Meige Syndrome: What’s in a Name?

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Abstract

Frequently, blepharospasm is associated with involuntary movements of the platysma, lower face and masticatory muscles. Similarly, masticatory dystonia may occur in isolation or in combination with dystonia of other cranial and cervical muscles. The non-possessive and possessive forms of Meige and Brueghel syndromes have been variably and imprecisely ascribed to various anatomical variations of cranio cervical dystonia. Herein, the origin of eponymic terms as applied to cranio cervical dystonia is reviewed as support for proposed elimination of these eponyms from clinical usage. Although the term “segmental cranio cervical dystonia” more accurately captures the combination of blepharospasm and dystonia of other head and neck muscles, delineation of cranio cervical subphenotypes is essential for etiological/genetic and treatment studies. To conclude, the clinical features, epidemiology, pathophysiology and therapeutic management of segmental cranio cervical dystonia are examined with a particular focus on “blepharospasm-plus” subphenotypes.

1. Introduction

The terms “Meige’s syndrome” and “Meige syndrome” are often used by neurologists and other clinicians to describe the combination of blepharospasm and involuntary movements of the lower facial and/or masticatory (jaw) muscles. Application of “Meige’s syndrome” and other eponyms to the various forms of dystonia is problematic for a multitude of reasons. First of all, Meige, a physician, did not suffer from the syndrome that bears his name. Along this line, the possessive form of eponyms has been discouraged by the Council of Science Editors [1] and the father of Online Mendelian Inheritance in Man®, the late Dr. Victor McKusick [2]. Second, Meige was not the first person to describe the combination of blepharospasm and dystonia of other cranial muscles [3]. Lastly, “Meige’s” or “Meige syndrome” could be confused with Meigs syndrome which is defined as the triad of a benign ovarian tumor, ascites and hydrothorax [4].

2. Historical Perspective

Dr. Horatio Wood, a Philadelphia neurologist, first drew attention to blepharospasm and other cranial dystonias in 1887 [3]. Wood briefly mentioned facial and oromandibular dystonia in his textbook on disorders of the nervous system [3]. He stated, “The contraction is tonic, causing a complete closure of the eye, and consequent blindness. This is accompanied by

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innumerable bizarre grimaces, due to the efforts of the antagonistic muscles to overcome the force which is closing the lids.” Clearly, his second sentence was incorrect.

In 1910, Henri Meige, a French neurologist, described approximately ten patients with involuntary closure of the eyelids [5]. Blepharospasm was associated with involuntary contractions of the jaw muscles in only one of these patients. Over 60 years later, an American neurologist, George Paulson, reported three patients with blepharospasm and oromandibular dystonia and emphasized the probability of a common pathophysiological basis [6].

In 1976, David Marsden, an English neurologist based in London, called attention to a work of art, De Gaper, by Pieter Brueghel the Elder, a Flemish Northern Renaissance painter, in an article on blepharospasm and oromandibular dystonia [7]. Brueghel the Elder was not a physician and his painting of a yawning subject has nothing to do with dystonia. Pieter Brueghel the Elder dropped the ‘h’ from his name in 1559, one year after painting the De Gaper [8].

Brueghel the Younger was also a painter, further confounding historically exact usage of this eponym [8]. Careful inspection of the relevant medical literature over the past 30 years indicates that “Brueghel” and “Meige” syndromes remain poorly delineated. One author, Dr. Gordon Gilbert, suggested that the essential sign of “Brueghel syndrome” is “a widely and dystonically opened jaw [9].” In reality, however, jaw-opening dystonia may occur in the setting of segmental, multifocal or generalized dystonia and may be associated with blepharospasm [10–12]; application of “Brueghel syndrome” to these cases would be unnecessarily complicated and confusing. Marsden, in the title of his 1976 article on the subject, actually defined blepharospasm-oromandibular dystonia syndrome as “Brueghel’s syndrome” and he did, in fact, use the possessive eponym [7].

The eponymous terms “Meige’s syndrome” and “Meige syndrome” are used much more frequently than the 4 variations of “Brueghel syndrome.” PubMed (www.ncbi.nlm.nih.gov) search (April 18, 2009) with the terms “Brueghel’s syndrome,” “Bruegel’s syndrome,” “Brueghel syndrome,” and “Bruegel syndrome” generated 9, 0, 5, and 0 hits, respectively. In contrast, PubMed search with the terms “Meige syndrome” and “Meige’s syndrome” generated 263 and 95 hits, respectively. For comparison, “cranio-cervical dystonia,” “craniocervical dystonia” and “cranial dystonia” produced 6, 29 and 77 hits, respectively. Even in recent years, application of the eponymous terms remains highly variable. “Meige syndrome” and “Meige’s syndrome” have been ascribed to both primary and secondary dystonias and diverse cranio-cervical anatomical patterns. For instance, Zesiewicz and colleagues reported substantial improvement in “Meige’s syndrome” with levetiracetam treatment although their patient also exhibited cervical dystonia [13]. For an even more divergent example, a 15-year-old boy with “Meige syndrome” was described as showing “a stiff face, labial incompetence, prominent mental creases and dimples with a lot of involuntary blinking and involuntary movements of the lower face [14].” Kraft and Lang [15] defined “Meige’s syndrome” as blepharospasm associated with dystonic movements of other muscle groups in the face, neck or limbs. Clearly, the time has come to terminate usage of poorly-defined eponymic terms for dystonia of the cranio-cervical region.

3. Anatomically-Based Classification of Dystonia by Distribution

In 1984, an Ad Hoc Committee of the Dystonia Medical Research Foundation developed a widely-accepted definition of dystonia and classification of dystonic movements [16]. Dystonia was defined as a motor syndrome characterized by sustained muscle contractions, usually producing twisting and repetitive movements or abnormal postures. It was noted that dystonia is often precipitated by action and almost all dystonic movements share a directional
quality that is typically sustained, sometimes for only an instant. The Ad Hoc committee classified dystonia by age at onset, etiology and distribution [16].

Classification by distribution includes the following categories: focal dystonia, segmental dystonia, generalized dystonia, multifocal dystonia and hemidystonia [16]. The term “focal dystonia” indicates involvement of a single body part. Common names such as blepharospasm, spasmodic dysphonia, writer’s cramp and spasmodic torticollis are often assigned to the focal dystonias. The term “segmental dystonia” denotes involvement of two or more contiguous regions of the body. The segmental dystonias are subdivided into regional categories: cranial, axial, brachial and crural [16]. Within this classification scheme, segmental “cranial” dystonia indicates involvement of any combination of musculature in the head and neck region. In reality, however, the neck and mandible are not parts of the cranium [17]. Therefore, the combination of blepharospasm, masticatory dystonia and cervical dystonia, for example, is more precisely classified as segmental “craniocervical” dystonia rather than segmental “cranial” dystonia [18]. Alternative terms such as “facio-cervical” are less precise since the masticatory muscles neither arise nor attach to the face. In fact, most facial muscles attach to the cranium and/or mandible. The term “segmental craniocervical” encompasses all muscle groups in this body segment with “cranial” serving as the rostral component of this segment and cervical forming the caudal portion.

The diagnosis and anatomical classification of dystonia remains a clinical exercise profoundly influenced by experience and training. Regional involvement may be subtle, intermittent and task-specific [19]. Moreover, the origins and insertions of many muscles are located in different anatomical regions of the body (e.g., levator scapulae, digastric, platysma, semispinalis capitis and longissimus capitis). Accordingly, clear demarcation of “focal” from “segmental” dystonia may be difficult in many patients. For instance, cervical dystonia patients with retrocollis often exhibit mild, electromyographically-demonstrable involvement of the upper thoracic paraspinal musculature.

There are several reasons why use of the term “segmental craniocervical dystonia” may be more accurate than “segmental cranial dystonia” in most patients with “blepharospasm-plus” subphenotypes. First, involuntary contractions of the platysma muscle can be seen in an important percentage of patients with blepharospasm. In these subjects, mild contractions of the platysma muscles may be time-locked with those of the orbicularis oculi muscles. The platysma is innervated by the facial nerve, the same nerve which innervates the orbicularis oculi muscles in the eyelids [17]. The platysma is a broad, thin, superficial muscle that extends from the upper chest, shoulder and clavicle upwards to the chin, mandible and lower face [17]. Second, the pharyngeal musculature, which can be affected in subjects with blepharospasm, encompasses both the cranial and cervical regions [17,20]. Similarly, several muscles involved in jaw-opening originate in the cervical region [17,21]. Based on these considerations, “segmental craniocervical dystonia” is an anatomically more precise term that envelops virtually all past clinical utilization of the terms “Meige syndrome” and “Breughel syndrome.”

The anatomical complexity of the craniocervical region also confounds employment of currently-available rating scales for dystonia [22–24]. The widely-used Burke-Fahn-Marsden (BFM) rating scale includes the following regions: eyes, mouth, speech and swallow, neck, right arm, left arm, trunk, right leg and left leg. For each region, severity ratings range from 0 (none) to 4 (severe dystonia). In addition, provoking factors are rated from 0 to 4 for each region. Scores for the eyes, mouth and neck are multiplied by 0.5 whereas the score for speech and swallow is multiplied by 1.0. Clearly, the BFM does not allow for unambiguous differentiation of masticatory, lingual and pharyngeal dysfunction. Lingual involvement, for
instance, is infrequent in primary blepharospasm-plus dystonia [11,25]. On the other hand, upper facial dystonia may occur without involvement of the orbicularis oculi muscles [26].

The Unified Dystonia Rating Scale (UDRS) was “designed to include a more detailed assessment of individual body areas, including separate ratings for proximal and distal limbs, and elimination of the subjective patient rating for speech and swallowing” included in the BFM rating scale [23]. Eyes and upper face, lower face, jaw and tongue, and larynx are among the 14 body areas included in the UDRS. The Global Dystonia Severity Rating Scale (GDS) is a simplified version of the UDRS and includes the same body areas. The GDS rates the maximal dystonia for each body area, but, unlike the UDRS, does not include a separate duration factor. The Jankovic Rating Scale (JRS) was designed to access the frequency and severity of blepharospasm and/or oromandibular dystonia [24]. For illustration, JRS severity category 3B is defined as “moderate movements or spasms of mouth, jaw, or tongue, interfering with speech, voice, chewing, or swallowing, causing moderate drooling; moderately disabling.” In patients with complex segmental cranio cervical dystonia, the UDRS, GDS and JRS are unmistakenly compromised by many of the same problems as the BFM. In addition, none of these scales provide due consideration to dyspnea and involvement of respiratory muscles, including the diaphragm, which may be affected in some patients with dystonia [27–29]. Complaints of dyspnea, often with breathing arrests, are not unusual in patients with cranio cervical dystonia [28]. The BFM and UDRS are viable rating scales for DYT1 and other forms of generalized dystonia which predominantly affect the appendicular musculature but are less desirable for adult-onset primary dystonia which is concentrated in the cranio cervical region. For these reasons, there is an evident need for improved methods of measuring the severity and anatomical distribution of cranio cervical dystonia.

4. Clinical Features of Segmental Cranio Cervical Dystonia

Patients with blepharospasm may also manifest other types of cranio cervical involvement including lower facial, masticatory, lingual, pharyngeal, laryngeal or cervical dystonia. With the passage of time, involvement of the lower facial and masticatory muscles becomes fairly common in patients with blepharospasm [30–32]. Involuntary lower facial and masticatory movements may include lip pursing, chewing, jaw thrusting, grimacing, jaw opening and jaw closing/clenching [15]. In some patients, the lower facial and jaw movements may be rhythmic or tremor-like. In addition, the involuntary lower facial and jaw movements seen in patients with blepharospasm may not result in sustained postures, and, as such, may not be compatible with the definition of dystonia. Instead, these involuntary movements are oftentimes described as dyskinesias, a poorly-defined term which encompasses several forms of involuntary movements (e.g., chorea, athetosis and myoclonus), each of which carries a more precise meaning.

Most of the time, dystonia in the cranio cervical region begins focally. Over time, however, dystonia may spread to involve other muscles of the body. Most commonly, dystonia spreads to contiguous muscles. For example, when blepharospasm does spread, it typically spreads to the lower face and/or masticatory muscles [30–32]. Rarely, cranio cervical dystonia may spread to more distant muscles in the arms and legs [30–32]. Although the probability of spread is highest within the first 3 years after dystonia onset, spread may occur a decade or more later [30,31]. In patients with blepharospasm, older age-of-onset, female gender and history of head trauma may increase the risk of spread [33]. Overall, patients with initial onset of dystonia in the eyelids (i.e., blepharospasm) have at least a 50% lifetime probability of spread [30–34].

Patients with cranio cervical dystonia may report the presence of useful geste antagonistes or sensory tricks [35,36]. Touching the periorbital region and biting a toothpick are commonly employed tricks. Other tricks include touching the chin, lips or back of the head. Patients with
blepharospasm-plus subphenotypes many benefit from whistling, humming, singing, looking downwards or chewing gum.

Segmental cranio-cervical dystonia should be diagnosed and managed by a clinician with extensive experience in movement disorders. Occasionally, patients with segmental cranio-cervical dystonia are treated by general ophthalmologists and otolarynogologists without adequate workups for secondary or neurodegenerative etiologies. For example, segmental cranio-cervical dystonia may be associated with one of the spinocerebellar ataxias [37] or a neurodegenerative disorder such as progressive supranuclear palsy [38]. Not infrequently, segmental cranio-cervical dystonia is caused by medications which block dopamine receptors in the brain such as antiemetics (e.g., metoclopramide) or antipsychotics (e.g., haloperidol) [39]. Oftentimes, a brain MRI scan and blood tests are ordered to exclude the possibility of a heredodegenerative or secondary cause such as Wilson disease [40] or an ischemic stroke [41], respectively. The etiological classification and differential diagnosis of cranio-cervical dystonia is presented in Table 1. Ordinarily, all diagnostic studies will prove to be normal and the affected subject will be diagnosed with primary dystonia.

The term “primary dystonia” does not preclude a distinct genetic etiology or genetic contributions. Blepharospasm and segmental cranio-cervical dystonia clearly have a hereditary component [25,34,42–47]. In particular, some studies have reported that over 10% of patients with blepharospasm and other forms of cranio-cervical dystonia have at least one first- or second-degree relative with dystonia [25,34,45–47]. Moreover, subjects with the classic DYT1 ΔGAG deletion may rarely present with cranio-cervical dystonia [48–50] and the majority of patients with mutations in THAP1 (DYT6) exhibit some form of cranio-cervical dystonia [51].

Blepharospasm and segmental cranio-cervical dystonia are significantly more common in women with a male:female ratio of roughly 1:2 [25,30–34,42,49]. The average age of onset for blepharospasm is around 55 years whereas the average age of onset for jaw dystonia is only a couple of years earlier [25,30–34,46,49]. In comparison, cervical and focal hand/arm dystonia begin approximately one and two decades earlier, respectively [30–34,46]. Of note, these are only averages, and, occasionally, patients may have disease onset in their twenties or seventies. Patients with blepharospasm or blepharospasm-plus subphenotypes of cranio-cervical dystonia have a small (<10%) chance of spontaneous remission [52].

Prevalence estimates for blepharospasm and segmental dystonia vary widely [53,54]. True differences in prevalence can be ascribed to the effects of race and ethnicity. Diverse ascertainment methods, diagnostic criteria and sample sizes have contributed to false variability in crude prevalence estimates. Prevalence measures are especially problematic in the context of blepharospasm-plus subphenotypes. Record-linkage studies based on the review of charts from several medical specialities could generate unreliable estimates for segmental cranio-cervical dystonia as a consequence of treatment focus on particular anatomical regions (e.g., eyes, jaw, neck). In addition, all forms of segmental dystonia are lumped together in most published studies [53,54]. Crude prevalence estimates for blepharospasm range from 16 to 133 per million [55]. Overall prevalence for all anatomical patterns of segmental dystonia in eight European countries has been estimated at 32 per million [53].

5. Etiopathogenesis and Pathophysiology of Segmental Cranio-Cervical Dystonia

Given that the anatomical distributions of DYT1, DYT3 and DYT6 dystonia often incorporate parts of the cranio-cervical musculature, molecular, cellular and systems studies of torsinA, TAF1 and THAP1, respectively, are pertinent to understanding the molecular and cellular biology of segmental cranio-cervical dystonia [48,51,56]. Gene expression profiles in rats and
Functional neuroimaging in humans have provided evidence that DYT1 dystonia is a 
neurodevelopmental network disorder [57,58]. At the cellular level, torsinA appears to mediate 
interactions between the nuclear envelope and cytoskeleton [59]. As such, mutant torsinA could 
indirectly perturb movement of transcription factors and transcripts in and out of the nucleus, 
respectively. Transcriptional dysregulation may be a common underlying pathophysiological 
mechanism in many forms of primary dystonia given that TAF1 and THAP1 are transcription 
factors expressed in the central nervous system.

The sporadic occurrence of most primary focal dystonias and incomplete penetrance and 
variable expressivity of several hereditary dystonias indicates that environmental factors may 
play an important role in the pathophysiology of this movement disorder. Maladaptive 
sensorimotor plasticity to peripheral sensorimotor perturbations may be implicated in all focal 
dystonias [60]. For example, cases of blepharospasm often begin with symptoms of ocular 
irritation due to conditions such as dry eye or blepharitis [61]. These patients typically exhibit 
increased blink frequency (an adaptive response) prior to the development of full-blown 
blepharospasm (a maladaptive response). In similar fashion, most patients with primary 
oromandibular dystonia have experienced blunt facial trauma or dental procedures prior to the 
onset of their movement disorder [62] and, in some series, more than 20% of patients with 
cervical dystonia reported substantial prior cervical trauma [63]. Based on this clinical 
information, a reasonable case has been made that dystonia is a disorder of abnormal 
sensorimotor integration [64].

Relatively few hypothesis-driven pathophysiological studies have specifically focused on 
segmental craniocervical dystonia or included subjects with blepharospasm-plus phenotypes 
[65–67]. Nevertheless, investigations of blepharospasm, masticatory and cervical dystonia are 
clearly pertinent to our understanding of segmental craniocervical dystonia since the focal 
dystonias share genetic and physiological underpinnings. Physiological studies have 
demonstrated abnormal excitability of brainstem interneuronal pathways and sensorimotor 
areas of cerebral cortex in patients with focal dystonias of the craniocervical region [65–68]. 
Brainstem interneuronal pathways have been studied with the blink reflex and masseter 
inhibitory reflex. The recovery cycles of the R2 component of the blink reflex and the SP2 
component of the masseter inhibitory reflex are enhanced in patients with craniocervical 
dystonia. Even subjects with isolated cervical dystonia show enhanced R2 recovery, indicating 
that abnormal interneuronal excitability extends beyond regions of clinical involvement. Dresel 
and colleagues [68] used silent event-related functional MRI to compare three experimental 
groups: isolated blepharospasm, blepharospasm plus oromandibular dystonia and controls. 
Both dystonia groups showed increased activation of somatosensory and caudal supplementary 
motor cortices during a whistling task. Cortical silent period shortening in blepharospasm and 
blepharospasm plus oromandibular dystonia experimental groups is consistent with 
hypoexcitability of cortical inhibitory neurons in cranial dystonia.

6. Treatment of Segmental Craniocervical Dystonia

Segmental craniocervical dystonia is commonly treated with injection of botulinum toxins. 
Successful treatment of dystonia with injection of botulinum toxins is both art and science. 
Results depend on accurate targeting of affected muscles with an appropriate amount of toxin. 
Electromyographic guidance is frequently used when injecting masticatory, laryngeal and 
cervical muscles [69–71]. Unfortunately, many patients with segmental craniocervical 
dystonia are forced to see two or more physicians for their botulinum toxin injections. For 
example, in the worse case scenario, a single patient may see an ophthalmologist for 
blepharospasm, an otorhinolaryngologist for spasmodic dysphonia and a neurologist for 
cervical dystonia. In patients with blepharospasm, attention to concomitant masticatory and 
lower facial involvement is often highly variable and dictated by the skill and experience of
the treating physician along with patient expectations. Injections of botulinum toxin into the
perioral, masticatory and platysma musculature in patients with coexisting blepharospasm can
provide significant subjective clinical benefit with a low risk for side effects [72–74].

Botulinum toxin type A is approved by the United States Food and Drug Administration (FDA)
for the treatment of blepharospasm and cervical dystonia and botulinum toxin type B is FDA-
approved for cervical dystonia. Injections into lower facial, masticatory, laryngeal and lingual
musculature are off-label applications of botulinum toxin in the United States. In comparison
with isolated blepharospasm, excellent subjective and objective improvement with injections
of botulinum toxin is less common in blepharospasm-plus subphenotypes [75–78]. For
instance, Van den Bergh and colleagues [75] reported dramatic improvement in patients with
blepharospasm (79%) but only moderate improvement in patients with “Meige’s syndrome
(53%).” On average, patients with blepharospasm-plus subphenotypes may have more severe
blepharospasm than individuals with isolated blepharospasm. In addition, blepharospasm may
be accompanied by either jaw-opening or jaw-closing dystonia [11,35]. In comparison to jaw-
closing dystonia, jaw-opening dystonia can be difficult to treat with injections of botulinum
toxin [37,78].

An extensive list of oral medications has been used to treat segmental craniocervical dystonia;
however, there are no multi-center, placebo-controlled, double-blind studies to reference in
this regard. A single-center, double-blind crossover study showed no benefit of sodium
valproate in “Meige syndrome [79].” Similarly, a single-center, randomized, placebo-
controlled, crossover trial showed that super blue-green algae was not an effective treatment
for patients with blepharospasm or “Meige syndrome [80].” Recent publications described the
benefits of zolpidem and levetiracetam in isolated cases of “Meige syndrome [13,81,82].”
Unfortunately, the magnitude of improvement typically obtained with commonly used drugs
such as the anticholinergics (e.g., trihexyphenidyl and benztropine), benzodiazepines (e.g.,
clonazepam and lorazepam), baclofen, and tetrabenazine is often modest, at best [10,83].
Although side-effects are often problematic, anticholinergics have proven value in segmental
cranio-cervical dystonia [84–87]. In many patients, low-dose clonazepam is also efficacious
[88,89]. Moreover, the side effects associated with benzodiazepines are usually more tolerable
than those due to anticholinergics. Many of the medications that have been used to treat
blepharospasm and other cranio-cervical dystonias are listed in Table 1 [10,81,84,90–97].

In recent years, deep brain stimulation (DBS) has garnered increasing attention as a therapeutic
choice in patients with intractable dystonia. Clearly, DBS is an important therapeutic option
in patients with DYT1 generalized dystonia [98]. Currently available data suggests that DBS
is also an effective treatment for many, but not all patients with segmental cranio-cervical
dystonia [99–102]. Most commonly, the internal segment of the globus pallidus (GPi) has been
targeted in patients with primary adult-onset segmental cranio-cervical dystonia [98]. Bilateral
stimulation of the GPi may be required for control of axial symptoms [103]. Unlike the situation
for Parkinson disease and essential tremor, the benefits associated with DBS for dystonia often
develop gradually over several months [104]. Interestingly, long-term GPi DBS may correct
those neural networks abnormalities responsible for the appearance of dystonia such that
continued stimulation may ultimately prove unnecessary [105].

DBS is associated with a small risk of stroke, infection and the development of new
neurological signs including but not limited to hemiparesis, visual field deficits, dysarthria and
dysphagia. In some patients with dystonia, stimulation of the GPi can produce mild worsening
of motor function in previously non-dystonic body regions [101]. Based on these
considerations, DBS should be seriously considered in patients with segmental cranio-cervical
dystonia only if other treatment options, administered by skilled and experienced neurologists,
are ineffective.

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7. Summary

The eponymic terms Meige syndrome and Brueghel syndrome are imprecise, have been used inconsistently for decades, and should be avoided in the classification of craniocervical dystonia. The term segmental craniocervical dystonia faithfully incorporates various blepharospasm-plus subphenotypes which appear to share common genetic and physiological underpinnings. Confident identification of genetic and environmental risk factors for segmental craniocervical dystonia may permit the developmental of better treatments which target pathways of cellular dysfunction within the central nervous system.

Acknowledgments

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References


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Table 1
Etiological Classification and Diagnosis of Craniocervical Dystonia

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<thead>
<tr>
<th>Etiological Classification</th>
<th>Diagnosis of Craniocervical Dystonia</th>
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<tr>
<td><strong>Primary craniocervical dystonia:</strong> syndromes in which dystonia is the sole phenotypic manifestation with the exception that tremor can be present as well</td>
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<td><strong>Secondary craniocervical dystonia:</strong> due to structural lesions and/or neural insults</td>
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<td>vascular (e.g., ischemic stroke, hemorrhagic stroke, cerebral palsy)</td>
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<td>infectious (e.g., human immunodeficiency virus, arboviruses)</td>
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<td>toxins (e.g., manganese, carbon disulfide)</td>
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<td>medications (e.g., neuroleptics, antiemetics, anticonvulsants)</td>
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<td>autoimmune/inflammatory (e.g., multiple sclerosis, lupus erythematosus, Behçet disease)</td>
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<td>metabolic (e.g., hypoxia, extra-pontine myelinolysis)</td>
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<td>neoplasms (e.g., glioblastoma, metastatic tumor, meningioma)</td>
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<td><strong>Craniocervical dystonia-plus:</strong> disorders distinct from primary dystonia and heredodegenerative diseases with dystonia</td>
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<td>dopa-responsive dystonia (DYT5)</td>
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<td>myoclonus-dystonia syndrome (DYT11)</td>
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<td><strong>Heredodegenerative diseases with craniocervical dystonia:</strong> typically associated with pathological changes in brain tissue and may be hereditary (e.g., progressive supranuclear palsy, Parkinson disease, multiple system atrophy, corticobasal ganglionic degeneration, spinocerebellar ataxias, Huntington disease, Lubag [DYT3], rapid-onset dystonia parkinsonism [DYT12], Wilson disease, Lesch-Nyhan syndrome, pantothenate kinase-associated neurodegeneration, mitochondrial encephalopathies, Niemann-Pick type C, neuronal ceroid lipofuscinosis)</td>
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<td><strong>Psychogenic craniocervical dystonia:</strong> dystonia primarily due to psychological factors</td>
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Table 2
Oral Medications for Blepharospasm and Other Cranial Dystonias

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<tr>
<th>Class</th>
<th>Names</th>
<th>Mechanism(s) of action</th>
<th>Most frequent side effects</th>
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<tr>
<td>Anticholinergic [84]</td>
<td>trihexyphenidyl, benztropine</td>
<td>block acetylcholine receptors</td>
<td>dry mouth, constipation, blurred vision, mild memory impairment</td>
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<td>Benzodiazepine [63]</td>
<td>clonazepam, lorazepam, diazepam</td>
<td>potentiate the effects of GABA on GABA&lt;sub&gt;A&lt;/sub&gt; receptors</td>
<td>drowsiness, disequilibrium</td>
</tr>
<tr>
<td>GABA&lt;sub&gt;B&lt;/sub&gt; receptor agonist [90]</td>
<td>baclofen</td>
<td>stimulates GABA&lt;sub&gt;B&lt;/sub&gt; receptors</td>
<td>drowsiness, disequilibrium, weakness</td>
</tr>
<tr>
<td>Dopamine precursor [91]</td>
<td>levodopa</td>
<td>converted to dopamine</td>
<td>nausea</td>
</tr>
<tr>
<td>Dopamine receptor agonist [92]</td>
<td>bromocriptine</td>
<td>stimulates D&lt;sub&gt;2&lt;/sub&gt; dopamine receptors, 5-HT&lt;sub&gt;2&lt;/sub&gt; antagonist</td>
<td>nausea, lightheadness, drowsiness</td>
</tr>
<tr>
<td>Neuroleptic [93]</td>
<td>pimozide, haloperidol</td>
<td>blocks dopamine receptors (D&lt;sub&gt;2&lt;/sub&gt; &gt; D&lt;sub&gt;3&lt;/sub&gt; &gt; D&lt;sub&gt;1&lt;/sub&gt; &amp; D&lt;sub&gt;4&lt;/sub&gt;)</td>
<td>tardive dyskinesias **</td>
</tr>
<tr>
<td>Monoamine depletor [93]</td>
<td>tetrabenazine</td>
<td>inhibits monoamine transporters in the brain</td>
<td>depression, drowsiness, Parkinsonism</td>
</tr>
<tr>
<td>Anticonvulsant [81]</td>
<td>levetiracetam</td>
<td>binds to the synaptic vesicle protein SV2A</td>
<td>irritability, headaches</td>
</tr>
<tr>
<td>Imidazopyridine [94]</td>
<td>zolpidem</td>
<td>binds to the benzodiazepine receptor 1</td>
<td>drowsiness, dizziness, headache</td>
</tr>
<tr>
<td>Atypical antipsychotic [95]</td>
<td>clozapine</td>
<td>blocks dopamine receptors (D&lt;sub&gt;2&lt;/sub&gt; &gt;&gt; D&lt;sub&gt;3&lt;/sub&gt;, D&lt;sub&gt;2&lt;/sub&gt;, D&lt;sub&gt;3&lt;/sub&gt;, &amp; D&lt;sub&gt;4&lt;/sub&gt;), partial 5-HT&lt;sub&gt;1A&lt;/sub&gt; agonist, cholinergic and histaminergic antagonist</td>
<td>constipation, sedation, agranulocytosis</td>
</tr>
<tr>
<td>Serotonin receptor antagonist [96]</td>
<td>cyproheptadine</td>
<td>5-HT&lt;sub&gt;2&lt;/sub&gt; antagonist, antihistaminic</td>
<td>drowsiness, nausea</td>
</tr>
<tr>
<td>Antiarrhythmic agent [97]</td>
<td>mexiletine</td>
<td>inhibits inward sodium currents</td>
<td>nausea, dizziness, tremor</td>
</tr>
</tbody>
</table>

* None of these medications are FDA approved treatments for blepharospasm

** Tardive dyskinesias may be a permanent side effect