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NEUROLOGY AND PRECLINICAL NEUROLOGICAL STUDIES - ORIGINAL ARTICLE

Evaluation of botulinum toxin effects in hemifacial spasm patients: correlation between clinical rating scales and high-speed video system measurements

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Abstract

The purpose of this study was to compare the scores of two clinical rating scales and high-speed video system measurements obtained during spontaneous eyelid movements in hemifacial spasm (HFS) patients before and after treatment. Patients were evaluated before and 30 days after receiving treatment with onabotulinumtoxinA injections. Using a high-speed video system, the eyelid movements were recorded bilaterally for 3 min and the energy power generated by the upper eyelid during spontaneous eyelid movements was assessed before and after treatment. The scores of the Jankovic rating scale (JRS) and Hemifacial Spasm Grading System (HSGS) were also assessed before and after treatment. The authors studied 22 patients. Significant reduction in JRS and HSGS scores and in the energy generated by the upper eyelid was observed after treatment. A power spectrum of less than 23,000 was associated with JRS and HSGS scores less than 4 and 6.25, respectively and a power spectrum greater than or equal to 23,000 was associated with JRS and HSGS scores greater than or equal to 4 and 6.25, respectively ($p < 0.0001$ and $p = 0.0025$). Rating systems are easy to use, but they may exhibit limitations in sensitivity to assess differences between distinct disease patterns and between subtle differences in treatment responses. The high-speed video system permits a greater degree of accuracy, which allows for the assessment of differences in eyelid movement patterns and would permit better tailoring of treatment to patients. However, simpler devices employing this system would need to be developed, so that it could be used in clinical practice.

Keywords Hemifacial spasm · Eyelid movements · Eyelid spasms · Botulinum toxin · Jankovic rating scale · Hemifacial spasm grading system

Introduction

Hemifacial spasm (HFS) is characterized by unilateral, involuntary, and tonic or clonic contractions of the muscles innervated by the facial nerve. Botulinum toxin-A (BoNT-A) injections into the affected muscles are the treatment of choice for this condition (Green et al. 2017; Kollewe et al. 2010; Ross et al. 2011; Kenney et al. 2008; Abbruzzese et al. 2011).

In a recent report, the researchers intended to compare the outcomes of various botulinum toxins and to report on their efficacy in treating hemifacial spasm and benign essential blepharospasm (BEB), and for this purpose, they reviewed 13 studies. In these studies, the efficacy of botulinum toxin administration was assessed using relevant rating scales. The Jankovic rating scale (JRS) was found to be the most widely used clinical rating system, especially for BEB (Bilyk et al.

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2018). Recently, a clinical scale for HFS (hemifacial spasm grading system [HSGS]) has been validated (Tambasco et al. 2019). However, in contrast to blepharospasm, there is no consensus on main clinical rating scales for this condition (Wabbels et al. 2011; Wabbels and Roggenkämper 2012). Duration of effect and global rather than disease-specific rating scales have been used to assess the outcome in most of the studies with botulinum toxins for HFS (Wabbels and Roggenkämper 2012). In previous studies, rating scales that were originally developed for other conditions were also used for HFS patients (Wabbels and Roggenkämper 2012; Di Stadio et al. 2019). JRS is considered to be the most adequate clinical scale to assess the severity and frequency of essential blepharospasm and its use has also been recommended to assess the severity and frequency of HFS patients (Wabbels et al. 2011; Wabbels and Roggenkämper 2012).

Although associated with some drawbacks, grading systems are quick and easy to apply in clinical practice. Objective approaches permit more accurate assessment of botulinum toxin injections, however, these are usually more time-consuming and associated with more complex methods. The purpose of this study was to compare the scores of a commonly used rating scale (JRS), a recently validated scale for HFS (HSGS), and the energy generated by the upper eyelid during the spontaneous eyelid movements using a high-speed video system before and after botulinum toxin injections.

Methods

This prospective interventional study was conducted at the Division of Ophthalmic Plastic and Reconstructive Surgery, Department of Ophthalmology and Visual Sciences, Federal University of S. Paulo. After obtaining prospective Institutional Review Board approval and written informed consent, 22 HFS patients were recruited to participate in this study. All the subjects were treated in accordance with the tenets of the Declaration of Helsinki.

The exclusion criteria included prior eyelid or ocular surgeries; ocular surface conditions, including punctate keratopathy, dry eye with surface irregularity, and corneal opacities; eyelid conditions, including blepharoptosis, chalazion, eyelid tumors, ectropion, entropion, and trichiasis; strabismus; usage of contact lenses; previous treatment with BoNT-A fewer than 5 months prior to the study; allergies to botulinum toxin or to any other component of the drug; pregnancy; breastfeeding; bilateral HFS; secondary dystonias or neuropathic diseases comorbid with HFS; and the use of drugs that could interfere with neuromuscular transmission.

We included patients whom we had already been treating with BoNT-A for at least 1 year before the study began. Two authors (THO and MHO) have been directly following-up the patients included in the present study. This implies that the authors already knew the patients' disease severity before the study began and that all patients received customized doses for their level of disease severity, ie, doses that had already been adjusted to relieve their symptoms.

The patients were treated with administration of onabotulinumtoxinA (Botox®, Allergan, Irvine, CA) into the affected muscles. A single investigator (MHO) performed all the steps involved in preparing and administering the BoNT-A based on the following standardized protocol: immediately before administration, each vial was reconstituted with normal saline without the addition of preservatives to obtain a final concentration of 50 U/mL. An insulin syringe and a 30-gauge needle were used to inject the drug into the affected muscles with the patient seated. All patients received BoNT-A doses based on their previous responses to the medication and the dose varied according to each patient's clinical condition. The mean volume injected per application site was 2.5 U, and the total dose varied from 25 to 35 U.

At baseline and at the 30-day timepoint after the botulinum toxin injections, two investigators assessed the patients using the JRS and HSGS, and video recordings were obtained. The baseline videos and clinical scores were obtained immediately before the BoNT-A injections were administered. To assure that the data (video recordings and scores) to be analyzed represented the frequency and severity of spasms that each patient reported presenting along the day, after each recording, it was checked with all patients if the eyelid spasms during the recording period corresponded to their symptoms along the day. If not, a second video was recorded.

Eyelid movements were recorded bilaterally in a standard manner using a high-speed video system for 3 min while the subjects watched a commercial movie. A small blue light-emitting diode (LED) measuring 2 × 1 × 1 mm with a brightness of 100 mcd was placed on the pretarsal region of both the upper eyelids (Fig. 1). The LED was connected to an electronic circuit through which its brightness could be adjusted. A commercially available high-speed camera (Point Grey Research® Inc, model FL3-U3-13S2C-CS) was aligned

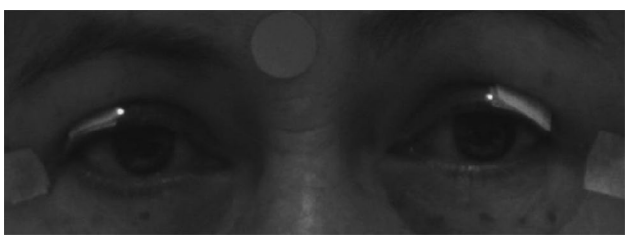

Fig. 1 Small blue light-emitting diodes placed on the pretarsal region of both upper eyelids

with the small LED in the patients' primary position of gaze. The patients were seated in front of a slit lamp under uniform lighting conditions. All the recordings were captured in the same exam room and at the same time to standardize the environmental conditions. A camera was coupled to a laptop computer and was used to register the upper eyelid motion in both eyes based on red, green, and blue (RGB) colored images (800×350 pixels, 150 dpi resolution) at 120 frames/s. This method was developed by one of the authors (D.M.G.) and the tracing of the spontaneous eyelid movements was obtained using an image processing technique that has been previously described (Wambier et al. 2014).

Eyelid kinematics analysis

All the steps involved in processing the signals were performed using Matlab Software R2015a (MathWorks, Natick, MA, U.S.A.) and were performed by a physicist (D.M.G.). Eyelid movement analysis is usually performed by taking into consideration the amplitude and velocity properties of a characteristic spontaneous blinking movement. However, in HFS, the presence of high-frequency anomalous eyelid movements is the main concern. These anomalous movements cannot be considered blinks. Thus, to numerically quantify these movements, the Fast Fourier Transform algorithm (FFT) was used to convert the signal from the time domain to the frequency domain. The result of this quantification represents the energy power distribution across the frequencies of the eyelid movements (blink and anomalous eyelid movements) registered. The total sum of the power spectrum was calculated to assess the activity associated with the eyelid movement. Power spectrum refers to a mathematical nomenclature and clinically represents the energy associated with the eyelid movements, being thus related to the level of the orbicularis *oculi* muscle contraction. Intrasubject variability was assessed before and after treatment comparing the energy generated between the first and the third minutes for both the affected and non-affected eyes.

The results are expressed as median (interquartile range, IQR). For the JRS, HSGS scores and intraindividual difference within the recording time, the Wilcoxon Signed Rank test was used. χ^2 tests were performed to assess if JRS and HSGS scores were associated with the total sum of the power spectrum of the upper eyelid movement. All calculations were performed with the JMP software version 10.0 (SAS Institute Inc., Cary, NC, U.S.A.).

Results

The mean age of the patients (13 females) was 63.95 ± 10.51 years (range 42–84 years). At the 30-day timepoint, all patients subjectively reported experiencing significant improvement with regard to the spasms. Only mild and transitory ecchymosis was observed at one of the injection sites in three patients. No complications, such as lagophthalmos, blepharoptosis, or diplopia, were observed during the follow-up period.

In two patients, a second video was recorded at baseline, because during the first recording, the frequency and severity of the spasms were lower than these patients reported along the day and lower than they usually presented in previous visits before treatment.

The eyelid motion traces obtained demonstrate that, beyond spontaneous blinking (Fig. 2a), HFS patients present complex and heterogeneous patterns: all patients presented nonconjugate spasms in the affected eyes (Fig. 2b), and 77% of the patients also presented high-frequency and low-amplitude eyelid twitches (Fig. 2c).

Tables 1, 2 and 3 present the total sum of the power spectrum of the upper eyelid movements recorded during spontaneous blinking, and the JRS and HSGS scores analysis, respectively, at baseline and the 30-day timepoint after the botulinum toxin injections. After the treatment, the total sum of the power spectrum of the upper eyelid movements, the JRS and HSGS scores were significantly reduced ($p < 0.05$) on the affected side.

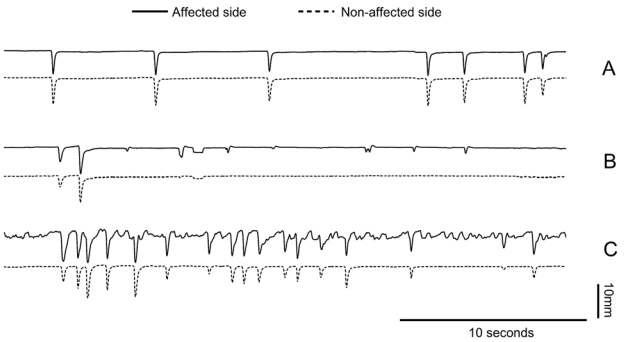

Fig. 2 Heterogeneous eyelid movements patterns observed in hemifacial spasm patients. **a** Normal spontaneous blinking. **b** Nonconjugate blink-like spasms on the affected side. **c** Spontaneous blinking mixed with high-frequency and low-amplitude eyelid twitches on the affected side

Table 1 Total sum of the power spectrum (mm^2/s) during upper eyelid movements before and after the botulinum toxin injections

Group	Pre		Post		*p* value
	Mean	SE	Mean	SE	
HFS (affected)	46,999.5	8075.4	21,463.8	5358.6	0.0022*
HFS (unaffected)	32,274.3	6762.0	27,527.5	5074.2	0.4961

HFS hemifacial spasm, *SE* standard error

*Statistically significant

Table 2 Jankovic rating scale (JRS) scores

Pre		Post		*p* value
Median	IQR	Median	IQR	
6.5	1.38	2.75	2.0	< 0.0001*

IQR interquartile range
*Statistically significant

Table 3 Hemifacial spasm grading system (HSGS) scores

Pre		Post		*p* value
Median	IQR	Median	IQR	
9	0	5	1.88	< 0.0001*

IQR interquartile range
*Statistically significant

Table 4 Intraindividual variability in energy generation between the 1st and 3rd min

Eye	Period	1st min Median (IQR)	3rd min Median (IQR)	Paired test *p* value*
Affected	Pre	3644.8 (3101.9)	3132.2 (3053.3)	0.84
Affected	Post	886.5 (1503.6)	1558.4 (1866.2)	0.22
Unaffected	Pre	2109.8 (2539.3)	2315.6 (2470.7)	0.81
Unaffected	Post	1478.7 (2564.7)	2548.8 (3041.5)	0.09

IQR Interquartile range
*Wilcoxon Signed Rank test

Interobserver agreement was 0.95 ($p < 0.0001$) for JRS and 0.96 ($p < 0.0001$) for HSGS scores. Spearman correlation between JRS and HSGS scores was 0.92 ($p < 0.0001$).

To assess if JRS and HSGS scores were associated with the total sum of the power spectrum of the upper eyelid movements, χ^2 tests were performed. Power spectrum lower than 23,000 was associated with JRS and HSGS scores lower than 4 and 6.25, respectively and power spectrum higher or equal to 23,000 was associated with JRS and HSGS scores higher or equal to 4 and 6.25, respectively ($p < 0.0001$ and $p = 0.0025$).

Table 4 lists the mean intrasubject variability (median values and interquartile range) of the energy generated during the first and third minutes of examination. No significant differences were observed during these two phases of the registration for the affected and unaffected eyes.

Discussion

To the best of our knowledge, no previous study has compared these two clinical grading scales to high-speed video system measurements to assess HFS patients. In the present study, the HSGS was compared with an established rating scale scale (JRS) and with the energy generated by the upper eyelid during eyelid movements. Although not originally developed to assess HFS (Jankovic et al. 1987), our results confirm that JRS can be a good tool to assess eyelid spasms in this condition. In addition, the authors found that the JRS permitted a more accurate assessment of HFS than HSGS. First, because the HSGS has only two-point scales for intensity and frequency, which permits poor differentiation between mild and moderate cases, especially after treatment when an improvement is usually noted. Moreover, it does not take into consideration the presence of high-frequency and low-amplitude eyelid fluttering, which was observed in most of HFS patients before treatment and was shown to be reduced after BoNT-A injections. Additionally, in HSGS, there is no rate for absence of spasms, making HFS assessment flawed especially in those patients who present with absence of eyelid spasms after treatment. It is important to mention, however, that HSGS was not developed to be used as assessment of outcomes of BoNT treatment.

In addition to HSGS, the HFS-30 and HFS-7 are specific evaluation tools that were validated in Asian populations to assess HFS (Tan et al. 2004, 2008). However, because they are based on patient reporting, they are more useful for assessing quality-of-life measures. To compare two rating scales that are in the same category (based on examiner evaluation, rather than based on patient response), we chose to use the HSGS in the present study.

Although rating systems are easy to use in clinical practice, they may exhibit limitations in sensitivity to assess differences between distinct disease patterns and between subtle differences in BoNT-A treatment responses. HFS patients present complex and heterogeneous patterns of eyelid movements, including spontaneous blinking and anomalous eyelid movements. Regarding the latter, besides nonconjugate spasms (Fig. 2b), most of the HFS patients also present high-frequency eyelid twitches on the affected eyes (Fig. 2c), which makes it challenging to accurately assess this condition using conventional methods that are used to assess normal individuals. These two types of anomalous movements observed in HFS patients are characterized by lower amplitudes and velocities (Osaki et al 2020).

Previously employed objective approaches to assess BoNT-A therapeutical effects in HFS were based on electromyography, less accurate systems based on reviewing videotapes, or other indirect approaches (Di Stadio et al. 2019; Yoshimura et al. 1992; Osaki et al. 2016). The duration of improvement or relief is stated as the primary outcome for efficacy in several studies, however it is mostly evaluated subjectively as the interval from treatment to the patient reported decrease in the effect or until the patient requests another treatment (Wabbels and Roggenkämper 2012). Objective assessment of the duration that

is associated with BoNT-A treatment has only been indirectly assessed in previous studies that analyzed changes in eyelid morphometric patterns and in corneal topography patterns in HFS patients over a 4-month period (Osaki et al. 2016).

The high-speed video system permitted a greater degree of accuracy in detecting eyelid movement, which allowed for the assessment of differences in anomalous eyelid movement patterns and to detect underlying eyelid movement abnormalities that could remain undetected by less accurate methods. This system permits a more accurate assessment of BoNT-A treatment response and could, therefore, allow better treatment tailoring. Nevertheless, simpler devices employing this system would need to be developed, so that it could be adopted in clinical practice. This system could also be used in comparative studies to improve or develop more accurate grading systems.

In the present study, the eyelid movements were recorded during a 3-min period because in a previous study performed by part of the present study group (Wambier et al. 2014), it had been observed that this period would be enough to evaluate the kinematics of eyelid movements. In both studies, the recording was performed in standardized and equivalent manners: while the subjects watched a commercial movie and using a front and chin support. A slit lamp (device used in the present study) has characteristically a front and chin support, equivalent to the support used in the paper by Wambier et al.

Time of pupil occlusion is a parameter that could be theoretically analyzed in HFS patients. However, in contrast to analysis in healthy individuals, due to the very heterogeneous array of eyelid movements in HFS patients, a manual and much more complex analysis would have to be performed for every single movement in these patients. Furthermore, high-frequency and low-amplitude eyelid twitches do not occlude the pupil and, therefore, this type of anomalous movement (shown to be present in most of the HFS patients), would not be accounted if this parameter was analyzed. In contrast, evaluation of the energy generated during eyelid movements permits to assess all types of eyelid movement (normal blinking, nonconjugate blink-like spasms, high-frequency and low-amplitude eyelid twitches—Fig. 2). For this reason, we chose to analyze energy generation in the present paper.

The energy generation associated with the eyelid movements is a novel approach to quantify the eyelid movements in HFS. Single analysis of blink parameters (amplitude and velocity) would not permit to directly quantify the effect of botulinum toxin in HFS. Moreover, in this condition there is a high rate of anomalous movements that cannot be considered to be blinks. With the Fourier transform, it was possible to evaluate the energy associated with all kinds of eyelid movements, regardless if they are considered as a blink or not.

As displayed in Table 4, the intrasubject variability between the first and third minutes of registration differed before and after treatment. However, these differences were not statistically significant.

The limitations of this study include the fact that assessments of HFS are challenging because the associated symptoms may vary depending on the time of day, patient stress level, lack of sleep, and environmental stimuli (Wabbels and Roggenkämper 2012). In the present study, the patients were evaluated in the same location and at the same time of the day; however, it was not possible to control all of the non-medication-related factors that might have influenced the eyelid spasms during video recording. Furthermore, although in HFS, muscles in the midface and in the lower third of the face may also be affected, this system was developed to assess orbicularis *oculi* spasms only, since eyelid spasms can lead to visual impairing. Development of a system that could detect the whole hemiface would be useful for future studies.

In conclusion, both grading systems and objective measures have advantages and disadvantages. Rating systems are quick and easy to use in clinical practice and can provide general assessment of HFS, but they may exhibit limitations in sensitivity to assess differences between distinct disease patterns and between subtle differences in treatment responses. The high-speed video system presented herein permits a greater degree of accuracy in detecting eyelid movement, which allows for the assessment of differences in eyelid movement patterns and to detect underlying eyelid movement abnormalities (that could remain undetected by an examiner using a simple videotape review method). This permits a more accurate assessment of BoNT-A treatment response and would, therefore, allow better treatment tailoring. Future development of simpler devices using this system could permit an easier and more accurate assessment of HFS to be used in routine clinical practice. Assessment of the energy generated by the eyelid during spontaneous eyelid movements could also be used in future comparative studies to improve or develop more accurate grading systems.

Author contributions THO: (1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the first draft; B. Review and approval of the final version. MHO: (1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: C. Review and Critique; (3) Manuscript Preparation: B: Review and Critique; approval of the final version. DG: (1) Research project: C. Execution; (2) Statistical Analysis: A. Design, B. Execution; Manuscript Preparation: B: Review and Critique; approval of the final version. TO: (1) Research project: B. Organization, C. Execution; (2) Statistical Analysis: C. Review and Critique; (3) Manuscript Preparation: B: Review and Critique; approval of the final version. LEO: (1) Research project: C. Execution; (2) Statistical Analysis: C. Review and Critique; (3) Manuscript Preparation: B: Review and Critique; approval of the final version. RB Jr: (1) Research project:

A. Conception; (2) Statistical Analysis: C. Review and Critique; (3) Manuscript Preparation: Review and Critique; approval of the final version. AAC: (1) Research project: A. Conception, B. Organization; (2) Statistical Analysis: C. Review and Critique; (3) Manuscript Preparation: Review and Critique; approval of the final version.

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Compliance with ethical standards

Conflict of interest Tammy H. Osaki declares that she has no conflict of interest. Midori H. Osaki declares that she has no conflict of interest. Denny Garcia declares that he has no conflict of interest. Teissy Osaki declares that she has no conflict of interest. Lilian E. Ohkawara declares that she has no conflict of interest. Rubens Belfort Jr declares that he has no conflict of interest. Antonio Augusto Cruz declares that he has no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the UNIFESP IRB (number 1322/2016) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

Abbruzzese G, Berardelli A, Defazio G (2011) Hemifacial spasm. Handb Clin Neurol 100:675–680

Bilyk JR, Yen MT, Bradley EA, Wladis EJ, Mawn LA (2018) Chemodenervation for the treatment of facial dystonia: a report by the American Academy of Ophthalmology. Ophthalmology 125(9):1459–1467

Di Stadio A, Dipietro L, Gambacorta V, Cristi MC, Faralli M, Della Volpe A, Ricci G (2019) Can the Jankovic-assessment be used as an alternative to electromyography? A cross-sectional study on facial dystonia patients treated with Botulinum toxin. Am J Otolaryngol. https://doi.org/10.1016/j.amjoto.2019.102278

Green KE, Rastall D, Eggenberger E (2017) Treatment of blepharospasm/hemifacial spasm. Curr Treat Options Neurol 19(11):41–55

Jankovic J, Orman J (1987) Botulinum A toxin for cranial-cervical dystonia: a double-blind, placebo-controlled study. Neurology 37(4):616–623

Kenney C, Jankovic J (2008) Botulinum toxin in the treatment of blepharospasm and hemifacial spasm. J Neural Transm (Vienna) 115(4):585–591

Kollewe K, Mohammadi B, Dressler D (2010) Hemifacial spasm and reinnervation synkinesias: long-term treatment with either Botox® or Dysport®. J Neural Transm 117(6):759–763

Osaki T, Osaki MH, Osaki TH, Hirai FE, Nallasamy N, Campos M (2016) Influence of involuntary eyelid spasms on corneal topographic and eyelid morphometric changes in patients with hemifacial spasm. Br J Ophthalmol 100(7):963–970

Osaki MH, Osaki TH, Garcia DM, Osaki T, Gameiro GR, Belfort R Jr, Cruz AAV (2020) Analysis of blink activity and anomalous eyelid movements in patients with hemifacial spasm. Graefes Arch Clin Exp Ophthalmol 258(3):669–674

Ross AH, Elston JS, Marion MH, Malhotra R (2011) Review and update of involuntary facial movement disorders presenting in the ophthalmological setting. Surv Ophthalmol 56:54–67

Tambasco N, Simoni S, Sacchini E, Eusebi P, Marsili E, Nigro P, Brahimi E, Paoletti FP, Romoli M, Calabresi P (2019) Validation of the Hemifacial Spasm Grading Scale: a clinical tool for hemifacial spasm. Neurol Sci 40(9):1887–1892

Tan EK, Fook-Chong S, Lum SY, Lim E (2004) Botulinum toxin improves quality of life in hemifacial spasm: validation of a questionnaire (HFS-30). J Neurol Sci 219(1–2):151–155

Tan EK, Hameed S, Fook-Chong S, Hussein K, Lum SY, Chan LL (2008) Treatment outcome correlates with knowledge of disease in hemifacial spasm. Clin Neurol Neurosurg 110(8):813–817

Wabbels B, Jost WH, Roggenkämper P (2011) Difficulties with differentiating botulinum toxin treatment effects in essential blepharospasm. J Neural Transm (Vienna) 118(6):925–943

Wabbels B, Roggenkämper P (2012) Botulinum toxin in hemifacial spasm: the challenge to assess the effect of treatment. J Neural Transm (Vienna) 119(8):963–980

Wambier S, Ribeiro SF, Garcia DM et al (2014) Two-dimensional video analysis of the upper eyelid motion during spontaneous blinking. Ophthal Plast Reconstr Surg 30:146–151

Yoshimura DM, Aminoff MJ, Tami TA, Scott AB (1992) Treatment of hemifacial spasm with botulinum toxin. Muscle Nerve 15(9):1045–1049