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Incidence of Increased Intraocular Pressure after Subtenon Injection of Triamcinolone Acetonide

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Abstract

Purpose: To determine the incidence of eyes that have an increase in the intraocular pressure (IOP) after subtenon injections of triamcinolone acetonide (TA).
Methods: The medical records of 147 patients treated with single or multiple subtenon injections of TA (10 mg) were reviewed. The incidence of an IOP elevation (ΔIOP) ≥5 mmHg or an IOP of >21 mmHg was determined. The peak ΔIOP, defined as the difference in the IOP at the peak to the baseline IOP, was also evaluated. Multivariate analyses were used to evaluate the relation between the IOP elevation and the age, gender, refractive error, and lens status.
Results: A ΔIOP ≥5 mmHg was found in 75 eyes (46%), and an IOP >21 mmHg was found in 48 eyes (30%) after a single injection of TA. The IOP increased within 3 months in 39 eyes (81%) and after 4 months in 9 eyes (19%). The IOP began to increase significantly from 2 weeks up to 5 months ($P<0.05$) and returned to the baseline IOP in 10 months. The incidence of ΔIOP ≥5 mmHg or an IOP of >21 mmHg after multiple subtenon injections of TA was significantly higher than after a single injection (62%; $P=0.027$, 47%; $P=0.013$, respectively). The incidence of IOP >21 mmHg and the peak ΔIOP were significantly related with younger age ($P=0.002$, $P=0.021$, Forward stepwise regression analysis). A weak but significant negative correlation was found between the peak ΔIOP and the age ($r=-0.216$, $P=0.006$, Pearson's correlation coefficient test), and the peak ΔIOP and the refractive error ($r=-0.198$; $P=0.018$).
Conclusion: Repeated injections of TAs and injection of younger patients or myopic eyes increase the incidence of an IOP elevation.

Introduction

Corticosteroids are known to reduce inflammation, but systemic administration of corticosteroids can also lead to serious systemic side effects. For the eye, triamcinolone acetonide (TA), a corticosteroid, has been topically used to treat chalazions and eyelid angiomas, and the efficacy of intravitreal or subtenon injections of TA for various vitreoretinal diseases has been reported.[1–4]

An intravitreal injection is less frequently used because of the risk of endophthalmitis and retinal detachments, and a subtenon injection is preferred because of its safety and convenience.[5,6] It has been reported that an increase in the intraocular pressure (IOP) can develop after injections of TA and other corticosteroids to cause steroid-induced ocular hypertension.[7,8] Since TA is weakly water soluble and long-acting, the IOP elevations can occur several months after the injection, and the increase in the IOP can last for several months. This complication can result in some eyes having to undergo laser treatment and/or filtering surgery.[9–12] In spite of the earlier studies, the exact incidence of eyes that have an increase in the IOP after a subtenon injection of TA has not been published.[13]

The purpose of this study was to determine the incidence of an elevation of the IOP after single or multiple injections of TA. To accomplish this, we reviewed the medical records of cases that had received either single or multiple subtenon injections of TA for several retinal disorders associated with major retinal vascular pathologies.

Methods

Subjects

A retrospective case series study was conducted on 162 eyes of 147 patients (79 men, 68 women) who had received single or multiple subtenon injections of 10 mg TA. There

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were 38 eyes of 26 patients with diffuse diabetic macular edema, 64 eyes of 63 patients with branch retinal vein occlusion, 10 eyes of 9 patients with central retinal vein occlusion, 39 eyes of 38 patients with exudative age-related macular degeneration, 7 eyes of 7 patients with idiopathic choroidal neovascularization, and 4 eyes of 4 patients with macular edema by other ocular diseases that were treated with TA.

The patients had been treated at the Keio University Hospital between June 2002 and January 2007 and were followed for at least 4 months. None of the patients had received an earlier subtenon injection of other corticosteroids. The baseline IOP was measured at least twice at different times on different days before the injection, and patients in whom glaucoma was diagnosed or had a baseline IOP >21 mmHg were excluded. The anterior chamber angle of all patients was open without any evidence of neovascularization.

A written informed consent was obtained from all patients after a full explanation of the purpose and possible complications of the subtenon TA injection. The Ethics Committee of Keio University approved the use of TA including possible additional treatments based on recommendation of the Institutional Review Board. The procedures used conformed to the tenets of the Declaration of Helsinki.

Procedures for subtenon TA injections

To prepare 10 mg of TA, 0.25 mL containing 10 mg of TA (Kenacort-A®, 40 mg/mL; Bristol Myers KK, Tokyo, Japan) was aspirated into a 1 mL syringe. The syringe was placed in a holder for several minutes, and after the crystals of TA had settled on the bottom, the supernatant was reduced to a volume of 0.1 mL. Immediately before the subtenon injection, the mixture in the syringe was shaken well to make a uniform suspension of the TA crystals.

Before the TA injection, the eye was anesthetized with several drops of 4% lidocaine. An eye speculum was used, and the patient was asked to look inferonasally to expose the superotemporal bulbar conjunctiva. A 26-gauge needle was inserted superotemporally into the subtenon space by gently moving the tip of the needle to avoid penetrating the globe. The tip of the needle was not sharp and was similar to the needle attached to a tuberculin syringe.

IOP measurements

The IOP was measured by Goldmann aplanation tonometry. Patients were examined at ~2 weeks and at 1 month after the TA injection. Thereafter, the follow-up examinations were done monthly. The incidence of IOP elevation (ΔIOP) ≥5 mmHg from the IOP before the injection (baseline IOP) and the incidence of IOP increased to >21 mmHg in any period after TA injection were evaluated. The peak ΔIOP, defined as the difference in the IOP at the peak elevation from the baseline IOP, was also evaluated. If the IOP exceeded 25 mmHg, topical beta-blockers, prostaglandin derivatives, or carbonic anhydrase inhibitors were given. If the IOP continued to be elevated, different combinations of these drugs were used. Selective laser trabeculoplasty (SLT) was usually performed if the IOP continued to be higher than 40 mmHg despite the maximum medication including systemic carbonic anhydrase inhibitors. The eyes that underwent SLT were included in the analysis on the ΔIOP but not included in the analysis evaluating the course of the IOP elevation after the treatments with SLT. The eyes that underwent cataract and/or vitreous surgery during the observation period or simultaneously with the TA injection were excluded to eliminate bias of the host factors.

The topical medication score was defined as the number of anti-glaucoma eye drops being used, and the scores were assessed before and after the TA injection. Statistical analyses were performed by a commercial statistical software package. Paired *t*-tests were used to assess the significance of differences in the IOPs before and after the TA injections. Fisher's exact probability tests were used to evaluate the significance of the ΔIOP. Forward stepwise regression analysis was used to evaluate the relationship between IOP elevation (IOP >21 mmHg or ΔIOP ≥5 mmHg, or the peak ΔIOP) and age, gender, refractive error, and lens status. Pearson's correlation coefficient test was used to determine the relationship between the age and the refractive error, or the age and the peak ΔIOP. The level of significance was 0.05 for all statistical tests.

Results

Incidence of elevation in IOP

A total of 311 subtenon TA injections were given to the 162 eyes. The mean age of the patients was 62.9±11.9 years (±standard deviation) with a range from 30 to 86 years. The mean baseline IOP before a single TA injection was 14.4±3.5 mmHg with a range from 8 to 21 mmHg (Table 1). A ΔIOP ≥5 mmHg was found in 75 eyes (46%), and an IOP >21 mmHg was found in 48 eyes (30%) after a single injection of TA. After a single injection of TA, a ΔIOP ≥5 mmHg was observed at 2 weeks to 8 months (mean 2.2 months) after the injection (Fig. 1). The mean IOP was elevated significantly for 2 weeks to 5 months. The mean peak ΔIOP was 17.3±6.0 mmHg (range from 8 to 62 mmHg), which was attained at 2 months after the TA injection. The mean IOP

TABLE 1. INCIDENCE OF INTRAOCULAR PRESSURE ELEVATION AFTER SUBTENON TRIAMCINOLONE ACETONIDE INJECTION

	Numbers of eyes	*baseline IOP (mmHg)*	*ΔIOP ≥5 mmHg*	*IOP >21 mmHg*	*IOP >30 mmHg*
Total injections	162	14.4±3.5	101 (62%)	73 (45%)	17 (10%)
Initial single injection	162	14.2±2.9	75 (46%)[a]	48 (30%)[b]	13 (8%)[c]
Repeated multiple injections	77	14.6±3.5	48 (62%)[a]	36 (47%)[b]	5 (6%)[c]

[a]$P=0.027$.
[b]$P=0.013$.
[c]$P=0.797$, Fisher's exact probability test.
IOP, intraocular pressure; ΔIOP, IOP elevation from the baseline IOP.

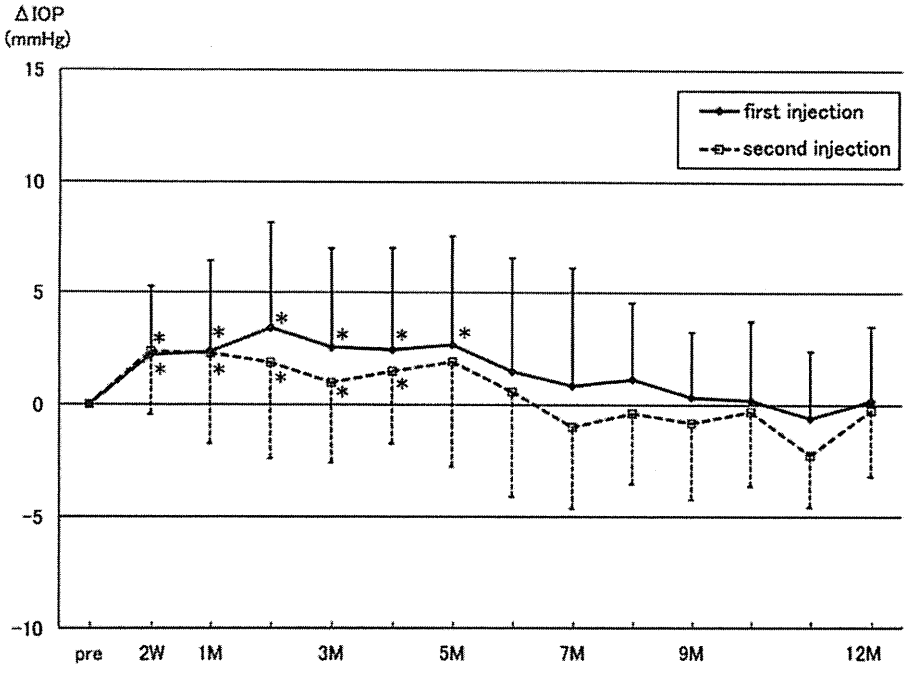

FIG. 1. Mean intraocular pressure (IOP) before and after a single and a second injection of TA. The IOPs at 2 weeks, and 1, 2, 3, 4, and 5 months after the injection of TA are significantly higher than the baseline IOP after a single injection. The IOPs at 2 weeks, and 1, 2, 3, and 4 months are significantly higher than the baseline after a second injection (*$P<0.05$, error bar: standard deviation, Paired t-tests). W, week, M, month; TA, triamcinolone acetonide.

decreased to 15.8±4.7 mmHg (ranged 9 to 35 mmHg) at 6 months after the TA injection, and it was not significantly different from that of the baseline IOP. The mean IOP returned to 14.2±3.1 mmHg (approximate the mean baseline IOP) with reduced numbers of medications at 10 months after the TA injection.

The IOP began to increase within 3 months in 60 (80%) of the 75 eyes with an IOP elevation ≥5 mmHg after the single TA injection. The increase in the IOP began at 4 months after the injection in the other 15 eyes (20%). The IOP increased to >21 mmHg after a single injection within 3 months in 39 eyes (81%) and in 4 months in the remaining 9 eyes. In 13 of the 162 eyes (8%), the IOP increased to >30 mmHg at 4 months after the injection.

In the 75 eyes with a ΔIOP ≥5 mmHg after a single injection, topical anti-glaucoma medications were given to 33 eyes (44%). The topical medication score was 0 at baseline and increased to 1.1 at 5 months after the single injection (Fig. 2). The score gradually decreased to 0.2 at 10 months after the injection. After a single subtenon injection of TA, SLT was performed on 3 eyes, and the IOPs of all 3 eyes were controlled without any medication at 6 months after the TA injection.

In the eyes that required 2 TA injections, the IOP increased significantly from 2 weeks after the second injection, but the IOP was not significantly higher at 5 months after the injection (Fig. 1). Seventy-seven of the 162 eyes received multiple subtenon injections of TA (Table 1). The incidence of a ΔIOP ≥5 mmHg after multiple subtenon injections of TA

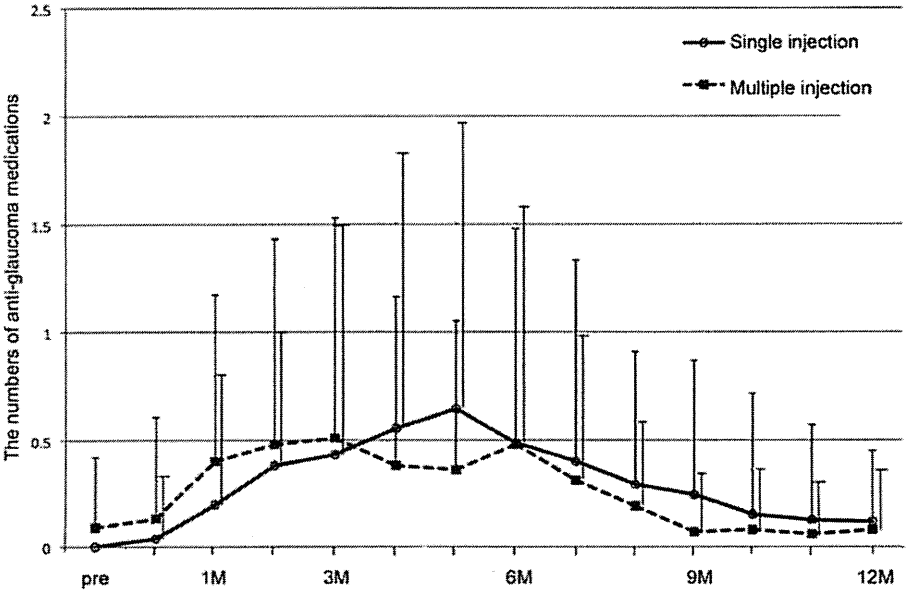

FIG. 2. Topical medication score before and after single and multiple injection of TA. The mean number of glaucoma medications increases from 0 to 1.1 at 5 months after the single injection and gradually decreased to 0.2 at 10 months after the injection. The topical medication score was <0.1 before the multiple injections, 0.5 at 4 months after the injection, and 0.2 at 8 months after the injection. The topical medication score rapidly increased compared with eyes with the single injection (error bar: standard deviation, Paired t-tests).

was significantly higher than that after a single injection ($P=0.027$, Fisher's exact probability test). The incidence of an IOP increasing to >21 mmHg was significantly higher than that after a single injection ($P=0.013$), but the difference in the incidence of an IOP increasing to >30 mmHg was not significant ($P=0.797$). In the 5 eyes whose IOP increased to >30 mmHg, the IOP elevation was seen within 3 months after the last injection.

Among the 48 eyes whose ΔIOP increased by ≥5 mmHg after multiple injections, anti-glaucoma topical drops were prescribed to 22 eyes (46%). The topical medication score was <0.1 before the additional injections, 0.5 at 4 months after the last injection, and 0.2 at 8 months after the last injection (Fig. 2). The topical medication score was higher than that after the initial single injection although the scores were relatively low.

One hundred and one eyes (62%) of 91 patients with a mean age of 63.3 years including 50 men and 41 women had a ΔIOP ≥5 mmHg at least once after the subtenon injections of TA. Sixty-one eyes (38%) of 56 patients with a mean age of 62.9 years including 29 men and 27 women did not show a ΔIOP ≥5 mmHg after the subtenon injections of TA. There were 15 cases that had subtenon TA injections in both eyes (Table 2), and the incidence of IOP >21 mmHg was 27% (8 eyes) of bilateral injections comparing with 30% (40 eyes) of unilateral injections ($P=0.826$, Fisher's exact probability test). In 8 eyes with bilateral injections with IOP increased to >21 mmHg, the IOP increased bilaterally in 3 cases (60%) and unilaterally in 2 cases (40%). However, there was a selection bias because both eyes from 15 patients were included in this analysis.

Relationship between change in IOP elevation and refractive error

One hundred and forty-two of the eyes (88%) of 127 patients were phakic, and 20 eyes of 20 patients were pseudophakic. None of the eyes was aphakic. The effect of the refractive error was only evaluated for the phakic eyes. The mean refractive error in the phakic subjects was −2.3±3.8 diopters (D) with a range from −19.0 D to +2.5 D. In 142 phakic eyes, 91 eyes (64%) of 85 patients including 55 eyes of 50 men and 36 eyes of 35 women had a ΔIOP ≥5 mmHg after single or multiple subtenon injections of TA. The mean refractive error (spherical equivalent) with a ΔIOP ≥5 mmHg was −2.4±3.3 D, and the mean age was 60.5 years. The mean refractive error without a ΔIOP ≥5 mmHg was −2.1±4.7 D, and the mean age was 62.3 years. Forward stepwise regression analysis showed a significant negative correlation between the age and IOP >21 mmHg ($P=0.002$), and the age and peak ΔIOP ($P=0.021$, Table 3). The relationship between the age and the peak ΔIOP was calculated by Pearson's correlation coefficient test, and a weak but significant negative correlation was found ($r=-0.216$, $P=0.006$; Fig. 3). A weak but significant negative correlation was also found between the refractive error and the peak ΔIOP ($r=-0.198$, $P=0.018$; Fig. 4). This indicated that the IOP was more likely to be elevated after a TA injection in younger patients and eyes with higher myopia.

TABLE 2. INCIDENCE OF INTRAOCULAR PRESSURE ELEVATION AFTER SUBTENON TRIAMCINOLONE ACETONIDE INJECTION

	Number of cases	*Number of eyes*	*Baseline IOP (mmHg)*	*IOP >21 mmHg (eyes)*
Unilateral Injection	132	132	14.2±3.0	40 (30%)[a]
Bilateral injections	15	30	14.6±2.7	8 (27%)[a]
Total injections	147	162	14.2±2.9	48 (30%)

[a]6 eyes of 3 cases and 2 eyes of 2 cases, $P=0.826$, Fisher's exact probability test.

Discussion

An increase in the IOP is the most frequent complication of TA use. The increase in the IOP is usually transient, and the patient is often asymptomatic even when the IOP is elevated to 50 to 60 mmHg, a characteristic of steroid glaucoma.[7] The effect of TA has been reported to last from 3 to 8 months.[14] Thus, careful attention should be paid to the IOP after both types of TA injection, because an increase in the IOP can lead to irreversible optic nerve atrophy, and the elevated IOP can be controlled by topical anti-glaucoma drugs in most cases. However, some cases may require filtering surgery to normalize the IOP.

Helm and Holland reviewed 20 eyes that had received subtenon injections of TA, and they reported that an elevated IOP was found in 6 patients (30%), and 2 of the 6 eyes had received several injections.[13] Mueller and associates studied 54 steroid nonresponders and reported that a subtenon injection of TA (40 mg) was safe and did not cause an increase in the IOP when the deposit was injected into the subtenon space.[15] Levin and associates reported an increase in the IOP in 4 of 9 patients (44%) who were steroid-responders and 7 of 55 patients (13%) who were steroid nonresponders.[16] Some patients had an IOP elevation after a subtenon injection of TA even in steroid nonresponders. These findings indicated that the conventional steroid response test cannot clearly differentiate the eyes that will have an elevation of the IOP after subtenon TA.

TABLE 3. MULTIVARIATE ANALYSIS WITH INTRAOCULAR PRESSURE INCREASE

	Standard partial regression coefficient	F *value*	P *value*
IOP >21 mmHg			
Age	−0.266	10.313	0.002
Gender	−0.023	0.087	0.768
Refractive error	−0.122	2.446	0.120
Phakia/aphakia	0.140	2.872	0.092
ΔIOP ≥5 mmHg			
Age	−0.069	0.656	0.419
Gender	0.067	0.690	0.407
Refractive error	−0.075	0.861	0.355
Phakia/aphakia	−0.015	0.031	0.861
Peak ΔIOP			
Age	−0.196	5.473	0.021
Gender	0.106	1.808	0.181
Refractive error	−0.035	0.201	0.655
Phakia/aphakia	0.028	0.114	0.736

Forward stepwise regression analysis.

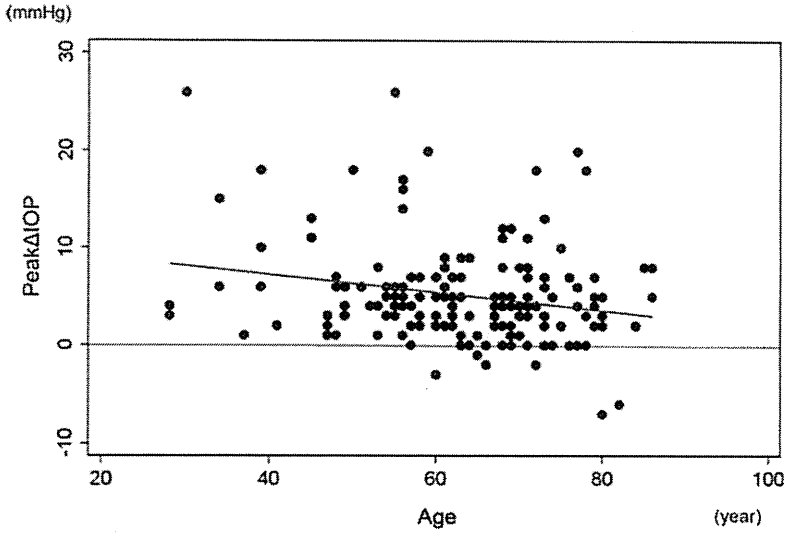

FIG. 3. Relationship between the change in the peak ΔIOP (the peak elevation from the baseline IOP) and age. A significant negative correlation exists between the peak ΔIOP and the age, indicating that the IOP increased in younger patients more often than in older patients ($P=0.006$; $r=-0.216$, Pearson's correlation coefficient test). ΔIOP, incidence of IOP elevation.

Ito and associates reported that the IOP increased to >21 mmHg in 41 eyes (34.5%) of 119 eyes after intravitreal and subtenon injections of TA, and an IOP increased by >5 mmHg from the baseline was found in 59 eyes (49.6%).[17] It has also been reported that the ΔIOP was higher in younger patients and also after repeated injections.[17] Jonas and associates also reported that the IOP increased to >21 mmHg in 39 (52%) of 75 eyes after an intravitreal injection of TA, and one of these cases required trabeculectomy.[7,18] The dose of TA for subtenon injection was usually 20 to 40 mg, which was more than that of an intavitreal injection of 4 to 20 mg. An intravitreal injection of TA is believed to affect the trabecular meshwork in the angle more directly than the subtenon injection. This may be why a delayed IOP elevation was observed after subtenon TA injection in our study.

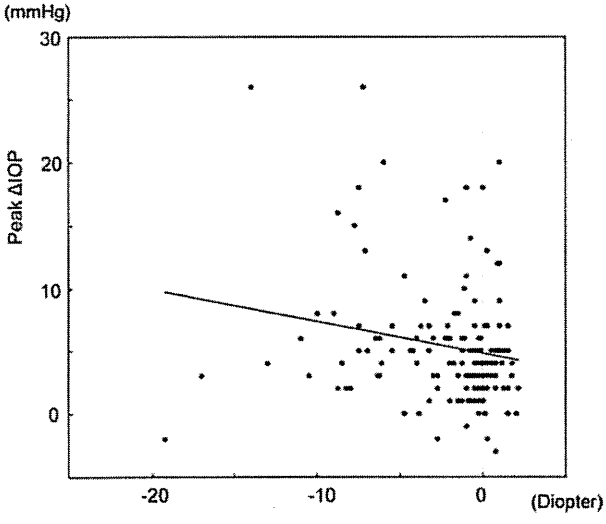

FIG. 4. Relationship between the change in the peak ΔIOP (the peak elevation from the baseline IOP) and refractive error. A significant negative correlation exists between the peak ΔIOP and the refractive error, indicating that the IOP in myopic eyes increased more often than in eyes with higher refractive errors ($P=0.018$; $r=-0.198$, Pearson's correlation coefficient test).

We injected the TA into the posterior subtenon space around the equator of the eye, and 46% of the cases had an elevated IOP within 2 months after the initial subtenon injection of TA. By 3 months, 80% of the eyes had developed an IOP elevation. However, cases of late-onset IOP elevation were present in our series, and repeated injections of TA may increase the risk of an IOP elevation. An IOP elevation was observed in 20% of our cases beginning 4 months after the TA injection. This suggests that a repeat TA injection within 4 months of a previous injection might increase the risk of IOP elevation. There may be a potential bias in our delay in giving the second injection when the IOP had risen after the initial injection. Thus, the incidence of IOP elevation after repeated injections would be higher than that stated earlier. Thus, repeated injections should be considered more carefully to avoid the risk of ocular hypertension.

A significant correlation was found between an IOP elevation and younger age and gender.[19] A weak but significantly negative correlation between refractive error and IOP elevation was found in our cases, indicating that more attention should be paid to younger patients and those with high myopia. In an earlier report, the authors recommended that patients should be tested for the presence of a positive steroid response by applying a topical steroid before the use of TA, and TA should be avoided if the patient was a steroid-responder.[16] However, our results showed that the IOP elevation could be controlled in most of the cases by topical anti-glaucoma drugs. In addition, we found that some patients had an elevation of the IOP unilaterally after a bilateral injection of TA. Thus, we believed that an elevated IOP after TA is probably more complex than expected from the presence of topical steroid response. The mechanism for the significant correlation between high myopia and an elevation of the IOP requires further study.

In conclusion, a subtenon injection of TA has been used for treatment, but can be a high risk of an IOP elevation. However, the elevated IOP is transient. We recommend frequent measurements of the IOP and long-term observations

in patients who have had a subtenon or an intravitreal injection of TA, because cases with late-onset increases in the IOP can be present and retreatment with TA increases the risk of IOP elevation.

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Author contributions

Design of the study (R.K., M.I., K.S., K.T.); Conduct of the study (R.K., M.I., K.S., S.I., K.T.); Collection and Analysis of the data (R.K., H.S., Y.I.); Literature Search (R.K., M.I., K.S.).

Author Disclosure Statement

No competing financial interests exist.

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Stiles–Crawford effect in focal macular ERGs from macaque monkey

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Background: To determine whether the focal macular electroretinograms (FMERGs) are affected by the angle of incidence of the stimulating light on the retina, i.e., the Stiles–Crawford effect (SCE). *Methods*: FMERGs were elicited by focal stimulation of the macula in three light-adapted macaque monkeys. The incidence of the light on the retina was varied from 0 to ±11.7°. The effects of the incidence and wavelengths of the stimulus on the SCE were determined. *Results*: The amplitudes of the FMERG components were largest when the stimulus beam entered the eye on the visual axis and passed through the center of the pupil. The amplitudes gradually decreased as the stimulus beam passed through the pupil more eccentrically and fell on the retina more obliquely. All components of the FMERGs were decreased with the decrease least for the amplitude of the d-wave. *Conclusions*: The decrease in the amplitudes of the FMERGs as the angle of incidence of the stimulus beam on the retina increases demonstrates that the SCE can be detected in adult macaque monkeys. This objective method of assessing the SCE suggests that this technique can be used to assess the alignment of cones in humans with different types of macular diseases.

Keywords: Stiles–Crawford effect, focal macular electroretinogram, ERG

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Introduction

Focal macular electroretinograms (FMERGs) have been used to assess the physiological condition of different retinal neuronal cells including the photoreceptors in the macular area (DeLint, Berendschot, & van Norren, 1998; Kondo, Miyake, Horiguchi, Suzuki, and Tanikawa, 1998). In most experimental and clinical studies, FMERGs have been recorded, and the effects of the Stiles–Crawford effect (SCE), a decrease in the luminous efficiency of light entering the edge of the pupil, were not examined. However with focal stimulation, the direction of the incidence beam becomes more important.

Evidence has been obtained that the directional sensitivity of the cones to light stimuli is responsible for the SCE (Alpern, 1986; Alpern, Kitahara, & Fielder 1987; Alpern & Kitahara, 1983; Stiles & Crawford, 1933). The SCE is generally determined by psychophysical tests (Alpern, 1986; Alpern et al., 1987; Alpern & Kitahara, 1983; DeLint, Vos, Berendoschot, & van Norren, 1997), and the subjects are required to actively participate in the examination. Thus, high level of concentration and good visual acuity are required to perform the tests.

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The SCE has been examined objectively in humans by only a few investigators. DeLint et al. analyzed the SCE by measuring the visual pigment density with different incidences of the bleaching and reflected light (DeLint et al., 1998). Birch et al. stimulated focal macular areas with a steady-state flickering light through a two-channel Maxwellian-view optical system to elicit focal ERGs (Birch, Sandberg, & Berson, 1982). They showed that the SCE could be demonstrated at the fovea in normal subjects. However, they isolated the b-waves by using band-pass filters, and a separation of a-wave and d-wave components was not possible. The FMERGs in our study enabled us to isolate the a-, b-, and d-waves, and we were able to analyze each component to determine whether each showed the SCE effect.

We have developed an FMERG system that is integrated into a slit lamp that allowed us to stimulate the retina with a spot of light at any incidence (Choshi, Matsumoto, & Nakatsuka, 2003; Yamada, Matsumoto, & Nakatsuka, 2006). This FMERG stimulating and recording system prompted us to assess the SCE objectively with long-duration stimuli. This system allowed the ERG recordings to be performed under direct fundus observation, and each component of the FMERGs could be analyzed separately.

Thus, the purpose of this study was to determine whether the SCE was present in the foveal area of macaque monkeys. To accomplish this, we elicited FMERGs from three macaque monkeys by light of different incidences on the retina. We shall show that all components of the FMERGs were affected by the SCE with the d-wave least affected.

Materials and methods

Animals

Focal macular ERGs (FMERGs) were recorded from 3 eyes of 3 adult (ages 6, 6, and 8 years) male macaque monkeys (*Macaca fuscata*). All experimental and animal care procedures adhered to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research and were approved by the Institutional Animal Care Committee of Oita University.

FMERG recordings

The monkeys were initially anesthetized by an intramuscular injection of a mixture of ketamine (7 mg/kg), xylazine (0.6 mg/kg), and butorphanol tartrate (0.04 mg/kg) and maintained on an infusion of the same proportions of ketamine, xylazine, and butorphanol tartrate per hour. The depth of the anesthesia was maintained at a level sufficient to inhibit the corneal reflex and eye movements. The pupils were dilated with topical tropicamide (0.5%) and phenylephrine hydrochloride (5%), and the cornea was anesthetized with topical oxybuprocaine hydrochloride (0.4%). The non-stimulated eye was covered with an opaque patch.

Photopic stimuli

An optical system was built to deliver focal stimuli to the macula under direct fundus observation. The system was designed so that the stimulus light passed through the center of the pupil, i.e., on the visual axis, or through different parts of the pupil from the temporal to nasal edge in 0.5-mm steps. The light sources were from hyper-bright light-emitting diodes (LEDs; NSPW500BS, NICHIA, Tokushima, Japan), and the stimuli positioning unit was a motorized helicoid stage (Sigma Koki, Saitama, Japan) with a telescopic optical system mounted on the stage. The stage moved the telescope so that the stimulating beam entered the pupil from the temporal to nasal sides across the visual axis in 0.5-mm steps. The movement of the stage had an accuracy of 0.05 mm.

The fundus observation system was composed of a near-infrared CCD camera (Hitachi, Japan) integrated on a customized slit lamp microscope (Carl-Zeiss, Germany). The position of the light spot on the macular area was monitored during all of the recordings. The stimulus spot was 5° in diameter. To examine the effects of the wavelength of the stimulus on the SCE, red (λ_{max} = 644 nm, half-amplitude bandwidth of 634 to 655 nm, TLRH180P, TOSHIBA, Tokyo, Japan), amber (λ_{max} = 590 nm, half-amplitude bandwidth of 585 to 596 nm, TLYE260A, TOSHIBA, Tokyo, Japan), green (λ_{max} = 523 nm, half-amplitude bandwidth of 512 to 545 nm, SLA580EC4T, ROHM, Kyoto, Japan), and blue (λ_{max} = 470 nm, half-amplitude bandwidth of 460 to 482 nm, NSPB500S, NICHIA, Tokushima, Japan) LEDs were used to elicit the FMERGs.

The white light stimulus intensity was set to 38 cd/m^2. The spectral characteristics (bandwidth and λ_{max}) of the LEDs used in this study were measured with a spectral colorimeter PR-650 SpectraScan and analyzed with SpectraView software (Photoresearch, CA, USA).

To determine whether the ERGs were focal, the 5° stimulus spot was projected onto the optic nerve head, and FMERGs were elicited by decreasing stimulus intensities. The FMERGs recorded by the stimulus projected on the optic nerve head became non-recordable when the intensity was ≤38 cd/m^2 indicating that this stimulus intensity would provide a focal response from the macula with negligible effect of stray light (Choshi et al., 2003; Yamada et al., 2006). The intensity of each colored light stimulus was matched by neutral density filters to elicit approximately the criteria amplitude of b-wave (1 μV) as elicited by the white stimulus whose luminance was

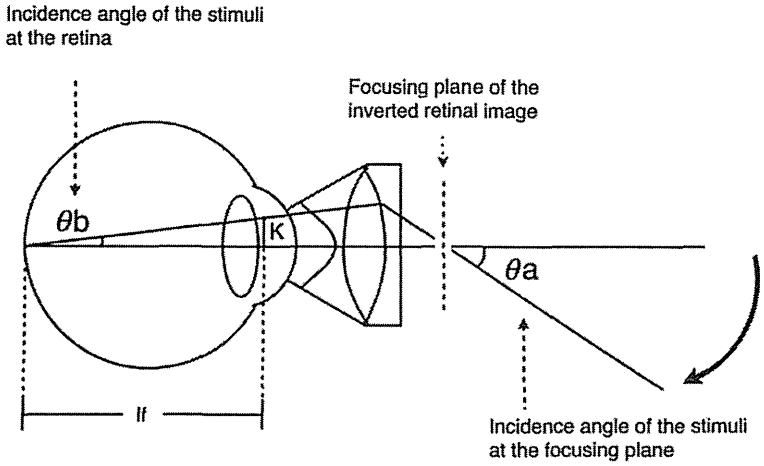

Figure 1. Relationship between the angle of incidence of the light beam on the focusing plane of the inverted retinal image. IF = IF distance, i.e., the axial length minus the corneal thickness and anterior chamber depth and K = distance of the stimulus beam from the visual axis in the iris plane in millimeters.

$\leq$38 cd/m^2. The FMERG waveforms were comprised of on and off waves. The adjusted intensity elicited no ERGs when the stimulus spot was projected onto the optic nerve head.

A gold-foil bipolar contact lens (Mayo, Nagoya, Japan) coupled with a mini-pan fundus lens was placed on the cornea of the examined eye (Figure 1). This provided an inverted real image of the ocular fundus projected approximately 3.5 mm in front of the contact lens unit. The relationship between the angle of incidence of the light beam on the focusing plane of the inverted retinal image and that on the retinal surface was calculated as shown in Figure 1. When the light beam fell on the temporal side of the real image at an angle of θ_a, then the light beam will be projected from the nasal side onto the retinal surface at an angle of θ_b. The relationship between θ_a and θ_b was calculated by

$$[\tan\theta_b = C(\tan\theta_a)], \quad (1)$$

with θ_b being the angle of incidence on the retina, θ_a being the angle of incidence on the focusing plane of the inverted retinal image, and C being the lens magnification constant. Thus, θ_b was determined by the telescope angle and C by the lens magnification constant (0.39).

The distance between the center of the pupil and the stimulus beam was measured as shown in Figure 1. The iris–fovea distance, IF, was calculated by

$$IF = K/(\tan\theta_b), \quad (2)$$

with K equal to the distance of the light beam from the visual axis in the iris plane, and IF equal to the distance of the axial length with the subtraction of corneal thickness and the anterior chamber depth. A correction for light transmission through the cornea and the lens was not done. The axial length, corneal thickness, and the anterior chamber depth were measured by A-mode ultrasound echography (Compuscan LT, Stortz, St. Louis, MO, USA).

The stimulus duration was 100 ms and the stimulus interval was 150 ms, and thus, the frequency of stimulation was 4 Hz. This stimulus pattern of 100 ms on and 150 ms off was used for each wavelength stimulus. A white light of 35 cd/m^2 for 15 min was used for light adaptation before recording with each wavelength. We believe that the off duration was long enough because the depolarization of the cone is much faster than 150 ms.

FMERG recordings and analyses

A bipolar contact lens electrode (Mayo, Nagoya, Japan) was used to pick up the FMERGs. The ground electrode was attached to the right ear lobe. After centering and focusing the stimulus spot on the macula, the eye was light adapted with 35 cd/m^2 for 15 min. Then, the FMERGs were elicited by different stimulus intensities and wavelengths. The responses were amplified with a NeuropackΣ bioamplifier (MEB-5500, Nihon Kohden, Tokyo), A/D converted at 16 bits (PCI-16/16UD, Contec, Japan), and averaged by a customized signal processing program (MTS, Japan). More than forty responses were averaged, and the sampling rate was 10 kHz (every 0.1 ms). The responses were filtered from 0.5 to 200 Hz with a hardwired band-pass filter. With this system, the noise level with the electrode placed on the cornea and no stimulus was less than 0.1 μV.

The amplitude of the a-wave was measured from the baseline to the trough of the a-wave, and the amplitude of the b-wave was measured from the trough of the a-wave

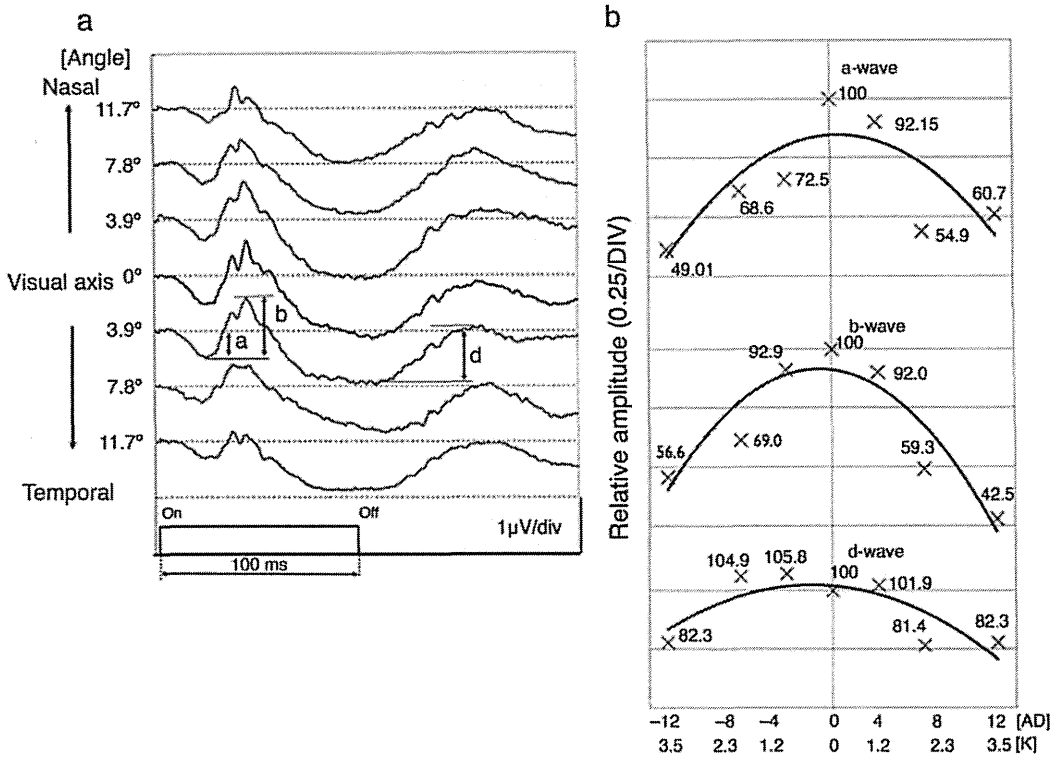

Figure 2. (a) Representative FMERGs elicited by white stimuli entering the pupil at different distances (ordinate) from the visual axis (0) for up to 11.7 degrees. The amplitudes of the a- and b-waves of the FMERGs decrease with increasing distance from the visual axis. (b) The amplitudes of the a-, b-, and d-waves were measured from ERGs such as those from the three monkeys, and the relative amplitudes are plotted on the right. One division of the graph is equal to 25%. *K* represents the distance of the entrance beam to the visual axis in the iris plane in millimeters; AD represents the mean angle of incidence in degrees of stimulus spot from the axis. The blue LED has a peak at 470 nm with a half-amplitude bandwidth between 442 and 520 nm. The green LED has a peak at 523 nm with a half-amplitude bandwidth between 480 and 620 nm. The yellow–orange LED has a peak at 590 nm with a half-amplitude bandwidth between 470 and 620 nm. The red LED has a peak at 644 nm with a half-amplitude bandwidth between 580 and 675 nm.

to the following positive peak (Figure 2). The amplitude of the d-wave was measured from the trough just preceding the d-wave to the positive peak after the stimulus offset.

All of the results are expressed as means ± standard deviations (*SD*s). The polynomial fit of the data was made with the Excel program, ver. 12.0. The polynomial fit was at order 2 for all data.

Results

The amplitudes of the a- and b-waves of the FMERGs were largest when the stimulus beam entered the eye on the visual axis ($K = 0$ mm, retinal angular incidence = 0 degree), and they decreased progressively as the stimulus beam entered more eccentrically up to the edge of the pupil. For example with white light, the average ($n = 3$) relative amplitude of the a-wave at 11.7° was approximately one-half of that at 0°. In the same way, the average ($n = 3$) of the relative amplitude of the b-wave at 11.7° was approximately one-half of that at 0°. Similar changes were found for the d-wave although the degree of change (reduced by 17.7 to 18.6%) was smaller (Figure 2 and Supplementary Table 1). With other wavelengths, the changes depended on the stimulus angle, but the relative amplitude of the d-wave was not evident.

The relative amplitudes of the FMERGs elicited by different wavelengths with peak transmission at 470 nm, 524 nm, 590 nm, and 644 nm are shown in Figure 3. As with the white stimuli, the amplitudes of the a- and b-waves were largest when the light beam entered the pupil on the visual axis and decreased with greater eccentricities. However, the degree of the SCE was not significantly affected by the wavelength of the stimuli (Figure 3).

When the relative amplitude difference was compared between the b-wave and d-wave, significant differences were found for each wavelength used. The relative amplitude differences was calculated as the relative amplitude by the stimulus at 0*K*—that by the stimulus at

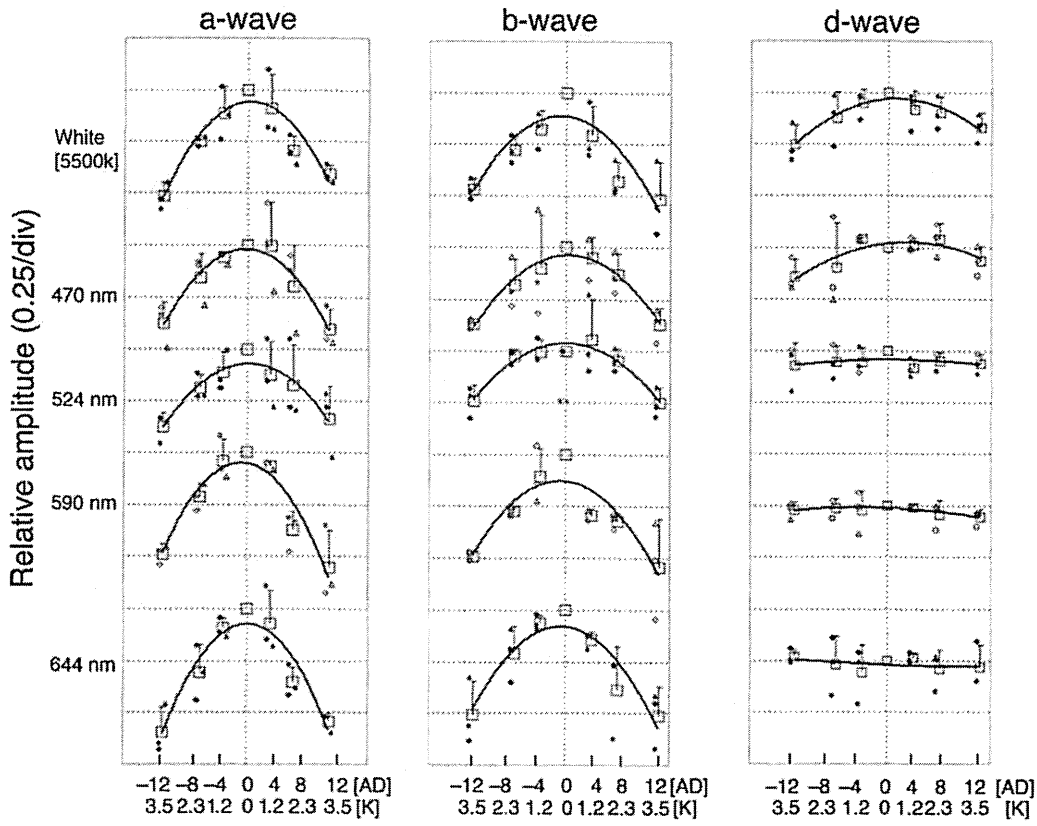

Figure 3. Relative amplitudes of the a-, b-, and d-waves elicited by different wavelengths of the stimulus. The λ_{max} of the stimuli was at 470 nm, 524 nm, 590 nm, and 644 nm. The small symbols (circles, triangles, and asterisks) represent the individual monkeys, the large squares are the averages, and the bars are the standard error of the means. One division of the graph is equal to 25%. *K represents the mean distance of the entrance beam to the visual axis in the iris plane in millimeters; [†]AD represents the mean angle of incidence in degrees of stimulus spot from the axis.

3.5K (Supplementary Table 1). The relative amplitude difference between maximal incidence stimuli and minimal incidence stimuli was significantly larger for the b-wave than for the d-wave for all wavelengths (Supplementary Table 1). Thus, the d-wave amplitude at the maximal stimulus incidence did not decrease as much as that of the b-wave suggesting that the SCE was larger for the b-waves than for the d-waves.

Discussion

Our results showed that the amplitudes of the a-wave and b-waves of the FMERGs were largest when the stimulus beam entered the eye through the center of the pupil and struck the retina perpendicularly. The amplitudes decreased progressively with increasing eccentricities of the stimulus beam. This is comparable to the SCE obtained psychophysically, and our results demonstrated that the SCE can be measured objectively using the FMERGs to assess the response of the retina.

The SCE is based on the ability of the photoreceptors to absorb photons passing through the outer segments, and the chances of a photon striking a photopigment increase when the beam passes perpendicularly through the entire extent of the outer segments. This explains why the FMERGs are largest when the stimulating beam entered the eye along the visual axis.

More than 25 years earlier, Birch et al. (1982) showed that the SCE can be demonstrated in the focal ERGs elicited by flickering stimuli obtained from a two-channel Maxwellian-view optical system. Our results confirmed their findings and also provided new information on the characteristics of the different components of the ERG and the influence of the wavelength of stimulating light.

Our data showed a drop-off in amplitude of the FMERGs when elicited by stimuli entering the edge of the pupil was approximately 50% whereas it was reported that the decrease of sensitivity was 1 log unit psychophysically (Alpern & Kitahara, 1983) or by OCT (Gao, Cense, Zhang, Jonnal, & Donald, 2008). The discrepancy between perimetry or OCT and the FMERGs is most likely due to methodological differences, i.e., the

FMERGs were elicited by suprathreshold stimulus intensities from focal areas, whereas perimetry employs near threshold stimuli. The FMERGs sum the activity of all of activated cells in the retina, whereas the psychophysical threshold is determined by the activity of the most sensitive cells. An alternative explanation might be that the differences were due to the differences in the species studied.

The degree of the SCE was similar for the a- and b-waves but lower for the d-wave. The origin of each wave is thought to be different. The a- and b-waves receive input from postreceptoral cells including off bipolar cells (Bush & Sieving, 1994) and from on bipolar cell (Sieving, Murayama, & Naarendorp, 1994), respectively. The d-wave arises from the activity of both the photoreceptors and inner retinal neurons (Sieving et al., 1994).

The difference may be due to the distribution of the different types of cones in the macular area (Yamamoto, Gouras, & Lopez, 1995). Another and more likely explanation is that the difference arises from the complexity of the ERG responses with several ERG components interacting. The d-waves of the full-field ERGs result from an interaction of the cone photoreceptor recovery and on bipolar offset and off bipolar cell depolarization. For focal stimuli, the response might be complicated by the photopic negative response (PhNR), because the d-wave is abolished by TTX treatment (Kurimoto et al., 2009; Yamada et al., 2006). Further investigations must be done to determine the reason for the different properties of the d-waves.

Stiles (1937) showed that the SCE depended on the wavelength of the light stimuli, and Alpern and Kitahara (1983) demonstrated that the directional sensitivity parameter (P) is dependent on the wavelength, namely, P was high at short (400 nm) and long (700 nm) wavelengths and lower at middle (550 nm) wavelengths. Our methods were not sensitive enough to detect these differences for the different wavelengths of the stimuli, probably because the bandwidths of the stimuli were relatively broad in our study. This was a limitation of the FMERGs. We used 4 LEDs with different wavelength and white light, while Alpern and Kitahara used 30 different monochromatic stimuli. Although each LED provides irradiance with relative steep peak, the relative broad bandwidth in our study might reduce the sensitivity to determine the difference depending on the stimulus wavelength. Using shorter, e.g., 400 nm, and longer, e.g., 700 nm, wavelength stimuli might have increased the sensitivity.

In conclusion, our results showed that the SCE can be determined objectively by the FMERGs. They also indicate that the SCE must be considered in interpreting the results of electrophysiological studies, particularly when focal stimuli are used to assess the macular area. Because the SCE is dependent on the passage of light through the outer segments of the photoreceptors, the FMERGs can be used to examine the alignment and integrity of the photoreceptors of the fovea in different types of macular diseases.

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Outer Retinal Microstructure in a Case of Acute Idiopathic Blind Spot Enlargement Syndrome

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Key Words
Acute idiopathic blind spot enlargement syndrome · Optical coherence tomography · External limiting membrane · Inner and outer segment line · Cone outer segment tips

Abstract
Purpose: To present a patient with acute idiopathic blind spot enlargement syndrome who had abnormal changes in the outer retinal microstructure limited to areas with reduced responses on multifocal electroretinograms as well as to the area involving a scotoma.
Methods and Results: We report the case of a 44-year-old man who developed an arcuate scotoma which was associated with a physiological blind spot in the left eye. The ophthalmoscopic, fluorescein angiographic, and full-field electroretinogram findings were normal. The amplitudes of the multifocal electroretinograms were reduced in the area of the scotoma. Optical coherence tomography showed that both the external limiting membrane and the inner and outer segment (IS/OS) line were intact, but that the middle cone outer segment tip line between the IS/OS line and the retinal pigment epithelium was absent in the nasal macular area of the left eye.
Conclusions: These findings indicate that the integrity of not only the external limiting membrane and IS/OS line but also the cone outer segment tip line is important for the function of the retina.

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Introduction

The acute idiopathic blind spot enlargement (AIBSE) syndrome was first reported in 1988 by Fletcher et al. [1] as a clinical entity with sudden scintillations and a temporal scotoma centered on the blind spot in an otherwise normal fundus. Later, AIBSE was reported to belong to a family of pathologically and etiologically related retinal diseases, including acute zonal occult outer retinopathy (AZOOR), acute macular neuroretinopathy, multiple evanescent white dot syndrome, multifocal choroiditis, and panuveitis, called the AZOOR complex [2, 3]. Optical coherence tomography (OCT) studies of eyes with AZOOR or AZOOR complex disorders revealed abnormalities in the microstructures of the outer retina, e.g. the disruption or loss of the external limiting membrane (ELM) or the loss of the inner and outer segment (IS/OS) line in the areas of the visual field defects [4–9].

Spectral domain OCT (SD-OCT) can acquire higher-resolution images of the retina, and the IS/OS line, the ELM, and the Verhoeff's membrane can thus be easily differentiated [10–12]. Srinivasan et al. [10] used a high-speed, ultrahigh-resolution OCT to show that the Verhoeff's membrane was located at the cone outer segment tips (COSTs). Here, we present a patient with AIBSE at the convalescent stage whose SD-OCT images showed an intact ELM and a continuous IS/OS line but an absence of the COST line. These findings were found only in the retinal areas with reduced responses on multifocal electroretinograms (mfERGs) and in the area of the scotoma.

Case Report

A 44-year-old Japanese man presented with a blind area in his left visual field which he had discovered 10 years earlier. At that time, he visited a local eye clinic but was not diagnosed with any specific retinal disease. In August 2009, he noticed that the blind area had worsened and visited another eye clinic where he was diagnosed with left optic neuritis. A brain MRI showed no abnormalities, and the patient received systemic steroid therapy that was, however, not effective.

His symptom did not improve and he thus visited the Inoue Eye Clinic in March 2010. At the initial examination, his best-corrected visual acuity was 1.2 with a refractive error of –3.0 diopters in both eyes. The intraocular pressure was 11 mm Hg in the right and 10 mm Hg in the left eye. The anterior segment was normal. Ophthalmoscopy and fluorescein angiography revealed that the retina and choroid were normal (fig. 1). Goldmann visual field tests showed a relative arcuate scotoma associated with the physiological blind spot in the left eye. Single-flash, full-field mixed rod-cone electroretinograms (ERGs), photopic cone ERGs, and oscillatory potentials were normal in both eyes. However, the amplitudes of the mfERGs were reduced both in the area corresponding to the visual field defects in the left eye and in the central areas in both eyes.

The entire macular area was scanned by SD-OCT (Cirrus OCT; Carl Zeiss Meditec, Inc.) with scan lengths of 9 mm. High-quality images were obtained using the 5-line raster mode. Both the ELM and the IS/OS line were continuous and distinct in the SD-OCT images. However, the COST line in the nasal macular area of the left eye was not detected (fig. 2). When the retinal thickness was measured by the volume scan mode of the SD-OCT, a decrease in the mean thickness in the nasal, superior, and temporal areas of the 9 sectors of the Early Treatment Diabetic Retinopathy Study (ETDRS) was found (fig. 2). The thinning appeared to be due to a thinning of the outer nuclear layer (ONL). These findings did not change on all examinations during the 8 months of follow-up.

Discussion

Since we did not examine our patient during the acute phase of the disease, our diagnosis of AIBSE syndrome was based only on our findings at the chronic stage. Because there was an arcuate segmental visual field defect connected to the blind spot, with no abnormalities in the ophthalmoscopic and fluorescein angiographic findings but with mfERG abnormalities in the areas of the visual field defect, we diagnosed our patient as having the AIBSE syndrome. Several authors [1–4, 8] have suggested that the AIBSE syndrome belongs to a group of diseases including AZOOR, of which the primary pathological sites are photoreceptors. In support of this, in one study, time domain OCT showed a loss or irregularity of the IS/OS line in a patient with AZOOR, and the authors suggested that the primary lesion occurred in the photoreceptor outer segment [5].

Recent improvements in the resolution of OCT instruments have allowed investigators to obtain higher-resolution images of the intraretinal microstructure in several retinal diseases [12]. The OCT images have shown that the existence of a continuous IS/OS line is due to well-recovered photoreceptor cells [10], and that the integrity of the ELM is correlated with the morphologic changes in the photoreceptor cell bodies and Müller cells [13, 14]. Wakabayashi et al. [14] focused on the microstructure of the outer retinal layer in eyes with surgically closed macular holes, and they reported that the ELM and IS/OS line can recover in some cases, but that the latter rarely recovered without a recovery of the ELM. Spaide et al. [4] found that defects in the IS/OS line were associated with an enlargement of the blind spot in eyes with AZOOR complex diseases.

More recently, ultrahigh-resolution OCT and SD-OCT have been used to examine patients with AZOOR complex disorders, and not only a thinning of the ONL but also a loss of the IS/OS was observed [4, 9]. Our patient presented similar findings. The decrease in the thickness of the ONL plus the thinning of the inner nuclear layer in severe AZOOR cases have been thought to reflect a secondary degeneration after damage of the outer segments [5, 9]. The possibility that in some cases, the loss of outer segments in the COST line is secondary to a loss of photoreceptor cell bodies in the ONL cannot be denied. Further studies are needed to confirm this hypothesis.

Srinivasan et al. [10] reported that the highly reflective line between the IS/OS junction and the retinal pigment epithelium (RPE) was the COST line, and that it was visible because of the different lengths of the cone and rod outer segments. Recently, a third line between the IS/OS line and the RPE was noted and named the intermediate line or Verhoeff's line in several retinal diseases [11, 12, 15–17]. A correlation was found between the site of the visual impairments and the loss of the foveal COST line [15, 16].

Our findings are based on a single case of AIBSE, and thus they should not be extended to all AZOOR complex disorders until further studies are conducted. However, to the best of our knowledge, cases with similar findings have not been reported for any retinal disease. Our results support the earlier suggestion that the photoreceptors are the site of the primary lesion in AZOOR complex diseases [2–4]. In addition, the selective absence of the COST line and the regional cone dysfunction detected by mfERGs suggest that the photoreceptor cell bodies and rod outer segments were most likely morphologically intact. Whether the intact ELM and IS/OS line only appeared after the recovery or had been intact throughout the course of the disease process could not be determined. Further

longitudinal studies with large numbers of patients are required to identify the underlying pathology.

We conclude that examinations of the integrity of outer retinal microstructures including the ELM, IS/OS, and COST lines should provide information on the disease process and be clinically relevant to the understanding of the pathologic mechanisms and the severity or stage of different retinal diseases.

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Disclosure Statement

None of the authors has a financial or proprietary interest in any material or method mentioned.

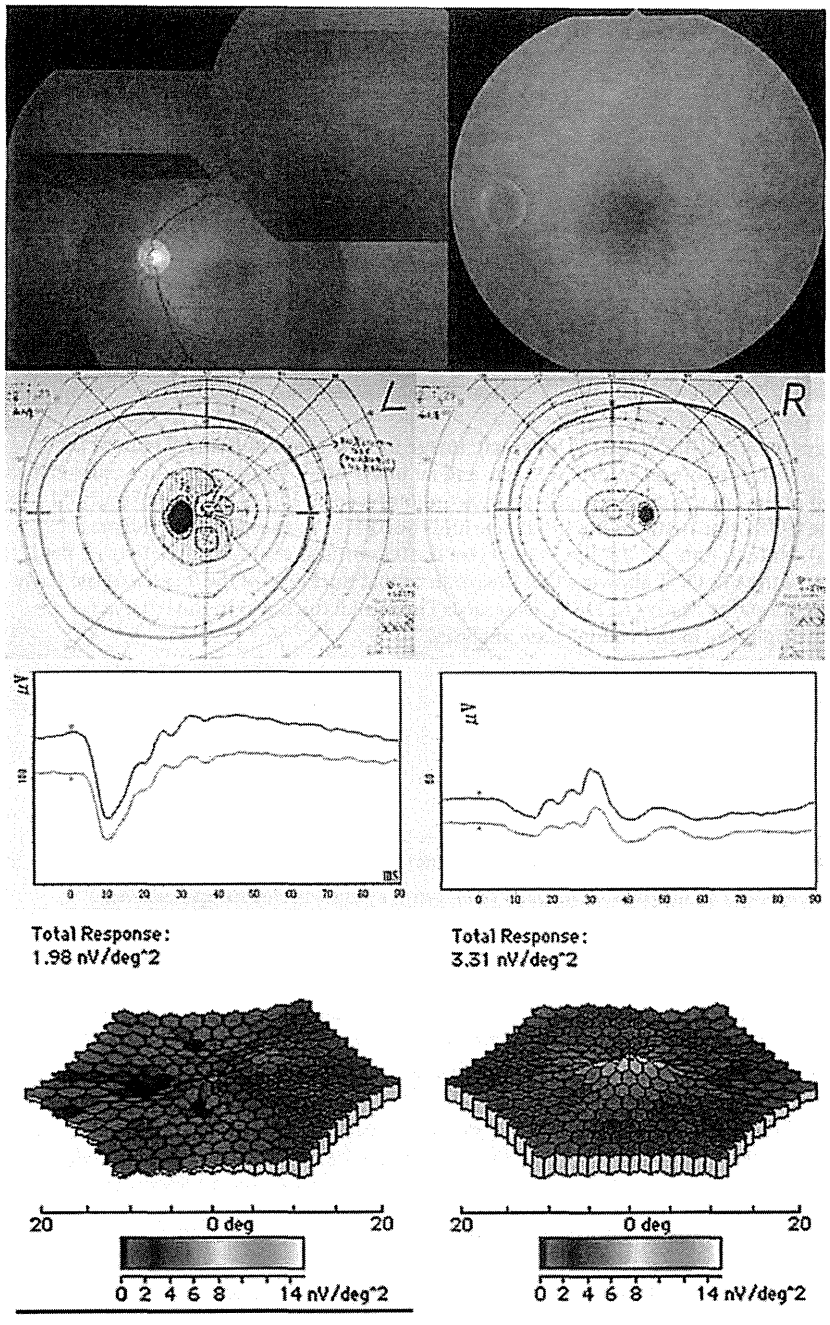

Fig. 1. Fundus photographs, fluorescein angiogram, and full-field and multifocal ERGs from the left eye of the patient with AIBSE syndrome. Top: fundus photographs and fluorescein angiogram showing no abnormal findings. Second row: Goldmann visual field of the affected eye demonstrates an arcuate scotoma connected to the physiological blind spot. Third row: full-field ERGs revealing normal mixed rod-cone ERG and photopic cone ERG results in both eyes. Bottom: mfERGs showing a reduced response density in the area of the scotoma in the left eye. The response density in the central area is reduced in both eyes.

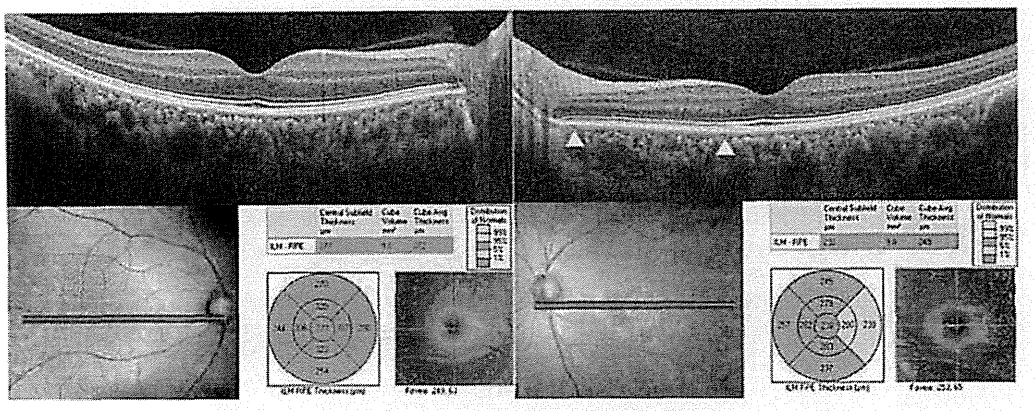

Fig. 2. SD-OCT images in our AIBSE patient. Upper left: image from a 9-mm horizontal scan of the right eye shows both an intact photoreceptor IS/OS line and an intact ELM. Upper right: image from a 9-mm horizontal scan of the left eye demonstrates an intact photoreceptor IS/OS line, an intact ELM and the absence of the COST line between the IS/OS line and the RPE in the nasal area of the macula (between arrowheads). Note that the COST line is intact on the temporal site with an intact visual field. Bottom: volume scans of the SD-OCT showing that the mean retinal thickness of the 9 areas of the Early Treatment Diabetic Retinopathy Study (ETDRS) decreased. The retinal thickness in the left eye is thinner than that of the right eye in the volume scan analyses.

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