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LITERATURE REVIEW

Research priorities in spasmodic dysphonia

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OBJECTIVE: To identify research priorities to increase understanding of the pathogenesis, diagnosis, and improved treatment of spasmodic dysphonia.

STUDY DESIGN AND SETTING: A multidisciplinary working group was formed that included both scientists and clinicians from multiple disciplines (otolaryngology, neurology, speech pathology, genetics, and neuroscience) to review currently available information on spasmodic dysphonia and to identify research priorities.

RESULTS: Operational definitions for spasmodic dysphonia at different levels of certainty were recommended for diagnosis and recommendations made for a multicenter multidisciplinary validation study.

CONCLUSIONS: The highest priority is to characterize the disorder and identify risk factors that may contribute to its onset. Future research should compare and contrast spasmodic dysphonia with other forms of focal dystonia. Development of animal models is recommended to explore hypotheses related to pathogenesis. Improved understanding of the pathophysiology of spasmodic dysphonia should provide the basis for developing new treatment options and exploratory clinical trials.

SIGNIFICANCE: This document should foster future research to improve the care of patients with this chronic debilitating voice and speech disorder by otolaryngology, neurology, and speech pathology.

Experts reviewed the current understanding of spasmodic dysphonia (SD), to identify gaps in knowledge and to develop recommendations for research on the pathogenesis and pathophysiology of the disorder for prevention and improved treatment.

DIAGNOSIS OF SPASMODIC DYSPHONIA

SD is a rare speech disorder that develops spontaneously in midlife. Symptoms are uncontrolled voice breaks[1] and a marked effort while speaking. Progression is gradual in the first year, then becoming chronic.[2] SD is usually idiopathic; symptoms rarely occur as a result of brain injury or neuroleptics. Women are affected more than men; between 60 percent and 85 percent female.[3,4]

Involuntary spasms in the laryngeal muscles cause intermittent voice breaks,[5] only during speech.[6] In adductor SD, spasmodic hyperadductions of the vocal folds produce voice breaks with a choked, strained quality. Abductor SD is less common, with hyperabduction (uncontrolled opening) of the vocal folds prolonging voiceless consonants before vowels.[7] Very rarely, adductor and abductor spasms occur in the same patient. Voice tremor is often present with SD. Diagnosis is difficult because other voice disorders have hyperfunctional voice, termed muscle tension dysphonia (MTD).[8] Patients with hyperfunctional voice alone do not have phonatory breaks.[1] SD responds well to local injection of botulinum toxin[9] but does not improve with voice therapy alone.[10] Hyperfunctional voice often improves with voice therapy, which is not beneficial in SD.[11] Vocal tremor with constant modulation of voice amplitude and frequency is most noticeable during prolonged vowels.[12] Tremor and SD often co-occur,[13] whereas hyperfunctional voice is rarely combined with tremor. The following recommendations for the diagnosis of SD comprise a major outcome of the meeting for research on SD.

Recommendations for Diagnosis

Based on a consensus among the participants, a three-tiered approach was recommended: screening questions to suggest *possible* SD; a speech examination to identify *probable* SD: and nasolaryngoscopy for a *definite* diagnosis. The value of the possible, probable, and definite diagnostic levels is to progressively narrow down the number of cases to be examined. An SD Study Group, to include neurologists, otolaryngologists, and speech pathologists with experts in design and statistical analysis,

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Table 1
Screening questions for spasmodic dysphonia

Question	Required for spasmodic dysphonia	Not expected for spasmodic dysphonia
1. Does it take a lot of work for you to talk?	Yes	No
2. Is it sometimes easier and sometimes more difficult to talk?	Yes	Sometimes entirely normal without treatment
3. How long has it been difficult for you to talk?	3 months or more, a chronic problem	Less than 3 months
4. Can you do any of the following normally?	Some of the following should be normal	Affected
Shout	Normal	Can't shout
Cry	Normal	Not normal
Laugh	Normal	Not normal
Whisper	Normal	Affected same as speech
Sing	Normal	More affected than speech
Yawn	Normal	Not normal

will need to design and conduct a validation study of these procedures.

Screening questionnaire (possible SD). Four screening questions could be made widely available for completion by prospective patients (Table 1). An affirmative answer to the first two questions and a duration greater than 3 months is required for possible SD; a positive answer to the fourth question is useful but not required. When SD is a possibility, patients should be examined by an otolaryngologist or neurologist specializing in SD.

Clinical speech examination (probable SD). A specialist will have the patient perform several speech tasks (Table 2). If patients have a strained effortful voice with voice breaks while speaking but not while shouting or whispering, SD is possible.

Sentences can elicit adductor voice symptoms and others can elicit abductor voice symptoms (Appendix A, http://journal.entnet.org). Patients should repeat sentences in their normal speaking voice and in a whisper. One or more voice breaks per three sentences during speaking and fewer during whispering are required. The clinician may use as many

Table 2
Speech examination findings expected for probable spasmodic dysphonia

Task	Required for spasmodic dysphonia	Hyperfunctional voice
Repeating adductor sentences (glottal stops and vowels)	Adductor type: breaks on vowels, 1 or more breaks per 3 sentences	Equal voice symptoms on vowels and voiceless consonants
Repeating abductor sentences (/p/, /t/, /k/, /s/, /h/, /f/)	Abductor type: prolonged voiceless consonants, 1 or more breaks per 3 sentences	Equal voice symptoms on vowels and voiceless consonants
Greater difficulty with 1 set of sentences	One set is more difficult than another	Both sets are equally affected, does not find 1 type of sentence more difficult
Shout	Normal	Affected same as speech
Strained choked voice	Less strain at a higher pitch	Consistent for all types of speech sounds and pitches
Prolonged vowel	May have tremor on prolonged vowels, prolonged vowels are less affected than speech	Prolonged vowels are similarly affected to speech, no tremor
Counting from 1 to 10	Breaks on vowels or prolonged voiceless consonants	No voice breaks

Table 3
Nasolaryngoscopy examination findings expected for definite spasmodic dysphonia

Task or finding	Required for spasmodic dysphonia	Expected for hyperfunctional voice
Structure	Normal	May have erythema or nodules
Vocal fold asymmetry	Normal	Normal
Whistling	Normal adductor and abductor movement	Normal adductor and abductor movement
Prolonged vowels	May have tremor or spasms in vocal folds	Consistent hyperfunctional posture
Adductor sentences	Adductor type: intermittent hyperadduction on vowels	Consistent hyperfunctional posture
Abductor sentences	Abductor type: Intermittent abduction on voiceless consonants (/p/, /t/, /k/, /s/, /h/, /f/)	Consistent hyperfunctional posture

sentences as required to confirm that particular symptoms are present. The numbers of breaks in 10 sentences will measure severity. Shouting "No" or "Not now" in a loud voice, should be symptom free.

To differentiate between adductor SD, abductor SD, and hyperfunctional voice, the patient repeats sentences from the adductor and abductor lists, indicating which type is more effortful. Adductor SD patients report more effort with adductor sentences, abductor SD patients with abductor sentences, and hyperfunctional voice patients report equal difficulty with both.

Ratings of a choked strained voice should be made on a visual analogue scale with anchors of "normal" on the left and "constantly severely strained" on the right to identify MTD without breaks. Prolonged vowels for 5 seconds, such as /i/ "tea," or /α/ "father" at a normal pitch can identify voice tremor, which usually reduces at high pitches.

Laryngeal examination (definite SD). Fiberoptic nasolaryngoscopy excludes other bases for the voice symptoms (Table 3) and is diagnostic. No anesthesia should be used; a video record is useful but not essential. No anatomic defects to account for abnormal voice and speech should be present; normal vocal fold movement is present during respiration, cough, throat clear, and whistling. Vocal fold tremor and spasms may be observed on prolonged vowels and during sentences.

The purpose of this procedure is to identify patients who have a diagnosis of SD for research. Therefore, patients with a probable SD result from the clinical examination who are not given a definite SD diagnosis should not be included for research studies on SD because they may have a different disorder or a combination of both SD along with another voice disorder.

Pilot Study of Diagnostic Validity

Thirty patients were recruited for the study who had previously been diagnosed with SD, MTD, or tremor based on a multidisciplinary examination and the patients' responses to treatment with botulinum toxin injection at the National Institutes of Health. All participants provided written informed consent to participate in an Internal Review Board–approved research protocol of the National Institute of Neurological Disorders and Stroke. They were examined with the use of the three-tiered approach; the patient screening questionnaire, speech recordings of sentences, and videotaped nasoendoscopy examinations. A speech pathologist scored the voice characteristics in sentences while blinded to subject identity. In addition, a team of two other speech pathologists and an otolaryngologist reviewed the nasoendoscopy recordings while blind to subject identity and came to a consensus on each of the measures. The ratings were entered into a stepwise linear discriminate function analysis aimed at identifying the factors that could identify the three groups based on the 25 items. The results identified two canonical factors with eigenvalues of 17.834 and 1.842 based on 13 of the 25 measures (Table 4) with canonical correlations of 0.973 and 0.803 and a Wilks's Lambda of 0.019, $F = 7.288$, $P < 0.0005$. The classification was 97% accurate; one SD patient was misclassified as having tremor (Fig 1).

As can be seen in Figure 1, the first factor (Set 1) displayed on the x axis differentiated the MTD group from the SD and tremor groups. As the group mean values on the individual measures in Table 4 demonstrate, the MTD group had high ratings for Constant Abnormal Laryngeal Posture During Voice and During Whisper in contrast with the SD and tremor groups. The second factor (Set 2) was useful for differentiating between the SD group and the tremor group on the y axis. High ratings for the SD group were found on Shouting Being Less Affected Than Speech, The Mean Number of Adductor Voice Breaks in Sentences, The Mean Number of Abductor Breaks in Sentences, and Functional Vocal Fold Asymmetry During Speech. In contrast, the tremor group had high ratings on Laughing Was Less Affected Than Speech, Whisper Was Less Affected Than Speech, Voice Tremor During Prolonged Vowels, and Vocal Tremor at Rest. A multicenter validation study is needed to examine these procedures further, although these initial results are promising.

Table 4
Results of discriminant function analysis canonical discriminant functions: Standardized by within variances with means for each measure for the three patient groups

Measure	Set 1	Set 2	Mean muscular tension dysphonia	Mean spasmodic dysphonia	Mean tremor
A lot of work to talk	3.035	0.283	71.9	70.1	59.0
Laughing less affected than speech	4.289	0.366	25.4	20.3	38.5
Crying less affected than speech	−2.320	0.153	32.7	28.4	34.2
Shouting less affected than speech	−2.384	0.740	36.9	62.5	44.8
Whisper less affected than speech	−1.892	−0.846	17.3	22.1	42.8
Mean number of abductor breaks in 20 sentences	−3.611	1.037	1.2	2.0	1.7
Mean number of adductor breaks in 20 sentences	3.851	−1.048	1.3	2.5	1.7
Voice tremor during prolonged vowel	−2.642	−0.384	21.3	29.9	52.0
Voice abnormality during shouting	1.227	−0.251	19.1	22.4	16.8
Functional vocal fold asymmetry	4.098	0.241	2.5	3.9	0.0
Vocal fold tremor at rest	−1.481	−0.108	3.0	5.4	22.8
Constant abnormal laryngeal posture during voice	1.354	−0.896	52.1	11.7	17.3
Constant abnormal laryngeal posture during whisper	−0.842	1.379	47.2	18.2	4.2
Group means:					
Muscular tension dysphonia	6.077	−0.231			
Spasmodic dysphonia	−2.249	1.065			
Tremor	−3.493	−2.318			

EPIDEMIOLOGY AND RISK FACTORS FOR SD

Limited data are available on prevalence, incidence, age of onset, gender, race, ethnic and regional variation, and risk factors.

Clinical and Epidemiologic Studies

SD is the third most prevalent form of focal dystonia (estimated at 1 per 100,000) after cervical dystonia and blepharospasm.[14] Underestimates are likely when derived from persons seeking medical attention. SD seems more frequent in persons of European descent[15]; no reports from Japan include persons with SD.[16] Reports of the female to male ratios vary from 1:1[17] to 7:1 in the United States.[3]

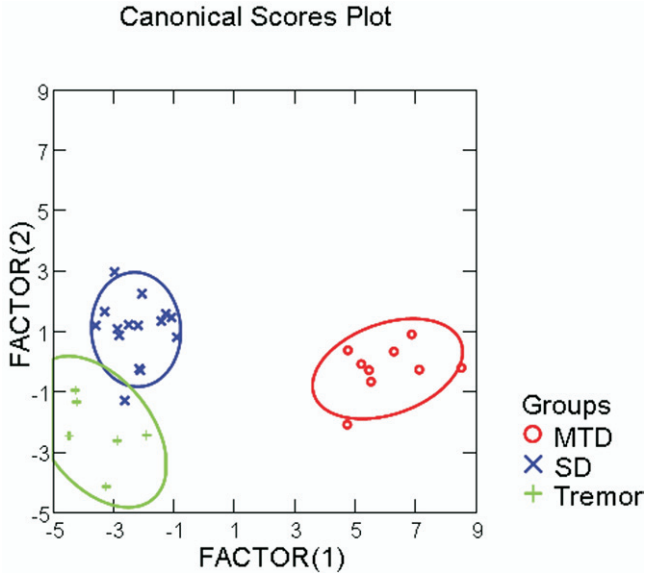

Figure 1 Discriminate function analysis results for three patient groups: muscular tension dysphonia (MDT); spasmodic dysphonia (SD), and tremor.

About 10 percent have a family history of dystonia[18] with onset in the forties.[3,14,18] Ninety percent have adductor SD; 26 percent also have essential tremor.[3] At least 30 percent report an upper respiratory tract infection or major life stress (21%) before onset,[3] although recall bias is likely. Because SD may not have a strong genetic component, investigation of potential environmental determinants may be fruitful. Although epidemiologic studies can only identify associations, they provide clues for animal models. Epidemiologic studies on SD will be challenging given the diagnostic difficulties, which also limit the accuracy of patient registries. Clinic-based populations are not generalizable whereas mandatory health care registries are representative but costly.

Rigorous epidemiologic studies are essential for identifying risk factors.[19] Patient recall bias is frequent[20] and interviewers seek information more intensely from patients than controls. Only prospective examination is verifiable. Incorporation bias depends on population characteristics; patients with SD seen in movement disorders clinics[21] may differ from those in voice centers.[3] Populations with free access to health care and interview studies can minimize this type of bias. Because SD is rare, studies within health care systems are more efficient than door-to-door surveys.

Genetic Studies of Dystonia

Fifteen "DYT" gene loci with variable penetrance and expressivity have been designated, six characterized by dys-

tonia, although none are specifically linked to SD.[22] No genetic studies have been reported in large families with just SD; most families have only a few affected members. Of the mapped primary dystonia genes, DYT-1 is associated with early onset dystonia below 13 years, affects the limbs and frequently generalizes although only 10 percent to 20 percent have voice symptoms similar to sporadic SD. DYT-6 and DYT-13 families have cervical, cranial, and arm involvement while late onset focal dystonia occurs with DYT-7. All three genes are autosomal dominant with reduced penetrance. Laryngeal involvement occurs in large DYT6 families although the voice symptoms have not been characterized.[23] DYT-4, a whispering dystonia, likely differs from sporadic SD.[24]

Previously, identifying genes depended on linkage analyses in large families. The use of single nucleotide polymorphisms (SNPs) allows for identifying genes from cohorts of unrelated patients.[25] Whole genome mapping can search for genetic association in a disease cohort compared with a control cohort. This method involves replication, requires a large number of patients with the same phenotype, and can be costly. Finding a gene makes it possible to develop animal and cellular models, study the biochemical cascade of events, hypothesize pathogenesis, and intervene in relevant pathways for prevention. Preclinical manifestations can be studied in persons predisposed to the disease to determine the interaction between environmental factors and genetic predisposition.

Recommendations for Population Research

Neuropathology studies. The SD patient and research community should collaborate with existing brain banks that store brains, archive data, and distribute tissue (Appendix B, http://journal.entnet.org). Annual examinations can determine the health histories of living donors and identify symptoms of other neurologic disorders, most notably Parkinson's disease, tremor, and dementia. Brains can be analyzed for neuropathologic markers (eg, torsin A) or neurotransmitter imbalances. Collecting postmortem larynges from SD patients may be fruitful. The SD Study Group should identify SD brain and tissue-banking sites for distribution to the research and patient communities.

Genetic research. Pursuing a genetic risk factor for SD is a million dollar experiment and considered premature without standardized diagnostic criteria. Although a common cause may exist between all forms of focal dystonia, this should be determined. For whole genome association studies, 500 cases and 500 controls are needed to identify a candidate gene, and then the same number are needed again to confirm identification through replication. Case collection on this scale for a rare disorder such as SD requires collaboration among centers and a dedicated research team. Standardized clinical criteria with family histories and storage of blood samples in a central public repository are needed.

Epidemiological study. Ongoing epidemiologic studies on the prevalence of different focal dystonias should include SD using procedures for possible, probable, and definite diagnosis. The SD Study Group could enhance continuing collaboration between the disciplines (neurology, otolaryngology, speech pathology) in planning epidemiologic studies.

Patient registries. A questionnaire on the National Spasmodic Dysphonia Association website, mailed to the membership or placed in voice clinics could establish a voluntary patient registry for research participation. The lack of accurate diagnosis of SD would make the data of little use for population research purposes. The goal is to identify patients willing to participate in clinical trials while protecting patient privacy.

PATHOPHYSIOLOGY OF FOCAL DYSTONIA

SD is likely similar to other focal dystonias with a related pathophysiology in the CNS controlling the laryngeal muscles during speech.

The Mammalian Vocalization System

Mammalian vocalization consists of a genetically preprogrammed system for the expression of emotional states, such as alarm, aggression, submission, comfort, or need for social contact.[26] This system is used for nonverbal emotional vocal utterances in human beings, such as laughter or crying. In contrast to this innate vocal system, the capacity to produce learned vocal utterances for speech is limited to human beings.

The entire forebrain, cerebellum, and rostral midbrain, shown as gray areas are dispensable for innate vocal patterns in the squirrel monkey (Fig 2A).[27,28] Structures indispensable for innate vocalization are: the motor neurons located in the lower brainstem (Ab, the nucleus ambiguus) and ventral horn of the spinal cord; the reticular formation (FR) of the lower brain stem[27]; the solitary tract nucleus (NTS), a somatosensory relay nucleus of proprioceptive input from the larynx and oral cavity, and stretch receptors in the lungs; and the periaqueductal gray (PAG) of the midbrain,[29] which triggers vocalization responses to external and internal (motivational) stimuli.[30]

Additional structures are involved in speech and not in innate vocal patterns (Fig 2B). With bilateral damage to the "face" area of the primary motor cortex (M1), patients cannot speak or sing. Direct outputs from the face motor cortex involve the pyramidal tract (Py) to the brain stem (shown in *brown*) while indirect pathways are via the putamen (Put) to the substantia nigra (SN) and reticular formation (FR). Two extensions of the indirect pathway shown in *pink* are through the putamen and may be important for learned vocalizations: back to motor cortex (via globus pallidus (GP) and ventrolateral thalamus, VL); and between the globus pallidus and subthalamic nuclei (St). The cere-

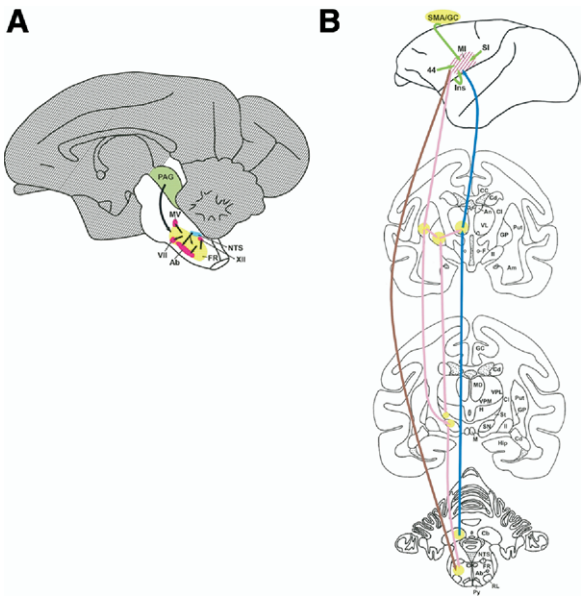

Figure 2 **(A)** The mammalian vocalization system includes areas not essential for innate vocalizations (*gray*). **(B)** Connections to the primary laryngeal motor control region in nonhuman primates include: the indirect pathway (*pink*), the cerebello-thalamo-cortical pathway (*blue*), and the corticobulbar pathway from M1 to the reticular formation in the brain stem (*brown*).

bellum (Cb) is also a pathway to the motor cortex (M1) via the ventrolateral thalamus (VL) shown in *blue*. Abnormalities within this framework should be studied in SD.

Animal models can provide valuable understanding of the complex sensory and motor relationships in SD. Although an animal model for SD is not currently available, several have been developed for other forms of dystonia.[31] In primates, the toxins MPTP and 3NPA can provoke generalized dystonia, often in combination with Parkinsonism.[32] Models for focal dystonias in primates include hand over-use,[33] and cervical dystonia due to midbrain lesions.[34] Rodent models are used for generalized, focal, and even paroxysmal dystonia.[31] A rat model for blepharospasm, a focal dystonia of the periocular muscles[35] may be relevant to SD. Partial striatal dopamine depletion combined with partial injury to the motor nerves to the orbicularis oculi muscles is involved. Similar strategies might generate animal models for SD.

Only speech is affected in SD, whereas innate vocalizations (laughing and crying) are spared. Because vocalizations in primates and rodents are innate rather than learned, it remains unclear if modeling a hypothesized defect in sensorimotor networks will produce a vocal defect that resembles SD.

Songbirds have both innate and learned vocalizations and may be considered for modeling SD.[36] The neuroanatomic basis for song and the molecular and cellular mechanisms underlying neural plasticity during song learning are well studied. The potential of the songbird model for SD depends on whether the neuroanatomic basis for vocalizations in birds is sufficiently homologous to human beings.

Dopaminergic Dysfunction in Focal Dystonia

Evidence for a specific neural pathway involved in dystonia has been emerging.[37] [18F] spiperone binds preferentially to D2-like dopamine receptors and had a 28 percent reduction in putamen uptake in persons with cranial or hand dystonia.[38] An animal model of transient dystonia found a reduction in D2-like dopamine receptors early after neurotoxin-induced nigrostriatal injury.[39] Dopaminergic abnormalities in the indirect pathway of the cortical-basal ganglia circuits may impair inhibition of unwanted muscle activity during intended movement in dystonia. The possibility of primary defects in this circuit producing behavioral abnormalities[37] needs to be examined in SD.

Pathophysiology of Focal Dystonias

The confluence of an inherent genetic factor and environmental modifiers may lead to SD. Three physiologic mechanisms may be involved in dystonia: decreased inhibition, increased plasticity, and abnormal sensory input. Loss of inhibition is well documented in dystonia and SD.[40] A variety of spinal and brain stem reflexes are abnormal, and the motor cortex also shows a loss of inhibition.[41,42] In patients with focal dystonias, measures of intracortical inhibition have revealed deficits.[43] Current treatments for dystonia generally increase inhibition or reduce excitability.[44] Center-surround inhibition, expected to play a role in fine motor movements, may be reduced in dystonia.[43] Motor training of individual finger movements for writer's cramp, developed out of ideas on center-surround inhibition, substantially improved patients' writing abilities.[45] Increased plasticity, as measured by excitability after paired associative stimulation, was demonstrated in writer's cramp.[46] In dystonia, increased plasticity could lead to an abnormal response to repetitive activity or increased use.[47]

Sensory abnormalities in hand dystonia include decreases in temporal and spatial discrimination.[48,49] Cerebral responses to vibrotactile hand stimulation were reduced in sensorimotor and supplementary motor areas in hand dystonia.[50] Sensory-evoked potentials from the fingers of both the symptomatic and asymptomatic hands had a deranged somatotopic map.[49] Because the sensory system is a prime driver of the motor system, disordered sensory input could lead to disordered motor output.

Laryngeal Pathophysiology in SD

SD symptoms are intermittent spasms in the laryngeal muscles.[5] Current therapies are targeted toward reduction of the impact of involuntary muscle spasms on voice. The emerging picture of SD is disordered inhibition in response to sensory feedback.[51] Muscles in the upper airway used for speech are also required for life-sustaining functions such as swallowing and breathing. Intervention in SD is complicated because of the need to maintain these life-sustaining functions.

The larynx is sensitive to many types of stimuli.[52] Sensory fibers in the internal branch of the superior laryngeal

nerve (SLN) terminate in the brain stem in the nucleus tractus solitarius[53] and include sensors for pressure on the laryngeal mucosa[54]; negative supraglottal pressure[55]; flow receptors[56]; a lack of chloride ions[57]; and muscle activity.[58] Proprioceptive information from the cricoarytenoid joint is conveyed via the SLN, and subglottal afferents are conveyed via the recurrent laryngeal nerve (RLN). Sensory input to the nucleus solitarius is relayed via interneurons to laryngeal motor neurons in the nucleus ambiguus.[59]

If SD is an abnormality of sensory gating, it may have a similar pathophysiology to other disorders of disinhibition such as chronic cough, tic doloureux, hiccup, and cricopharyngeal achalasia. The glottic-stop reflex in cough is similar to the laryngeal adductor reflex[60] elicited by SLN stimulation. Paroxysmal laryngospasm has been reported after injury to the SLN.[61]

Reduced inhibition of the laryngeal adductor response to paired electrical SLN stimulation occurred in SD.[51] Determining the roles of different neurotransmitters in modulating this reflex might identify new avenues for treatment.[62] Clinical methods for assessment of the laryngeal adductor response to air puff stimuli are available[63] and could identify abnormalities in sensorimotor gating in SD. Care must be taken to avoid the confounding effects of higher levels of motor neuron activity likely present in focal dystonia and SD that could augment motor responses in these patients independent from inhibitory gating abnormalities.

Recommendations for Research on the Pathophysiology of SD

Animal models. Although animal models may not precisely mimic the human condition, they can test predictions with respect to pathophysiology and treatment. No other mammals have learned vocalizations like human beings and cannot reproduce task specificity to speech, a hallmark of SD. However, if the pathophysiologic processes hypothesized to underlie SD can be reproduced, the resulting abnormalities could be endpoints for testing hypotheses about SD. Specifically, a model similar to the blepharospasm model with partial lesions of striatal dopamine and damage to laryngeal motor (or sensory) nerves could be considered.

The potential relevance of songbirds should be explored. The effects of specific types of pharmacologic and surgical lesions in songbirds should be reviewed from an SD perspective. Any findings suggestive of SD, such as muscle spasms that occur during song, should be examined further. Given the higher occurrence of SD and other focal dystonias in women, research into possible hormonal contributions and their direct/indirect effects on laryngeal sensorimotor control should be pursued.

Integrative systems research on the sensorimotor basis for vocalization. The mammalian vocalization system can be used to study the effects of environmental and neurochemical manipulations on laryngeal sensorimotor function. Fully understanding the anatomy and circuitry for the larynx in the brain is fundamental for further research. The anatomy of laryngeal reflexes, the sensory relay connections to the nucleus ambiguus and descending cortico-bulbar connections all require further investigation. Although rodents vs primates were debated, higher brain centers that modulate laryngeal motor neurons need to be identified. GABA receptor agonists or glutamate antagonists to block excitatory neurotransmission could determine defects that may be associated with SD. Brain regions identified in animal studies need to be examined in postmortem brains from SD patients.

Functional brain imaging. Two brain-imaging studies examined SD comparing brain activation before and after botulinum toxin injection.[64,65] Patients with SD had reduced brain activation in sensorimotor regions during symptoms. Studies should be performed to confirm that the pathophysiology in SD is analogous to other dystonias. Writer's cramp, a task specific focal dystonia, seems to have the closest potential similarity to SD.

As functional neuroimaging methods are applied to this disorder, care must be taken not to confound such studies because of increased speech effort in persons with voice disorders such as SD. Applying sensory stimuli at rest to examine central responses will avoid the confounding effects of the movement disorder. Investigations of selective neurotransmitter receptor systems may be useful, as in other focal dystonias.[66]

Other experiments. An autoimmune event may be associated with the development of SD. A study to examine whether a link exists would be worthwhile. Some patients with SD have had over 70 injections of botulinum toxin into their larynx. Animal studies that reproduce multiple injections could assess the cumulative long-term effects of botulinum toxin on laryngeal muscle physiology.

TREATMENT OF SPASMODIC DYSPHONIA

Botulinum Toxin Injections

The most common and effective treatment for SD is injection of botulinum toxin into the laryngeal muscles, for which SD is an off-label indication. By inhibiting acetylcholine release at the neuromuscular junction, the toxins reduce muscle activity. About 90 percent of patients with adductor SD improve for 3 to 12 months after receiving an injection of botulinum toxin type A,[18] although voice production is not normal.[67] The only randomized, controlled, and blinded trial in SD was small, and demonstrated greater symptom reduction with botulinum toxin type A injection than after saline.[9] Although the thyroarytenoid muscle is normally injected for adduc-

tor SD,[18] some benefit may occur with injecting other adductor muscles such as the lateral cricoarytenoid (LCA).[68] Patients with abductor SD also respond to botulinum toxin injection in the posterior cricoarytenoid (PCA), although treatment is less effective.[69]

Repeated botulinum toxin injections are needed every 3 to 6 months[18] and dosages range widely across patients. Periods of breathiness and occasional aspiration of liquids follow thyroarytenoid injection for adductor SD while stridor and airway obstruction can follow PCA injections for abductor SD. Long-term results and safety still need to be addressed. Botulinum toxin for patients with voice tremor has less predictable results.[70] The outcome may relate to the movement disorder characteristics.

Surgical Approaches

The initial surgical approach to symptom control in SD was unilateral RLN section, which was not long lasting[71] due to nerve reinnervation.[72] Current surgical approaches for SD include laryngoplasty,[73,74] myectomy,[75] myoplasty,[76] and denervation/reinnervation.[77] Laryngoplasty alters the cartilaginous skeleton of the larynx through anterior commissure push back, thyroid cartilage widening, or vocal fold medialization.[78] Patients with SD usually do not experience lasting benefit after anterior push back.[74] Myectomies to excise the thyroarytenoid, LCA, or PCA[76] may reduce breaks, although vocal harshness and lasting benefit have been unpredictable. The denervation/reinnervation procedure denervates the RLN branch to the thyroarytenoid muscle bilaterally and then sutures the nerve stump to the ansa cervicalis nerve.[77] The best candidates are female patients with adductor SD without tremor. Those with mixed adductor and abductor symptoms are not candidates, and men have less benefit than women. Later, LCA myotomy was added to improve outcome. Although 83 percent of respondents reported improvement for up to 49 to 52 months,[79] some continued to receive botulinum toxin injections and others reported mild swallowing difficulties. Controlled trials over 5-years are needed to determine the outcome of this surgery with independent blinded quantitative voice assessments, such as measures of mean number of voice breaks in sentences, the measure specific to SD in the diagnostic procedure (Table 4). Surgical procedures must be considered experimental for SD until controlled studies of the long-term voice outcomes are published.

Recommendations for Treatment Research in SD

Controlled treatment trials are needed to avoid placebo effects, which can be quite large in this patient group, while controlling for differences in previous treatments, concomitant signs, and symptoms. At least a 3-year follow-up is essential because SD is a chronic condition. Appropriate outcome measures include subjective rating scales,[80] objective acoustic measures,[1] and quality of life questionnaires.[81] Videotapes made before and after treatment can be randomized and rated by an uninvolved investigator. Because few trials of new treatment options have been conducted in this disorder, small, open-label Phase I trials should first explore new approaches before committing to large, randomized, placebo-controlled trials.

Pharmacological treatments for SD. Based on clinical observation, only tremor in SD has a modest response to beta-blockers and about 20 percent to 30 percent of patients may be receiving botulinum toxin injections combined with oral medications. Such combinations may be effective whereas a drug alone is not. Some patients report symptom improvement with alcohol, which suggests that processes affected by alcohol might respond to pharmacologic intervention. Systematic studies of combinations of botulinum toxin injections with oral medications are needed in SD. Immunosuppressive agents also may be worth evaluating particularly in patients with incipient SD. Small exploratory Phase I trials should be encouraged.

Surgical procedures. Both retrospective information on patients who have already received surgery and prospective studies are needed to determine if procedures are beneficial. Surgeries should be documented and standardized preoperative histories, assessments, and postoperative follow-up by blinded independent raters are needed to gather data on surgical outcomes for physicians and patients.

Trials to evaluate the efficacy of surgical procedures are needed. Surgical trials are difficult compared with medication trials because surgery is irreversible. To yield generalizable results, surgeons at several centers trained to perform similar procedures need to commit to following up patients at regular intervals. Animal studies could determine the short- and long-term physiologic effects of permanent alterations in laryngeal structure.

Deep brain stimulation. Deep brain stimulation (DBS) has proven effective in the internal globus pallidus in dystonia.[82] Exploratory Phase I trials should investigate the use of deep brain stimulation in patients with severe SD who are not adequately treated by botulinum toxin injection. Caution should be used, however, given the reduced benefit of DBS for voice and speech deficits in some cases[83] and the need for objective data on the effects of DBS in the internal globus pallidus for voice and speech in dystonia. Mapping speech/voice motor control within the basal ganglia may further both the understanding of SD and the potential effects of DBS.

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AUTHOR CONTRIBUTIONS

Christy L. Ludlow organized and ran the meeting and participated in and compiled data on the validation study. The following reviewed and presented data on topics as indicated: **Charles H. Adler** (botulinum toxin); **Gerald S. Berke** (surgical procedures); **Steven A. Bielamowicz** (diagnosis); **Andrew Blitzer** (epidemiology); **Susan B. Bressman** (genetics); **Mark Hallett** (pathophysiology); **H.A. Jinnah** (role of animal models); **Uwe Juergens** (neurologic control of the larynz); **Joel S. Perlmutter** (pathophysiology and neuroimaging results); **Christine Sapienza** (measurement of voice and speech disorders); **Andrew Singleton** (use of population-based genetics for movement disorders); **Caroline M. Tanner** (epidemiology of movement disorder); **Gayle E. Woodson** (upper airway hyper-reactivity disorders). All participated in the writing and revisions of the manuscript. **Sandra Martin** participated in and compiled the data on the validation study.

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APPENDIX A

(Adapted from Fairbanks, G.A. Drill and Articulation Workbook, 2nd ed, New York: Harper and Row; 1960. p. 36, 64, and 94.)

Adductor sentences (location of frequent voice breaks are underlined)

1. Tom wants to be in the army.
2. We eat eels every day.
3. He was angry about it all year
4. I hurt my arm on the iron bar.
5. Are the olives large?
6. John argued ardently about honesty.
7. We mow our lawn all year.
8. Jane got an apple for Ollie.
9. A dog dug a new bone
10. Everyone wants to be in the army.

Abductor sentences

1. He is hiding behind the house.
2. Patty helped Kathy carve the turkey.
3. Harry is happy because he has a new horse.
4. During babyhood he had only half a head of hair
5. Who says a mahogany highboy isn't heavy?
6. Boys were singing songs outside of our house.
7. The puppy bit the tape
8. See, there's a horse across the street.
9. Sally fell asleep in the soft chair.
10. The policy was suggested in an essay on peace

APPENDIX B

Location of brain banks for depositing dystonia brains

Brain and Tissue Bank for Developmental Disorders
University of Maryland, Baltimore
Director, H. Ronald Ziekle, Ph.D.
Pediatric Research Bressler Research Building
655 W. Baltimore Street
Baltimore, MD 21201-1559
Phone (410) 706-1755; (800) 847-1539; (410) 706-0020 FAX
email: btbumab@umaryland.edu

University of Miami
Director, Lillian Rodriguez, M.D.
Department of Pathology
1550 NW 10th Avenue, Room 410 Pap Building
Miami FL 33136
Phone 800-592-7246
Fax: 301-243-6970
email: btb@med.miami.edu

University of Miami
Brain Endowment Bank
Department of Neurology
1501 NW 9th Avenue
Room #4013, NPF Building
Miami, FL 33136
800-UM BRAIN
305-243-4678 FAX

The National Neurological Research Specimen Bank
NNRSB (127A)
Director, Wallace W. Tourtellotte, M.D., Ph.D.
W. Los Angeles VAMCV
11301 Wilshire Blvd.
Los Angeles, CA 90073
310-268-3536
310-268-4768 FAX

Harvard Brain Tissue Resource Center
McLean Hospital
115 Mill Street
Belmont, MA 02178-9106
617-855-3199
Sun Health Research Institute
10515 W. Santa Fe Drive
Sun City, AZ 85351
Thomas Beach, MD, Director
(623) 875-6503

For donations from individuals in Arizona only
Tourette Syndrome Association, Inc.
42-40 Bell Boulevard
Bayside, NY 11361-2999
718-279-9596 FAX