MAURICE HANSON, MD
Neurologist, Movement Disorders Program,
Cleveland Clinic Florida,
West Palm Beach, FL

Use of chemodenervation in dystonic conditions

ABSTRACT

Dystonia, an uncommon movement disorder that causes sustained muscle contractions and painful body positions, is a difficult diagnostic challenge; misdiagnosis is common. Classification may include etiology, area of physical involvement, or age of onset. Bodily distribution is varied, and dystonias can present as primary (genetic) or secondary (caused by other disease processes or use of neuroleptic drugs). Although there is no cure, the use of botulinum toxins for chemodenervation provides symptomatic relief and is considered the treatment of choice in focal dystonia. The dose of botulinum toxin may be titrated to provide significant relief for 12 weeks or more.

Dystonia is a movement disorder in which involuntary sustained muscle contractions cause twisting movements that place the body in abnormal, sometimes painful, positions. Dystonia is believed to arise from an abnormality in the basal ganglia and an inherent or acquired defect in the processing of neurotransmitters.[1]

Dystonia is uncommon, although its exact prevalence is unknown. Nutt et al concluded that at least 250,000 people were affected by idiopathic dystonia in the United States, but prevalence is likely higher because misdiagnosis is not uncommon.[2] A more recent European study found the prevalence of primary dystonia in the general population aged 50 years or more to be 732 per 100,000.[3] The Epidemiological Study of Dystonia in Europe (ESDE) Collaborative Group found that the estimated prevalence of cervical dystonia was 50 to 200 per 1 million individuals.[4] Also known as spasmodic torticollis, this is the most commonly diagnosed form of focal dystonia.

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CLASSIFICATION OF DYSTONIA

Accurate classification of dystonia is important, since this informs approaches to management as well as prognosis. The three most important means by which dystonia is classified are (1) etiology, including primary dystonia, which encompasses a variety of genetic variables, and secondary dystonia; (2) bodily distribution of symptoms; and (3) age at onset.

Etiology

Most primary or idiopathic dystonia appears to be hereditary. Early-onset primary dystonia is most frequently caused by a mutation in the *DYT1* gene, although other genetic mutations are possible.[5] Patients with primary dystonia have no other underlying disorder; involuntary muscle contractions are the sole symptom. A thorough history should include a review of perinatal and early developmental history, prior neurologic illness, and exposure to drugs known to cause acquired dystonia. Physical examinations (encompassing intellectual, pyramidal, cerebellar, and sensory domains) and laboratory tests reveal no specific cause for the dystonic symptoms. Primary dystonia is also most frequently action-induced; at rest, the affected body region may appear to be normal.

Secondary dystonia occurs as a symptom of another disease process. Multiple sclerosis or any one of several hereditary neurologic disorders, such as Wilson disease, may be implicated. Secondary dystonia also may result from trauma to the brain, as might occur during an automobile accident; from heavy-metal or carbon monoxide poisoning; or as an adverse effect of medication. It may be psychogenic or related to Parkinson disease or Parkinson-plus syndromes, a group of neurodegenerative disorders with parkinsonian features. Tardive dystonia, the most common adult form of secondary dystonia, may occur following exposure to certain neuroleptic drugs; tardive dystonia is a type of tardive dyskinesia that describes any involuntary neurologic movement disorder.

Bodily distribution

Dystonia is further classified by location of symptoms. Focal dystonias, which are usually primary dystonias, describe symptoms that are limited to a region of the body, such as a specific arm. There are several variations.

TABLE 1
Common dystonia misdiagnoses

Type of dystonia	Misdiagnosed as…
Blepharospasm	Tic, dry eye syndrome
Cervical dystonia	Arthritis, stiff neck, subluxation of cervical vertebrae, tumor of posterior fossa
Dystonia, all forms	Stress, anxiety, nervousness; psychogenic disorders
Laryngeal dystonia	Laryngitis, sore throat, vocal abuse
Oromandibular dystonia	Temporomandibular joint disorder
Writer's cramp	Carpal tunnel syndrome, muscle strain, lateral epicondylitis

Cervical dystonia affects the head and neck, is the most common adult-onset dystonia, and affects more women than men. Blepharospasm, or involuntary contractions of the eyelids, potentially leads to extended eye closure and functional blindness and often involves other facial muscles. Laryngeal dystonia affects the muscles in the larynx. Limb dystonia, such as writer's or musician's cramp, affects muscles in the arm, hand, leg, or foot. Limb dystonia is often task-specific action dystonia, and can be primary or secondary.

Segmental dystonia describes a group of involved muscles that are contiguous, such as cranial to neck to cervical to arm. Oromandibular dystonia, affecting the face, mouth, and jaw, often with unusual tongue movements (ie, lingual dystonia), is a type of segmental dystonia, although some consider it a focal dystonia. Meige syndrome is the combination of blepharospasm and oromandibular dystonia. Certain limb and cranial dystonias are considered segmental dystonias. Dystonia that affects two or more noncontiguous muscle groups in different parts of the body is multifocal. Hemidystonia describes unilateral symptoms.

Symptoms that have advanced from a focal presentation to affect additional regions of the body characterize generalized dystonia. The symptoms potentially advance to include the trunk and limbs. The muscular contractions are usually sustained, are often both repetitive and painful, and worsen with activity.[6] In severe cases, muscular contractions may occur even while resting. Early-onset myoclonus dystonia is a generalized hereditary dystonia whose symptoms include dystonic contractions of the neck and shoulders and rapid jerking movements.[7] Of note diagnostically, early-onset dystonia in a leg typically begins at age 8 to 9 years and is more likely than other early-onset presentations to progress to generalized dystonia. Early-onset dystonia that begins in an arm typically presents later, at age 12 to 14 years, and is less likely to progress to generalized dystonia. Late-onset dystonia (> 27 years of age), by contrast, rarely begins in a leg and tends to remain either focal or segmental.[8]

Age of onset

A third useful classification scheme identifies early-onset (childhood to young adult) and late-onset varieties of dystonia.

THE DIAGNOSTIC CHALLENGE

Accurate diagnosis of dystonia is challenging because of its relative rarity and the variety of etiologies that pertain to this heterogeneous family of disorders. Patterns of inheritance are not straightforward and primary dystonia can be difficult to diagnose even with the benefit of genetic testing. There is no identifiable pathologic abnormality in many patients, and negative genetic tests do not necessarily mean that the dystonia is not primary. In the face of these challenges it is not surprising that dystonia is frequently misdiagnosed **(Table 1)**. Nevertheless, certain findings can guide the diagnosis toward primary or secondary dystonia.

Consider primary dystonia if perinatal and developmental histories, intellect, strength, and perception of sensations are normal. There should be no prior history of neurologic illness or exposure to neuroleptic drugs whose adverse effects include secondary dystonia. In primary dystonia, diagnostic studies are negative and dystonia is the only symptom. If onset of symptoms is associated with activity, then primary dystonia should be considered. In the case of early- or late-onset limb dystonia, testing should be performed for the *DYT1* gene. If the results are negative, then a trial for dopa-responsive dystonia should be undertaken with levodopa.

Consider secondary dystonia if the patient has been exposed to neuroleptic drugs, symptoms are distributed unilaterally, or the presentation is unusual for age or distribution of symptoms. For example, cranial dystonia in a child would raise the index of suspicion for secondary dystonia. If tardive dystonia is part of the differential diagnosis, consider magnetic resonance imaging (MRI), serum ceruloplasmin measurement, or slit-lamp diagnostic testing. Suspicion of a structural lesion affecting the central nervous system warrants examination with MRI, computed tomography, or angiography. Certain metabolic and neurologic hereditary disorders cause secondary dystonia, in which case dopa-responsive dystonia should be ruled out. Psychometric testing should also be considered.

SYMPTOMATIC TREATMENT WITH CHEMODENERVATION

In the absence of a cure, treatment options for dystonia are necessarily symptomatic and supportive. Titratable chemodenervation agents are injected directly into the muscle or motor nerve, temporarily weakening the local muscle and easing dystonia symptoms. Chemodenervation agents include phenol, ethyl alcohol, and botulinum toxin types A (BTX-A; onabotulinumtoxinA, abobotulinumtoxinA, and incobotulinumtoxinA) and B (BTX-B; rimabotulinumtoxinB).

Phenol and ethyl alcohol injections targeted perineurally or as a motor point block have been employed for dystonia and cause nonselective tissue destruction, muscle necrosis, and highly variable durations of response. Perineural microcirculation may be damaged, possibly leading to long-term defects.

Clostridium botulinum bacteria produce seven serologically distinct neuroparalytic toxins. They are the most powerful such toxins currently known and temporarily prevent acetylcholine vesicles from docking into the presynaptic neuromuscular junction. Use of BTX-A for treatment of dystonia was recommended in a National Institutes of Health consensus statement in 1990.[9] It has been studied for a variety of dystonias, including blepharospasm, hemifacial spasm, laryngeal dystonia, oromandibular dystonia, and cervical dystonia, among other focal dystonias. Lew et al reported in 1997 on the successful use of BTX-B for cervical dystonia in a double-blind, single-treatment study,[10] and confirmatory studies followed.[11,12]

Varying indications for botulinum toxin

US Food and Drug Administration–approved indications for the toxins vary. The three BTX-A products and the single BTX-B product are approved for the treatment of cervical dystonia in adults to reduce the severity of abnormal head position and neck pain. OnabotulinumtoxinA is approved for treatment of blepharospasm and strabismus associated with dystonia; and incobotulinumtoxinA is approved for blepharospasm in patients who have previously been treated with onabotulinumtoxinA. BTX-A has also been found to be safe and effective for the management of focal dystonias. These botulinum toxin agents are not equivalent in dosing units, so caution must be observed when switching brands.

Patients selected to receive BTX for dystonia should meet three criteria:

- The dystonia should interfere with their functioning, comfort, or care to the degree that causes impairment and affects activities of daily living;
- Focal weakening following administration of the drug should not decrease their level of function; and
- The patient should understand that use of BTX may not completely address positioning, posturing, or secondary deformities.

Contraindications include pregnancy, lactation, comorbid neuromuscular disease (eg, amyotrophic lateral sclerosis or myasthenia gravis), and use of an aminoglycoside.

The need for BTX therapy should be reevaluated prior to each treatment; clinical benefit lasts 3 months or more. Electromyography may facilitate the location of target muscles, particularly since involved musculature may not be palpable and is often not superficial.[13] In-office tools that help document baseline and posttreatment results, including videotaping dystonic limb movements and the use of rating scales, can be important for evaluating the patient's progress.[14]

Relief for cervical dystonia

The treatment of choice for focal dystonias and focal aspects of generalized dystonia is BTX. Both BTX-A and BTX-B offer effective palliative treatments for cervical dystonia by improving neck position, reducing pain, and decreasing disability in sufferers.[11,15–18] The BTX solution is injected directly into the dystonic muscle at several locations, temporarily weakening the overactive muscle. The BTX dose is approximately proportional to the size of the muscle, although smaller muscles typically responsible for precision movement may require a relatively larger dose **(Table 2)**. Doses may be modified according to clinical factors such as muscle bulk and severity of dystonia **(Table 3)**.

TABLE 2
Botulinum toxin-A for cervical dystonia: Starting doses[a]

Potential muscles involved	Starting dose (units)	Starting range (units)	Approximate number of injection sites
Sternocleidomastoid	40	15–75	2
Scalene complex	30	15–50	3
Splenius capitis	60	15 or 30–100	4
Splenius cervicalis	30	20–60	2
Semispinalis capitis	60	30–100	4
Longissimus capitis	60	30–100	4
Trapezius	40	20 or 55–100	3
Levator scapulae	40	20–100	3

[a]In this example, the botulinum toxin-A is onabotulinumtoxinA.

TABLE 3
Potential botulinum toxin dose modifiers

Clinical situation	A *decrease* may be indicated	An *increase* may be indicated
Patient weight	Low	High
Likely duration of therapy	Chronic	Acute
Muscle bulk	Very small	Very large
Dystonia severity	Mild	Severe
Number of muscles injected	Many	Few

Relief following BTX injection for cervical dystonia occurs about 1 week later, with the greatest effect seen at about 2 to 6 weeks following injection; relief may last 12 to 16 weeks. Reinjections are not normally administered prior to 12 weeks' duration in order to reduce the possibility of antibody formation. Concomitant interventions addressing depression and anxiety may have a significant effect on overall quality of life.[19] Patients may also try several sensory tricks, called gestes antagoniste, which may temporarily reduce or alleviate the dystonia. However, these tactile procedures—such as placing a hand on top of the head—lose their effectiveness over time.

Treatment of blepharospasm, focal limb dystonia

The use of BTX-A for blepharospasm is a significant improvement over the former clinical reliance on various oral medications, which, with the exception of baclofen, proved largely ineffective.[20] Surgical treatments result in damage to muscular and nervous tissues, and so are reserved only for nonresponders to BTX-A therapy.[21]

BTX-A can provide effective relief and is the treatment of choice for focal limb dystonias.[22] Goals of treatment include functional improvement, correction of abnormal posture, and relief from discomfort. Although a variety of oral medications may also be prescribed, drug toxicity and adverse effects can outweigh the benefit and are usually only used in cases of severe dystonia. Oral medications used for limb dystonia include anticholinergics, dopamine agonists and antagonists, baclofen, clonazepam or other benzodiazepines, and muscle relaxants.

Antibodies may bind to the drug in a small percentage of patients who regularly receive injections of BTX, rendering additional injections of that specific serotype of BTX ineffective. This immunoresistance can be avoided if clinicians inject only the smallest quantity of BTX that achieves clinical efficacy, avoid administering booster injections before the end of the minimum 12-week lockout period, and extend the period between treatments as long as possible. If immunoresistance does occur, the BTX should be exchanged for a different serotype.

Testing for nonresponse

Patients are said to be nonresponders to BTX therapy if at 4 to 6 weeks following injection they show no reduction in muscle tone. A functional test for nonresponse is to inject a small amount of BTX into either the frontalis or sternocleidomastoid muscle prior to starting treatment; asymmetric weakness demonstrates a response, indicating that either injection technique or muscle selection is the problem. In addition to the development of neutralizing antibodies, other possible reasons for nonresponse include a dose that is too low or an alteration in the pattern of muscles involved in the dystonic movement.

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Correspondence: *Maurice Hanson, MD, Cleveland Clinic Florida, 525 Okeechobee Boulevard, City Place Tower, West Palm Beach, FL 33401; hansonm@ccf.org*