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Blepharospasm 40 Years Later

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Abstract

Forty years ago, C.D. Marsden proposed that blepharospasm should be considered a form of adult-onset focal dystonia. In the present paper, we provide a comprehensive overview of the findings regarding blepharospasm reported in the past 40 years. Although prolonged spasms of the orbicularis oculi muscles remain the clinical hallmark of blepharospasm, patients with blepharospasm may be characterized by various types of involuntary activation of periocular muscles. In addition to motor features, blepharospasm patients may also have nonmotor manifestations, including psychiatric, mild cognitive, and sensory disturbances. The various motor and nonmotor symptoms are not present in all patients, suggesting that blepharospasm is phenomenologically a heterogeneous condition. This emphasizes the need for tools for severity assessment that take into account both motor and nonmotor manifestations. The cause of blepharospasm remains elusive, but several lines of evidence indicate that blepharospasm is a multifactorial condition in which one, or several, as yet unknown genes together with epigenetic and environmental factors combine to reach the threshold of the disease. Although blepharospasm was originally believed to be solely a basal ganglia disorder, neurophysiological and neuroimaging evidence point to anatomical and functional involvement of several brain regions. The contribution of multiple areas has led to the hypothesis that blepharospasm should be considered as a network disorder, and this might reflect the varying occurrence of motor and nonmotor manifestations in blepharospasm patients. Despite advances in the aetiology and pathophysiology, treatment remains symptomatic.

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Blepharospasm is a movement disorder characterized by hyperactivity of the orbicularis oculi and of other muscles around the eyes. Although blepharospasm had been described in the later 19th century,[1] 40 years ago, C. D. Marsden[2] suggested that blepharospasm should be considered a focal form of dystonia together with other conditions such as oromandibular dystonia, cervical dystonia, and writer's cramp. Marsden also described a number of clinical characteristics, including female preference, peak age at onset between the 5th and 7th decade, a tendency to spread to adjacent body parts, and a possible association with tremor in the head or upper limbs. From a pathophysiological point of view, he also suggested that the basal ganglia play an important role in blepharospasm.

Including blepharospasm in the larger family of focal dystonias has helped us in understanding of the condition. In this paper, we provide a comprehensive overview of the new findings regarding blepharospasm in the past 40 years and highlight what gaps remain in our knowledge of this condition.

Demographic Data

The reported prevalence of blepharospasm ranges between 20 and 133 cases per million depending on the geographic area.[3] Blepharospasm is generally considered to be more frequent than laryngeal or focal hand dystonia, whereas international prevalence trends for blepharospasm and cervical dystonia appear to be discordant: cervical dystonia is reported to be more frequent than blepharospasm in the United States and northern Europe, but less frequent in Italy and Japan. Studies are concordant, indicating a preponderance of women in blepharospasm and a peak age at onset in the 6th decade.[4] Menopause might be a factor predisposing to blepharospasm in older women.[5]

Clinical Phenomenology

Motor Manifestations

Blepharospasm is not only characterized by involuntary spasms of the orbicularis oculi muscle but also by other motor manifestations, including "apraxia of eyelid opening" and an increased blink rate.

Orbicularis Oculi Spasms—As Marsden first highlighted,[2] blepharospasm is characterized by stereotyped, bilateral, and synchronous spasms of the orbicularis oculi (OO) muscles. Spasms may be brief or sustained and may induce narrowing or closure of the eyelids.[6] Tasks requiring attention usually reduce the duration and frequency of eyelid spasms. It is not known whether the different types of spasms become manifest sequentially during the course of the disease or aggregate in separate clusters that identify subpopulations of patients.

Apraxia of Eyelid Opening—Many patients with blepharospasm may have “apraxia of eyelid opening” (AEO)[7] characterized by transient failure to voluntarily reopen the eyes without an apparent spasm of the OO muscle and despite sustained frontalis muscle contraction. AEO results from an involuntary contraction of the pretarsal portion of the OO muscle that antagonizes eyelid reopening.[8] The beneficial effect of pretarsal injections of botulinum toxin on AEO in patients with blepharospasm as well as in some patients with isolated AEO strongly suggests that these patients actually have pretarsal blepharospasm.[9] When AEO occurs in isolation, it can also be a result of levator contraction failure.[10] AEO has been reported after deep brain stimulation (DBS) of the subthalamic nucleus (STN) in Parkinson disease (PD), but only rarely after DBS of the internal segment of the globus pallidus (GPi) in dystonic patients. AEO in PD likely arises as a result of changes in dopaminergic therapy after STN DBS more than as a direct consequence of DBS.[11] Nigro-striatal contribution to premotor control of eyelid coordination may also play a prominent role in the pathophysiology of AEO.[12] STN DBS may have detrimental effects on voluntary blinking thus contributing to AEO.[13] Evidence on AEO induced by GPi DBS in dystonic patients is limited to case reports.[14] In the case reported by Vagefi and colleagues,[14] the authors suggested that DBS stimulation of the GPi could have inhibited input from the prefrontal motor cortex to the basal ganglia, preventing activation of the levator palpebrae superioris and resulting in AEO or aggravation of a previously unrecognized AEO.

Increased Blinking—Bentivoglio and colleagues[15] demonstrated that the blink rate at rest and during conversation was higher in patients with blepharospasm than in healthy controls. The finding of an increased blink rate at rest was confirmed by Conte and colleagues.[16] Increased blinking may precede the appearance of OO spasms, thus representing a forme fruste of blepharospasm. However, prospective studies on patients with increased blinking alone are lacking.

Dystonia in Other Body Sites—Dystonia in patients with blepharospasm may display a greater tendency to spread to adjacent body parts (most frequently oromandibular and cervical regions) than in patients with other focal dystonias.[17,18] A retrospective analysis established that dystonia usually spreads within the first 5 years from symptom onset in approximately two thirds of patients with blepharospasm.[17,18] A genetic polymorphism of the *DYT1* gene, which is the gene known to predispose to some forms of early-onset generalized dystonia, was found to be related to the spread of dystonia in 2 controlled series of patients with blepharospasm, 1 from Italy and the other from the United States.[19] Age may be another factor that modulates the spread of dystonia. Indeed, the majority of spreading events in patients with blepharospasm and cervical dystonia have recently been reported to occur after the age of 50, regardless of the site of dystonia presentation and the age of dystonia onset.[20] Aging modulates basic mechanisms that appear to be dysfunctional in dystonia,[21,22] such as intracortical inhibitory pathways and cortical body maps in the primary sensory-motor cortices.[23–25] Healthy elderly persons display enlarged hand representations in the primary somatosensory cortex, possibly related to an age-related reduction in intracortical inhibition.[25] Age-related mechanisms implying cortical map reorganization and reduction in intracortical inhibition—that seem to be also dysfunctional in dystonia—make patients with blepharospasm “vulnerable” to spreading.

Nonmotor Manifestations

Sensory Symptoms—*S*ensory symptoms reported by patients with blepharospasm include a burning sensation and grittiness in the eye, dry eye, and photophobia. Across different series, 22% to 57% of patients complained of sensory symptoms.[20,26–30] Eye symptoms usually develop months or years before the onset of blepharospasm and are resistant to local therapy. Patients without ocular symptoms upon presentation rarely develop them subsequently.

Eye symptoms may belong to the clinical spectrum of blepharospasm or may result from eye diseases. The similar frequency of eye symptoms observed in the relatives of patients with focal dystonia and in healthy individuals suggests a common origin of eye symptoms in both groups.[29] Because chronic eye symptoms in healthy individuals are believed to be an expression of chronic diseases of the anterior segment of the eye, the same explanation may apply to the relatives of patients with focal dystonia.[31] Dry eye is a particularly common symptom, but objective measurements of tear production are often normal. There may be some abnormalities of the tear film itself or in the perception of dryness; clearly more work is needed in this area.

Ophthalmological disorders may trigger idiopathic blepharospasm in a substantial proportion of predisposed patients. This might be a result of increased reflex blinking to the sensory symptoms by analogy to task-specific hand dystonia because of repetitive performance of a specific task.

Patients with blepharospasm are considerably more sensitive to light than controls and as sensitive to light as patients with migraine.[32] The symptoms of photophobia in patients with blepharospasm may be reduced significantly by means of photochromatic modulation. FL-41 lenses, which block blue light, provide both subjective and objective benefits.[33] Photophobia in patients with blepharospasm may be associated with abnormal hyperactivity in the thalamus.[34]

A peculiar sensory-motor manifestation is the so-called sensory trick[35,36] that occurs in up to 70% of patients with blepharospasm.[37] Examples of alleviating maneuvres include a light touch to certain areas of the face or pulling on the upper eyelid or an eyebrow, wearing tinted lenses, talking, singing, or chewing/eating that enables a patient with blepharospasm to keep the eyes open.[37] Neurophysiological and functional imaging studies have shown that a light touch in a specific area of the body can reduce activation of the supplementary motor area and primary sensorimotor cortex in association with the attenuation of muscle activity.[38,39] The light touch reduced the blink reflex, and this was associated with the normal prepulse inhibition of trigeminofacial circuits.[40,41] Patients without a sensory trick had diminished prepulse inhibition. Sensory tricks might therefore decrease abnormal cortical facilitation.

Psychiatric Disturbances—Our review identified 6 controlled studies that dealt with psychiatric abnormalities in blepharospasm. These studies were heterogeneous with regard to the design, number of patients and controls examined, and the methodology adopted for the psychiatric assessment (Table 1).

The 3 controlled studies that evaluated depressive symptoms included 1 study that yielded a higher risk of lifetime depression in patients with blepharospasm than in disease-affected and healthy controls.[42] In contrast, 2 smaller studies failed to detect any risk for depressive symptoms.[43,44] Of the 6 controlled studies, 3 detected a higher risk of obsessive/compulsive symptoms in patients with blepharospasm than in disease-affected and healthy controls[43,45,46] using different psychiatric tools (Table 1). Yet another study on 76 patients with mixed types of isolated focal dystonia (including 50 patients with blepharospasm) was not considered in our analysis because data could not be extracted for patients with blepharospasm alone.[47] Last, no controlled studies detected a higher risk of anxiety symptoms in blepharospasm (Table 1).

In conclusion, depression and obsessive/compulsive symptoms probably represent a feature inherent to blepharospasm, whereas the relationship with anxiety is less certain and warrants further evaluation.

Sleep Abnormalities—Earlier polysomnographic observations in patients with cranial dystonia indicated that abnormal dystonic movements are still present during sleep, even though their frequency and duration may be markedly reduced.[48,49]

At least 50% of patients with cranial dystonia have impaired sleep quality compared with no more than 20% of controls.[50,51] In contrast, excessive daytime sleepiness seems to be uncommon in blepharospasm. Because sleep impairment appears to be independent of dystonia severity but correlates with depression, it is not yet clear whether a primary sleep abnormality is present in blepharospasm.

Cognitive Dysfunction—One study that tested executive functions using the frontal assessment battery in 22 patients with blepharospasm compared to 29 with hemifacial spasm did not detect any difference between the 2 groups.[52] A widespread cognitive assessment was performed by Alemán and colleagues[53] and Romano and colleagues.[54] Both studies pointed to an impairment in several specific cognitive domains that was not consistent with overt dementia but with multidomain mild cognitive impairment. Altered cognitive measures did not correlate with either the severity of motor impairment or with disease duration, thereby raising the possibility that altered cognitive functions are part of the clinical spectrum of idiopathic blepharospasm. A longitudinal study is needed to clarify the true incidence of cognitive impairment and to ascertain whether it is associated with an increased risk of dementia.

Clinical Evaluation Tools

Diagnosis

The diagnosis of blepharospasm is based on clinical grounds and is, therefore, open to disagreements. The most important causes of misdiagnosis are probably the phenomenological variability of blepharospasm upon presentation and the existence of a number of neurological and non-neurological conditions that mimic blepharospasm. A sensitive and specific diagnostic guideline founded on objective criteria has recently been developed.[55] The starting step is the recognition of “stereotyped, bilateral and synchronous

orbicularis oculi spasms." The next step is the identification of a "sensory trick" or "increased blinking." The algorithm yielded 93% sensitivity and 90% specificity in distinguishing blepharospasm from other conditions of involuntary lid closure, such as eyelid tics, hemifacial spasm, facial chorea, pure apraxia of eyelid opening, frequent blinking, or lid ptosis because of myasthenia. It is worth noting that there have been a small number of case reports of true blepharospasm associated with myasthenia.[56,57] Myasthenic oculomotor muscle fatigue may be corrected by increased synkinetic eye blinking, which might eventually lead to development of blepharospasm.

Severity Assessment

Historically, the most widely used severity scale is the Jankovic Rating Scale, which includes 2 subscales (both based on a 5-point grading system) that measure the intensity and frequency of eyelid spasms.[58] Although the Jankovic Rating Scale displays excellent internal consistency, data on its reliability and other clinimetric properties are not available.[58,59]

Most of the motor manifestations that characterize blepharospasm have been included in a more recent severity scale.[60] In this scale, the degree, duration, and frequency of eyelid closure caused by spasms are considered the core clinical hallmarks of blepharospasm severity, whereas AEO, the occurrence of spasms during writing, and increased blinking are considered as factors that can be used to grade severity. The scale yielded moderate to almost perfect reliability and acceptable clinimetric properties.

Other less-specific severity scales are the Burke-Fahn-Marsden Rating Scale, the Unified Dystonia Rating Scale, and the Global Dystonia Severity Rating Scale, all of which comprehensively measure not only the severity of blepharospasm but also that of dystonia in all body parts.[59] Severity grading in these scales is based on the intensity of dystonic contractions merged with (as in the Burke-Fahn-Marsden Rating Scale) or weighted by (as in the Unified Dystonia Rating Scale) the duration and daily frequency of the spasms. These scales all have excellent internal consistency, but their inter-rater agreement is not optimal for dystonia affecting the upper/lower face.

All of the existing scales may be subject to criticism to varying extents. Most important, all share a lack of attention to nonmotor manifestations. Given the influence that nonmotor symptoms are reported to exert on disability and quality of life, this is a gap that needs to be filled.

Etiology

Primary Blepharospasm

Although predominantly a sporadic disorder, up to 25% of patients with blepharospasm have 1 or more family members affected by dystonia.[61,62] An inheritance pattern compatible with an autosomal dominant trait and reduced penetrance has been detected in a few large families.[63] More often, however, no more than 1 affected first-degree relative has been found, and inheritance does not always appear to be Mendelian. Regardless of the number of relatives affected, proband–relative pairs may be phenotypically heterogeneous.[4] Recently

reported genetic mutations in guanine nucleotide binding protein (*GNAL*),[64] anoctamine 3 (*ANO3*),[65] tubulin beta4A (*TUBB4a*),[66] interacting zinc finger protein 1 (*CIZ1*)[67] occur in relatively few families and account for less than 2% of the genetic causes of adult-onset dystonia. None of these genes has been associated with pure blepharospasm, which could argue that a different group of genes may be chiefly responsible for blepharospasm.

Environmental factors may exert either protective or deleterious effects. Three case-control studies designed to compare patients with blepharospasm with patients with hemifacial spasm, healthy controls, or unaffected siblings found a significant association between blepharospasm and diseases of the anterior segment of the eye.[5,19,29] The association between blepharospasm and dry eye was further supported by a Japanese study that reported an 8.1% frequency of blepharospasm among participants suffering from dry eye.[68] Two case-control studies failed to find a relationship between blepharospasm and preceding head trauma.[19,69] Studies that investigated smoking and coffee drinking as putative protective environmental agents for blepharospasm yielded contrasting results. A study conducted on a cohort of mixed phenotypes of adult-onset idiopathic focal dystonia detected a significant inverse relationship between current smoking and patient status in the multivariate analysis.[19] However, when analyzed according to phenotype, the association did not hold true in the blepharospasm group. Smoking habits were investigated together with coffee drinking in 2 subsequent case-control studies.[61,70] The multivariate analysis in both studies showed an inverse (possibly protective) association between prior coffee consumption and blepharospasm, whereas the potential association between smoking and blepharospasm was, at least in part, confounded by coffee.

Secondary Blepharospasm

Secondary blepharospasm is much less common than idiopathic blepharospasm. Nevertheless, secondary cases may be important in providing clues as to the origin of the condition. Blepharospasm may follow focal lesions in multiple brain regions, including the thalamus, basal ganglia, lower brain stem, cerebellum, midbrain, and cortex,[71] or may develop in patients with PD[72] or tardive dyskinesia.[73] Finally, secondary blepharospasm may arise from conditions associated with lid weakness, such as facial palsy and myasthenia.[56,74]

Observations from secondary blepharospasm cases fit well with a 2-factor rodent model of blepharospasm that combines a small subclinical loss of striatal dopamine that reduces the tonic inhibition of trigeminal reflex blink circuits and a slight weakening of the lid-closing orbicularis oculi muscle leading to an adaptive increase in the drive on trigeminal sensory-motor blink circuits.[75] Neither individually causes spasms of lid closure, but together they induce bilateral forceful blinking and spasms of lid closure. The presence of blepharospasm in patients with PD and tardive dyskinesia may suggest a possible role of dopamine in the pathophysiological mechanisms of blepharospasm.

Pathophysiology

Neurophysiological Studies

Berardelli and colleagues[76] showed that inhibition of the R2 response evoked by electrical stimulation of the supraorbital nerve is decreased in patients with blepharospasm. This finding suggested that the interneurons that mediate the R2 response of the blink reflex in the brain stem are abnormal in blepharospasm (Table 2, Fig. 1).[6,16,77–79] As botulinum toxin treatment leaves the blink reflex recovery cycle unchanged but significantly improves OO muscle spasms,[79,80] the blink reflex abnormalities in patients with blepharospasm are likely to reflect a pathophysiological mechanism and not to be a consequence of dystonic activity in the OO muscle. The final conclusion shared by the authors of the various studies was that the facilitation of the blink reflex is a result of failure in inhibitory processes.

Plasticity in the blink reflex circuit is also abnormal in blepharospasm,[81] but a subsequent study challenged the possibility of inducing plasticity mechanisms in the trigeminal circuitry in healthy controls or in patients with blepharospasm.[82] Several studies have also shown that the enhanced excitability of interneurons in the brain stem extends outside the trigeminofacial circuitry to include an abnormal auditory startle reaction and an abnormal trigeminosternocleidomastoid reflex.[83,84] Patients with oromandibular dystonia, such as those with blepharospasm, have an enhanced blink reflex recovery cycle.[76,77]

Recordings of the EMG pattern of the OO and levator palpebrae muscles helped to classify patients with blepharospasm into 3 subclasses.[10] Patients with blepharospasm alone could have an abnormal R2 recovery index, whereas 75% of patients with blepharospasm with either involuntary levator palpebrae inhibition or disturbed reciprocal innervation, as well as all patients with involuntary levator palpebrae inhibition but no blepharospasm, had a normal R2 recovery index (Fig. 1). On the basis on these findings, the authors suggested that cranial dystonias are not pathophysiologically homogeneous. Consistent with this hypothesis, a recent study showed that the R2 recovery cycle, as tested by means of the blink reflex recovery curve, was normal in patients who were characterized by increased blinking although not by OO muscle spasms.[16] Thus abnormal blink reflex recovery cycle parallels the presence of OO muscle spasms.

Transcranial magnetic stimulation (TMS) has shown that excitability of the primary motor cortex activity is abnormal in blepharospasm, as demonstrated by reduced short-interval intracortical inhibition in the hand muscles and by the reduced duration of the cortical silent period in the cranial muscles of such patients.[85,86] Using paired associative stimulation (PAS), a technique that investigates cortical area plasticity, Quartarone and colleagues[87] observed that the plasticity of cortical motor areas is increased in the hand muscles of patients with blepharospasm. It is important, however, to mention that PAS abnormalities in focal dystonias including blepharospasm are variable.[88] The enhanced plasticity induced by PAS therefore cannot yet be considered a dystonic fingerprint.

Patients with different forms of focal dystonia, including blepharospasm, exhibit an increased somatosensory temporal discrimination threshold (STDT).[16,89–91] Increased STDT values are present in body parts that may be affected or unaffected by dystonia, do not

improve after botulinum toxin,[92] and do not correlate with severity scale scores. A recent study on patients with increased blinking and blepharospasm showed that STDT values are abnormal in both groups of patients,[16] thus suggesting that abnormal sensory abnormalities are shared both by patients who have increased blinking alone and by patients with blepharospasm. If increased blinking alone is considered a mild or early form of blepharospasm, then STDT is more sensitive than blink reflex recovery for identifying underlying pathophysiology.

Neuroimaging Studies

In 1 series of patients with blepharospasm, only a limited number had focal lesions visible by conventional imaging.[71]

Voxel-based morphometry (VBM) studies performed in patients with blepharospasm to investigate gray matter abnormalities failed to provide a common pattern of changes (Table 3).[93–98] Only 1 study reported gray matter volume changes in the basal ganglia alone.[93] The other studies detected gray matter volume changes in the basal ganglia as well in several cortical/subcortical areas[94,95] or in cortical regions alone.[96–98] Discrepancies across studies might be a result of a number of factors involved in data analysis or to differences in the treatment regimens or in the number of participants. In this regard, Table 3 clearly shows that an increase in the number of patients studied resulted in the detection of an increasing number of gray matter changes. It is yet unclear whether the imaging findings observed are primary or secondary. The lack of any correlation between severity/duration of blepharospasm and abnormal VBM imaging findings in some areas, such as the putamen, the premotor cortex, somatosensory integration areas, cingulate/paracingulate, and cerebellum, seem to suggest that the imaging abnormalities detected in these areas are probably not secondary manifestations.

The only blood flow positron emission tomography study performed to date on patients with blepharospasm revealed an abnormal activation pattern in the supplementary motor cortex, which probably reflected abnormal sensory processing during the execution of a vibrotactile stimulation task.[99]

Functional magnetic resonance imaging using blood oxygen level-dependent contrast detected regional changes in the oxygenation level of the blood in the putamen in one study based on a blink task,[100] and in the primary sensory cortex and supplementary motor cortex in another study based on whistling.[101]

Diffusion tensor imaging is a form of diffusion-weighted imaging that measures two indices, fractional anisotropy and mean diffusivity. No diffusion tensor imaging changes were observed in 3 studies in which 5 to 16 patients with blepharospasm were compared with healthy controls.[98,102,103] However, a more recent study based on 31 patients with blepharospasm revealed fractional anisotropy reductions in the white matter of the left anterior lobe of the cerebellum and in the right precuneus of the parietal lobe (abnormalities that significantly correlated with disease severity and duration) as well as increases in mean diffusivity in the right lentiform nucleus, thalamus, and insula.[104]

Management of Blepharospasm

Botulinum neurotoxin type A is considered the first-line drug in the treatment of blepharospasm.[105] Side effects such as transient ptosis, blurring of vision, or diplopia are relatively uncommon and usually improve spontaneously in a few weeks; long-term efficacy of botulinum neurotoxin type A treatment in blepharospasm has also been documented.[106,107] Despite apparently very good motor responses, however, several patients did not show satisfaction and consistent changes in quality of life.[108,109] This implies the need for interventions on nonmotor aspects in these patients.

An improvement obtained with commonly used drugs such as the anticholinergics (eg, trihexyphenidyl), benzodiazepines (eg, clonazepam and lorazepam), baclofen, and tetrabenazine is often modest at best and side effects may be often problematic.[110–112] In addition, there was only a single-center, placebo-controlled study to reference in this regard.[112]

In recent years, DBS has been tested in localized forms of dystonia, including patients affected by blepharospasm.[113–125] No study dealt with patients with isolated blepharospasm. Most patients underwent bilateral DBS of the GPi, and the benefits associated with DBS for dystonia often develop gradually over several months. On follow-up (ranging from 6–84 months), all patients showed substantial improvement in the severity of dystonia. Adverse events included local infections, AEO, and perioral tightness.

So far, only 1 study has assessed the effects of TMS and transcranial direct current stimulation in blepharospasm, 2 neuromodulation techniques that may have behavioral consequences and therapeutic efficacy.[126] This was a pilot study in 7 patients with blepharospasm who were treated with 3 different techniques aiming at reducing cortical excitability in the following 4 areas: primary motor cortex, anterior cingulate, and secondary motor areas, such as premotor and supplementary motor cortices. Continuous theta burst stimulation and transcranial direct current stimulation provided no significant change in any of the outcome measures, whereas low-frequency repetitive TMS improved not only the subjective patient rating but also physician rating and the blink reflex recovery curve.

Conclusions

Forty years of study have confirmed and enriched Marsden’s initial observations regarding motor manifestations of blepharospasm. In particular, subsequent studies have shown that OO spasms, the clinical hallmark of blepharospasm, may be characterized by significant phenomenological variability. Spasms may be brief or sustained, may lead to complete or incomplete eyelid rim closure, may be modulated by sensory tricks, or may be associated with AEO and increased blinking. No study, however, has yet evaluated whether the development of the various motor manifestations depends on the duration of the disease or whether motor signs aggregate in such a way as to allow specific clusters of patients to be identified. Nevertheless, the appearance of sensory tricks, AEO, increased blinking, and dystonia in adjacent body sites in a limited number of patients with blepharospasm raises the possibility that subpopulations of patients with blepharospasm do exist.

Patients with blepharospasm may also have nonmotor manifestations. Depressive and obsessive compulsive disorders and mild cognitive disturbances are more frequent in blepharospasm than in healthy and/or disease-affected controls and do not appear to correlate with severity/duration of motor signs, thus suggesting that these nonmotor manifestations contribute to the spectrum of blepharospasm. Motor and nonmotor aspects contributing to blepharospasm have the potential to substantially impact quality of life.[108,109]

The contribution of psychiatric and cognitive disturbances to the clinical spectrum of blepharospasm suggests that tools that take into account both motor and nonmotor manifestations are probably needed to accurately measure the severity of blepharospasm and its impact on quality of life. In addition, the substantial impact of blepharospasm on health status emphasizes the need for interventions even on nonmotor aspects in these patients.

It is worth bearing in mind that the various nonmotor symptoms involved in blepharospasm are not present in all patients and even may be independent of disease duration. This further supports the view that blepharospasm patients may be phenomenologically heterogeneous. It is not, however, known whether motor disturbances, either alone or in combination with nonmotor signs, form clusters in clinical subtypes.

Several lines of evidence suggest that blepharospasm is a multifactorial condition in which 1 or several as yet unknown genes together with epigenetic and environmental factors combine to reach the threshold that induces the disease.

Neurophysiological studies have identified several abnormalities, including loss of inhibition at different levels of the central nervous system, abnormal sensory-motor integration, and maladaptive plasticity. The fact that these abnormalities are shared by different forms of dystonia suggests a dystonic trait, although the role of each abnormality in determining specific motor symptoms is unclear.[63] Enhanced excitability and abnormal plasticity in the motor circuitry may intuitively explain the overflow of motor activation, but evidence showing that sensory abnormalities are also present in patients with blepharospasm as well as in other forms of focal dystonia suggests that blepharospasm is not simply a motor disorder, and this is the case with all forms of dystonia.

Because altered STDT does not correlate with clinical severity, the abnormal temporal processing of sensory information is likely to enhance the permissive environment that predisposes patients to the development of motor symptoms. Neurophysiological abnormalities in blepharospasm, as well as those in other forms of dystonia, seem to lie on different levels in the pathophysiological cascade, with some playing a permissive role and others reflecting a causative role. Which neurophysiological abnormalities in blepharospasm trigger motor symptoms on a permissive pathophysiological level is still unknown. Moreover, there is evidence suggesting that blepharospasm may not be pathophysiologically homogeneous.

Although blepharospasm was originally considered a basal ganglia disorder, the accumulating neuroimaging evidence points to the anatomical and functional involvement of several brain regions. The lack of any correlation between severity/duration of

blepharospasm and abnormal VBM imaging findings in some areas, such as the putamen, the premotor cortex, somatosensory integration areas, cingulate/paracingulate, and cerebellum, seem to suggest that the imaging abnormalities detected in these areas are probably not secondary manifestations. The concept that blepharospasm is exclusively a result of a basal ganglia dysfunction is further challenged by a recent review drawing attention to the fact that secondary blepharospasm is associated with structural lesions in several regions of the nervous system, including not only the basal ganglia but also the thalamus, lower brain stem, cerebellum, midbrain, and cortex.[71] Interestingly, brain regions associated with secondary blepharospasm correspond to some of the regions highlighted by nonconventional studies in idiopathic blepharospasm.[71]

The observation that several brain areas may contribute to blepharospasm has led to blepharospasm being considered as a network disorder resulting from the dysfunction of 1 node within the network or even from aberrant communication between different nodes. The same hypothesis has been formulated for other focal dystonias. Moreover, this network model might explain the varying occurrence of nonmotor manifestations in blepharospasm. The heterogeneity of blepharospasm with regard to both the motor and nonmotor domain may reflect the involvement of different brain regions. Structures that are functionally associated with emotional processing might be associated with psychiatric disorders; the cingulate and precuneus are critical to the functioning of the visuospatial system, which is altered in patients with blepharospasm. In addition, the anterior cingulate is the primary locus of cortical input to the OO muscles, which controls eyelid closure and plays a key role in the motor control of blinking. On the basis of postmortem studies, some authors have suggested that the cerebellum may be involved in adult-onset focal dystonia.[127,128] This observation is, however, currently limited to cervical dystonia, there being no evidence as yet of cerebellar involvement in idiopathic blepharospasm. Future studies designed to investigate cerebellar function in blepharospasm may clarify whether different forms of focal dystonia share the same dysfunctional circuits. In this regard, dystonia has recently been defined as a “communication node disorder.”[129]

Some of the challenges that warrant attention in future studies include better characterizing the phenomenological heterogeneity of blepharospasm, investigating the relationships between motor and nonmotor phenotypic domains, shedding light on the physiological interactions that result in different brain regions contributing to different clusters of motor and nonmotor symptoms, and clarifying the genetic basis. The development of comprehensive severity rating tools assessing both motor and nonmotor aspects of blepharospasm would be crucial to allow significant advances in all aspects.

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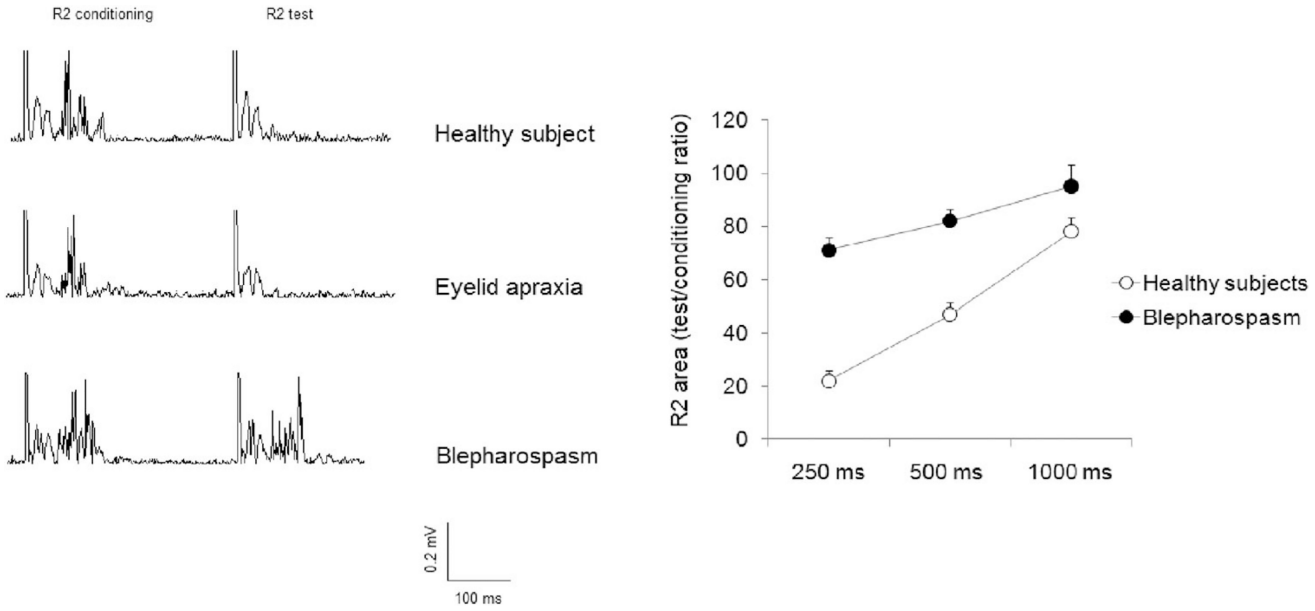

FIG. 1.

Left: electromyographic recordings of blink reflex recovery cycle at 250 milliseconds interstimulus interval in a healthy participant, a patient with eyelid apraxia, and a patient with blepharospasm. Right: blink reflex recovery cycle (250-millisecond, 500-millisecond, and 1000-millisecond interstimulus intervals) in healthy participants and patients with blepharospasm. Each point represents mean, bar represents standard error.

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TABLE 1

Controlled studies assessing psychiatric disturbances in patients with blepharospasm

Author, year, reference	Study participants (number in parentheses)	Higher risk for depressive symptoms (assessment tool)	Higher risk for anxiety symptoms (assessment tool)	Higher risk for obsessive compulsive symptoms (assessment tool)	Significant correlation between measures of BSP severity/duration and psychiatric measure
Bihari et al, 1992[45]	BSP (21) vs HC (19)	Not tested	Not tested	Yes (Maudsley OCD Questionnaire)	Not tested
Brookcs et al, 1998[43]	BSP (13) vs HFS (13)	No (SCID)	No (SCID)	Yes (Hamburg Obsession/Compulsion Inventory–Short Form)	Not tested
Munoz et al, 2005[130]	BSP (30) vs HFS (30)	Not tested	Not tested	No	Not tested
Fabbrini et al, 2010[42]	BSP (28) vs HFS (26) vs HC (23)	Yes (SCID)	No (SCID)	No (SCID)	No
Fontenelle et al, 2011[44]	BSP (22) vs HFS (31)	No (Beck Depression Inventory)	No (Beck Anxiety Inventory)	No (Obsessive/Compulsive Inventory Revised)	No
Barahona-Corrêa et al, 2011[46]	BSP (15) vs CD (46) vs HC (30)	Not tested	Not tested	Yes (Yale-Brown Obsessive/Compulsive Scale)	No

BSP, blepharospasm; HC, healthy controls; HFS, hemifacial spasm; CD, cervical dystonia; SCID, structured clinical interview for DSM.

TABLE 2

Neurophysiological abnormalities in patients with blepharospasm

Author, year, reference	Function	Findings	Correlation with disease severity
Berardelli et al, 1985[76]	Blink reflex recovery cycle	Enhanced	Not investigated
Tolosa et al, 1988[77]	Blink reflex recovery cycle	Enhanced	Not investigated
Valls-Solè et al, 1991[80]	Blink reflex recovery cycle	Enhanced	Not investigated
Conte et al, 2010[79]	Blink reflex recovery cycle	Enhanced	No correlation
Schwingenschuh et al, 2011[78]	Blink reflex recovery cycle	Enhanced	Not investigated
Conte et al, 2013[16]	Blink reflex recovery cycle	Enhanced in patients with OO spasms, normal in patients with increased blinking but no spasms	Not investigated
Quartarone et al, 2006[81]	Trigeminal circuits LTP-like plasticity	Enhanced	Not investigated
Zeuner et al, 2010[82]	Trigeminal circuits LTP-like plasticity	Responses similar to healthy participants	Not investigated
Müller et al, 2007[83]	Auditory startle reaction	Enhanced	Not investigated
Carella et al, 1994[84]	Exteroceptive suppression of the contracting sternocleidomastoid muscle	Enhanced	Not investigated
Sommer et al, 2002[85]	Intracortical inhibition with paired pulse TMS	Reduced	Not investigated
Currà et al, 2000[86]	Cortical silent period with TMS	Reduced duration	Not investigated
Quartarone et al, 2008[87]	Cortical silent period with TMS	Reduced duration	Not investigated
Quartarone et al, 2008[87]	Paired associative plasticity	Enhanced	Not investigated
Molloy et al, 2003[89]	Spatial discrimination threshold	Increased	No correlation
Fiorio et al, 2008[90]	Temporal discrimination threshold	Increased	No correlation
Scontrini et al, 2009[91]	Temporal discrimination threshold	Increased	No correlation
Conte et al, 2013[16]	Temporal discrimination threshold	Increased in patients with OO spasms and in patients with increased blinking but no spasms	No correlation

OO, orbicularis oculi; LTP, long-term potentiation; TMS, transcranial magnetic stimulation.

TABLE 3

Comparison of methodologies and results of previous voxel-based morphometry studies on blepharospasm

Author, year, reference	MRI	No. of patients/ healthy controls	Increased GMV	Decreased GMV	Correlation with disease severity and duration
Black et al, 1998[93]	1.5 T	5/	Putamen		No data
Etgen et al, 2006[94]	1.5 T	16/16	Putamen	L inferior parietal lobule	No relationships of any area with duration
Oberman et al, 2007[95]	1.5 T	11/11	Caudate, cerebellum	Putamen, thalamus	No data
Martino et al, 2011[96]	3 T	25/24	Middle frontal gyrus	L superior temporal gyrus, post central gyrus	No relationships of any area with duration; inverse correlation between R middle frontal gyrus and severity
Suzuki et al, 2011[97]	1.5 T	32/48	L cingulate, bilateral sensory-motor cortex		No data
Horovitz et al, 2012[98]	3 T	14/14	R postcentral gyrus, bilateral precuneus, L middle temporal gyrus	L primary motor cortex, R orbitofrontal cortex, L inferior frontal gyrus, R anterior cingulate, R occipital cortex	No relationships of any area with severity; inverse correlation between R occipital cortex and disease duration

R, right; L, left; GMV, gray matter volume.

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