online at http://aaojournal.org). During 23-year clinical follow-up, clumped pigmentation has appeared in the retinal degeneration and the cystic changes in the foveal region have become ambiguous (Fig 2). His latest vision was 0.5 in the right eye and 0.3 in the left eye at age 53.

Genetic analysis revealed a novel nucleotide substitution (c.151G>A) in exon 2 homozygously, resulting in a novel missense mutation (a glycine-to-arginine substitution) at amino acid position 51 (p.G51R; Fig 7; available online at http://aaojournal.org).

Case 2 was a 78-year-old woman.[3] Funduscopy showed diffuse mild retinal degeneration with no pigmentation in both eyes (Fig 8, available online at http://aaojournal.org). Optical coherence tomography showed a subtle foveal schisis in the left eye, although the structure of the retina including the outer nuclear layer in the macular area was relatively well maintained (Fig 8). After cataract surgery, her vision improved to 0.3 in the right eye and 0.2 in the left.

Genetic analysis revealed compound heterozygous mutations of c.142C>T (exon 2) and c.311G>A (exon 3), resulting in an arginine-to-cysteine substitution at amino acid position 48 (p.R48C) and an arginine-to-glutamine substitution at amino acid position 104 (p.R104Q; Fig 7).

A daughter of case 2 who was asymptomatic and had normal fundus appearance showed only the p.R48C mutation heterozygously, that indicated she was an unaffected carrier relative (Fig 7).

NR2E3 protein, a photoreceptor-specific orphan nuclear receptor, plays an important role in the development and differentiation of rods and all cone classes. NR2E3 has 2 functionally important domains, namely, the DNA-binding domain (DBD) and the ligand-binding domain (Fig 1). Mutations within these domains result in serious dysfunction of NR2E3 protein leading to abnormal process of development and differentiation of multipotent progenitor cells to rods and cones.

Genetic analysis revealed a homozygous mutation (p.G51R) in case 1 and compound heterozygous mutations of (p.R48C) and (p.R104Q) in case 2. Among these mutations, (p.G51R) and (p.R48C) are novel as causative mutations of ESCS.

The mutation (p.G51R) found in case 1 resides in the first zinc finger of the DBD, and the compound heterozygous mutations (p.R48C and p.R104Q), which were found in case 2 reside in the first and second zinc fingers of the DBD. Because the zinc fingers are necessary for maintenance the structure of NR2E3 protein, these mutations in the zinc fingers of NR2E3 result in phenotypes as ESCS (Fig 1).

Clinically, case 1 with a homozygous missense mutation (p.G51R) showed typical features as ESCS, whereas case 2 with compound heterozygous mutations (p.R48C and p.R104Q) showed mild retinal degeneration and has kept some level of vision and construction of the macula despite advanced age. In the past, the mutation (p.R104Q) has never been reported except in 1 case, which demonstrated the normal structure and function of the macula with recordable rod electrophysiology.[5] These facts indicate the mutation (p.R104Q) may be correlated with the relatively mild clinical findings as ESCS.

We identified 2 novel missense mutations (p.G51R and p.R48C) as causes of ESCS. To our knowledge, the finding of case 1 is the longest-observed clinical case ever reported, and case 2 is the oldest case among all the patients with ESCS so far reported.

KAZUKI KUNIYOSHI, MD,[1] TAKAAKI HAYASHI, MD,[2] HIROYUKI SAKURAMOTO, MD,[1] AKIRA NAKAO, MD,[1]
TAKASHI SATO, MD,[1] TOMOHIRO UTSUMI,[2] HIROSHI TSUNEOKA, MD,[2] YOSHIKAZU SHIMOMURA, MD[1]
[1]Department of Ophthalmology, Kinki University, Faculty of Medicine, Osaka, Japan; [2]Department of Ophthalmology, The Jikei University School of Medicine, Tokyo, Japan

References

1. Marmor MF, Jacobson SG, Foerster MH, et al. Diagnostic clinical findings of a new syndrome with night blindness, maculopathy, and enhanced S cone sensitivity. Am J Ophthalmol 1990;110:124–34.
2. Jacobson SG, Marmor MF, Kemp CM, Knighton RW. SWS (blue) cone hypersensitivity in a newly identified retinal degeneration. Invest Ophthalmol Vis Sci 1990;31:827–38.
3. Sato T, Kuniyoshi K, Nakao A, et al. Long-term observation of two cases of enhanced S-cone syndrome. J Jpn Ophthalmol Soc 2009;113:980–90.
4. Haider NB, Jacobson SG, Cideciyan AV, et al. Mutation of a nuclear receptor gene, *NR2E3*, causes enhanced S cone syndrome, a disorder of retinal cell fate. Nat Genet 2000;24:127–31.
5. Hayashi T, Gekka T, Goto-Omoto S, et al. Novel *NR2E3* mutations (R104Q, R334G) associated with a mild form of enhanced S-cone syndrome demonstrate compound heterozygosity. Ophthalmology 2005;112:2115–22.

Financial Support: This study was supported by grants from the Ministry of Health, Labour and Welfare of Japan and the Vehicle Racing Commemorative Foundation.

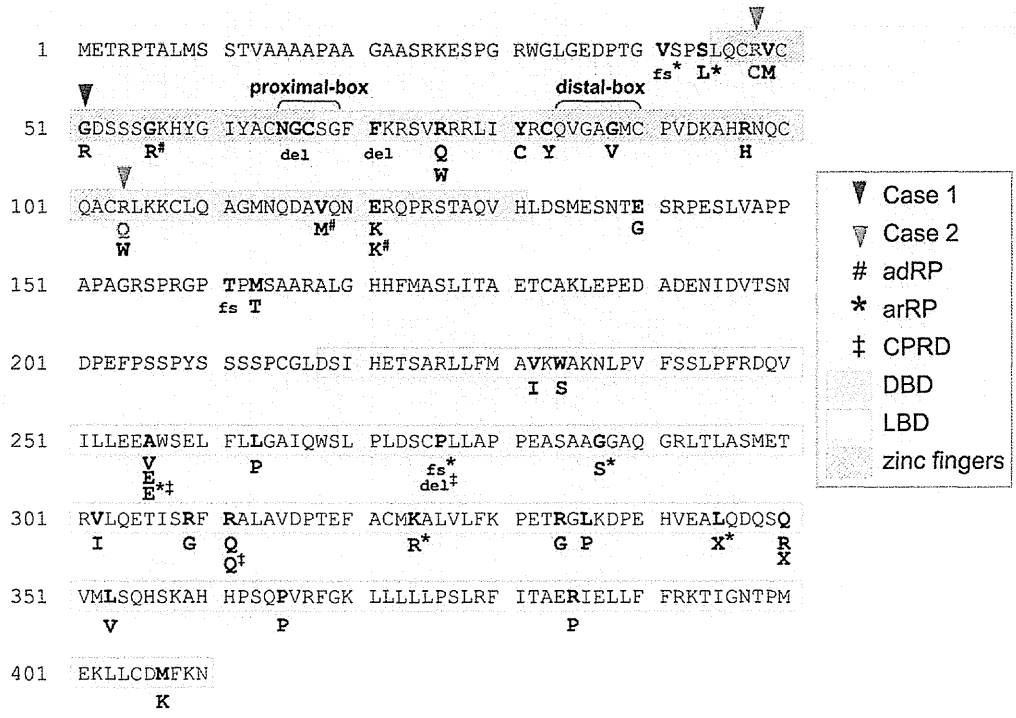
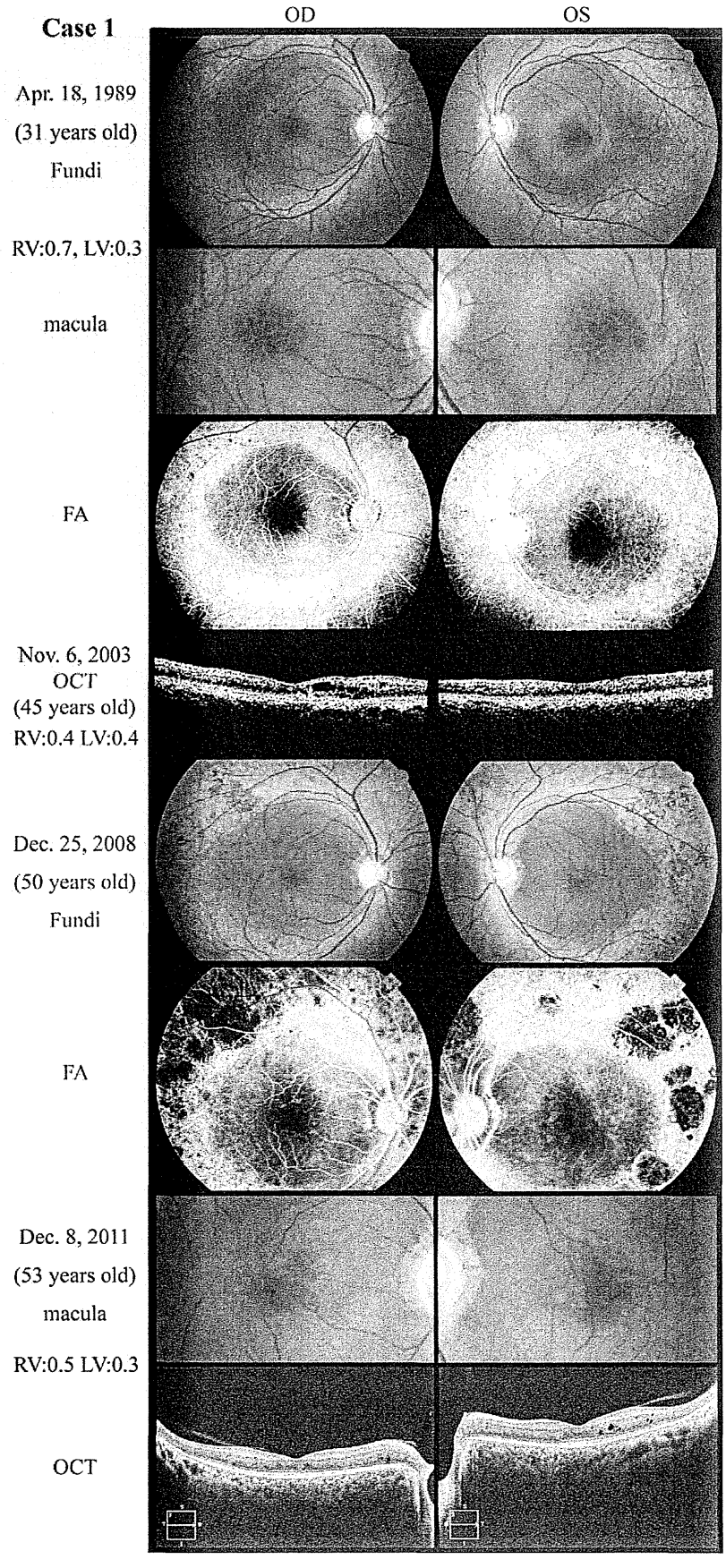


Figure 1. NR2E3 protein structure and mutations in cases presented in this letter and reported in past papers. Bold characters with no marks indicate mutations reported as a cause of enhanced S-cone syndrome (ESCS). Red characters and arrow indicate homozygous missense mutation discovered in Case 1 (p.G51R). Blue characters and arrows indicate compound heterozygous missense mutations discovered in case 2 (p.R48C and p.R104Q). p.G51R and p.R48C are novel mutations as causes of ESCS. adRP = autosomal-dominant retinitis pigmentosa; arRP = autosomal-recessive retinitis pigmentosa; CPRD = clumped pigmentary retinal degeneration; DBD = DNA-binding domain; del = deletion mutation; fs = frame shift of amino acids; LBD = ligand-binding domain.


Case 1
OD
OS
Apr. 18, 1989
(31 years old)
Fundi
RV:0.7, LV:0.3
macula
FA
Nov. 6, 2003
OCT
(45 years old)
RV:0.4 LV:0.4
Dec. 25, 2008
(50 years old)
Fundi
FA
Dec. 8, 2011
(53 years old)
macula
RV:0.5 LV:0.3
OCT

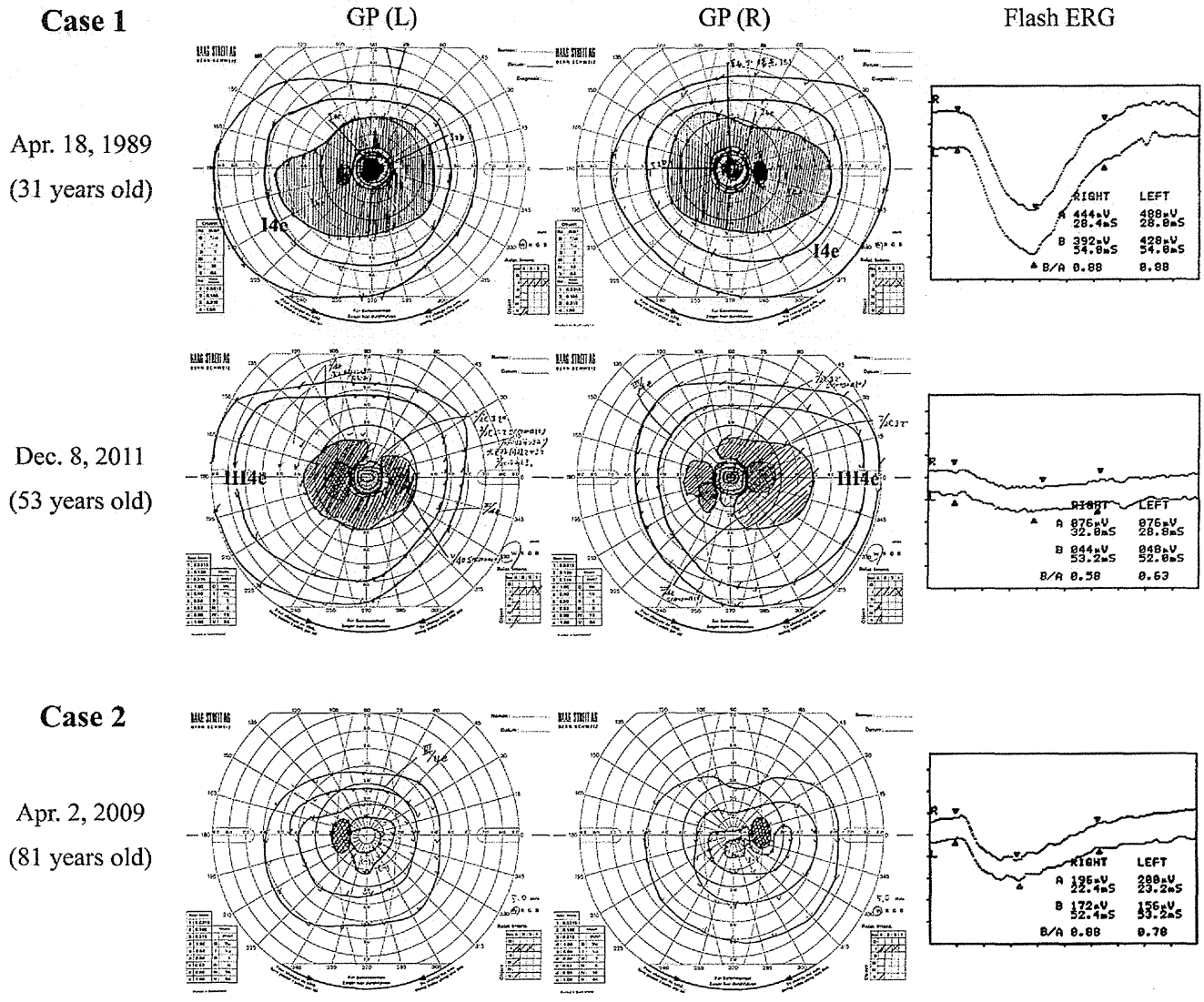


Figure 3. Results of Goldmann perimetry (GP) and flash electroretinography (ERG). In case 1, retinal sensitivity decreased and amplitude of ERG was attenuated during the 2-decade follow-up. In case 2, the visual field and the ERG findings were maintained relatively well in spite of her great age. This Figure was made with modification of Figures 2, 3, and 8 in Sato et al[3] with permission.

←

Figure 2. Results of fundus photography, fluorescein fundus angiography (FA) and optical coherence tomography (OCT) in case 1. At the initial visit (April 1989), cystic changes were observed in the fovea that became ambiguous 2 decades later; vision, however, did not improve. This figure was made with modification of Figures 1 and 6 in Sato et al,[3] with permission.

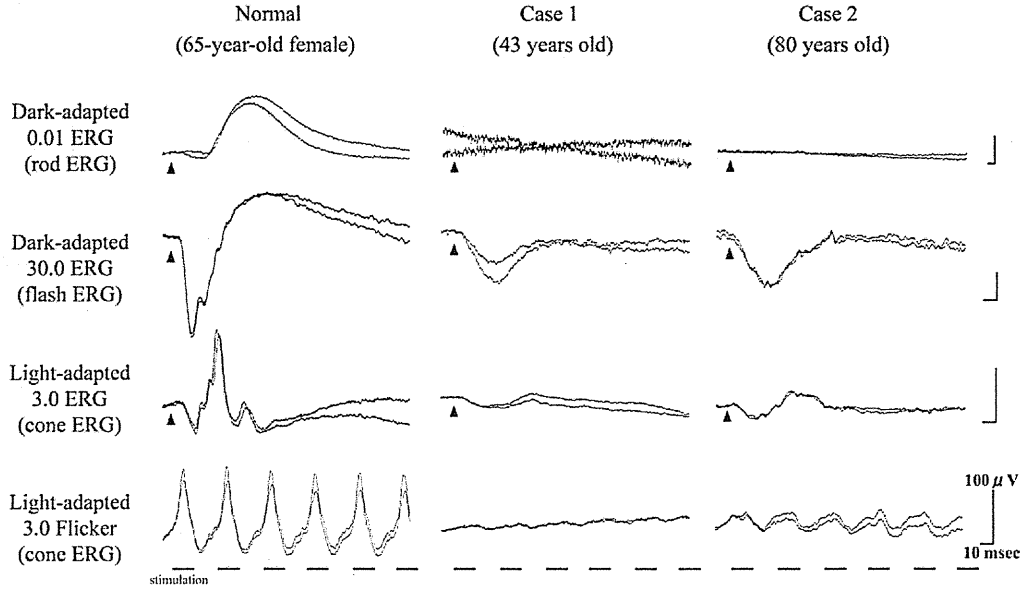


Figure 4. International Society for Clinical Electrophysiology of Vision (ISCEV)-standard electroretinography (ERGs) images. The 2 cases showed nonrecordable rod responses and significantly prolonged flash ERGs. Flicker ERGs derived from the middle- and long-wavelength-sensitive (M- and L-) cone systems were attenuated in these cases. These findings were consistent with enhanced S-cone syndrome. This figure was made with modification of Figure 4 in Sato et al[3] with permission.

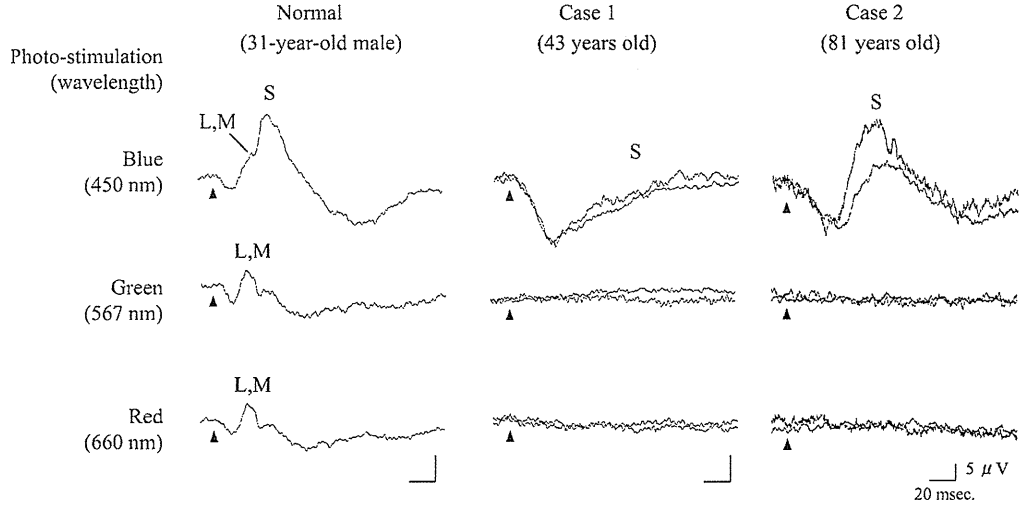


Figure 5. Color electroretinography (ERGs) images. The ERGs were recorded using 3-colored LED-built-in electrode (Kuniyoshi et al. Doc Ophthalmol 2003;106:311-8). The ERGs were elicited by 3 kinds of stimulus, namely, blue, green, and red light under the yellow background light. Luminance of the yellow background light was 670 cd/m^2 and duration of the stimulus was 2 milliseconds. The ERG waveform elicited by blue stimulus in the normal subject showed double-peaked, namely, rapid b-wave, which was derived from the L- and M-cone systems (L, M) followed by slow b-wave derived from the S-cone system (S). In cases 1 and 2, large b-wave with slow peak time was recorded with blue photostimulation, whereas no response was recorded with green and red photo stimuli. The intensity of the color stimulus was decided to elicit the rapid b-wave (L, M) with almost the same amplitude as in the normal subject. This Figure was made with modification of Figure 5 in Sato et al[3] with permission.

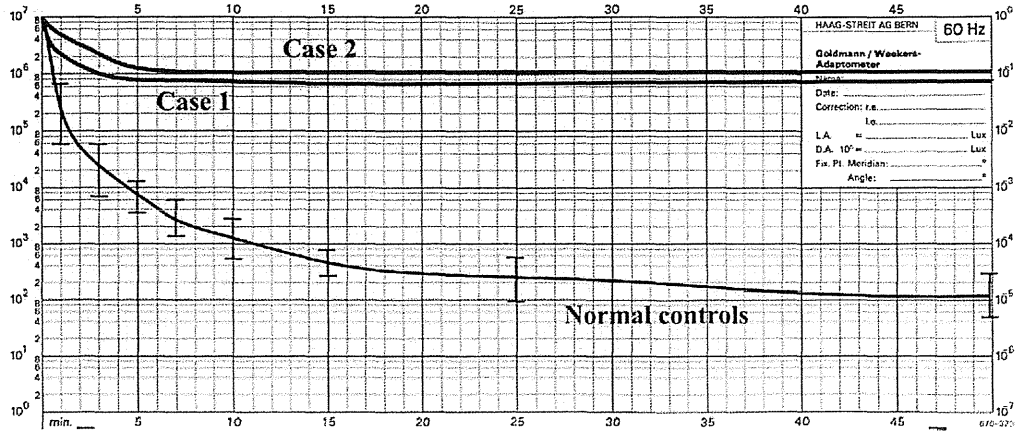


Figure 6. Results of Goldmann-Weekers dark adaptometry. Lower line indicates averaged value and its standard deviation resulted from normal controls.

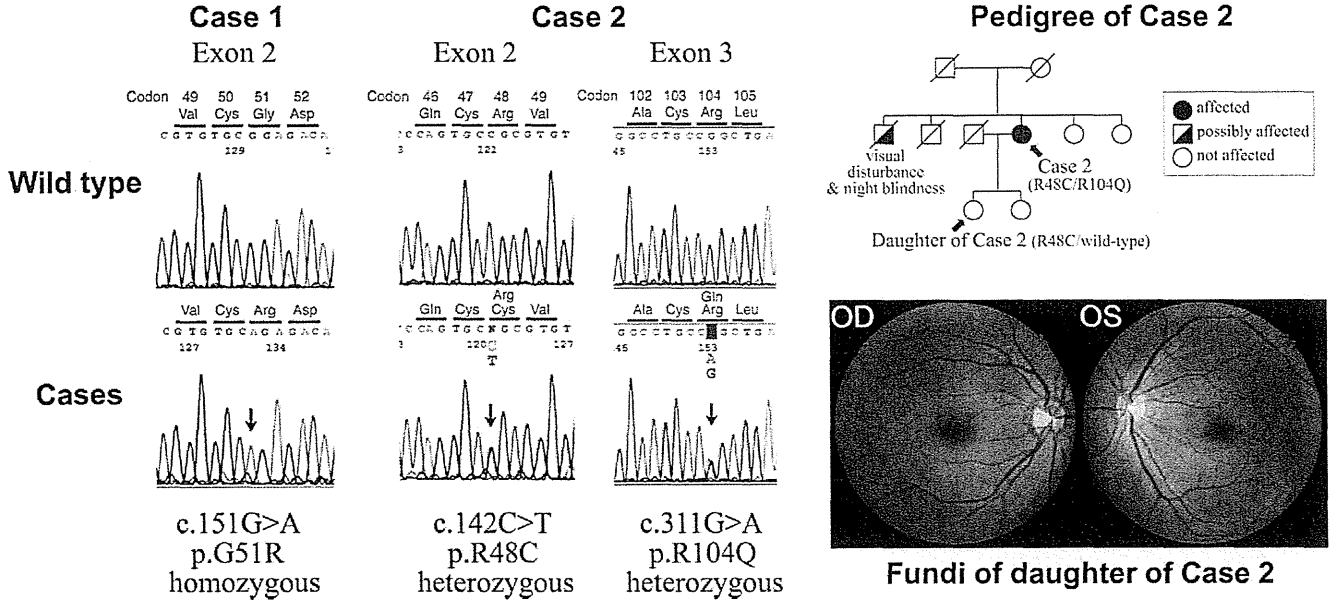


Figure 7. Results of DNA sequencing of the *NR2E3* gene in cases 1 and 2 (left), the pedigree of case 2, and fundus photographs of the daughter of case 2 (right). Mutation analysis identified a novel homozygous missense mutation of p.G51R, which resides in the DNA-binding domain (DBD) in NR2E3 protein in case 1. In case 2, heterozygous missense mutation of p.R48C and p.R104Q were identified, and the former is a novel mutation. A daughter of case 2 revealed heterozygous missense mutation of p.R48C and normal fundus appearance. In mutation screening of the *NR2E3* gene, all coding exons including exon/intron boundaries were amplified using polymerase-chain reaction (PCR) with primer pairs followed by sequencing. The primers and protocols used for PCR, and the procedures of PCR amplification and purification were the same as reported previously.[5]

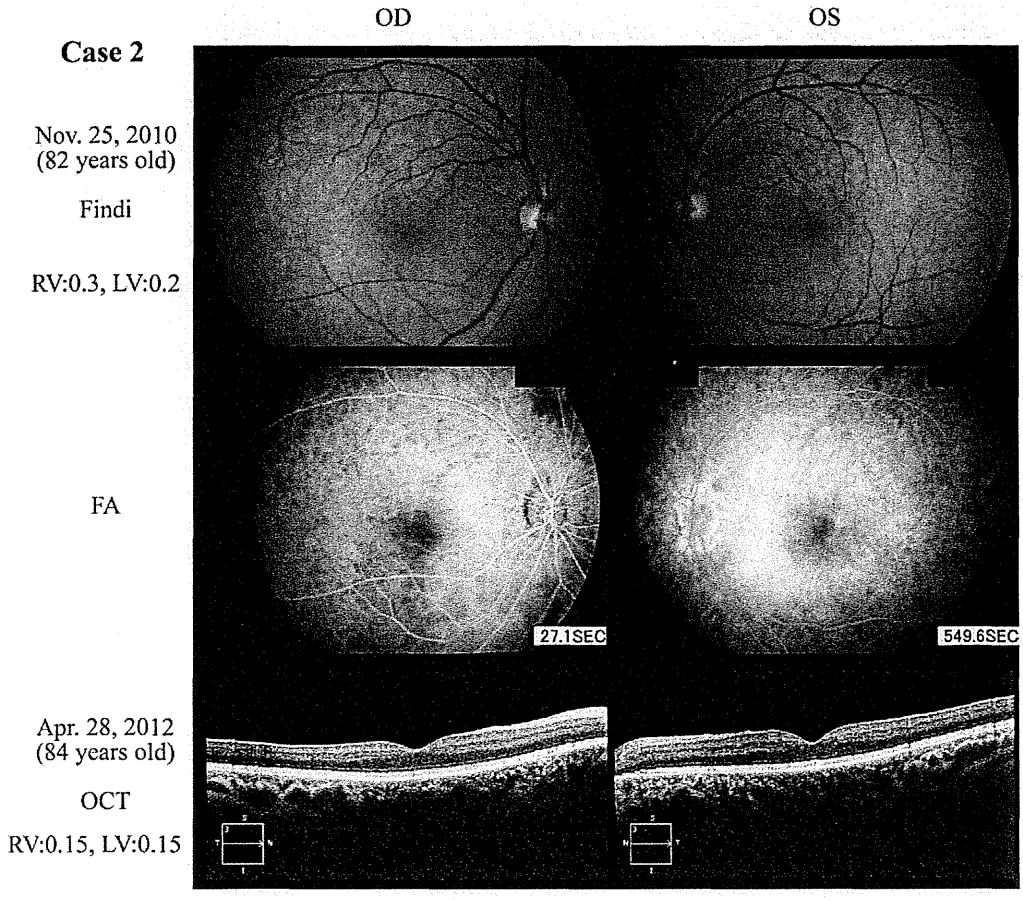


Figure 8. Results of fundus photography, fundus angiography (FA), and optical coherence tomography (OCT) in case 2. These photographs were taken after cataract surgery. The retinal degeneration was relatively mild with no pigmentation in both eyes. This Figure was made with modification of Figure 7 in Sato et al[3] with permission.

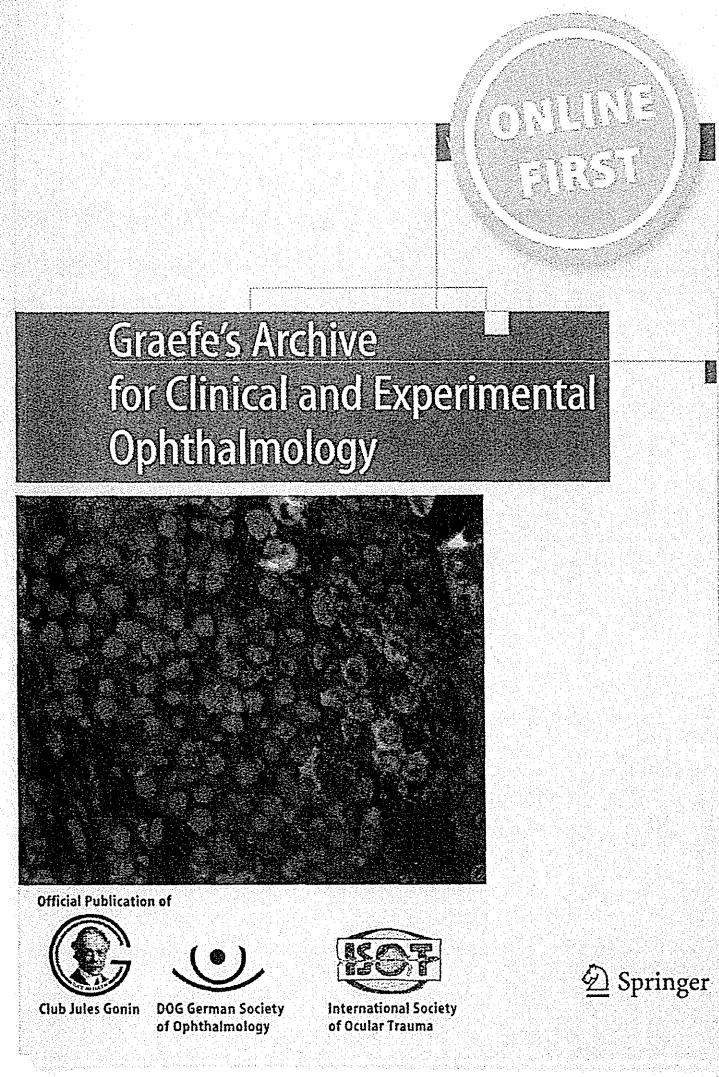
Improvement of visual acuity after transcorneal electrical stimulation in case of Best vitelliform macular dystrophy

Naoki Ozeki, Kei Shinoda, Hisao Ohde, Susumu Ishida & Kazuo Tsubota

Graefe's Archive for Clinical and Experimental Ophthalmology
Incorporating German Journal of Ophthalmology

ISSN 0721-832X

Graefes Arch Clin Exp Ophthalmol
DOI 10.1007/s00417-013-2341-4



Springer

Graefes Arch Clin Exp Ophthalmol
DOI 10.1007/s00417-013-2341-4

CASE REPORT

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

Naoki Ozeki · Kei Shinoda · Hisao Ohde · Susumu Ishida · Kazuo Tsubota

Received: 13 September 2012 / Revised: 23 March 2013 / Accepted: 2 April 2013

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.

N. Ozeki · K. Shinoda · H. Ohde · S. Ishida · K. Tsubota
Department of Ophthalmology,
Keio University School of Medicine, Tokyo, Japan

K. Shinoda (✉)
Department of Ophthalmology,
Teikyo University School of Medicine, 2-11-1 Kaga, Itabashi-ku,
Tokyo 186-8605, Japan
e-mail: shinodak@med.teikyo-u.ac.jp

H. Ohde
Makuhari Ode Eye Clinic, Chiba, Japan

S. Ishida
Department of Ophthalmology, Hokkaido University Graduate
School of Medicine, Sapporo, Japan

Published online: 19 April 2013

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.

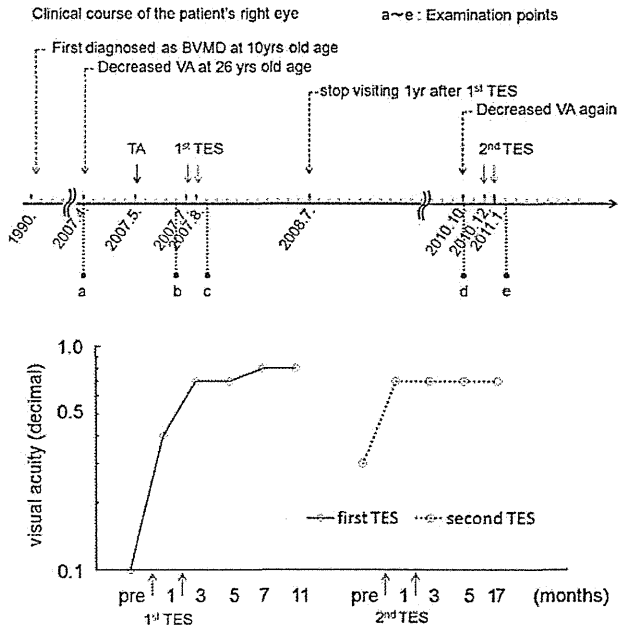


Fig. 1 Results from the right eye of a patient with Best vitelliform macular dystrophy. **a** Clinical course of the BCVA in the right eye of our patient. Scale shows 1 month intervals unless otherwise indicated. BVMD: Best vitelliform macular dystrophy, TES: transcorneal electrical stimulation, TA: 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

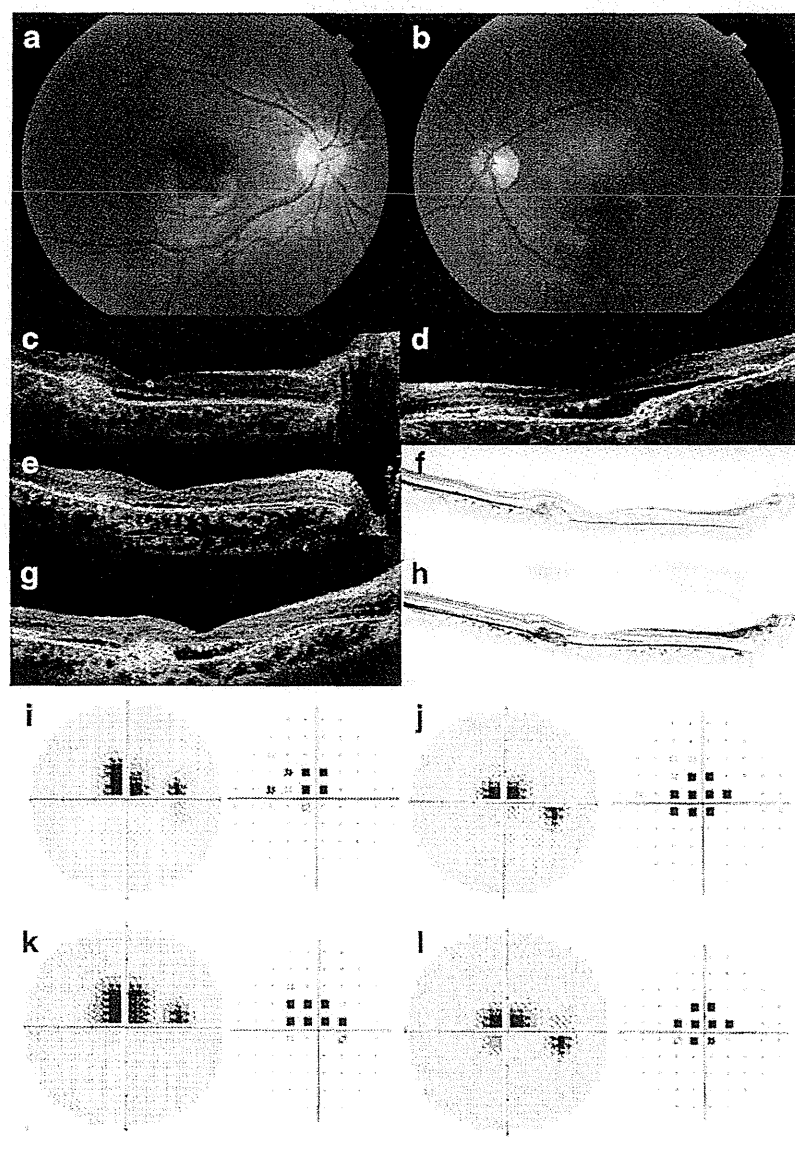


Fig. 2 Fundus appearance and morphological and functional evaluation of the right macula of a patient with Best vitelliform macular dystrophy (BVMD). **a** and **b** Fundus photograph of the right (**a**) and left (**b**) eyes taken when the BCVA was 20/200 at the initial examination at point '*a*' in 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.

Acknowledgments No author has a financial or proprietary interest in any material or method mentioned. Support of this study was provided by Research Grants on Sensory and Communicative Disorders from the Ministry of Health, Labor, and Welfare, Japan.

References

1. Potts AM, Inoue J, Buffum D (1968) The electrically evoked response of the visual system (EER). Investig Ophthalmol 7:269–278
2. Shimazu K, Miyake Y, Watanabe S (1999) Retinal ganglion cell response properties in the transcorneal electrically evoked response of the visual system. Vis Res 39:2251–2260
3. Fujikado T, Morimoto T, Matsushita K, Shimojo H, Okawa Y, Tano Y (2006) Effect of transcorneal electrical stimulation in patients with nonarteritic ischemic optic neuropathy or traumatic optic neuropathy. Jpn J Ophthalmol 50:266–273
4. Inomata K, Shinoda K, Ohde H, Tsunoda K, Hanazono G, Kimura I, Yuzawa M, Tsubota K, Miyake Y (2007) Transcorneal electrical stimulation of retina to treat longstanding retinal artery occlusion. Graefes Arch Clin Exp Ophthalmol 245:1773–1780
5. Schatz A, Röck T, Naycheva L, Willmann G, Wilhelm B, Peters T, Bartz-Schmidt KU, Zrenner E, Messias A, Gekeler F (2011) Transcorneal electrical stimulation for patients with retinitis pigmentosa—a prospective, randomized, sham-controlled exploratory study. Investig Ophthalmol Vis Sci 52:4485–4496
6. Fedorov A, Jobke S, Bersnev V, Chibisova A, Chibisova Y, Gall C, Sabel BA (2011) Restoration of vision after optic nerve lesions with noninvasive transorbital alternating current stimulation: a clinical observational study. Brain Stimul 4:189–201
7. Morimoto T, Miyoshi T, Matsuda S, Tano Y, Fujikado T, Fukuda Y (2005) Transcorneal electrical stimulation rescues axotomized retinal ganglion cells by activating endogenous retinal IGF-1 system. Investig Ophthalmol Vis Sci 46:2147–2155
8. Ni YQ, Gan DK, Xu HD, Xu GZ, Da CD (2009) Neuroprotective effect of transcorneal electrical stimulation on light-induced photoreceptor degeneration. Exp Neurol 219:439–452
9. Morimoto T, Miyoshi T, Sawai H, Fujikado T (2010) Optimal parameters of transcorneal electrical stimulation (TES) to be neuroprotective of axotomized RGCs in adult rats. Exp Eye Res 90:285–291
10. Inomata K, Tsunoda K, Hanazono G, Kazato Y, Shinoda K, Yuzawa M, Tanifuji M, Miyake Y (2008) Distribution of retinal responses evoked by transscleral electrical stimulation detected by intrinsic signal imaging in macaque monkeys. Investig Ophthalmol Vis Sci 49:2193–2200
11. Fujikado T, Morimoto T, Kanda H, Kusaka S, Nakauchi K, Ozawa M, Matsushita K, Sakaguchi H, Ikuno Y, Kamei M, Tano Y (2007) Evaluation of phosphenes elicited by extraocular stimulation in normals and by suprachoroidal-transretinal stimulation in patients with retinitis pigmentosa. Graefes Arch Clin Exp Ophthalmol 245:1411–1419

Case Reports in Ophthalmology

Case Rep Ophthalmol 2012;3:396–405
DOI: 10.1159/000345507

Published online:
November 20, 2012

ISSN 1663–2699
www.karger.com/cop

Acute Visual Field Defect following Vitrectomy Determined to Originate from Optic Nerve by Electrophysiological Tests

Atsuro Uchida[a] Kei Shinoda[a, b] Celso Soiti Matsumoto[b]
Miho Kawai[a] Sayaka Kawai[b] Hisao Ohde[a, d]
Yoko Ozawa[a] Susumu Ishida[e] Makoto Inoue[c]
Atsushi Mizota[b] Kazuo Tsubota[a]

[a]Department of Ophthalmology, Keio University School of Medicine, [b]Department of Ophthalmology, Teikyo University School of Medicine, University Hospital Itabashi, and [c]Department of Ophthalmology, Kyorin Eye Center, Kyorin University School of Medicine, Tokyo, [d]Makuhari Ode Eye Clinic, Chiba, and [e]Department of Ophthalmology, Hokkaido University School of Medicine, Sapporo, Japan

Key Words
Ischemic optic neuropathy · Proliferative diabetic retinopathy · Multifocal electroretinogram · Multifocal visual evoked potentials · Photopic negative response

Abstract
Purpose: To present our findings on the cause of an acute visual field defect (VFD) that developed in a patient on the day after vitrectomy for proliferative diabetic retinopathy.
Case: A 50-year-old man complained of a blind area in the superior visual field that developed one day after vitrectomy. The patient had undergone uncomplicated vitrectomy for a long-duration vitreous hemorrhage associated with proliferative diabetic retinopathy. Residual vitreous hemorrhage hampered a clear view of the fundus. Goldmann perimetry showed a horizontal VFD in the superior field. The area corresponding to the VFD was examined by multifocal electroretinograms (mfERGs) and multifocal visual evoked potentials (mfVEPs). The amplitudes of the mfVEPs were reduced with prolonged implicit times especially when the superior hemifield was stimulated, while the amplitudes and implicit times were within the normal range when other parts of the visual field were stimulated. In addition, the full-field photopic ERGs and photopic negative responses were attenuated in the right eye. These findings suggested that the VFD did not originate from alterations in the retinal inner and middle layer but in the ganglion cells. The visual acuity improved to 1.2 but his optic disc became pale and the VFD remained unchanged more than 12 years after the surgery.

Kei Shinoda, MD

Department of Ophthalmology
Teikyo University School of Medicine
2-11-1 Kaga, Itabashi-ku, Tokyo 173-8605 (Japan)
E-Mail shinodak@med.teikyo-u.ac.jp

Case Rep Ophthalmol 2012;3:396–405
DOI: 10.1159/000345507
Published online: November 20, 2012

ISSN 1663–2699
www.karger.com/cop

Conclusion: We suggest that vitrectomy can cause ischemic optic neuropathy by interfering with the circulation associated with diabetes mellitus. Evaluations by mfERGs, mfVEPs, and full-field photopic ERGs were helpful in making the diagnosis.

Introduction

The visual function after vitrectomy depends on many factors, e.g., the underlying vitreoretinal disease, surgical procedures, and complications in either the anterior or posterior segments of the eye. Visual field defects (VFDs) are known to be a postsurgical complication, and they can be caused by retinochoroidal circulatory disturbances [1, 2], nerve fiber damage due to excessive exposure to dry air [3–5], optic nerve damage due to retrobulbar anesthesia [6–9], phototoxicity [10], and elevation of the intraocular pressure [11]. We report our findings in a patient who developed a severe VFD on the day following an uncomplicated vitrectomy for a vitreous hemorrhage associated with proliferative diabetic retinopathy [12]. A tentative diagnosis of ischemic optic neuropathy (ION) was made from the acute onset, superior hemianopsia, and the results of electrophysiological tests. We re-examined the patient after 10 years, and the VFD and the electrophysiological results remained unchanged. We conclude that our original diagnosis was correct, and also that the electrophysiological findings were critical in determining the pathological site of the VFD.

Case Report

A 50-year-old man underwent uncomplicated vitrectomy on September 22, 1998 for a vitreous hemorrhage of 2 months duration which was associated with proliferative diabetic retinopathy. His preoperative best-corrected visual acuity (BCVA) was hand movements in the right eye and 1.2 in the left eye. He underwent conventional pars plana vitrectomy, and no complications were encountered during the surgical procedures. His blood pressure increased to 176/107 mm Hg just before the surgery, but it decreased and became stable between 116–140/70–90 mm Hg intra- and postoperatively.

The patient complained of a blind area in the superior visual field of the right eye on the day after the vitrectomy (fig. 1a). His decimal BCVA was 0.02 in the right eye. The residual vitreous hemorrhage hampered a clear view of the fundus. On the second day after surgery, flash visual evoked potentials (VEPs) and full-field single-flash electroretinograms (ERGs) were recorded simultaneously [13]. The recording electrodes for the ERGs were attached to the surface of the lower eyelids to avoid using a contact lens electrode.

The implicit times of the flash VEPs were slightly delayed in both eyes and no difference was found between the eyes (fig. 2). The amplitudes of the a- and b-waves of the full-field ERGs were normal but the oscillatory potentials were slightly reduced in both eyes. However, no differences were found between the eyes (fig. 2). At that time, we did not evaluate the photopic negative response (PhNR) because its origin had not fully been determined.

Blood tests showed no abnormalities in the erythrocyte sedimentation rate, blood coagulation factor, C-reactive protein, and complete blood count. The results for antinuclear antibody were negative. ION was suspected because of the acute onset, horizontal hemianopsia, normal full-field ERGs, and diabetes.

Oral carbazochrome and kallidinogenase were started. The fundus became more visible one week after the surgery, and the BCVA improved to 0.7. Ophthalmoscopy showed localized edema adjacent