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# What Is New in Laryngeal Dystonia: Review of Novel Findings of Pathophysiology and Novel Treatment Options

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## Abstract

**Purpose of Review** The aim of this review is to present the current literature on pathophysiology, evaluation, and management of laryngeal dystonia.

**Recent Findings** Recent evidence suggests loss of cortical inhibition, and sensory dysfunction plays an important role in the pathophysiology of laryngeal dystonia. New treatments addressing these changes include electrical stimulation for neuromodulation of the larynx, vibrotactile therapy, and sodium oxybate. Preliminary investigations are promising and these may impact the future of care for laryngeal dystonia patients.

**Summary** The current literature emphasizes a new understanding of the pathophysiology of laryngeal dystonia which has led to investigation of novel therapies.

**Keywords** Spasmodic dysphonia · Laryngeal dystonia · Novel treatment · Surgery · Pathophysiology

## Introduction

Laryngeal dystonia (LD), also known as spasmodic dysphonia, is a task-specific focal movement disorder primarily effecting voice production [1]. The dystonic movements of the vocal folds result in a varied phenomenology, typically hard vocal breaks and strain in the adductor-type laryngeal dystonia (ADLD), and breathy breaks or aphonia in the abductor-type laryngeal dystonia (ABLD). More than 80% of patients have suffered from ADLD [2]. By comparison, 17% of patients have suffered from ABLD [1]. In addition to these two main types of LD, there are also uncommon forms such as mixed adductor/abductor laryngeal dystonia, singer's dystonia, and adductor respiratory dystonia.

The disease was first described 150 years ago and recognized as a psychogenic origin disorder. In 1980 Moore's high-speed laryngeal imaging confirmed the vocal breaks in ADLD were due to irregular contractions of the vocal fold adductor muscles [3, 4].

Laryngeal dystonia is listed as a rare disease by the National Institutes of Health with an incidence of 1–4/100,000 primarily affecting women (2.5:1) [5, 6]. The average age of onset is 30–50 years old.

While a causative relationship has not been established, many environmental factors associated with the disease have been identified. Twenty-one percent of patients chronologically associate the onset of symptoms with a significantly stressful emotional event. It has been hypothesized this stress has a disease triggering neuroplastic effects on the brain. A recent upper respiratory tract infection is also one of the trigger events observed in 30% of patients [7]. Sixty-five percent of LD patients previously had measles or mumps in a survey study, compared with a national average of 15% at that time [7]. These findings raise the question of the role of viral infections in causing or triggering LD. While there is not a direct connection between viral infections and LD, it is well known they can cause significant neurologic insult and lead to

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peripheral and central nervous system disorders such as progressive multifocal leukoencephalopathy, subacute sclerosing panencephalitis, and multiple sclerosis.

## Pathogenesis

The precise pathophysiology of LD is still unclear. The first report suggesting a neurological origin of the disease was in 1960 showing abnormalities on electroencephalography in the temporal area of patients with LD [8]. This was further confirmed by Dedo who demonstrated improvement of the voice after RLN sectioning [9]. As the abnormal motor activity was thought to be the cause of symptoms, further treatment efforts were targeted at the motor dysfunction. In 1988, this led to the treatment of LD by injections of botulinum toxin (BTX) into the laryngeal muscles which showed improvement in the voice [1]. Botulinum toxin remains the primary treatment for LD today. Recent studies confirm that LD is somatosensory disorder resulting from a neurologic network dysfunction along the pathways connecting the cortex, thalamus, basal ganglia, and cerebellum [10•]. These disparate abnormalities may be the reason for some of the differences in patients' phenotypical presentations and may present opportunities for new treatments.

### Neurologic Pathophysiology

#### Neural Network Dysfunction

The knowledge of the pathophysiology of LD has been evolving quickly over the last decade. Present evidence suggests dystonia as a functional network disorder [11]. Multiple structural abnormalities that underlie the speech sensorimotor network have been identified as possible contributors to the pathophysiology in patients with LD compared with healthy subjects. These structural changes exist in both white and gray matter in focal dystonias [12••, 13–20]. Gray matter anomalies in LD patients relative to healthy controls have been reported to include bilateral primary sensorimotor and premotor cortex, superior/medium temporal, supramarginal, inferior frontal gyri, inferior parietal lobule, insula, putamen, thalamus, and cerebellum whereas alterations in white matter include the genu of the internal capsule, inferior frontal gyrus and associative pathways, lentiform nucleus, thalamus, and cerebellum. In a recent study, Bianchi et al. analyzed phenotypes and genotype-specific structural differences in large samples of ADLD, ABLD, and sporadic versus familial LD using high-resolution MRI and diffusion-weighted imaging [12••]. Using these modalities, they showed that evaluation of structural abnormalities alone allows for the differentiation of ADLD from ABLD and sporadic from familial LD.

Moreover, it has been shown that abnormal functional connectivity within the sensorimotor and frontoparietal networks exists in LD patients relative to normals. Evaluation of these alterations allows for differentiation of LD patients from normal subjects with 71% accuracy. It also allows for discrimination of adductor from abductor types of LD with 71% accuracy [21, 22••].

These studies emphasizing the varying structural changes with these specific network dysfunctions could be used as a biological diagnostic tool for phenotype-based characterization of disease pathophysiology [22••].

It is possible that the structural changes related to LD are the result of neural network dysfunction [23••]. It remains unclear if these structural changes represent regional abnormalities or abnormal hubs of a large-scale structural dystonic network. A very recent study has tried to answer this pathophysiologic question examining inter-regional white matter connectivity of the whole-brain structural network in writer's cramp and laryngeal dystonia, compared with healthy individuals [23••]. They discovered connectomes in both types of focal dystonia were defined by a series of unique changes of hubs and nodes. The most prominent regional abnormalities in the LD structural network were the supplementary motor area known to regulate the planning, initiation, and selection of actions during speech production [24–26]. As a result, this study offers new evidence that LD and other focal dystonias are network disorders at both the structural and functional levels.

#### Loss of Cortical Inhibition

Loss of cortical inhibition appears to occur in motor and sensory systems in dystonia patients. Transcranial magnetic stimulation can be used to evaluate cortical inhibition by measuring the cortical silent period (CSP) [27]. Compared with patients with muscle tension dysphonia and healthy controls, decreased CSPs in the masseter and first dorsal interosseous muscle have been shown in ADLD patients [28]. Shortened CSP indicates less cortical inhibition in phenotypically unaffected muscles. Decreased CSP is not specific to LD; it has been shown in other focal dystonias like cervical dystonia [29]. These changes in CSP show an association between the loss of cortical inhibition and focal dystonia. Yet, it is unclear if there is a causative relationship. It could be speculated to be a predisposing factor for the disease rather than a cause [10•]. The presence of a shorter CSP in unaffected muscles suggests less cortical inhibition suggests a global, GABA dysfunction [6]. This is further supported by the phenomenon of the alcohol responsive focal dystonia patients. Alcohol consumption, which is an indirect GABA agonist, has been shown to improve voice in more than 50% of LD patients [30]. Although the mechanism by how alcohol consumption improves the symptoms of LD is not yet known, it is postulated to be due to this modulation of GABAergic transmission [30].

### Somatosensory Dysfunction

Evidence of somatosensory abnormalities is seen both in the central nervous system (CNS) and the periphery. The earliest suggestion of this peripheral proprioceptive dysfunction was in 1995 and was thought to be due to abnormal muscle spindle function [7]. This proprioceptive dysfunction is not limited to the area affected by focal dystonia but is global, including in LD [31–33]. Konczak et al. showed LD patients have impaired limb proprioception, relatively to healthy controls [31]. There are also abnormalities of tactile and visual temporal discrimination in focal dystonia [34, 35].

There is also radiologic evidence of abnormalities in cortical sensory areas. In a functional MRI study of ADLD patients, a positive correlation between symptom severity (i.e., number of voice breaks) and increased activation intensity in the left primary somatosensory cortex was shown [36]. A H215O PET study showed speech-related cortical blood flows in heteromodal sensory areas decreased significantly in people with ADLD relative to volunteers. After either unilateral or bilateral BTX injection, the blood flow in patients increases in unimodal and heteromodal sensory areas regions (left dorsal postcentral, left posterior supramarginal, left posterior middle temporal gyri) regardless of the injection side [37]. These positive changes correlate with clinical improvement. In the same study, there were changes in motor-associated regions too; however, these regions (left anterior cingulate, left dorsal precentral gyrus) are not typically associated with control of laryngeal muscles but oro-motor control [37].

Further support of somatosensory dysfunction in LD comes from the response to treatment from BTX or peripheral stimulation. The target of both therapies, whose manipulations result in symptomatic improvement, appears to be due to treatment of proprioceptive dysfunction, not motor dysfunction. Studies show direct effects on the muscle spindle as well as normalization of cortical sensory organization and function that parallel symptomatic improvement [37–40, 41•, 42].

**Genetic** While 12% of LD patients have a family history of dystonia, a specific gene for LD has not been identified. Dystonia has had more than 20 genes associated with it but the genes shown to be LD-related are limited to TOR1A (DYT1), THAP1 (DYT6), and TUBB4A (DYT4) and GNAL (DYT25) [22••]. These genes mostly cause generalized or segmental familial dystonia associated with LD. THAP1 mutation is linked to various focal dystonias, including LD. Mutations in TUBB4A are linked to the autosomal dominant form of oro-lingual dystonia with a rare type of LD, whispering LD [22••, 43]. Mutations in the GNAL gene have been associated with cervical or cranio-cervical segmental dystonia including LD. A carrier mutation in this gene has been found in a patient with isolated ADLD [44, 45]. Not only are the mutations in specific genes linked with dystonia but polymorphisms also play a role. While mutations of the TOR1A gene are responsible for early onset segmental dystonia that rarely involves laryngeal dystonia, polymorphisms in the same gene have been associated with adult onset, primarily focal dystonia, including LD and even a decreased risk of developing dystonia [46–48].

Genotypic specific structural changes have also been identified in the extra-Sylvian regions and their connecting pathways. These findings suggest a possible role of the temporal lobe in pathophysiology of this subtype of LD [12••].

Although evidence of a clear link between specific genes and larynx-involving dystonia has been shown, the diagnostic and prognostic utility of genetic screening in clinical settings is still not clinically impactful [6]. These genotype-specific changes, however, can provide an important step toward future description of imaging markers and potential targets for new spasmodic dysphonia diagnostics and therapeutic interventions.

## Treatment

Botulinum toxin has been used for the treatment of LD since 1988 [2, 49]. Since then, BTX injection of laryngeal musculature has been recognized as the gold standard treatment for LD. However, there are many undesirable side effects including breathy dysphonia and dysphagia. The procedures are unpleasant and need to be repeated approximately every 3 months. Optimal voicing is only achieved during 30% of each injection cycle due to the delayed onset of BTX effects and return of symptoms prior to repeated injection [50]. Due to these shortcomings, physicians continue to research new treatments.

### Surgical Treatment

The first attempt at surgical treatment was described by Dedo in 1976. He was inspired by improvement in his patients' symptoms after recurrent laryngeal nerve (RLN) block [9]. This led to him performing RLN section for ADLD. However, the long-term results for RLN sectioning have not been promising with a 64% failure rate. Despite this, the concept of mechanically preventing excessive glottal closure or inhibiting abnormal motor signals from reaching the laryngeal muscles has remained the goal of newer surgical treatments and BTX injections [51].

In 1999, selective laryngeal adductor denervation-reinnervation (SLAD-R) surgery was described for ADLD with 90% success rate in 3-year follow-up [52]. Their 7-year follow-up study reveals that while about 80% of the patients have decreased symptoms, 20% of the patients had unsatisfactory results with moderate to severe breathiness [52].

Despite the relative success, only few laryngologists routinely perform this technique for treatment of their LD patients.

Another surgical technique was reported by Isshiki et al. in 2000, midline lateralization thyroplasty (form II thyroplasty), for ADLD [53]. Type II thyroplasty is intended to prevent the spasmodic overclosure of the glottis during phonation. Substantial failure rates have been shown in the literature and may be associated with technical difficulty. Recently, the authors who described the technique have shared modifications of it [54]. New studies are needed for more conclusive results.

Novel techniques of surgical treatment have not been limited to the transcervical approach. Su et al. described the transoral laser thyroarytenoid (TA) myoneurectomy in 2007 [55]. This surgery targets the end organ of ADLD by removing the muscle, terminal nerves, and neuromuscular junction of the thyroarytenoids. In an attempt to prevent muscle compensation causing a recurrence of symptoms, the surgeon resects most of the TA muscle, potentially resulting in a long-lasting effect [55]. While 92% of patients had benefit from the surgery in the original study, voice deterioration was observed in 45% of patients during follow-up after initial good short-term outcomes. A stable voice outcome was only achieved in 55% of patients after 12 months [56•]. No worsening of the symptoms or complications was reported in the study. TA myoneurectomy may be a potential treatment for ADLD, but long-term results and the outcome of revision TA myoneurectomy surgeries should be evaluated.

Although novel surgical techniques mostly focus on for ADLD, there are several surgical treatments suggested for ABLD as well. Surgical techniques proposed for ABLD are unilateral type 1 thyroplasty, bilateral medialization laryngoplasty, PCA myoplasty with medialization thyroplasty, and endoscopic partial posterior cricoarytenoid myectomy [57–63]. None of the surgical techniques has been widely accepted by laryngologists at this time. Botulinum toxin injection stills remain as the standard treatment for ABLD.

## Novel Treatment Options

Multiple new treatments have been studied over the last few years. These novel approaches are either intended to cure the disease or aid in more effective treatment. These treatments can be divided into two main categories: those treating at the CNS or the end organ at the larynx.

### Central Nervous System

**Deep Brain Stimulation** Deep brain stimulation (DBS) is performed by surgically implanting a device into the brainstem that delivers electrical stimulation to modulate the neuronal circuits. Revolutionized in the last 30 years, DBS has been and effective treatment for severe movement disorders [64]. The FDA has approved it for Parkinson's disease and essential tremor. It is approved for dystonia but only with special permission [65]. There have been several anecdotal reports indicating that basal ganglia DBS improves patients' LD symptoms [66]. In these cases, the patients have confounding symptoms such as essential tremor, focal dystonia, or local dystonia. A clinical trial named Thalamic Deep Brain Stimulation for Spasmodic Dysphonia (DEBUSSY Trial) was recently launched; however, no report has been released [67]. If the findings are positive, such a trial could result in the incorporation of DBS as a treatment option for LD.

**Pharmacological Treatment with Sodium Oxybate** Traditional pharmacological intervention for dystonia has been considered unsuccessful for task-specific dystonia. Recent investigations have focus on sodium oxybate, as alcohol consumption has long been known to improve with the symptoms of more than 50% patients with LD [30].

Sodium oxybate (Xyrem ®), the sodium salt of gamma hydroxybutyric acid (GHB), mimics some of the effects of alcohol. Sodium oxybate is quickly absorbed when ingested orally, crosses the blood-brain barrier, and transforms into GABA within the brain. Sodium oxybate has FDA approval for cataplexy and severe daytime narcolepsy sleepiness. In a recent open-label clinical trial of sodium oxybate for patients with alcohol-responsive LD with or without tremor, 82% had an improvement in their symptoms [68••]. The medicine's effect started in less than 40 min and continued for approximately 3.5 h. Almost half of the patients experienced mild lightheadedness in the first hour after administration. A new randomized placebo-controlled double-blind clinical trial has recently been launched which is expected to be completed in August 2022. (ClinicalTrials.gov Identifier: NCT03292458) [69]. If the trial ends with encouraging results, patients with alcohol-responsive LD may have a therapy that can function alone as need or in conjunction with BTX injection.

### Laryngeal Treatments

**Vibrotactile Stimulation of the Larynx** Abnormal proprioceptive muscle spindle activity of non-dystonic limbs has been observed in LD and other types of focal dystonia such as blepharospasm and cervical dystonia [70]. This suggests that somatosensory dysfunction could be a target for disease treatment, much like sensory tricks are found to relieve symptoms in patients with focal dystonia [70]. A recent study has shown that a one-time 40-min application of non-invasive laryngeal vibrotactile stimulation (VTS) resulted in a significant improvement in symptoms in 69% of patients with carryover effect lasting for at least 20 min after VTS was discontinued. This improvement was accompanied by positive changes in the somatosensory region of the motor cortex [71••]. Following these promising results, a new clinical trial was lunched to provide scientific evidence for assessing the

appropriate dose of VTS therapy for effective improvement of voice symptoms in LD (ClinicalTrials.gov Identifier: NCT03746509) [72]. Successfully completing the planned study will be a significant step toward promoting laryngeal VTS as a therapeutic intervention. Theoretically, the developed neck collar could be worn to apply the treatment as need, resulting in a vocal "boost" for a meeting or phone call or social function.

### Laryngeal Neuromodulation with Electrical Stimulation

Electrical stimulation of the larynx has been studied as a method of neuromodulation, treating the muscle spindle and associated proprioceptive and somatosensory abnormalities in LD. Previously, electrical stimulation was investigated for the treatment of focal dystonia in patients with writer's cramp disease. Patients treated with transcutaneous electrical stimulation have significant improvement of their symptoms compared with placebo. The positive carry over effect persisted for 3 weeks after the treatment ended [73]. Similar results have also been shown in electrical stimulation for cervical dystonia [42]. In 2014, this was investigated in the larynx for ADLD [74••]. In this study, electrical stimulation was delivered to the left thyroarytenoid muscle by a hooked electrode. The stimulation was at below the level of motor neuron activation and was performed 1 h per day for five consecutive days. Outcome measures, including spasm counts, patient-reported outcomes, and the blinded evaluation by a speech language pathologist, showed significant patient improvement. In four of the five patients, improvement lasted 3 to 14 days after stimulation was discontinued. At present, a second and larger study is underway. If viable, an implanted electrical stimulator would allow for intermittent treatment as needed, by the patient instead of the physician. They would activate the stimulator when their voice began to deteriorate, allowing the patient to maintain a stable vocal improvement compared with the peaks and valleys of BTX injections.

## Conclusions

The loss of sensorimotor inhibition and neural network abnormalities is crucial to the pathophysiology of LD and to the direction of future therapies. Studies focused on further elucidating these structural and functional abnormalities are essential to enhancing our understanding of the disease. Improved insight will allow for the development of novel treatments, some already under investigation, that will better address the needs of patients suffering from LD.

## Compliance of Ethical Standards

**Conflict of Interest** Necati Enver declares no conflict of interest.

Michael J. Pitman has a royalty and patent interest with MedEl in the use of electrical stimulation for laryngeal and focal dystonia.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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