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Spasmodic dysphonia: An overview of clinical features and treatment options

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ABSTRACT

Spasmodic dysphonia (SD) is considered a rare focal laryngeal dystonia characterized by task-specific voice dysfluency resulting from selective intrinsic laryngeal musculature hyperfunction. Symptoms may be attenuated by a sensory trick. Although SD can be seen at times in generalized dystonia syndrome, it is typically a sporadic phenomenon, and the involvement of the laryngeal adductor muscles is more common than that of the abductor muscles. This research reviews the literature for the pathogenesis, clinical characteristics, treatment options, and current management methods of SD. Technological advances have enabled clinicians to better understand the connection between laryngeal function and dysfunction. Refinements in imaging and genetic investigation techniques have helped better understand the underlying mechanisms of this neurolaryngology disorder. Currently, the standard of care for SD is the symptomatic management of botulinum toxin (BT) chemodenervation. This is supported by a large body of literature attesting to its efficacy in many different research studies, particularly in the uncomplicated adductor form of the disorder. Efforts towards surgical treatment predate the development of BT treatment by a decade, but the long-term efficacy has not been proven and, further research is expected. Symptom relief in patients with abductor SD and dystonia with tremors after surgical and BT treatments and those in patients remains suboptimal.

1. Introduction

This review focuses on spasmodic dysphonia (SD). SD is a task-specific focal dystonia characterized by intermittent and involuntary spasms of the intrinsic laryngeal muscles during phonation. Dystonia is a neurological disorder of the central nervous system (CNS) characterized by muscle spasms caused by task-specific movements. After the physicians recognized that SD was not a symptom related to psychiatric disorders, the initial treatment for this disease focused on surgically resolving vocal symptoms. However, the long-term results from this approach were not promising, and this procedure was largely replaced by temporary chemodenervation with botulinum toxin (BT). This was consistent with the initial surgical results and provided reproducible long-term benefits against retreatment. For most patients, BT treatment has proven to be a satisfactory means of achieving relief from symptoms. However, predictable control of voice symptoms may remain difficult in some patients, especially those with abductor SD or involuntary laryngeal movements with significant tremor.

2. Background

Laryngoscopic visualization of abnormal spasms in the adductor muscles of the vocal folds during speaking was first re-

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ported around 150 years ago [1]. Abnormal vocal fold movements were characterized as dystonia in the 1980s [2]. Currently, SD is recognized as an idiopathic focal dystonia affecting the intrinsic laryngeal muscles. It is classified as a rare disease with a prevalence of 3.5 to 7.0 in 100,000 predominantly affecting women (4.1 to 4.4 times more likely to suffer from this disorder than men) [3]. The age of onset is reportedly 30.9 years. SD presents with two main phenotypes: (a) adductor SD, which is the most common, and (b) abductor SD, which is relatively rare. Mixed SD involves the characteristics of both. Vocal tremors often coexist with SD.

3. Pathogenic factors

Robe et al. reported that, of the 10 patients diagnosed with SD, all had signs of CNS abnormalities [4]. Further evidence suggested a neurological component when Dedo temporarily paralyzed the recurrent laryngeal nerve (RLN) and subsequently cut it open, after which half of the treated patients regained their normal voice [5].

Early electromyographic studies have indicated abnormalities in the motor control system [6]. Subsequently, dystonic movements were treated by injecting BT into the affected muscle. BT inhibits the release of acetylcholine from the presynaptic terminal to the neuromuscular junction, causing temporary paralysis, and early results showed that BT was effective in improving voice symptoms following injection [7,8]. Currently, BT is the primary treatment for SD worldwide [9,10].

In recent years, SD has been considered a result of basal ganglia abnormalities, while the pathogenesis of SD is currently considered to involve genetic and environmental factors [11].

SD is characterized by its multifactorial etiology, and genetic variants are considered important risk factors for the development of this disorder. Additionally, 25.3% of SD patients reportedly have a family history of dystonia and 11.8% have a family history of other movement disorders [12–14]. Among other forms of dystonia-causing gene mutations that have been identified, laryngeal involvement has been reported in patients with generalized and segmental dystonia who are carriers of the DYT1, DYT4, DYT6, DYT25, and DYT28 mutations [15–17]. Currently, only one case of adductor SD has been sequenced; the patient had the DYT25 (*GNAL*) mutation, with no other concomitant dystonia, and no family history of dystonia or other movement disorders has been reported [18]. This finding pointed to a genetic overlap between SD and other forms of dystonia, and suggested that gene mutations may underlie even sporadic SD presentation due to reduced penetrance. It was proposed that the stratification of patients into truly sporadic and familial cases would remain arbitrary, pending the discovery of causative gene mutations specific to SD [18].

Previous neuroimaging studies have suggested that SD is associated with abnormal sensorimotor integration in the primary sensorimotor cortex, basal ganglia, thalamus, and cerebellum [19–21]. These studies are important because they suggest that the pathogenesis of SD is an abnormality in the brain region that regulates speech production. Furthermore, Simonyan and Ludlow [19] deliberately trained healthy participants to 'imitate' the typical voice patterns of SD patients and measured their brain activity using functional magnetic resonance imaging (fMRI). The authors observed increased activation in the primary sensorimotor cortex, insula, superior temporal gyrus, basal ganglia, thalamus, and cerebellum in SD patients compared with that in controls. More recently, functional connectivity analysis using resting-state fMRI has been used as an alternative imaging method to overcome the inherent problems in comparing SD patients with healthy or non-SD participants. Particularly, Battistella et al. [22] showed abnormal functional connectivity within the sensorimotor and frontoparietal networks in patients compared to that observed in healthy individuals.

4. Clinical characteristics

Dystonia may be generalized or restricted to one functional muscle group. When involving the larynx, it is usually focal to that organ. SD, like other dystonias, is task-specific: that is, it affects only one type of activity performed by the larynx. Most patients usually experience the onset of symptoms beginning in their mid-30s and cases in women are more common [3,23,24]. Approximately 8 of the 10 patients have adductor SD, which causes improper glottal closure, and, consequently, strangled breaks in connected speech. Nevertheless, abductor SD causes inappropriate glottal opening, breathy breaks, etc. Because of the compensatory manipulation or mixed dystonic features, the voice patterns encountered clinically may not always be typical or easily identifiable.

Diagnosis is based on the clinical history and examination of the larynx during various laryngeal tasks during phonation. Typical history includes deterioration of voice quality due to stress or telephone calls. Some patients find that certain tactile or proprioceptive maneuvers, so-called sensory tricks, such as chewing or supporting the head, can improve speech. The mechanism underlying this phenomenon is unknown. Singing or laughing may also improve the fluency of speech, perhaps taking advantage of the task-specific nature of dystonia. Occasionally, the diagnosis of SD can be difficult. There are no relevant signs in the SD patient's history or examination. Essential voice tremor and muscle tension dysphonia (MTD), a functional disorder, can cause voice breaks and form the most important entities in the differential diagnosis of this disease. The hyperadduction of MTD is generally persistent and spasmodic, whereas the dyskinesia of essential tremors are rhythmic and often involve the pharyngeal and strap muscles. Neither tremors nor MTD exhibits task specificity, but both disorders can be exacerbated by stress on the voice. In a pilot study, Kodama et al. demonstrated that voice therapy was useful in differentiating between adductor SD and MTD [25]. Hyodo et al. formulated diagnostic criteria for SD based on the characteristics of clinical symptoms, response to treatment, and differential diagnosis and severity classification, using information from a nationwide epidemiological survey in Japan [3,26]. These diagnostic criteria need to be evaluated

for validity and reliability, and a study using a disease registry is expected.

5. Treatment options

It is most likely due to Dedo's contribution that SD was again conceptualized as a medical disorder, when he proposed RLN section of the adductor form in 1976, after an attempt at a temporary lidocaine block [5]. Biller et al. [27] were the first to report a widespread recurrence of symptoms after RLN crush, which was initially thought to be equally effective, with a success rate of 13% at 3 years. Other researchers have noted recurrence in long-term follow-up, even with a complete RLN section [28,29]. In 1983, Aronson and DeSanto [30] reported a 64% recurrence rate at 3 years after superb initial results. Although some authors have obtained more stable long-term results, unsuccessful salvage strategies are being reported. These included ipsilateral superior laryngeal nerve transection, partial myectomy of the thyroarytenoid muscle, and more aggressive re-resection of the RLN [28,31–33].

Voice therapy does not result in marked improvement by itself, but may be useful when administered in addition to BT [34], perhaps by addressing the compensatory behaviors that are superimposed on SD. Voice therapy is the principal therapy for MTD; however, it may be helpful as a diagnostic maneuver in ambiguous cases [25].

Because of the promising results of BT treatment for blepharospasm and torticollis, two focal dystonias affecting the periocular and cervical muscles, BT was first performed in SD patients in 1984. Blitzer's experience with laryngeal electromyography needles allowed him to deliver the BT into the intrinsic laryngeal muscles, effectively performing a chemical neurectomy and successfully relieving symptoms [35]. The principle of this treatment, denervation, is the same as that of the RLN section, except that the relief of symptoms is temporary, but can be repeated indefinitely.

5.1. Botulinum toxin

The widespread success of BT as a treatment for focal dystonia may be due to the specificity, repeatability, and reversibility of chemodenervation. Nerve terminal recovery from poisoning is a continuous, multiphase process, beginning practically as soon as acetylcholine release is blocked [36]. The cycle of recovery and reinjection by BT may not overcome denervation because the CNS never reaches a stable plateau. The voice effects of this injection were sometimes found to be greater than expected from the observed *in vitro* activity of BT, suggesting that its clinical effect may be more than simple acetylcholine blockade at the neuromuscular junction. Some authors have hypothesized that BT may also affect neurotransmission in afferent systems [37,38]. In SD patients, changes in muscle activation are observed in both injected and non-injected muscles, further suggesting a central effect [6,39].

Although the treatment cycle of recovery and re-injection results in some clinical fluctuations in voice quality, the results are generally satisfactory, as seen in post-treatment clinician's assessment of voice function and, more importantly, patient self-assessment. Recent studies, measured using the Voice-Related Quality of Life questionnaire, a standardized patient-based outcome inventory, have demonstrated continued, albeit somewhat heterogeneous, benefits across multiple treatment sessions in patients with adductor SD [40,41].

In 2002, a regimen of alternating unilateral injections has been offered as a means of controlling symptoms of glottic insufficiency, such as breathy voice or dysphagia, in patients with adductor SD by Bielamowicz et al. [42]. This study was reported based on the treatment of 45 patients. The same research group conducted a similar evaluation based on the course of treatment of 272 patients (total 4023 injections) [43]. They reported that optimal effect duration was more commonly seen in bilaterally injected patients (55%) compared to the unilaterally injected patients (47%) and the optimal side effect duration was better for the unilaterally injected patients (77%) compared to the bilaterally injected patients (73%). These results suggested that bilateral injections were more effective than unilateral injections. Hyodo et al. [10] conducted a multicenter, placebo-controlled, randomized, double-blind, parallel-group/open-label clinical trial to gain approval for BT treatment for SD in Japan. Regarding this study, BT injections into unilateral and bilateral thyroarytenoid muscles for Adductor SD were approved in Japan.

5.2. Evolving perspectives in surgical treatment

SD has poor results associated with surgical neurolysis, as do other types of dystonia, such as blepharospasm or torticollis. Electromyographic and clinical evidence suggests that recurrence of the symptoms is due to reinnervation [29,32,44,45]. To prevent this, Berke et al. [46] proposed selective sectioning of the distal branches of the RLN leading to the thyroarytenoid and sometimes the lateral cricoarytenoid muscle, with immediate reinnervation using a nonlaryngeal nerve, generally the sternohyoid branch of the ansa cervicalis. Thus, they attempted to prevent the reestablishment of abnormalities in central motor control by connecting the laryngeal musculature to a nerve supply that was not affected by the disorder. Their initial report presented favorable voice results in 21 adductor SD patients dissatisfied with BT treatment who were followed for an average of 3 years postoperatively. Most voices were markedly improved according to both professionals and patients. Only one patient required further BT injections. Most patients experienced breathiness for 3–6 months, but only one developed difficult aspiration. Berke and Blumin [47] subsequently reported formally on 50 additional patients with similar results. Conversely, repeatability is an important initial test for any new approach, and the literature contains reports of the same surgical results by another group. Allegretto et al. [48] treated six patients without complications and with generally favorable results, as rated by patients and both trained and untrained listeners. Five of the six patients no longer require BT treatment. Patients were followed up for a mean of 20 months.

A transoral partial thyroarytenoid muscle myectomy and neurectomy has been reported [49–53]. While this procedure is considered relatively safe, effective, and technically simple, a postoperative breathy voice was given as the greatest disadvantage of this procedure. Tsuji et al. [50,51] evaluated the vocal quality in patients who underwent partial myoneurectomy and found a clear difference between The Voice Handicap Index (VHI) scores before and after surgery. Schuering et al. compared the long-term results of endoscopic laser thyroarytenoid myoneurectomy and BT treatment in 22 patients with the same adductor SD and observed no significant difference. However, at the postoperative follow-up, 10 of 22 patients (45%) required a second procedure after a mean of 18 months (interquartile range, 13–22 months) because of the recurrence of original voice symptoms [52].

Finally, Isshiki et al. [54,55] presented a mechanical solution to the problem of excessive adduction in patients with adductor SD: type 2 thyroplasty with midline division of the thyroid cartilage. Surgical success depends on maintaining a permanent left-to-right opening of the thyroid cartilage incision, and a titanium bridge was developed [56]. Recently, titanium bridges have been improved following clinical studies and have been commercialized as medical devices [57]. Sanuki and Yumoto [58] have successfully reported 47 surgical cases, employing the VHI-10 to assess the subjective symptoms of patients and the condition of the wound. The mean duration of follow-up was 41.3 months. Nomoto et al. [53]. compared thyroarytenoid muscle myectomy with type 2 thyroplasty and found that thyroarytenoid muscle myectomy tended to improve strangulation, interruption, and tremor; however, it tended to worsen breathiness postoperatively. Postoperative VHI-10 scores did not differ significantly between the two procedures. Given the favorable improvement rates, both surgical procedures were considered effective.

Early success and subsequent disappointment are characteristic of surgical approaches to dystonias, including SD, perhaps because the static nature of the intervention eventually allows the CNS drive to reexpress itself in the larynx over time. Against this background, any new intervention must pass a test of long-term efficacy; experience with RLN sectioning suggests that a minimum of 3 years follow-up is required. Furthermore, for the adductor SD, it would be necessary to see the postoperative voice quality compared not only to that before the operation but also to that obtained after BT treatment. This is essential if surgery is to be used as a primary treatment alternative to BT treatment, as Berke and Blumin [47] have proposed. A recent report suggests that BT treatment after RLN section can be somewhat less satisfactory than surgery [45]. The burden remains on the physician to avoid harm.

A slightly different surgical approach intended to address abductor SD involves attachment of the posterior cricoarytenoid muscle to the arytenoid cartilage [59]. Unlike selective adductor reinnervation, this is initially performed unilaterally to avoid airway problems, although it is sometimes combined with medialization. Shaw et al. [59] presented three cases in which a favorable voice result was eventually obtained, as judged by counting voice breaks in a standardized voice sample 1 year postoperatively. One patient underwent simultaneous posterior cricoarytenoid muscle section with ipsilateral medialization, another followed an initial muscle section with a contralateral muscle section and medialization 5 months later, and a third underwent muscle section with contralateral BT treatment. This patient required tracheostomy until the effects of the toxin were abated. Abductor SD remains a challenge to treat both surgically and by chemodenervation.

6. Conclusion

SD is most likely a disorder of the basal ganglia rather than the larynx, and interventions at the end organ are unlikely to offer a true cure. The pathophysiology underlying dystonia, which was exclusively a subject for speculation when recurrent nerve sections and, later BT treatment was introduced, is becoming better understood because of discoveries in genetically based forms of the disorder. The elucidation of the function of the protein products of several genes may reveal the underlying mechanism of dystonia and offer a route to definitively relieve patient symptoms.

Currently, the standard treatment for SD is symptomatic management through BT chemodenervation. This is supported by a large body of literature attesting to its effectiveness in many different studies, especially in the uncomplicated adductor form of the disorder. Efforts towards surgical treatment predate the development of BT treatment by a decade, but long-term efficacy has not been proven, and so further research is expected. Symptom relief in patients with abductor SD and dystonia with tremor after either surgical intervention or BT treatment remains suboptimal.

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Declaration of Competing Interest

The author has no conflicts of interest directly relevant to the content of this article.

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