Blepharospasm plus Cervical Dystonia with Predominant Anterocollis: A Distinctive Subphenotype of Segmental Cranio cervical Dystonia?

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Abstract

Background: Dystonia of the eyelids often spreads to affect other muscles in the cranio cervical region. Certain blepharospasm-plus subphenotypes may be clinically unique.

Methods: Seven subjects with the subphenotype of late-onset blepharospasm with apraxia of eyelid opening and cervical dystonia with predominant anterocollis were identified from a database of over 1800 patients with primary dystonia.

Results: Blepharospasm was the first affected site in 6/7 subjects, followed by spread of the disease to the cervical muscles. Although four patients also had other forms of dystonia (laryngeal, lower face), none showed spread outside the cranio cervical region. A family history of dystonia was present in 4/7. No mutations were identified in THAP1 or TOR1A. Overall, blepharospasm was difficult to treat, typically requiring both myectomy and substantial doses of botulinum toxin into the pretarsal orbicularis oculi muscles. In one subject, anterocollis markedly improved after deep brain stimulation.

Discussion: Delineation and characterization of cranio cervical dystonia subphenotypes may serve to guide genetic and therapeutic studies, in addition to clinical interventions. The blepharospasm with apraxia of eyelid opening and anterocollis subphenotype can be therapeutically challenging.

Keywords: anterocollis; blepharospasm; cranio cervical dystonia; THAP1; TOR1A


Introduction

Blepharospasm and cervical dystonia are two familiar manifestations of late-onset primary dystonia. 1 Blepharospasm and cervical dystonia may occur in isolation or as part of more extensive anatomical involvement as segmental, multifocal, or generalized dystonia. 2 Late-onset primary dystonia is concentrated in the cranio cervical region of the body; the arms and legs are less frequently affected. 1,3 Dystonia of the cranio cervical region may involve contiguous or non-contiguous areas: (eyes and upper face) +/- (lower face) +/- (jaw and tongue) +/- (larynx) +/- (neck). Although various groupings of anatomical areas are possible in individual patients during the course of their disease, certain patterns do appear to be distinctive and have captured the attention of neurologists for over 100 years: Meige syndrome, Brueghel syndrome, and “blepharospasm-plus,” for example. 2,4,5 Unfortunately, the non-possessive and possessive forms of Meige and Brueghel syndromes have been ambiguously ascribed by neurologists to anatomical variations of cranio cervical dystonia that include the combination of blepharospasm and involuntary movements of lower facial and/or masticatory (jaw) muscles. 2
Late-onset primary focal dystonia, particularly blepharospasm, may spread to adjoining or distant body parts. Most commonly, dystonia with onset in the eyelids (blepharospasm) extends to the lower face and masticatory muscles. In an important subset of patients, blepharospasm may also spread to the neck. In a retrospective study of 78 patients with blepharospasm in the United States, 31% developed manifest dystonia in the neck within 5 years of onset in the eyelids. Similar results were obtained in Italy, with 21% of 124 blepharospasm patients showing spread to the neck with follow-up periods of up to 15 years. Unfortunately, these reports did not detail the severity and positional characteristics of cervical dystonia in those subjects with concomitant blepharospasm.

In subjects with primary dystonia limited to the cervical region, isolated or predominant anterocollis is uncommon. In most neurology practices, the majority of subjects with anterocollis have a neurodegenerative disorder, or secondary cervical dystonia due to neuroleptic or antiepileptic exposure. In two independent clinical series, 6.8% and 25% of subjects with cervical dystonia exhibited anterocollis, most commonly in combination with laterocollis and/or rotational torticollis. Conventionally, anterocollis can be difficult to treat with botulinum toxin. In fact, most clinical studies of chemodenervation for cervical dystonia have excluded subjects with isolated or predominant anterocollis.

Herein, we describe the demographics and clinical features of seven patients with well-characterized primary late-onset segmental cranio cervical dystonia with a distinctive combination of blepharospasm with apraxia of eyelid opening (AEO) and anterocollis. Given that the early-onset primary dystonias driven by Mendelian inheritance tend to exhibit characteristic clinical phenotypes, it is possible that subphenotypes of late-onset dystonia are also driven by relatively specific genetic variants and/or pathophysiological processes. Therefore, recognition and characterization of subphenotypes may prove useful for genetic, physiological, and therapeutic studies of dystonia.

**Methods**

Human studies were performed in accordance with institutional review board guidelines, and all subjects gave informed consent for genetic analyses, disclosure of medical and demographic information, and use of photographs. A total of 170 subjects with segmental dystonia were identified from our biorepository of over 1800 subjects. Among the group of subjects with segmental dystonia, 114 had “blepharospasm-plus” subphenotypes of segmental cranio cervical dystonia, of whom seven had a distinctive combination of anterocollis and blepharospasm. This subgroup was chosen for presentation because of their relatively unique combination of clinical features, including severe blepharospasm with AEO, limited or absent response to sensory tricks, and absence of head and appendicular tremors. Moreover, all patients were examined by the senior author before injections of botulinum toxin. Subjects were also examined by the senior author for the presence of nonphysiological head and appendicular tremors (essential, dystonic, and other).

**Results**

Table 1 summarizes the demographic and clinical data of the seven subjects included in this study. In male subjects, dystonia first became manifest in their fourth or early fifth decade (44–52 years of age). In contrast, dystonia onset was 60 and 65 years, respectively, in the two female patients. At the time of this report, dystonia duration was between 7 and 15 years in all subjects. No subject showed clinical evidence of Parkinsonism, ataxia, spasticity, or posterior cervical (extensor) myopathy. Four patients had other sites of involvement, all within the craniocervical region. During the course of their disease, all subjects were given trials of oral agents for their dystonia and AEO. Treatments included benzodiazepines, tetrabenazine, anticholinergic agents, an analeptic (modafinil), a dopamine agonist (pramipexole), levodopa, and muscle relaxants. In aggregate, oral pharmacotherapy was only mildly beneficial in our cohort. Injections of onabotulinumtoxin A were employed to relieve the symptoms of blepharospasm (range: 47–110 units) and cervical dystonia (100–255 units). All patients received injections into the pretarsal portions of the OO muscles. Although complemented by the effects of botulinum toxin injections, all subjects required surgical intervention in the form of OO myectomy or blepharoplasty for adequate control of blepharospasm.

Subject #1 (Figure 1A–1C) is a Caucasian male with type II diabetes and hyperlipidemia. Blepharospasm onset was mildly asymmetrical, initially presenting in the left eye, followed by right eye involvement a few months later. Cervical dystonia, manifest as isolated anterocollis, appeared 5 years later. The severity of both blepharospasm and anterocollis has progressed slowly over time. Neither blepharospasm nor anterocollis has responded to trials of clonazepam (maximum dosage: 1 mg t.i.d.), tetrabenazine (maximum dosage: 25 mg t.i.d.), or trihexyphenidyl (maximum dosage: 5 mg t.i.d.). Baclofen (10 mg b.i.d.) has been associated with mild improvement in neck discomfort. This patient did not obtain satisfactory clinical improvement with injections of onabotulinumtoxin A and underwent limited OO myectomy at age 50 and, more extensive, integrated upper eyelid myectomy at age 56. Bilateral electromyographically (EMG)-guided injections of onabotulinumtoxin A (178–255 units) into the sternocleidomastoid, scalene, levator scapulae, longus colli, and longus capitis muscles were performed on three occasions, but provided only minimal benefit. In contrast, since
his second myectomy procedure, this patient’s blepharospasm and AEO have responded well to injections of onabotulinumtoxin A (8 units each upper eyelid pretarsal OO muscle, 47 units total).

Subject #2 (Figure 1D–1F), a Caucasian male, has had dry eye symptoms that were treated with punctal plugs and, eventually, tear duct cauterization. Mild but non-sustained improvements in both

<table>
<thead>
<tr>
<th>Data</th>
<th>Subject #1</th>
<th>Subject #2</th>
<th>Subject #3</th>
<th>Subject #4</th>
<th>Subject #5</th>
<th>Subject #6</th>
<th>Subject #7</th>
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<tr>
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<td>62</td>
<td>71</td>
<td>59</td>
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<td>Father - segmental craniocervical dystonia</td>
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Abbreviations: BSP, blepharospasm; CD, cervical dystonia; EMG, electromyography; NA, not available or applicable; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale.

Tremor and Other Hyperkinetic Movements
http://www.tremorjournal.org
blepharospasm and cervical dystonia were noted with benzodiazepines (clonazepam and alprazolam) and trihexyphenidyl. AEO showed no reliable response to amphetamines. A bedtime dose of cyclobenzaprine has helped to reduce nocturnal neck discomfort. Slight improvement in AEO and blepharospasm was noted after a limited bilateral OO myectomy and frontalis muscle sling procedure. Over the past 4 years, this patient's bilateral blepharospasm and AEO have responded satisfactorily to injections of onabotulinumtoxinA (20 units each upper eyelid pretarsal OO muscle, 94 units total). In contrast, cervical dystonia with severe anterocollis has shown only modest improvements with EMG-guided injections of onabotulinumtoxin A. Current medical problems include hyperlipidemia, hypertension, and type II diabetes mellitus. The patient's sister had a single episode of bilateral eyelid closure suggestive of blepharospasm that lasted approximately 3 months and resolved without specific treatment.

Subject #3, a Caucasian female with long-standing type I diabetes mellitus, noticed the simultaneous onset of segmental cranio cervical dystonia (blepharospasm and cervical dystonia) at the age of 60, 2 weeks after the loss of her spouse. Blepharospasm and AEO did not improve with clonazepam or modafinil, but have responded well to injections of onabotulinumtoxinA (10 units each upper eyelid pretarsal OO muscle, 73 units total). Peri-oral dystonia has been well controlled with injections of onabotulinumtoxin A. Bilateral dermatochalasis was treated with blepharoplasty. In general, better clinical results were obtained with injections of onabotulinumtoxin A after blepharoplasty. Cervical dystonia manifest as anterocollis with minimal left rotational torticollis has responded well to EMG-guided injections of onabotulinumtoxinA (up to 220 units).

Subject #4, an African-American male, gets limited relief of both blepharospasm and cervical dystonia symptoms when he touches his left lateral brow. He was treated with limited OO myectomy at 47 years of age. His blepharospasm and AEO have been successfully managed with injections of onabotulinumtoxin A (16 units each upper eyelid pretarsal OO muscle, 100 units total) and low-dose trihexyphenidyl (2–4 mg daily). He has declined injections of botulinum toxin for treatment of his cervical dystonia, although it has become more severe over the past several years. A younger sister has isolated blepharospasm, reportedly responsive to injections of onabotulinumtoxin A.

Subject #5 (Figure 1G–1I), a Caucasian female, did not benefit from various combinations of medications including trihexyphenidyl, clonazepam, modafanil, pramipexole, levodopa, and cyclobenzaprine. Injections of onabotulinumtoxin A were moderately beneficial for blepharospasm, but produced minimal improvement in cervical dystonia. Additional reductions in blepharospasm severity and improved responses to injections of onabotulinumtoxin A were apparent after extensive integrated OO myectomy.25 However, owing to progression of anterocollis and persistent need for onabotulinumtoxin A injections to control blepharospasm, the subject underwent bilateral microelectrode-guided placement of bilateral globus pallidus pars interna (GPi) electrodes (Medtronic Kinetra). The benefits of surgery were apparent within weeks, and with her current settings

Figure 1. Photographs of Three Subjects with Blepharospasm and Anterocollis
Frontal, lateral, and posterior views of subjects #1 (A–C) and #2 (D–F). Subject #5 before (H) and after ([I] 1 month; [J] 2 months) bilateral GPi DBS.
Distinctive Subphenotype of Craniocervical Dystonia

Wahl O, LeDoux MS

Anterocollis is an uncommon form of primary cervical dystonia. Additionally, no explicit data on the combination of blepharospasm with subtypes of cervical dystonia have been published. Is the combination of blepharospasm and anterocollis a phenotype of segmental craniocervical dystonia that is physiologically, molecularly, and genetically unique and distinct, or simply two different focal manifestations of dystonia randomly affecting the same individual? Even though our data and study design do not answer those questions, the combination of blepharospasm and anterocollis does show evidence, albeit uncontrolled, of characteristic clinical features, including AEO, difficult-to-treat blepharospasm, absence of head and appendicular tremors, frequent family history of dystonia, and infrequent response to sensory tricks. From physiological and evolutionary perspectives, eyelid closure and anterocollis provide a coordinated motor plan to protect the eyes and face from oncoming threats. Ultimately, n-dimensional cluster analysis of high-resolution phenotypic data derived from a large multi-center cohort of subjects with segmental craniocervical dystonia will be required to determine whether creation of subphenotypes is scientifically valid. Although potentially limited by recall and referral bias, our descriptive analysis of a putative subphenotype does provide motivation for more exacting characterization of primary dystonia, which, at present, remains a clinical diagnosis, based solely on positive motor manifestations.

Our descriptive, largely retrospective report has several limitations. First, a rating scale for blepharospasm was not employed, and the TWSTRS was not completed at each visit. Second, the TWSTRS was not completed after washout of medications, including botulinum toxin. Third, the collection of subjects described herein may over-represent particularly complex cases owing to referral bias. Fourth, we did not compare our cohort with subjects with blepharospasm plus other forms of cervical dystonia. Lastly, our data do not allow us unambiguously to argue that the blepharospasm with AEO and anterocollis is a discrete entity rather than a probabilistic collection of numerous possible combinations of segmental craniocervical dystonia.

EMG showed tonic firing patterns in muscles known to generate head flexion. In addition, none of our patients had evidence of a focal or generalized myopathy with weakness of their posterior (extensor) cervical musculature. The marked improvement of cervical dystonia with deep brain stimulation (DBS) in subject #3, and positive response to injections of onabotulinumtoxin A injections in subjects #2, #3, and #6, also argue that the anterocollis noted in our cohort was actually driven by dystonia of the cervical musculature.

Although the treatment of anterocollis is notoriously difficult, recent advances in neuromodulation and botulinum toxin injection techniques are encouraging. The success of GPi DBS in subject #5 offers hope to patients similarly affected. Recent series support the efficacy of DBS in patients with blepharospasm, cervical dystonia, and more complex segmental craniocervical dystonia.27-29 However, the treatment of cervical dystonia predominantly manifest as anterocollis has not been explicitly reported. The use of EMG guidance for injections

Discussion

Late-onset primary dystonia most commonly begins in the craniocervical region, and, although it may spread, tends to remain isolated to the craniocervical region. Isolated or disproportionate
of botulinum toxin into the deep cervical musculature, particularly when coupled with imaging (e.g., fluoroscopy or computed tomography), may improve therapeutic outcomes.\textsuperscript{19,30}

Concomitant AEO can be a major contributor to botulinum toxin refractoriness in a subset of patients with blepharospasm.\textsuperscript{31} Although the relative roles of the pretarsal OO and levator palpebrae (LP) muscles in AEO is rarely established in routine clinical practice, a significant percentage of patients do improve with pretarsal injections of botulinum toxin and/or upper eyelid myectomy.\textsuperscript{31,32} Although simultaneous OO and LP EMG was not performed in our cohort of subjects, the positive response to injections of botulinum toxin suggests that dystonic discharges of the OO muscle contributed to their AEO.\textsuperscript{32,33} Alternatively, reduced contraction of the pretarsal OO that dystonic discharges of the OO muscle contributed to their AEO. A formal blepharospasm rating scale was not used to assess our subjects since their condition often demanded injections of botulinum toxin at intervals of less than 12 weeks, before the beneficial effects of toxin had entirely waned. Anecdotally, anterocollis contributed to disability by constricting normal access to upper portions of the visual fields.

Spread of dystonia to other sites after onset as blepharospasm has been well documented.\textsuperscript{6–8} For example, Svetel and colleagues\textsuperscript{7} observed 132 patients with primary blepharospasm and reported spread of dystonia in 33.3\%, with the second site being affected in 1.2 years, on average, and the highest chance of spread occurring within the first 5 years after disease onset. In similar work, Abbruzzese et al.\textsuperscript{8} reported that only 3.4\% of their patients demonstrated spread of dystonia outside the craniocervical region. Based on these data, the spread of blepharospasm to other cranio cervical sites becomes increasingly uncommon with the passage of time and spreading outside the cranio cervical region is distinctly unusual. Given the long duration of blepharospasm in our cohort of subjects (7–15 years), additional spread of dystonia is improbable.

Four of our subjects had a positive history of dystonia with variable expressivity and reduced penetrance. We offer the hypothesis that blepharospasm with AEO and anterocollis is a unique subphenotype of adult-onset primary cranio cervical dystonia that might be due to distinct sequence variants in genes yet to be causally associated with dystonia. In this regard, phenotype-genotype correlations are well established in dystonia: early-onset leg involvement in DYT1 dystonia, writer’s cramp and cervical dystonia in the myoclonus-dystonia (DYT11), and predominant cranio cervical manifestations in DYT6 dystonia.\textsuperscript{5} Cranio cervical subphenotype-genotype correlations should become possible as the genetic underpinnings of late-onset primary dystonia are exposed. Physiologically, we should consider the possibility that focal and segmental dystonias may be localized manifestations of generalized neural dysfunction.

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References


