NATIONAL SPASMODIC DYSPHONIA ASSOCIATION

Spasmodic Dysphonia Research
Past, Present, and Future

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Research Growth on Spasmodic Dysphonia over the Past 67 Years

For this review, all papers published in the medical literature from 1950 to 2017 that contained "spastic or spasmodic" and "dysphonia" were examined to determine how our understanding and knowledge of spasmodic dysphonia (SD) has promoted emerging medical research. A total of 734 papers have been published in the past 67 years starting with a few papers per year before 1976, to over 40 papers each year in 2017 *(Figure 1)*. This reflects an increase in interest in the disorder and hope for those living with SD.

Assessing the Past

Research on SD from 1950 through 2010 fell into three distinct categories:

- First was the identification of **SD as a neurological disorder**.
- This was followed by the introduction of various **temporary treatments** that reduced nerve conduction to the laryngeal muscles and muscle spasms that disrupt voice during speech.
- The third phase has focused on trying to **understand the neurological system abnormalities underlying SD voice abnormalities**. This last phase is essential to understanding what could cause SD and how to treat it for long term results.

Phase One: Spasmodic Dysphonia as a Neurological Disorder

In 1960, Robe, Brumlik, and Moore published the first paper to propose that SD is a neurological disorder[1.]. Then in 1968, Aronson and colleagues[2, 3] described how SD is related to voice tremor and differed from psychological disorders affecting the voice; both issues still being investigated today. It was Marsden who first proposed that SD was a form of dystonia specific to the laryngeal muscles occurring only during speech and voice[4].

Our understanding of SD and the accepted explanation today is that it is a dystonia focal to the laryngeal muscles and that the spasms only occur during speech and voice and not during emotional voice expression such as laughter and crying.

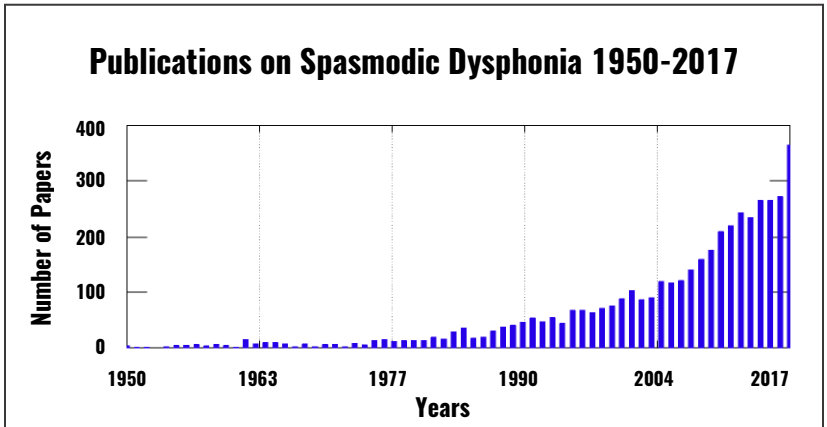

Figure 1: *Distribution of 734 Papers published in the medical literature between 1950 and 2017, showing growth from 5 to over 250 per year, reflecting increased interest in studying spasmodic dysphonia.*

Phase Two: Denervation of the Laryngeal Muscles to Reduce Spasms

Treatment for SD was first introduced in 1976 when Dedo reported that cutting the recurrent laryngeal nerve on one side of the larynx could disrupt the muscle spasms[5]. However, there was less enthusiasm when it was realized that benefit became reduced three years later when the recurrent nerve grew back and spasms returned[6-8]. Although doing more extensive nerve excision has been tried, it is recognized that a prolonged unilateral laryngeal paralysis also reduces voice function due to persistent breathiness and swallowing difficulties.

In 1987, the first article was published reporting the use of botulinum toxin injections in adductor SD patients improving their voice function[9]. The injection of botulinum toxin into the laryngeal muscles chemically blocked communication between the nerve and muscle and reduced voice spasms in SD patients[9]. This was followed by studies demonstrating that the voice breaks were reduced in adductor SD[10], and that 90 % of persons with adductor SD reported significant benefits for three months[11, 12], but dosages and results varied considerably.[13, 14] Different methods of muscle injection are used and the side effects of transient breathiness and swallowing difficulties can vary. Only a very small controlled trial (comparing the effects of saline injections with botulinum toxin injections) has objectively evaluated the degree to which botulinum toxin injections benefit patients with adductor SD[15].

Botulinum toxin injections for adductor SD remain the treatment of choice today. They can produce a significant reduction in voice breaks and speaking effort although the results vary even when the same physician employs the same dosage at regular intervals. Both the duration and degree of voice improvement varies as do the temporary side effects of breathiness and swallowing difficulties.

Patients with other forms of SD such as abductor SD require different muscle injections and have much less benefit, sometimes only for short periods[16, 17]. Voice tremor patients also vary in their benefit particularly when additional muscles outside the larynx have tremor[18, 19]. To maintain a benefit, botulinum toxin re-injections are needed every few months. These can be costly and may not maintain good voice function over time.

Surgical approaches to treatment aim to provide long term benefits. These are highly skilled requiring denervation of the vocal fold muscle on each side with reinnervation with another nerve, referred to as selective laryngeal adductor denervation-reinnervation: SLAD-R[20, 21]. Care is needed in selecting patients as the results can vary. However, long term benefits have been found without further treatment in many cases. Other surgical approaches that have been used but not well evaluated include midline lateralization thyroplasty[22]. Recently, six cases of abductor SD were benefitted by bilateral vocal fold medialization surgery, which needs further study[23].

Phase Three: Neurological Abnormalities Producing SD Voice Abnormalities

Although treatment of SD has focused on disrupting the communication between the brain and the laryngeal muscles, the underlying neurological abnormality producing the spasms is in the brain. The third phase of research was focused on pathophysiology, i.e. studying the brain irregularities in SD patients as compared to normal subjects to determine abnormalities. If brain abnormalities can be identified, then, in theory, these could be targeted for treatment. Methods for studying brain function include examining sensory motor reflexes and studying brain function using functional neural imaging techniques (Positron Emission Tomography - PET and Functional Magnetic Resonance Imaging - fMRI).

To study reflexes, sensory nerves are stimulated and the parts of the brain that connect the sensory input from the larynx with output to the laryngeal muscles can be identified. In 1994-1995 studies were done using electrical stimulation to activate sensory input, and the laryngeal muscle responses in adductor and abductor SD were found to be hyperactive[24, 25]. In addition, blink reflexes were also hyperactive in adductor SD demonstrating that brain stem reflex circuits for the larynx and the eyes were less controlled in SD[26].

Functional neural imaging compared brain functioning in persons with SD with persons without SD while both groups were speaking. PET functional imaging showed SD patients had cortical abnormalities such as increased right premotor, increased left somatosensory, and increased cerebellar activity[27] *(Figure 2)*. However, the speaking difficulties of people with SD in comparison with those who did not have SD might account for some of the findings. Contrary to previous assumptions held that SD is a basal ganglia disorder, few basal ganglia abnormalities were found in this study[27].

To examine the central effects of botulinum treatment, a 2006 study found the motor hyperexcitability in the brain decreased and sensory activation increased, demonstrating cortical changes with botulinum toxin[27]. However, reductions in speech effort in persons with adductor SD after botulinum toxin injection, could itself account for brain function changes after treatment.

Assessing Present Research Measuring the Severity of SD

Studies of methods for measuring the severity of SD have been particularly active in the last seven years. To compare different treatments, it is essential to measure changes in the severity of a patient's voice disorder.

The methods of voice measurement used in persons with SD that are reliable (i.e. when used by two persons or repeated by the same person produce the same result) and valid (voice measures that differentiate persons with SD from persons without a voice disorder) are summarized in Table 1.

Table 1: Review of Voice Assessment Tools Evaluated in Spasmodic Dysphonia or Voice Tremor

Measure	Reliability	Validity
Patient Quality of Life -Voice-Related Quality of Life (V-RQOL)[28]	√	√
Voice Handicap Index 10[29, 30]	√	
Perceptual/Acoustic Measures of Voice Breaks([10, 31]	√	√
Cepstral Peak Prominence in Voiced Speech[32]	√	√
Rating Tremor in Prolonged Vowels[33]	√	√
Clinician Perceptual Ratings, CAPE V[28]	√	√
Unified Spasmodic Dysphonia Rating Scale[34]		√

Classification of Adductor SD, Abductor SD, Voice Tremor or Muscular Tension Dysphonia

Accurate identification of who has adductor SD, abductor SD, voice tremor or muscular tension dysphonia (another voice disorder), is important as the best treatment differs between these disorders. Ninety percent of adductor SD patients benefit from botulinum toxin injection while persons with abductor SD or voice tremor usually need different muscles injected. Surgical options are mostly available for adductor SD while muscular tension dysphonia usually responds to voice therapy. Patients see many professionals before their disorder is identified and they can receive treatment[35]. A recent study found that experts, even from the same voice centers and/or profession, did not agree on classification[36].

Because of this, over 50 experts on SD developed definitions of each disorder and a set of 19 attributes were identified for classifying the disorders using the Spasmodic Dysphonia Attributes Inventory. Hopefully this checklist will be useful in future research for classifying patients who have adductor SD, abductor SD, voice tremor, muscular tension dysphonia or combinations of each[36].

Pathogenesis of Spasmodic Dysphonia

Pathogenesis is the study of factors that might cause spasmodic dysphonia. This is essential to be able to identify long-term treatments or to prevent SD from developing.

Some studies looking at the brain structure and potential functional differences have been published. fMRI measures of brain structure and function when persons are at rest and not speaking can compare the structure and function of brain regions of persons with SD and those without a voice disorder. A network involving the left inferior parietal and sensorimotor regions had higher levels of activity in persons with SD and could separate patients from normal speakers with 71% accuracy[37]. Further, the results could differentiate adductor from abductor SD and those with a family history of SD from those without a family history[37].

Transcranial magnetic stimulation of brain regions to elicit muscle responses in the hand in SD and controls found that the cortical silent period was shorter in persons with SD than in controls, showing reduced cortical inhibition in persons with adductor SD[38]. Others found this difference was most pronounced during language tasks[32]. In addition, structural differences in the brain have been found in SD.

Two studies showed reduced white matter tracts in the right internal capsule in SD[39, 40].

Considerable attention has been given to possible genetic mutations that could lead to specific types of dystonia, including SD. Genetic mutations for four dystonia types that include voice disorders have been reported. However, when the genes of persons with SD were examined, very few people with SD had these mutations.

- **DYT1** is an early onset torsion dystonia with voice abnormalities; but a study of 422 people with SD found none had the gene mutation referred to as *TOR1A*[41].
- **DYT4** is a whispering dysphonia with jaw involvement, but none of 57 people with SD had the *TUBB4A* mutation[42].
- **DYT6** is primary torsion dystonia with frequent laryngeal involvement, but only two of 422 people with SD had *THAP1* variations[43].
- **DYT25**, is primary torsion dystonia with cranio-cervical dystonia with *GNAL*, but this mutation was only found in one of 57 people with SD[42].

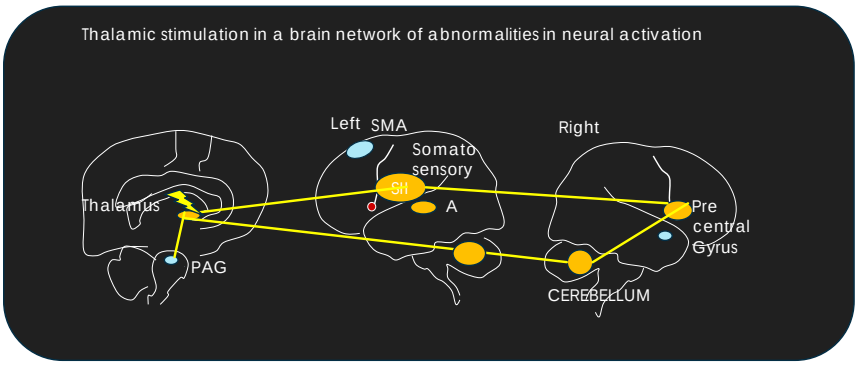

Figure 2: *Based on functional brain imaging research, regions in orange have been found hyperactive in studies of speaking and at rest in SD including the somatosensory area (SII), the auditory association area (A) on the left, the precentral gyrus in the right and the cerebellum and the thalamus bilaterally. Regions that have been found to have decreased in activity in SD include the peri-aquaductal gray (PAG), the left supplementary motor area (SMA), and an auditory area on the right. As suggested here, continued stimulation in the thalamus could possibly reset the network abnormalities in the brain in persons with SD or voice tremor that might improve voice functioning.*

Hope for the Future

Research is continuing to try to identify the brain basis for SD and hopefully new treatment methods that will improve the quality of life for those with SD.

Comparisons of Treatments for Adductor SD

Studies have shown that persons with adductor SD can benefit from either botulinum toxin injections, laryngeal muscle excisions (myectomy), or laryngeal repositioning (type II Thyroplasty), but information is not available comparing the benefits and side effects of each. Thus, patients have no information on which treatment approach might be best for their particular type of SD. Only two authors have compared different treatment types for adductor SD. When thyroarytenoid muscle myectomy and Type II Thyroplasty were compared, patient ratings found both were equally beneficial, however, myectomy was more helpful in severe cases[30].

A literature review compared the benefits of botulinum toxin injection with surgical procedures including myectomy, thyroplasty, SLAD-R, or recurrent nerve crush or resection for treatment of adductor SD. No differences were found based on a meta-analysis[44]. However, prospective studies are needed to compare the outcomes of different treatments for SD on long term control of symptoms with fewer side effects.

Deep Brain Stimulation for Voice Tremor & SD

Deep brain stimulation (DBS) involves the surgical implantation of stimulating electrodes into regions deep in the brain. Using brain imaging this surgical technique places electrodes into specific regions of structures. The electrodes stimulate those centers to alter the brain network dysfunction and control symptoms. An example is bilateral stimulation of the subthalamic nucleus (STN) used for treatment of dyskinesia in Parkinson's 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 does. However, one study reported that a patient with adductor SD had a marked benefit[45].

Control of arm tremor can be benefitted by stimulating the ventral intermediate (Vim) nucleus of the thalamus bilaterally; and reduced voice tremor in two patients[46-48]. The same region was implanted in a patient with SD who also had arm tremor, and there was a voice benefit[49]. These are only single cases but suggest that DBS may be helpful in people with voice tremor and SD by stimulating one part of the brain to reset abnormalities in the brain networks in SD or voice tremor *(Figure 2*). 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[50]. A study on DBS in six patients with SD is currently being conducted with results expected to be published next year.

Conclusions

As summarized, a great deal has been accomplished over the last forty years through research on SD. The National Spasmodic Dysphonia Association has contributed significantly by providing seed money for the initiation of much of this research. However, there is much more work to be done.

By improving diagnostic accuracy, understanding the brain abnormalities and developing methods for treating those brain abnormalities, the prospects for helping patients with these disorders will improve dramatically. The long-term goal of determining what causes this disorder could lead to the prevention of SD, an ideal for us all.

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