OPEN ACCESS Freely available online

Tremor and Other Hyperkinetic Movements

Reviews

Diagnosis and Treatment of Laryngeal Dystonia: Past, Present and Future Directions

Niv Mor[1*] **& Andrew Blitzer**[2]

[1] Maimonides Medical Center, Voice and Swallowing Disorders, Division of Otolaryngology—Head and Neck Surgery, New York, NY, USA, [2] New York Center for Voice and Swallowing Disorders, New York, NY, USA

Abstract

Background: Laryngeal dystonia is a task-specific focal dystonia of the internal laryngeal muscles.

Methods: Peer-reviewed articles on laryngeal dystonia from PUBMED were identified. Manuscripts that supported selected points of discussion were chosen. Illustrative figures and videos from the authors' personal files support selected ideas.

Results: This manuscript presents a comprehensive overview of the diagnoses and treatment of laryngeal dystonia and includes a brief history of the terminology, genetic mutations, and common misdiagnosis. In addition, the manuscript provides an in-depth description of the use of botulinum toxin (BoNT), including the mechanism of action, techniques for injections, and outcomes.

Discussion: Laryngeal dystonia is a complex clinically heterogeneous disorder. BoNT injection provides targeted therapy to the laryngeal muscles and has shown great efficacy in improving voice fluidity. Nevertheless, BoNT provides only symptomatic relief without altering the underlying disorder. Future therapeutic options that target the central nervous system may help clinicians better understand the pathophysiology of this condition.

Keywords: Laryngeal dystonia, spasmodic dysphonia, botulinum toxin

Citation: Mor N, Blitzer A. Diagnosis and treatment of laryngeal dystonia: past, present and future directions. Tremor Other Hyperkinet Mov. 2016; 6. doi: 10.7916/D8G160J5

*To whom correspondence should be addressed. E-mail: nivmor73@gmail.com.

Editor: Elan D. Louis, Yale University, USA

Received: September 16, 2015 **Accepted:** December 11, 2015 **Published:** March 16, 2016

Funding: None.

Financial Disclosures: None.

Conflict of Interest: The authors report no conflict of interest.

Ethics Statement: All patients that appear on video have provided written informed consent; authorization for the videotaping and for publication of the videotape was provided.

Introduction

Laryngeal dystonia is a clinical syndrome characterized by involuntary hyperfunctional contraction of the internal laryngeal muscles. The prominent feature of laryngeal dystonia is task specificity. Speaking is the most commonly affected task and is referred to as spasmodic dysphonia (SD). SD generally comes in two subtypes: adductor SD and abductor SD. Adductor SD is caused by inappropriate hyperadduction of the vocal folds leading to a strained and strangled voice quality. Adductor SD is five times more common than abductor SD.[1] Abductor SD is caused by inappropriate hyperabduction of the vocal folds and is heralded by intermittent breathy phonation when attempting to articulate voiceless consonants.

Throughout the years the etiology, terminology, characteristics, and treatment of SD have been debated. In this manuscript we present a comprehensive overview of laryngeal dystonias beginning in 1871 when the condition was first described by Taube. We have also included exemplary figures and videos, which give support to understanding the disorder and help differentiate it from other common laryngeal movement disorders.

Methods

The authors reviewed the literature onlaryngeal dysphonia. Peer-reviewed articles from PUBMED were identified. Additional books and supportive manuscripts were supplemented. Articles that best-support points of discussion were chosen. Illustrative figures and videos from the authors' personal files have been included to support selected ideas.

History and terminology

In 1871, Taube was the first to characterize SD when he described a "hysterical" girl with strained high-pitched hoarseness and called the disorder "spastic dysphonia".[2] Not yet recognized as a dystonia, the disorder was thought to be a result of muscular spasticity. Since that time the disorder has been described under multiple names, including spastic aphonia, lalophobia, aphthongia, and psychophonasthenia.[3–8] In 1887, Frankel noted a correlation between SD and another dystonic disorder, mogigraphia (occupational writers' cramp). He therefore called the disorder mogiphonia.[3,9] In 1973, Aronson was the first to group the disorder into the two subtypes, adductor subtype and abductor subtype, and in 1981 Aronson and Hartman recognized the disorder to be associated with a vocal tremor.[10,11]

Blitzer emphasized that the term "spastic dysphonia" was incorrect.[12] While spasticity is restricted voluntarily movement resulting from increased muscle tone, spasticity shows resistance to passive movement and is not task specific. Dystonic contractions are task-specific action-induced muscle spasms. Reciprocal inhibition results in co-contraction of opposing agonist and antagonist muscles. Restriction to passive movement is not seen in dystonia. In 1985 Blitzer used laryngeal electromyography (LEMG) to confirm SD as a dystonic disorder. Thus, the most accurate description of the disorder is "focal laryngeal dystonia."[12] In keeping with the spirit of Taube's originally coined term, the disorder was renamed "spasmodic dysphonia." While "laryngeal dystonia" broadly describes involuntary dystonic contractures to the laryngeal muscles without identifying the involved task, SD refers to laryngeal dystonia triggered by speech.

Epidemiology

SD is a rare disorder, and it is difficult to estimate its exact prevalence. According to the National Spasmodic Dysphonia Association, approximately 50,000 people in North America are affected by SD, with an estimated prevalence of 0.009%.[13,14] Taking into account that SD is often misdiagnosed, the true prevalence is likely somewhat higher. The majority of cases are in women (63%), and most (82.5%) are classified as primary idiopathic. The average age of onset is 39 years of age.[1] The first attack of SD may occur suddenly or can be triggered by a seemingly unrelated occurrence, such as trauma,[15–18] or viral illness.[19,20] Trauma is accepted as the inciting trigger when the onset of the dystonia occurs within 6–12 months of an identified injury. In some cases, the injury may be so mild that it is overlooked.[21]

Secondary SD is caused by a known underlying source. In most cases, secondary SD is due to a neurological disease, such as Wilson's disease, multiple sclerosis, or storage diseases. Rarely life-threatening, laryngeal dystonia occurs as an adverse side effect to certain neuroleptic medications.[22,23]

Genetics

While the cause of SD is still unknown, 20% will have a known dystonia gene mutation and 12% of patients will have a positive family history.[1] Hereditary dystonias are usually autosomal dominant and less frequently autosomal recessive or X-linked.

Genetic mutations are entitled "DYT," which stands for dystonia. DYT1 is caused by a mutation to torsinA and is the most common genetic cause of dystonia.[24–29] Although the role of torsinA in cellular function is not fully understood, its amino acid sequence is similar to that of heat shock proteins. Patients with DYT1 mutations present with early-onset dystonia before 10 years of age, and affected children usually progress to a more generalized dystonia.[26] Most DYT1 mutations are autosomal dominant; however, reduced penetrance within families may occur with some carriers having no clinical symptoms. DYT1 mutations are five to 10 times more common in the Ashkenazi Jewish population,[30–34] and 10–20% of patients will have voice symptoms.

A mutation to the tubulin beta-4A (TUBB4A) gene is associated with DYT4. Beta tubulin is primarily expressed in the central nervous system where it forms heterodimers with alpha-tubulin and is responsible for microtubule assembly. The mutation was first reported as "whispering dystonia" with autosomal dominant inheritance in an Australian family.[35] Patients in this family also have characteristics of Wilson's disease.[36] The observed whispering phenomenon has been recognized as adductor SD with compensatory whispering as a response to involuntary laryngeal hyperadduction. DYT4 dystonia also commonly affects the face and many will eventually develop generalized dystonia and dysphagia.

Mutations to the thanatos-associated protein domain containing apoptosis associated protein 1 (THAP1) have been identified as the basis for DYT6 dystonia. THAP1 is expressed in both the central and the peripheral nervous systems and is involved in transcriptional regulation, apoptosis, and cell-cycle control. The mutation was first recognized in Amish-Mennonites in the United States and has since been identified in a multitude of familial and sporadic cases from different racial and ethnic groups.[37–40] Inheritance is autosomal dominant with reduced penetrance and variable expressivity. Mutations to THAP1 are associated with adductor laryngeal dystonia.[37,41,42] The first signs of DYT6 dystonia are usually in the larynx, face, and neck with eventual progression towards segmental or generalized dystonia.

DYT25 is associated with a mutation in the guanine nucleotide binding protein alpha activating polypeptide (GNAL) gene. GNAL is involved in dopamine type 1 receptor function and olfactory signal transduction.[37] Inheritance is autosomal dominant and affected family members present with cervical or cranial–cervical dystonia. A few sporadic cases with similar phenotypes have also been reported.[43–45] Forty percent of patients with DYT25 mutation will also develop SD.[44,46]

Although there are already 27 known DYT gene mutations, reduced penetrance, variable expressivity, and rarity of this disorder make it difficult to provide the exact genetic or inherited prevalence.[47] Dystonia that is without a known genetic mutation or secondary cause is labeled as idiopathic. However, neither negative family history nor negative genetic testing can definitively exclude a genetic cause. Negative family history may result from reduced penetrance, late onset, early death, or a spontaneous mutation. It is also likely that some mutations have yet to be identified. We recently presented a review of 57 patients with isolated

laryngeal dystonia and found no carriers of TOR1A (DYT1), TUBB4A (DYT4), or THAP1 (DYT6) mutations. One patient was a carrier of a GNAL (DYT25) mutation without a familial history of dystonia.

Clinical characteristics

Patients with laryngeal dystonia have normal development and intellect. About 15% of patients with focal laryngeal dystonia will eventually develop dystonic contractions in areas other than the larynx.[1]

SD is the most common laryngeal dystonia. Although conversational speech is affected, breathing, coughing, laughing, yelling, crying, singing, and swallowing are normal. SD generally falls into one of two broad categories: adductor SD and abductor SD. Although rare, there are also cases of mixed SD showing characteristics of both adductor and abductor SD. Patients with SD often have an associated vocal tremor resulting from co-contraction of opposing muscle groups. Unlike the vocal tremor in essential tremor, the vocal tremor in SD is irregular. In some patients the vocal tremor can be subtle and may be overlooked on examination.

Adductor spasmodic dysphonia

Adductor SD involves contracture of the laryngeal muscles responsible for closing the vocal folds. These include the thyroarytenoid (TA), lateral cricoarytenoid (LCA), transverse arytenoid, and possibly the cricothyroid muscles (Figure 1A,C). Patients with adductor SD have difficulty when articulating consonants that require vocal closure. Clinically they have a choked, strained, and strangled voice with voice breaks during phonation. Glottic closure during swallowing and coughing are uninvolved. The laryngeal examination can be subtle or may show hyperfunctional closure of the true and false vocal folds or excessive vocal fold tension with voicing that normalizes with other tasks such as coughing, breathing, or swallowing (Video 1).

Abductor spasmodic dysphonia

Abductor SD involves contracture of the posterior cricoarytenoid (PCA) muscles, which are the sole muscles responsible for opening the glottis (Figure 1B, C). When phonating a voiceless consonant (/h/, /p/, /t/)

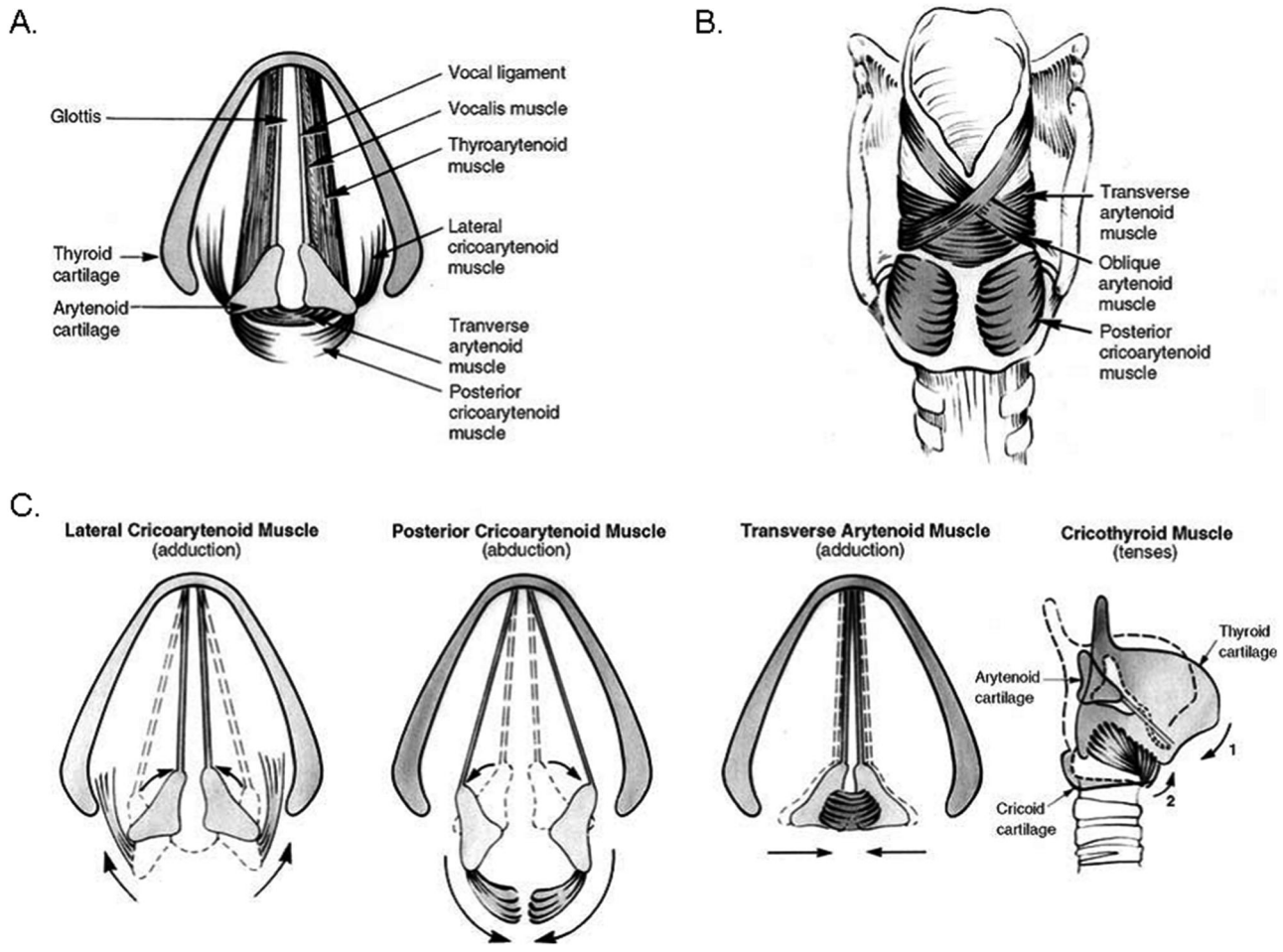
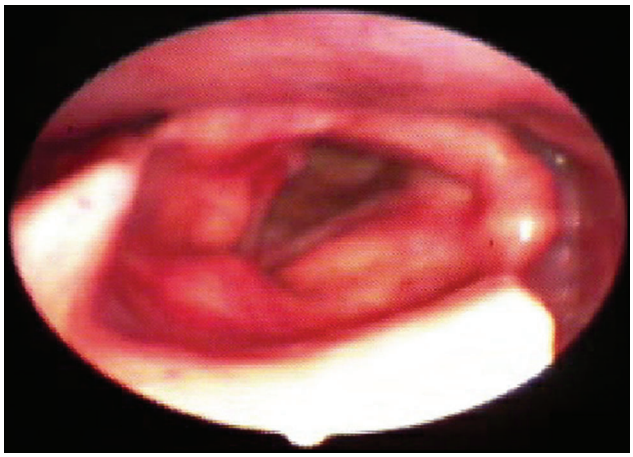
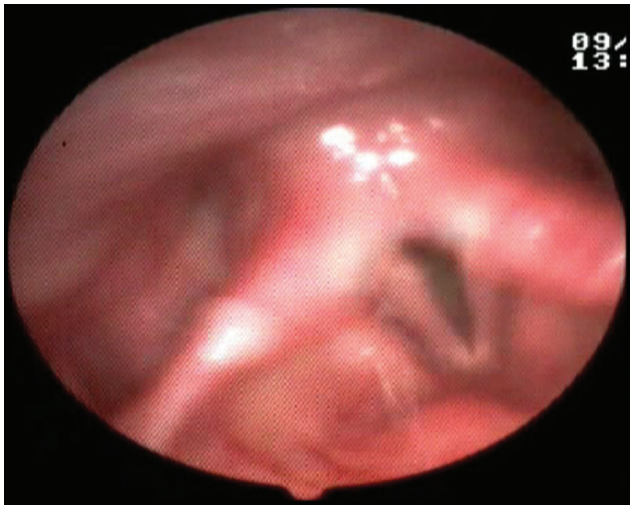


Figure 1. **Intrinsic Laryngeal Muscles and Effect on Vocal Fold Position.** Intrinsic muscles of the larynx (A,B) and the movement of the vocal folds caused by their contraction (C). Dashed lines indicate position of vocal folds and arytenoid cartilages before movement caused by contraction of the muscles (arrows). Solid lines indicate position of vocal cords and arytenoid cartilage after contraction. Cricothyroid muscle, 1 and 2 indicate movements of cartilages. With permission from Cooper MH. Anatomy of the Larynx In: Blitzer A, Brin MF, Sasaki CT, Fahn S, Harris K, editors. Neurological disorders of the larynx. New York: Thieme; 1992. p 6.



Video 1. Adductor Speech and Laryngeal Examination. Patients with adductor spasmodic dysphonia. Note the normal appearance to the larynx prior to phonation. This patient has a strained and strangled voice with voice breaks.



Video 2. Abductor Speech and Laryngeal Examination. Patients with abductor spasmodic dysphonia. Note the normal appearance to the larynx prior to phonation and with breathing. This patient has breathy voice breaks with phonation. She has normalization of voice with voiced consonants and severe whispered voice breaks with voiceless consonants.

the glottis must open widely. The vocal folds of patients with abductor SD persist in the open position resulting in a prolonged, effortful, aphonic, and breathy voice quality. The laryngeal examination may show hyperfunctional abduction of one or both vocal folds and voicing with normal glottic opening during inspiration or coughing (Video 2).

Mixed and compensatory spasmodic dysphonia

Some patients show characteristics of both adductor and abductor SD, which makes diagnosing the correct SD subtype challenging. The diagnosis of mixed SD is often made when one subtype gets worse or is revealed following successful treatment of the other subtype. Patients with mixed SD often require treatment to both adductor and abductor muscles.[1] We have also observed patients convert from pure adductor SD to pure abductor SD, and the other way around, following years of successful treatment.

Some patients have compensatory behaviors to a particular SD subtype and are mistakenly categorized as having mixed SD. For instance, compensatory pseudo-abductor dysphonia occurs when patients with adductor SD initiate words with a whisper to prevent the onset of adductor spasms while voicing. This was recognized as the phenomenology in DYT4 dystonia. Compensatory pseudo-adductor dysphonia is less common. In this instance, patients with severe abductor SD phonate before voiceless consonants to overcome involuntary breathy voice breaks.[48–50]

Cannito and Johnson[51] proposed that SD should be seen on a continuum and cannot be placed neatly into strict categories such as adductor SD, abductor SD, or mixed SD. They suggest that an individual's symptomatology depends on their directional preponderance. Findings by Hillel[52] also suggest that SD may be a more heterogeneous disorder. He found that patients with adductor, abductor, and mixed SD each have abnormal LEMG signals in all intrinsic laryngeal muscles during both phonatory and non-phonatory tasks.

Task specificity

The prominent feature of laryngeal dystonia is that of task specificity. Speaking is the most commonly affected task with preservation of a normal cough, laugh, and singing voice. Less commonly, alternate laryngeal tasks are implicated. We have reported on cases of respiratory adductor laryngeal dystonia where involuntary vocal fold adduction occurs upon inspiration.[53–56] These patients have normal laryngeal function when speaking, singing, coughing, and swallowing.

Occupational dystonia

The term occupational dystonia refers to the development of dystonic movements to highly skilled tasks usually involving a repetitive motor activity.[57,58] Musicians are often affected. Although the precise pathophysiology of occupational dystonia remains unclear, observations of musicians suggest that increased corticospinal excitability and reduced cortical inhibition play a role.[59–61] The observed sensorimotor reorganization likely facilitates the acquisition of uninhibited motor skills necessary in expanding a musician's creativity at the expense of potentially developing a focal dystonia while playing an instrument.[62–66] We have reported on cases of "singer's dystonia," where patients have a fluent voice quality with conversational speech and laryngeal hyperkinesias solely with singing.[67,68] "Singer's dystonia" is viewed as an occupational dystonia.

Sensory trick

Geste antagonistique, or sensory trick, consists of maneuvers that stimulate tactile proprioceptive signals and temporarily ameliorate

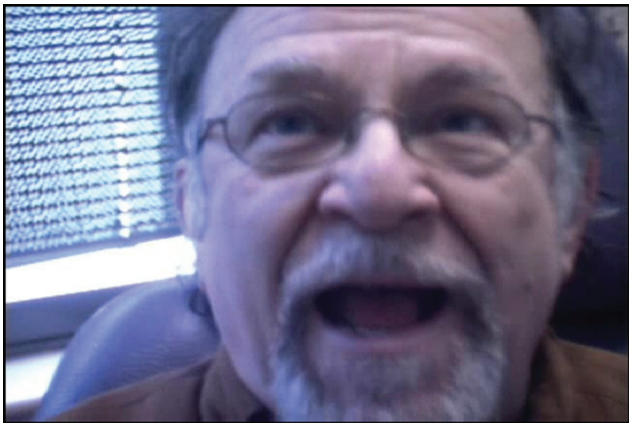
the dystonic movements.[69] While the physiological mechanism of the sensory tricks is unknown, it is likely a result of temporary alterations to the afferent feedback.[70,71] Patients with SD have reported improved symptoms by various maneuvers, including pinching the nares, placing pressure on their head, abdomen, or clavicle, or pulling their ear.[72,73] The sensory trick is such a powerful exercise that some patients have reported reduced dystonic activity by simply thinking of their particular sensory trick.[74] Over time, the sensory trick generally loses its effectiveness. The reason for this is also unknown, but is likely a result of central nervous system adaptation. The video below depicts a patient with adductor SD who achieves fluidity of speech with palatal elevation (Video 3).

Pathophysiology

Although the clinical symptoms in laryngeal dystonia are well described, the pathophysiology of the disorder is unknown. Task specificity suggests a central cause. SD likely involves abnormalities to areas in the brain responsible for learned voice production, explaining why areas responsible for innate vocalizations, such as crying and laughing, are unaffected. Recent studies have demonstrated altered brain activity by functional magnetic resonance imaging (fMRI) in patients with SD compared with normal controls.[75] Laryngeal feedback to the brain was the most impaired function and may play a key role. Surprisingly, differences in brain activity were noted during both symptomatic and asymptomatic tasks. Structural differences connecting the cortex to the brain stem were also observed in patients with SD.[76]

Diagnosis

The diagnosis of SD is made primarily on the perceptual analysis of the voice in the absence of secondary causes. Laryngeal examination may show hyperadduction or prolonged abduction of the vocal folds with phonation but may also be normal. Although LEMG may show intrusion of spasmodic bursts, these findings are not consistently found in all patients.[12] Currently, the use of imaging is limited to scientific research studies. As such, there are no good objective studies to diagnose SD. Making the correct diagnosis relies on an experienced clinician with a good ear.



Video 3. Sensory Trick. This video depicts a patient with adductor spasmodic dysphonia who can achieve fluidity of voice with palatal elevation.

Alternate diagnosis

As stated above, the diagnosis of SD is ultimately made from patients' clinical symptomatology and relies on an experienced physician with a trained ear. Objective studies may be normal, making it difficult to differentiate SD from other laryngeal voice disorders like essential vocal tremor, or muscle tension dysphonia.[77]

Vocal tremor

The vocal tremor in SD is a result of isometric co-contraction of antagonistic muscles. However, vocal tremors can be seen in other disorders such as essential tremor, Parkinson's disease, Tourette's syndrome, vocal tics, cerebellar ataxia, and flaccid dysarthria.[78–80] Vocal tremor in SD is a consequence of loss of reciprocal inhibition resulting in an irregular isometric tremor. Essential laryngeal tremor is characterized by reciprocal oscillatory movement of antagonistic muscles and shows regular rhythmic 4–12 hertz frequency tremors. Laryngeal examination often shows vertical or horizontal movement of the larynx with speaking or with quiet respirations[81–84] (Video 4). Although much less common, periods of co-contraction have been reported in essential tremor and regular periodic tremors have been observed in SD.[12]

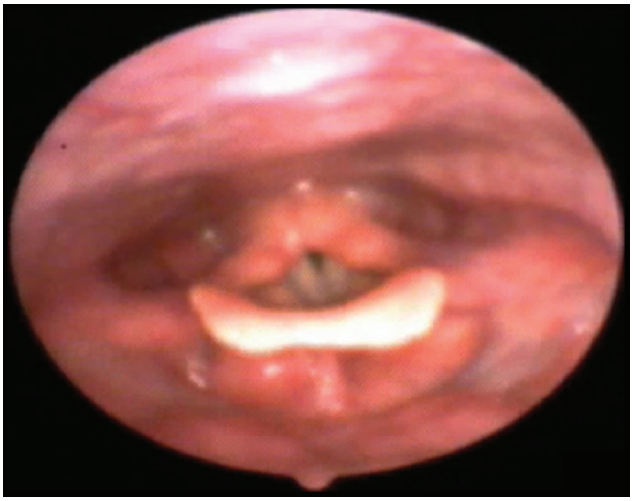
Muscle tension dysphonia

Muscle tension dysphonia occurs when patients squeeze the laryngeal muscles while speaking. Patients often produce voice with muscles that are not meant for voice production. Excessive laryngeal squeezing causes a strained, tight, and tense voice quality that could be mistaken for adductor SD. Most commonly, misuse includes vibration of the ventricular vocal folds (false vocal folds). Patients may also incorporate muscle activity from the laryngeal strap muscles or the sternocleidomastoid muscles and may report tenderness of the cervical muscles.[85] Laryngeal muscle misuse generally develops as a persistent adaptation to a temporary injury, infection, or paresis. In most instances, the diagnosis of muscle tension dysphonia can be made by physical examination findings. Muscle tension dysphonia is best treated with voice therapy. Infrequently we have injected botulinum toxin (BoNT) into the ventricular vocal folds in cases of severe refractory muscle tension dysphonia (Video 5).

Treatment

Surgery

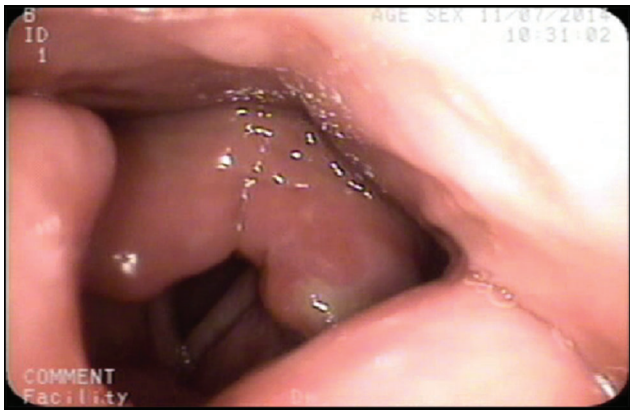
In 1976, Dedo[86] reported normalization of voice quality following unilateral section of the recurrent laryngeal nerve (RLN). Surgery was performed with hopes of relieving aberrant laryngeal muscle activity at the cost of unilateral vocal fold paralysis. Initial studies reported an 85–90% success rate; however, a 3-year follow-up showed that 64% of patients had a return of pathologic voice quality.[87–89] Several procedures designed to mechanically relax the vocal folds through alterations in the laryngeal framework also failed to demonstrate long-term success.[90,91]



Video 4. Essential Vocal Tremor. Note the oscillatory rhythmic vertical and horizontal movement of the larynx with a sustained phonation in this patient with essential vocal tremor. The patient has adapted quick bursts of staccato speech and voices in-between rhythmic tremors to mask her disorder. Also note the presence of a tremor at both arytenoids during quiet respiration.

Part of the dramatic initial improvement seen with surgery could be attributed to acute alterations in peripheral proprioceptive signals similar to a sensory trick. Nevertheless, the peripheral alteration is fixed, and central adaptation may explain the high rate of recidivism.

In 1986, Blitzer found dramatic improvement in voice quality following direct injection of BoNT into the affected laryngeal muscles.[48] Unlike neuronal surgery, BoNT injection is selective. In addition, the toxin is continuously metabolized, thus the ever-changing effect does not allow for central adaptation. However, the response to BoNT is temporary, necessitating repeat injection. In an attempt to provide permanent selective denervation, Berke et al.[92] performed a selective denervation–reinnervation procedure. The branches of the RLN responsible for innervating only the adductor laryngeal muscles were cut and then anastomosed to a branch of the ansa cervicalis.[92]



Video 5. Muscle Tension Dysphonia Speech and Laryngeal Examination. Laryngeal exam of a patient with severe muscle tension dysphonia with sphincteric supraglottic squeezing and a strangulated voice quality. Notice that voice fluidity is improved following exercises that loosen his laryngeal muscles.

Critics of RLN transection claimed that recidivism resulted from persistent hyperadduction from the unaffected nerve. Berke thus performed the denervation–reinnervation procedure bilaterally, and the procedure was only performed in patients with adductor SD. Although initial results are promising, long-term results show the return of voice breaks in 26% and a breathy voice quality in 30%.[93]

Voice therapy

Voice therapy may be useful in preventing unwanted compensatory voice patterns and results are usually discouraging.[94]

Systemic oral medications

Systemic medications generally act on the central nervous system and reduce excess muscle and nerve activity. Although the medications discussed below are commonly used in SD, none is approved by the United States Food and Drug Administration for use in dystonia.

Anticholinergic agents act centrally and peripherally, and although they are the most successful systemic medications their side-effects (flushing, hyperthermia, dry skin, urinary retention, tachycardia, confusion, agitation, and hallucinations) are not always tolerated.[95] The most commonly used medications in dystonia act centrally on gamma-aminobutyric acid (GABA) neurotransmitters (benzodiazepines, baclofen, and gabapentin).[95,96] Common side effects of these medications include sleepiness, depression, loss of balance, and confusion. Medications that modulate GABA must be used with caution as they carry a risk of dependence, and sudden withdrawal could incite serious life-threatening complications such as seizures.[97–99] Levodopa, commonly used in treating Parkinson's disease, increases centrally available dopamine and is occasionally also used in dystonia.[95] Carbidopa, often used in combination with levodopa, inhibits the peripheral conversion of levodopa and reduces the peripheral side effects of dopamine.

No systemic oral medication is uniformly effective in treating laryngeal dystonia, and they are mostly used adjectively to prolong the duration of BoNT.

Botulinum toxin

The gold standard for treatment of laryngeal dystonia is EMG-guided BoNT injections directed to the affected muscle.

Mechanism of action

BoNT is a 150-kD exotoxin produced from *Clostridium botulinum*, whose action is mediated through the cleavage of docking proteins responsible for membrane fusion of pre-synaptic vesicles. Type A botulinum toxin (BoNT-A) cleaves the membrane-associated protein "synaptosomal-associated protein"[25] (SNAP-25), which is a member of the "soluble *N*-ethylmaleimide-sensitive factor attachment protein C receptor" (SNARE) protein. Type B botulinum toxin (BoNT-B) cleaves synaptobravin, which is part of the vesicular-associated membrane protein. Cleavage of these docking proteins leads to inhibition of acetylcholine release at the neuromuscular junction, and subsequent muscle weakness.

Chemodenervation of aberrant laryngeal muscle activity does not fully explain the clinical effects of BoNT in SD, as evidenced by the efficacy of unilateral injections. The likely effect of BoNT also includes modulation to the afferent sensory feedback from peripheral muscles to the central nervous system.[100–102] BoNT also decreases the activation of muscle spindles directly through its effect on intrafusal afferent sensory fibers.[103,104] Lastly, the effect of BoNT is constantly changing over the course of 12 weeks, making central adaptation difficult.[105] If the effect of BoNT also imposes a sensory trick, then the effect will be sustained throughout the entire biological activity of the toxin.

Injection technique

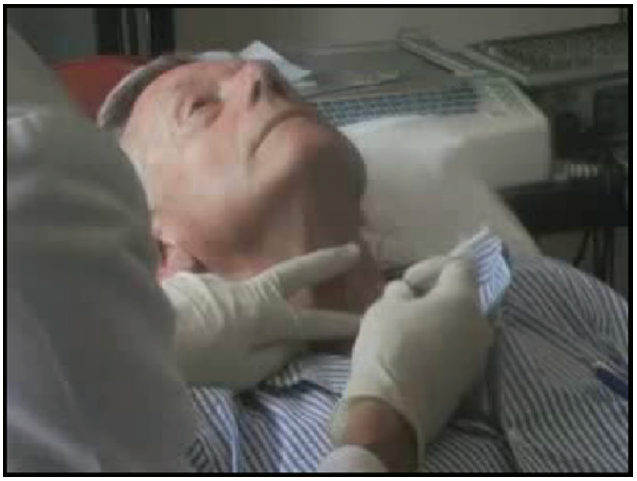
The most common approach to BoNT laryngeal injections is via transcutaneous EMG-guided needle injection to the affected laryngeal muscle. We advocate using low-volume injections to prevent diffusion to neighboring muscles, which can lead to unnecessary side effects.[106] Patient follow-up is 2 weeks after the initial injection for dosage adjustment. Once an effective dose is established, patients generally follow-up every 12 weeks for repeat injections. SD, like all dystonias, is a dynamic disorder and the severity of symptoms may progress or improve over time. We therefore make dose adjustments at every follow-up visit on the basis of each individual patient's symptoms.

The TA or LCA muscles are targeted for adductor SD (Figure 1A). The most common approach is through the cricothyroid membrane and injections are generally well tolerated. Our initial dose is 1 unit to each TA or LCA, and the dose is adjusted on subsequent visits. On average, the response to therapy begins 2.4 days after TA/LCA injection[1] (Video 6).

The PCA muscle is targeted for abductor SD (Figure 1B). The larynx is rotated and injection is achieved transcutaneously through the pyriform sinus. EMG confirmation is obtained with the electrode against the posterior cricoid cartilage while the patient abducts their vocal folds by sniffing though their nose (i.e., PCA contraction) (Figure 1C). In difficult cases, access to the PCA can be achieved transcutaneously through the cricothyroid membrane. In such cases, the injection needle is extended into the lumen of the subglottis and directed 30 degrees off midline towards the posterior cricoid ring. The posterior cricoid cartilage is punctured, and BoNT is injected upon EMG confirmation from the PCA. Before every PCA injection, we perform a dynamic laryngeal examination to assess airway patency. We only perform unilateral injections to the PCA and inject the more active side to prevent excessive airway narrowing. Our starting dose is 3.75 units. High-dose injections risk excessive airway narrowing and in rare cases may necessitate tracheotomy. High-volume injection may diffuse inferiorly and may risk dysphagia from effects to the cricopharyngeal muscle. On average, the response to therapy begins 4.1 days after PCA injections[1] (Video 7).

Outcomes

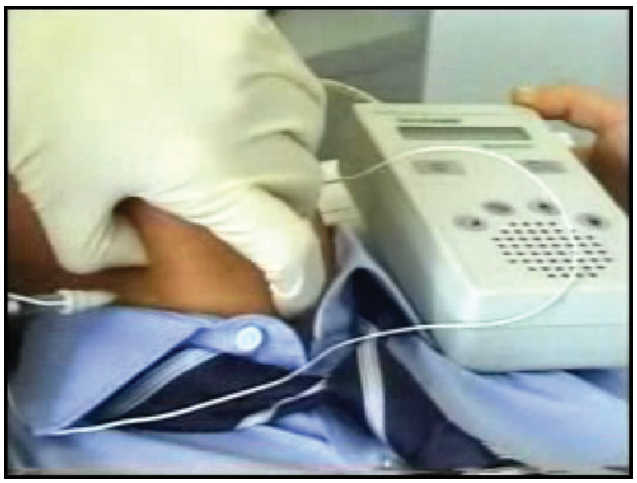
In general patients have good clinical responses to BoNT, and they are able to regain the fluidity in their voice (Video 8). In our series of 901 patients treated for over 12 years (6,280 sessions), we found that patients with abductor SD do not achieve the same degree of voice



Video 6. Cricothyroid Injection Technique for Adductor Spasmodic Dysphonia. Transcutaneous electromyography (EMG)-guided botulinum toxin injection into the thyroarytenoid muscles through the cricothyroid membrane. Note confirmation of intramusclar placement by audible EMG signal.

normalization as adductor SD patients.[1] Patients with abductor SD reported improvement to 66.7% of normal function lasting on average 10.5 weeks compared with nearly 90% of normal function lasting on average 15.1 weeks in patients with adductor SD. It is therefore not surprising that 30% of patients with abductor SD supplement BoNT injections with systemic oral medication.[106]

Novakovic et al.[105] found that 28.5% of patients with adductor SD will have an initial decline of function with a breathy voice quality before improving (Figure 2B). The initial functional decline lasts approximately 2 weeks and they are at risk of aspiration during this period.[1,106] Voice quality generally normalizes thereafter with maximal benefit sustained over approximately 6 weeks. This period is followed by a slow decline



Video 7. Posterior Cricoarytenoid Injection Technique for Abductor Spasmodic Dysphonia. Transcutaneous botulinum toxin injection into the posterior cricoarytenoid. The larynx is rotated and injection is achieved through the pyriform sinus. Electromyography confirmation is obtained while the patient is asked to sniff.

Video 8. Before and After Botulinum ToxinInjection. This video depicts a patient with abductor spasmodic dysphonia before and after botulinum toxin injection. Note that the patient has severe breathy voice breaks before injection and has regained fluidity of his voice following botulinum toxin injection.

over 4 weeks.[105] Although not all patients responded with an initial decline of function, those who did ultimately achieved a higher percentage of normal function than those who did not (Figure 2A, B).

Poor clinical response to BoNT occasionally occurs and is usually due to inadequate dosing, inappropriate technique, or dynamic changes of the underlying laryngeal dystonia. Injection of supraglottic muscles, the cricothyroid muscle, or transverse arytenoid musclehas demonstrated some benefit in refractory cases.[107,108] In rare instances, patients with SD may become secondarily non-responsiveness to BoNT following an initial good response. This effect likely results from the development of anti-BoNT antibodies.[109–111] Over time and following the removal of the antigenic stimulus, patients will revert back to negative antibody status and have a good clinical response to re-injections. During the cessation period, patients will respond well to BoNT injection of a different serotype. Clinicians should be aware that different BoNT serotypes have their own dosing regimen, onset, and duration.[112]

Future therapeutic options

A recent survey showed that 55.9% of patients with SD have improvement of voice following ingestion of alcohol.[113] In this study, the duration of benefits was between 1 and 3 hours, with the maximal effect occurring after two drinks. The effect of alcohol in SD may be related to the effect of alcohol on GABA receptors. A metabolite of sodium oxybate, used to treat excessive daytime sleepiness in narcolepsy, also acts on GABA receptors and is currently being investigated in treating selected patients with SD whose dystonia improves following ingestion of alcohol.[114–117]

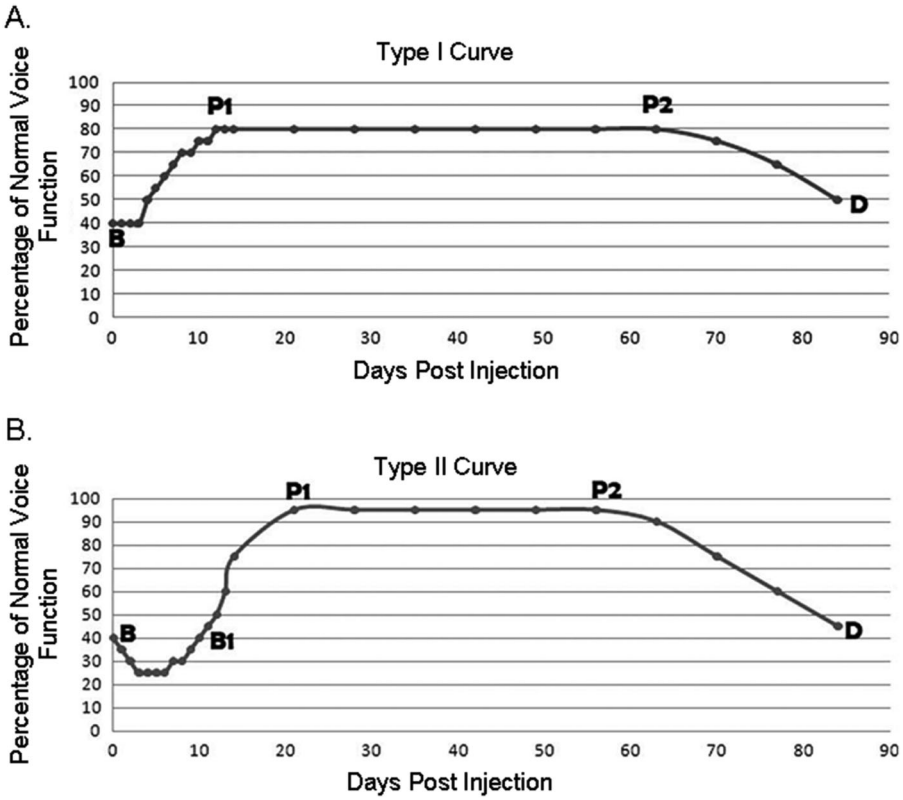


Figure 2. Vocal Function Over Time. The above graph represents percentage of normal voice function from the time of initial Botulinum Toxin Injection against time. Two general configurations are represented. (A) Type I curves shows 80% normal voice function in the plateau phase without initial breathiness. (B) Type II cures show an initial decline of function, but patients ultimately achieved higher percent of normal function in the plateau phase. B, Baseline; B1, Return to Baseline; P1–P2, Plateau Phase; P2-D, Decline Phase.

Scientists are searching formore efficient forms of BoNT with improved efficacy at a lower therapeutic dose.[118,119] Future developments in bioengineering will likely unleash recombinant neurotoxins capable of increased specificity for targeting only certain cells or areas of the body.

Conclusion

Laryngeal dystonia is a task-specific focal disorder of the central nervous system that affects the laryngeal muscles. Spasmodic dysphonia is when laryngeal dystonia affectsvolitional speech. Mechanical alterations temporarily elude the central nervous system and abolish the aberrant signal. However the brain eventually adapts to static changes. BoNT injection provides targeted therapy to the laryngeal muscles and has shown great efficacy in improving voice fluidity. Nevertheless, BoNT provides only symptomatic relief without altering the underlying disorder. Future therapeutic options that target the central nervous system may help clinicians better understand the pathophysiology of SD and may add to our therapeutic armamentarium.

References

1. Blitzer A, Brin MF, Stewart CF. Botulinum toxin management of spasmodic dysphonia (laryngeal dystonia): A 12-year experience in more than 900 patients. *Laryngoscope* 1998;108:1435–1441. doi: 10.1097/00005537-199810000-00003.

2. Traube L. Zur Lehre von den larynxaffectionen beim ileotyphus. Berlin: Verlag Van August Hisschwald; 1871. p674–678.

3. Arnold GE. Spastic dysphonia: Changing interpretations of a persistent affliction. *Logos* 1959;2:3–14.

4. Schnitzler J. Aphonia spastica. *Wien. Med. Presse* 1875;16:429–432. 477–479.

5. Coen R. Pathologie und Therapie der Sprachanomalien. Vienna: Urban and Schwarzenberg; 1886.

6. Gutzmann H. Zur Heilung der Aphonia spastica. *Maschr. Ges. Sprachheilk* 1898;8:8–15.

7. Greene JS. Psychiatric therapy for dysphonia, aphonia, psychophonasthenia, falsetto. *Arch Otolaryng* 1938;28:213–221.

8. Bicknell JM, Greenhouse AH, Pesch RN. Spastic dysphonia. *J Neurol Neurosurg Psychiatry* 1968;31:158–161.

9. Frankel B. Uber die Beschaftigungsschwahe der stimme: Mogiphonie. *Dtsch. med. Wschr* 1887;13:121–123.

10. Aminoff MJ, Dedo HH, Izdebski K. Clinical aspects of spasmodic dysphonia. *J Neurol Neurosurg Psychiatry* 1978;41:361–365.

11. Aronson AE, Hartman DE. Adductor spastic dysphonia as a sign of essential (voice) tremor. *J Speech Hear Disord* 1981;46(1):52–58.

12. Blitzer A, Lovelace RE, Brin MF, Fahn S, Fink ME. Electromyographic findings in focal laryngeal dystonia (spastic dysphonia). *Ann Otol Rhinol Laryngol* 1985;94:591–594.

13. National Spasmodic Dysphonia Association. Spasmodic dysphonia. Research, Awareness, and Support for People Living with Spasmodic Dysphonia; 2015. Retrieved from https://www.dysphonia.org/spasmodic-dysphonia.php.

14. North America Population 2015. Work Population Review WPR; 2015. Retrieved from http://worldpopulationreview.com/continents/north-america-population/.

15. Brin MF, Fahn S, Bressman SB, Burke RE. Dystonia precipitated by peripheral trauma. *Neurology* 1986;36:119.

16. Jankovic J. Can peripheral trauma induce dystonia and other movement disorders? Yes! *Mov Disord* 2001;16:7–12.

17. O'Riordan S, Hutchinson M. Cervical dystonia following peripheral trauma—a case-control study. *J Neurol* 2004;251:150–155.

18. Weiner WJ. Can peripheral trauma induce dystonia? No! *Mov Disord* 2001;16:13–22.

19. Teoh KH, Christakis GT, Weisel RD, et al. Dipyridamole preserved platelets and reduced blood loss after cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 1988;96:332–341.

20. Schaefer SD. Neuropathology of spasmodic dysphonia. *Laryngoscope* 1983; 93:1183–1204. doi: 10.1288/00005537-198309000-00015.

21. Schott GD. The relationship of peripheral trauma and pain to dystonia. *J Neurol Neurosurg Psychiatry* 1985;48:698–701. doi: 10.1136/jnnp.48.7.698.

22. Warren J, Thompson P. Drug-induced supraglottic dystonia and spasmodic dysphonia. *Mov Disord* 1998;13:978-979. doi: 10.1002/mds.870130623.

23. Newton-John H. Acute upper airway obstruction due to supraglottic dystonia induced by a neuroleptic. *BMJ* 1988;297:964–965. doi: 10.1136/bmj.297.6654.964.

24. Bressman SB, De Leon D, Raymond D, et al. Secondary dystonia and the DYTi gene. *Neurology* 1997;48:1572–1577. doi: 10.1212/WNL.48.6.1571.

25. Ozelius LJ, Hewett JW, Page CE, et al. The gene (DYT1) for early-onset torsion dystonia encodes a novel protein related to the Clp protease/heat shock family. *AdvNeurol* 1998;78:93–105.

26. Kramer PL, de Leon D, Ozelius L, et al. Dystonia gene in Ashkenazi Jewish population is located on chromosome 9q32–34. *Ann Neurol* 1990;27:114–120. doi: 10.1002/ana.410270203.

27. Ozelius LJ, Kramer PL, de Leon D, et al. Strong allelic association between the torsion dystonia gene (DYT1) and loci on chromosome 9q34 in Ashkenazi Jews. *Am J Hum Genet* 1992;50:619–628.

28. Rostasy K, Augood SJ, Hewett JW, et al. TorsinA protein and neuropathology in early onset generalized dystonia with GAG deletion. *Neurobiol Dis* 2003;12:11–24.

29. Ozelius LJ, Hewett JW, Page CE, et al. The early-onset torsion dystonia gene (DYT1) encodes an ATP-binding protein. *Nat Genet* 1997;17:40–48. doi: 10.1038/ng0997-40.

30. Ozelius L, Kramer PL, Moskowitz CB, et al. Human gene for torsion dystonia located on chromosome 9q32-q34. *Neuron* 1989;2:1427–1434. doi: 10.1016/0896-6273(89)90188-8.

31. Gasser T, Bove CM, Ozelius LJ, et al. Haplotype analysis at the DYT1 locus in Ashkenazi Jewish patients with occupational hand dystonia. *Mov Disord* 1996;11:163–166. doi: 10.1002/mds.870110208.

32. Risch NJ, Bressman SB, deLeon D, et al. Segregation analysis of idiopathic torsion dystonia in Ashkenazi Jews suggests autosomal dominant inheritance. *Am J Hum Genet* 1990;46:533–538.

33. Klein C, Brin MF, de Leon D, et al. De novo mutations (GAG deletion) in the DYT1 gene in two non-Jewish patients with early-onset dystonia. *Hum Mol Genet* 1998;7:1133–1136. doi: 10.1093/hmg/7.7.1133.

34. Lee WW, Ahn TB, Chung SJ, Jeon BS. Phenotypic differences in Dyt1 between ethnic groups. *Curr Neurol Neurosci Rep* 2012;12:341–347. doi: 10.1007/s11910-012-0285-4.

35. Lohmann K, Wilcox RA, Winkler S, et al. Whispering dysphonia (DYT4 dystonia) is caused by a mutation in the TUBB4 gene. *Ann Neurol* 2013;73:537–545. doi: 10.1002/ana.23829.

36. Parker N. Hereditary whispering dysphonia. *J Neurol Neurosurg Psychiatry* 1985;48:218–224.

37. Petrucci S, Valente EM. Genetic issues in the diagnosis of dystonias. *Front Neurol* 2013;4:34. doi: 10.3389/fneur.2013.00034.

38. LeDoux MS, Xiao J, Rudzińska M, et al. Genotype-phenotype correlations in THAP1 dystonia: molecular foundations and description of new cases. *Parkinsonism Relat Disord* 2012;18:414–425.

39. Blanchard A, Roubertie A, Simonetta-Moreau M, et al. Singular DYT6 phenotypes in association with new THAP1 frameshift mutations. *Mov Disord* 2011;26:1774–1776. doi: 10.1002/mds.23641.

40. Bonetti M, Barzaghi C, Brancati F, et al. Mutation screening of the DYT6/THAP1 gene in Italy. *Mov Disord* 2009;24:2424–2427. doi: 10.1002/mds.22640.

41. Djarmati A, Schneider SA, Lohmann K, et al. Mutations in THAP1 (DYT6) and generalised dystonia with prominent spasmodic dysphonia: A genetic screening study. *Lancet Neurol* 2009;8:447–452. doi: 10.1016/S1474-4422(09)70083-3.

42. Xiao J, Zhao Y, Bastian RW, et al. Novel THAP1 sequence variants in primary dystonia. *Neurology* 2010;74:229–238. doi: 10.1212/WNL.0b013e3181ca00ca.

43. Charlesworth G, Plagnol V, Holmstrom KM, et al. Mutations in ANO3 cause dominant craniocervical dystonia: Ion channel implicated in pathogenesis. *Am J Hum Genet* 2012;91:1041–1050.

44. Fuchs T, Saunders-Pullman R, Masuh I, et al. Mutations in GNAL cause primary torsion dystonia. *Nature Genet* 2013;45:88–92. doi: 10.1038/ng.2496.

45. Xiao J, Uitti RJ, Zhao Y, et al. Mutations in CIZ1 cause adult onset primary cervical dystonia. *Ann Neurol* 2012;71:458–469. doi: 10.1002/ana.23547.

46. Bressman SB, Heiman GA, Nygaard TG, et al. A study of idiopathic torsion dystonia in a non-Jewish family: Evidence for genetic heterogeneity. *Neurology* 1994;44:283–287. doi: 10.1212/WNL.44.2.283.

47. Zech M, Lam DD, Francescatto L, et al. Recessive mutations in the alpha-3 (VI) collagen gene COL6A3 cause early-onset isolated dystonia. *Am J Hum Genet* 2015;96:883–893. doi: 10.1016/j.ajhg.2015.04.010.

48. Blitzer A, Brin MF, Fahn S, Lovelace RE. Clinical and laboratory characteristics of laryngeal dystonia: A study of 110 cases. *Laryngoscope* 1988;98:636–640. doi: 10.1288/00005537-198806000-00012.

49. Brin MF, Fahn S, Blitzer A, Ramig LO, Stewart C. Movement disorders of the larynx. In: Blitzer A, Brin MF, Sasaki CT, Fahn S, Harris K, editors. Neurological disorders of the larynx. New York: Thieme; 1992. p240–248.

50. Blitzer A, Brin MF. Laryngeal dystonia: A series with botulinum toxin therapy. *Ann Otol Rhinol Laryngol* 1991;100:85–90. doi: 10.1177/000348949110000201.

51. Cannito MP, Johnson P. Spastic dysphonia: Acontinuum disorder. *J Comm Disord* 1981;14:215–223.

52. Hillel AD. The study of laryngeal muscle activity in normal and laryngeal dystonia using multiple fine-wire electromyography. *Laryngoscope* 2001;11:1–47.

53. Grillone GA, Blitzer A, Brin MF, Annino DJ Jr, Saint-Hilaire MH. Treatment of adductor laryngeal breathing dystonia with botulinum toxin type A. *Laryngoscope* 1994;104:30–32. doi: 10.1288/00005537-199401000-00007.

54. Brin MF, Blitzer A, Braun N, Stewart C, Fahn S. Respiratory and obstructive laryngeal dystonia treatment with botulinum toxin (Botox). *Neurology* 1991;41:293.

55. Baer JW, Braun N, Brin MF, Stewart C, Austin J, Blitzer A. Disordered diaphragmatic motion in patients with cranial dystonia: Afluoroscopic study. *Neurology* 1992;42:240.

56. Braun N, Abd A, Baer J, Blitzer A, Stewart C, Brin M. Dyspnea in dystonia. A functional evaluation. *Chest* 1995;107:1309–1316.

57. Gatto EM, Pardal MMF, Reisin RC, Pardal AM. Playing harp, another unusual task-specific dystonia. *Mov Disord* 2001;16:778–779. doi: 10.1002/mds.1134.

58. Ragothaman M, Sarangmath N, Jayaram S, Swaminath PV, Muthane U. Task-specific dystonia in tabla players. *Mov Disord* 2004;19:1254–1256. doi: 10.1002/mds.20195.

59. Rosenkranz K, Williamon A, Butler K, Cordivari C, Lees AJ, Rothwell JC. Pathophysiological differences between musician's dystonia and writer'-scramp. *Brain* 2005;128:918–931. doi: 10.1093/brain/awh402.

60. Quartarone A, Bagnato S, Rizzo V, et al. Abnormal associative plasticity of the human motor cortex in writer's cramp. *Brain* 2003;126:2586–2596. doi: 10.1093/brain/awg273.

61. Stinear CM, Byblow WD. Impaired modulation of corticospinal excitability following subthreshold rTMS in focal hand dystonia. *Hum Mov Sci* 2004;23:527–538. doi: 10.1016/j.humov.2004.08.022.

62. Torres-Russotto D, Perlmutter JS. Task-specific dystonias. *Ann NY Acad Sci* 2008;1142:179–199. doi: 10.1196/annals.1444.012.

63. Hallett M. Pathophysiology of writer's cramp. *Hum Mov Sci* 2006;25:454–463. doi: 10.1016/j.humov.2006.05.004.

64. Schicatano EJ, Basso MA, Evinger C. Animal model explains the origins of the cranial dystonia benign essential blepharospasm. *J Neurophysiol* 1997;77:2842–2846.

65. Evinger C. Animal models of focal dystonia. *NeuroRx* 2005;2:513–524. doi: 10.1602/neurorx.2.3.513.

66. Byl N, Wilson F, Merzenich M, et al. Sensory dysfunction associated with repetitive strain injuries of tendinitis and focal hand dystonia: Acomparative study. *J Orthop Sports Phys Ther* 1996;23:234–244. doi: 10.2519/jospt.1996.23.4.234.

67. Chitkara A, Meyer T, Keidar A, Blitzer A. Singer's dystonia: First report of a variant of spasmodic dysphonia. *Ann Otol Rhinol Laryngol* 2006;115:89–92. doi: 10.1177/000348940611500201.

68. Grillone GA, Blitzer A, Brin MF, Annino DJ Jr, Saint-Hilaire MH. Treatment of adductor laryngeal breathing dystonia with botulinum toxin type A. *Laryngoscope* 1994;104:30–32.

69. Wissel J, Muller J, Ebersbach G, Poewe W. Trick maneuvers in cervical dystonia: Investigation of movement-and touch-related changes in polymyographic activity. *MovDisord* 1999;14:994–999. doi: 10.1002/1531-8257(199911)14:6<994::AID-MDS1013>3.0.CO;2-K.

70. Meige H. Les convulsions de la face: Une forme clinique de convulsions faciales, bilatérale et médiane. *Rev Neurol* 1910;21:437–443.

71. Tolosa E, Marti MJ. Blepharospasm-oromandibular dystonia syndrome (Meige's syndrome): Clinical aspects. *Adv Neurol* 1988;49:73–84.

72. Aronson AE, Peterson HW, Litin EM. Voice symptomatology in functional dysphonia and aphonia. *J Speech Hear Disord* 1964;29:367–380. doi: 10.1044/jshd.2904.367.

73. Brin MF, Blitzer A, Velickovic M. Movement disorders of the larynx. In: Blitzer A, Brin MF, Ramig LO, editors. Neurologic disorders of the larynx. New York: Thieme; 2009.p 160–195.

74. Greene PE, Bressman S. Exteroceptive and interoceptive stimuli in dystonia. *Mov Disord* 1998;13:549–551. doi: 10.1002/mds.870130329.

75. Simonyan K, Ludlow CL. Abnormal activation of the primary somatosensory cortex in spasmodic dysphonia: An fMRI Study. *Cerebral Cortex* 2010;20:2749–2759. doi: 10.1093/cercor/bhq023.

76. Simonyan K, Tovar-Moll F, Ostuni J, et al. Focal white matter changes in spasmodic dysphonia: A combined DTI and neuropathological study. *Brain* 2008;131:447–459.

77. Barkmeier JM, Case JL, Ludlow CL. Identification of symptoms for spasmodic dysphonia and vocal tremor: Acomparison of expert and nonexpert judges. *J Commun Disord* 2001;34:21–37. doi: 10.1016/S0021-9924(00)00039-3.

78. Aronson AE. Clinical voice disorders. New York: Thieme; 1985.

79. Brown JR, Simonson J. Organic voice tremor: Atremor of phonation. *Neurology* 1963;13:520–525. doi: 10.1212/WNL.13.6.520.

80. Ardran G, Kinsbourne M, Rushworth G. Dysphonia due to tremor. *J Neurol Neurosurg Psychiatry* 1966;29:219–223. doi: 10.1136/jnnp.29.3.219.

81. Critchley E. Clinical manifestations of essential tremor. *J Neurol Neurosurg Psychiatry* 1972;35:365–372. doi: 10.1136/jnnp.35.3.365.

82. Davis CH, Kunkle CE, Durham NC. Benign essential (heredofamilial) tremor. *Trans Am Neurol Assoc* 1951;56:87–89.

83. Marshall J. Pathology of tremor. In: Findley LJ, Capildeo R, editors. Movement disorders: Tremor. New York: Oxford University Press; 1984. p 95–123.

84. Marshall J. Observations on essential tremor. *J Neurol Neurosurg Psychiatry* 1962;25:122–125. doi: 10.1136/jnnp.25.2.122.

85. Roy N, Gouse M, Mauszycki SC, Merrill RM, Smith ME. Task specificity in adductor spasmodic dysphonia versus muscle tension dysphonia. *Laryngoscope* 2005;115:311–316. doi: 10.1097/01.mlg.0000154739.48314.ee.

86. Dedo HH. Recurrent laryngeal nerve section for spastic dysphonia. *Ann Otol Rhinol Laryngol* 1976;85:451–459. doi: 10.1177/000348947608500405.

87. Dedo HH, Izdebski K. Problems with surgical (RLN section) treatment of spastic dysphonia. *Laryngoscope* 1983;93:268–271. doi: 10.1288/00005537-198303000-00002.

88. Aronson AE, De Santo LW. Adductor spastic dysphonia: Three years after recurrent laryngeal nerve resection. *Laryngoscope* 1983;93:1–8. doi: 10.1288/00005537-198301000-00001.

89. Weed DT, Jewett BS, Rainey C, et al. Long-term follow-up of recurrent laryngeal nerve avulsion for the treatment of spastic dysphonia. *Ann Otol Rhinol Laryngol* 1996;105:592–601. doi: 10.1177/000348949610500802.

90. Isshiki N, Yamamoto I, Fukagai S. Type 2 thyroplasty for spasmodic dysphonia: Fixation using a titanium bridge. *Acta Otolaryngol* 2004;124:309–312. doi: 10.1080/00016480410016261.

91. Tucker HM. Laryngeal framework surgery in the management of spasmodic dysphonia. Preliminary report. *Ann Otol Rhinol Laryngol* 1989;98:52–54. doi: 10.1177/000348948909800111.

92. Berke GS, Blackwell KE, Gerratt BR, Verneil A, Jackson KS, Sercarz JA. Selective laryngeal adductor denervation-reinnervation: A new surgical treatment for adductor spasmodic dysphonia. *Ann Otol Rhinol Laryngol* 1999;108:227–231. doi: 10.1177/000348949910800302.

93. Chhetri DK, Mendelsohn AH, Blumin JH, Berke GS. Long-term follow-up results of selective laryngeal adductor denervation-reinnervation surgery for adductor spasmodic dysphonia. *Laryngoscope* 2006;116:635–642. doi: 10.1097/01.MLG.0000201990.97955.E4.

94. Fabron EMG, Marino VCC, Nobile TC, Sebastiao LT, Onofri SMM. Medical treatment and speech therapy for spasmodic dysphonia: Aliterature review. *Rev CEFAC* 2013;15:713–724. doi: 10.1590/S1516-18462013005000034.

95. Cloud LJ, Jinnah HA. Treatment strategies for dystonia. *Expert Opin Pharmacother* 2010;11:5–15. doi: 10.1517/14656560903426171.

96. Tallman JF, Gallager DW. The gaba-ergicsystem: A locus of benzodiazepine action. *Ann Rev Neurosci* 1985;8:21–44. doi: 10.1146/annurev.ne.08.030185.000321.

97. Hellwig TR, Hammerquist R, Termaat J. Withdrawal symptoms after gabapentin discontinuation. *Am J Health Syst Pharm* 2010;67:910–912. doi: 10.2146/ajhp090313.

98. Petursson H. The benzodiazepine withdrawal syndrome. *Addiction* 1994;89:1455–1459.

99. Evans K, Sullivan, M J. Withdrawal and medical issues. Dual diagnosis: Counseling the mentally Ill substance abuser. 2nd edition. New York: Guilford Press; 2001. p 52–53.

100. Ludlow CL, Hallett M, Sedory SE, Fujita M, Naunton RF. The pathophysiology of spasmodic dysphonia and its modification by botulinum toxin. In: Berardelli A, Benecke R, Manfredi M, Marsden CM, editors. Motor disturbances II. New York: Academic Press; 1990. p 273–288.

101. Zwirner P, Murry T, Swenson M, Wooodson GE. Effects of botulinum toxin therapy in patients with adductor spasmodic dysphonia: Acoustic, aerodynamic, and videoendoscopic findings. *Laryngoscope* 1992;102:400–406. doi: 10.1288/00005537-199204000-00006.

102. Borg-Stein J, Pine ZM, Miller JR, Brin MF. Botulinum toxin for the treatment of spasticity in multiple sclerosis: New observations. *Am J Phys Med Rehabil* 1993;72:364–368. doi: 10.1097/00002060-199312000-00005.

103. Brin MF, Blitzer A, Stewart C, Fahn S. Treatment of spasmodic dysphonia (laryngeal dystonia) with local injections of botulinum toxin: Review and technical aspects. In: Blitzer A, Brin MF, Sasaki CT, Fahn S, Harris KS, editors. Neurological disorders of the larynx. New York: Thieme; 1992. p 214–228.

104. Filippi GM, Errico P, Santarelli R, Bagolini B, Manni E. Botulinuma toxin effects on rat jaw muscle spindles. *Acta Otolaryngol* 1993;113:400–404. doi: 10.3109/00016489309135834.

105. Novakovic D, Waters HH, D'Elia JB, Blitzer A. Botulinum toxin treatment of adductor spasmodic dysphonia: Longitudinal functional outcomes. *Laryngoscope* 2011;121:606–612. doi: 10.1002/lary.21395.

106. Meyer T, Blitzer A. Spasmodic dysphonia. In: Stacy M, editor. Handbook of dystonia. 1st edition. London: CRC Press; 2006. p 179–188.

107. Bielamowicz S, Stager SV, Badillo A, Godlewski A. Unilateral versus bilateral injections of botulinum toxin in patients with adductor spasmodic dysphonia. *J Voice* 2002;16:117–123. doi: 10.1016/S0892-1997(02)00080-2.

108. Hillel AD, Maronian NC, Robinson L, Waugh PF, Klotz DA. Treatment of the interarytenoid muscle with botulinum toxin for laryngeal dystonia. *Ann Otol Rhinol Laryngol* 2004;113:341–348. doi: 10.1177/000348940411300501.

109. Atassi MZ. Immune recognition of BoNTs A and B: How anti-toxin antibodies that bind to the heavy chain obstruct toxin action. *Toxicon* 2009;54:600–613. doi: 10.1016/j.toxicon.2009.02.034.

110. Atassi MS, Dolimbek BZ, Jankovic J, Steward LE, Aoki KR. Regions of botulinum neurotoxin A light chain recognized by human anti-toxin antibodies from cervical dystonia patients immunoresistant to toxin treatment. The antigenic structure of the active toxin recognized by human antibodies. *Immunobiology* 2011;216:782–792. doi: 10.1016/j.imbio.2010.12.009.

111. Atassi MZ. Basic immunological aspects of botulinum toxin therapy. *Mov Disord* 2004;19:S68–84. doi: 10.1002/mds.20020.

112. Blitzer A. Botulinum toxin A and B: Acomparative dosing study for spasmodic dysphonia. *Otolaryngol Head Neck Surg* 2005;133:836–838.

113. Kirke DN, Frucht SJ, Simonyan K. Alcohol responsiveness in laryngeal dystonia: Asurvey study. *J Neurol* 2015;262:1548–1556. doi: 10.1007/s00415-015-7751-2.

114. FDA Approval Letter for Xyrem; Indication: EDS (excessive daytime sleepiness) associated with narcolepsy. US Food and Drug Administration. 2005-11-18. Retrieved 2010-10-03. http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2005/021196s005ltr.pdf.

115. FDA Approval Letter for Xyrem; Indication: Cataplexy associated with narcolepsy. US Food and Drug Administration. 2002-07-17. Retrieved 2010-10-03. http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2002/21196ltr.pdf.

116. Health Canada. Summary basis of decision (SBD): Xyrem. Health Canada. 2006-03-22. Retrieved 2012-11-02. http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/sbd_smd_2006_xyrem_088659-eng.php.

117. Simonyan K, Frucht SJ. Long-term effect of sodium oxybate (XyremH) in spasmodic dysphonia with vocal tremor. *Tremor Other Hyperkinet Mov* 2013;3. doi: 10.7916/D8CJ8C5S.

118. Ibanez C, Blanes-Mira C, Fernandez-Ballester G, Planells-Cases R, Ferrer-Montiel A. Modulation of botulinum neurotoxin a catalytic domain stability by tyrosine phosphorylation. *FEBS Lett* 2004;578:121–127.

119. Masuyer G, Thiyagarajan N, James PL, Marks PM, Chaddock JA, Acharya KR. Crystal structure of a catalytically active, non-toxic endopeptidase derivative of Clostridium botulinum toxin A. *Biochem Biophys Res Commun* 2009; 381:50–53. doi: 10.1016/j.bbrc.2009.02.003.