

Neurological Voice Disorders: A Review

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ABSTRACT

Aim: To provide an overview of neurological disorders affecting the larynx, either primarily or as part of a systemic disease process. In this review, we first present an overview of the approach to diagnosis and treatment of neurological diseases of the larynx, and then move on to discuss individual conditions in more detail.

Background: Neurolaryngology focuses on the neuromuscular function of the larynx. Laryngeal issues such as cough, aspiration, and hoarseness are among the most common problems in ambulatory medicine and aspiration is the leading cause of morbidity and mortality in the geriatric population and is especially prevalent in neurodegenerative disease.

Review results: Neurological voice disorders can be divided into three categories: those that originate from the central nervous system, those that originate from the peripheral nervous system, and those that are functional or behavioral in nature. Several central nervous system disorders have manifestations in the larynx—the disorders most commonly seen by otolaryngologists are: dystonia, essential tremor, Parkinson's disease, and stroke. Laryngeal disorders originating from the peripheral nervous system include vocal fold paresis/paralysis and myasthenia gravis. Functional voice disorders include muscle tension dysphonia and paradoxical vocal fold motion.

Conclusion: Neurological voice disorders can originate from the central or peripheral nervous system, or be functional in nature. It is important for the otolaryngologist to be able to be familiar with history and physical examination findings that suggest neurological pathology, and also be able to recognize specific findings pertinent to each individual condition.

Clinical significance: Patients with central nervous system disorders can often have laryngeal complaints as their first presenting symptom. Therefore, the otolaryngologist can sometimes be the first physician to diagnose such conditions, and plays an important role in coordinating and providing therapies that significantly improve quality of life for these patients. Current research involving machine learning and functional neuroimaging may greatly improve the diagnosis of many of these disorders in the near future.

Keywords: Central nervous system, functional voice disorder, larynx, neurological, peripheral nervous system, review, voice disorders.

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INTRODUCTION

Neurolaryngology focuses on the neuromuscular function of the larynx. Laryngeal issues such as cough, aspiration, and hoarseness are among the most common problems in ambulatory medicine and aspiration is the leading cause of morbidity and mortality in the geriatric population and is especially prevalent in neurodegenerative disease. The mechanisms of laryngeal control by the nervous system are still being elucidated, and the complex and reflexive interaction of the laryngeal, respiratory, and swallowing systems are poorly understood.

Neurological voice disorders can be divided into three categories: those that originate from the central nervous system, those that originate from the peripheral nervous system, and those that are functional or behavioral in nature. Many of these neurological disorders affect the body systemically, but patients will often complain of dysphonia before other symptoms develop.¹ The otolaryngologist can therefore be the first physician to diagnose such neurological conditions, and must be familiar with their signs and systems, and take a systematic approach to the examination of the pharynx and larynx.² In this review, we first present an overview of the approach to diagnosis and treatment of neurological diseases of the larynx, and then move on to discuss individual conditions in more detail.

Approach to Diagnosis

During the history-taking for a patient with a suspected neurological voice condition, the clinician should be sure to ask

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about the following symptoms, as they often suggest an underlying neurological pathology: vocal fatigue, increased effort for speech, pitch breaks, lack of voice inflection, tremor, tightness, dysarthria, oral incompetence, dysphagia, aspiration, fluctuating inspiratory stridor, and weak cough.^{2,3} Friends and family are good sources for observation about communication difficulties, and specific situational examples can be informative such as difficulty with phone use, public speaking, or noisy environments.

The physical examination should start with the clinician listening to the patient's speech.² The clinician should assess for abnormalities in fluidity (whether there are breaks or spasms), articulation, cadence, rate of speech, and quality. In terms of vocal quality, the presence of roughness signifies turbulent airflow, which can be a sign of aperiodic vibration of the vocal folds. A very breathy voice is a sign of a glottic gap. A strained voice typically is caused by excessive muscle activity.¹

Next, the physician should perform a targeted neurological examination of the sensation, motion, strength, and symmetry of the oral cavity (lips, hard palate, and tongue) and oropharynx (soft palate). Athetoid movements are suggestive of tardive dyskinesia. Fasciculations of the tongue suggest ALS. Jaw and tongue thrusting suggest oromandibular dystonia. Slow, repetitive jerking suggests palatal myoclonus.³ Rapid repetition of certain syllables ("pah" to test the lips, "tah" to test the tip of the tongue, "gah" to test the posterior tongue) also provides information about central and peripheral motor control. A lower motor neuron disorder causes hypophonia, an upper motor neuron disorder decreases the rate of the repetition, and a cerebellar disorder can cause an irregular rhythm.²

The laryngeal exam should be performed with a flexible laryngoscope, and follow a systematic process. The soft palate should first be observed for weakness, tremor or spastic movement at rest.¹ Having the patient swallow and repeat the syllable "ka" will test the symmetry and completeness of velopharyngeal closure. The base of tongue should then be observed during phonation of the sounds "ee" and "ah," which should move the tongue anteriorly and then posteriorly, respectively. The patient is then asked to phonate at the highest pitch they can muster, and the squeezing action of the pharyngeal muscles are observed for any weakness. The hypopharynx is examined for pooling of secretions, which can be due to impaired swallow. The larynx is then observed during respiration, observing for any tremors of the vocal folds. The patient is then asked to phonate and cough, both of which assess the mobility of the larynx. Asking the patient to phonate from lowest to highest pitch tests the function of the cricothyroid muscle.³ Stroboscopy can also be performed to detect laryngeal structural abnormalities, examine glottic closure and evaluate symmetry in tension and mucosal wave.²

Approaches to Treatment

Neurological impacts on laryngeal function can be broadly categorized into two main groups based on hypo- or hyper-activity. Hyperactive disorders of the larynx result in spasms, tremor, dyskinesia, and dystonia. Spasmodic dysphonia, vocal tremor, myoclonus, muscle tension dysphonia, and paradoxical vocal fold motion can be viewed from the lens of hyperactive disorders. The laryngeal exam in the hyperactive disorders shows vocal fold overclosure, excessive and disorganized muscle contractions, and inefficient function. In contrast, hypoactive or hypotonic neurolaryngological disorders result in diminished coordination and strength with resulting paresis, weakness, and/or reduced velocity. Laryngeal problems generally viewed in the hypoactive group include vocal fold paralysis and paresis and laryngeal dysfunction from most neurodegenerative disease such as Parkinson's disease and muscular dystrophies. Laryngeal examination shows reduced tone, atrophy, reduced velocity, and range of motion of the vocal folds, and incomplete glottal closure. This categorization system is useful as a framework when considering treatment options. Although specific and comprehensive recommendations on all neurological disorders are difficult to describe, when evaluating the larynx in this broad way, laryngeal treatment options generally also fall into two categories: augmentation to address weakness and botulinum toxin to address spasm.

Initial approaches to treatment involve carefully assessing symptoms and maximizing medical and physical therapy options. Almost all neurolaryngological disorders will benefit from careful screening and work with a speech language pathologist (SLP). Early

evaluation of swallowing, speech, and voice function by a therapist is recommended before initiating surgical and procedural intervention.

Botulinum toxin is a neurotoxin that specifically target the neuromuscular junction with a titratable weakening effect that can be used to temporarily chemodenervate muscle groups in hyperactive disorders. Targeted chemodenervation can be used to diminish hyperactivity and rebalance the larynx in an adducted or abducted fashion. Injecting muscles of adduction in the larynx, such as the thyroarytenoid, lateral cricoarytenoid, and interarytenoid muscles can cause lateralization and reduce overclosure. The side effects of toxin injections must be taken into account, especially aspiration risk and a modified barium swallow in the setting of suspected aspiration should be considered on at-risk patients. Botulinum toxin injections are contraindicated in certain neuromuscular disorders such as myasthenia gravis.

Augmentation laryngoplasty is often helpful in hypoactive neurolaryngological disorders that result in aspiration, glottal insufficiency, and weak voice. Augmentation of the vocal folds can be performed with a temporary injectable in the office setting that can address glottal closure, reduce glottal atrophy, and improve cough and voice strength. If temporary injection improves symptoms, longer term materials and more permanent surgery should be considered.

CENTRAL NERVOUS SYSTEM DISORDERS WITH MANIFESTATIONS IN THE LARYNX

There are several disorders of the central nervous system that can have manifestations in the larynx. Some of these disorders include: dystonia, pseudobulbar palsy, amyotrophic lateral sclerosis, primary lateral sclerosis, postpolio syndrome, Arnold-Chiari malformations, stroke, Parkinson disease, multiple sclerosis, essential tremor, and myoclonus.³ The disorders most commonly seen by otolaryngologists are described below.

Dystonia

Dystonia is a movement disorder that is characterized by sustained muscle contractions, twisting and repetitive movements, and abnormal postures. The etiology of dystonia is dysfunction of neuronal networks in the basal ganglia, cerebellum, thalamus, and cortex, which causes abnormal motor function.⁴ Spasmodic dysphonia is a focal dystonia of the larynx.⁵ It manifests as task-specific involuntary contractions of the laryngeal muscles, which causes irregular voice breaks that occur only during speech.⁵⁻⁷ This disease manifests primarily in females (over 65% of patients), with an average age of onset of 45 years. It has a prevalence of one per 100,000.⁵

Spasmodic dysphonia most often presents as the adductor type (about 83% of cases), due to muscle spasms of the laryngeal adductor muscles.^{8,9} These patients have a strangled, harsh-sounding voice, with inappropriate pitch or pitch breaks. Abductor spasmodic dysphonia is caused by spasms of the posterior cricoarytenoid muscles, which are the sole laryngeal abductor muscles. Patients present with a breathy, soft voice that requires a lot of effort. Patients can also have a mixed adductor/abductor spasmodic dysphonia, with a combination of breathy and harsh voice breaks.¹⁰ About one-third of spasmodic dysphonia patients have coexisting vocal tremor.¹¹

Ludlow et al.⁷ suggest a 3-tiered approach to the diagnosis of spasmodic dysphonia. The diagnosis begins with screening questions (see Table 1). If patients answer affirmatively to the first

Table 1: Screening questions for spasmodic dysphonia

| Question | Consistent with spasmodic dysphonia | Not consistent with 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 | 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 the same as speech |
| Sing | Normal | More affected than speech |
| Yawn | Normal | Not normal |

Adapted from Ludlow et al. Research priorities in spasmodic dysphonia. *Otolaryngol Head Neck Surg.* 2008 Oct; 139:(4) 495–505

two questions and have a duration of symptoms greater than 3 months, spasmodic dysphonia is a strong possibility.

Next, a clinical speech evaluation is performed.⁷ Giving the patient-specific vocal tasks that isolate the abductor and adductor laryngeal muscles can be helpful in identifying adductor spasms and abductor spasms.¹ Having the patient count from 60–70 and then from 80–90 is one such task.³ A patient with adductor spasmodic dysphonia may have voice breaks and strains during the 80–90 counting, as this task contains many-voiced vowels, causing the vocal folds to hyperadduct.³ A patient with abductor spasmodic dysphonia may have breathy voice breaks during the 60–70 counting, as this task contains many voiceless consonants, which can elicit spasms of the true vocal folds while they are in abduction.³ Greater than one voice break per three sentences in a normal speaking voice is required for a diagnosis of spasmodic dysphonia. In this condition, patients will be less symptomatic while whispering, and should have no symptoms while shouting.⁷

Flexible laryngoscopy exam should demonstrate no structural lesions that could account for the patient's dysphonia. The vocal folds should have normal movement during breathing, coughing, throat clearing, and whistling. Spasms may be observed during speech.⁵

The mainstay of treatment for spasmodic dysphonia is botulinum toxin injection into the affected laryngeal muscles. Botulinum toxin exerts its effect by inhibiting the release of acetylcholine at the neuromuscular junction, causing a flaccid paralysis.¹² For adductor-type spasmodic dysphonia, the bilateral thyroarytenoid and/or lateral cricoarytenoid muscles are most commonly injected.¹³ This is done under EMG guidance, *via* a percutaneous approach, through the cricothyroid membrane.¹³ The average onset to action is 2.4 days, average duration is 15 weeks, and average improvement is to 91% of normal voice function. Adverse effects include breathy voice and cough with drinking fluids, which can last up to 2 weeks.¹⁴

For abductor-type spasmodic dysphonia, the posterior cricoarytenoid muscle is injected.¹³ This is also done in a percutaneous fashion, with the needle entering behind the posterior edge of the thyroid lamina and advancing to the cricoid cartilage to access the PCA muscle.¹² As the PCA is the lone laryngeal abductor, the clinician should start with unilateral injections until the patient's reaction to the injections are known, in order to reduce the chance of airway compromise.¹³ The average onset of action is 4 days, average duration is 10.5 weeks, and average improvement is to 70% of normal voice function. Adverse effects include mild exertional wheezing and mild transient dysphagia to solids.⁸

Surgical treatments for spasmodic dysphonia have been attempted, but with mixed outcomes. Recurrent laryngeal nerve transection has been tried with an initial reported 85–90% success rate, but 64% of patients had eventual return of symptoms.⁶ Selective laryngeal adduction denervation and reinnervation is another surgical procedure, which involves transection of the bilateral branches of the recurrent laryngeal nerve that innervate the adductor laryngeal muscles. To prevent reinnervation and muscle atrophy, the cut nerve branches are anastomosed to a branch of the ansa cervicalis. Results from this procedure were promising, but long-term results demonstrated that 30% of patients had breathiness postoperatively, and 26% of patients still had voice breaks.^{6,15}

There have not been any well-established medical treatments for spasmodic dysphonia. Alcohol has been shown to improve voice symptoms in 58% spasmodic dysphonia patients, with benefits lasting from 1–3 hours. This is obviously not a practical long-term treatment. Recently, sodium oxybate has demonstrated good efficacy in alcohol-responsive movement disorders such as essential tremor and myoclonus. This is an oral medication that is chemically identical to gamma-hydroxybutyric acid, which is an inhibitory neurotransmitter that produces effects similar to those of alcohol. This drug exerts its effects within 30–45 minutes, and lasts about 3.5–4 hours. A recent open-label study by Rumbach et al., demonstrated that sodium oxybate was successful in 82% of alcohol-responsive spasmodic dysphonia patients in significantly reducing the number of adductor and abductor spasmodic dysphonia voice breaks and the severity of coexisting vocal tremor. Sodium oxybate also showed to improve vocal tremor symptoms in patients who had persistent vocal tremor after successful botox injections for their spasmodic dysphonia.¹¹

The application of functional MRI to neuroimaging in dystonia is an exciting recent development. Functional MRI is able to detect changes in the hemodynamic response during different types of neuronal activity. Thus, it can be used to identify alterations in normal neuronal activity during tasks that provoke dystonic movements.¹⁶ Such functional MRI imaging was shown to be able to detect specific neuronal changes in abductor and adductor spasmodic dysphonia—the changes in adductor spasmodic dysphonia were found in the frontal cortex, whereas the changes in abductor spasmodic dysphonia were found in the cerebellum and putamen.¹⁷ The combination of functional MRI technology and machine learning has recently been studied by several groups. One such study was able to demonstrate 71% accuracy in classifying laryngeal dystonia patients vs healthy controls. This technology could result in a powerful diagnostic tool based on neuroimaging biomarkers.¹⁶

Stroke

Speaking is a very complex action that is produced by multiple cranial nerves working in conjunction to perform a sequence

of tasks including: respiration, vocal fold movement, shaping sound, and articulation.¹⁸ Voice impairments after cerebrovascular accidents are dependent on the location of the event in the brain. Spastic voice changes are seen with upper motor neuron lesions, with speech characterized by slowed articulation, strained quality, and hypernasality.¹⁸ Cerebrovascular accidents of the vertebrobasilar circulation affect the brainstem—specifically, the tracts providing sensory information to the pharynx and larynx.¹³ Such strokes result in flaccid voice changes, from a loss of muscle tone and reflexes. Speech in this case would be breathy and hypophonic. Although rare, vocal fold paralysis can also occur. Cerebrovascular accidents can also cause dysphagia and aspiration due to weak or poorly coordinated pharyngeal muscular activity, or lack of pharyngeal/laryngeal sensation.¹⁸

Videolaryngoscopy and stroboscopy are important aspects of the otolaryngology exam in a stroke patient. Sensation of different laryngeal structures can be tested by using the endoscope tip. Pooling of secretions suggests impairment of sensation or ineffective swallow. Stroboscopy can identify subtle paresis or atrophy of the vocal fold. Laryngeal EMG can also be helpful in assessing vocal fold mobility, cricopharyngeus muscle activity, motor pathway to the supraglottis, and supraglottic/glottic sensation. Aspiration/dysphagia is assessed with modified barium swallow study, flexible endoscopic swallow evaluation, and manometry.¹⁸

Speech pathologists play a key role in the rehabilitation of most speech and swallowing disorders after stroke, and speech/swallow therapy can help with aphasia, apraxia speech, dysarthria, and dysphagia.² The otolaryngologist can play a role when surgical intervention may be beneficial.¹⁸ In thinking about treatment, otolaryngologists should prioritize the laryngeal functions of protection, respiration, and phonation, in that order.¹⁸ The laryngeal paralysis of a stroke is often severe, and can lead to phonation difficulties and aspiration that is not improved by thyroplasty or injection laryngoplasty alone. Arytenoid adduction is the most effective means of closing the glottic gap in these patients, usually in combination with type I thyroplasty.² In patients who have pooling of secretions due to paralysis of the pharyngeal muscles, redundant hypopharyngeal tissue can be removed to decrease pooling and improve pharyngeal transit time.¹⁸ However, with severe aspiration that does not respond to smaller surgical interventions, some patients ultimately need to undergo laryngectomy.²

Essential Tremor

Essential tremor is an involuntary, oscillatory rhythmic movement that occurs during directed movement and posture-holding.¹ For patients with essential tremor, about 90% are affected by hand tremor, 30% have head tremor, and 20% have voice tremor.¹⁹ Patients can also present with isolated vocal tremor.²⁰ The vocal symptoms are caused by tremor in the muscles of the larynx, pharynx, soft palate, or strap muscles.² Vocal tremor is thought to be due to dysfunction in the central networks of the basal ganglia, and the cerebello-thalamo-cortical system.¹² In about half of cases, it is inherited in an autosomal-dominant fashion, with age of onset peaking at both the 2nd and 6th decades. It is thought that 5% of people older than 65 years of age may have an essential tremor.¹⁹

Patients will generally report symptoms of voice shaking, weakness, instability, or hoarseness.²¹ Most patients complain of variations in volume and increased effort required for speech. Patients also complain of dyspnea while speaking and difficulty raising voice volume.²¹ Patients will report symptoms that

slowly worsen over months to years, with symptoms that are aggravated by anxiety or stress and improved with alcohol and benzodiazepines.^{1,13} On exam, symptoms will be present across all vocal tasks, with no spontaneous intervals of clear voice.²¹ On flexible laryngoscopy, there may be rhythmic, oscillatory motion of the palate, pharynx, or vocal folds, which will be symmetrically affected.^{1,21} Laryngeal EMG can be helpful in cases in which the diagnosis is unclear, and will demonstrate waxing and waning adductor muscle activation.²¹

Pharmacological treatment includes propranolol (a Beta-adrenergic blocker) and primidone (a neuroleptic). These medications have been shown to be effective treatments for hand and head tremor. However, these medications are often less impactful for voice tremor—they are effective in up to 50% of patients.^{1,2,22} As mentioned in the previous section on spasmodic dysphonia, sodium oxybate is a newer oral agent that has recently been shown to reduce vocal tremor. Botulinum toxin can be an effective treatment of essential voice tremor by decreasing the severity of the tremor, but it does not eliminate it. For patients who have tremor in the horizontal plane (side to side oscillations), botulinum toxin is injected into one or both thyroarytenoid muscles.²² Laryngeal tremor in the vertical plane (up and down oscillations) can be treated by botulinum toxin injections into the strap muscles.²² Side effects of botulinum toxin injections include breathiness (thyroarytenoid injection), and dysphagia (strap muscle injection).²²

Over the last two decades, deep brain stimulation has been successfully used for several different movement disorders, including Parkinson's disease, essential tremor, and dystonia. This procedure involves implanting electrodes into the thalamus to selectively electrically simulate and modify activity in the target area.¹⁹ A study specifically examining deep brain stimulation for voice tremor showed that 86% of patients showed improvement, with a mean follow-up of 10 months. Literature generally supports the efficacy of deep brain stimulation for vocal tremor, but there have only been few studies (with small numbers of patients) on this subject.²³

Parkinson's Disease

Parkinson's disease is a movement disorder caused by the degeneration of the extrapyramidal areas of the brain, particularly the substantia nigra.²⁴ The major symptoms include slowed movement, resting tremor, rigidity, and loss of coordination during movement. Speech is often affected, and vocal impairment may be an early symptom of the disease.²⁴ It is estimated that 70–89% of Parkinson's disease patients will experience vocal impairment as the disease progresses, and greater than 30% of these patients find it to be the most bothersome of all of their symptoms.^{1,24} Patients with Parkinson's disease have a characteristic voice that is soft, monotonous, breathy, and harsh.²⁴ Patients often have difficulty initiating speech, speak in short rushes of words, have inappropriate silences, have a variable speaking rate, and can have a vocal tremor.^{24–26}

On flexible laryngoscopy exam, patients have been found to have pooled hypopharyngeal secretions, diminished sensation, weak cough and swallowing reflexes, and aspiration.¹ Videostroboscopy is also helpful in making the diagnosis. Characteristic findings include: vocal fold bowing, glottic gap on phonation, and slowed vibration.¹ Laryngeal EMG shows reduced thyroarytenoid muscle activity.⁹ Patients who have Parkinson's disease as well as autonomic nervous system dysfunction are said to have multiple system atrophy. One form of multiple system atrophy is Shy-Drager syndrome, in which patients have limited vocal fold abduction with inspiration, which gets worse during sleep and may necessitate tracheostomy.¹²

Levodopa is considered to be the most effective medical treatment of Parkinson's disease. Levodopa is an amino acid precursor of dopamine, and is converted in the brain to dopamine (which is depleted in Parkinson's disease).²⁷ The literature shows inconclusive results in regards to levodopa's effects on speech improvement in Parkinson's. A recent systematic review demonstrated that objective voice quality measurements were improved after administration of levodopa, but this study was limited by the poor quality of and small numbers of patients in the included studies, as well the great heterogeneity of methods used in the studies.²⁸ Most studies have shown that levodopa does not result in an improvement of speech as measured by objective acoustic measures.^{27,29} It is hypothesized that this finding is due to the fact that the treatment of Parkinson's disease with levodopa results in improvement of symptoms that result from degeneration of the nigrostriatal system (bradykinesia, rigidity, and tremor). However, symptoms like abnormal gait/postural instability, speech impairment, and cognitive impairment are thought to be caused by lesions that affect areas of the brain that do not rely on dopamine, and thus it is logical that these symptoms would not respond to treatment with dopamine replacement.²⁹

The Lee Silverman voice treatment program (LSVT), developed in 1987, is an intensive speech therapy program that focuses on a set of tasks designed to maximize phonatory and respiratory functions. Patients are constantly instructed to produce a loud voice with maximum effort during vocal tasks, and are reminded to monitor the loudness of their voice and the effort it takes to produce it.³⁰ There have been many studies that have demonstrated significant improvement in glottic closure, vocal fold vibratory movements, sound pressure level, voice fundamental frequency range, voice quality, and speech intelligibility after LSVT. These effects have been shown to persist in long-term 2-year follow-up.³⁰

Deep brain stimulation in the subthalamic nucleus (STN-DBS) has been shown to be an effective treatment for patients with advanced Parkinson's disease, greatly improving bradykinesia, rigidity, and tremor.³¹ However its effects on speech have been variable—some studies have demonstrated improvement in voice,³¹ while others have showed worsening of speech intelligibility after STN-DBS.³²

Injection laryngoplasty can help to improve hypophonia in patients with glottal insufficiency, with studies demonstrating improvement in 61–75% of patients.^{25,33} Because Parkinson's disease is a progressive disorder, injection with temporary substances are more ideal, as they can be more easily revised as the patient's motor function deteriorates.²⁵ It has been shown that patients with advanced neurologic disease with aphonia, difficulty with speech initiation, dysphagia, or ambulatory difficulty are less likely to respond to treatment with injection laryngoplasty.³³

PERIPHERAL NERVOUS SYSTEM DISORDERS

Vocal Fold Paresis/Paralysis

Vocal fold immobility is a common and significant clinical problem given the critical role that vocal folds play during phonation, respiration, and airway protection during swallowing. Even mild vocal fold motion impairment can manifest as severe symptomatology during speaking, breathing, and/or swallowing. Vocal fold immobility is a broad term that includes impaired motion from either a neurogenic or a mechanical cause, such as arytenoid dislocation or joint fixation.¹² When a motion abnormality is deemed permanent and due to a neurologic issue, the terms

paresis and paralysis are used for partial or total loss of vocal fold motion, respectively.³⁴

Vocal fold paresis/paralysis can occur due to dysfunction of either the brainstem nuclei, the vagus nerve, the recurrent laryngeal nerve, or the vocal folds themselves. Therefore, a myriad of etiologies can cause vocal fold paresis/paralysis, such as: iatrogenic vagal/recurrent laryngeal nerve injury, vagal/recurrent laryngeal nerve tumor invasion, central nervous system disease, and trauma.³⁵ Bilateral vocal fold paralysis most often results from surgical injury to the bilateral vagus/recurrent laryngeal nerves¹³ but can also occur in diseases that affect the skull base and brainstem such as neurofibromatosis type 2 and neurosarcomatoid.^{36,37}

The primary symptom of vocal fold paresis/paralysis is dysphonia. The range of dysphonia can be very large—it can range from vocal fatigue in mild or well-compensated cases, to almost complete aphonia in severe cases. The quality of the voice is determined by the muscular tone and position of the affected vocal fold, as well as how much compensatory glottic and supraglottic hyperfunction has occurred. It is also common for patients to report having symptoms of aspiration with liquids, as well as a weak cough.³⁸ In bilateral vocal fold paralysis, the voice may be minimally affected, but patients can develop significant airway compromise due to the inability to abduct their vocal folds.¹³ For progressive neuromuscular diseases such as Charcot Marie Tooth, initial unilateral vocal fold paresis can present with voice loss, but airway symptoms predominate as bilateral paresis unfolds.³⁹

The physical examination should include a thorough neck exam, as compressive neck masses can cause vocal fold paralysis. A cranial nerve exam should also be performed, as findings of palatal paralysis can indicate a high vagal lesion, and involvement of cranial nerves 11 and 12 may signify a lesion at the level of the skull base.³⁸ Flexible laryngoscopy should then be performed, during which the patient is asked to alternate between sniffing and saying "ee." This maneuver causes the vocal folds to alternately adduct and abduct maximally, which emphasizes any deficits in movement. A paralyzed vocal fold can either be located in the lateral, paramedian, or median position, depending on the degree of reinnervation and synkinesis present.³⁸ The vocal process is often displaced inferiorly, resulting in a vertical mismatch or misalignment with the working fold. Videostroboscopy is a helpful part of the workup, because in many cases of vocal fold paralysis, the paralyzed vocal fold shows a hyperdynamic or flaccid mucosal wave because the denervated vocalis muscle is atrophic. In cases of mild or moderate vocal fold paresis, the increased amplitude on stroboscopy may be the only sign of vocal fold weakness.¹³ Videostroboscopy can also detect other subtle findings in paresis, like mild bowing of the vocal fold and asynchronous mucosal wave.³⁸

Laryngeal EMG can be very useful in the diagnosis of vocal fold immobility. Findings of spontaneous activity, polyphasic motor action potentials, and a neuropathic interference pattern strongly suggest a neurological cause of the immobility.⁴⁰ LEMG, when performed between 1 and 6 months postinjury, can provide reasonably accurate (75–100%) prognostic information about recovery after vocal fold paralysis.^{38,40} This allows the clinician to determine which patients will not recover vocal fold motion; these patients can then be offered an early definitive procedure.⁴⁰

When the cause of vocal fold paralysis is not obvious, further workup, including imaging, is used rule out other causes (like a compressive mass lesion). Computed tomography or MRI from the skull base to the chest is indicated in order to examine the full course

of the recurrent laryngeal nerve. Blood tests such as rheumatoid factor, Lyme, and antinuclear antibody tests are performed if clinical history suggests they may be warranted.¹²

For patients with a new diagnosis of unilateral vocal fold paralysis, the treatment is based on symptoms and needs and can include: (1) observation for 9–12 months for spontaneous return of vocal fold movement or compensation by the contralateral vocal fold, (2) speech pathology evaluation for voice strengthening or swallow therapy, (3) injection laryngoplasty with a temporary substance to improve the position of the paralyzed vocal fold to facilitate glottic closure and improve voice (while waiting for return of function or compensation), or (4) permanent strategies like injection laryngoplasty of the vocal fold with a long-term substance, medialization laryngoplasty (with or without arytenoid adduction), or laryngeal reinnervation.^{38,41}

Temporary injection laryngoplasty is most commonly performed with either carboxymethylcellulose or hyaluronic acid gels. Long-term injection laryngoplasty is most commonly performed with calcium hydroxyapatite, autologous fat, and polydimethylsiloxane.

See Table 2 for specific characteristics of each of these injectable substances.³⁴

Medialization thyroplasty is considered to be the gold standard surgical treatment for UVFP, and it has been shown in the literature to have good long-term voice outcomes.⁴¹ This procedure involves the creation of a window in the thyroid cartilage and insertion of a permanent implant to medialize the vocal fold.⁴¹ Currently, the two most commonly used implants are Gore-Tex and Silastic.¹³ Arytenoid adduction is an important adjunct to medialization thyroplasty in select patients who have a lack of vocal process contact during phonation, and those with vocal folds at different levels. This operation involves placement of a suture from the muscular process of the arytenoid to the thyroid cartilage. This simulates the action of LCA contraction. The resulting effect is an arytenoid cartilage that is rotated, and a vocal process that is elevated, medialized, and stabilized.⁴²

The goal of laryngeal reinnervation is to maintain vocal fold bulk, stiffness, and tension by providing nerve supply to the thyroarytenoid muscle.⁴¹ The different approaches to reinnervation include: primary anastomosis of the transected recurrent laryngeal

nerve, nerve-muscle pedicle transfer to the thyroarytenoid muscle, direct ansa cervicalis nerve implantation onto the thyroarytenoid muscle, and anastomosis between a donor nerve and the recurrent laryngeal nerve.⁴¹ All of the above reinnervation techniques have demonstrated positive effects on UVFP in terms of acoustic, perceptual, electromyographic, and visual outcomes, but the overall quality of the current literature is poor, and more studies are warranted.⁴³

In bilateral vocal fold paralysis, if airway compromise is severe, a tracheotomy may be required.¹³ In less emergent circumstances, other vocal fold lateralization procedures can be considered. These include partial or total arytenoidectomy, posterior cordotomy, an external lateralization stitch, or botulinum toxin injection. These procedures attempt to increase the glottic aperture without compromising phonation.¹³

Future directions in vocal fold paralysis involve improving diagnosis through machine learning. Two recent studies describe the creation and application of an open-source, machine learning algorithm that is able to track true vocal fold edges from videolaryngoscopy.^{44,45} From videolaryngoscopy, this tool is able to calculate the anterior glottic angle between the true vocal folds—a measurement that was shown to be significantly different between control patients and patients with unilateral vocal fold paralysis. This machine learning tool was able to predict unilateral vocal fold paralysis with a sensitivity of 77% and specificity of 92%. Such technology may result in a future tool for automated diagnosis of vocal fold paralysis based on algorithmic analysis of videolaryngoscopy.

Myasthenia Gravis and Eaton-Lambert Disease

Myasthenia gravis is an autoimmune disorder that affects 14–20/100,000 people. This disease involves auto-antibodies directed against the postsynaptic acetylcholine receptors, which competitively inhibit acetylcholine from binding, and lead to a decrease in the number of receptors at the motor endplate.^{13,46}

Patients complain of weakness that worsens at the end of the day, or with repeated activity. Proximal muscles are affected more than distal muscles, and extraocular muscle weakness is often seen as an early symptom.¹³ It is reported that 6% of patients have dysphonia as their presenting symptom, and 60% develop dysphonia eventually. These patients complain of vocal fatigue, difficulty with voice projection, breathiness, difficulty sustaining high pitches, hypernasality, and difficulty with enunciation.⁴⁶

Laryngoscopy of the pharynx and larynx reveals fatigue with repetitive movements.² Videostroboscopy is an important tool during the physical examination, as it can detect fluctuating variations in vocal fold mobility as well as incomplete glottic closure, which are both seen in myasthenia gravis.⁴⁶

The Tensilon test is the most reliable diagnostic test for Myasthenia gravis. It involves administration of edrophonium, an anticholinesterase. The test is considered positive if improvement in strength occurs in response to the drug. The sensitivity of this test is improved by using laryngeal EMG to directly measure improvement in laryngeal function in response to edrophonium.⁴⁶ Antibodies against the acetylcholine receptor are detectable in the serum of up to 90% of patients with generalized myasthenia, but it is much less sensitive in patients who have laryngeal or ocular symptoms alone.⁴⁶

Early detection of this disorder is of the utmost importance, because most patients have good responses to medical treatment with cholinesterase inhibitors. Other effective drugs include prednisone and cyclophosphamide. Thymectomy is recommended

Table 2: Materials for injection laryngoplasty

| Temporary injectable substances | Description | Length of effect |
|---------------------------------|--|--|
| Carboxymethylcellulose | Organic polymer | 2–3 months |
| Hyaluronic acid gel | Organic polymer | 3–14 months, depending on which particular product |
| Long-term injectable substances | | |
| Calcium hydroxyapatite | Calcium and phosphate | 8–36 months |
| Autologous fat | Usually harvested from abdomen | Highly variable (due to unpredictable resorption rates): 6 months to permanent |
| Polydimethylsiloxane | Silicone particles suspended in a hydrogel | Permanent (does not undergo resorption) |

for most patients, as ten percent of patients have a thymic tumor, and 70% have thymic hyperplasia.²

FUNCTIONAL VOICE DISORDERS

Muscle Tension Dysphonia

Muscle tension dysphonia (MTD) is a pathological condition in which excessive tension of the laryngeal and paralaryngeal musculature leads to a disturbed voice.⁴⁷ Primary MTD involves dysphonia in the absence of concurrent organic vocal fold pathology. Secondary MTD is dysphonia in the presence of an underlying vocal fold pathology, which leads to excessive laryngeal and paralaryngeal activity as compensation.⁴⁷ MTD typically results from hyperfunctional vocal patterns in efforts to meet high vocal demands of daily life. Patients present with altered pitch and voice quality, vocal fatigue, and pain or discomfort. The onset is usually gradual, and the problem is consistent. Patients may report a globus sensation. It has a presentation similar to spasmodic dysphonia, and it can be difficult to distinguish the two disorders.⁴⁸

From a neurology perspective, primary MTD may be categorized as a type of functional dystonia. Functional dystonias are considered to be disorders that straddle the line between neurological and psychiatric. They may resemble other forms of dystonia, but the management of these disorders is very different, as functional dystonias frequently require cognitive behavioral psychotherapy approaches.⁴⁹

Physical examination may reveal tension in the head and shoulders and a raised position of the larynx. Palpation of the larynx will often reveal minimal thyrohyoid space, sensitivity of the thyrohyoid lamina on palpation, and rigidity of the larynx when trying to move it side to side.⁴⁸ The voice may sound breathy, hoarse, rough, strained, or harsh. The patient may have excessively high or low pitch, and reduced vocal range.⁴⁸ A patient with MTD will have a strained voice (and no voice breaks) that does not change significantly during different vocal tasks—unlike the spasmodic dysphonia patient, who will have voice breaks triggered by certain vocal tasks.^{1,37} Patients will have normal or greatly improved voice during reflex activities like coughing, laughing, or yawning, or with distraction such as performing a cognitive task.⁴⁹ Flexible laryngoscopy will reveal sustained lateral or anterior-posterior hyperfunction of the larynx, without spasms. Some patients will have severe hyperfunction of the anterior vocal folds and false vocal folds.⁴⁹

The mainstay of treatment of MTD is voice therapy. These techniques attempt to reduce vocal strain, improve efficiency, and relax the laryngeal muscles. Adjuvant medical treatments can include sensory nerve blocks, if there is a significant pain component to the spasms. Botulinum toxin injections can also be used to weaken and rebalance muscle groups.⁴⁹ In secondary MTD, the primary laryngeal condition must also be addressed.

Paradoxical Vocal Fold Motion

Paradoxical vocal fold motion (PVFM) is a disorder of episodic inappropriate adduction of the vocal folds on inspiration, which manifests as glottic obstruction. Patients will present with a rapid onset of dyspnea (with more difficulty getting air in than out), a choking sensation, and stridor.⁵⁰ These episodes can be precipitated by anxiety, odors, exposure to chemicals, strong emotions, changes to humidity or temperature.^{50,51} Exercise-induced PVFM disorder represents a subset of patients with PVFM who only develop symptoms with exertion. For these patients, symptom onset is rapid,

and resolves within minutes of exercise cessation.⁵¹ PVFM is often mistaken for asthma due to the similar presentation (and increased symptoms after methacholine challenge) but it does not respond to typical asthma medications.^{50,52} In fact, the majority of patients with PVFM have been treated for refractory asthma.⁵³

On flexible laryngoscopy, there may be inappropriate adduction of the vocal folds on inspiration, and/or a more marked adduction on exhalation.^{50,54} If not present at rest, most patients with PVFM will demonstrate inappropriate adduction with provocative maneuvers (Valsalva, strong odors, exercise).⁵⁰ Of note, patients with PVFM do not have any deficit in vocal fold mobility, and so full abduction must be seen at some point during the examination to differentiate PVFM from vocal fold paralysis/paresis.⁵⁰ Flow-volume spirometry can help with the diagnosis, and will show a “flattening” of the inspiratory aspect of the curve, representing an extrathoracic airway obstruction.⁵⁴ Pulmonary function testing will be normal.⁵⁰

The etiology of PVFM is thought to be multifactorial. It is more common among women (81%) and people age 50 or older (60%).⁵⁵ Up to 70% of patients have been reported to have an underlying psychological diagnosis (conversion disorder) as the etiology. This is thought of as primary PVFM. However, it has been shown that 70% of these patients have an associated medical condition like chronic laryngitis, reflux, laryngeal sicca, or asthma that contributes to the PVFM. These conditions must be treated as part of the management of PVFM.⁵³ The mainstay of treatment in patients with primary PVFM consists of speech therapy, specifically laryngeal control therapy (LCT). This therapy emphasizes relaxation techniques, stress reduction, and conscious control over breathing. It focuses on attack prevention as well as rescue techniques. Some of the maneuvers include deep nasal breathing and pursed lip expiration.⁵¹ This has shown to be effective in up to 95% of patients.⁵⁰ Further psychotherapy, including cognitive-behavioral therapy, has also shown to be effective.⁵⁵

There is a subset of PVFM patients (25% in one large prospective series) who have normal psychological testing, and are thought to have secondary PVFM, either due to laryngeal hyperreactivity (sensory abnormality) or a neurologic etiology (motor abnormality).⁵³ Patients with laryngeal hyperreactivity manifest symptoms of PVFM in response to laryngeal irritants, such as chemical exposures, strong scents, GERD, laryngeal candidiasis, laryngeal sicca, and tobacco. Avoidance of irritants, as well as medical management of coexisting irritating conditions is key to treatment.⁵³ However, sometimes an initial inflammatory insult to the larynx can result in a persistent hyperresponsiveness of the larynx (even without exposure to irritants) and a chronic cough. This is known as laryngeal sensory neuropathy.⁵⁰ Neuromodulating agents, such as gabapentin have been used with success in such patients.⁵³ The neurologic etiology of PVFM is known as respiratory-type laryngeal dystonia. The patient will have continual, varying degrees of restricted breathing during the day, but never while sleeping. These patients usually respond dramatically to unilateral vocal fold injections of botulinum toxin A.⁵⁶

CONCLUSION

In conclusion, neurological voice disorders can originate from the central or peripheral nervous system, or be functional in nature. It is important for the otolaryngologist to be able to be familiar with history and physical examination findings that suggest neurological pathology, and also be able to recognize specific findings pertinent to each individual condition. Patients with central nervous system disorders can often have laryngeal complaints as their first presenting

symptom. Therefore, the otolaryngologist can sometimes be the first physician to diagnose such conditions, and plays an important role in coordinating and providing therapies that significantly improve the quality of life for these patients. Current research involving machine learning and functional neuroimaging may greatly improve the diagnosis of many of these disorders in the near future.

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