Update on blepharospasm

Report from the BEBRF International Workshop

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ABSTRACT

This review updates understanding and research on blepharospasm, a subtype of focal dystonia. Topics covered include clinical aspects, pathology, pathophysiology, animal models, dry eye, photophobia, epidemiology, genetics, and treatment. Blepharospasm should be differentiated from apraxia of eyelid opening. New insights into pathology and pathophysiology are derived from different types of imaging, including magnetic resonance studies. Physiologic studies indicate increased plasticity and trigeminal sensitization. While botulinum neurotoxin injections are the mainstay of therapy, other therapies are on the horizon. ***Neurology*® 2008;71:1275–1282**

GLOSSARY

BFMDRS = Burke-Fahn-Marsden dystonia rating scale; **BoNT** = botulinum neurotoxin; **DBS** = deep brain stimulation; **DTI** = diffusion tensor imaging; **FDG** = ^{18}fluorodeoxyglucose; **VBM** = voxel-based morphometry.

Blepharospasm is a focal dystonia manifested by involuntary eyelid closure.[1] The primary form, the focus of this update, is often called benign essential blepharospasm (BEB) even though the term has been criticized since blepharospasm is rarely benign and never "essential." Involuntary eyelid closure can be due to spasms of the orbicularis oculi or to failure of levator palpebrae contraction. This failure is called apraxia of eyelid opening, and is particularly common in Parkinson disease or other parkinsonian disorders such as progressive supranuclear palsy, but can be seen in isolation.[2] Apraxia of eyelid opening is an important consideration when botulinum neurotoxin (BoNT) fails to improve blepharospasm despite the production of eyelid weakness. A diagnosis of apraxia is often made in error because selective contraction of the pretarsal portion of the orbicularis oculi can be responsible for eyelid closure. Unless this portion is injected specifically with BoNT, treatment will fail.[3] Injection into Riolan's muscle, at the lid margin, may be particularly useful in this regard.[4]

There are, however, true cases of apraxia. Unequivocal proof of this depends on the demonstration by EMG of levator muscle inactivity despite an attempt of the patient to open the eyes. Because this is a specialized ophthalmologic procedure, the diagnosis remains largely based on careful clinical assessment and observation of delayed eye opening, with possible supplementation with EMG recordings from the pretarsal orbicularis oculi. Treatment of apraxia of eyelid opening is difficult, and logically BoNT cannot work unless the apraxia is "triggered" by voluntary or involuntary eyelid closure. Surgical approaches with shortening of the levator tendon or a frontalis sling may help some patients.[5] Using glasses fitted with wire loops to press against the brow (Lundie loops) or to lift the upper eyelid (eyelid crutch) may help.[6] Such loops may also function by a sensory trick mechanism.

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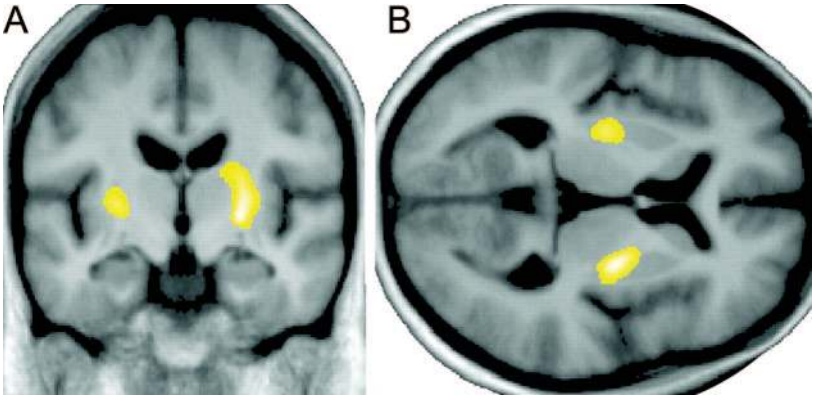
ANATOMY AND PATHOLOGY The cortical control of eyelid closure is not well understood. Only relatively recently has there been the finding that a major source is the cingulate cortex (M3) as well as lesser sources in primary motor cortex (M1).[7] This was first defined in the primate, and then confirmed in humans with both transcranial magnetic stimulation mapping[8] and functional MRI.[9] It will be valuable to know the inputs to M3. New findings show a major input from the amygdala which presumably plays a role in behaviors such as emotional facial expressions.[10] Whether either cortical area plays a direct role in the pathophysiology is not known.

While the primary dystonias are generally assumed to have their origin in pathology of the basal ganglia, this has not been proven. In fact, the recent report of pathology in Oppenheim or DYT1 dystonia (early onset autosomal dominant generalized dystonia) shows pathology mainly localized to the brainstem.[11] Knowing where to look for pathology should be helpful and new MRI techniques are valuable in this regard. Voxel-based morphometry (VBM) is an MRI technique to compare structural anatomy between patients and normal controls. One study compared 16 patients and a matched set of healthy subjects.[12] In patients there was a bilateral increase in gray matter in the putamen, and a gray matter decrease in the left inferior parietal lobule (figure 1). In another study of 11 patients, there was increased gray matter in the caudate head and cerebellum bilaterally and a decrease in the putamen and thalamus bilaterally.[13] In interpreting VBM studies, location of the abnormality is most important, increases or decreases might occur depending on the details of the MR sequence. Diffusion tensor imaging (DTI), another MRI technique that assesses the integrity of white matter tracts, shows abnormalities in some forms of dystonia.[14] This approach has not yet been applied to blepharospasm. Clearly, one of the next steps must be to look for histopathology in blepharospasm brains.

Figure 1 **Gray matter increase bilaterally in the putamen in blepharospasm**



Results are projected on (A) coronal and (B) axial slices of the study-specific averaged T1-image in a standard stereotactic space derived from all the 32 study participants. Reported from Etgen et al.[12] with permission from BMJ Publishing Group Ltd.

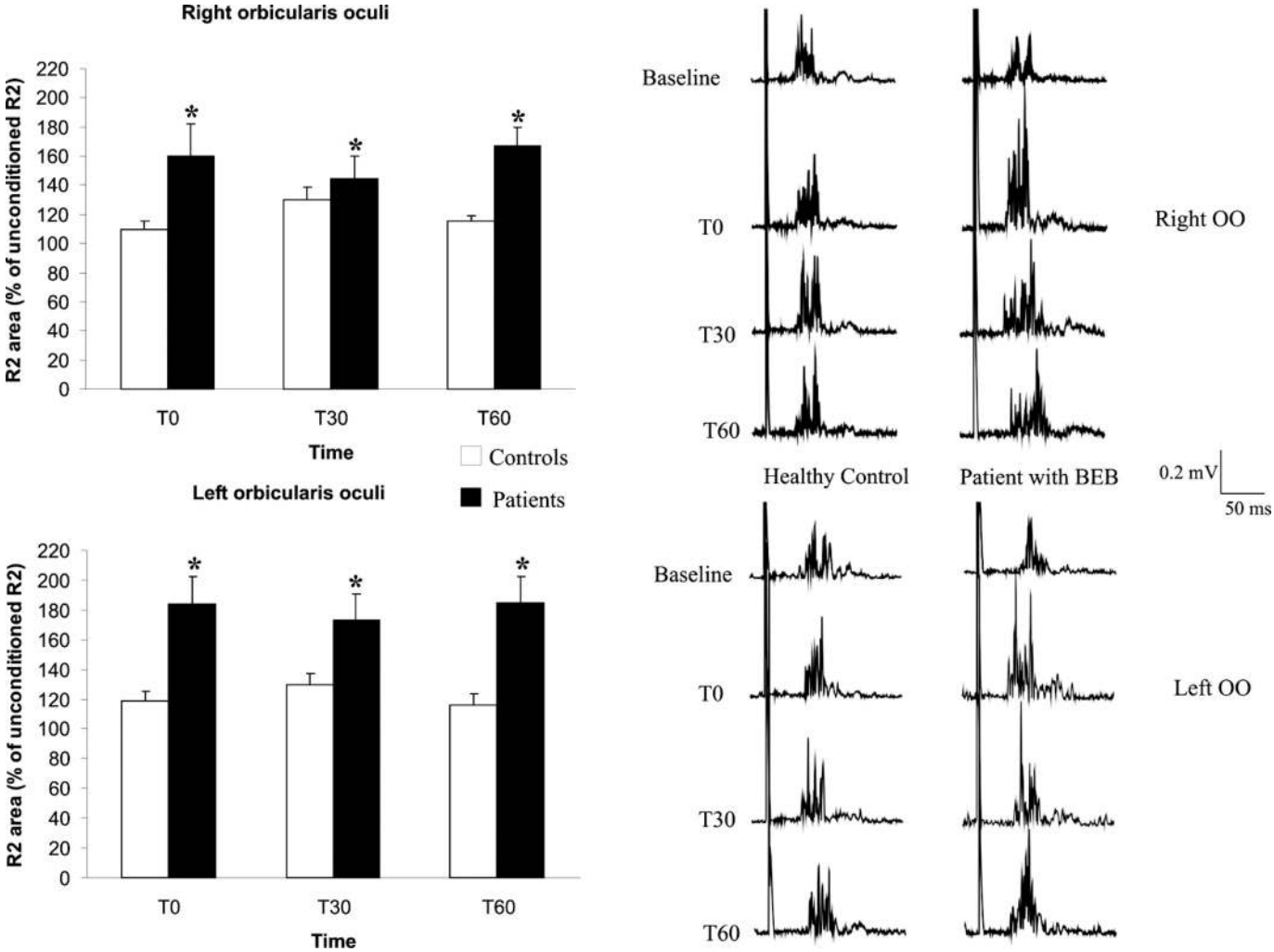
PATHOPHYSIOLOGY There are many investigations of the focal dystonias using clinical neurophysiology, and much of this is likely relevant to blepharospasm since the focal dystonias are certainly related to each other.[15,16] Some work is being done in blepharospasm itself. Blink rates were compared during rest, conversation, and reading in 50 patients with blepharospasm and in 150 healthy subjects.[17] Blink rate both at rest and during conversation was higher in patients. Moreover, 76% of patients blinked more at rest than during conversation, whereas 74% of controls blinked more during conversation than at rest. This reversal in the usual pattern of blinking suggests that conversation may reduce the excitability of eyelid closure and accounts for the common observation that patients with blepharospasm talk more than those without it. The sensitivity and specificity of the two features (number of blinks at rest and the pattern of blinking) in discriminating patients and controls were found to be best with a resting blink rate above 27 blinks per minute.

Patients with focal dystonias have sensory disorders as well as the more obvious motor dysfunction. Patients with focal hand dystonia have been shown to have deficits in tactile temporal discrimination,[18] and now this has been demonstrated for patients with blepharospasm as well.[19] The temporal discrimination deficit appears due to a loss of a short latency inhibitory mechanism,[20] and thus is related to the fundamental deficit in focal dystonia of loss of inhibition.[15]

There is considerable evidence that patients with dystonia exhibit increased plasticity.[21] This has been demonstrated in blepharospasm by coupling a train of electric shocks to the supraorbital nerve during the R2 (the second and major response) of the blink reflex.[22] This causes an increase in the R2 amplitude that is enhanced in patients relative to control subjects (figure 2). Linking these findings to the underlying pathology and to therapy remain challenges.

PET neuroimaging with ^{18}fluorodeoxyglucose (FDG) was performed in 11 patients and a similar number of matched controls.[23] Brain areas with the most significant clusters of increased glucose uptake were the right caudate, inferior frontal gyri, right posterior cingulate gyrus, left middle occipital gyrus, fusiform gyrus of the right temporal lobe, and left anterior cingulate gyrus. Areas with the most significant clusters of decreased glucose uptake were the left

Figure 2 Enhanced long-term potentiation-like plasticity of the trigeminal blink reflex circuit in blepharospasm



Magnitude of the R2 component of the blink reflex at baseline (T0) and 30 minutes (T30) and 60 minutes (T60) following a session of high frequency stimulation of the supraorbital nerve timed to occur during the blink reflex. Average data on the left and individual data on the right. Reprinted from Quartarone et al.[22] with permission from the *Journal of Neuroscience*.

inferior cerebellum, thalamus, and inferior frontal gyri, ventral to the area of increased glucose metabolism. A second study examined FDG PET in patients whose symptoms were suppressed by an injection of botulinum-A toxin in order to avoid a confound caused by sensory feedback from the dystonic movements (although the intervention itself might be a confound).[24] Twenty-five patients were compared with 38 normal volunteers. A significant increase in glucose metabolism was seen in the thalamus and pons in the patients. The inconsistent results of these studies make their interpretation unclear.

Functional MRI studies of blinking in patients with blepharospasm have not been done, but a study was done with whistling as part of a study of cranial dystonia (previously also referred to as Meige syndrome).[25] Comparing patients with blepharospasm with controls, there was overactivity of the post-central gyrus and caudal SMA bilaterally, the left dorsolateral prefrontal cortex and the left paravermal cerebellum, and there was less activation in the left cerebellum and the left fusiform gyrus. Overactivity of the primary sensory cortex is commonly seen with motor tasks in patients with focal dystonias, providing further evidence for the idea that dysfunction of the sensory system is important in the pathophysiology of this apparently motor disorder.

ANIMAL MODELS Better animal models for blepharospasm would be useful in identifying new clinical approaches to blepharospasm. Consistent with the imaging studies describing abnormal cerebellar activity with blepharospasm,[13,24] recent animal models of dystonia indicate that the cerebellum might be a possible site of pathology.[26,27]

An in vitro rat preparation has been used to look at the circuit between trigeminal input and

facial nerve output, with the hope that the information learned will be useful in developing ideas about circuits that might become pathologic in blepharospasm. This is done with brainstem "slabs" from P7–P15 rats containing a functional neural circuit comprised of the trigeminal nerve, spinal trigeminal nucleus, reticular interneurons, and facial motoneurons to the vibrissae.[28] Stimulation of the trigeminal nerve generated EPSPs in facial motoneurons mediated by activity of spinal trigeminal neurons. Trigeminal nerve stimulation at frequencies above 2 Hz produced rapid depression of the facial motoneuron EPSPs, reducing the gain of the sensorimotor loop and preventing the sensorimotor loop from creating uncontrollable spasms. The investigators hypothesized that blepharospasm might arise because of an exceptionally high gain for the blink sensorimotor loop created by a loss of this synaptic depression.

A common explanation for the ocular discomfort of photophobia, often experienced by patients with blepharospasm, is that central visual neurons excite nociceptor centers in the ophthalmic region of the spinal trigeminal complex. Another proposal is that the excessive pupil constriction evoked by bright lights activates nociceptors associated with the iris. To distinguish between different hypotheses for the neural basis of photophobia, Evinger (personal communication) developed an anesthetized rat model of photophobia. He utilized the observations from humans that trigeminal stimuli elicit blinks larger than spontaneous blinks and that people exhibit a higher spontaneous blink rate in the presence of lights reported as uncomfortable or painful.[29] Thus, it is possible to quantify photophobia by measuring the change in trigeminal reflex blink amplitude and the increase in spontaneous blinking as a function of light intensity. Photophobia was quantified before and after lesioning both optic nerves in this model. This lesion only reduced photophobia by approximately 30%. These data indicated that a significant portion of photophobia did not involve central visual pathways or pupil constriction. The simplest explanation of these results was that intraocular trigeminal nociceptors responding to retinal activity produced the majority of the photophobia. This hypothesis can explain the occurrence of photophobia sometimes reported in blind patients.[30] Based on this hypothesis, Evinger proposed that the central trigeminal sensitization associated with blepharospasm would produce an elevated response to intraocular nociceptors, a hypersensitivity to light.

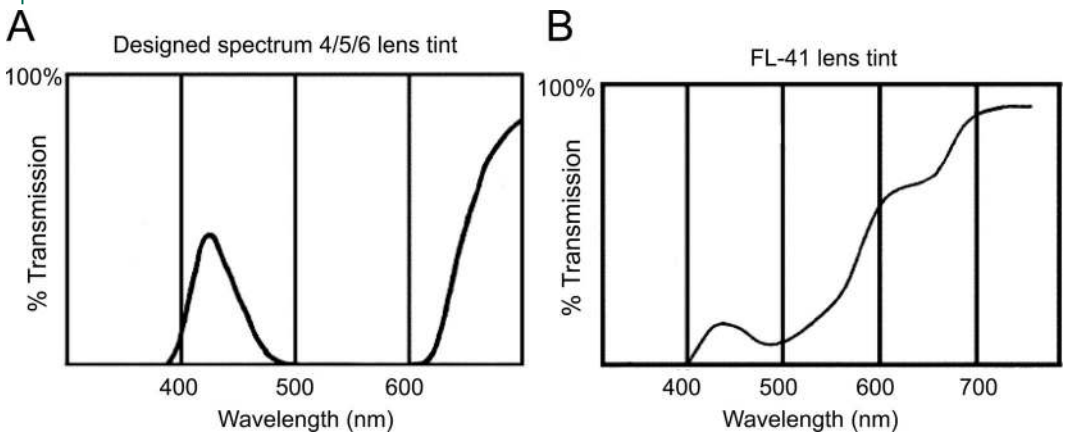
DRY EYE Many patients complain of dry eye, but objective findings are much less than the frequency of complaints. Dryness may have less to do with the amount of tears, and more to do with the makeup of the tear film and its dynamics.[31,32] Studies are being conducted looking at the pattern of tear break-up, the osmolarity of the liquid layer, and the composition and thickness of the lipid layer. Whether any of these abnormalities are common in patients with blepharospasm and the extent to which these abnormalities may be etiologic are important issues needing further investigation.

PHOTOPHOBIA Photophobia is a prominent complaint in patients with blepharospasm. Light is not only unpleasant, it also precipitates eyelid spasms. The visible spectrum of light is from about 380 to 750 nm, and frequent, but anecdotal, reports suggest that filtering the light may improve symptoms of blepharospasm. One important question is whether symptoms are better relieved by reducing light in a specific region of the spectrum or just the net flux.

In one study designed to quantify light sensitivity in blepharospasm, 24 patients and 10 controls were evaluated with seven different chromatic lenses.[33] Without a lens, the light tolerated by the two groups was similar. The light intensity tolerated by the normal subjects grew to 3.5 times that tolerated by the blepharospasm group when there was only a limited portion of high wavelength light transmitted. Although the highest intensity of light tolerated by the patients was measured with lens 6 (filtering light at $<$400 nm and 500–600 nm), 71% of patients with blepharospasm reported the greatest relief of photophobia with the FL-41 lens (figure 3). The FL-41 lens filters well $<$400 nm, and moderately between 400 and 550 nm. Consistent with the observation that the sensitivity to photophobia peaks at about 500 nm and increases monotonically for wavelength $<$460 nm in control subjects,[34] these findings in patients with blepharospasm suggest that sensory photophobia may be related as much to the wavelength as to the intensity of the light exposure.

Another case-controlled study compared 87 subjects in three groups: blepharospasm, migraine, and normal control subjects.[35] A slit-lamp was used to measure light sensitivity thresholds without spectacles, with gray-tinted spectacles, and with FL-41 tinted spectacles. Light discomfort thresholds for subjects with blepharospasm were significantly lower compared with normal control subjects and similar to the migraine group. Both gray and FL-41 tinted lenses improved light sensitivity thresholds in all groups. There was no observed difference in the improvement in light sensitivity when the gray and FL-41 tinted lenses were compared. In contrast to

Figure 3 Spectral transmission characteristics of lens tint 6 (A) and FL-41 lens (B)



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Herz and Yen,[33] the Adams et al.[35] study implies that the relevant feature for photophobia is the light intensity and not the wavelength. More work is necessary to understand the basis of the photophobia present in blepharospasm.

The studies involving pathophysiology, animal models, dry eye, and photophobia suggest that sensitization of the trigeminal system plays a role in blepharospasm. The increased plasticity of the blink reflex identified by Quartarone et al.[22] reflects a change in the trigeminal system.[36] The in vitro model of vibrissae control developed by Nguyen and Kleinfeld[28] suggests that blepharospasm arises from a change in the trigeminal input to the facial nucleus. As dry eye or ocular irritation sensitizes the trigeminal system,[37] the linkage between blepharospasm and ocular symptoms[38] points to the importance of trigeminal sensitization in blepharospasm. The similarity of light sensitivity exhibited by patients with blepharospasm and migraine[35] suggests that patients with blepharospasm share the trigeminal sensitization present in patients with migraine.[39] More work is necessary to understand the role of trigeminal sensitization.

EPIDEMIOLOGY Age appears to be more of a risk factor in the development of blepharospasm than other types of focal dystonia. An investigation carried out in 14 families with primary focal dystonias and compared with a meta-analysis of 83 published series including 5,057 patients[40] showed that the mean age at onset of writer's cramp was 38.4 years, cervical dystonia 40.8 years, spasmodic dysphonia 43.0 years, and blepharospasm together with cranial dystonia 55.7 years.

A validated questionnaire was administered to 165 Italian patients with blepharospasm and 180 age- and gender-matched control patients with hemifacial spasm particularly to assess ocular symptoms prior to the onset of blepharospasm.[38] Logistic regression analysis indicated a significant association between ocular symptoms starting in the year preceding disease onset (short-latency symptoms). In addition, the age at onset played a role since the association was stronger when the short-latency symptoms developed from 40 to 59 years of age.

In another multicenter case control study in Italy, prior coffee drinking and cigarette smoking habits were investigated in 166 patients with blepharospasm, 228 control patients with hemifacial spasm, and 187 healthy control subjects.[41] Unadjusted logistic regression analysis showed that prior coffee drinking and cigarette smoking was associated with reduced likelihood of blepharospasm compared with the control groups. After adjustment for age, sex, referral center, disease duration, years of schooling, and ever coffee drinking/cigarette smoking, as appropriate, only the association of coffee intake and blepharospasm survived. The strength of the relationship between blepharospasm and coffee intake increased with the average number of cups of coffee per day, and there was a significant correlation between age at blepharospasm onset and number of cups per day. This finding is similar to what has been found in Parkinson disease[42] and remains unexplained.

Patients who develop blepharospasm may experience spread of the dystonia to other body parts. One study followed 602 patients with primary dystonias.[43] Patients with blepharospasm were more likely to spread (31% past the head) than those with cervical dystonia (9%), laryngeal dystonia (12%), or upper extremity dystonia (16%). Most spread occurred in the first 1 to 2 years after onset of blepharospasm, whereas the risk of spread was relatively constant over time in the other dystonias. In another study, 124 patients presenting with blepharospasm, 73 patients with cervical dystonia, and 24 patients with focal

hand dystonia, all with 10 years or more of symptom duration, were compared.[44] Age at dystonia onset, age at initial spread, and the risk of initial spread were higher and the time from onset to initial spread was shorter for the patients with blepharospasm. This greater risk of spread in blepharospasm was mainly evident in the first 5 years of the disorder. Similar findings were seen in a group of 132 patients followed for a mean of 7.5 years.[45]

GENETICS A recent study re-evaluated the genetic influence in blepharospasm based on the examination of the first-degree relatives of 56 probands.[46] The 56 families included 436 first-degree relatives of whom 296 were alive and 233 were examined. The proportion of probands with at least one first-degree relative affected by some form of focal dystonia was 27%. Importantly, there was considerable phenotypic variability of dystonia within families. Assuming autosomal dominant transmission, penetrance was about 20%. It seems clear that all the focal dystonias are related to each other.[16]

Since polymorphisms of the genes encoding TorsinA (DYT1) and the D5 dopamine receptor (DRD5) have been associated with lifetime risk for focal dystonia, these genes were investigated in two independent cohorts of Italian and North American patients with blepharospasm.[47] While no association was identified, analysis of the Italian group separately revealed an association with the same risk genotype in DYT1 as previously described in an Icelandic population.

TREATMENT Although there is paucity of well-designed, double-blind, controlled studies, BoNT injections into the eyelids and eyebrows are now generally considered as the treatment of choice.[48] Patients who fail to obtain satisfactory control of their blepharospasm with BoNT may be candidates for surgical treatment. Myectomy should be a consideration. Deep brain stimulation (DBS) has been found to be effective in the treatment of generalized dystonia and cervical dystonia. Recently, it was used to treat patients with disabling cranial dystonia, including blepharospasm, who have become refractory to other forms of therapy. Two early reports of pallidal DBS in patients with cranial dystonia showed a mild positive effect.[49,50] A more successful case was a 47-year-old patient with a 5-year history of progressively severe, bilateral craniofacial dystonia, refractory to medications and to BoNT injections.[51] DBS was done in the right posteroventral GPi for 6 months with about 40% improvement, and then left GPi DBS was added with improvement advancing to about 75%. Recently, six patients with cranial-cervical dystonia underwent bilateral GPi DBS.[52] At 6 months, patients showed a 72% mean improvement in the Burke-Fahn-Marsden dystonia rating scale (BFMDRS) total movement score. There was also a trend to improvement in the mean BFMDRS disability score. It is important to note that despite improvement in cranial-cervical dystonia, there was mild worsening of motor function in previously non-dystonic body regions in four patients. Very few patients have been studied so far, but given the clear utility of DBS for dystonia, further studies for blepharospasm will certainly be undertaken.

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APPENDIX

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