Laryngeal Dystonia

16

Justin M. Hintze, Christy L. Ludlow, and David G. Lott

Spasmodic dysphonia almost ended my career. After 6 years of doctors telling me it was 'all in my head,' two physicians … finally diagnosed spasmodic dysphonia. I was given my first injection of Botox that very day. Three weeks later I was back on the air.

Diane Rehm
Talk show host (now retired)
National Public Radio

Introduction

Spasmodic dysphonia (SD), a form of laryngeal dystonia, is a task-specific focal dystonia characterized by irregular and uncontrolled voice breaks that interrupt normal speech flow and effortful phonation [1–3]. There are, broadly speaking, two different types of SD based on the predominant spasms present: adductor SD (AdSD) and abductor SD (AbSD), with AdSD being more common than AbSD. The former is typified by adductor spasms causing choked, harsh voice breaks, especially on vowels and voiced phonemes, while the latter is characterized by hyperabduction of the vocal folds leading to prolonged voiceless consonants [3, 4] (Table 16.1). In some instances, both types of SD can occur in the same patient.

First accounts of SD hypothesized a psychosomatic cause for the pathogenesis of SD. This changed in 1960 when Robe et al. postulated a central nervous system (CNS) etiology [5]. Since then, environmental, genetic, and neurologic risk factors have been proposed.

Table 16.1 Differences between adductor and abductor spasmodic dysphonia

Adductor spasmodic dysphonia	Abductor spasmodic dysphonia
"Sentences loaded with voiced segments will worsen symptoms"	"Difficulty with voice onset following voiceless sounds"
Intermittent glottal stops (vowel breaks) in vowels on voiced sentences	Intermittent breathy breaks in voiceless consonants before vowels in sentences
Strain-strangled, effortful, tight voice quality	Symptoms most evident during connected speech
Patient report of speaking effort	Few symptoms on prolonged vowels
Symptoms reduced during whisper	Intermittent abductor spasm of the vocal folds or arytenoids during speech
Intermittent vocal fold or arytenoid hyperadduction	

J. M. Hintze · D. G. Lott (✉)
Department of Otolaryngology–Head and Neck Surgery, Mayo Clinic Arizona, Phoenix, AZ, USA
e-mail: lott.david@mayo.edu

C. L. Ludlow
Department of Communication Sciences and Disorders (retired), James Madison University, Harrisonburg, VA, USA

P. A. Weissbrod, D. O. Francis (eds.), *Neurologic and Neurodegenerative Diseases of the Larynx*,
https://doi.org/10.1007/978-3-030-28852-5_16

Epidemiology

SD is a rare clinical condition. Prevalence estimates vary between 1 in 100,000 and 2.9 per 1,000,000 persons [6, 7]. Roughly two-thirds of all patients affected are female, predominantly in their middle decades of life [1, 8]. Several case series have identified a range of female predominance between 62% and 80% [8–12] and a mean onset between 45 and 51 years of age [8, 10–12]. AdSD occurs more frequently than AbSD, with reported AdSD percentages ranging from 82% to 96.6% [8, 9, 12]. Vocal tremor can also coexist with SD and has been described as occurring in 29–55% of SD patients [8, 13] with a slightly higher incidence in females noted by one study [8].

Frequently described risk factors include a personal or family history of cervical dystonia or tremor [8, 13], previous sinus or throat infections, mumps or rubella infections [12], extensive voice use, and stress [14]. The link between viral illnesses and neurological sequelae is established in other diseases such as Ramsay Hunt syndrome, virus-induced vocal fold paralysis, and long-term neurological deficits following meningitis or encephalitis, but not as yet found in SD [12, 15]. Controlled epidemiological studies are needed to identify genetic and environmental risk factors for SD. Such findings might help to identify "at-risk" patient populations for SD and might eventually contribute to the diagnosis of SD.

Genetics

There has been significant growing interest in the possible association of genetic factors with the development of SD. This is in part due to accessible genetic testing and recent evidence that certain polymorphisms in generalized dystonia-causing genes can affect the risk of developing focal or segmental dystonias [16]. Four different genes have been found to be related to familial dystonias with varying degrees of dysphonic features: *TUBB4A, THAP1, TOR1A,* and *GNAL.*

The *TUBB4A* gene is responsible for tubulin beta-4a chain proteins, which are major components of microtubules. *TUBB4A* mutations can lead to atrophy in the basal ganglia and cerebellum. This gene has been shown to contribute to an autosomal-dominant dysphonia that has a "whispering" voice quality and is distinct from the sporadic forms of AdSD and AbSD [17].

The *THAP1* gene regulates endothelial cell proliferation. Its mutation can lead to a generalized form of dystonia, DYT6, that frequently has laryngeal features [16].

TOR1A mutations can lead to a different form of generalized dystonia that frequently manifests in childhood or early adulthood [16].

GNAL encodes Gαolf, a G protein (guanine nucleotide–binding protein) that mediates odorant signaling in the olfactory epithelium. Although the G protein subunit Gαs is the predominant stimulatory G protein subunit in the brain, Gαolf replaces Gαs in striatal medium spiny neurons and couples with dopamine type 1 receptors. Gαolf is also expressed in striatal cholinergic interneurons. Various *GNAL* mutations have been found in families with primary torsion dystonia, *DYT25* [18].

One study examined *TUBB4A*, *THAP1*, and *TOR1A* in 86 patients with SD and found that none had mutations in these three genes, although two patients (2.3%) had novel/rare variants of the *THAP1* gene [16]. Another study of 57 patients with SD examined *TUBB4A, THAP1, TOR1A,* and GNAL and found that one patient with SD but without *DYT25* was a *GNAL* mutation carrier, indicating that *GNAL* mutation may represent a rare genetic factor contributing to SD risk [19]. These studies suggest that further work is needed. As with other forms of dystonia, there may be sporadic and genetically determined types of SD. The genetic patterns may become more apparent with further genetic research.

Pathophysiology

Most recent evidence supports the idea that SD is a focal dystonia affecting primarily the laryngeal musculature and is task specific, i.e., only evident during certain types of speech [20]. Three differ-

ent neurological mechanisms have been proposed in the pathophysiology of SD: loss of cortical inhibition, sensory processing abnormalities, and neuroanatomical and neurophysiological differences from normal [1–3].

Loss of Cortical Inhibition

Research on other focal dystonias, such as cervical dystonia, focal hand dystonia, blepharospasms, and oromandibular dystonia, has demonstrated reduced cortical inhibition when transcranial magnetic stimulation is used to measure short-interval intracortical inhibition (SICI) and cortical silent periods (CSPs) [21]. Samargia et al. found reduced CSP in the masseter and first dorsal interosseous muscles in patients with AdSD when compared to controls [22]. As unaffected muscles also seem to demonstrate shorter CSPs in SD, this might suggest a GABA-ergic dysfunction. One case report indicated reduced voice symptoms in neuroleptic-induced dysphonia following administration of a GABA antagonist, clozapine [23]. A questionnaire study in an SD patient registry found reduced symptoms reported following the consumption of alcohol in 55.9% of patients [24].

Sensory Processing Abnormalities

Sensory processing disturbances have been found in patients with SD when compared to controls on visual temporal discrimination testing [25]. Patients with SD required longer intervals between two flashing lights to be able to discern the difference between the two. These were similar findings of impaired somatosensory temporal discrimination in SD to those previously found in cervical dystonia [26].

Studies of sensorimotor reflex inhibition for the laryngeal adductor response to electrical stimulation of laryngeal sensory nerves showed reduced central inhibition in AdSD [27] and AbSD [28]. Similar abnormalities in blink reflex conditioning were found in patients with SD [29].

Neuroanatomical and Neurophysiological Differences

Neuroimaging studies have found neuroanatomical and neurophysiological differences from healthy controls in patients with SD that pertain to the pathophysiology of SD. Functional magnetic resonance imaging studies have shown increased activation in the primary somatosensory cortex, insula, and superior temporal gyrus during symptomatic and asymptomatic tasks and decreased activation extent in the basal ganglia, thalamus, and cerebellum during asymptomatic tasks in AdSD and AbSD [30]. Increased activation intensity in SD patients was found only in the primary somatosensory cortex during symptomatic voice production, which correlated with AdSD symptom severity [30]. In another study, diffusion tensor imaging of white matter tracts in a group of AdSD patients and a neuropathological investigation in a single case found altered microstructural integrity along the right genu of the internal capsule of the corticobulbar tract [31]. Deficits along these tracts could interfere with neural control between cortical and subcortical brain regions that are essential for voluntary voice production (Fig. 16.1) [1, 31].

Diagnostic Considerations in SD

Diagnosis of SD can be difficult given the complex symptom presentations and lack of awareness among clinicians. Diagnostic difficulties can lead to significant delays in treatment, with one study reporting delays up to 4.5 years [32]. Since this disorder is not common in the general population, many clinicians, including otolaryngologists and speech-language pathologists (SLPs) not specializing in voice disorders, are unfamiliar with the disease. Therefore, diagnostic teams should ideally include a multidisciplinary team of otolaryngologists, SLPs, and neurologists [33]. While the inclusion of a neurologist in the multidisciplinary team is not universal, some advocate the addition of a neurologist with special interest in dystonias to help rule out other neurologic disorders since there is an increased incidence in this patient population.

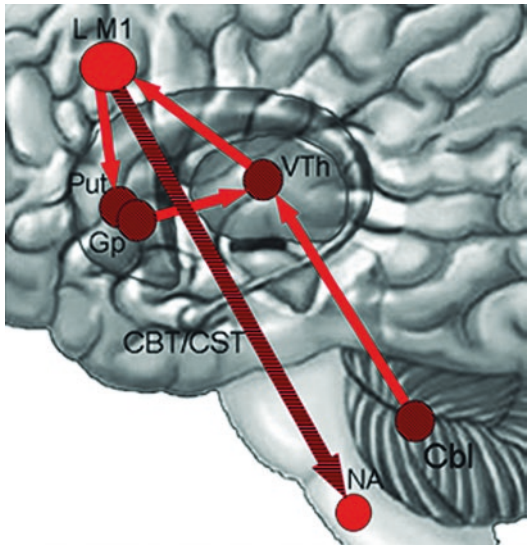

Fig. 16.1 Neural network of voluntary laryngeal control: LM1 (laryngeal motor cortex) to phonatory motor nuclei (nucleus ambiguus, NA), descending via the corticobulbar/corticospinal tract (CBT/CST). Cbl cerebellum, Gp globus pallidus, Put putamen, VTh ventral lateral thalamus. (Adapted from Simoyan et al. [31], with permission Oxford University Press)

Diagnosis of SD can still be quite difficult even when a multidisciplinary team is used. A recent multicenter study across four voice centers specializing in SD examined classification agreement for voice disorders including AdSD, AbSD, vocal tremor, and MTD based on reviewing voice and nasolaryngoscopy video recordings of 178 patients without standardized criteria [34]. There was poor agreement between specialists regardless of profession (otolaryngology, speech-language pathology, or neurology with special interest in voice) or whether specialists were from the same or different voice centers. As a result, a four-stage Delphi method was employed to determine group consensus on criteria for classifying the various voice disorders among 46 specialists in SD across the United States [34]. There was good agreement on the top features for AbSD, "intermittent breathy breaks" (97%) and "symptoms most evident in speech" (76%); however, there was relatively low agreement on features for AdSD, "intermittent glottal stops" (53%) and "patient report of speaking effort" (47%) [34]. Thus, there seems to be a better agreement on the features of AbSD than AdSD. Based on the results, a multidisciplinary group consisting of 12 specialists from four voice centers was able to develop a spasmodic dysphonia attribute inventory (SDAI), where a small number of attributes were selected to help identify each disorder [34]. The main attributes selected for AdSD and AbSD can be seen in Table 16.1 [34].

The primary technique for diagnosing SD includes a combination of speech examination and transnasal laryngoscopy. In 2008, Ludlow et al. recommended the addition of a screening questionnaire to help identify probable SD [3]. While the screening questionnaire is not considered standard of care, it is a tool that may help improve diagnostic accuracy and communication for both voice experts and nonexperts. This three-tiered approach (screening questionnaire, speech examination, and transnasal laryngoscopy) is described below.

Screening Questionnaire

Initial screening questions aim to determine the likelihood of an SD diagnosis and involve questions regarding the presence of effortful phonation, persistence or variability of symptoms, duration of symptoms (greater than 3 months), and if some tasks are less affected than speech (including shouting, crying, laughing, whispering, and singing) [34].

Speech Examination

The speech examination focuses on typical presentations of the SD variants and other possible confounding voice disorders, such as MTD or vocal tremor. Symptoms of SD are usually characterized by uncontrolled voice breaks due to laryngeal muscular spasms and complaints that phonation is effortful. The voice breaks are most prominent during connected speech. With both AdSD and AbSD, sentences performed in a shouted and/or whispered voice should elicit

fewer symptoms than in conversational speech at a normal volume [3].

In AdSD, voice breaks are evident during voiced vowel segments with a choked, strained characteristic, whereas in AbSD, breathy breaks occur following voiceless consonants preceding vowels [4] (see Table 16.1). During voice breaks in AdSD, quick glottic closures interrupt airflow and phonation, leading to breaks during vowels in speech. In AbSD on the other hand, prolonged vocal fold abduction during voiceless consonants interferes with the rapid onset of vowels resulting in breathy voice breaks during voiceless consonants (/h/, /s/, /f/, /p/, /t/, /k/). A rare form of SD is the mixed type, where patients display features of both AdSD and AbSD.

SD can be easily confused with muscle tension dysphonia (MTD). Additionally, MTD can sometimes be superimposed on SD. However, the vocal tasks in MTD do not alter between speech sounds (vowels or consonants) or among voice tasks such as shouting or singing. MTD patients tend to find all aspects of connected speech and vocalizations equally difficult. Such patients are usually responsive to voice therapy alone [35, 36]. In SD patients on the other hand, symptoms tend to be task-dependent, are most prominent during connected speech, and do not respond to voice therapy alone [37] (see Table 16.2).

Table 16.2 Differences between spasmodic dysphonia and muscle tension dysphonia

Characteristic	Spasmodic dysphonia	Muscle tension dysphonia
Glottal stops and vowels	Breaks on vowels	Equal symptoms on vowels and voiceless consonants
Shout/whisper	Less affected	Equally affected
Strained voice	Less strained at high frequency	Constant strain
Vocal fold tremor	May coexist	Not present
Laryngoscopy	Normal structure and symmetry at rest	Supraglottic compression obscuring vocal folds during voice production
Voice therapy	Poorly responsive	Responsive

Vocal tremor often coexists with SD, complicating diagnosis and management. It can be characterized by regular pitch and/or amplitude oscillation during a sustained vowel, visible laryngeal tremor on nasolaryngoscopy, tremor of the pharyngeal constrictor muscles, and possible additional bobbing of the laryngeal position during voicing [34]. This has been reported to occur in 29–54% of patients with SD [8, 13]. Large sex differences have also been reported by Patel et al., with 60% of females and 32.8% of males with AdSD having concurrent vocal tremor [8]. There is also some suggestion that botulinum neurotoxin (BoNT) injections are less effective in patients with concurrent vocal tremor [38].

Transnasal Laryngoscopy

Laryngoscopy is performed to rule out other structural/functional disorders that may be causing the patient's symptoms. Since SD is a disorder of connected speech, laryngoscopy should be performed transnasally to allow for visualization during connected speech. The vocal folds should appear normal during quiet breathing and have full range of motion during coughing and whistling [3, 39]. No masses or lesions should be evident. One study found that only 10% of video-only clips of patients with SD were correctly classified as SD, whereas 73% of audio-only clips were correctly identified, highlighting the importance of the clinical speech examination in the classification of SD.

Supportive Diagnostic Procedures

Occasionally, tremor or spasms may be difficult to visualize during adductor or abductor sentences. Either videokymography (Fig. 16.2) or high-speed videolaryngoscopy can help identify such movement [40]. These methods are not widely available in the clinical setting and currently mostly confined to research centers.

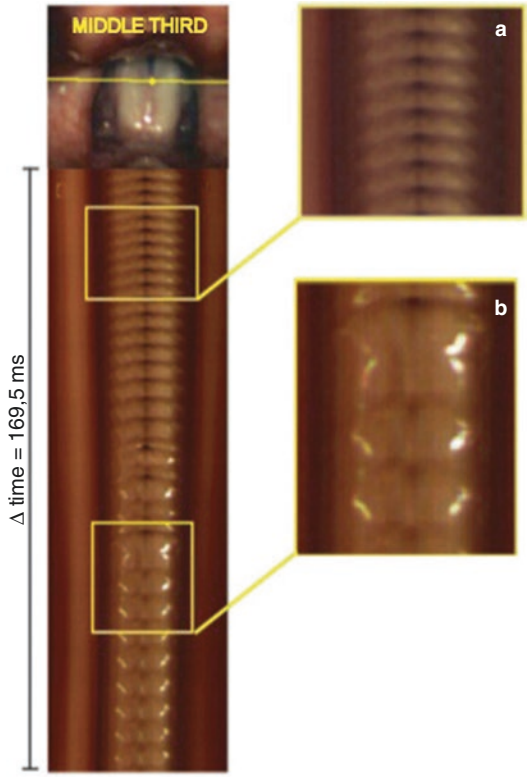

Fig. 16.2 High-speed videokymography of a patient with AdSD showing reduction in vibration amplitude and propagation of the mucosal wave, as well as longer duration of the closed phase compared to the total duration of the cycle, (**a**). Spasms can be observed in detail, (**b**). (From Tsuji et al. [40] with permission from Thieme)

Electromyographic (EMG) methods can be used to detect characteristic motor activation patterns in laryngeal muscles. Some suggest that the thyroarytenoid muscle is hyperactive in patients with SD [41]; however, others have found this to not be the case when compared to controls [42]. Increased muscle latencies have been found in patients with SD, as well as overactivity of the cricothyroid muscle in AbSD [43]. When combined, these EMG characteristics can be used to help identify the specific muscles contributing to SD and monitor treatment response [44]. However, EMG is invasive and can be time-consuming, and abnormal muscle activation is usually not restricted to a single muscle. A neurolaryngology study group in 2009 investigated the use of EMG in SD and concluded that there is insufficient evidence for EMG to be used as a diagnostic tool by itself [45].

Medical Management

Both medical and surgical treatments for SD have focused on denervation of one or more of the laryngeal muscles to reduce muscle force and the impact of muscle spasms on phonation. Such treatment approaches, however, may not alter the central neural control abnormalities causing muscle spasms but only reduce the impact of the CNS abnormalities on voice production.

Blitzer in 1985 reported early EMG results in patients with SD indicating an abnormality in the motor control system [46]. These findings were then followed by early attempts at reducing dystonic movements using BoNT injections into affected laryngeal musculature [47, 48]. BoNT inhibits release of acetylcholine from the presynaptic terminals into the neuromuscular junction, causing a temporary partial paralysis. These effects usually last between 3 and 4 months as reinnervation occurs and symptoms return [49]. BoNT remains the most commonly used treatment for SD today.

Several studies have shown improvement in acoustic, aerodynamic, and perceptual characteristics of voice after BoNT injection [50]. Table 16.3, adapted from Murry [2], outlines some of the acoustic and physiological changes that occur after BoNT injections. A study by Rojas et al. used acoustic voice analysis and found significant reductions in changes in the intensity contour and breaks in the fundamental frequency (fo) contour and reduced rhythmic variations in intensity and fo on a sustained vowel /a/. The patients reduced their Voice Handicap Index (VHI) scores at 30 days post-injection, but not 120 days post-injection [51]. Airflow rates also increase after BoNT injection, but these plateau after a few weeks [50].

Although the primary basis for improvement of AdSD symptoms after BoNT injection is due to reduction in local vocal fold muscle activation [52], there may also be some central effects

Table 16.3 Acoustic differences after botulinum neurotoxin (BoNT) injection

Parameter	Findings
Prolonged vowels	
Fo	Unchanged
Jitter	Lower post BoNT
Shimmer	Lower post BoNT
Harmonic/noise ratio	Improved post BoNT
Subglottic pressure	Lower post BoNT
Airflow rate	Higher post BoNT (normalized by ~2 weeks)
Voice breaks	Fewer post BoNT
Tremor	Reduced post BoNT in some cases
Speech sentences	
Mean *Fo*	Unchanged
Speech rate	Increased speech rate post BoNT
Airflow rate	Higher post BoNT
Voice breaks	Fewer post BoNT

Adapted from Murry [2], with permission

on the origin of muscle spasms after BoNT injection [53]. Following a unilateral thyroarytenoid muscle injection, spasms in contralateral, non-injected vocal fold muscles are reduced [54]. This potentially highlights the more complex neural network that is involved in the pathophysiology of SD. Previous basic research has shown that BoNT can be transported from the site of muscle injection centrally to motor neurons in the brain stem altering muscle spasms [55–57], although it is not known if this occurs in the human.

BoNT injections can either be unilateral or bilateral and are usually guided by EMG or nasolaryngoscopy [58]. Doses for BoNT injection may vary from 0.1 to 7.5 units per side [58], with median starting doses per side ranging from 0.25 to 1.5 units [59]. As reinnervation usually occurs in 3–4 months resulting in return of symptoms, repeat injections are required over time. A recent systematic review found that the duration of effect ranged between 14.66 and 18.03 weeks [58]. However, laryngeal EMG demonstrated that effects on motor unit physiology can still be present one year later. Based on a series of 900 patients with SD reported by Blitzer et al. [49], no clinical impressions indicated that there was a need to increase BoNT doses over time to achieve the same clinical benefit. While generally considered safe, a histopathological study of the effects on eye muscles after repeated injection for blepharospasm found muscular atrophy, scarring, and fibrosis in orbicularis oculi muscles [60]. For patients with AbSD, most laryngologists in the United States (79% in one study) advocate unilateral BoNT injections into one posterior cricoarytenoid muscle first. The reported mean starting dose was higher in AbSD patients at 5 units per side and ranged from 1 to 15 units. Most laryngologists (92%) prefer to target the posterior cricoarytenoid muscle alone [59].

In 2007 speech benefits of supraglottic injection were found in four AdSD patients with sphincteric supraglottic contraction of the ventricular fold obscuring the view of the vocal folds during phonation [61]. Using EMG control and a thyrohyoid approach, a traditional injection in the upper portion of the adductor muscles (the thyroarytenoid and lateral cricoarytenoid muscles) with BoNT did not result in significant voice benefit. In contrast when the oblique portion of the lateral cricoarytenoid muscles was injected with BoNT, all four patients demonstrated improved voice quality post-injection into the supraglottic region. More recently, ratings of voice function and patient completion of VHI scales were administered to evaluate the outcome of 198 supraglottic injections of BoNT injection into the false vocal folds, also termed supraglottic injection in AdSD patients [62]. The intended benefits are a reduced incidence of breathy voice after injection and the preservation of fo control during singing. Slightly higher doses were used for these injections (mean dose 6.94 units per side), with an average interval between injections of 15.6 weeks [62]. Most patients (74%) reported no post-injection voice decline that can sometimes accompany BoNT injections. However, given the wide variation in the extent of muscle fibers in the ventricular fold and the supraglottic region in the human larynx [63], the diffusion pattern of injection into muscle fibers in the supraglottic region is unknown.

Surgical Management

The first reported procedure for reducing vocal spasticity, reported in 1976 by Dedo, involved sectioning of the recurrent laryngeal nerve [64]. However, recurrence of symptoms was found 3 years later in a high proportion of patients [65] due to reinnervation of the thyroarytenoid muscle by the recurrent laryngeal nerve [66]. Since then, other surgical alternatives have been described, including thyroarytenoid myotomy, type 2 laryngoplasty, selective laryngeal adductor denervation-reinnervation, laryngeal nerve crush [58], and extensive avulsion of the recurrent laryngeal nerve on resection [67, 68].

Tsuji et al. investigated using endoscopic neurectomy of the thyroarytenoid branch of the recurrent laryngeal nerve, combined with partial myectomy of the thyroarytenoid muscle using CO2 laser for patients with AdSD [69]. Neurectomy was performed by directing an electrocautery tip between the perichondrium of the thyroid cartilage and the fasciae of the lateral cricoarytenoid and thyroarytenoid muscles [69]. A significant improvement in the Voice Handicap Index (VHI) was found postoperatively (mean preoperatively, 99; mean postoperatively, 24) in a cohort of 15 patients. Similar results were reported by Gandhi et al. in 2014, with an improvement of VHI noted from 70 to <25 [70].

Type 2 laryngoplasty has also been described. A midline thyrotomy is performed and the edges are separated between 2 and 5 mm, either with a titanium bridge [71] or with a T-shaped Silastic shim [72]. In a study by Sanuki et al. in 2017 of 47 patients with AdSD, 69% of patients reported a reduction in glottal tightness, strangulated voice, and phonation difficulties [71]. VHI-10 scores improved from 26.8 to 9.4 and these changes were maintained up to 36 months [71]. Nomoto et al. in 2014 compared thyroarytenoid muscle myectomy with type 2 laryngoplasty and found no overall significant difference postoperatively, but scores for strangulation, interruption, and tremor were lower in the myectomy group [73]. Importantly, postoperative complications were significantly increased in the myectomy group, in particular breathiness, and these changes were irreversible [73]. Although laryngoplasty is considered reversible, extensive scar tissue can interfere with surgery.

In 1999, Berke et al. described a selective laryngeal adductor denervation-reinnervation (SLAD) surgery, whereby the thyroarytenoid branch of the recurrent laryngeal nerve is divided before insertion into the muscle and the sternohyoid or sternothyroid branch of the ansa cervicalis is used for thyroarytenoid reinnervation. It is believed that by reinnervating the muscle with a different nerve, the ansa cervicalis, spontaneous RLN reinnervation is less likely and spasms are less likely to recur in the majority of patients. Follow-up of 136 patients who underwent this type of surgery found that VHI-10 scores improved from a mean of 36.6 preoperatively to 14.27 postoperatively. Moderate to severe postoperative breathiness occurred in 20% of patients and appeared to be related to lateral cricoarytenoid myotomy [74]. In one case however, described by deConde et al. in 2011, SD symptoms recurred 9 years after SLAD surgery. This might have been due to progression of the focal laryngeal dystonia to a more regional dystonia involving motor neurons to the ansa cervicalis [75].

To date there have been no studies comparing the voice outcomes of BoNT with voice characteristics following various surgical interventions and it is not clear if surgery should be considered as an adjunct to BoNT or as an alternative. It is important to note that to date most surgical interventions have not been demonstrated to have permanent long-term benefits on voice in SD.

Frontiers

Pathogenesis

The pathogenesis of SD is still poorly understood and is likely multifactorial in nature. It can be viewed as a multiple-hit mechanism with some endogenous predispositions and environmental triggers combined to produce the SD phenotype.

Genetic screening for mutations known to produce various familial dystonias in SD patients

have only found mutation of *GNAL* in one patient with SD and some variants of *THAP1* in a couple of SD patients. In general, familial cases with SD are rare and most cases seem to be sporadic in nature. Further advances in identifying genetic factors in other types of dystonia may shed some light on additional genetic influences in SD.

Pathophysiology

Neuroanatomical and neurophysiological research has highlighted the complex neurophysiological nature of SD. SD is likely a complex neural network disorder involving basal ganglia, cerebellum, and cortical mechanisms, rather than one single neuroanatomical defect (see Fig. 16.1).

Experimental neurophysiological techniques using EMG of laryngeal muscles and transcortical magnetic stimulation to quantify the CSP have found that the period is shortened in patients with SD [76], and the CSP in hand muscles differentiates between SD and MTD [22]. The CSP could potentially be used as diagnostic adjunct and also to monitor central changes following BoNT therapy [77].

Previous evidence of dopaminergic dysfunction comes from case reports of the effects of antipsychotics such as haloperidol and dopamine antagonists causing acute laryngeal dystonic reactions [78]. A recent neuroimaging study using positron emission tomography quantified raclopride (RAC) uptake to examine striatal dopaminergic neurotransmission at rest, while producing sentences, and during finger tapping in SD patients. Compared to healthy controls, the patients had bilaterally decreased RAC binding to striatal dopamine receptors by 29.2% while speaking, but increased RAC in the bilateral striatum during asymptomatic tapping. Patients with more severe voice symptoms had greater RAC differences, and those with longer SD duration had a decrease in task-induced RAC. Decreased dopaminergic transmission during speech may be pathophysiological in SD, whereas increased dopaminergic function during unaffected task performance may be compensatory. These differences may represent neurochemical alterations in this disorder. Other results have highlighted the role of the thalamus and cerebellum in the pathophysiological processes of SD [53]. Any dysfunction along the laryngeal neural network could contribute to the occurrence of SD symptoms (see Fig. 16.1).

As previously highlighted, there may be underlying reduced cortical inhibition and GABA-ergic dysfunction in SD, evidenced by the benefit experienced by some patients taking clozapine or consuming alcohol [23, 24]. These pathways may offer potential treatment targets in the future.

Diagnosis

In cases where there still is not a definitive diagnosis following speech examination using SD sentences and nasolaryngoscopy, additional procedures may be available in the future. This is especially important, given the difficulty in diagnosing SD and the lack of objective testing. Automated acoustic analysis tools such as the cepstral spectral index of dysphonia (CSID) developed by Awan and colleagues can now be performed on connected speech which is most affected in SD [79, 80]. Such measures can be used to determine the severity of voice disorders. However, the automated tool was only able to achieve sensitivity of 67% and specificity of 64% in differentiating SD from MTD, indicating that it is a measure of dysphonia but not specific to SD [37]. Previous research by Rees et al. has demonstrated the value in using spectrographic features in SD. SLPs were able to correctly distinguish AdSD from MTD in 96% of cases using spectrograms [81].

Another approach used for the differentiation of SD from other voice disorders was the use of a telephone-screening interview. Experienced clinicians from the same voice center were able to correctly identify patients as having SD or voice tremor with 90% sensitivity and 95% specificity [82]. Further validation across multiple voice centers is required to determine if this approach could be used to screen patients for possibly having SD before scheduling them for clinical evaluation.

Treatment

Currently, the main treatment modality for SD involves BoNT injection and less frequently surgery. While patients with AdSD have an average benefit of 90%, AbSD patients only experience a 66% benefit [9]. Large-scale multicenter comparisons of quantitative and qualitative measures of immediate and long-term voice outcomes in SD patients following BoNT (as a gold standard) and each of the different surgical techniques is urgently needed for patients and clinicians to make informed treatment decisions.

Deep Brain Stimulation for Voice Tremor and Spasmodic Dysphonia

Deep brain stimulation (DBS) involves the surgical implantation of stimulating electrodes into specific brain regions such as the basal ganglia and thalamus. The electrodes stimulate in one region to alter the brain network dysfunction and improve symptoms. An example is bilateral stimulation of the subthalamic nucleus (STN) used for the treatment of dyskinesia in Parkinson disease. The stimulation does not alter the disease; it only alters the abnormalities in brain function to reduce symptoms. DBS in the globus pallidus internus (GPi) is now used in generalized dystonia but speech and voice difficulties may not benefit as much as walking. However, one study reported that a patient with adductor SD had a marked benefit [83].

Control of arm tremor can be benefitted by stimulating the ventral intermediate (Vim) nucleus of the thalamus bilaterally, and it was found to benefit voice tremor in two patients with both arm and voice tremor [84–86]. A similar approach was used in a patient with essential tremor and coincident AdSD undergoing deep brain stimulation (DBS) and investigated the effects on vocal function. The target of the DBS was the left thalamic ventral intermediate nucleus and ventral oralis anterior nucleus. They found significant improvements in the SD symptoms, both qualitatively and quantitatively, in the form of the voice-related quality of life and the Unified Spasmodic Dysphonia Rating Scale [87]. Interestingly, they did not find any benefit when the ventral oralis anterior nucleus was stimulated alone (palladial outflow), whereas the best clinical effects occurred when the ventral intermediate nucleus (cerebellar outflow) was stimulated. These are only single cases but suggest that this may be helpful in a few persons with voice tremor and SD by stimulating one part of the brain to reset abnormalities in the brain networks (see Fig. 16.1). However, great care must be taken as surgical implantation of electrodes in these small brain regions may injure the brain causing significant side effects such as slurred speech (dysarthria). Very refined stimulation techniques are needed to reduce side effects [88].

Summary

SD is a focal dystonia characterized by irregular and uncontrollable voice breaks. There are two types of SD, abductor and adductor SD, typified by different muscle spasms, leading to different voice symptoms.

SD is a rare clinical condition, with an estimated prevalence as high as 1 in 100,000. It predominantly occurs in females in their middle decades of life. Limited case series have indicated possible risk factors associated with the occurrence of SD, including a personal or family history of other types of movement disorders, previous viral illnesses, extensive voice use, and stress. While genetic testing has identified polymorphisms in other focal dystonias, only a *GNAL* mutation has been found in one patient with SD and variants in *THAP1* in a couple of cases. In general, most cases of SD appear to be sporadic. Only a few are familial and may be genetically determined. Other pathophysiological mechanisms have been identified, including sensory processing disturbances, reduced cortical inhibition, and neurophysiological increases in excitability in the primary somatosensory cortex. Few neuroanatomical abnormalities have been found, including white matter reduction in the right genu of the internal capsule. Overall, SD is likely a complex neural network disorder, rather than one single neuroanatomical defect.

Diagnosis of SD is frequently delayed and should involve a multidisciplinary team. Diagnosis involves speech examination, a diagnostic nasolaryngoscopy, and occasionally a screening questionnaire. However, there can still be poor agreement between voice specialists. This has led to the development of a score sheet to aid in the identification of SD and other voice disorders based on certain attributes, and validation and generalizability is still under investigation.

The mainstay of treatment of SD is BoNT injections into the affected muscle(s), which need to be repeated every 3–4 months to control symptoms. Surgical options include manipulation of the larynx, either by neurectomy/denervation, myectomy of the thyroarytenoid muscle, or thyroplasty. Experimental methods for future exploration include DBS and GABA antagonists.

References

1. Hintze JM, Ludlow CL, Bansberg SF, Adler CH, Lott DG. Spasmodic dysphonia: a review. Part 1: pathogenic factors. Otolaryngol Head Neck Surg. 2017;157(4):551–7.
2. Murry T. Spasmodic dysphonia: let's look at that again. (The G. Paul Moore Lecture, 42nd annual symposium: care of the professional voice, Philadelphia, PA, 1 Jun 2013). J Voice. 2014;28(6):694–9.
3. Ludlow CL, Adler CH, Berke GS, Bielamowicz SA, Blitzer A, Bressman SB, et al. Research priorities in spasmodic dysphonia. Otolaryngol Head Neck Surg. 2008;139(4):495–505.
4. Edgar JD, Sapienza CM, Bidus K, Ludlow CL. Acoustic measures of symptoms in abductor spasmodic dysphonia. J Voice. 2001;15(3):362–72.
5. Robe E, Brumlik J, Moore P. A study of spastic dysphonia. Neurologic and electroencephalographic abnormalities. Laryngoscope. 1960;70:219–45.
6. Castelon Konkiewitz E, Trender-Gerhard I, Kamm C, Warner T, Ben-Shlomo Y, Gasser T, et al. Service-based survey of dystonia in Munich. Neuroepidemiology. 2002;21(4):202–6.
7. Nutt JG, Muenter MD, Melton LJ 3rd, Aronson A, Kurland LT. Epidemiology of dystonia in Rochester, Minnesota. Adv Neurol. 1988;50:361–5.
8. Patel AB, Bansberg SF, Adler CH, Lott DG, Crujido L. The Mayo Clinic Arizona spasmodic dysphonia experience: a demographic analysis of 718 patients. Ann Otol Rhinol Laryngol. 2015;124(11):859–63.
9. Blitzer A. Spasmodic dysphonia and botulinum toxin: experience from the largest treatment series. Eur J Neurol. 2010;17(Suppl 1):28–30.
10. Childs L, Rickert S, Murry T, Blitzer A, Sulica L. Patient perceptions of factors leading to spasmodic dysphonia: a combined clinical experience of 350 patients. Laryngoscope. 2011;121(10):2195–8.
11. Schweinfurth JM, Billante M, Courey MS. Risk factors and demographics in patients with spasmodic dysphonia. Laryngoscope. 2002;112(2):220–3.
12. Tanner K. Epidemiologic advances in spasmodic dysphonia. Perspect Voice Voice Disord. 2012;22(3):104. https://doi.org/10.1044/vvd22.3.104.
13. Tanner K, Roy N, Merrill RM, Sauder C, Houtz DR, Smith ME. Case-control study of risk factors for spasmodic dysphonia: a comparison with other voice disorders. Laryngoscope. 2012;122(5):1082–92.
14. Izdebski K, Dedo HH, Boles L. Spastic dysphonia: a patient profile of 200 cases. Am J Otolaryngol. 1984;5(1):7–14.
15. Blitzer A, Jahn AF, Keidar A. Semon's law revisited: an electromyographic analysis of laryngeal synkinesis. Ann Otol Rhinol Laryngol. 1996;105(10):764–9.
16. de Gusmao CM, Fuchs T, Moses A, Multhaupt-Buell T, Song PC, Ozelius LJ, et al. Dystonia-causing mutations as a contribution to the etiology of spasmodic dysphonia. Otolaryngol Head Neck Surg. 2016;155(4):624–8.
17. Lohmann K, Wilcox RA, Winkler S, Ramirez A, Rakovic A, Park JS, et al. Whispering dysphonia (DYT4 dystonia) is caused by a mutation in the TUBB4 gene. Ann Neurol. 2013;73(4):537–45.
18. Fuchs T, Saunders-Pullman R, Masuho I, Luciano MS, Raymond D, Factor S, et al. Mutations in *GNAL* cause primary torsion dystonia. Nat Genet. 2013;45(1):88–92.
19. Putzel GG, Fuchs T, Battistella G, Rubien-Thomas E, Frucht SJ, Blitzer A, et al. GNAL mutation in isolated laryngeal dystonia. Mov Disord. 2016;31(5):750–5.
20. Jinnah HA, Berardelli A, Comella C, Defazio G, Delong MR, Factor S, et al. The focal dystonias: current views and challenges for future research. Mov Disord. 2013;28(7):926–43.
21. Butefisch CM, Boroojerdi B, Chen R, Battaglia F, Hallett M. Task-dependent intracortical inhibition is impaired in focal hand dystonia. Mov Disord. 2005;20(5):545–51.
22. Samargia S, Schmidt R, Kimberley TJ. Shortened cortical silent period in adductor spasmodic dysphonia: evidence for widespread cortical excitability. Neurosci Lett. 2014;560:12–5.
23. Lanzaro M, Petrone R, D'Ambrosio A. Successful treatment with clozapine in a patient with neuroleptic-induced acute laryngeal dystonia. Eur Psychiatry. 2001;16(4):261–2.
24. Kirke DN, Frucht SJ, Simonyan K. Alcohol responsiveness in laryngeal dystonia: a survey study. J Neurol. 2015;262(6):1548–56.
25. Termsarasab P, Ramdhani RA, Battistella G, Rubien-Thomas E, Choy M, Farwell IM, et al. Neural correlates of abnormal sensory discrimination in laryngeal dystonia. Neuroimage Clin. 2016;10:18–26.

26. Antelmi E, Erro R, Rocchi L, Liguori R, Tinazzi M, Di Stasio F, et al. Neurophysiological correlates of abnormal somatosensory temporal discrimination in dystonia. Mov Disord. 2017;32:141–8.
27. Ludlow CL, Schulz GM, Yamashita T, Deleyiannis FW. Abnormalities in long latency responses to superior laryngeal nerve stimulation in adductor spasmodic dysphonia. Ann Otol Rhinol Laryngol. 1995;104(12):928–35.
28. Deleyiannis FW, Gillespie M, Bielamowicz S, Yamashita T, Ludlow CL. Laryngeal long latency response conditioning in abductor spasmodic dysphonia. Ann Otol Rhinol Laryngol. 1999;108(6):612–9.
29. Cohen LG, Ludlow CL, Warden M, Estegui MD, Agostino R, Sedory SE, et al. Blink reflex curves in patients with spasmodic dysphonia. Neurology. 1989;39:572–7.
30. Simonyan K, Ludlow CL. Abnormal activation of the primary somatosensory cortex in spasmodic dysphonia: an FMRI study. Cereb Cortex. 2010;20(11):2749–59.
31. Simonyan K, Tovar-Moll F, Ostuni J, Hallett M, Kalasinsky VF, Lewin-Smith MR, et al. Focal white matter changes in spasmodic dysphonia: a combined diffusion tensor imaging and neuropathological study. Brain. 2008;131(Pt 2):447–59.
32. Creighton FX, Hapner E, Klein A, Rosen A, Jinnah HA, Johns MM. Diagnostic delays in spasmodic dysphonia: a call for clinician education. J Voice. 2015;29(5):592–4.
33. Whurr R, Lorch M. Review of differential diagnosis and management of spasmodic dysphonia. Curr Opin Otolaryngol Head Neck Surg. 2016;24(3):203–7.
34. Ludlow CL, Domangue R, Sharma D, Jinnah HA, Perlmutter JS, Berke G, et al. Consensus-based attributes for identifying patients with spasmodic dysphonia and other voice disorders. JAMA Otolaryngol Head Neck Surg. 2018;144:657–65.
35. Roy N, Bless DM, Heisey D, Ford CN. Manual circumlaryngeal therapy for functional dysphonia: an evaluation of short- and long-term treatment outcomes. J Voice. 1997;11:321–31.
36. Roy N, Ford CN, Bless DM. Muscle tension dysphonia and spasmodic dysphonia: the role of manual laryngeal tension reduction in diagnosis and management. Ann Otol Rhinol Laryngol. 1996;105:851–6.
37. Roy N, Mazin A, Awan SN. Automated acoustic analysis of task dependency in adductor spasmodic dysphonia versus muscle tension dysphonia. Laryngoscope. 2014;124(3):718–24.
38. Novakovic D, Waters HH, D'Elia JB, Blitzer A. Botulinum toxin treatment of adductor spasmodic dysphonia: longitudinal functional outcomes. Laryngoscope. 2011;121(3):606–12.
39. Hintze JM, Ludlow CL, Bansberg SF, Adler CH, Lott DG. Spasmodic dysphonia: a review. Part 2: characterization of pathophysiology. Otolaryngol Head Neck Surg. 2017;157(4):558–64.
40. Tsuji DH, Hachiya A, Dajer ME, Ishikawa CC, Takahashi MT, Montagnoli AN. Improvement of vocal pathologies diagnosis using high-speed videolaryngoscopy. Int Arch Otorhinolaryngol (New York: Thieme). 2014;18(3):294–302.
41. Yang Q, Xu W, Li Y, Cheng L. Value of laryngeal electromyography in spasmodic dysphonia diagnosis and therapy. Ann Otol Rhinol Laryngol. 2015;124(7):579–83.
42. Van Pelt F, Ludlow CL, Smith PJ. Comparison of muscle activation patterns in adductor and abductor spasmodic dysphonia. Ann Otol Rhinol Laryngol. 1994;103:192–200.
43. Kraft S, Childes J, Hillel A, Schindler J. Refractory dysphonia due to isolated cricothyroid muscle dystonia. J Voice. 2016;30(4):501–5.
44. Ludlow CL, Naunton RF, Terada S, Anderson BJ. Successful treatment of selected cases of abductor spasmodic dysphonia using botulinum toxin injection. Otolaryngol Head Neck Surg. 1991;104(6):849–55.
45. Sataloff RT, Mandel S, Mann EA, Ludlow CL. Practice parameter: laryngeal electromyography (an evidence-based review). Otolaryngol Head Neck Surg. 2004;130(6):770–9.
46. Blitzer A, Lovelace RE, Brin MF, Fahn S, Fink ME. Electromyographic findings in focal laryngeal dystonia (spastic dysphonia). Ann Otol Rhinol Laryngol. 1985;94(6 Pt 1):591–4.
47. Adler CH, Bansberg SF, Krein-Jones K, Hentz JG. Safety and efficacy of botulinum toxin type B (Myobloc) in adductor spasmodic dysphonia. Mov Disord. 2004;19(9):1075–9.
48. Ludlow CL, Naunton RF, Sedory SE, Schulz GM, Hallett M. Effects of botulinum toxin injections on speech in adductor spasmodic dysphonia. Neurology. 1988;38(8):1220–5.
49. 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(10):1435–41.
50. Adams SG, Durkin LC, Irish JC, Wong DL, Hunt EJ. Effects of botulinum toxin type A injections on aerodynamic measures of spasmodic dysphonia. Laryngoscope. 1996;106(3 Pt 1):296–300.
51. Rojas GV, Ricz H, Tumas V, Rodrigues GR, Toscano P, Aguiar-Ricz L. Vocal parameters and self-perception in individuals with adductor spasmodic dysphonia. J Voice. 2017;31(3):391.e7–391.e18.
52. Mor N, Simonyan K, Blitzer A. Central voice production and pathophysiology of spasmodic dysphonia. Laryngoscope. 2018;128(1):177–83.
53. Ali SO, Thomassen M, Schulz GM, Hosey LA, Varga M, Ludlow CL, et al. Alterations in CNS activity induced by botulinum toxin treatment in spasmodic dysphonia: an H215O PET study. J Speech Lang Hear Res. 2006;49(5):1127–46.
54. Bielamowicz S, Ludlow CL. Effects of botulinum toxin on pathophysiology in spasmodic dysphonia. Ann Otol Rhinol Laryngol. 2000;109(2):194–203.
55. Pastor AM, Moreno-Lopez B, De la Cruz RR, Delgado-Garcia JM. Effects of botulinum neurotoxin type A on abducens motoneurons in the cat: ultra-

structural and synaptic alterations. Neuroscience. 1997;81:457–78.
56. Moreno-Lopez B, De la Cruz RR, Pastor AM, Delgado-Garcia JM. Effects of botulinum neurotoxin type A on abducens motoneurons in the cat: alterations of the discharge pattern. Neuroscience. 1997;81:437–55.
57. Moreno-Lopez B, Pastor AM, de la Cruz RR, Delgado-Garcia JM. Dose-dependent, central effects of botulinum neurotoxin type A: a pilot study in the alert behaving cat. Neurology. 1997;48(2):456–64.
58. van Esch BF, Wegner I, Stegeman I, Grolman W. Effect of botulinum toxin and surgery among spasmodic dysphonia patients. Otolaryngol Head Neck Surg. 2017;156(2):238–54.
59. Shoffel-Havakuk H, Rosow DE, Lava CX, Hapner ER, Johns MM III. Common practices in botulinum toxin injection for spasmodic dysphonia treatment: a national survey. Laryngoscope. 2019;129:1650–6.
60. Borodic GE, Ferrante R. Effects of repeated botulinum toxin injections on orbicularis oculi muscle. J Clin Neuroophthalmol. 1992;12(2):121–7.
61. Young N, Blitzer A. Management of supraglottic squeeze in adductor spasmodic dysphonia: a new technique. Laryngoscope. 2007;117(11):2082–4.
62. Simpson CB, Lee CT, Hatcher JL, Michalek J. Botulinum toxin treatment of false vocal folds in adductor spasmodic dysphonia: functional outcomes. Laryngoscope. 2016;126(1):118–21.
63. Kotby MN, Kirchner JA, Kahane JC, Basiouny SE, El-Samaa M. Histo-anatomical structure of the human laryngeal ventricle. Acta Otolaryngol. 1991;111:396–402.
64. Dedo HH. Recurrent laryngeal nerve section for spastic dysphonia. Ann Otol Rhinol Laryngol. 1976;85(4 Pt 1):451–9.
65. Aronson AE, Desanto LW. Adductor spasmodic dysphonia: three years after recurrent nerve section. Laryngoscope. 1983;93:1–8.
66. Fritzell B, Hammarberg B, Schiratzki H, Haglund S, Knutsson E, Martensson A. Long-term results of recurrent laryngeal nerve resection for adductor spasmodic dysphonia. J Voice. 1993;7:172–8.
67. Netterville JL, Stone RE, Rainey C, Zealear DL, Ossoff RH. Recurrent laryngeal nerve avulsion for treatment of spastic dysphonia. Ann Otol Rhinol Laryngol. 1991;100(1):10–4.
68. Weed DT, Jewett BS, Rainey C, Zealear DL, Stone RE, Ossoff RH, et al. Long-term follow-up of recurrent laryngeal nerve avulsion for the treatment of spastic dysphonia. Ann Otol Rhinol Laryngol. 1996;105(8):592–601.
69. Tsuji DH, Takahashi MT, Imamura R, Hachiya A, Sennes LU. Endoscopic laser thyroarytenoid myoneurectomy in patients with adductor spasmodic dysphonia: a pilot study on long-term outcome on voice quality. J Voice. 2012;26(5):666.e7–12.
70. Gandhi S, Remacle M, Mishra P, Desai V. Vocal outcome after endoscopic thyroarytenoid myoneurectomy in patients with adductor spasmodic dysphonia. Eur Arch Otorhinolaryngol. 2014;271(12):3249–54.
71. Sanuki T, Yumoto E. Long-term evaluation of type 2 thyroplasty with titanium bridges for adductor spasmodic dysphonia. Otolaryngol Head Neck Surg. 2017;157(1):80–4.
72. Chan SW, Baxter M, Oates J, Yorston A. Long-term results of type II thyroplasty for adductor spasmodic dysphonia. Laryngoscope. 2004;114(9):1604–8.
73. Nomoto M, Tokashiki R, Hiramatsu H, Konomi U, Motohashi R, Sakurai E, et al. The comparison of thyroarytenoid muscle myectomy and type II thyroplasty for spasmodic dysphonia. J Voice. 2015;29(4):501–6.
74. 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(4):635–42.
75. DeConde AS, Long JL, Armin BB, Berke GS. Functional reinnervation of vocal folds after selective laryngeal adductor denervation-reinnervation surgery for spasmodic dysphonia. J Voice. 2012;26(5):602–3.
76. Chen M, Summers RL, Goding GS, Samargia S, Ludlow CL, Prudente CN, et al. Evaluation of the cortical silent period of the laryngeal motor cortex in healthy individuals. Front Neurosci. 2017;11:88.
77. Suppa A, Marsili L, Giovannelli F, Di Stasio F, Rocchi L, Upadhyay N, et al. Abnormal motor cortex excitability during linguistic tasks in adductor-type spasmodic dysphonia. Eur J Neurosci. 2015;42(4):2051–60.
78. Payne S, Tisch S, Cole I, Brake H, Rough J, Darveniza P. The clinical spectrum of laryngeal dystonia includes dystonic cough: observations of a large series. Mov Disord. 2014;29(6):729–35.
79. Peterson EA, Roy N, Awan SN, Merrill RM, Banks R, Tanner K. Toward validation of the cepstral spectral index of dysphonia (CSID) as an objective treatment outcomes measure. J Voice. 2013;27(4):401–10.
80. Awan SN, Roy N. Outcomes measurement in voice disorders: application of an acoustic index of dysphonia severity. J Speech Lang Hear Res. 2009;52(2):482–99.
81. Rees CJ, Blalock PD, Kemp SE, Halum SL, Koufman JA. Differentiation of adductor-type spasmodic dysphonia from muscle tension dysphonia by spectral analysis. Otolaryngol Head Neck Surg. 2007;137(4):576–81.
82. Johnson DM, Hapner ER, Klein AM, Pethan M, Johns MM 3rd. Validation of a telephone screening tool for spasmodic dysphonia and vocal fold tremor. J Voice. 2014;28(6):711–5.
83. Risch V, Staiger A, Ziegler W, Ott K, Scholderle T, Pelykh O, et al. How does GPi-DBS affect speech in primary dystonia? Brain Stimul. 2015;8(5):875–80.
84. Yoon MS, Munz M, Sataloff RT, Spiegel JR, Heuer RJ. Vocal tremor reduction with deep brain stimulation. Stereotact Funct Neurosurg. 1999;72(2–4):241–4.

85. Ho AL, Choudhri O, Sung CK, DiRenzo EE, Halpern CH. Deep brain stimulation for essential vocal tremor: a technical report. Cureus. 2015;7(3):e256.
86. Ho AL, Erickson-Direnzo E, Pendharkar AV, Sung CK, Halpern CH. Deep brain stimulation for vocal tremor: a comprehensive, multidisciplinary methodology. Neurosurg Focus. 2015;38(6):E6.
87. Poologaindran A, Ivanishvili Z, Morrison MD, Rammage LA, Sandhu MK, Polyhronopoulos NE, et al. The effect of unilateral thalamic deep brain stimulation on the vocal dysfunction in a patient with spasmodic dysphonia: interrogating cerebellar and pallidal neural circuits. J Neurosurg. 2018;128(2):575–82.
88. Barbe MT, Dembek TA, Becker J, Raethjen J, Hartinger M, Meister IG, et al. Individualized current-shaping reduces DBS-induced dysarthria in patients with essential tremor. Neurology. 2014;82(7):614–9.