Benign Essential Blepharospasm: What We Know and What We Don't

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Introduction

Benign essential blepharospasm (BEB) is a cranial dystonia that can have debilitating functional and social effects. While previously considered a disease of psychogenic origin, much has been learned about the disease in the past 4 decades within the field of neurology and ophthalmology and several treatment advances have been made.

Despite this progress, several questions remain regarding the neurophysiology and genetic basis of the disease, as well as the effectiveness of treatments. Many patients with BEB remain difficult to treat. The purpose of the present chapter is to summarize what has been learned and has what yet to be discovered in this transitioning field of research.

Clinical Presentation and Patient Evaluation

BEB is a disorder characterized by sustained, involuntary spasms of the orbicularis oculi, corrugator, and procerus muscles resulting in partial or total eyelid closure. The prevalence of BEB ranges from 1.4 to 13.3 cases per 100,000 people with onset typically between the fifth and seventh decades of life.[1] Symptoms often range from mildly increased blink rate to forceful eyelid closure sometimes leading to functional blindness. Patients with BEB may also develop mid-facial or lower-facial spasms, often referred to as Meige syndrome.[2] Another associated finding in a subset of patients is apraxia of eyelid opening (AEO), which is a nonparalytic inability to open the eyelids in the absence of muscle spasm due to loss of co-inhibition between eyelid protractors and retractors. AEO associated with BEB is, therefore, not a true apraxia and should be distinguished from other paralytic causes.[3]

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The majority of patients report symptoms of dry eyes, irritation, and photophobia at the time of presentation.[2,4,5] Patients may also have sensory tricks that help break spasms or reduce the frequency of spasms such as traction on the eyelids, talking, singing, humming, or looking downward.[6] Chronic blepharospasm may lead to functional eyelid disorders including dermatochalasis, blepharoptosis, entropion, ectropion, or brow ptosis.[2,7]

Several clinical rating scales are available to measure severity of BEB: the Jankovic Rating Scale, Blepharospasm Disability Scale, the Functional Disability Score, the Blepharospasm Disability Index, and a more recently validated blepharospasm severity scale developed by Defazio and colleagues.[8–12] Although the Jankovic Rating Scale has been used frequently in clinical trials, only the Blepharospasm Disability Index and the recent severity scale by Defazio and colleagues have undergone successful clinometric testing and validation.[13,14]

What We Don't Know

The clinical manifestations of blepharospasm are characteristic, but limited evidence exists to explain the heterogeneity in disease severity between patients. It is unknown if AEO, which occurs in a minority of patients, represents a more severe spectrum of the disease, or a separate category of disease unto itself. Although ratings scales and electromyography (EMG) have been used to track the course of the disease and response to treatments, no singular objective measure has been able to consistently yield a quantifiable data point for researchers to study in this complex disease, which has many unique manifestations.

■ The Neurophysiology of Blepharospasm

Overend first postulated the existence of a blink reflex motor pathway in humans in 1896,[15] and subsequent EMG studies have elucidated 2 components of the reflex in response to a facial tap.[16] The R1 component is recognized as an early response ipsilateral to the stimulus preceding the blink, and the R2 component is a late bilateral second response coinciding with the blink. This pathway is currently referred to as the trigeminal blink reflex. Other EMG studies have demonstrated abnormalities in both R1 amplitude and duration as well as R2 reflex duration and recovery in BEB. Inhibition of the R2 response is believed to be decreased in patients with BEB.[17–19]

Dopamine levels within basal ganglia (BG) pathways may be a key factor in BEB and other forms of dystonia. Early clinical observations in both rat studies and patients with dopamine-related disorders suggested a relationship between blepharospasm and dopamine insufficiency.[20,21]

Schicatano and colleagues proposed a 2-factor rodent model for the pathophysiology of BEB. First, loss of dopamine in the substantia nigra may create a permissive environment in the trigeminal circuits. Second, weakening of the orbicularis oculi combined with dopamine loss led to characteristic findings of BEB in rats.[22]

Progressive loss of dopamine in the substantia nigra occurs with aging and is associated with increasing trigeminal reflex blink excitability, peaking in the fifth decade of life, which coincides also with the typical age of onset in BEB.[23–26] The presence of BEB in patients with Parkinson disease (PD) and tardive dyskinesia as well as patients with focal brain lesions involving areas such as the BG and thalamus also support a purported pathophysiologic role for dopamine in BEB.[27–29] Two recent interventional case series have demonstrated improvement in BEB symptoms with administration of oral methylphenidate, which increases intrasynaptic dopamine by blocking dopamine transmitters.[30,31]

Forty years ago, Marsden[32] argued that blepharospasm, like other focal dystonias, was linked to dysfunction of the BG. His argument was supported by subsequent work suggesting BG dysfunction as the underlying cause of BEB,[18,22,33] but the current leading theory argues that BEB is a result of defective neural circuitry rather than dysfunction at a single locus.[18,34–36]

What We Don't Know

Despite significant advances in the understanding of the neurophysiology of blepharospasm, no unifying theory has emerged. Blepharospasm patients have heterogenous clinical presentations, and the defective neural pathways underlying the disease may be heterogenous as well. The emerging paradigm for blepharospasm and dystonia is the neural node hypothesis, which explains why many regions of the brain may be involved, and why patients may have different manifestations of the disease.[29]

■ Pathophysiology: Genetics of Blepharospasm

BEB is generally considered to be a sporadic disorder, but up to 27% of patients have one or more family members with dystonia, suggesting some genetic predisposition.[37,38] Animal models and population studies have suggested that predisposing genes are inherited in an autosomal dominant fashion with low penetrance.[39–41] Studies have shown polymorphisms in the D5 dopamine receptor (DRD5), and a group of DYT polymorphisms have been linked to inherited dystonias, but results have been inconsistent.[41–43] Several other genetic mutations have been hypothesized as potential etiologies of BEB and other primary focal

dystonias, but no association between pure BEB and these mutations has been found.[44–50]

What We Don't Know

Despite identification of genetic loci associated with the disease, BEB does not have a strong genetic basis, and environmental stimuli clearly play a role in the manifestations of the disease. However, our understanding of the disease will evolve as we understand more about the interactions between known and as-yet-unknown genetic loci and the epigenetic phenomena occurring in response to the environment. At this point, we have limited information regarding clinical genetics that is useful for patient counseling.

■ Pathophysiology: Neuroimaging of Blepharospasm

Advances in neuroimaging have suggested potential pathways for blepharospasm. Early studies using voxel-based morphometry to investigate gray matter abnormalities found increased gray matter volume in the putamen.[51,52] Subsequent studies have also found gray matter abnormalities in multiple areas of the cerebral cortex, but there are no common patterns based on voxel-based morphometry studies at this time.[53–56]

More recent functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies have demonstrated abnormalities in the thalamus, pons, cerebellum, BG, and sensorimotor cortices. Together this data suggests that an abnormal cortico-striato-pallido-thalamic loop may be associated with the pathophysiology of BEB.[57–67] However, recent diffusion tensor imaging studies have been unable to clearly identify involvement of white matter tracts in BEB.[56,68–70]

What We Don't Know

Neuroimaging has made several advances since early studies of blepharospasm patients that suggested involvement of the BG in the pathogenesis of the disease. However, subsequent work has shown that the loci of the disease in the brain may be decentralized, with many areas of involvement including the BG and cerebellum. Neuroimaging may eventually provide insight into the etiology of BEB, but studies thus far have not identified a distinct pathway or locus to explain the manifestations of the disease.

■ Treatment of Blepharospasm

Conservative Management Options

Upon initial presentation, we provide all patients with information about the Benign Essential Blepharospasm Research Foundation (BEBRF). Anderson et al[2] found that 90% of patients had improvement in symptoms through the BEBRF. Ocular surface disease should be treated using artificial tears, eyelid hygiene, and temporary or permanent punctal occlusion.[71] Glasses tinted with FL-41 have been shown to improve subjective and objective symptoms.[72]

Neurotoxin Injection

Since the introduction of botulinum neurotoxin (BoNT) as a nonsurgical treatment for BEB, it has become the treatment of choice for BEB. Use of BoNT in treating BEB involves addressing the overactive efferent motor limb of the blink reflex pathway. By causing flaccid paralysis of facial muscles via chemodenervation, symptoms of orbicularis oculi muscle spasms are reduced or eliminated temporarily. After local infiltration of BoNT into the synaptic space, the light-chain of BoNT is translocated into the presynaptic bouton where it cleaves the SNARE proteins required for exocytosis of ACh, resulting in a nonfunctional complex and attenuation of extracellular neurotransmitter release.[73] Diminished ACh release decreases the probability of firing an action potential required for muscle fiber contraction and results in localized flaccid paralysis.

The FDA approved BoNT for BEB and facial spasm in 1989 after a double-blind, placebo-controlled study demonstrated improvement in blepharospasm symptoms in 100% of patients compared with placebo.[8] Currently 3 brands of BoNT serotype A (BoNT-A) and one brand of serotype B (BoNT-B) have been approved by the FDA for the treatment of BEB and cervical dystonias. Studies have demonstrated similar efficacy between serotypes A and B and BoNT-B may be useful in patients who become refractory to BoNT-A.[74] However, BoNT-B may have a shorter duration of action and higher complication rates.[75]

Follow-up studies of BoNT have reported a response rate of around 90%.[76–81] However, many of the studies had small sample sizes and were based on patient-reported improvement. A 2005 Cochrane Review concluded that current studies suggested that BoNT was both highly effective and safe for BEB, but no high-quality randomized, controlled trials existed. Given the efficacy of BoNT, however, placebo-controlled trials may now be unethical to perform.[82]

Comparative studies of BoNT preparations have shown similar efficacy and safety between onabotulinum A toxin (BOTOX; Allergan Inc., Irvine, CA) and abobotulinum A toxin (Dysport; Ipsen Ltd., Paris, France).[78,83–86]

However, these studies used different dosing conversion ratios and a true equivalent dose ratio is still unknown. Two studies comparing BOTOX and incobotulinum A toxin (Xeomin, Merz Pharmaceuticals, Frankfurt, Germany) also showed similar efficacy and adverse effect rates using a 1:1 dosing ratio.[87,88]

On the basis of findings of recent published studies, the American Academy of Neurology has published practice guidelines for the use of BoNT for the treatment of blepharospasm, giving BOTOX and Xeomin Level B (probably effective) recommendations, Dysport Level C (possibly effective) recommendations, and concluded there was insufficient evidence to support the use of Myobloc in the treatment of BEB.[89] Benefits from BoNT may last as long as 15 years, but patients may require increasing doses over time to achieve the same benefit. Although rare, the most commonly reported adverse effects include periorbital hematoma, ptosis, dry eye, and blurry or double vision.[90]

Oral Pharmacologic Agents

Historically, oral pharmacologic agents were first-line treatment for BEB before the era of BoNT. Older studies have suggested that trihexylphenidyl, baclofen, and benzodiazepines may be effective in treating BEB symptoms.[2,6,91,92] Others have recommended fluoxetine, clozapine, and the combination of valproate and baclofen to treat BEB symptoms.[20,93,94] Lithium has also been considered an effective treatment for BEB symptoms.[95] Although contradictory, treatments with both anticholinergic and cholinergic medications, as well as both dopamine agonists and antagonists, have been shown to help with BEB symptoms.[91,95]

Results from a more recent study showed that zolpidem may also be helpful in improving symptoms of blepharospasm and other dystonias by enhancing inhibitory pathways in the BG motor loop.[96] In 2 case series, oral methylphenidate has shown promise in treatment of BEB cases refractory to BoNT.[30,31]

At present, there is limited high-quality evidence to support the widespread use of oral pharmacologic therapies in BEB.[97] As BoNT has surpassed oral medications as the treatment of choice for BEB, oral pharmacologic treatments may be considered in cases refractory to BoNT and before pursuing surgical intervention.

Deep Brain Stimulation (DBS)

In 2003, the FDA granted limited approval for DBS in treatment of certain types of dystonia. DBS has been studied mostly for movement disorders such as essential tremor or PD. Prior studies have included blepharospasm within the context of other dystonias, but few have studied DBS for pure BEB.

Multiple case reports have reported promising results for the use of DBS in treating medically refractory focal dystonias, including Meige syndrome.[98–101] Placement of unilateral DBS electrodes within the globus pallidus internus (GPi) showed bilateral benefit, although some cases required eventual bilateral lead placement. A recent report described successful bilateral GPi DBS surgery for a patient with isolated blepharospasm refractory to oral pharmacologic therapy, BoNT injection, myectomy and frontalis suspension surgery. DBS improved symptom severity and the patient had regained full independence after being functionally blind from the disease.[102]

Despite reports of DBS successfully treating medically refractory blepharospasm either alone or within other focal dystonias, there have also been studies stating that DBS may induce blepharospasm after stimulation of the subthalamic nucleus (STN), which is the preferred target in DBS for PD. It is known that blepharospasm is more common after STN DBS compared with GPi DBS.[25,103–105] STN DBS can reportedly induce tonic motor contraction of the facial muscles causing blepharospasm and AEO.[103,106] Complications of DBS surgery, although rare, may be severe and include hemorrhagic stroke and paralysis (1% risk per brain hemisphere), hematoma, infection, and hardware-related problems.[107,108]

Surgery

Before the introduction of botulinum toxin injection for the treatment of blepharospasm, surgery was a common treatment modality. Differential sectioning of the facial nerve was first described in the early 1900s with good initial results.[109] Several others have described similar methods for facial nerve denervation including resection or injection of alcohol.[110,111] However, facial nerve surgery had a high rate of recurrence of symptoms from nerve regeneration as well as surgical complications related to the induced palsy.

Anderson and colleagues first described orbicularis myectomy in 1981 and it has become a mainstay of surgical treatment for BEB.[7] McCord et al[112] studied outcomes of facial nerve dissection compared with the Anderson myectomy technique and found patients who had undergone myectomy had lower rates of recurrence and required fewer additional procedures. Currently, myectomy is done in cases of BoNT injection failure, AEO associated with blepharospasm, and patients who are unable to receive BoNT injections.[113]

Traditionally, full myectomy involves removal of the pretarsal, preseptal, and orbital portions of both upper and lower eyelid orbicularis oculi muscle through blepharoplasty incisions as well as removal of the procerus and corrugator muscles.[7] More recently, upper eyelid myectomy alone has been shown to be effective in alleviating blepharospasm symptoms in the majority of patients, although some will require

eventual lower eyelid myectomy.[114] Upper and lower eyelid myectomy should be staged and performed at least 6 months apart to prevent lymphedema and scarring. Furthermore, the continued use of BoNT injection after upper eyelid myectomy may prevent or delay the need for lower eyelid myectomy and the effects of BoNT may last significantly longer after limited upper eyelid surgery.[115,116]

What We Don't Know

The most significant advance in the treatment of blepharospasm has undoubtedly been BoNT therapy. Despite the efficacy of BoNT in many patients, however, there are still patients that remain symptomatic despite therapy, and require second-line treatments. Surgical myectomy has shown efficacy for patients with severe blepharospasm, but can induce cicatricial lagophthalmos. Postmyectomy patients may still require BoNT injections, albeit usually at a lower dose.[116] In both BoNT and surgical myectomy, the treatment has been directed at the motor neuron endplate and orbicularis muscle, and not at the underlying dysfunction of the blink reflex. Oral therapies have shown some promise for treating the underlying dysfunction in small case series, and deep brain stimulation has shown some isolated success. More work is needed in determining whether other oral agents, or emerging treatments such as transcranial magnetic stimulation, may help patients who do not respond to BoNT.[117]

■ Conclusions

Many advances have been made in the understanding and treatment of benign essential blepharospasm since Marsden[32] classified the disease as a form of dystonia over 40 years ago. Despite these advances, many patients still remain difficult to treat and suffer significant functional disability from the disease. As much as we have learned about the disease, still more remains unanswered.

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■ References

1. Steeves TD, Day L, Dykeman J. The prevalence of primary dystonia: a systematic review and meta-analysis. *Mov Disord*. 2012;27:1789–1796.
2. Anderson RL, Patel BCK, Holds JB, et al. Blepharospasm: past, present, and future. *Ophthal Plast Reconstr Surg*. 1998;14:305–317.
3. Goldstein JE, Cogan DG. Apraxia of Lid Opening. *Arch Ophthalmol*. 1965;73:155–159.

4. Elston JS, Marsden CD, Grandas F, et al. The significance of ophthalmological symptoms in idiopathic blepharospasm. *Eye*. 1988;2:435–439.
5. Evinger C, Bao J, Powers AS, et al. Dry eye, blinking, and blepharospasm. *Mov Disord*. 2002;17(suppl 2):S75–S78.
6. Simon GJB, Mccann JD. Benign essential blepharospasm. *Int Ophthalmol Clin*. 2005; 45:49–75.
7. Gillum WN, Anderson RL. Blepharospasm surgery: an anatomical approach. *Arch Ophthalmol*. 1981;99:1056–1062.
8. Jankovic J, Orman J. Botulinum a toxin for cranial-cervical dystonia: a double-blind, placebo-controlled study. *Neurology*. 1987;37:616–623.
9. Lindeboom R, De Haan R, Aramideh M, et al. The Blepharospasm Disability Scale: an instrument for the assessment of functional health in blepharospasm. *Mov Disord*. 1995;10:444–449.
10. Grivet D, Robert P, Thuret G, et al. Assessment of blepharospasm surgery using an improved disability scale: study of 138 patients. *Ophthal Plast Reconstr Surg*. 2005;21: 230–234.
11. Jankovic J, Kenney C, Grafe S, et al. Relationship between various clinical outcome assessments in patients with blepharospasm. *Mov Disord*. 2009;24:407–413.
12. Defazio G, Hallett M, Jinnah HA, et al. Development and validation of a clinical scale for rating the severity of blepharospasm. *Mov Disord*. 2015;30:525–530.
13. Albanese A, Sorbo FD, Comella C, et al. Dystonia rating scales: critique and recommendations. *Mov Disord*. 2013;28:874–883.
14. Pietracupa S, Bruno E, Cavanna AE, et al. Scales for hyperkinetic disorders: a systematic review. *J Neurol Sci*. 2015;358:9–21.
15. Overend W. Preliminary note on a new cranial reflex. *Lancet*. 1896;1:619.
16. Kugelberg E. Facial reflexes. *Brain*. 1952;75:385–396.
17. Hallett M. Blepharospasm: recent advances. *Neurology*. 2002;59:1306–1312.
18. Grandas F, Alfredo T, Fernando A, et al. Blink reflex recovery cycle in patients with blepharospasm unilaterally treated with botulinum toxin. *Clin Neuropharmacol*. 1998; 21:307–311.
19. Ross AH, Elston JS, Marion M, et al. Review and update of involuntary facial movement disorders presenting in the ophthalmological setting. *Surv Ophthalmol*. 2011;56:54–67.
20. Schrieber S, Pick C. Fluoxetine for blepharospasm: interaction of serotonin and dopamine. *J Nerv Ment Dis*. 1995;183:719–721.
21. Hotson J, Boman D. Memory-contingent saccades and the substantia-nigra postulate for essential blepharospasm. *Brain*. 1991;114:295–307.
22. Schicatano EJ, Basso MA, Evinger C, et al. Animal model explains the origins of the cranial dystonia benign essential blepharospasm. *J Neurophysiol*. 1997:2842–2846.
23. Fearnley J, Lees A. Aging and Parkinson's disease: substantia nigra regional selectivity. *Brain*. 1991;114:2283–2301.
24. Perlmutter JS, Stambuk MK, Markham J, et al. Decreased [18 F] spiperone binding in putamen in idiopathic focal dystonia. *J Neurosci*. 1997;17:843–850.
25. Jinnah HA, Berardelli A, Comella C, et al. The focal dystonias: current views and challenges for future. *Mov Disord*. 2013;28:926–943.
26. Basso MA, Powers AS, Evinger C. An explanation for reflex blink hyperexcitability in Parkinson's disease. I. Superior colliculus. *J Neurosci*. 1996;16:7308–7317.
27. Rana A-Q, Kabir A, Dogu O, et al. Prevalence of blepharospasm and apraxia of eyelid opening in patients with Parkinsonism, cervical dystonia and essential tremor. *Eur Neurol*. 2012;68:318–321.
28. Zádori D, Veres G, Szalárdy L, et al. Drug-induced movement disorders drug-induced movement disorders. *Expert Opin Drug Saf*. 2015;14:877–890.

29. Defazio G, Hallett M, Jinnah HA, et al. Blepharospasm 40 years later. *Mov Disord*. 2017;32:498–509.
30. Price K, Ramey N, Richard M, et al. Can methylphenidate objectively provide relief in patients with uncontrolled blepharospasm? A pilot study using surface electromyography. *Ophthal Plast Reconstr Surg*. 2010;26:353–356.
31. Eftekhari K, Choe CH, Vagefi MR, et al. Oral methylphenidate for the treatment of refractory facial dystonias. *Ophthal Plast Reconstr Surg*. 2015;31:e65–e66.
32. Marsden CD. Blepharospasm-oromandibular dystonia syndrome (Brueghel's syndrome): a variant of adult-onset torsion dystonia? *J Neurol Neurosurg Psychiatry*. 1976; 39:1204–1209.
33. Berardelli A, Rothwell JC, Day BL, et al. Pathophysiology of blepharospasm and oromandibular dystonia. *Brain*. 1985;108:593–608.
34. Quartarone A, Angelo AS, Battaglia F, et al. Enhanced long-term potentiation-like plasticity of the trigeminal blink reflex circuit in blepharospasm. *J Neurosci*. 2006; 26:716–721.
35. Digre KB. Benign essential blepharospasm—there is more to it than just blinking. *J Neuroopthalmol*. 2012;35:379–381.
36. Peterson DA, Sejnowski TJ. A dynamic circuit hypothesis for the pathogenesis of blepharospasm. *Front Comput Neurosci*. 2017;11:1–11.
37. Defazio G, Livrea P, De Salvia R, et al. Prevalence of primary blepharospasm in a community of Puglia region, Southern Italy. *Neurology*. 2001;56:1579–1581.
38. Defazio G, Martino D, Aniello MS, et al. A family study on primary blepharospasm. *J Neuro*. 2006;77:252–254.
39. Stojanovic M, Cvetkovic D, Kostic V. A genetic study of idiopathic focal dystonias. *J Neurol*. 1995;242:508–509.
40. Defazio G, Brancati F, Valente EM, et al. Familial blepharospasm is inherited as an autosomal dominant trait and relates to a novel unassigned gene. *Mov Disord*. 2003;18:207–212.
41. Clarimon J, Brancati F, Peckham E, et al. Assessing the role of DRD5 and DYT1 in two different case–control series with primary blepharospasm. *Mov Disord*. 2007; 22:162–166.
42. Misbahuddin A, Placzek M, Chaudhuri K, et al. A polymorphism in the dopamine receptor DRD5 is associated with blepharospasm. *Neurology*. 2002;58:124–126.
43. Hague S, Klaffke S, Clarimon J, et al. Lack of associate with TorsinA haplotype in German patients with sporadic dystonia. *Neurology*. 2006;66:951–952.
44. Phukan J, Albanese A, Gasser T, et al. Primary dystonia and dystonia-plus syndromes: clinical characteristics, diagnosis, and pathogenesis. *Lancet Neurol*. 2011; 10:1074–1085.
45. Fuchs T, Saunders-pullman R, Masuho I, et al. Mutations in GNAL cause primary torsion dystonia. *Nat Genet*. 2012;45:88–92.
46. Charlesworth G, Plagnol V, Holmstrom K, et al. Mutations in ANO3 cause dominant craniocervical dystonia: ion channel implicated in pathogenesis. *Am J Hum Genet*. 2012;91:1041–1050.
47. Hersheson J, Mencacci NE, Davis M, et al. Mutations in the autoregulatory domain of b-Tubulin 4a cause hereditary dystonia. *Ann Neurol*. 2013;73:546–553.
48. Xiao J, Uitti RJ, Zhao Y, et al. Mutations in CIZ1 cause adult onset primary cervical dystonia. *Ann Neuro*. 2012;71:458–469.
49. Xiao J, Zhao Y, Bastian RW, et al. Novel THAP1 sequence variants in primary dystonia. *Neurology*. 2010;74:229–238.
50. Xiromerisiou G, Dardiotis E, Tsironi EE, et al. THAP1 mutations in a Greek primary blepharospasm series. *Park Relat Disord*. 2013;19:404–405.
51. Black KJ, Ongiir D, Perlmutter JS. Putamen volume in idiopathic focal dystonia. *Neurology*. 1998;51:819–824.

52. Etgen T, Gaser C, Sander D. Bilateral grey-matter increase in the putamen in primary blepharospasm. *J Neurol Neurosurg Psychiatry*. 2006;77:1017–1020.
53. Obermann M, Yaldizli O, De Greiff A, et al. Morphometric changes of sensorimotor structures in focal dystonia. *Mov Disord*. 2007;22:1117–1123.
54. Martino D, Giorgio A Di, Ambrosio ED, et al. Cortical gray matter changes in primary blepharospasm: a voxel-based morphometry study. *Mov Disord*. 2011;26:1907–1912.
55. Suzuki Y, Kiyosawa M, Wakakura M, et al. Gray matter density increase in the primary sensorimotor cortex in long-term essential blepharospasm. *Neuroimage*. 2011;56:1–7.
56. Horovitz SG, Ford A, Najee-ullah MA, et al. Anatomical correlates of blepharospasm. *Transl Neurodegener*. 2012;1:1–7.
57. Baker RS, Andersen AH, Morecraft RJ, et al. A functional magnetic resonance imaging study in patients with benign essential blepharospasm. *J Neuroopthalmol*. 2003;23:11–15.
58. Schmidt KE, Linden DEJ, Goebel R, et al. Striatal activation during blepharospasm revealed by fMRI. *Neurology*. 2003;60:1738–1743.
59. Dresel C, Haslinger B, Castrop F, et al. Silent event-related fMRI reveals deficient motor and enhanced somatosensory activation in orofacial dystonia. *Brain*. 2006;129:36–46.
60. Yang J, Luo C, Song W, et al. Altered regional spontaneous neuronal activity in blepharospasm: a resting state fMRI study. *J Neurol*. 2013;260:2754–2760.
61. Zhou B, Wang J, Huang Y, et al. A resting state functional magnetic resonance imaging study of patients with benign essential blepharospasm. *J Neuroopthalmol*. 2013;33:235–240.
62. Esmaeli-Gutstein B, Nahmias C, Thompson M, et al. Positron emission tomography in patients with benign essential blepharospasm. *Ophthal Plast Reconstr Surg*. 1999;15: 23–27.
63. Feiwell RJ, Black KJ, McGee-Minnich LA, et al. Diminished regional cerebral blood flow response to vibration in patients with blepharospasm. *Neurology*. 1999;52: 291–297.
64. Hutchinson M, Nakamura T, Moeller JR, et al. The metabolic topography of essential blepharospasm: a focal dystonia with general implications. *Neurology*. 2000;55: 673–677.
65. Kerrison JB, Lancaster JL, Zamarripa FE, et al. Positron emission tomography scanning in essential blepharospasm. *Am J Ophthalmol*. 2003;136:846–852.
66. Suzuki Y, Mizoguchi S, Kiyosawa M, et al. Glucose hypermetabolism in the thalamus of patients with essential blepharospasm. *J Neurol*. 2007;254:890–896.
67. Murai H, Suzuki Y, Kiyosawa M, et al. Positive correlation between severity of blepharospasm and thalamic glucose metabolism. *Case Rep Ophthalmol*. 2011;2:50–54.
68. Fabbrini G, Pantano P, Totaro P, et al. Diffusion tensor imaging in patients with primary cervical dystonia and in patients with blepharospasm. *Eur J Neurol*. 2008;15:185–189.
69. Pinheiro GLS, Guimara RP, Piovesana LG, et al. White matter microstructure in idiopathic craniocervical dystonia. *Tremor Other Hyperkinet Mov*. 2015;5:1–6.
70. Yang J, Luo C, Song W, et al. Diffusion tensor imaging in blepharospasm and blepharospasm-oromandibular dystonia. *J Neurol*. 2014;261:1413–1424.
71. Martino D, Defazio G, Alessio G, et al. Relationship between eye symptoms and blepharospasm: a multicenter case-control study. *Mov Disord*. 2005;20:1564–1570.
72. Blackburn MK, Lamb RD, Digre KB, et al. FL-41 tint improves blink frequency, light sensitivity, and functional limitations in patients with benign essential blepharospasm. *Ophthalmology*. 2009;116:997–1001.
73. Turton K, Chaddock JA, Acharya KR. Botulinum and tetanus neurotoxins: structure, function and therapeutic utility. *Trends Biochem Sci*. 2002;27:552–558.

74. Dutton JJ, Fowler AM. Botulinum toxin in ophthalmology. *Surv Ophthalmol*. 2007;52:13–31.
75. Dutton JJ, White JJ, Richard MJ. Myobloc® for the treatment of benign essential blepharospasm in patients refractory to Botox®. *Ophthal Plast Reconstr Surg*. 2006;22: 173–177.
76. Dutton JJ, Buckley E. Long-term results and complications of botulinum A toxin in the treatment of blepharospasm. *Ophthalmology*. 1988;95:1529–1534.
77. Hsiung GR, Das SK, Ranawaya R, et al. Long-term efficacy of botulinum toxin A in treatment of various movement disorders over a 10-year period. *Mov Disord*. 2002;17:1288–1293.
78. Bentivoglio AR, Fasano A, Ialongo T, et al. Fifteen-year experience in treating blepharospasm with Botox or Dysport: same toxin, two drugs. *Neurotox Res*. 2009;15: 224–231.
79. Cillino S, Raimondi G, Guepratte N, et al. Long-term efficacy of botulinum toxin A for treatment of and spastic entropion: a multicentre study using two drug-dose escalation indexes. *Eye*. 2010;24:600–607.
80. Ababneh OH, Cetinkaya A, Kulwin DR. Long-term efficacy and safety of botulinum toxin A injections to treat blepharospasm and hemifacial spasm. *Clin Exp Ophthalmol*. 2014;42:254–261.
81. Silveira-moriyama L, Goncalves LR, Chien HF, et al. Botulinum toxin A in the treatment of blepharospasm: a 10-year experience. *Arq Neuropsiquiatr*. 2005;63: 221–224.
82. Costa J, Espírito-santo CC, Borges AA, et al. Botulinum toxin type A therapy for blepharospasm (review). *Cochrane Database Syst Rev*. 2004;2:1–11.
83. Sampaio C, Ferreira JJ, Simões F, et al. DYSBOT: a single-blind, randomized parallel study to determine whether any differences can be detected in the efficacy and tolerability of two formulations of botulinum toxin type A—Dysport and Botox—assuming a ratio of 4:1. *Mov Disord*. 1997;12:1013–1018.
84. Nussgens Z, Roggenkämper P. Comparison of two botulinum-toxin preparations in the treatment of essential blepharospasm. *Graefe's Arch Clin Exp Ophthalmol*. 1997;235: 197–199.
85. Bihari K. Safety, effectiveness, and duration of effect of BOTOX after switching from Dysport to blepharospasm cervical dystonia, and hemifacial spasm. *Curr Med Res Opin*. 2005;21:433–438.
86. Marchetti A, Magar R, Findley L, et al. Retrospective evaluation of the dose of dysport and BOTOX in the management of cervical dystonia and blepharospasm: the real dose study. *Mov Disord*. 2005;20:937–944.
87. Wabbels B, Reichel G, Fulford-Smith A, et al. Double-blind, randomised, parallel group pilot study comparing two botulinum toxin type A products for the treatment of blepharospasm. *J Neural Transm*. 2011;118:233–239.
88. Saad J, Gourdeau A. A direct comparison of OnabotulinumtoxinA (Botox) and IncobotulinumtoxinA (Xeomin) in the treatment of benign essential blepharospasm: a split-face technique. *J Neuroopthalmol*. 2014;34:233–236.
89. Simpson DM, Hallett M, Ashman EJ, et al. Practice guideline update summary: Botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache. *Neurology*. 2016;86:818–826.
90. Kollewe K, Mohammadi B, Kohler S, et al. Blepharospasm: long-term treatment with either Botox(R), Xeomin(R) or Dysport(R). *J Neural Transm*. 2015;122:427–431.
91. Balash Y, Giladi N. Efficacy of pharmacological treatment of dystonia: evidence-based review including meta-analysis of the effect of botulinum toxin and other cure options. *Eur J Neurol*. 2004;11:361–370.
92. Jankovic J. Medical treatment of dystonia. *Mov Disord*. 2013;28:1001–1012.

93. Hazari N, Kate N, Grover S. Clozapine and tardive movement disorders: a review. *Asian J Psychiatr*. 2013;6:439–451.
94. Sandyk R. Blepharospasm—successful treatment with baclofen and sodium valproate. A case report. *S Afr Med J*. 1983;64:955–956.
95. Cramer H, Otto K. Meige's syndrome: Clinical findings and therapeutic results in 50 patients. *J Neuroopthalmol*. 1986;6:3–15.
96. Miyazaki Y, Sako W, Asanuma K, et al. Efficacy of zolpidem for dystonia: a study among different subtypes. *Front Neurol*. 2012;3:1–5.
97. Albanese MA, Barnes MP, Bhatia KP, et al. A systematic review on the diagnosis and treatment of primary (idiopathic) dystonia and dystonia plus syndromes: report of an EFNS/MDS-ES Task Force. *Eur J Neurol*. 2006;13:433–444.
98. Capelle H, Weigel R, Krauss JK. Bilateral pallidal stimulation for blepharospasm—oromandibular dystonia (Meige syndrome). *Neurology*. 2017;60:2017–2018.
99. Vidailhet M, Vercueil L, Houeto J-L, et al. Bilateral deep-brain stimulation of the globus pallidus in primary generalized dystonia. *N Engl J Med*. 2005;352:459–468.
100. Foote KD, Sanchez JC, Okun MS. Staged deep brain stimulation for refractory craniofacial dystonia with blepharospasm: case report and physiology. *Neurosurgery*. 2005;56:E415.
101. Blomstedt P, Tisch S, Mi H. Pallidal deep brain stimulation in the treatment of Meige syndrome. *Acta Neurol Scand*. 2008;5:198–202.
102. Santos AF, Veiga A, Augusto L, et al. Successful treatment of blepharospasm by pallidal neurostimulation. *Mov Disord Clin Pr*. 2016;3:409–411.
103. Umemura A, Toyoda T, Yamamoto K, et al. Apraxia of eyelid opening after subthalamic deep brain stimulation may be caused by reduction of levodopa. *Park Relat Disord*. 2008;14:655–657.
104. Weiss D, Wachter T, Breit S. Involuntary eyelid closure after STN-DBS: evidence for different pathophysiological entities. *J Neurol Neurosurg Psychiatry*. 2010;81: 1002–1007.
105. Bologna M, Fasano A, Modugno N, et al. Effects of subthalamic nucleus deep brain stimulation and l-dopa on blinking in Parkinson's disease. *Exp Neurol*. 2012;235: 265–272.
106. Tommasi G, Krack P, Fraix V, et al. Pyramidal tract side effects induced by deep brain stimulation of the subthalamic nucleus. *J Neurol Neurosurg Psychiatry*. 2008;79: 813–819.
107. Hariz MI. Complications of deep brain stimulation surgery. *Mov Disord*. 2002;17: S162–S166.
108. Ostrem JL, Starr PA. Treatment of dystonia with deep brain stimulation. *Neurotherapeutics*. 2008;5:320–330.
109. Frazier CH. The surgical treatment of blepharospasm. *Ann Surg*. 1931;XCIII: 1121–1125.
110. Gurdjian E, Williams HW. The surgical treatment of intractable cases of blepharospasm. *JAMA*. 1982;91:2053–2056.
111. Harvey HK. Resection of the facial nerve for blepharospasm. *Arch Ophthalmol*. 1971;86:178–181.
112. Mccord CD, Coles WH, Shore JW, et al. Treatment of essential blepharospasm. I. Comparison of facial nerve avulsion and eyebrow-eyelid muscle stripping procedure. *Arch Ophthalmol*. 1984;102:266–268.
113. Pariseau B, Worley MW, Anderson RL. Myectomy for blepharospasm 2013. *Curr Opin Ophthalmol*. 2013;24:488–493.
114. Georgescu D, Vagefi MR, McMullan TFW, et al. Upper eyelid myectomy in blepharospasm with associated apraxia of lid opening. *Am J Ophthalmol*. 2008;145: 541–547.

115. Mauriello JA, Keswani R, Franklin M. Long-term enhancement of botulinum toxin injections by upper-eyelid surgery in 14 patients with facial dyskinesias. *Arch Otolaryngal Head Neck Surg*. 1999;125:627–631.
116. Kent TL, Petris CK, Holds JB. Effect of upper eyelid myectomy on subsequent chemodenervation in the management of benign essential blepharospasm. *Ophthal Plast Reconstr Surg*. 2015;31:222–226.
117. Kranz G, Shamim EA, Lin PT, et al. Transcranial magnetic brain stimulation modulates blepharospasm A randomized controlled study. *Neurology*. 2010;75: 1465–1471.