

## LARYNGEAL DYSTONIA: A SERIES WITH BOTULINUM TOXIN THERAPY

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Laryngeal dystonia is a syndrome characterized by action-induced, involuntary spasms of the laryngeal muscles. Most patients have involvement of the adductor laryngeal muscles producing uncontrolled spasms during phonation, and a "strains-strangle" speech pattern commonly termed "spastic dysphonia." Other patients have involvement of the abductor muscles producing "whispering dysphonia." Rare patients have paradoxical vocal cord motion during respiration with adductor spasms on inspiration. Over the past 5 years we have used botulinum toxin (BOTOX) to treat more than 200 patients with laryngeal dystonia. This group includes patients with adductor involvement (phonatory dystonia, recurrent laryngeal nerve section failure, respiratory dystonia) and those with abductor involvement (whispering dystonia). Patients received benefit within 24 to 72 hours, with sustained improvement for 2 to 9 months with an average of 4 months. Patients improved to an average of 90% of normal function. Clinically significant adverse effects included extended breathy dysphonia and mild choking on fluids. BOTOX has become our treatment of choice for dystonic conditions of the larynx.

KEY WORDS — botulinum toxin, laryngeal dystonia, spastic dysphonia.

Laryngeal dystonia is a neurologic disorder of central motor processing characterized by action-induced spasms of the vocal cords. The spasms are poorly controlled by the patient, and the symptoms are exacerbated by stress. These spasms produce a clinical voice syndrome often termed spasmodic dysphonia (SD) or spastic dysphonia, which is characterized by a choked, constrained voice pattern with breaks in vocalization.<sup>1,2</sup> In addition, the voice pattern may also be tremulous with inhalation phonation, harshness, and audible grunts. In addition to the adductor form of laryngeal dystonia, approximately 10% of patients will present with the abductor form. In this form of phonation, the cords will have a spasmodic motion of the posterior cricoarytenoid (PCA) muscles, producing a breathy voice. The history of observations of SD has previously been reported.<sup>3-6</sup> Our group and others<sup>7-12</sup> have linked SD to dystonia, a central nervous system disorder. Dystonia may manifest itself in other focal and segmental presentations, including blepharospasm (forced, involuntary eye closure), oromandibular dystonia (face, jaw, or tongue involvement), torticollis (twisting of the neck), and writer's cramp (action-induced dystonic contractions of the hand muscles).<sup>13-16</sup> Laryngeal dystonia may present focally or in association with other dystonic movements.

Vocal analysis of the adductor SD patients reveals harshness, usually a tremor, inappropriate pitch or pitch breaks, groaning, breathiness, and glottal fry.<sup>17,18</sup> The voice arrests come from hyperadduction of the true and false vocal cords. Some of the patients with tremor have synchronous involvement of the pharynx, face, masticatory muscles,

etc.<sup>19,20</sup> The abductor SD patients were described by Aronson et al<sup>10</sup> in 1968 as a group with a whispering dysphonia or aphonia. This may be the earliest report of the true abductor SD. Many of these patients may be misdiagnosed as having a vocal cord paralysis.

Our electromyography (EMG) data also showed 17% of patients with enlarged potentials, as well as 11% with polyphasic potentials.<sup>9,21</sup> This finding is indicative of some reorganizational activity, perhaps denervation and reinnervation.

In addition we have identified two other variations of presentation. The term compensatory abductor dysphonia refers to those patients with such severe adductor spasms that they voluntarily produce a breathy voice by not contracting their vocal cords in order to prevent the spasms and the broken speech pattern. Patients with compensatory abductor dysphonia are those severe abductors who try to prevent the breathiness by tightly contracting their vocal cords.<sup>1</sup>

Psychotherapy, speech therapy, and biofeedback are generally unsuccessful methods of treating SD. Recurrent laryngeal nerve section has a long-term success rate of about 36%,<sup>21</sup> with continued vocal cord paralysis. We have postulated<sup>20</sup> that this failure rate is related to hyperfunction of the opposing hyperfunctional dystonic muscle, which usually exaggerates the dystonic symptoms. Our series<sup>1</sup> has shown poor results of treatment of adductor dystonia with medication, although there was a 33% response rate in the abductor type. We therefore established a program of treatment of laryngeal dystonia with botulinum toxin (BOTOX) injections.

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## METHODS

## CLINICAL DATA

This study (approved by our Institutional Review Board) consists of a group of 260 primary and 60 secondary laryngeal dystonia patients, of whom 210 patients had the presumptive diagnosis of SD (adductor or abductor laryngeal dystonia) when referred. Patients were evaluated with a detailed history and physical examination including direct fiberoptic laryngoscopy with video recording, a complete neurologic examination, and laryngeal EMG; some had brain stem audiometric evoked response and magnetic resonance imaging scans. In questionable cases, the videotapes were reviewed to confirm the diagnosis. Patient data are stored in a Foxbase data base.

Initially we only invited patients who had previously failed treatment with pharmacotherapeutic agents. BOTOX has been so successful as compared to other modalities, with few clinically significant side effects, that we began to offer BOTOX as primary therapy. We also have offered BOTOX therapy to patients who have failed surgical therapy (recurrent laryngeal nerve section and anterior commissure release procedures), patients with abductor laryngeal dystonia, and patients with dystonic respiratory laryngeal dysrhythmias.

## INJECTION TECHNIQUE

**Adductor.** Each patient had injections that were individualized with doses of 1.25 U to 3.75 U. Injections were given percutaneously with EMG guidance as we have previously reported.<sup>23</sup>

**Abductor.** The first abductor patient was initially treated with BOTOX via a direct laryngoscopy and injection into the PCA muscle. This was not possible to do with EMG control, and besides the patient discomfort, very little improvement was noted. We next began EMG-guided percutaneous injection. The larynx is manually rotated away from the side of intended injection and the hollow EMG needle with syringe is placed posterior to the posterior edge of the thyroid lamina. The needle is advanced to the cricoid cartilage and then moved out under EMG guidance to the optimum position in the PCA muscle.

## RATING

Patient's voices were scored in a nonblinded fashion by means of a subjective rating scale estimating the percent of normal speech, with 0% representing no speech or full disability and 100% representing normal speech. Patients scored themselves before each injection, and a videotaping and voice recording were performed. In addition, the physicians made a similar rating and the most conservative rating was recorded and used as the percent improvement in all cases. Patients kept diaries of vocal function, noting the time of onset of vocal weakness,

## DYSTONIA AT COLUMBIA-PRESBYTERIAN MEDICAL CENTER

	Laryngeal Dystonia (N = 320)		All Dystonia (N = 1,926)	
	Primary	Secondary	Primary	Secondary
N	260 (81%)	60 (19%)	1,350 (70%)	570 (30%)
F	152 (58%)	39 (65%)	813 (60%)	328 (57%)
M	108 (42%)	21 (35%)	543 (40%)	244 (43%)
F:M	1.4	1.3	1.5	1.3
Jewish	60 (23%)	13 (22%)	325 (24%)	112 (20%)
Non-Jewish	200 (77%)	47 (78%)	1,031 (76%)	458 (80%)
J:NJ	0.30	0.28	0.32	0.25
Positive family history	44 (17%)	5 (8%)	248 (18%)	48 (8%)
Focal	168 (65%)	15 (25%)	770 (57%)	186 (33%)
Segmental				
cranial	43 (17%)	6 (10%)	191 (14%)	55 (10%)
All segmental hemidystonia	70 (27%)	18 (30%)	431 (32%)	203 (36%)
Generalized	20 (8%)	23 (38%)	138 (10%)	138 (24%)

peak weakness, duration of breathy hypophonia, duration and severity of choking with liquids, and any other notable events. No correlation was made between the observed improvement and vocal cord paralysis, since with our technique, paralysis is very rare. Postinjection EMG studies were performed on the 2-week follow-up visit in a limited number of patients early in our study. The studies were not carried out in all patients since they did not appear to have direct clinical relevance.

## RESULTS

## CLINICAL CHARACTERISTICS

**Laryngeal Dystonia Data.** Of the 1,926 cases of dystonia registered at the Dystonia Clinical Research Center, 320 cases (16.6%) had vocal involvement. Of these 320 patients, 260 (81%) had primary dystonia and 60 (19%) had secondary dystonia (see Table). Of the primary group, 152 (58%) were female and 108 (42%) were male. This is very similar to the 60% female/40% male ratio found in the entire group of primary dystonias. The Jewish/non-Jewish ratio for primary laryngeal dystonia was 23%/77%, which is consistent with the 24%/76% found in the entire primary dystonia group.

In the group of 320 patients with laryngeal dystonia, 270 (84.4%) had adductor vocal involvement ("spastic dysphonia"); 47 (14.6%) had abductor vocal involvement ("whispering dysphonia"); and 3 (1%) had adductor breathing dystonia. The average age at onset of SD patients was 38. The three patients with laryngeal adductor breathing dystonia were 27, 55, and 56 years of age at onset. Of interest was the fact that 27 patients of the primary dystonia group (10.4%) had laryngeal involvement first and then went on to have involvement of another neuromuscular system. The importance of family history is illustrated by the fact that 44 of the 260 (17%) patients who had primary laryngeal dystonia had a family history of dystonia.

## BOTULINUM TOXIN THERAPY

**Adductor Laryngeal Dystonia.** Of the 320 cases of laryngeal dystonia recorded in our data base, we have injected 210 patients since April 1984. At the inception of our study, there were no previous guidelines for laryngeal BOTOX injections and therefore our dose schedule was empiric. Recognizing that the vocalis-thyroarytenoid complex consists of small muscles, we planned small doses with the goal of minimizing adverse effects and vocal trauma. Our first approach was to inject 8.5 U into one vocal cord. This injection had little effect. We then gave an additional 7.5 U, which caused a vocal cord paresis and a period of breathy dysphonia but 90% improvement of vocal function. In keeping with our goal of minimizing the total exposure to BOTOX, we decided to explore bilateral, low-dose injections. This decision also paralleled our theory that weakening or paralyzing one vocal cord stresses the remaining vocal cord and exaggerates the dystonic symptoms. We therefore initiated a first-treatment program of injecting both vocalis muscles with 3.75 U. All patients experienced benefit. Initially there was an effect within the first 24 hours, followed by a hypophonia that was maximum at the third post-injection day. This breathy speech typically lasted 4 to 14 days and was mild, but lasted 57 days in one patient. Some patients also experienced a mild choking sensation when drinking fluids, although there were no cases of aspiration. Patients found that drinking slowly compensated adequately for this symptom until it resolved. Patients' speaking improved from 60% to 100% of normal function with a mean of 90%, and the duration of effect was from 3 to 4 months. Patients often requested reinjection before returning to their pretreatment level of functioning. When we performed 2-week follow-up laryngeal EMC, occasional evidence of denervation could be found.

Owing to the prolonged period of breathy hypophonia in some of the patients receiving 3.75 U per vocal cord, we modified our first treatment protocol by reducing the dose to 2.5 U per vocal cord. Although there was a trend for decreased duration of breathiness, choking, and duration of benefit at 2.5 U, the differences were not statistically significant. Two patients, however, failed to have any noticeable effect at the lower dose and had to be reinjected. Because of the lack of significant difference in the duration or degree of benefit of these two doses, our current protocol is to initially inject 2.5 U per cord except when the patient finds it impossible to make a return visit in 2 weeks should the injection have no effect. In these patients a dose of 3.75 U per cord is given. For repeat injections, we initially injected either 3.75 or 2.5 U per cord. We have begun to give some patients 2.5 U unilaterally or 1.25 U bilaterally on follow-up to minimize the length of hypophonia, since there often appears to be some residual weakness at the time of the follow-

up injection.

The adverse effects from laryngeal BOTOX injections included a mild breathy dysphonia for a short period of time in 45% of patients and mild choking on fluids for the first several days in 22%. Several patients hyperventilated and became dizzy trying to speak while hypophonic. Several patients coughed up blood-tinged sputum and/or had a sore throat. One patient had itching but no rash.

**Nerve Section.** Of the adductor vocal group, nine were patients who had failed a recurrent laryngeal nerve section. This group, previously reported,<sup>26</sup> included four men and five women ranging in age from 36 to 62 with a mean of 50. They all failed RLN section from 0 to 4 years postoperatively (mean, 1.8 years). Four of the patients had more than one procedure performed on the nerve or vocal cord to try to turn failure into success. Laryngeal EMC was performed on all patients; most showed signs of chronic denervation with few and very small potentials and occasional fibrillation potentials. We injected most of the patients with 2.5 U unilaterally. This was given in the functional cord in most patients with an improvement of 0% to 100% with a mean of 81% as compared to 10% to 80% with a mean of 59% when the paralyzed cord was injected.

**Anterior Commissure Release.** In addition to the nerve section failures we have treated three patients who failed an anterior commissure release procedure. In these patients the larynx appeared foreshortened, but the adductor spasms were as intense as in the nonoperated group. These patients were also given 2.5 U per vocal cord, and all experienced benefit. The spasms remitted, but because of the laxity of the vocal cord from the release, most noticed a narrowed pitch range. The duration of the breathy hypophonia also was extended in this group.

**Abductor Laryngeal Dystonia.** With our growing experience, we cautiously elected to treat abductor laryngeal dystonia with injection of BOTOX into the PCA muscle. We informed the patients that excessive weakening of the PCA muscle might cause airway distress and might necessitate a temporary tracheostomy. Doses of 1.25 to 5 U were given in one to four treatments to weaken one or both PCA muscles in 12 patients. Marked improvement was seen in 8, with a mean improvement to 57% and a return of mean maximal functional performance to 80% of normal. Follow-up treatments required smaller toxin doses. The adverse effects included brief choking on fluids without aspiration and mild stridor on exertion in 2 patients. There were no significant breathing difficulties, even in the cases in which both PCA muscles were injected.

**Adductor Laryngeal Breathing Dystonia.** In addition to the patients who had phonatory symptoms

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#### CARE OF THE PROFESSIONAL VOICE

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due to laryngeal dystonia, we identified three patients who had paradoxical motion of the vocal cords during respiration. These patients were not hypoxic, but produced moderate to severe inspiratory stridor. This symptom disappeared as soon as the patients went to sleep, and took a short while after a waking in the morning to reappear. After a thorough otolaryngologic, neurologic, and pulmonary workup, we treated two of these patients with BOTOX with decrease or cessation of the symptoms. A complete description of these patients and their test results will be published separately.

#### DISCUSSION

The data from our previous publications,<sup>1,12,19,21,22</sup> our current series, and reports of other authors support the conclusion that "spastic dysphonia" and "whispering dysphonia" are focal laryngeal forms of dystonia. Our data on age of onset, sex preponderance, Jewish/non-Jewish ratio, family history, and involvement of other body parts are consistent with those of other authors and with those of our total dystonia group.

The average age at onset in our entire group was 38 for both the adductor and abductor forms. The average age of patients who had primary dystonia of the larynx and another body part was 31, since patients with early-onset disease are more likely to have more than one site involved.

Of the 260 patients who had the larynx as their primary site of onset, 27 (10.4%) had spread to another body part. These data suggest that patients should be advised of possible spread and be followed and reexamined on a regular basis for signs of other dystonic involvement. The family history was also significant, with 44 of 260 patients (17%) with primary laryngeal dystonia having a family history of dystonia. Family studies of childhood onset idiopathic dystonia show an autosomal dominant inheritance with reduced penetrance. A gene locus marker located on the 9q chromosome has just recently been established by our group and others, and this finding opens new doorways for the understanding and possible treatment of the disorder.<sup>24</sup> Therefore, it is of paramount importance to obtain a family history and have genetic counseling provided where necessary.

Recurrent laryngeal nerve section originally seemed to be the treatment of choice for SD. However,

many late failures were found leaving a poor voice with a continued paralyzed vocal cord. We believe that the return of symptoms in these patients is due to stressing the remaining functioning vocal cord, thereby intensifying the dystonic symptoms.

Ludlow et al<sup>24</sup> and Miller et al<sup>24</sup> have injected higher doses of toxin (up to 80 U over three visits) into one vocalis muscle in patients with SD. Since the goal of this treatment method is unilateral vocal cord paralysis, we see little advantage of this technique over recurrent laryngeal nerve section. We have theorized that surgical therapy may ultimately fail because the contralateral functioning vocal cord hyperadducts. This hyperadduction stresses the remaining functional vocal cord and exaggerates the underlying dystonic state, causing additional dysfunction and a return of the dysphonia.

Our experience with 210 patients has shown that local injections of BOTOX into laryngeal muscles is a relatively safe and effective mode of therapy for laryngeal dystonia. In contrast to surgical therapy, BOTOX injections have the advantage of being given on an ambulatory basis; both vocal cords can be treated; and the toxin is given under EMG control for precise localization of the most active part of the muscle complex. Graded weakening can be achieved by using low dosages and repeating the injections to achieve the optimum weakness desired. If too much weakness is produced, the strength gradually returns with time. The procedure is very acceptable to patients with very satisfactory vocal results. It is too soon to tell whether patients will become refractory to this form of therapy. To date we have not found anyone who has become refractory with laryngeal injections or sustained a disability from laryngeal toxin injections.

#### CONCLUSION

Laryngeal dystonia is a disorder of central motor processing that can cause adductor spasms ("spastic dysphonia"), abductor spasms ("whispering dysphonia"), and adductor breathing dystonia. Laryngeal BOTOX injections are performed percutaneously, on an ambulatory basis under EMG control. Graded weakening can be achieved by using small dosages and injecting additional toxin as needed. If too much weakness is produced, the strength gradually returns with time. Our data suggest that BOTOX injection is the treatment of choice for dystonic symptoms of the larynx.

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