

Vagal Neuropathy After Upper Respiratory Infection: A Viral Etiology?

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Purpose: To describe a condition that occurs following an upper respiratory illness, which represents injury to various branches of the vagus nerve. Patients with this condition may present with breathy dysphonia, vocal fatigue, effortful phonation, odynophonia, cough, globus, and/or dysphagia, lasting long after resolution of the acute viral illness. The patterns of symptoms and findings in this condition are consistent with the hypothesis that viral infection causes or triggers vagal dysfunction. This so-called postviral vagal neuropathy (PVVN) appears to have similarities with other postviral neuropathic disorders, such as glossopharyngeal neuralgia and Bell's palsy.

Materials and Methods: Five patients were identified with PVVN. Each patient's chart was reviewed, and elements of the history were recorded.

Results: Each of the 5 patients showed different features of PVVN.

Conclusions: Respiratory infection can trigger or cause vocal fold paresis, laryngopharyngeal reflux, and neuropathic pain.

(Am J Otolaryngol 2001;22:251-256. Copyright © 2001 by W.B. Saunders Company)

Cranial nerves are known to be affected by inflammatory neuropathic processes. Bell's palsy, trigeminal neuralgia, and glossopharyngeal neuralgia are examples of such cranial neuropathies. These represent isolated nerve injuries that result in motor and sensory dysfunction (eg, paralysis, pain), depending on the nerves affected. Other cranial neuropathies have also been described.^{1,2}

Of particular interest to the otolaryngologist is the existence of vagal neuropathy. This entity presumably represents the consequence of a disease process affecting the vagus nerve, leading to nerve dysfunction, such as vocal fold paresis or paralysis. The etiology of vagal neuropathy is uncertain, although viral infection has been suggested as a possible cause.³⁻⁵

This article describes 5 cases of vagal neu-

ropathy occurring after a viral upper respiratory infection (URI) (Table 1). In each case, unilateral or bilateral vocal fold paresis, documented by electromyography, and other manifestations of vagal dysfunction were observed after the URI. This report focuses on the spectrum of symptoms that may result from such an injury, which include breathy dysphonia, vocal fatigue, effortful phonation, odynophonia, and symptoms of laryngopharyngeal reflux (LPR). In addition, severe neuropathic-type pain may be associated with postviral vagal neuropathy (PVVN). In each case, the symptoms and findings appear to represent dysfunction of specific vagal branches. The workup and treatment of PVVN are emphasized.

CASE REPORTS

Case 1

A 67-year-old man was referred to our voice center in 1994 with complaints of fever, sore throat, dysphagia, breathy hoarseness, and left-sided otalgia of 1 week's duration. He also complained of aspiration with cough when swallowing liquids. Except for adult-onset diabetes, the patient's past medical history was unremarkable.

Examination showed ruptured vesicles on the left tympanic membrane (but not on the

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Presented as a poster at the annual meeting of the Southern Section of the Triologic Society, St. Petersburg, FL, January 11-13, 2000.

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0196-0709/01/2204-0005\$35.00/0
doi:10.1053/ajot.2001.24823

TABLE 1. Summary of Findings in Reported Patients

Patient No.	Right Vocal Fold Paresis	Left Vocal Fold Paresis	LPR	Neuropathic Pain
1	-	+	-	-
2	+	+	+	+
3	+	+	+	-
4	-	+	+	-
5	+	+	+	-

Abbreviation: LPR, laryngopharyngeal reflux.

ear canal), left trigeminal hypesthesia, decreased left-sided pharyngeal tone, and a left vocal fold paralysis. The patient was aphonic. The paralyzed vocal fold was in a lateral position with a wide-open posterior commissure, and it was severely bowed. Secretions pooled in the hypopharynx and spilled over into the endolarynx.

Laryngeal electromyography (LEMG) showed spontaneous activity in both the left cricothyroid and thyroarytenoid muscles. There was reduced (2+) recruitment in the left cricothyroid muscle and no voluntary motor units (0+ recruitment) in the left thyroarytenoid muscle. Thus, the patient had evidence of a combined left superior and recurrent laryngeal neuropathy, with the left recurrent nerve being severely affected. Magnetic resonance imaging (MRI) of the brain, skull base, neck, and upper chest was normal.

The vocal paralysis did not recover; subsequently, the patient underwent a successful left medialization laryngoplasty and arytenoid adduction procedure. The procedure corrected his aspiration and restored his voice. Years later, he remains asymptomatic.

This patient was referred to us with a diagnosis of herpetic polyneuritis. Although we were never able to prove that diagnosis, the etiology of his problems was almost certainly viral. It is particularly interesting that this patient had involvement of multiple cranial nerves and several branches of the vagus nerve.

Case 2

A 46-year-old man presented in September 1998 with complaints of dysphonia, vocal fatigue, effortful phonation, odynophonia, and neck and jaw pain for almost 10 years. He also complained of symptoms of chronic throat

clearing, dysphagia, globus pharyngeus, and heartburn. He reported that his symptoms began in the winter of 1989 after an acute URI. His past medical history was otherwise unremarkable. In 1989, he had been seen by another laryngologist who had diagnosed bilateral fold paresis and LPR.

At the time of his presentation to our voice center, he was only able to speak for 1 to 2 minutes before experiencing severe burning and lancinating pain. The pain involved his neck and jaw bilaterally, the roof of his mouth, and his right ear. The vocal symptoms and pain were so persistent and severe that the patient, a self-employed businessman, was virtually disabled.

Examination via transnasal fiberoptic laryngoscopy with stroboscopy showed bilateral vocal fold paresis (limited and asymmetric vocal fold mobility with bilateral bowing and decreased tone of the right vocal fold) and LPR. The patient had a 24-hour, double-probe pH study, which confirmed the presence of LPR. LEMG showed bilateral cricothyroid and right thyroarytenoid muscle weakness (ie, neuropathy involving both superior laryngeal nerves and the right recurrent laryngeal nerve). There was no evidence of ongoing neural degeneration or regeneration in any of the muscles tested (ie, this neuropathy had not occurred recently).

Initial treatment of the LPR with proton pump inhibitors improved the patient's LPR symptoms; however, the dysphonia, effortful phonation, vocal fatigue, and pain persisted. A bilateral medialization laryngoplasty was performed, which dramatically improved his voice symptoms; however, he continued to have pain. He was then referred to a neurology pain center. The consultant believed that the symptoms were consistent with neuropathic pain and the patient was started on gabapentin 300 mg 3 times daily. The pain responded to the medication, and the patient has subsequently returned to full-time work with minimal symptoms.

In this case, the onset of voice symptoms, reflux symptoms, and pain all appeared after an acute URI. After effective treatment of the LPR and paresis, it became clear that although the pain was triggered by voice use, it was out of proportion to the laryngeal and voice findings. Other features also indicated that the

pain was neuropathic (eg, its persistence, anatomic distribution, and intensity).

Case 3

A 68-year-old woman presented in January 1999 with complaints of chronic hoarseness and vocal fatigue. Four years before presentation, she suffered an URI, after which she developed her symptoms. Before the illness her voice had been normal, and she had had no other throat complaints. Her past medical history was otherwise unremarkable.

Initial office examination showed evidence of bilateral vocal fold paresis with bowing. In addition, the evidence of LPR included pseudo-sulcus vocalis, ventricular obliteration, and diffuse laryngeal edema and erythema. LEMG confirmed bilateral vocal fold paresis. Double-probe pH testing confirmed LPR. Manometry and barium swallow showed abnormal esophageal pressures and motility. Although the patient responded well to proton pump inhibitors, she required bilateral medialization laryngoplasty to restore her voice.

In this case, the patient experienced the onset of multiple problems after a viral illness. Objective evidence shows the presence of abnormalities in multiple and bilateral branches of the vagus nerve.

Case 4

A 50-year-old woman presented in April 1999 with a 5-month history of hoarseness, vocal fatigue, effortful phonation, odynophonia, cough, dysphagia, globus, and heartburn. All of these symptoms began after a viral URI with severe cough. Persistent chronic cough and dysphagia were her most troubling symptoms. Before her illness, the patient denied ever having any of the above symptoms, and her past medical history was otherwise non-contributory.

Examination showed the typical inflammatory findings of LPR and sluggish mobility and bowing of the left vocal fold. Chest radiographs were normal. The patient underwent LEMG, which confirmed a left thyroarytenoid muscle paresis (ie, left recurrent laryngeal neuropathy). Double-probe pH testing was grossly abnormal, with the finding of severe

esophageal and pharyngeal acid exposure. Esophageal manometry was also abnormal.

In this case, the onset of severe LPR after URI suggests the possibility that viral inflammation may involve vagal branches supplying the esophageal body and its sphincters.

Case 5

A 78-year-old woman was in good health until she became ill with an URI on December 16, 1998. She presented to her local otolaryngologist with fever, coryza, sore throat, and cough. On initial examination, she reportedly had bilateral vesicular eruptions in her throat. Thereafter, she developed severe breathy hoarseness, vocal fatigue, effortful phonation, odynophonia, chronic throat clearing, dysphagia, globus pharyngeus, cough, and heartburn. Most disturbing, however, was the development of severe aspiration and cough.

After her acute symptoms subsided, she had persistent symptoms of vocal fold paresis, LPR, dysphagia, and aspiration. By March 1999, 3 months after the URI, the patient's aspiration was unimproved. Barium swallow showed gross laryngeal and tracheal penetration, and her physician was concerned about the possibility that she might develop aspiration pneumonia. At that time, the physician considered recommending that a feeding tube be placed, and the patient was referred to our center for evaluation.

Our initial examination showed bilateral vocal fold paresis, with the right vocal fold almost paralyzed. Both vocal folds were bowed, and there was pooling of secretions in the hypopharynx and larynx. Severe inflammatory findings of LPR were present; the entire larynx was red and swollen, especially posteriorly.

LEMG showed bilateral vocal fold paresis. Reduced recruitment was seen in both cricothyroid muscles and both thyroarytenoid muscles. Most severely affected was the right thyroarytenoid muscle, which showed ongoing degeneration. The waveform morphology of the left thyroarytenoid muscle showed low-amplitude polyphasic motor units, which indicated ongoing neural regeneration. The LEMG was interpreted as showing bilateral combined superior and recurrent laryngeal

neuropathies with an uncertain prognosis for recovery.

An MRI of the head and skull base, and a computed tomography scan (skull base through superior mediastinum) were normal. Modified barium swallow showed poor pharyngeal phase function with vallecular and piriform sinus stasis, and aspiration. Pharyngeal and upper esophageal sphincter (UES) manometry showed extremely low resting tone of the UES, with extremely poor pharyngeal contractions. The peak pharyngeal contraction amplitudes were 40 mm Hg (normal being 50 to 250 mm Hg).

A right medialization laryngoplasty was performed, and the patient was started on omeprazole 20 mg 2 times daily and gabapentin 100 mg 3 times daily. One week later, the patient's swallowing and voice were improved. Four months later, the patient was seen in follow-up. At that time, she was eating normally, and repeat pharyngeal and UES manometry showed peak pharyngeal contractions in the normal range (150 mm Hg).

This patient appears to have developed bilateral PVVN affecting the entire laryngopharynx. Her aspiration was probably the result of the combination of inadequate pharyngeal propulsion, UES dysfunction, LPR, and glottal incompetence. The glottal closure was improved by a medialization procedure, and pharyngeal function improved as well. Whether the recovery was entirely spontaneous or related in part to the medical treatment remains uncertain.

DISCUSSION

Unilateral or bilateral vocal fold paresis is a relatively common clinical entity, and in most cases, the causes are trauma, tumor, or an iatrogenic cause; however, some are considered idiopathic. Most series report that between 15% and 20% of cases fit into this latter category⁶⁻⁸; although the incidence has been reported as high as 41%.⁹ It also has been postulated that some of these idiopathic cases are related to viral infection. Clerf³ attributed 45 of 293 cases to be secondary to viral infection. Although unproven, the theory that viruses can cause vocal fold weakness or paralysis has been reiterated by several authors.^{5,10,11} A typical history of persistent

hoarseness after the resolution of acute laryngitis is noted in these patients. Physical examination showed evidence of vocal fold paresis or paralysis.

The theory of viral illnesses causing neuropathy is not without precedent. Viral infection has been proposed as the possible etiology in Bell's palsy. Similarly, Guillain-Barre syndrome is widely believed to be caused by viral-induced inflammation. Two mechanisms whereby viral infection may cause neuritis or neuropathy have been proposed: (1) direct infection and inflammation of a nerve, or (2) by the induction of a nonspecific inflammatory response that secondarily involves a nerve.

The thought that viruses may infect nerves directly has been studied in relation to the herpes simplex virus (HSV) (eg, postherpetic neuralgia). Notably, it has been shown that the vagus nerve can be infected by HSV.¹² Gesser et al¹³ were able to show the presence of HSV in vagal sensory ganglia after oral and esophageal inoculation of the virus in mice. They postulated that the virus directly entered nerve endings during the mucosal infection stage and then traveled by axonal transport to the proximal ganglia.

The other potential mechanism (ie, nerve injury as a result of the inflammatory cascade) has been studied as it relates to Guillain-Barre syndrome.¹⁴ Presumably, the proximity of the nerve to the site of infection allows exposure to various inflammatory mediators, such as cytokines. These mediators may cause indiscriminate damage to the nerve through demyelination and axonal loss or may lead to the production of cross-reacting antibodies, which may subsequently damage the nerve. In addition, there is evidence that the acute inflammatory response may also temporarily slow nerve conduction.¹⁵

The neuropathy is not always limited to the initial affected nerve. With Guillain-Barre syndrome, neuropathy may be progressive and may affect multiple nerves. Similarly, in the case of trigeminal neuralgia, although HSV may initially invade a single branch of the nerve, it appears to lead to the development of symptoms in other divisions as well. There is some evidence that Bell's palsy, which is traditionally believed to be a mononeuropathy, is actually a polyneuropathy, because some pa-

tients have symptoms and findings consistent with involvement of other cranial nerves.¹⁶

Each of the 5 patients described in this article prove this point to a different extent. Although all had documented abnormalities on LEMG, 4 patients also had evidence of new onset LPR, 1 patient had neuropathic pain, and 1 had involvement of the trigeminal nerve. This implies that the initial neuropathic process may have spread to other nerves and/or ganglia, causing abnormalities in other systems.

Although the mechanism of postviral onset of LPR is unknown, we postulate that it results from dysfunction of the UES and/or changes in other reflux-protective mechanisms of the esophagus, such as esophageal acid clearance. Indeed, 3 of the 5 patients in this study showed abnormalities on manometry, such as very low resting UES tone and poor esophageal peristalsis (abnormal esophageal motility). Although it is possible that LPR was an unrelated, coexistent disease, all the patients in this series had no LPR symptoms before they developed the URI.

Pain associated with voice use was also a prominent clinical feature in 1 patient. Although patients with vocal fold paresis and paralysis may have odynophonia, in this case the pain was described as severe, sharp, and radiating. This type of pain is different from the discomfort associated with muscle tension and fatigue, and is consistent with the definition of neuropathic pain. In this case, the patient continued to experience neuropathic pain with voice use after his voice had been restored by a medialization procedure.

The likely mechanism for the development of neuropathic pain has been studied in other parts of the body.¹⁷ It is postulated that in response to the injury, the proximal axonal stumps begin to undergo a series of changes, including the expression of transcription and nerve growth factors. If the injury to the nerve is severe, the axons do not have a proper roadmap to guide them. This may lead to rearrangement in organization within peripheral nerves, in which certain fibers may sprout into terminals normally occupied by other types of fibers. This may lead to abnormal functioning of distal muscle bundles, or in the case of injury to afferent nerves, may lead to chronic neuropathic pain.¹⁷ In addition, it has

been shown that neuropathic pain may be caused by the production of tumor necrosis factor-alpha in regions of axonal damage¹⁸ and by the stimulation of sympathetic sprouting.¹⁷

As mentioned, the key element of the disease process in these patients is the finding of vocal fold paresis. Although paresis is often obvious on telescopic examination, the diagnosis in these patients was confirmed by LEMG. This confirmation allows the physician to gather objective proof of neuromuscular weakness, while ruling out cricoarytenoid joint fixation or pericapsular fibrosis as possible causes of hypomobility of the vocal folds. In addition, LEMG may provide prognostic information, which would help determine the therapy offered to the patient.¹⁹

Treatment for patients with PVVN should take into consideration each individual symptom or finding, because each is treated in a different manner. The paresis, LPR, and neuropathic pain (when present) should each be individually addressed. Symptomatic vocal fold paresis or paralysis may be effectively treated with injection augmentation or medialization procedures.²⁰ LPR should be treated with dietary changes and proton pump inhibitors. Neuropathic pain may be more difficult to treat; we have found that gabapentin may be useful in the treatment of such pain. In some cases, referral to a specialized pain clinic may be indicated.

It must be pointed out that confirmatory evidence of a viral etiology of PVVN is not available, because this would require biopsy of the affected nerves. This was not possible, and certainly is not advisable, because it would only worsen the patient's symptoms. Serology is unreliable, and, even if positive, would not prove an etiologic link between the virus and the neuropathy. The authors strongly believe that the history in these patients is clear and represents the best evidence for a viral etiology.

CONCLUSIONS

PVVN appears to have identifiable clinical components. Patients presenting with the sudden onset of voice problems, LPR, and/or painful phonation may represent a group of patients who have sustained postviral injuries

to one or both vagus nerves, with incomplete or aberrant regeneration. Patients with PVVN require therapy that addresses the following sequelae: (1) vocal fold paresis, (2) LPR, (3) dysphagia, and (4) neuropathic pain.

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