Hindawi Publishing Corporation
Case Reports in Medicine
Volume 2014, Article ID 786578, 6 pages
http://dx.doi.org/10.1155/2014/786578

Hindawi

Case Report

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

Gaku Terauchi,[1] Celso Soiti Matsumoto,[1,2] Kei Shinoda,[1] Harue Matsumoto,[2] Yutaka Imamura,[3] Emiko Watanabe,[1] Takaaki Kondo,[1] and Atsushi Mizota[1]

[1] *Department of Ophthalmology, Teikyo University School of Medicine, 2-11-1 Kaga, Itabashi-ku, Tokyo 173-0003, Japan*
[2] *Matsumoto Eye Clinic, Tokushima 771-1705, Japan*
[3] *Department of Ophthalmology, Teikyo University School of Medicine, University Hospital Mizonokuchi, Kanagawa 213-8507, Japan*

Correspondence should be addressed to Kei Shinoda; shinodak@med.teikyo-u.ac.jp

Received 14 August 2013; Revised 13 December 2013; Accepted 27 December 2013; Published 30 April 2014

Academic Editor: Marco A. Zarbin

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

1. Introduction

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

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

2. Materials and Methods

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

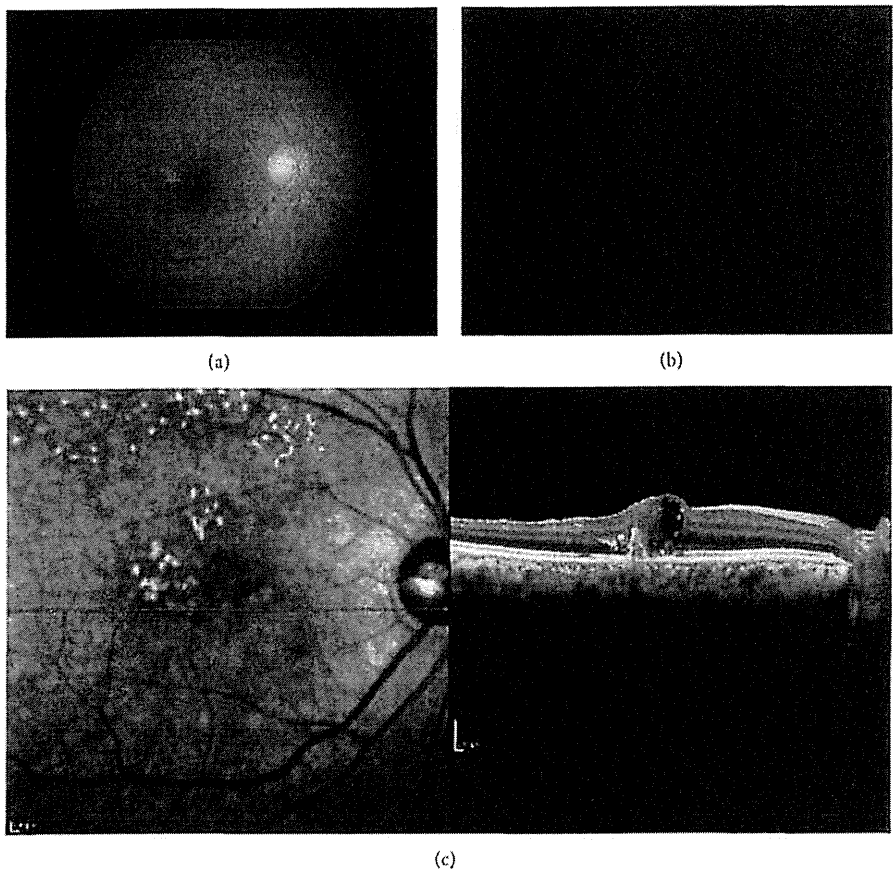

FIGURE 1: Finding of the right eye of Patient 1 with idiopathic macular telangiectasis (MacTel) type 1 on her first visit. Her best-corrected visual acuity (BCVA) was 20/100. (a) Fundus photograph showing hard exudates associated with telangiectasia temporal to the fovea. (b) Fluorescein angiogram showing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

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

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

3. Case Reports

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

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

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

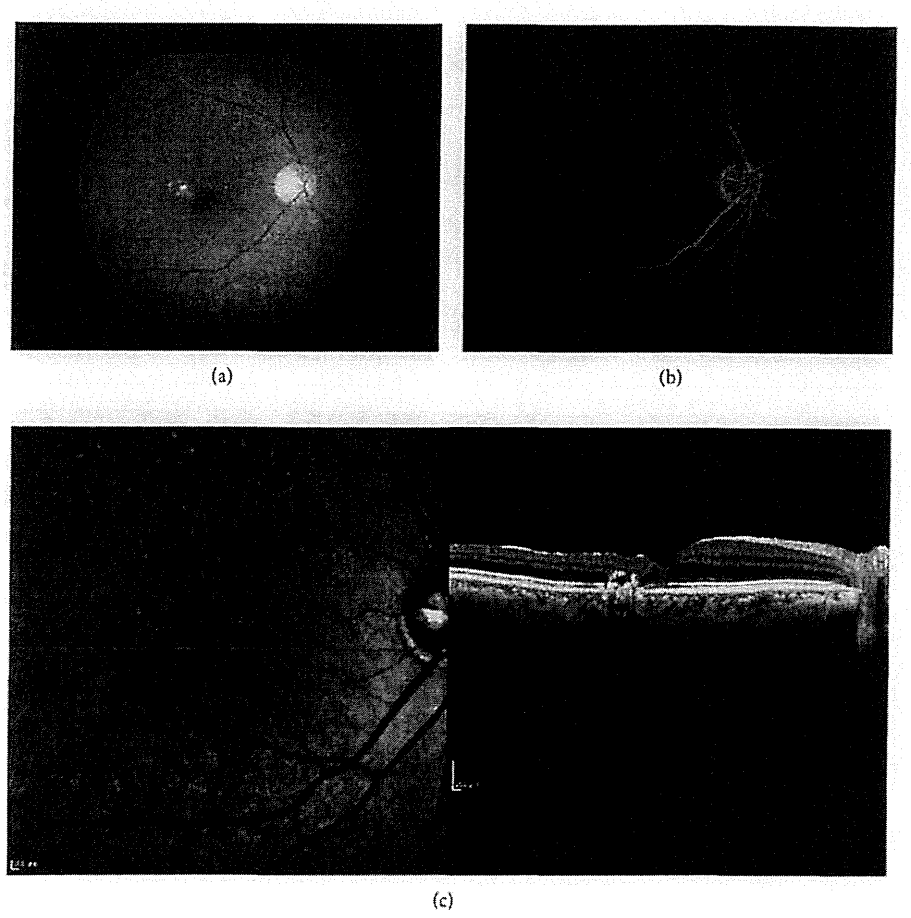

FIGURE 2: Findings of the right eye of Case 1 taken 3 months after surgery. The BCVA has improved to 20/25. (a) Fundus photograph showing localized area of scars from the laser photocoagulation temporal to the fovea. (b) Fluorescein angiogram showing the absence of fluorescein leakage in the late phase.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

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

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

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

4. Discussion

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

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

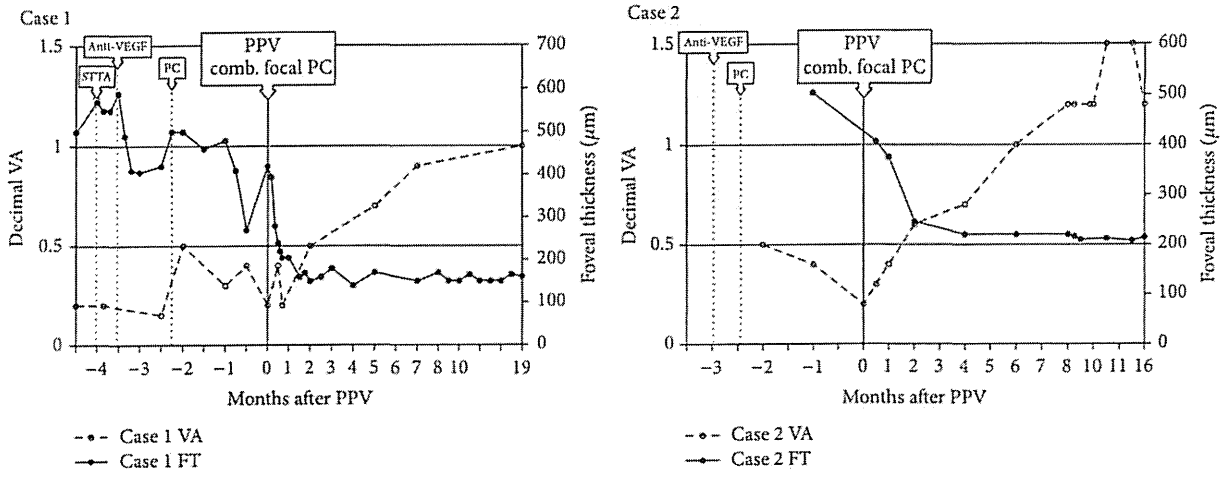

FIGURE 3: Clinical course of the affected eyes in two cases of MacTel type 1. In Case 1, the visual acuity improved to 20/20 and foveal thickness was reduced to 140 μm at 19 months after surgery. In Case 2, the visual acuity improved to 20/13 and foveal thickness to 208 um at 13 months after surgery.

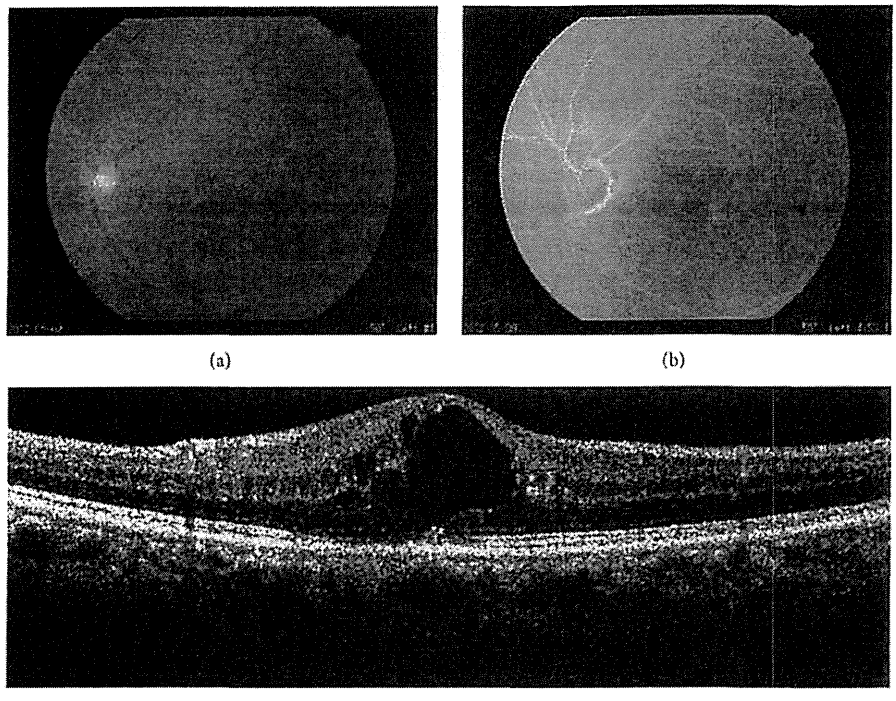

FIGURE 4: Findings of the left eye at the first visit of Case 2. The BCVA was 20/50. (a) Fundus photograph showed hard exudates associated with telangiectasia inferior temporal to the fovea. (b) Fluorescein angiogram showing fluorescein leakage in a circular pattern in the late phase. (c) Optical coherence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

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

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

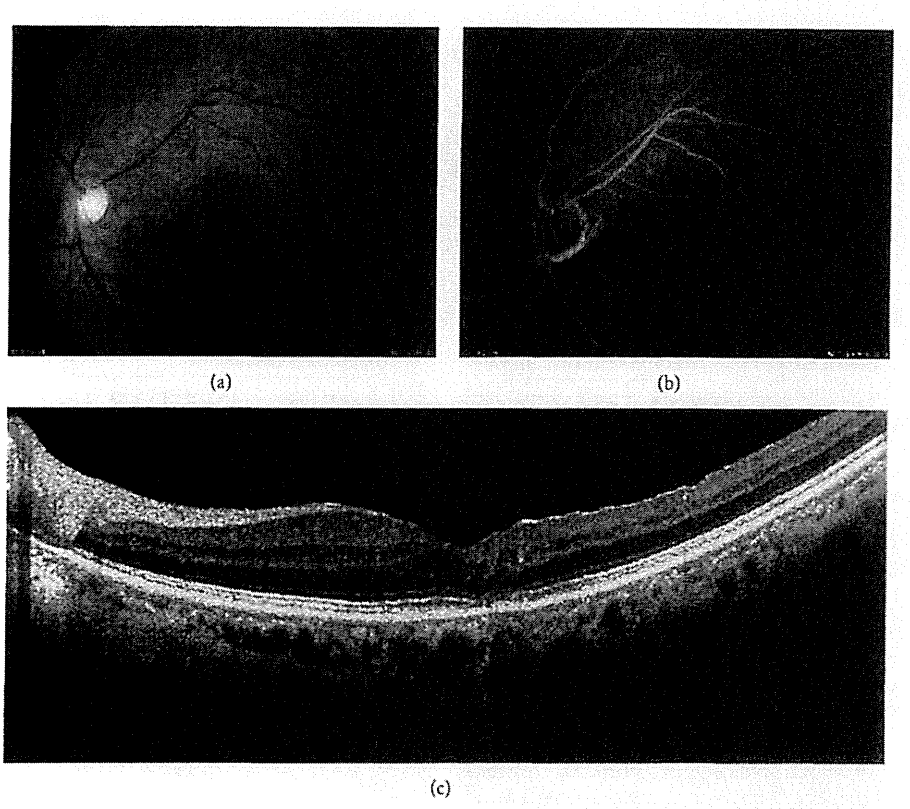

FIGURE 5: Fundus appearance of the left eye of Case 2 six months after surgery. Visual acuity has improved to 20/13. (a) Fundus photograph showed localized area of scarring by laser photocoagulation inferior-temporal to the fovea. (b) Fluorescein angiogram showing the disappearance of fluorescein leakage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

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

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

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

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

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

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

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

Conflict of Interests

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

Acknowledgments

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] J. D. Gass and R. T. Oyakawa, "Idiopathic juxtafoveolar retinal telangiectasis," *Archives of Ophthalmology*, vol. 100, no. 5, pp. 769–780, 1982.

[2] J. D. M. Gass and B. A. Blodi, "Idiopathic juxtafoveolar retinal telangiectasis: update of classification and follow-up study," *Ophthalmology*, vol. 100, no. 10, pp. 1536–1546, 1993.

[3] L. A. Yannuzzi, A. M. C. Bardal, K. B. Freund, K.-J. Chen, C. M. Eandi, and B. Blodi, "Idiopathic macular telangiectasia," *Archives of Ophthalmology*, vol. 124, no. 4, pp. 450–460, 2006.

[4] A. Chopdar, "Retinal telangiectasis in adults: fluorescein angiographic findings and treatment by argon laser," *British Journal of Ophthalmology*, vol. 62, no. 4, pp. 243–250, 1978.

[5] Y. Hirano, T. Yasukawa, Y. Usui, M. Nozaki, and Y. Ogura, "Indocyanine green angiography-guided laser photocoagulation combined with sub-Tenon's capsule injection of triamcinolone acetonide for idiopathic macular telangiectasia," *British Journal of Ophthalmology*, vol. 94, no. 5, pp. 600–605, 2010.

[6] J. A. Martinez, "Intravitreal triamcinolone acetonide for bilateral acquired parafoveal telangiectasis," *Archives of Ophthalmology*, vol. 121, no. 11, pp. 1658–1659, 2003.

[7] K. K. W. Li, T. Y. H. Goh, H. Parsons, W. M. Chan, and D. S. C. Lam, "Use of intravitreal triamcinolone acetonide injection in unilateral idiopathic juxtafoveal telangiectasis," *Clinical and Experimental Ophthalmology*, vol. 33, no. 5, pp. 542–544, 2005.

[8] M.-A. Gamulescu, A. Walter, H. Sachs, and H. Helbig, "Bevacizumab in the treatment of idiopathic macular telangiectasia," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 246, no. 8, pp. 1189–1193, 2008.

[9] B. G. Moon, Y. J. Kim, Y. H. Yoon, and J. Y. Lee, "Use of intravitreal bevacizumab injections to treat type 1 idiopathic macular telangiectasia," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 250, pp. 1697–1699, 2012.

[10] A. Ciarnella, S. Verrilli, V. Fenicia et al., "Intravitreal ranibizumab and laser photocoagulation in the management of idiopathic juxtafoveolar retinal telangiectasia type 1: a case report," *Case Reports in Ophthalmology*, vol. 3, pp. 298–303, 2012.

[11] D. W. Park, H. Schatz, H. R. McDonald, and R. N. Johnson, "Grid laser photocoagulation for macular edema in bilateral juxtafoveal telangiectasis," *Ophthalmology*, vol. 104, no. 11, pp. 1838–1846, 1997.

[12] U. Mester and P. Dillinger, "Vitrectomy with arteriovenous decompression and internal limiting membrane dissection in branch retinal vein occlusion," *Retina*, vol. 22, no. 6, pp. 740–746, 2002.

[13] A. Gandorfer, E. M. Messmer, M. W. Ulbig, and A. Kampik, "Resolution of diabetic macular edema after surgical removal of the posterior hyaloid and the inner limiting membrane," *Retina*, vol. 20, no. 2, pp. 126–133, 2000.

[14] M. S. Mandelcorn and R. K. Nrusimhadevara, "Internal limiting membrane peeling for decompression of macular edema in retinal vein occlusion: a report of 14 cases," *Retina*, vol. 24, no. 3, pp. 348–355, 2004.

[15] E. J. Sigler, J. C. Randolph, J. I. Calzada, and S. Charles, "Comparison of observation, intravitreal bevacizumab, or pars plana vitrectomy for non-proliferative type 2 idiopathic macular telangiectasia," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 251, no. 4, pp. 1097–1101, 2013.

Graefes Arch Clin Exp Ophthalmol (2013) 251:1867–1870
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 / Published online: 19 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

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.

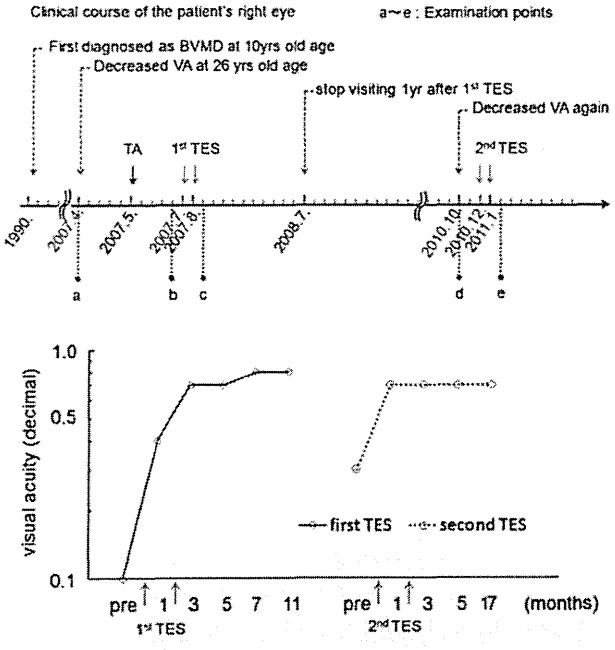

Fig. 1 Results from the right eye of a patient with Best vitelliform macular dystrophy. a Clinical course of the BCVA in the right eye of our patient. Scale shows 1 month intervals unless otherwise indicated. BVMD: Best vitelliform macular dystrophy, TES: transcorneal electrical stimulation, TA: Subtennon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

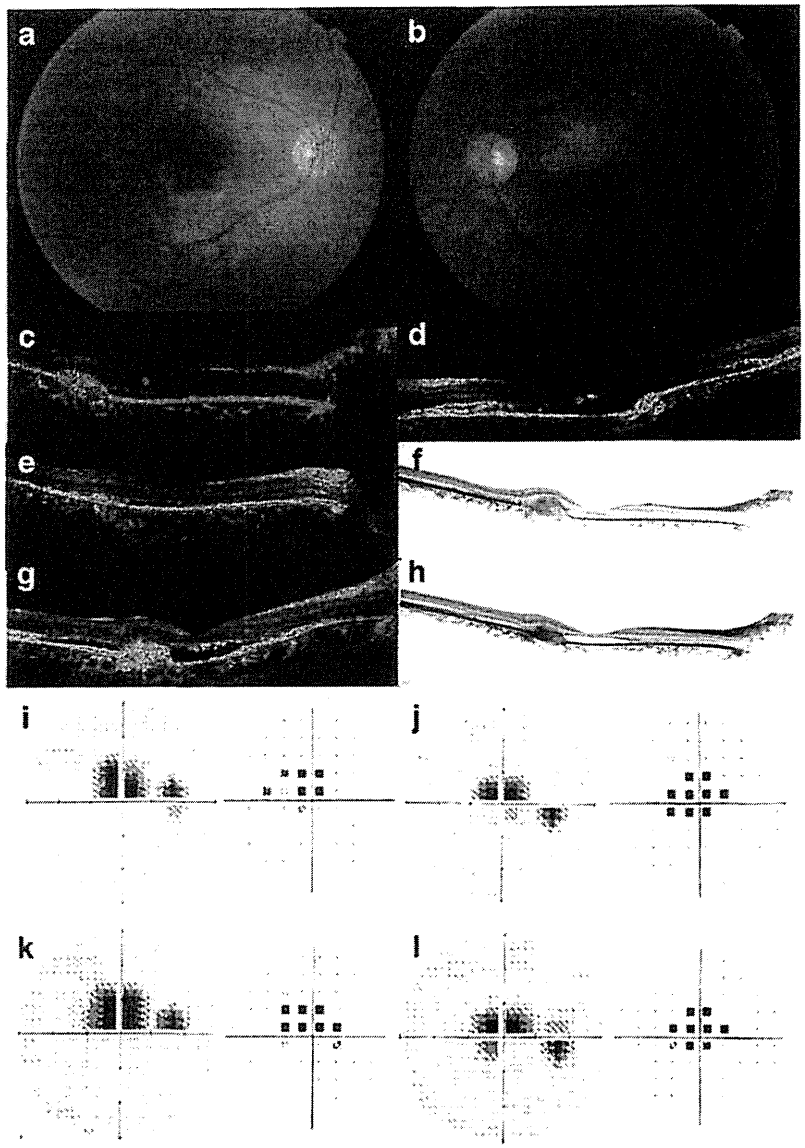

Fig. 2 Fundus appearance and morphological and functional evaluation of the right macula of a patient with Best vitelliform macular dystrophy (BVMD). **a** and **b** Fundus photograph of the right (**a**) and left (**b**) eyes taken when the BCVA was 20/200 at the initial examination at point '*a*' in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

QUANTIFICATION OF METAMORPHOPSIA IN CHRONIC CENTRAL SEROUS CHORIORETINOPATHY AFTER HALF-DOSE VERTEPORFIN PHOTODYNAMIC THERAPY

KYOKO FUJITA, MD, PHD,* YUTAKA IMAMURA, MD, PHD,† KEI SHINODA, MD, PHD,*‡ CELSO SOITI MATSUMOTO, MD, PHD,‡ YOSHIHIRO MIZUTANI, MD, PHD,* ATSUSHI MIZOTA, MD, PHD,‡ MITSUKO YUZAWA, MD, PHD*

Purpose: To determine the degree of metamorphopsia before and 1 year after half-dose verteporfin photodynamic therapy in eyes with chronic central serous chorioretinopathy.

Methods: This was a retrospective, noncomparative, interventional case series. Forty-five eyes of 45 consecutive patients with chronic central serous chorioretinopathy were evaluated. The degree of metamorphopsia was measured with M-CHARTS before and at 1, 3, 6, 9, and 12 months after half-dose verteporfin photodynamic therapy. The best-corrected visual acuity was also measured.

Results: Forty of the 45 eyes had a complete resolution of the serous retinal detachment at 1 month, 1 eye at 3 months, and 3 eyes at 6 months. The serous retinal detachment in one eye persisted throughout the follow-up period. The mean horizontal metamorphopsia score improved significantly from 0.61 ± 0.52° at baseline to 0.49 ± 0.56° at 12 months (P = 0.04). The vertical metamorphopsia score improved significantly from 0.52 ± 0.53° at baseline to 0.33 ± 0.46° at 12 months (P = 0.005).

Conclusion: Half-dose verteporfin photodynamic therapy for chronic central serous chorioretinopathy results in significant improvements of metamorphopsia at 1 year, especially in eyes with good best-corrected visual acuity at the baseline. Half-dose verteporfin photodynamic therapy can be a therapeutic option for patients with good visual acuity who complain of metamorphopsia.

RETINA 34:964–970, 2014

Central serous chorioretinopathy (CSC) is characterized by a serous retinal detachment (SRD) in the macular area.[1] Although CSC has been described as a benign and self-limiting disease, a persistent SRD can lead to poor vision and foveal atrophy. The foveal atrophy is most likely because of photoreceptor and retinal pigment epithelium damage that is caused by the prolonged separation of the photoreceptors from the retinal pigment epithelium.[2–4]

Photodynamic therapy (PDT) has been reported to enhance the absorption of fluid from the subretinal space in eyes with CSC by remodeling the structures of the choroidal vasculature. The remodeling causes alterations in the choroidal vascular hyperpermeability.[5] Several studies have reported favorable outcomes after PDT.[6–8] In addition, the safety and beneficial effects of "safety-enhanced" half-dose verteporfin (Visudyne; Novartis AG, Bulach, Switzerland) PDT have been demonstrated for both acute and chronic CSC.[9–11] However, there are patients who still complain of metamorphopsia even after a complete resolution of the SRD.

Amsler charts are widely used to detect metamorphopsia.[12] The Amsler chart is a useful method to establish the presence of metamorphopsia, but it does not allow a quantification of the degree of metamorphopsia and is therefore difficult to use for follow-up studies. Matsumoto et al have developed a new metamorphopsia chart called M-CHARTS (Inami Co, Tokyo, Japan) to evaluate the degree of metamorphopsia quantitatively (Figure 1).[13–17]

The purpose of this study was to determine the degree of metamorphopsia by the M-CHARTS before and after

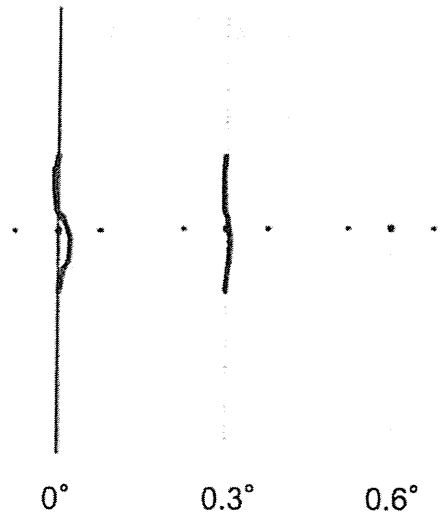

Fig. 1. Dotted lines are shown to the subject one after another, until the subject reports that the line is straight. In this case, the vertical solid line was distorted at 0.3°, after lines with larger dot intervals were recognized as less distorted. Line 0.6° was recognized as straight, thus the MV score is 0.6°.

half-dose verteporfin PDT in patients with chronic CSC. In addition, the relationship between the metamorphopsia and the integrity of the microstructures of the photoreceptors at the macula was evaluated.

Patients and Methods

We studied a series of consecutive patients who had undergone half-dose verteporfin PDT for chronic CSC between November 2009 and March 2011 and were followed for at least 12 months after the PDT. All of the patients had a history of CSC characterized by visual disturbances persisting for more than 6 months or had a recurrent history of CSC. The inclusion criteria were presence of leakage and multifocal or diffuse retinal pigment epithelium decompensation on fluorescein angiography, choroidal vascular hyperpermeability, and abnormal dilatation of the choroidal vasculature on indocyanine green angiography. In addition, all of the eyes had a SRD that overlapped the fovea. Eyes that had been treated with laser photocoagulation and those with recurrent CSC were included. The exclusion criteria were severely myopic or hyperopic eyes with refractive errors (spherical equivalent) of more than 6 diopters, had evidence of choroidal neovascularization, presence of any other ocular diseases that could affect the visual acuity, and presence of media opacities such as cataracts that could interfere with obtaining high quality optical coherence tomographic images, fluorescein angiography, and indocyanine green angiography images. Eyes with a decimal best-corrected visual acuity (BCVA) of <0.1 (Snellen equivalent of 20/200) were excluded because the limit of the decimal BCVA that M-CHARTS could detect metamorphopsia has been reported to be 0.1.[14]

All the patients completed the 12 months of follow-up examinations. The examinations included dilated fundus examination, measurement of the BCVA, and OCT (Spectralis HRA + OCT; Heidelberg Engineering GmbH, Heidelberg, Germany) scanning at the baseline and at 1, 3, 6, 9, and 12 months after the half-dose verteporfin PDT.

We used the M-CHARTS to quantify the degree of metamorphopsia. This chart is based on the fact that patients with metamorphopsia perceive a straight line as a curved or an irregular line.[14,15] When the straight line is replaced with a dotted line and the dot interval is changed from fine to coarse, the distortion of the line decreases with increasing dot intervals until the dotted line appears straight. The M-CHARTS was designed based on this, and 1 set consisted of 19 charts with each chart having a dotted line of different dot intervals. The angular separation of the dots ranged from 0.2° to 2.0°. The examination distance was 30 cm, and the refraction of the eye was adjusted to this distance. In the M-CHARTS test, a vertical straight line (0°) was first shown to the patient, and if the patient reported the straight line as being straight, the metamorphopsia score was 0°. If the patient reported the straight line as distorted, the next chart with a greater separation of the dots was shown. The dot intervals changed from fine to coarse, and the charts were shown one after another until the patient reported perceiving the dotted line as being straight. The visual angle that was reported to be straight was considered to be the M-CHARTS score. The M-CHARTS score was determined for both vertical and horizontal lines (Figure 1).

To reduce the test variations, both vertical and horizontal tests were repeated at least two times for each subject, and the average of the two test scores was used. An M-CHARTS score >0.2° was defined as a positive detection of metamorphopsia.

From the *Department of Ophthalmology, Surugadai Nihon University Hospital, Tokyo, Japan; †Department of Ophthalmology, Teikyo University School of Medicine, University Hospital Mizonokuchi, Kawasaki-shi, Japan; and ‡Department of Ophthalmology, Teikyo University School of Medicine, University Hospital Itabashi, Tokyo, Japan.

Supported by Researches on Sensory and Communicative Disorders from the Ministry of Health, Labor, and Welfare, Japan.

None of the authors have any conflicting interests to disclose.

Reprint requests: Kei Shinoda, MD, PhD, Department of Ophthalmology, Teikyo University School of Medicine, Kaga 2-11-1, Itabashi-ku, Tokyo 173-8606, Japan; e-mail: shinodak@med.teikyo-u.ac.jp

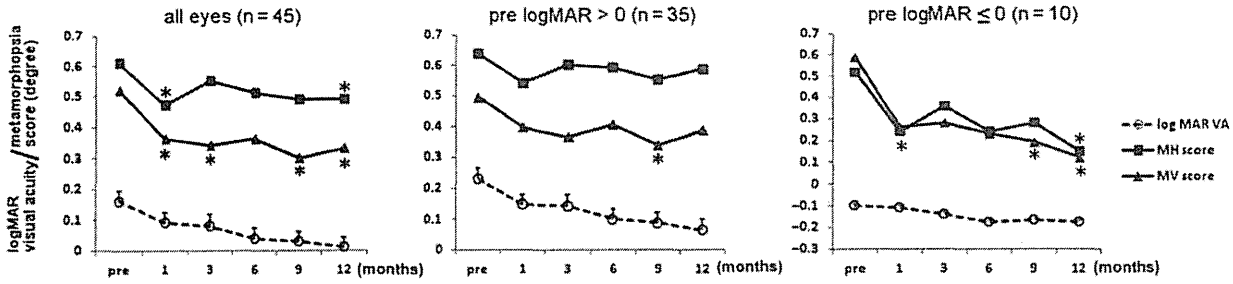

Fig. 2. Changes of the mean metamorphopsia score and mean best-corrected visual acuity before and after half-dose photodynamic therapy for chronic central serous chorioretinopathy. Left: The horizontal metamorphopsia (MH) and vertical metamorphopsia (MV) scores for all eyes. Significant improvements were observed in the MH scores at 1 and 12 months and in the MV scores at 1, 3, 9, and 12 months compared with the baseline scores. Middle: Comparison of the metamorphopsia scores and BCVA before and after half-dose photodynamic therapy for chronic central serous chorioretinopathy in eyes with decimal BCVA <1.0 (Group B). Significant improvement was not observed at all follow-up times for both the MH and MV scores except at 9 months in the MV score compared with the baseline scores. Right: Comparison of the metamorphopsia scores and BCVAs before and after half-dose photodynamic therapy for chronic central serous chorioretinopathy in eyes with decimal BCVA ≥1.0 at baseline (Group A). Significant improvement was observed at 12 months in the MH score and at 1, 9, 12 months in the MV score comparing with the baseline scores. *$P < 0.05$.

Spectral domain optical coherence tomographic images were recorded from a 9 × 9 mm area centered on the fovea. Horizontal and vertical scans through the fovea were recorded for each eye. The status of the photoreceptor inner/outer segment (IS/OS) line and the cone outer segment tips (COST) line at 12 months was classified as follows: eyes with an intact IS/OS line in both horizontal and vertical scans were classified as having an intact IS/OS line, and eyes in which the IS/OS line was not detected in at least 1 scan was classified as an absent IS/OS line. Each eye also was classified based on the status of the COST line beneath the macula using the same criteria described for the IS/OS line. The morphologic changes of the macular photoreceptor microstructures were evaluated by two masked investigators (K.F. and Y.M.) independently.

Photodynamic therapy was performed using half-dose verteporfin. For this, 3 mg/m^2 body size of verteporfin was infused intravenously more than 10 minutes, and 15 minutes after beginning the infusion, the laser treatment was begun. The total light energy delivered to the area of hyperpermeability detected on the indocyanine green angiography images was 50 J/cm^2. The spot size covered the areas with choroidal hyperpermeability on the indocyanine green angiography.

The study protocol was approved by the Ethics Committee of the Surugadai Nihon University Hospital, and a written informed consent was obtained from all patients. All experiments were performed in accordance with the Declaration of Helsinki for research involving human subjects.

The BCVA was measured with Landolt charts, and the decimal values were converted to logarithm of the minimum angle of resolution (logMAR) units. Student *t*-tests were used to assess the significance of the changes in the BCVA, and the Wilcoxon signed-rank tests were used to assess the changes of the metamorphopsia scores. For comparisons between 2 groups that were classified according to the baseline BCVA, that is, those with BCVA ≥1.0 (Snellen equivalent of 20/20) or <1.0 (20/20), we used the Wilcoxon signed-rank tests. Mann–Whitney *U* tests were used to compare the horizontal metamorphopsia (MH) and vertical metamorphopsia (MV) scores between presence or absence of the IS/OS line and COST line at 12 months. A $P < 0.05$ was taken to be statistically significant. The analyses were performed using StatView version 5.0 (SAS Inc, Cary, NC).

Results

Forty-five eyes of 45 consecutive patients met the inclusion criteria for this study. The mean age of the 45 patients with chronic CSC was 53.0 ± 9.7 years (range, 36–75 years) and consisted of 43 men and 2 women. Although all patients either stopped or did not have a history of corticosteroid use before the half-dose verteporfin PDT, one patient had used corticosteroid cream for the skin for at least 1 year. The mean duration of the symptom before treatment was 49 months (range, 6–240 months). All patients met each scheduled follow-up visit and underwent all examinations.

The SRD was resolved at 1 month in 40 eyes, at 3 months in 1 eye, and at 6 months in 3 eyes. One eye had a persistent SRD throughout the follow-up period. We did not repeat the PDT in this patient because the macula was already atrophic, and we believed that the BCVA would not improve. During the follow-up period of 1 year, a recurrence of the SRD occurred in 2 eyes. In 1 eye, the SRD was absorbed in 6 months but recurred at 9 months This SRD was spontaneously resorbed at 14 months. In the other eye, the SRD was resorbed in 1 month and recurred at 6 months. The

SRD persisted, and 24 months later, PDT was successfully performed to resolve the SRD. No side effects due to half-dose verteporfin PDT were observed in all the cases.

The patients' postoperative BCVA ranged from 0.15 to 1.5 (from 20/130 to 20/13). Therefore, M-CHARTS examination was performed on all patients. The mean baseline BCVA was 0.16 ± 0.23 logMAR units (equivalent to 20/100), and there was a significant improvement to 0.09 ± 0.22 at 1 month, 0.08 ± 0.24 at 3 months, 0.04 ± 0.22 at 6 months, 0.03 ± 0.22 at 9 months, and 0.01 ± 0.23 logMAR units at 12 months (20/25, 20/24, 20/22, 20/21, and 20/20, respectively; $P < 0.05$ for all comparisons, paired t-tests).

Eighteen of 45 eyes had an improvement of the MH score ≥0.2°, 19 eyes had no change, and 8 eyes had a worse score at 12 months. Twenty-one of 45 eyes had an improvement in the MV score of ≥0.2°, 18 eyes had no change, and 6 eyes had a worse score. The mean MH score was 0.61 ± 0.52° at the baseline, 0.47 ± 0.53° at 1 month, 0.55 ± 0.49° at 3 months, 0.51 ± 0.52° at 6 months, 0.49 ± 0.45° at 9 months, and 0.49 ± 0.56° at 12 months (Figure 2). The mean MH score did not improve significantly at 3, 6, and 9 months ($P > 0.05$, Wilcoxon signed-rank test), but it improved significantly between the baseline and 1 and 12 months ($P < 0.05$, Wilcoxon signed-rank test).

The mean MV scores in degrees were 0.52 ± 0.53° at the baseline, 0.36 ± 0.31° at 1 month, 0.34 ± 0.34° at 1 month, 0.36 ± 0.43° at 6 months, 0.30 ± 0.37° at 9 months, and 0.33 ± 0.46° at 12 months. The mean MV scores improved significantly at 1, 3, 9, and 12 months compared with the baseline score ($P < 0.05$, Wilcoxon signed-rank test) but did not improve

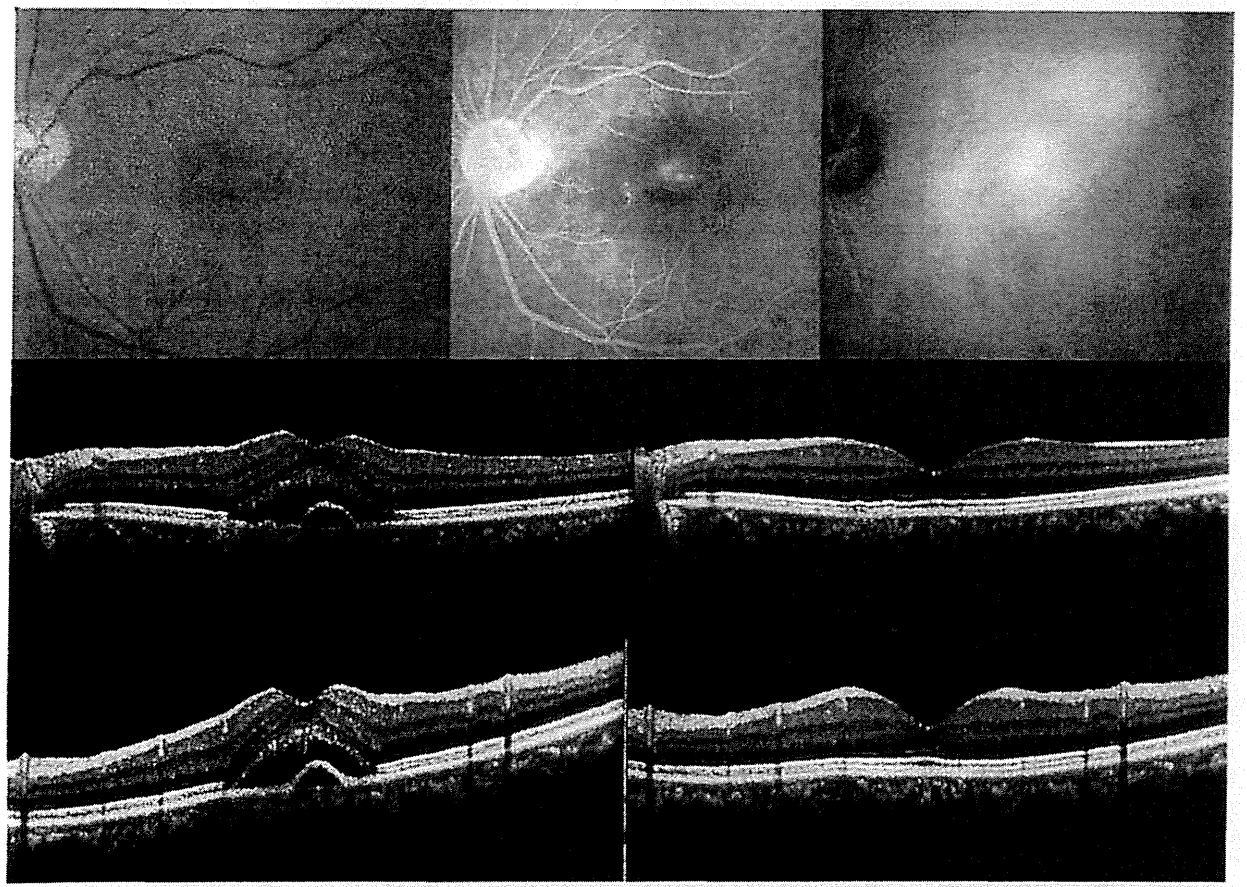

Fig. 3. Representative case from Group A that had an improvement in the metamorphopsia score after half-dose verteporfin photodynamic therapy. A 57-year-old man with chronic central serous chorioretinopathy with a baseline decimal visual acuity of 1.2. Upper left: His MH score and MV score at baseline were 0.9° and 1.0°, respectively. Both scores were improved to 0° at 12 months. Baseline color fundus photograph showing SRD at the macular area including pigment epithelial detachment (PED). Upper middle: Baseline fluorescein angiography showed some focal leakage at the macula. Upper right: Baseline indocyanine green angiography showing choroidal hyperpermeability at the macula. Middle left: Baseline spectral domain optical coherence tomographic (SD-OCT) image of horizontal scan through the fovea showing the SRD and PED. Middle right: SD-OCT image of horizontal scan through the fovea obtained at 12 months showing complete resolution of the SRD and PED. Bottom left: Baseline SD-OCT image of vertical scan through the fovea showed SRD and PED. Bottom right: SD-OCT image of vertical scan through the fovea obtained at 12 months showing complete resolution of the SRD and PED.

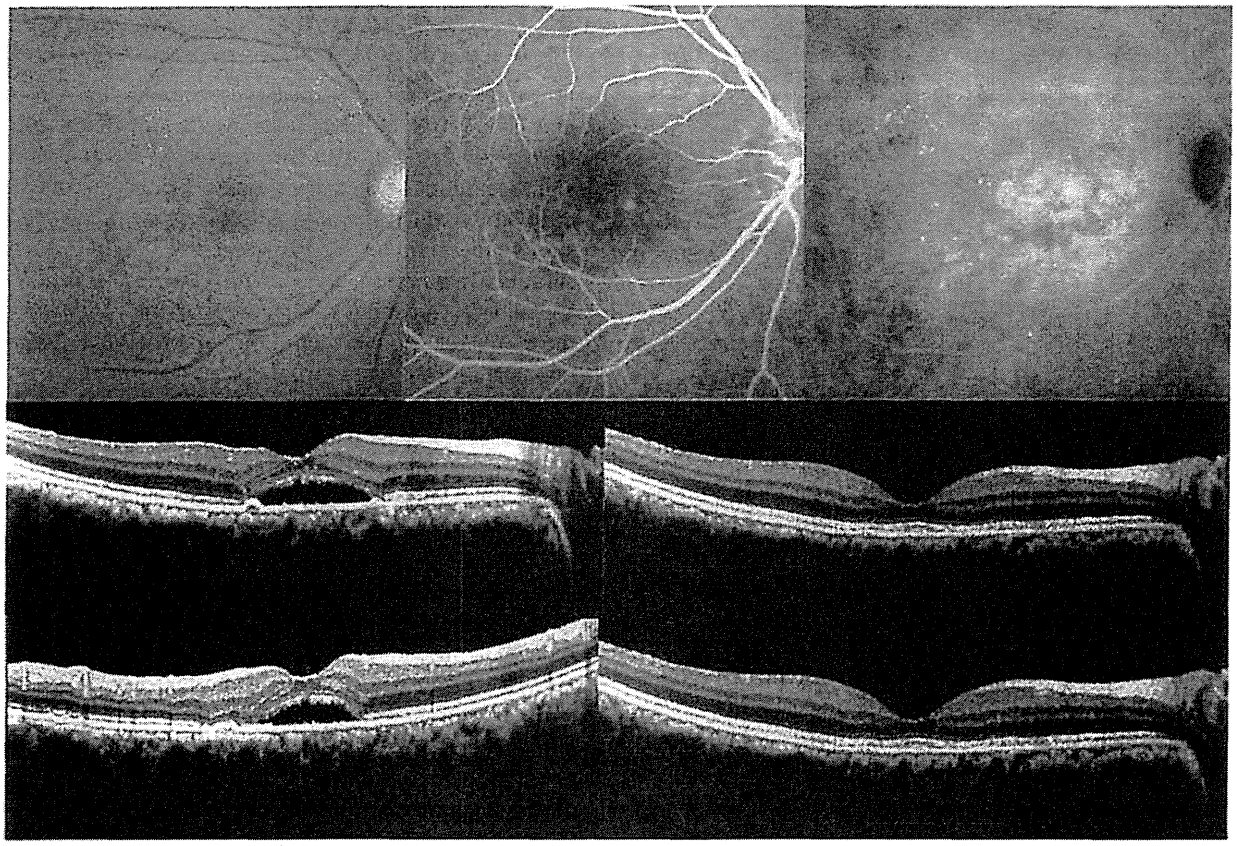

Fig. 4. Representative case from Group B. A 61-year-old woman with chronic central serous chorioretinopathy. Her visual acuity at baseline was 0.5, and her horizontal metamorphopsia (MH) and vertical metamorphopsia (MV) score at baseline were 0.4° and 0.5°, respectively. At 12 months, MH score and MV score were 0.5° and 0.6°, respectively. Upper left: Baseline color fundus photograph showing a serous retinal detachment (SRD) at the macular area. Upper middle: Baseline fluorescein angiography showed some focal leakage at the macula. Upper right: Baseline indocyanine green angiography showed choroidal hyperpermeability at the macula. Middle left: Baseline spectral domain optical coherence tomography (SD-OCT) image of horizontal scan through the fovea showed SRD. Middle right: SD-OCT image of horizontal scan through the fovea obtained at 12 months showing complete resolution of the SRD. Bottom left: Baseline SD-OCT image of vertical scan through the fovea showed SRD. Bottom right: SD-OCT image of vertical scan through the fovea obtained at 12 months showing complete resolution of the SRD.

significantly at 6 months ($P > 0.05$, Wilcoxon signed-rank test; Figures 2 and 3).

We divided the eyes according to the BCVA at baseline; there were 10 eyes with a BCVA of ≤0 logMAR units (Group A) and 35 eyes with a BCVA of >0 logMAR units (Group B). In Group A, the mean MH scores improved significantly from 0.52 ± 0.53° to 0.15 ± 0.25° ($P = 0.04$, Wilcoxon signed-rank test), and the mean MV score improved significantly from 0.59 ± 0.59° to 0.12 ± 0.21° at 12 months ($P = 0.04$, Wilcoxon signed-rank test) compared with that at the baseline (Figures 2 and 3). In Group B, neither the mean MH scores (from 0.64 ± 0.52° to 0.59 ± 0.59°, $P > 0.05$, Wilcoxon signed-rank test) nor the mean MV scores (from 0.49 ± 0.52° to 0.38 ± 0.50°) improved significantly ($P > 0.05$, Wilcoxon signed-rank test; Figures 2 and 4).

The spectral domain optical coherence tomographic images showed that 36 eyes had an intact IS/OS line, and 17 eyes had an intact COST line at 12 months (Table 1). The BCVA was significantly higher in eyes with an intact IS/OS line (n = 36) than in eyes without it (n = 9; $P = 0.0002$, *t*-test) and also significantly higher in eyes with an intact COST line (n = 17) than in eyes without it (n = 26; $P = 0.001$, *t*-test). The MH and MV scores were not significantly different between eyes with (n = 36) and without (n = 9) an intact IS/OS line ($P > 0.05$, for both comparisons, Mann–Whitney *U* test). The MH and MV sores were not significantly different between eyes with (n = 17) and without (n = 28) an intact COST line ($P > 0.05$, for both comparisons, Mann–Whitney *U* test).

Discussion

Our findings showed that both the MV score and the MH score were significantly improved at 12 months

Table 1. Comparisons of Visual Acuity, Horizontal, and Vertical Metamorphopsia Scores Between Eyes With and Without the IS/OS Junction and the COST Lines at 12 Months After Half-Dose PDT

	IS/OS			COST		
	Present (n = 36)	Absent (n = 9)	P*	Present (n = 17)	Absent (n = 28)	P*
LogMAR VA: min–max (mean ± SD)	−0.17 to 0.39 (−0.06 ± 0.15)	−0.07 to 0.69 (0.30 ± 0.27)	0.0002	−0.17 to 0.04 (−0.13 ± 0.07)	−0.17 to 0.69 (0.09 ± 0.25)	0.001
Snellen VA: min–max (mean)	20/50 to 20/13 (20/17)	20/100 to 20/17 (20/40)		20/22 to 20/13 (20/15)	20/100 to 20/13 (20/25)	
MH score: min–max (median)	0 to 2.0 (0.35)	0 to 1.9 (0.60)	0.357	0 to 2.0 (0.30)	0 to 1.9 (0.50)	0.372
MV score: min–max (median)	0 to 2.0 (0.10)	0 to 2.0 (0.40)	0.75	0 to 2.0 (0.20)	0 to 2.0 (0.10)	0.774

LogMAR VA, logarithm of minimal angle resolution visual acuity; SD, standard deviation; min, minimum; max, maximum.
*Statistical comparison was made using Student *t*-test for logMAR VA and Mann–Whitney *U* test for MH and MV scores.

after the half-dose verteporfin PDT for eyes with chronic CSC. For eyes whose baseline decimal BCVA was ≥1.0, both the MV and MH scores improved significantly after the PDT. The presence of the IS/OS line and COST line at 12 months was significantly correlated with the improvement of BCVA, but it was not significantly correlated with the MH or MV scores.

Photodynamic therapy with verteporfin has been shown to improve the visual acuity and reduce the subretinal fluid in eyes with chronic CSC.[6–9,11] Despite the anatomical success and improvement of the visual acuity, patients often complain of metamorphopsia as seen in eyes after successful removal of the epiretinal membrane.[18]

Metamorphopsia has been suggested to result from a displacement of the photoreceptors and a false localization of the image seen by these displaced photoreceptors.[12] The mechanism of metamorphopsia in CSC has not been definitively determined, but a possible explanation is that the regular intervals between adjacent photoreceptors are disrupted by the subretinal fluid. We found that the correlations between the integrity of the IS/OS line and the COST line and the metamorphopsia score were not significant. Ooto et al[19] reported that the adaptive optics scanning laser ophthalmoscope images showed abnormal cone mosaic patterns and reduced cone densities in eyes with resolved CSCs. It is highly likely that three-dimensional alterations of the photoreceptors would not be visible in the images obtained by the spectral domain optical coherence tomography that we used.

Our findings, that eyes with a significant improvement of the mean horizontal and vertical metamorphosia scores at 12 months had baseline decimal BCVA of ≥1.0, suggest that an earlier intervention by PDT would be better. Most published studies suggest that PDT with verteporfin is a safe and efficacious treatment in CSC and that complications are rare, especially when total energy delivered to the retina is reduced.[9–11]

This study has several limitations. This was a retrospective study with no control group. In addition, the number of patients was relatively small. Therefore, further studies with larger sample sizes are needed to confirm these results.

In conclusion, half-dose verteporfin PDT for chronic CSC resulted in significant improvements of the metamorphosia score at 12 months. The improvements of both the MH and MV were significant in eyes with BCVA 1.0. We conclude that the use of M-CHARTS is a useful way to quantify metamorphopsia in CSC undergoing half-dose verteporfin PDT. We recommend half-dose verteporfin PDT for patients with CSC of good vision, particularly when metamorphopsia is present.

Key words: metamorphopsia, M-CHARTS, optical coherence tomography, photodynamic therapy, chronic central serous chorioretinopathy.

References

1. Gass JD. Pathogenesis of disciform detachment of the neuroepithelium. Am J Ophthalmol 1967;63(suppl):1–139.
2. Wang MS, Sander B, Larsen M. Retinal atrophy in idiopathic central serous chorioretinopathy. Am J Ophthalmol 2002;133: 787–793.
3. Piccolino FC, de la Longrais RR, Ravera G, et al. The foveal photoreceptor layer and visual acuity loss in central serous chorioretinopathy. Am J Ophthalmol 2005;139:87–99.
4. Imamura Y, Fujiwara T, Spaide RF. Fundus autofluorescence and visual acuity in central serous chorioretinopathy. Ophthalmology 2011;118:700–705.
5. Chan WM, Lam DS, Lai TY, et al. Choroidal vascular remodeling in central serous chorioretinopathy after indocyanine green angiography guided photodynamic therapy with verteporfin: a novel treatment at the primary disease level. Br J Ophthalmol 2003;87:1453–1458.
6. Cardillo Piccolino F, Eandi CM, Ventre L, et al. Photodynamic therapy for chronic central serous chorioretinopathy. Retina 2003;23:752–763.
7. Yannuzzi LA, Slakter JS, Gross NE, et al. Indocyanine green angiography guided photodynamic therapy for treatment of chronic central serous chorioretinopathy: a pilot study. Retina 2003;23:288–298.
8. Taban M, Boyer DS, Thomas EL, Taban M. Chronic central serous chorioretinopathy: photodynamic therapy. Am J Ophthalmol 2004;137:1073–1080.
9. Lai TY, Chan WM, Li H, et al. Safety enhanced photodynamic therapy with half dose verteporfin for chronic central serous chorioretinopathy: a short-term pilot study. Br J Ophthalmol 2006;90:869–874.
10. Chan WM, Lai TY, Lai RY, et al. Half dose verteporfin photodynamic therapy for acute central serous chorioretinopathy. Ophthalmology 2008;115:1756–1765.
11. Chan WM, Lai TY, Lai RY, et al. Safety enhanced photodynamic therapy for chronic central serous chorioretinopathy. Retina 2008;28:85–93.
12. Amsler M. Earliest symptoms of diseases of the macula. Br J Ophthalmol 1953;37:521–537.
13. Matsumoto C, Arimura E, Hashimoto S, et al. A new method for quantification of metamorphopsia using M-CHARTS. Rinsho Ganka 2000;54:373–377.
14. Matsumoto C, Arimura E, Okuyama S, et al. Quantification of metamorphopsia in patients with epiretinal membranes. Invest Ophthalmol Vis Sci 2003;44:4012–4016.
15. Arimura E, Matsumoto C, Okuyama S, et al. Retinal contraction and metamorphopsia scores in eyes with idiopathic epiretinal membrane. Invest Ophthalmol Vis Sci 2005;46: 2961–2966.
16. Arimura E, Matsumoto C, Okuyama S, et al. Quantification of metamorphopsia in a macular hole patient using M-CHARTS. Acta Ophthalmol Scand 2007;85:55–59.
17. Kinoshita T, Imaizumi H, Okushiba U, et al. Time course of changes in metamorphopsia, visual acuity, and OCT parameters after successful epiretinal membrane surgery. Invest Ophthalmol Vis Sci 2012;53:3592–3597.
18. Okamoto F, Okamoto Y, Hiraoka T, Oshika T. Effect of vitrectomy for epiretinal membrane on visual function and vision-related quality of life. Am J Ophthalmol 2009;147: 869–874.
19. Ooto S, Hangai M, Sakamoto A, et al. High-resolution imaging of resolved central serous chorioretinopathy using adaptive optics scanning laser ophthalmoscopy. Ophthalmology 2010; 117:1800–1809.

Jpn J Ophthalmol
DOI 10.1007/s10384-013-0300-6

THE OFFICIAL INTERNATIONAL JOURNAL OF THE JAPANESE OPHTHALMOLOGICAL SOCIETY

CLINICAL INVESTIGATION

Autoantibodies to transient receptor potential cation channel, subfamily M, member 1 in a Japanese patient with melanoma-associated retinopathy

Yukiko Morita · Kazuhiro Kimura · Youichiro Fujitsu · Atsushi Enomoto · Shinji Ueno · Mineo Kondo · Koh-Hei Sonoda

Received: 23 May 2013 / Accepted: 3 December 2013

Abstract
Purpose To report a case of melanoma-associated retinopathy (MAR) in a Japanese patient found to have autoantibodies to transient receptor potential cation channel, subfamily M, member 1 (TRPM1).
Case An 82-year-old man presented with blurred vision OS as well as night blindness and photopsia OU. Fundus photography, fluorescein angiography, and spectral domain-optical coherence tomography findings were essentially normal. Goldmann perimetry revealed a relative central scotoma, including the blind spot in the right eye, as well as a relative scotoma around a blind spot OS. The full-field scotopic electroretinograms showed a "negative-type" pattern OU, suggestive of extensive bipolar cell dysfunction. Systemic examination revealed that the patient had malignant melanoma of the anus with lung metastasis. Autoantibodies to TRPM1 were detected in the serum of the patient by immunoblot analysis. Vitreous opacity developed during follow-up. The visual symptoms and vitreous opacity of the patient were markedly improved after oral prednisolone therapy. The patient died as a result of widespread metastasis of the melanoma at 11 months after his first visit.
Conclusion The present case is the first reported instance of MAR positive for autoantibodies to TRPM1 in an Asian patient.

Keywords Melanoma-associated retinopathy · Electroretinogram (ERG) · Transient receptor potential cation channel, subfamily M, member 1 (TRPM1) · Paraneoplastic retinopathy

Y. Morita · K. Kimura (✉) · Y. Fujitsu · K.-H. Sonoda
Department of Ophthalmology, Yamaguchi University Graduate School of Medicine, 1-1-1 Minami-Kogushi, Ube, Yamaguchi 755-8505, Japan
e-mail: k.kimura@yamaguchi-u.ac.jp

A. Enomoto
Department of Pathology, Nagoya University Graduate School of Medicine, Nagoya, Japan

S. Ueno
Department of Ophthalmology, Nagoya University Graduate School of Medicine, Nagoya, Japan

M. Kondo
Department of Ophthalmology, Mie University Graduate School of Medicine, Tsu, Japan

Introduction

Melanoma-associated retinopathy (MAR) is a paraneoplastic autoimmune manifestation of melanoma that is characterized by various visual signs and symptoms including night blindness, photopsia, visual field defects, and abnormal color vision [1–8]. Patients with MAR also have characteristic electroretinograms (ERGs). The scotopic full-field ERG elicited by a bright flash stimulus shows a "negative-type" pattern with an a-wave of normal amplitude and a b-wave smaller than the a-wave [1–6], suggesting that in MAR patients, the retinal bipolar cells are affected. Historically, autoantibodies to bipolar cells have been recognized as markers of MAR, but the specific bipolar cell antigen has not been identified [8–12].

We and others recently identified autoantibodies specific for transient receptor potential cation channel, subfamily M, member 1 (TRPM1) in the serum of MAR patients [13, 14]. TRPM1 is specifically expressed in retinal ON bipolar cells and functions as a component of the transduction channel in these cells [15–17]. All four MAR

Published online: 29 January 2014

patients with autoantibodies to TRPM1 in these previous reports were Caucasian [13, 14], and individuals with TRPM1-related MAR have not been described for other ethnic groups. Malignant melanoma is rare in the Japanese population, with a prevalence of only 0.002 %, compared with a frequency of 0.015 % in white populations.

We now report a case of MAR positive for serum autoantibodies to TRPM1 in a Japanese individual with melanoma of the anus and metastasis to the lung.

Case report

An 82-year-old man visited Yamaguchi University Hospital with complaints of blurred vision OS as well as night blindness and photopsia OU with a duration of about 1 month. He had not recently been diagnosed with any ocular or systemic disease, including any malignant tumors. His family history revealed no members with any eye diseases. Our initial examination found that his best corrected visual acuity (BCVA) was 1.2 OD and 0.6 OS. Slit-lamp assessment, intraocular pressure measurement, fundus examination, and fluorescein angiography findings were essentially normal OU (Fig. 1a, b). Spectral domain-optical coherence tomography (SD-OCT) (Cirrus HD-OCT; Carl Zeiss Meditec, Dublin, CA, USA) revealed a normal macular structure, with the exception of a slight irregularity of the retinal pigment epithelium in both eyes (Fig. 1c). The thickness of the parafoveal nasal inner nuclear layer (INL) was 40 μm OD and 36 μm OS. Given that the normal thickness of the parafoveal nasal INL was previously determined to be ~40 μm [18], there did not appear to be any thinning of the INL in this patient.

Goldmann perimetry revealed that the visual fields manifested general depression OU. A relative central scotoma including a blind spot was detected OD, and a relative scotoma around the blind spot was detected OS, with the I-4e target (Fig. 2a). Color vision tested with Ishihara color plates was normal, but the Standard Pseudoisochromatic Plates part 2 (SPP-2) test and the panel D-15 test revealed a mild blue-yellow defect OS. A dark-adaptation test revealed a poorly defined red-cone break and elevated threshold level, with a log threshold (arbitrary units) value of 6 after 40 min. Full-field ERGs were recorded with a bright flash stimulus of 20 J after 20 min of dark adaptation. They showed a normal a-wave and a b-wave with a markedly reduced amplitude, giving rise to a "negative-type" pattern OU (Fig. 2b).

On the basis of these ophthalmological and electrophysiological findings, we tentatively diagnosed the patient with paraneoplastic retinopathy and performed systemic examinations. Whole-body computed tomography (CT) revealed a tumor in his right lung (Fig. 2c). Biopsy specimens were obtained from a hilar lymph node in the right lung by bronchoscopy, and histology revealed the mass to be a malignant melanoma (Fig. 2d). Positron emission tomography was performed, but the site of the primary tumor was not identified. There was physiological accumulation of the tracer in the bladder. We consulted a dermatologist, and the patient was then treated with DAV-Feron (dacarbazine, nimustine hydrochloride, vincristine, and interferon-β) chemotherapy. His BCVA remained at 1.0 OD and 0.7 OS, but vitreous opacity appeared OS and perimetry revealed enlarged blind spots OU.

Given that autoantibodies to TRPM1 have been detected in patients with paraneoplastic retinopathy associated with dysfunction of retinal ON bipolar cells [13, 14], we examined whether such autoantibodies were also present in the serum of our MAR patient. Immunoblot analysis revealed that serum from the patient yielded a pronounced immunoreactive band with lysates of cells transfected with an expression vector for human TRPM1 (Fig. 3). Negative control serum did not show such reactivity. These results suggested that the serum of the proband contained autoantibodies to TRPM1.

The patient received oral prednisolone at 40 mg/day for treatment of his MAR. Four weeks after the onset of prednisolone therapy, the vitreous opacity had disappeared and the blind spot enlargement was markedly attenuated OU. Four months after his initial visit, the patient was diagnosed with anal malignant melanoma, with the late diagnosis being attributable to the misidentification of his anal tumor as a hemorrhoid. The lung tumor was thus likely a metastasis from anal malignant melanoma. The patient died at 11 months after his first visit as a result of metastasis to the brain, lung, liver, bilateral hilar lymph nodes, mediastinal lymph nodes, and inguinal lymph nodes.

Discussion

The patient presented with blurred vision, night blindness, and photopsia associated with a "negative-type" ERG, indicative of dysfunction of retinal bipolar cells. Systemic examination revealed malignant melanoma in the lung and anus. The serum of the patient was also positive for autoantibodies to TRPM1. On the basis of these findings, we diagnosed the patient with MAR likely caused by autoantibodies to TRPM1. Only four patients with TRPM1-related MAR have been reported to date, all of whom were Caucasian [13, 14]. The present Japanese patient thus represents the first case of TRPM1-related MAR in an ethnic group other than Caucasian. Our findings suggest that autoantibodies to TRPM1 may play an important role in the pathogenesis of MAR regardless of ethnicity.