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Respiratory Laryngeal Dystonia: Characterization and Diagnosis of a Rare Neurogenic Disorder

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Objective/Hypothesis: Respiratory laryngeal dystonia (RLD) is poorly understood and rarely reported in the literature. Patients have atypical laryngeal movement resulting in airway obstruction. This motion is neurogenic in nature, is constant while awake, non-episodic, and non-trigger dependent. Given its rarity, it is often misdiagnosed for inducible laryngeal obstruction; however, it is refractory to medical and behavioral management. Although this condition has been addressed in the literature, this report is the largest case series characterizing presenting symptomology, multimodal treatment outcomes, and longitudinal course of these patients, and proposes a set of diagnostic criteria to aid in clinical identification of RLD patients. Our objectives were to characterize RLD clinically and offer diagnostic guidelines to clinicians.

Study Design: A prospective case series with a retrospective analysis at a tertiary referral center.

Methods: A review of clinical records and videostroboscopic analysis of 16 patients treated for respiratory laryngeal dystonia from October 2005 to October 2018 was performed.

Results: Sixteen patients with respiratory laryngeal dystonia were included. The common features of this group were persistent, non-episodic dyspnea and stridor with laryngoscopic evidence of paradoxical vocal fold motion. Our patients had no structural neurologic abnormalities. These patients typically failed respiratory retraining therapy and medical management of laryngeal irritants. In our series, 100% of patients underwent respiratory retraining therapy, 68.8% received laryngeal botulinum toxin injection, and 31.3% required tracheostomy.

Conclusions: RLD is a rare and challenging condition. The disorder can be severely disabling, and treatment options appear limited. A multidisciplinary approach may be helpful. Some patients responded to laryngeal botulinum injection and medical management, whereas others required tracheostomy for symptom control.

Key Words: Respiratory laryngeal dystonia, functional dysphonia, laryngeal, stroboscopy, laryngology, laryngeal retraining, speech and language pathology.

INTRODUCTION

Dystonia is an abnormal, involuntary, and recurring muscle contraction causing twisting and repetitive movements or abnormal postures. This is a neurologic movement disorder, and can be more pronounced in states of fatigue, stress, emotion, and motor activity.1,2 Dystonia can be focal, affecting isolated muscles group; multifocal, affecting multiple muscles groups; and generalized, affecting most muscles in the body. Laryngeal dystonia is a focal variant that affects laryngeal muscles in isolation or accompanied by other dystonias. The most common form of laryngeal dystonia is spasmodic dysphonia. This form of laryngeal dystonia primarily affects the vocal folds during voice and speech production resulting in a dystonic voice.

There are two types of spasmodic dysphonia, adductor and abductor, depending on the laryngeal muscles affected.

There are, however, other forms of laryngeal dystonia that are less common, poorly understood, and rarely reported in the literature. These can be particularly debilitating when the normal respiratory function of the larynx is affected. One rare laryngeal dystonia has been described by several names, including but not limited to adductor laryngeal breathing dystonia, spasmodic laryngeal dyspnea, and respiratory type focal laryngeal dystonia.1 Overall, this condition is adequately described as respiratory laryngeal dystonia (RLD).

Patients with RLD typically present with dyspnea, desynchronized breathing, inspiratory stridor, dysphonia, and paradoxical vocal fold motion (PVFM) or inducible laryngeal obstruction (ILO).3,4 This is a condition where supraglottic structures and not the vocal folds obstruct the airway. Symptoms occur continuously while the patient is awake and typically not observed during sleep. Diagnosis is suggested by history, presentation, and physical examination. However, endoscopic observation of the larynx showing adduction of the true vocal folds during inspiration is the critical component for diagnosis. Treatment of this condition is challenging and is usually conducted based on provider comfort without guidelines or clear treatment algorithms. Respiratory retraining therapy and
different medication protocols have been employed in these patients, but have largely shown to be ineffective. Botulinum toxin A injection to the laryngeal adductor musculature may be beneficial; however, tracheostomy is required for some patients with severe disability.

This research introduces diagnostic criteria for RLD and describes a series of patients treated in our institution’s voice center over the past 13 years including presenting symptoms, treatment patterns, and outcomes.

MATERIALS AND METHODS
A prospective case series with a retrospective analysis was performed with approval from our institutional review board. Diagnostic criteria were proposed based on a review of the literature\textsuperscript{1,2,5,6} and are listed in Table I. Sixteen patients were identified and found to have symptoms consistent with RLD. All patients underwent complete otolaryngological and speech-language pathology evaluation at the Voice Center of the Head and Neck Institute, Cleveland Clinic (Cleveland, OH). Respiratory retraining therapy was attempted on all patients. This consisted of identification and attempted elimination of abnormal or inefficient breathing patterns and exercises to establish abdominal breathing control, pursed lip and straw breathing exercises, and breathing hygiene coaching. Clinical records including videostroboscopic analysis of all 16 patients treated for RLD were reviewed from October 2005 to October 2018.

RESULTS
Sixteen patients with RLD were included based on our criteria for diagnosis (Table I). A summary of patient characteristics, treatments, and outcomes can be found in Table II. The cohort consisted of 11 females (69%) and five males (31%). The age of diagnosis ranged from 13 to 77 years, with a mean age of 48.5 years and standard error of 4.5 years. Patients were observed for between 1 and 13 years during the study, with average observation of 5.25 years and a standard error of 0.8 years. The common features of this group at time of diagnosis include a persistent nonepisodic, non–trigger-dependent dyspnea, and laryngoscopic evidence of glottic adduction during respiration as defined by the diagnostic criteria. Symptoms at presentation include 16 (100%) patients with dyspnea; 13 (81%) with stridor; and 14 (88%) with dysphonia, of whom one (6%) also had a component of spasmodic dysphonia. Eight (50%) patients had hoarseness, one (6%) had lingual dysarthria, five (31%) had headache, eight (50%) had cough, six (38%) had wheezing, 10 (63%) had fatigue, and four (25%) had dysphagia on presentation. Interestingly, two (13%) patients were felt to have normal voice quality limited only by respiratory difficulty.

Of the nine patients who had neurological imaging as part of their diagnostic evaluation for RLD, all were negative for neurological cause of dystonia. One of these nine patients did have deep brain stimulator in situ for the treatment of cluster headaches that predated diagnosis. Eleven patients were seen in consultation with neurology (69%). Nine patients (56%) were seen in consultation with pulmonology, and of those, seven (44%) had a concomitant diagnosis of asthma and three (19%) had concurrent diagnosis of chronic obstructive pulmonary disease. Five patients (31%) had other dystonias (affecting the hands (one patient) and cervical and facial muscles (four patients). No patients had concurrent respiratory dystonias affecting the diaphragm or chest-wall musculature.

Respiratory retraining therapy was attempted in all patients (100%), but none were felt to have adequate response to this therapy. Four patients (25%) had some improvement from laryngeal retraining therapy but required additional therapeutic measures (two botulinum toxin injection, one neuromodulator medication, one tracheostomy) to reach an acceptable level of symptoms. Five patients (31%) received medical therapy but declined or were ineligible for botulinum toxin injection and declined tracheostomy. Of these five patients, two had severe dysphagia precluding botulinum toxin injection, and three had relatively mild symptoms and declined treatment. Empiric acid suppression was employed in 12 patients (75%) but was felt to yield no improvement in symptoms of dyspnea. Neuromodulators including gabapentin, tricyclic antidepressants, and tramadol were used and trialed in 12 patients (75%) but were ineffective in treating respiratory dystonia. One patient reported improvement in dyspnea with gabapentin therapy and declined further

<table>
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<th>TABLE II. Subject Characteristics and Treatment Outcomes (N = 16).</th>
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<tr>
<td>Female</td>
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<td>Age at diagnosis, yr</td>
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<td>Period of observation, yr</td>
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<td>Symptoms at presentation, n (%)</td>
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<tr>
<td>Dyspnea</td>
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<td>Stridor</td>
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<td>Dysphagia</td>
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<td>Normal voice</td>
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<td>Treatment, n (%)</td>
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<tr>
<td>Respiratory retraining</td>
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<tr>
<td>Botulinum toxin injection</td>
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<tr>
<td>Medical treatment</td>
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<td>Tracheostomy</td>
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1. Adduction of the true vocal folds or prolapse of the supraglottic structures during inspiration on laryngoscopy
2. Symptoms are nonepisodic while awake and last more than 4 weeks\textsuperscript{*}
3. Symptoms are non–trigger dependent
4. Failure to resolve after respiratory retraining therapy
5. No evidence of neurologic lesions or anatomic abnormalities known to cause dysphonia

\textsuperscript{*}Symptoms may worsen with respiratory effort, but do not remit and then reoccur during the symptomatic period.
interventions despite persistent laryngoscopic findings. Laryngeal botulinum toxin injections into the bilateral thyroarytenoid muscles were employed in 11 (69%) patients and were adequate for controlling symptoms in six of these (54% of those treated). Doses were initiated between 1 and 2 U per side, and dosage was titrated upward to a desired patient response. Notably, two of these six also received cervical muscle (sternocleidomastoid and trapezius) injections concurrently for coincident cervical dystonia. Four patients were initially treated unilaterally, but symptom progression led to bilateral injections in all 11 patients. Tracheostomy was performed in four (25%) patients, and of these, two had failed botulinum toxin injection. One patient went on to have a cordotomy and her tracheostomy was then successfully decannulated. Two showed spontaneous improvement and were decannulated with some residual RLD not requiring tracheostomy. One patient was tracheostomy dependent but eventually improved after a laryngeal denervation/renervation surgery and was eventually decannulated. One patient failed to improve with any intervention and remains tracheostomy dependent.

DISCUSSION

There are many movement disorders that affect the larynx including tics, tremor, rigidity, bradykinesia, tardive movements, decreased reflexes, and dystonias. The most common of these is spasmodic dysphonia. This condition is a focal laryngeal dystonia, which rarely affects respiratory function of the larynx. Respiratory laryngeal dystonia presents with focal laryngeal dystonia of the adductor muscles during respiration and may be accompanied by dysphonia. Few reports of RLD exist in the literature, and among these there are differing opinions of what defines RLD. Both focal and multifocal muscular involvement has been described.1,12 There have been reports of dystonias affecting the laryngopharyngeal musculature and diaphragmatic muscles simultaneously.7,8

RLD appears distinct from these dystonias in that it primarily affects a patient’s laryngeal airway, with variable effect on phonation.1,6 Although many RLD patients express voice complaints, only one of our patients had spasmodic dysphonia in addition to respiratory dystonia. Typically, patients with RLD will have respiratory distress in varying degrees due to vocal fold adduction on inspiration, with a reduced glottic airway.2 Involuntary, inappropriate vocal fold adduction or adduction of the supraglottis on inspiration results in dyspnea, gasping, cough, and some speech interruption.5,6,8 The symptoms are typically continuous in the wakeful state, but will dissipate during sleep in the majority of patients, similar to other dystonias.5–11 Unsurprisingly, these symptoms can cause severe disability as patients may truly gasp for every breath leading to respiratory fatigue. Some of our patients prefer tracheostomy over the symptoms of RLD disease, and one of our patients remains tracheostomy dependent at the time of publication.

A multidisciplinary approach to diagnosis and treatment is recommended and involves otolaryngology, speech language pathology, pulmonology, and neurology. Diagnosis of RLD is achieved through history, physical examination, and laryngoscopy to confirm respiratory adduction of the larynx. In our experience, many patients are initially misdiagnosed with paradoxical vocal fold motion disorder or asthma and are correctly diagnosed after failing therapies for these diseases. Much like RLD, the most common form of ILO will have a flat inspiratory arm on spirometry and laryngeal behavior with atypical adduction of the vocal folds on inspiration.6,7 However, ILO is characterized by episodic trigger-dependent attacks in contrast to the unremitting symptoms of RLD.11 PVFM is usually treated via respiratory and laryngeal training exercises. Laryngeal electromyography (EMG) will show electrical activity of the adductor muscles during the inspiratory phase of the breathing cycle in patients with RLD. Patients with ILO will only exhibit muscle activation on inspiration if the patient is symptomatic at the time of the EMG testing. In patients with RLD, however, the paradoxical movement of the vocal folds or supraglottic contractions are nonepisodes, non–trigger dependent, and not consistently responsive to medical or behavioral intervention. For example, one of our patients had a known diagnosis of sarcoidosis. Initially it was postulated that her respiratory dystonia could have been related to sarcoid involvement of the brain. This was suggested because it has been reported that ILO can be associated with neurogenic abnormalities such as brain stem compression, organic cortical injury, or nuclear and lower motor neuron injury,12 and it follows that the same care should be taken for RLD. In our patient, we did not find evidence to support this, and both computed tomography and magnetic resonance imaging of the brain were negative. An important diagnostic feature of RLD is that these patients do not have any underlying structural or anatomic neurologic abnormalities that might cause dystonic motor symptoms. Oftentimes, this is proven in consultation with neurology via neuroimaging. In our series, all related neuroimaging was negative except for one patient with a deep brain stimulation implant in place.

Treatment of RLD is challenging, and options remain limited. Typically, patients with RLD will first be treated with respiratory retraining. However, this intervention was largely ineffective in our sample. One of our patients showed some improvement in symptoms after respiratory retraining and required no further intervention, even though the vocal fold adduction on inspiration continued as confirmed with laryngeal endoscopy. In addition, four patients endorsed some improvement with retraining alone but required additional therapies. Benzodiazepine, antireflux medications, anticholinergics, dopamine blockers, neurogenic modulators, and tricyclic antidepressants were prescribed to our patients but failed to improve symptoms in the majority of our patients. These medications have shown limited success in our experience and the experience of others.1,10

To date, the most effective treatment of RLD has been botulinum toxin injections into the adductor compartment to affect the lateral cricothyroid muscles and thyroarytenoid muscles.6 Interarytenoid injection and ventricular fold injections have been reported to improve
function in some patients. Using botulinum toxin injection to treat RLD was first described by Grillone et al., Blitzer and Brin, and Brin et al. It has been shown to reduce the quantity and quality of spasms and therefore produce noticeable improvement in breathing. Botulinum toxin takes effect after an average of 43.2 hours, with maximal effect after 2 weeks. Symptomatic improvement lasts an average of 13.8 weeks (range, 6–26 weeks). Adverse effects of this treatment include cough, dysphagia, and breathy dysphonia. These side effects will typically resolve after 2 weeks and can be limited by injecting the lowest possible dose of toxin that will provide maximal benefit. There was some consideration in the literature concerning whether this treatment should be unilateral or bilateral. Eleven of our patients received bilateral thyroarytenoid botulinum toxin injections. Of these, six patients reported near complete resolution with injections alone during the therapeutic window. All of our patients treated with botulinum toxin required bilateral injections for symptom relief.

In total, five of our 16 patients failed to improve despite multiple therapeutic measures and declined escalation to tracheostomy. Two of these patients were poor candidates for botulinum toxin injection due to concurrent severe dysphagia, and the remaining three had more mild disease and were able to manage symptoms without intervention. All five of these patients were offered tracheostomy and declined.

Although botulinum toxin injections have been reported as successful treatment options, our experience has been less efficacious; 54% of patients receiving botulinum toxin injections experienced remarkable improvement. Additionally, two of our patients decompensated after laryngeal botulinum toxin injection. One patient had pronounced symptoms of RLD after injection as well as laryngoscopic evidence of supraglottic airway prolapse and required a planned surgical airway shortly after initial botulinum toxin injection. A second developed a vocal fold hematoma and required hospitalization for monitoring without surgical intervention. The baseline dyspnea within this patient group makes laryngeal intervention higher risk than other laryngeal dystonia patients, and they should be closely monitored following injection. Four of our patients required tracheotomy at some point in their care. At the time of publication, three patients with tracheotomies had been successfully decannulated. The final patient remains a poor candidate for decannulation due to concurrent pulmonary disease. Interestingly, three of our patients experienced spontaneous improvement of symptoms after 3, 5, and 7 years, respectively. None of our patients experienced complete resolution of symptoms. All patients were undergoing treatment for comorbid conditions, and it is unclear whether this improvement is based on medical therapies for other diseases, changes in laryngeal neuropathology, or unknown contributing factors.

CONCLUSION

Respiratory laryngeal dystonia is a rare and challenging condition. The disorder can be severely disabling, and treatment options are limited. A multidisciplinary approach may be helpful. Some patients respond to laryngeal botulinum toxin injections and medical management, whereas others with more severe disability require tracheostomy for symptom control.

BIBLIOGRAPHY