Study in Patients With Unilateral Horner Syndrome Supports the Role of Müller's Muscle in the Eyelid-Dark Reflex

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Purpose. A previous study demonstrated upper eyelid retraction synchronized with pupil dilation following a transition from photopic to scotopic conditions. The current study aimed to evaluate the role of Müller's muscle as the efferent arm of this suggested reflex arc.

Methods. A video scan of both eyes of patients with unilateral Horner syndrome was performed using optical coherence tomography infra-red mode to document the transition between photopic and scotopic conditions. The affected side with sympathetic denervation was the study group, whereas the contralateral unaffected side of the same patients served as the control group. The pupil diameter, upper eyelid margin-to-reflex distance 1, lower eyelid margin-to-reflex distance 2, and vertical palpebral fissure height were measured. The control group was compared to the healthy subjects of a previous study to verify any compensatory changes to the side contralateral to denervation.

Results. Ten patients with unilateral Horner Syndrome were included in the study. Transitioning from photopic to scotopic conditions, the mean change in margin-to-reflex distance 1 in the study and control groups was 315 ± 276 µm ($P < 0.05$) and 723 ± 432 µm ($P = 0.005$), respectively. Margin-to-reflex distance 1 and palpebral fissure height were significantly higher in the control group both in photopic ($P = 0.005$ and $P = 0.017$, respectively) and scotopic conditions ($P = 0.005$ and $P = 0.007$, respectively). The change in margin-to-reflex distance 1 and palpebral fissure height following the transition from light to dark was significantly greater in the control group ($P = 0.022$).

Conclusions. Reflexive eyelid retraction following a transition from photopic to scotopic conditions was significantly diminished in eyelids with sympathetic denervation compared with the unaffected contralateral side of the same patients. This study provides further evidence that the sympathetically innervated Müller's muscle serves as the efferent arm of this reflex.

Keywords: Horner syndrome, eyelid dark reflex, Müller's muscle

The pupillary light reflex involves afferent stimulation of the visual pathway to the pretectal nucleus of the midbrain in response to photopic conditions. This results in efferent parasympathetic activation of ipsilateral and contralateral sphincter muscles, causing bilateral and consensual pupillary constriction.[1] The pupillary dark reflex, a sympathetically dominated reflex arc, results in afferent stimulation of the hypothalamus in response to scotopic conditions with eventual contraction of the dilator pupillae muscle via the long ciliary nerves, resulting in bilateral pupillary dilation.[1,2] Furthermore, the latter results in the pupil's sphincter muscle passively returning to its relaxed state, as well as inhibition of tonically active midbrain nuclei.[1]

Horner syndrome is caused by disruption of the oculosympathetic pathway, resulting in the classical triad of ptosis, myosis, and anhidrosis.[3,4] Overall, oculosympathetic paresis results in ipsilateral ptosis due to denervation of the Müller's muscle, whereas disrupted sympathetic innervation to the lower lid retractors results in lower lid reverse ptosis, resulting in narrowing of the vertical palpebral fissure height.[4,5] Furthermore, unopposed parasympathetic innervation to the iris constrictor muscle results in ipsilateral miosis, which is most apparent in scotopic conditions.[4,6]

We previously demonstrated eyelid retraction synchronized with pupil dilation after transitioning from photopic to scotopic conditions and described this phenomenon as an "eyelid-light reflex."[7] We hypothesized that the sympathetically innervated Müller's muscle contracts involuntarily during scotopic conditions, which provides a larger aperture for light to enter the eye.

The purpose of the current study was to examine if the sympathetic system and Müller's muscle serve as the efferent arm of this reflex arc by evaluating this reflex in patients with Horner syndrome, as well as cross-validating any compensatory changes on the opposite side to denervation.

Methods

The study was conducted in accordance with good clinical practice guidelines and adhered to the tenets of the Declaration of Helsinki. Ethical approval was granted by the institutional review board, and written informed consent was obtained from all participants. Patients with unilateral Horner syndrome were recruited. A neuro-ophthalmologist examined all patients, and appropriate pharmacological testing confirmed the diagnosis of unilateral Horner syndrome. Exclusion criteria included any history of eyelid surgery, intra-ocular surgery 1 year prior to the study examination, chronic or recent topical eye treatment, and history of eyelid trauma.

The examination and measurement methods were consistent with those described in our previous study.[7] A video scan of the anterior segment was performed using a Heidelberg Spectralis optical coherence tomography (OCT) infrared mode in photopic and scotopic conditions, and the transition between the two conditions was recorded. We aimed the scanner at each eye while the patient was instructed to fixate with the contralateral eye at a distant, non-accommodative target. Patients were instructed to blink as needed to remain comfortable during the scan, and to avoid using brow or forehead muscles. The test commenced under light conditions and transitioned to dark in order to avoid reflexive and unintentional orbicularis activation in response to sudden bright light. Both eyes of each patient were examined and recorded separately. The affected side with sympathetic denervation was designated as the study group, whereas the contralateral, unaffected side of the same patient was assigned to the control group.

The researchers reviewed the recorded video and selected two frames of minimal and maximal pupil diameter to represent light and dark conditions, respectively, and verified that they were not taken in the course of a blink. The pupil diameter, upper eyelid margin-to-reflex distance 1, lower eyelid margin-to-reflex distance 2, and vertical palpebral fissure height were measured using the Heidelberg company software (see the Fig.). Furthermore, the control group's (unaffected eyes) measurements were compared to the healthy subjects of our previous study to confirm any compensatory changes to the side contralateral to denervation.[7] The researchers who performed the video recording and measurements were blinded to the patients' clinical data and the laterality of Horner syndrome.

Statistical Analysis

The minimum sample size for 80% power and 0.05 alpha was estimated based on previous observations of margin-to-reflex distance 1 changes among healthy controls.[8] Using

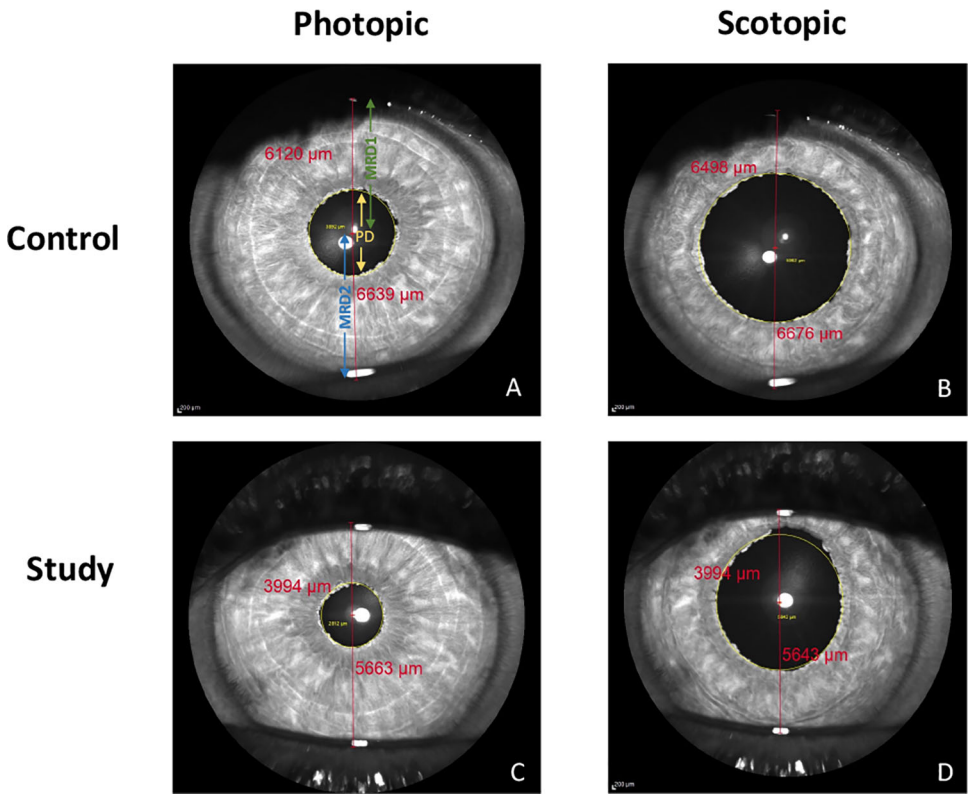

Figure. Infrared photos of a patient's control eye (**A** and **B**) and sympathetically denervated eye (**C** and **D**) in photopic and scotopic conditions. Images were taken by Heidelberg Spectralis optical coherence tomography with an anterior segment lens. Pupil diameter, upper-eyelid margin-to-reflex distance 1, lower eyelid margin-to-reflex distance 2, and vertical palpebral fissure height were measured using Heidelberg company software. This patient demonstrates a larger pupil dilation amplitude and an increase in upper-eyelid margin-to-reflex distance 1 in the control eye (**A** and **B**) compared to the eye affected by Horner syndrome (**C** and **D**).

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Statulator (https://statulator.com), we calculated that at least 10 cases are needed for a paired-sample comparison, assuming a mean change in margin-to-reflex distance 1 of 348 ± 311 µm. We increased the number of cases by 30% to account for potential patient dropouts. The statistical software SPSS version 25.0 (SPSS, Inc., Chicago, IL, USA) was used for data analysis. Given the small sample size, nonparametric tests were used. Changes in pupil diameter and eyelid positions between photopic and scotopic conditions in the study group were compared using the Wilcoxon signed-rank test. Statistical significance was set at $P < 0.05$. A secondary analysis compared the extent of change within our study group versus healthy controls data using the Mann-Whitney test.[8]

Results

Thirteen patients were diagnosed with Horner syndrome and recruited to the study. Of these, three patients were unable to appropriately complete the examination procedure: two due to cognitive limitations and one due to preexisting significant bilateral ptosis with obstruction of the visual axis. Ten patients were therefore included in the study. The average age was 56 ± 13.2 years, comprising 5 men and 5 women. Horner syndrome was demonstrated on the right side in six patients and the left side in four patients. Causes of Horner syndrome included carotid artery dissection (4 patients), neck surgery (2 patients), Pancoast tumor (1 patients), cerebrovascular accident (1 patients), and unknown (2 patients).

Mean pupil diameter, margin-to-reflex distance 1, margin-to-reflex distance 2, and palpebral fissure height for both the study and control groups in both photopic and scotopic conditions are listed in the Table. Transitioning from photopic to scotopic conditions, the pupillary diameter in the study and control groups increased by 1974 ± 725 microns ($P = 0.005$) and 2006 ± 745 microns ($P = 0.005$), respectively. Concurrently, the mean change in margin-to-reflex distance 1 in the study and control groups was 315 ± 276 microns ($P < 0.05$) and 723 ± 432 microns ($P = 0.005$), respectively, whereas palpebral fissure height increased by 219 ± 374 microns ($P = 0.005$) and 642 ± 719 ($P < 0.05$), respectively. There was no statistically significant change in margin-to-reflex distance 2 between photopic and scotopic conditions.

When comparing the measured values between the study and control groups, margin-to-reflex distance 1 and palpebral fissure height were significantly higher both in photopic conditions ($P = 0.005$ and $P = 0.017$, respectively) and scotopic conditions ($P = 0.005$ and $P = 0.007$, respectively) in the control group (see the Table, Fig.). There was no difference in the measurements of margin-to-reflex distance 2 between the groups. The change in margin-to-reflex distance 1 and palpebral fissure height following the transition from light to dark was significantly greater in the control group than in the study group ($P = 0.022$ for both).

We compared the measurements of the control group (unaffected eyes) with those of the healthy subjects reported in our previous study.[8] Despite a significant age difference (mean age of 41.4 vs. 56 years, $P = 0.003$), there were no significant differences in measurements of pupil diameter, margin-to-reflex distance 1, margin-to-reflex distance 2, or palpebral fissure height compared with the current study's control group.

Discussion

This study examined changes in upper eyelid position after transitioning from photopic to scotopic conditions in patients with unilateral Horner syndrome. We found that upper eyelid retraction was diminished in the affected side compared to the contralateral, uninvolved eye.

We previously documented upper eyelid retraction synchronously with pupillary dilation following the transition from light to dark conditions in a cohort of healthy individuals.[7] This synchronicity led us to hypothesize that this reflex shares a common pathway with the "pupillary-light reflex" and that the Müller's muscle and its oculosympathetic innervation serve as the efferent arm. This phenomenon may be the mature form of the "eye-popping reflex" observed in infants initially described by Perez et al.[8] We also suggested a possible mechanism to explain the physiologic advantage of such a reflex. As the pupil dilates in the dark, the palpebral aperture needs to widen to avoid peripheral scotoma. However, based on these observations alone, we could not demonstrate the involvement of either the Müller's muscle

Table. Measurements of Pupillary Diameter and Eyelid Position in Patients With Unilateral Horner Syndrome

		Measurements (Mean ± SD), µm			
Group Horner		**Pupillary Diameter**	**Upper Eyelid Margin-to-Reflex Distance 1**	**Lower Eyelid Margin-to-Reflex Distance 2**	**Vertical Palpebral Fissure Height**
Control	Photopic	2779 ± 528	2637 ± 979	6206 ± 745	8843 ± 1026
	Scotopic	4752 ± 1000	2952 ± 942	6110 ± 770	9062 ± 1005
	Mean change	**1974 ± 725 ($P = 0.005$)**	**315 ± 276 ($P < 0.05$)**	96 ± 386 ($P = 0.575$)	**219 ± 374 ($P = 0.005$)**
Horner	Photopic	3592 ± 567	4055 ± 898	6494 ± 884	10549 ± 1289
	Scotopic	5598 ± 1184	4777 ± 889	6413 ± 1148	11191 ± 1698
	Mean change	**2006 ± 745 ($P = 0.005$)**	**723 ± 432 ($P = 0.005$)**	−81 ± 402 ($P = 0.508$)	**642 ± 719 ($P < 0.05$)**
Horner versus control					
	Photopic	**$P = 0.005$**	**$P = 0.005$**	$P = 0.646$	**$P = 0.017$**
	Scotopic	**$P = 0.017$**	**$P = 0.005$**	$P = 0.508$	**$P = 0.007$**
	Mean change	$P = 0.959$	**$P = 0.022$**	$P = 0.646$	**$P = 0.022$**

The P values in bold face represent statistical significance.

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or associated sympathetic pathways. Furthermore, we could not exclude the contribution of other upper eyelid retractors, such as the levator palpebrae superioris (LPS), frontalis, or brow muscles.[9]

The current study was designed to isolate the contribution of Müller's muscle to the upper eyelid retraction we observed following a transition from light to dark conditions. Müller's muscle consists of thin, smooth muscle fibers and is sympathetically innervated through the oculosympathetic pathway, whereas LPS is a striated muscle that receives motor innervation from the oculomotor nerve.[9–11] Although it is difficult to isolate the action of Müller's muscle in clinical practice, pharmacological testing, or direct measurements of eyelid function, in its absence, it may provide clinical information regarding the muscle's functional ability.[12,13] Phenylephrine, an alpha-adrenergic agonist, stimulates the sympathetically innervated Müller's muscle independent of levator function.[12,13] Alternatively, in patients with Horner syndrome, disruption of sympathetic innervation to Müller's muscle results in relatively mild ptosis with preserved LPS function.[3,4] Therefore, the current study was designed to compare the amplitude of the eyelid reflex between both upper eyelids: one with intact and one with disrupted sympathetic innervation. Overall, we found that the observed reflex was significantly diminished in the sympathetically denervated side compared to the unaffected, contralateral eye. This supports the role of the sympathetic nervous system and the Müller's muscle in this reflexive adjustment of the upper eyelid position.

Nevertheless, this calls for a renewed discussion on the nature of this reflex. The term "pupillary light reflex" describes the reflex arc that causes miosis in response to light as a result of parasympathetic stimulation.[1] Conversely, the "pupillary dark reflex" triggers mydriasis during the transition to scotopic conditions and involves a separate pathway of third-order oculosympathetic fibers that collectively innervate the dilator pupillae muscle.[7,14] This common sympathetic pathway also projects terminating fibers to Müller's muscle, resulting in sympathetically driven muscle contraction during dark conditions.[1,2] Therefore, the term "eyelid-dark reflex" seems more appropriate to describe the reflex we documented in both studies.

This study and its methodology may have some limitations. Patient imaging was performed in our institution's imaging suite, where only relative scotopic conditions could be achieved. Furthermore, despite identical conditions and instructions to patients, strict compliance of patients during imaging may have varied between subjects and, therefore, affected measurement accuracy. Additionally, Horner syndrome is a clinical diagnosis that may have different levels of sympathetic denervation, with some patients retaining partial function of their Müller's muscle. However, several aspects of our study's design and conclusions enhance our results' internal and external validity. In both groups, we found a significant change in pupil diameter when transitioning from light to dark conditions, validating an adequate change in lighting conditions. Furthermore, our measurements found significant ptosis and miosis in the eye affected by Horner syndrome compared with the unaffected side, confirming that clinically significant Horner syndrome was present at the time of imaging. Last, there were no significant differences in pupil diameter, margin-to-reflex distance 1, margin-to-reflex distance 2, or palpebral fissure height measurements when we compared the unaffected eyes with those of the healthy subjects reported in our previous study.

In conclusion, this study provides further evidence that the sympathetically innervated Müller's muscle serves as the efferent arm of a reflexive upper eyelid retraction in response to the transition from light to dark. We believe the term "eyelid-dark reflex" may describe this phenomenon more accurately. The clinical significance of this reflex remains to be elucidated, but warrants further investigations to better understand the function of the oculosympathetic chain. Furthermore, reduced eyelid retraction in patients with oculosympathetic disruption may assist in the clinical diagnosis of patients with suspected but unclear Horner syndrome.

Acknowledgments

Ethics Statement: The study was conducted in accordance with good clinical practice guidelines and adhered to the tenets of the Declaration of Helsinki, as well as the Sheba Medical Center Institutional Review Board (IRB).

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