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Primary Blepharospasm
Diagnosis and Management

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Contents

Abstract

Primary blepharospasm is an adult-onset focal dystonia characterised by involuntary contractions of the orbicularis oculi muscles. Patients may have various types of movements arising from the different parts of the orbicularis oculi muscle. These include typical blepharospasm associated with Charcot's sign, pretarsal blepharospasm and flickering of the eyelids. Primary blepharospasm may be associated with so-called apraxia of eyelid opening as well as dystonia in the lower face, jaw or cervical muscles. Unless there are clinical clues to a symptomatic cause, adults presenting with blepharospasm do not require extensive aetiological investigation because the condition is rarely due to an identifiable condition. As the aetiology of primary blepharospasm is largely unknown, therapeutic approaches are symptomatic, with type A botulinum toxin being the treatment of choice.

Blepharospasm refers to excessive involuntary closure of the eyelids as a result of spasms of the orbicularis oculi muscles. It may occur in a variety of CNS diseases or secondarily to ocular disorders.[1-4] However, the most common form of blepharospasm, primary blepharospasm, is an adult-onset focal dystonia that usually starts between the fifth and the seventh decade, with women being more likely to be affected than men.[1-3] The cause of primary blepharospasm is largely unknown, but a role for both genetic and environmental factors is suspected.[5,6]

The crude prevalence of primary blepharospasm has been determined as 12 per million population in Japan, 17 per million in Rochester, MN, USA, 30 per million in Northern England, 36 per million in the Epidemiological Study on Dystonia in Europe and 133 per million in a region in Southern Italy.[7] Evidence from a recent study on primary adult-onset dystonia performed in Northern Italy suggests that the prevalence of blepharospasm may be >3000 per million in those aged over 50 years.[8] It is unclear whether these geographic differences in prevalence are real or reflect data acquisition bias and differences in physician education on blepharospasm.[7]

There are observations, in fact, suggesting that blepharospasm, as well as other focal dystonias, may be frequently misdiagnosed even in neurological settings.[9]

This article reviews the pathophysiology, clinical course, differential diagnosis and treatment of primary blepharospasm in order to provide a clinically oriented guide to the management of this often disabling movement disorder.

1. Pathophysiology

Primary blepharospasm may start unilaterally but, usually, contractions become bilateral and synchronous within a few months.[2,3] In examining patients, various types of involuntary movements can be observed, arising from different parts of the orbicularis oculi muscle and involving, to a variable degree, the levator palpebrae superior (LPS) muscles.[10]

The orbicularis oculi muscle consists of three basic and functionally distinct portions: orbital, preseptal and pretarsal.[11] The orbital and preseptal motor units are mainly involved in spontaneous or voluntary sustained unilateral or bilateral narrowing or closure of the eyelids; hence, their contraction results in Charcot's sign, the clinically visible lowering of the brows beneath the superior orbital rim. The pretarsal fibres are mainly responsible for spontaneous, voluntary or reflex blinking. Involuntary contractions of the orbital/preseptal muscle fibres induce prolonged forceful spasm of eyelid closure or persistent narrowing of the palpebral fissure without complete eyelid closure, both associated with Charcot's sign.[10] This is the typical blepharospasm, as shown in figure 1a. Involuntary contractions restricted to the pretarsal portion induce episodes of involuntary eyelid closure with no Charcot's sign (pretarsal blepharospasm).[12] Brief clonic repetitive movements of upper eyelids on both sides without Charcot's sign (flickering of the eyelids) are the consequence of alternating dystonic discharges in the pretarsal orbicularis oculi and the LPS muscles.[10,13]

Some patients, once their eyes close because of tonic or clonic spasm, have difficulty in reopening their eyes even though there is no concomitant overt spasm of the orbicularis oculi (figure 1b). The clinical appearance in these cases is similar to the so-called apraxia of eyelid opening (AEO),[14] with the delay in eyelid reopening being due to pretarsal motor persistence or transient involuntary LPS inhibition.[13]

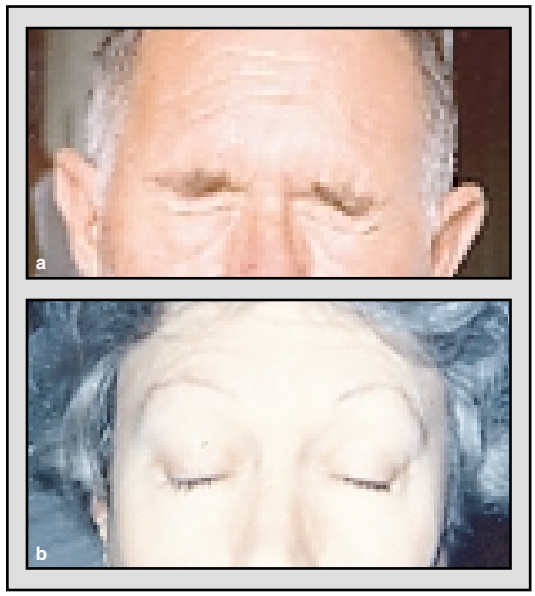

Fig. 1. Clinical appearance of (**a**) typical blepharospasm, and (**b**) so-called apraxia of eyelid opening.

Primary blepharospasm occurs spontaneously, but can be aggravated by bright light, irritants to the eye (smoke, wind), stress, looking upward/downward, walking, reading or watching television. Performing tasks requiring concentration may reduce blepharospasm, whereas relaxation tends to worsen contractions.[2,3,15] The spasms are thought to disappear during sleep, but a polysomnographic study documented their persistence during sleep in at least in some patients, although the frequency was reduced.[16] At times, the spasms disappear for a few hours or days for no obvious reasons.

During clinical examination, manoeuvres that can be helpful in triggering the spasms in otherwise asymptomatic patients include: opening/closing eyes (firmly or gently) several times at a rate of one repetition per second; looking upward/downward;

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or shining a bright light in front of the patient's eyes. A highly characteristic feature is the amelioration of contractions with sensory tricks (geste antagonistique) such as touching the forehead or the eyebrow.[2,3,15] The physiology of sensory tricks is poorly known,[17] but the response seen suggests the involvement of the sensory system in the pathophysiology of this apparently pure motor disorder. Most patients have sensory symptoms at the onset and/or during the course of the blepharospasm condition, such as dryness of the eyes, grittiness, irritation or photophobia.[2,3,18] These findings have been interpreted as indicating that eye diseases trigger blepharospasm in predisposed individuals[18] or, alternatively, that these sensory symptoms are subtle signs or 'formes frustes' of blepharospasm.[5]

2. Clinical Course

Primary blepharospasm may begin with increased eyelid blinking.[2,3] As the disorder develops, sustained nonforceful contractions occur. In many patients, as the condition worsens, there are longer periods of sustained eyelid closure and even forceful orbicularis oculi contractions. Eye closure can be so severe as to make vision and activities of daily living difficult. The condition may take several years to worsen, and it will progress only partially in some patients and can plateau at any stage. Spontaneous remission occurs rarely, most often within the first 5 years.[15]

In a significant number of patients, dystonia may spread to other muscles.[19] This usually occurs during the initial 5 years after the onset of blepharospasm. There is a greater and earlier involvement of lower face and oromandibular muscles compared with cervical and limb muscles.[19,20] Older age at onset, female sex and prior head/face trauma are suspected to be risk factors for spread of dystonia.[20]

3. Differential Diagnosis

Diagnosis of blepharospasm is based on clinical grounds and can be affected by several factors, including test circumstances and the psychological status of the patient. It is, therefore, open to bias. A recent study showed that neurologists may have different attitudes with regards to recognising blepharospasm.[9]

It is not always straightforward to distinguish dystonic blepharospasm from non-dystonic conditions that can cause the eyelids to close,[21] including: (i) weakness or paralysis of the LPS muscle resulting in ptosis; and (ii) involuntary contractions of the orbicularis oculi of peripheral, ocular, muscular or central origin (table I). Electromyographic recordings from the orbicularis oculi and LPS muscles can distinguish the patterns of involuntary muscle activity corresponding to the various types of movements arising from different parts of the orbicularis oculi muscle,[13] but such expertise is not readily available in all settings.

It is beyond the scope of this article to discuss the clinical differences between dystonic blepharospasm and all causes of eyelid closure. However, so-called AEO, hemifacial spasm and dry eye are reviewed briefly.

So-called AEO[14] is a nonparalytic movement disorder frequently found in association with blepharospasm, with which it may be readily confused. It is characterised by the transient inability to raise the eyelids after voluntary closure despite marked frontalis muscle overaction and the absence of signs of ongoing orbicularis oculi contractions

Table I. Differential diagnosis of eyelid closure

Cause	Disorder
Weakness of levator palpebrae superior	Ptosis
Involuntary contractions of the orbicularis oculi arising from:	
the CNS	Dystonia (blepharospasm), tics, chorea, so-called apraxia of eyelid opening, myoclonus
the peripheral nervous system	Hemifacial spasm, facial synkinesis, facial myokymia
muscular disease	Myotonia
ocular disease	Kerato conjunctivitis

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such as Charcot's sign (figure 1b). As suggested by electromyographic studies,[13] some patients cannot reopen their eyelids because the activity of the LPS muscles is somehow inhibited (involuntary LPS inhibition); others are unable to inhibit the voluntary discharges in the pretarsal orbicularis oculi responsible for voluntary eye closure despite normal activity of the LPS (pretarsal motor persistence). Clinically, patients with involuntary LPS inhibition show episodes of drooping of the eyelids while the eyes are open because of loss of tonic activity of the LPS.[13] Patients with pretarsal motor persistence do not show drooping of the eyelids because the tonic activity of the LPS is intact and the pretarsal orbicularis oculi muscles exhibit no involuntary discharges as long as the eyelids are open.[13] In contrast, patients with pretarsal blepharospasm[12] who experience episodes of eyelid closure (without Charcot's sign) caused by involuntary discharges in the pretarsal orbicularis oculi are able to reopen their eyes with no difficulty after voluntary closure of the eyelids inbetween the spasms.

Hemifacial spasm refers to involuntary episodic tonic or clonic movements of the facial muscles innervated by the seventh cranial nerve on one side.[22] This condition is attributed to compression of the facial nerve by neurovascular anomalies, cerebellopontine angle tumours or it can develop following peripheral facial nerve palsy. Hemifacial spasm frequently begins in the eyelid and occasionally occurs bilaterally. Like blepharospasm, it is often seen in an older population and may be worse with emotional or social stress. Differentiation of blepharospasm from the rare event of bilateral hemifacial spasm may be difficult, but the contractions of the two sides of hemifacial spasm are usually not synchronous.

Dry eye[23] is commonly misdiagnosed as primary blepharospasm. This is probably because dry eye can cause increased blinking and involuntary forced closure of the eyelids. In addition, patients with primary blepharospasm may have sensory symptoms resembling dry eye at the onset and/or during the course of their illness.[18] Activation of the trigeminal-palpebral reflex is usually responsible for reflex blepharospasm of ocular origin.[4] When the cause of the symptoms is uncertain, routine dry eye treatment with artificial tears, warm compresses and ointment placed in the eyes can be used as a diagnostic test for dry eye. Absence of improvement suggests that primary blepharospasm may be causing the patient's symptoms.[23]

Having established the clinical diagnosis of dystonic blepharospasm, the next step is to determine the aetiology. The vast majority of patients have primary blepharospasm. In the biased samples of patients referred to specialised clinics, about 10% of patients have secondary blepharospasm.[2,3,24-26] Causes of secondary blepharospasm include acquired conditions (tardive dystonia following antipsychotic drug treatment, or basal ganglia or brainstem lesions of inflammatory or vascular origin) or, less frequently, inherited metabolic/neurodegenerative conditions (Wilson's disease, dopa-responsive dystonia, myoclonus-dystonia, Huntington's disease and parkinsonian conditions in which blepharospasm may be a neurological sign of either the disease or treatment with dopaminergic drugs).

In the past there was a tendency to label primary blepharospasm as a psychogenic problem. It was about a quarter of century ago that Marsden[27] definitively established its neurological nature. However, in a few patients, dystonia may be the manifestation of a hysterical conversion reaction, malingering or even Munchausen syndrome.[28]

Because blepharospasm is rarely due to an identifiable condition, patients do not require extensive aetiological investigation unless there are clinical clues (incongruous aspects of the history of the illness and/or presence of neurological signs other than those that can be attributed directly to dystonia) to a symptomatic and possibly treatable cause.[25] All patients should undergo a careful history and general physical/neurological examination, but a minimal laboratory and imaging investigation (including computed tomography and/or magnetic resonance imaging scan of the head, full blood count and serology) should be done only on presentation under the age of 50 years to substantiate the absence of any structural cause and to exclude Wilson's

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disease.[25] Psychogenic dystonia can only be diagnosed with confidence retrospectively, when appropriate psychiatric, psychotherapeutic or placebo treatment has led to complete resolution of the problem.[28]

4. Treatment

Botulinum toxin A is considered the treatment of choice for primary blepharospasm.[29,30] The therapeutic value of botulinum toxin A is attributable to its ability to cause chemodenervation and produce local paralysis when injected into a muscle. A double-blind, placebo-controlled trial[31] and numerous open-label trials support the efficacy and safety of this treatment.[32]

Botulinum toxin A treatment can be performed in an outpatient setting. A detailed knowledge of the functional anatomy of the orbicularis oculi and neighbouring muscles is needed,[11] but electromyographic guidance is generally unnecessary. Although a wide range of injection techniques has been reported, there is no standard treatment protocol for injection location and number, dilution schedule and dosage. Rather, injections must be planned to meet the need of the individual patient.

To weaken the orbital/preseptal part of the orbicularis oculi (involved in typical blepharospasm), injections should be placed in the upper eyelid above the eyebrow, medially and laterally, and in the lower eyelid laterally only.[32] To weaken the pretarsal part of the orbicularis oculi (involved in pretarsal blepharospasm and flickering of the eyelids) botulinum toxin A is injected subcutaneously into the mid upper eyelid close to the eyelash line.[33,34]

Botulinum toxin A can diffuse from the site of injection, with the size of the denervation field being largely determined by the volume and dose.[35] Thus, injection dose and volume should be adequate to weaken specific portions of the orbicularis oculi muscle, and to limit diffusion of the toxin to nearby muscles. It is important to note that the biological activity of the toxin produced in the US (Botox®[1], Allergan Inc., Irvine, CA, USA) is different from the toxin produced in the UK (Dysport®, Ipsen Ltd, Slough, UK).[36] The clinically observable activity of 1U of Botox® is roughly equivalent to approximately 2.5–3U of the Dysport® product.[36] Botox® 20U per eye and Dysport® 50U per eye are commonly used, with higher dosages being nevertheless used in some patients. Most clinicians dilute Botox® at a rate of 25 U/mL and Dysport® at 200 U/mL.

The improvement in blepharospasm induced by botulinum toxin A is difficult to express numerically. In many patients the benefit is obvious because treatment enables them to work, drive, watch television or read. To date, there is only a validated clinical scale to assess the impact of treatment on the severity of eyelid spasms and patient's activities of daily living.[37] Moderate to marked improvement of both frequency and severity of eyelid spasms is noted in over 94% of patients treated with botulinum toxin A, with an average duration of benefit of 3–4 months.[32] Of note, botulinum toxin A cannot relieve dry eye complaints.[38] Evidence of the long-term effectiveness and safety of botulinum toxin A in reducing blepharospasm has been provided.[39,40]

Causes of botulinum toxin A treatment failure include inappropriate dose or injection sites, association of blepharospasm with so-called AEO, eyelid deformities (such as disinsertion of the levator aponeurosis caused by repeated orbicularis oculi contractions) and formation of antibody to botulinum toxin A.[41-43] In patients in whom blepharospasm and so-called AEO coexist, additional botulinum toxin A administration in the pretarsal orbicularis oculi may reduce disability only if pretarsal motor persistence is responsible for the inability to raise eyelids.[33,34,41] Development of secondary resistance to botulinum toxin A is a highly improbable event during blepharospasm treatment. To date, it has been reported in only two patients,[44,45] versus approximately 5% of patients receiving botulinum toxin A for cervical dystonia.[46] In fact, risk factors for development of immune resistance to botulinum toxin A include booster injections, botulinum toxin A dosages greater than those injected in the

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orbicularis oculi muscles and young age.[42-46] Type B botulinum toxin (Myobloc™ [previously Neurobloc®], Elan Pharmaceuticals, South San Francisco, CA, USA) can be used for treating patients who develop resistance to botulinum toxin A.[47]

Local adverse effects can be caused by unwanted diffusion of botulinum toxin to nearby muscles, including the LPS muscle (ptosis), extraocular muscles (blurring of vision or diplopia) and lower face muscles (lower facial palsy), and the drug can cause excessive weakness of the orbicularis oculi muscles (tearing). Local complications occur in 15–25% of patients, but usually improve spontaneously in 2–3 weeks; interference with daily activities and social tasks occurs only in a minority of patients.[32]

The frequency of ptosis and lower face palsy actually decreases after repeated treatments. This is probably because of greater experience and improved injection technique with repeated administration.[39,40] Injection with less diluted toxin may reduce local diffusion, allowing greater safety and a more effective response.[32] Avoiding the midline levator, or injecting botulinum toxin in the pretarsal rather than preseptal/orbital orbicularis oculi, can also prevent ptosis.[48] In contrast, blurring of vision or diplopia tend to recur on reinjection, sometimes with a prolonged recovery time. It is probable that the extraocular muscles of some patients are more susceptible to chemodenervation than others, or that botulinum toxin may diffuse to extraocular muscles more readily in some patients than in others.[49]

Generalised weakness as a systemic complication of botulinum toxin is unlikely during the treatment of blepharospasm because of the low dosages used.[32]

The advent of botulinum toxin, and the demonstration of its efficacy and safety, unfortunately has not stimulated studies on the central pharmacology of blepharospasm and other focal dystonias. Thus, availability of alternative medication is limited.[50] Among clinical trials performed on primary blepharospasm from 1975 to 2003, only a few (mostly uncontrolled) studies dealt with oral medication; those studied included dopaminergic and antipsychotic drugs, anticholinergics such as trihexyphenidyl, and benzodiazepines such as clonazepam.[51-54] Overall, previous studies suggest that a minority of patients may gain some benefit from one of these oral medications, but neither reliable criteria for predicting a favourable response to a particular treatment nor evidence of long-term effectiveness have been provided. The possibility of undesirable adverse effects may further limit the use of oral medication.

Trihexyphenidyl is the only drug whose efficacy in different forms of dystonia, including blepharospasm, has been supported by a double-blind study.[55] High dosages (60–100 mg/day) are usually necessary for trihexyphenidyl to provide partial relief from dystonia.[53] Although trihexyphenidyl is generally well tolerated when the dosage is increased slowly, older patients may nevertheless experience confusion, memory difficulty and hallucinations. Clonazepam may provide additional benefits for patients with unsatisfactory response to anticholinergic drugs, but sedation may be important limiting factor.[54] Although extensively used in the past, antipsychotic drugs should no longer be administered for the treatment of blepharospasm because of the possibility of tardive dystonia.[26] Recently, nicotine nasal spray was anecdotally reported to ameliorate blepharospasm,[56] but this was not confirmed by a later study.[57]

Other therapeutic approaches include chemomyectomy with doxorubicin and surgery. Chemomyectomy with the muscle-necrotising drug doxorubicin has proven to be effective in blepharospasm but severe local skin irritation has limited its acceptance.[58] An eyebrow-eyelid muscle-stripping surgical procedure yields improvement in approximately 90% of patients, but complications include numbness of the forehead, chronic lymphoedema of the periorbital region and, less often, exposure keratitis, ptosis or eyelid retraction.[59] In addition, patients may require secondary surgical procedures to correct one or more of the complications of the original procedure. Surgical reinsertion may also be helpful in the case of disinsertion of the levator aponeurosis

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because of the repeated orbicularis oculi contractions caused by blepharospasm.

5. Conclusion

Primary blepharospasm is an often disabling, adult-onset, focal dystonia that is probably more frequent than is conventionally thought. Patients may have various involuntary movements, arising from different parts of the orbicularis oculi muscles. Diagnosis of the condition is mainly based on clinical grounds and is open to bias. Clinicians should carefully distinguish dystonic blepharospasm from several other conditions characterised by eyelid closure. Because the condition is rarely due to an identifiable condition, adults presenting with dystonic blepharospasm do not require extensive aetiological investigation unless there are clinical clues to a symptomatic cause. Because the aetiology and pathophysiology of primary blepharospasm remain poorly understood, therapeutic approaches are symptomatic, with botulinum toxin A being the treatment of choice.

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