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Effect of light on blinking in patients with idiopathic isolated blepharospasm

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Abstract

Objective: Melanopsin may be involved in the pathophysiology of photophobia in idiopathic isolated blepharospasm. We assessed the efficacy of blocking wavelengths of melanopsin absorption to reduce blinking in blepharospasm as a possible surrogate for photophobia.

Methods: Twenty-one participants (11 blepharospasm and 10 healthy controls) were studied. There were three sessions: (1) a baseline condition to measure the blink rate (BR) without intervention; (2) two conditions where the participants received intermittent light stimuli with high or low intensity without wearing study lenses; (3) four conditions in which the participants received intermittent light stimuli with high intensity while wearing one of four different lenses: tinted lenses with neutral gray or FL-41, or coated lenses that block 480-nm or 590-nm wavelength. The primary outcome measure was the BR.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.parkreldis.2019.09.010>.

Results: The blepharospasm group blinked more frequently than controls in dim room conditions. Patients reported greater photosensitivity compared to controls based on the questionnaire and exhibited a higher BR with intermittent light stimuli. The BR decreased for both groups when using 480-nm and 590-nm blocking lenses. In the patients, 480-nm and 590-nm blocking lenses reduced the mean BR by 9.6 blink/min and 10.3 blink/min, respectively, while in the control group, the mean BR decreased by 4.4 blink/min and 4.3 blink/min, respectively.

Conclusions: Blepharospasm patients had increased BR with light stimuli which decreased with 590-nm and 480-nm blocking lenses. The 480-nm- and 590-nm- coated lenses might have therapeutic potential in treating photophobia although BR does not appear to be an optimal biomarker for photophobia.

Keywords

Blepharospasm; Dystonia; Photophobia; Blink rate

1. Introduction

Idiopathic isolated blepharospasm (here just called blepharospasm) is characterized by involuntary orbicularis oculi spasms that are usually bilateral, synchronous, and symmetrical [1,2]. Photophobia, also called “photoallodynia”, is defined as a sensory state in which light causes discomfort in the eye or head; it may also cause an avoidance reaction without overt pain [3]. Nearly 94% of patients report light sensitivity and up to 74% have photophobia [4]. Furthermore, photophobia is considered the second most common factor which can impact blepharospasm patients’ quality of daily life [5]. However, the mechanism of photophobia is still elusive.

Melanopsin-containing intrinsically photosensitive retinal ganglion cells (ipRGCs) are atypical retinal photoreceptors separate from classical rod and cone photoreceptors. Melanopsin is activated with light at 480-nm and requires light at 590-nm to be restored to its baseline state [6]. Evidence accumulating from animal models shows that ipRGCs are involved in photophobia of rod- and cone deficient mice [7,8]. In humans, ipRGCs have been implicated in photoallodynia since migraine patients who are blind from a complete lack of rod and cone function still experience photoallodynia compared with patients with enucleated eyes [9]. Using the photic blink reflex, one study tried to objectively quantify the ocular sensitivity to red (640 nm) and blue (485 nm) light in patients with light sensitivity and normal subjects. The data demonstrated an increased photic blink reflex to blue light as opposed to red light in light-sensitive patients [10]. These results suggest that the melanopsin signaling system may control light aversion and the ipRGC may be the most important photoreceptor cell in the pathophysiological mechanism of photophobia. The pathophysiology of photophobia in isolated blepharospasm is still unclear, but may relate to this observation. A previous study demonstrated that FL-41 lenses, which block wavelengths around 480 nm, the wavelength at which ipRGCs are maximally sensitive, reduced mean blink rate and eyelid contraction force more than standard sunglasses in blepharospasm patients [11]. Another study showed that patients with blepharospasm have less photophobia when wearing FL-41 lenses [12]. The reason why FL-41 lenses relieve blepharospasm symptoms is still not certain and not every BEB patient experiences benefit from wearing

FL-41 lenses which may be related to the fact that FL-41 lenses block the wavelengths around 480 nm non-selectively and weakly.

We hypothesized that blink rate would be a biomarker for photophobia, and that strongly and selectively blocking the wavelength specific to the melanopsin system would reduce blink rate in blepharospasm patients. In this exploratory study, we aimed to investigate melanopsin's role in the pathophysiology of photophobia in blepharospasm patients with implications for potential therapeutic interventions.

2. Methods

2.1. Standard protocol approvals and patient consent

This study was approved by the Institution Review Board of National Institute of Health. Written informed consent was obtained from all participants prior to the experiment.

2.2. Study participants

Blepharospasm patients having a history of involuntary contraction of the orbicularis oculi for one year or more were recruited from the National Institute of Neurological Disorders and Stroke outpatient clinic with help from the Benign Essential Blepharospasm Research Foundation. The clinical diagnosis of blepharospasm was based on the standard criteria by senior movement disorder specialists [13]. Study participants with segmental dystonia, psychiatric conditions (based on self-report and the medical records), migraine, parkinsonian disorders, meningitis, subarachnoid hemorrhage, pituitary tumors or apoplexy, ophthalmologic disorders (other than blepharospasm and dry eye), positive history of traumatic brain injury, contact lens use and laser refractive surgeries were excluded. Two of the patients had sensory tricks according to their self-report. All but one blepharospasm patient were on a regimen of botulinum toxin injections in the affected muscles every 12–20 weeks. The experiment was performed at least 11 weeks after the most recent injection. The control study participants, free of neurological, psychiatric disorders or ophthalmologic disorders, were recruited from the National Institutes of Health (NIH) Healthy Volunteer Center.

2.3. Clinical assessments

Demographic data and detailed clinical history were collected in a face-to-face interview. The severity of the blepharospasm was assessed using the Jankovic Rating Scale (JRS) [14] and the Blepharospasm Disability Index (BSDI) [15] in patients. Each participant provided his or her subjective perception of light sensitivity by using the Photosensitivity Assessment Questionnaire (PAQ) [16] (Supplementary Material 1), which can identify study participants' behaviors that actively avoid light, termed photophobia (PAQ-Pho) and those that actively search light, described as photophilia (PAQ-Phi).

2.4. Lenses

Our study utilized two tinted lenses with neutral gray and FL-41, and two coated lenses designed to block 480-nm and 590-nm wavelengths (Optical Shop at the University of Utah, Salt Lake City, UT). While the tints absorb unwanted wavelengths, the thin-film coatings

reflect the unwanted wavelengths of light. The neutral gray lenses are tinted to equally absorb all wavelengths across the visible spectrum. The FL-41 blocks wavelengths around 480 nm as well as some of the other shorter wavelengths. All lenses have the same optical density of 30%, which means that the four lenses block the same amount of the light in total, but differ in their transmission of various wavelengths within the visible spectrum. All lenses were examined for spectral characteristics using a spectrophotometer [Lambda 9; PerkinElmer Optoelectronics, Fremont, Calif]. The absorption spectra were compared, and the average percent visible transmission from 400 to 700 nm was calculated for each lens. It is worth noting that FL-41 blocks some light near 480 nm and the 480 nm glasses are more precise at the melanopsin peak and block substantially more light at that frequency. The characteristics of spectral transmission of different lenses are shown in Fig. 1.

2.5. Photic-stimulator procedure

A photic-stimulator (Grass PS22 photic stimulator) was mounted 20 cm from the subject's eyes. Electromyography (EMG) surface electrodes were attached to the inferior-lateral quadrant of the orbicularis oculi and the reference electrode was placed on the forehead. All study participants were tested in a supine position and were instructed to look down 15–20° to eliminate background EMG activity in orbicularis oculi. All tests were carried out in a dark room except for the low background illumination created by the test instrumentation. Study participants were given 10 min to adapt to the darkness before receiving the light stimuli. The experiment was performed during 3 different sessions using 7 different conditions (Fig. 2). To avoid habituation of the light stimulation, we conducted the first and second sessions in one day and study participants returned for a third session on a separate day. Session 1 was a baseline condition to measure the blink rate (BR) without any intervention. Session 2 included two separate conditions wherein the participants received light stimuli of high or low intensity without wearing study lenses. In this session, single-pulse light stimuli with a 10 msec duration were delivered 10 times at fixed intervals of 30 ± 3 s with high or low light intensity (5.5 or 22 lumen sec/ft [2]). The stimulation protocol was designed to avoid adaptation and habituation to light based on some preliminary observations in pilot studies [17]. Session 3 included four conditions in which the participants wore different study lenses (neutral gray, FL-41, 480-nm, 590-nm blocking lenses) in randomized order and received the same light intensity (22 lumen sec/ft [2]). The interval between two different conditions was at least 5 min. The blink rates were counted for the entire 5 min of stimulation under each of 7 conditions. During the experiments, the study participants were not permitted to wear their prescription eyewear.

2.6. EMG data acquisition and analysis

The EMG signal was amplified using D360 amplifiers, with a low-frequency filter of 20 Hz and a high-frequency filter of 2000 Hz and stored in a computer for offline analysis using Spike2 software (Cambridge Electronic Design, UK). The raw blink recordings were rectified, and BR was counted manually. We defined synchronized EMG discharges of the orbicularis oculi from both sides as one blink. If the interval of two consecutive EMG discharges was less than 100 msec, we defined it as a single blink. Blinks to the light flashes were not counted. The main outcome measure was the blink rate (BR) during different experimental conditions.

2.7. Statistical analysis

Since this is an exploratory study, descriptive statistics were used, such as mean and standard deviation to characterize the demographic and clinical profile of the participants. To evaluate the difference in BR between blepharospasm and control groups, two-sample *t*-test and Fisher's exact test were used for quantitative and binary variables, respectively. Pearson's correlation analysis was performed to examine the relationship between the PAQ-phi and the BR. A two-way repeated-measures analysis of variance (ANOVA) was performed to evaluate the interaction between group and light conditions on the BR. The group with two levels (blepharospasm vs. control) was a between-subject factor and light with seven levels (Baseline, White-Low, White-High, Neutral gray-High, FL-41-High, 590-nm-High, 480-nm-High) was a within-subject factor. Compound symmetry (CS) was used as a covariance structure with different parameters for blepharospasm and control group considering that the variation within blepharospasm was greater than that within the control group. Age and sex were considered as covariates and dropped ($p > 0.15$). To evaluate the effect of light condition within group, one-way repeated ANOVA with CS covariance structure was performed for blepharospasm and control group separately. Dennett's method was used for testing the difference between baseline (or White-High) and each of the other light conditions. $P = 0.05$ was used as significance level. Statistical analyses were performed using SAS version 9.2.

3. Results

3.1. Demographics and clinical data

Our sample consisted of 11 blepharospasm patients (9 female, 2 male, mean age \pm SD 68 ± 6 years, blepharospasm mean onset \pm SD age 56 ± 6 years) and 10 controls (6 female, 4 male, mean \pm SD age 64 ± 5) (Table 1). None of the patients had a family history of focal dystonia; however, 2 patients (18%) had first-degree relatives diagnosed with essential tremor (ET). All patients complained that "the light bothers my eyes" or "the light triggers my eyelid spasm". By history, the onset of eyelid spasm preceded the photophobia in all the patients. None of the controls complained of photophobia. Not surprisingly, total scores on the PAQ-Pho were significantly higher in patients with blepharospasm compared to healthy controls ($P < 0.001$); the total scores on PAQ-Phi were significantly higher in healthy controls ($P = 0.03$). All patients except one had been on a regimen of botulinum toxin injections. None of the patients believed that photophobia was ameliorated by botulinum toxin injection. About half the patients (45%) wore prescribed FL-41 lenses outdoors and/or indoors for symptomatic management, and 27% of them subjectively reported that they benefited from wearing them. Most of the patients told us that they did not wear the glasses all the time, but we have no quantitative data.

3.2. The correlation between BR and the severity of blepharospasm

Blepharospasm severity scores (Jankovic Rating Scale and Blepharospasm Disability Index) showed no relationship with either baseline BR or BR under light stimulation (Supplementary Material 2-A 2-B). Additionally, blepharospasm severity scores were not correlated with photophobia severity scores (Supplementary Material 2-C).

Effect of light stimuli with different intensity on blink rate (BR).

The blepharospasm group blinked more frequently than controls in dim room conditions (29 vs 14 blink/min, $p = 0.028$). The effect of light intensity differed between groups (two way repeated measures ANOVA $F_{6, 82} = 4.3$, $p = 0.008$ for the interaction), such that there was no effect of light intensity in the control group ($p = 1.0$ white-low, $p = 0.93$ white-high), but a significant increase in blink rate in the blepharospasm group ($p = 0.02$ white-low, $p < 0.001$ white-high). Table 2 lists the least squares mean values of BR in patients and controls in different experimental conditions and Dunnett's adjusted p-values.

3.3. Reduction of the blink rate with tinted lenses

Dunnett's test using white-high baseline as a control showed that the BR decreased when both patients and controls wore 480-nm and 590-nm blocking lenses. In the control group, the BR reduced from 15 to 11 with ($p = 0.04$ and $p = 0.03$, respectively). There was also a reduction in the blepharospasm group, from 48 to 37 and 38 ($p = 0.03$ and $p = 0.05$) with 590 and 480 nm blocking lenses. There was a trend towards improvements with FL-41 in both the patient group and controls reducing the mean BR 6 blink/min and 4 blink/min respectively. However, there was no significant difference in BR when neutral gray lenses were worn (Table 2).

4. Discussion

Our study demonstrated three important aspects of photophobia in blepharospasm. First, blepharospasm patients reported greater photosensitivity compared to healthy controls based on the questionnaire and had higher BR using intermittent light stimuli. BR significantly increased with intermittent light stimuli in blepharospasm patients while this was not observed in healthy controls. Second, blepharospasm severity scores showed no relationship with either baseline BR or BR under light stimulation. The likely reason for this is that blepharospasm severity scores include not only the frequency of eyelid spasms, but also the intensity of eyelid spasms and other related factors. Moreover, blepharospasm severity scores are not correlated with photophobia severity scores. The results imply that the severity of blepharospasm does not affect independently the light sensitivity (photophobia). Third and most importantly, BR in the blepharospasm patients decreased when wearing the 480- and 590-nm blocking lenses while neutral gray and FL-41 did not have significant effect.

We used intermittent light stimuli rather than constant flux for several reasons. First, intermittent pulsed light may be more effective in resetting the blink generator in the brainstem. A previous study showed that spontaneous eyeblink activity is changed by a sudden increase in light levels more than background light conditions [18]. Second, the ipRGCs have a high threshold for activation, long response latency, and prolonged duration of firing before returning to baseline; therefore, using intermittent stimuli is more suitable for differentiating the melanopsin specific system [3,19]. We did not count the photic blink reflex itself for the same reason because the immediate response to photic stimulation is likely due to rods and cones activation rather than direct ipRGCs stimulation.

Our study demonstrated that BR can be modulated more by specific wavelength than by the net light flux (at least within the range of our light stimuli). A previous study showed that FL-41 tint, moderately blocking short wavelength, reduced the number of blinks in blepharospasm patients [12]. Additionally, studies using fMRI suggest that there may be different physiological responses to spectrally-specific tints compared to neutral density filtering (which attenuates all wavelengths equally) [20]. However, our study showed that wearing the FL-41 was not effective in reducing the BR compared to 480-nm and 590-nm blocking lenses. This is inconsistent with a previous study done by Blackburn et al. that showed FL-41 to be effective in the treatment of blepharospasm [12]. The main reason of the inconsistent results may be due to the differences of the research methods. We monitored the subjects while they were supine and provoked increased blinking with a photic stimulator; in the previous study, patients were monitored in constant light while reading. It is possible, however, that our study did not have enough power to detect an effect. FL-41 did show a trend to reduce BR for both blepharospasm (from 47 to 41) and controls (from 15 to 11), but did not reach statistical significance in our sample.

The 480-nm and 590-nm blocking lenses utilized in our study are formulated based on the discovery of ipRGCs and the molecular mechanism of melanopsin. The ipRGCs contain the photopigment melanopsin that are “intrinsically photosensitive”, meaning they can be stimulated by light in the absence of input from the traditional photoreceptors, rods and cones [21]. The action spectrum of ipRGCs peaks at 480 nm, midway between the action spectrum of green and blue cones [22]. Once activated, rhodopsin and cone opsins must be recycled back to their active, 11-cis state by the retinal pigment epithelium. Unlike these opsins, melanopsin is a biphasic molecule, meaning that different wavelengths of light move melanopsin between its all-trans and 11-cis isomers[1]. In fact, melanopsin is recycled from its inactive, all-trans isomer back to its active, 11-cis isomer by 590 nm light, a wavelength closer to the orange end of the visible spectrum [23]. Our results showed 590 nm blocking lenses have the same effect in reducing the blink rate as does the 480 nm blocking lenses likely based on the bistable property of melanopsin. Blocking 480 nm wavelength leads to a smaller amount of melanopsin transiting to the high state, and ultimately reduces the blink rate. On the other hand, blocking the 590 nm wavelength results in less melanopsin reverting to the low state and, thus, less melanopsin will be available to be activated.

Our study has limitations. This is an exploratory study with a small number of study participants. Also, we did not include blepharospasm patients without photosensitivity. We intended to recruit blepharospasm patients regardless of presence of photosensitivity, but all patients complained of light sensitivity. This is consistent with a previous report that 94% of blepharospasm patients have photosensitivity. Inclusion of blepharospasm without photosensitivity would have better clarified whether increase in BR to light stimulation is related to blepharospasm mechanism or merely depends on the presence of photosensitivity. However, the lack of this information does not affect our study conclusion.

In summary, our findings show that BR in blepharospasm patients is more sensitive to light than in normal study participants and both 480-nm and 590-nm- wavelength appears to play an important role. Our study suggests that 480-nm- and 590-nm- coated lenses might have therapeutic potential in treating spasm and photophobia in blepharospasm patients and could

be better than FL-41. Unfortunately, there is no good evidence for a correlation between photic-blink reflex and photophobia either in previous literature or our own study. Better objective measures are needed for the evaluation of photophobia in the future. Additionally, further studies will be required to evaluate whether such lenses can reduce photophobia in blepharospasm patients in daily living activities, such as reading and driving.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Mark Hallett may accrue revenue on US Patent: Immunotoxin (MAB-Ricin) for the treatment of focal movement disorders, and US Patent: Coil for Magnetic Stimulation and methods for using the same (H-coil); in relation to the latter, he has received license fee payments from the NIH (from Brainsway). Research funds have been granted by Medtronic, Inc., for studies of deep brain stimulation, Merz for treatment studies of focal hand dystonia, Allergan for studies of methods to inject botulinum toxins, and CALA Health to study a device for the treatment of essential tremor.

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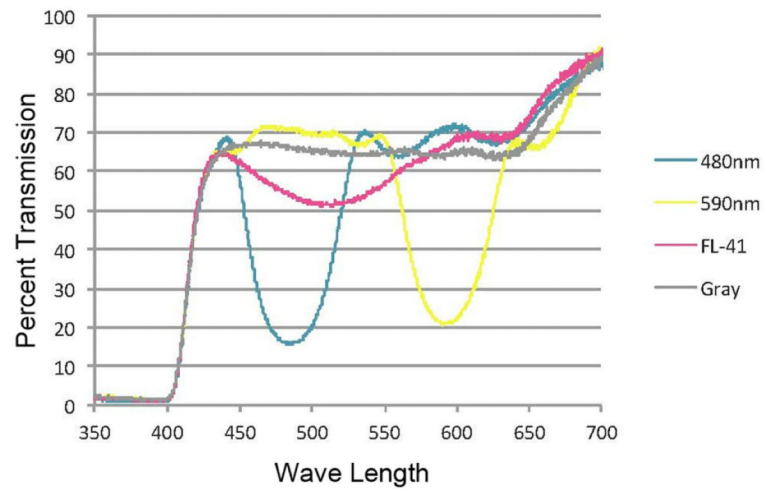


Fig. 1. Transmittance vs. wavelength for 4 different lenses. 480 nm: 480-nm-coated lenses; 590 nm: 590-nm-coated lenses; FL-41: FL-41 lenses; Gray: neutral gray-tinted lenses.

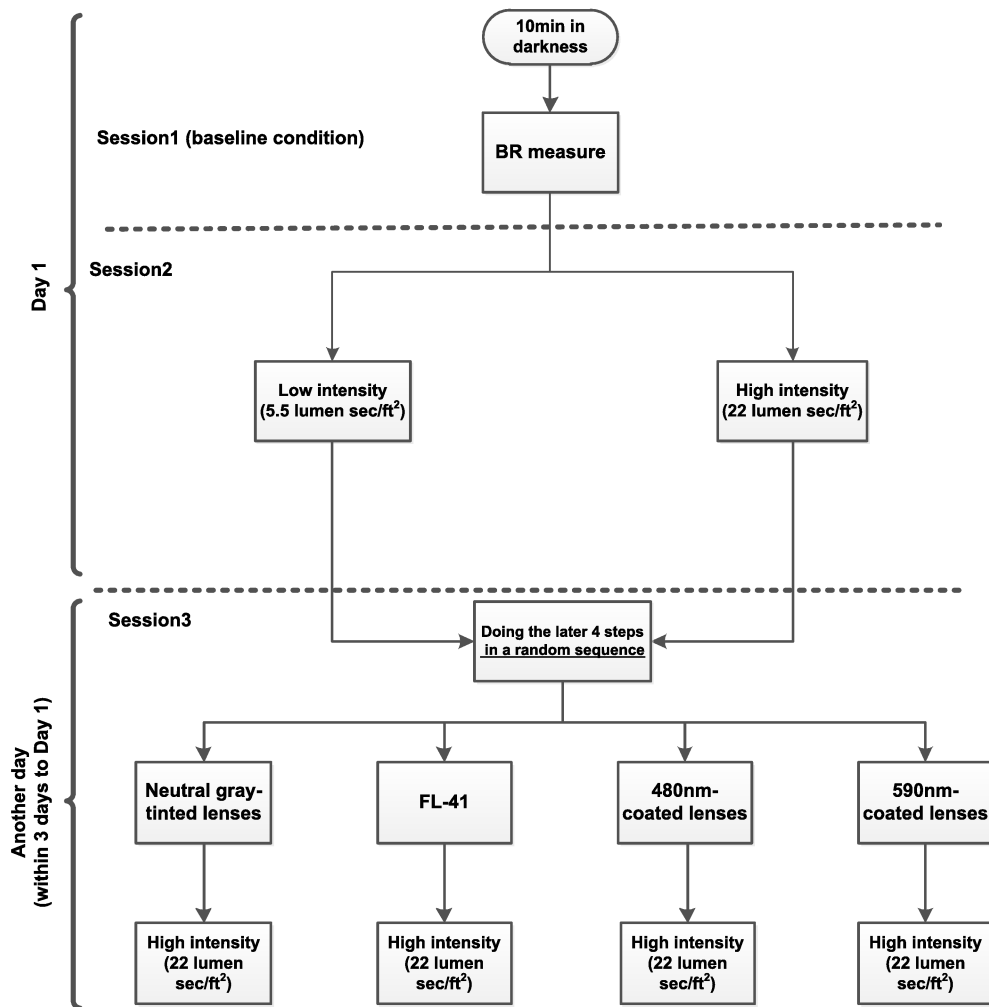


Fig. 2. Photic-stimulator procedure. The experiment was performed during 3 different sessions using 7 different conditions. BR: blink rate; Low-intensity: single-pulse light stimuli with a 10 msec duration were delivered 10 times at fixed intervals of 30 ± 3 s under the light stimuli with lower intensity (5.5 lumen sec/ft [2]); High-intensity: single-pulse light stimuli with a 10 msec duration were delivered 10 times at fixed intervals of 30 ± 3 s under the light stimuli with higher intensity (22 lumen sec/ft [2]); Lenses: Neutral gray-tinted lenses, FL-41, 590-nm-coated lenses, 480-nm-coated lenses.

Table 1

Demographic and clinical characteristics of participants.

	Blepharospasm patients (n = 11)	Healthy controls(n = 10)	Significance level, $p < 0.05$
Mean age (years) (SD)	68.27(6.23)	64.50(5.12)	$p = 0.15^a$
Female/male (%)	9/2(81%)	6/4(60%)	$p = 0.36^b$
Family history of BEB [*] , n (%)	0(0%)	0(0%)	–
Blepharospasm - onset (years) (SD)	56.09(6.36)	–	–
Blepharospasm - duration (years)(SD)	12.36(5.59)	–	–
Photophobia ^{**} - onset (years) (SD)	57.18(4.12)	–	–
Photophobia ^{**} - duration (years)(SD)	11.27(6.34)	–	–
Latest botulinum toxin injection (weeks) ^c (SD)	16.40(5.73)	–	–
Wearing FL-41, occasionally or usually N(%)	5/11(45.45%)	–	–
Mean PAQ-Pho score(SD)	0.65(0.24)	0.03(0.08)	$p < 0.001^a$
Mean PAQ-Phi score(SD) Mean JRS scores(SD)	0.30(0.17)	0.53(0.27)	$p = 0.03^a$
JRS sum score	5(1.61)	–	–
JRS severity subscore	2.45(0.93)	–	–
JRS frequent subscore	2.36(0.67)	–	–
Mean BSDI(I(SD)	1.65(0.81)	–	–

Blepharospasm: Idiopathic isolated blepharospasm; JRS: Jankovic Rating Scale; PAQ: photosensitivity assessment questionnaire; Pho: photophobia; Phi: photophobia; BSDI: Blepharospasm disability index

^{*} 2 patients reported a family history of essential tremor in a first-degree relative

^{**} according to the patients' self-report

^a two-sample *t*-test

^b Fisher's exact test

^c one patient who had never received botulinum toxin injection was not included in the analysis.

Effect of spontaneous blink rate in blepharospasm and control subjects under different conditions of light.

Table 2

Conditions	Least squares means		Adjusted Dunnett's p-value			
	Blepharospasm	Control	Control=Baseline		Control=White-High	
			Blepharospasm	Control	Blepharospasm	Control
Baseline	29.27	13.88	-	-	<.001	0.93
White-Low	39.91	13.98	0.02	1.00	0.19	0.95
White-High	47.28	15.12	<.001	0.93		
Neutral gray-High	45.57	13.26			0.99	0.70
FL-41-High	41.54	11.58			0.41	0.12
590-nm-high	36.94	10.78			0.03	0.04
480-nm-high	37.71	10.68			0.05	0.03

Blepharospasm: Idiopathic isolated blepharospasm; Baseline: not under light stimuli and without wearing lenses; White-Low: under light stimuli with lower intensity and without wearing lenses; White-High: under the light stimuli with higher intensity and without wearing lenses; Neutral gray-High, FL-41-High, 590-nm-High, 480-nm-High: under the light stimuli with higher intensity and with wearing 4 different lenses [Neutral gray-tinted lenses, FL-41, 590-nm-coated lenses, 480-nm-coated lenses]. One-way repeated measures ANOVA was performed to evaluate the effect of light condition on BR for Blepharospasm and control group separately, followed by Dunnett's test with baseline or white-high as a control. The standard deviation is 8.03 for the Blepharospasm group and 1.59 for the control group.