

# Evidence for Sensory Neuropathy and Pharmacologic Management

Scott M. Greene, C. Blake Simpson, MD\*

## KEYWORDS

- Postviral vagal neuropathy • Chronic cough • Irritable larynx
- Laryngeal sensory neuropathy

Postnasal drip, cough-variant asthma, and gastroesophageal reflux disease are the cause of chronic cough in 86% of adult patients. This percentage increases to over 99% when evaluating immunocompetent nonsmokers with normal chest radiograph findings and no history of angiotensin-converting enzyme-inhibitor use.<sup>1</sup> Despite this, a significant number of patients continue to have unexplained cough after an exhaustive workup and failed empiric treatments. Recently, a body of literature has emerged supporting a sensory or motor neuropathy responsible for many of the previously refractory cases of chronic cough. First introduced by Morrison and colleagues<sup>2</sup> in 1999, the idea of the irritable larynx has been redefined throughout the years, holding various titles for the same suspected cause: postviral vagal neuropathy (PVVN), sensory neuropathic cough and laryngeal sensory neuropathy (LSN). Many recent studies not only identify the at-risk population, but the common presenting symptoms, potential pathophysiology behind vagal neuropathy, and several promising medical interventions. The purpose of this article is to emphasize that postviral vagal neuropathy may be a distinct and treatable cause of chronic idiopathic cough while reviewing common clinical presentations and potential treatments. See the article by Irwin elsewhere in this issue for another perspective of the role of sensory neuropathy in the unexplained chronic cough.

The idea of postviral neuropathies has been well studied in various other disease processes, such as Bell palsy, Guillain-Barré syndrome, and postherpetic neuralgias. Of interest to otolaryngologists is the small, but significant, subset of patients with treatment-resistant chronic cough that have been identified with clinical or objective evidence suggesting an underlying vagal neuropathy. PVVN is a condition of vagal nerve injury or dysfunction following an antecedent viral illness. Vagal neuropathy

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The Department of Otolaryngology—Head and Neck Surgery, The University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78229, USA

\* Corresponding author.

E-mail address: [simpsonc@uthscsa.edu](mailto:simpsonc@uthscsa.edu) (C.B. Simpson).

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may affect the motor branches of the vagus nerve, resulting in vocal fold paralysis or paresis, or it may affect the sensory branches, inducing a throat tickle, globus sensation, excessive throat mucous, odynophonia, chronic cough, or laryngospasm. These symptoms may be aggravated by sensory stimuli such as laughing, prolonged phonation, and noxious stimuli, and has been described being elicited clinically by palpation at the cricoid level.<sup>1,3,4</sup>

In 2001, Amin and Koufman<sup>5</sup> first described the association of neuropathic cough and previous upper respiratory tract infection. They described a case report of five patients presenting over 5 years with similar symptoms consisting of chronic cough, globus, dysphagia, vocal fatigue, and effortful phonation, persisting long after resolution of their acute viral illness. Subsequent investigation through videostroboscopy and laryngeal electromyography (LEMG) revealed varied presentations: (1) vocal fold paresis, (2) neuropathy-induced laryngopharyngeal reflux disease, (3) dysphagia, and (4) neuropathic pain.

Two potential mechanisms by which viral infection may cause nerve injury have been described: (1) direct infection and inflammation of the nerve or (2) induction of a nonspecific inflammatory response that secondarily involves a nerve.<sup>5</sup> In either situation, viral involvement lowers the threshold of both the efferent and afferent arms, sensitizing the nerves to previously ignored stimuli. In 2009, Rees and colleagues<sup>2</sup> made clinical distinction between the motor and sensory components of vagal neuropathy. In a prospective cross-sectional series of 44 patients presenting with persistent cough, throat clearing, dysphonia, and vocal fatigue following a previous upper respiratory infection, 45% with motor and sensory neuronal involvement, 41% with isolated sensory nerve involvement, and 14% with isolated motor nerve involvement. Rees and colleagues<sup>3</sup> concluded “cough, throat clearing, and globus are considered primarily sensory symptoms while loss of voice and vocal fatigue are considered primarily motor symptoms,” which all may be attributed to vagal nerve dysfunction. Unfortunately, it may never be possible to definitely establish this causal relationship, as vagal nerve biopsy remains the only means of definitive diagnosis. As more case studies and prospective analysis emerge, greater support appears for a clinical diagnosis of PVVN.

## CLINICAL EVALUATION

In diagnosing PVVN, the clinician must maintain a high level of suspicion. As with all clinical diagnoses, a thorough history is essential in providing clues to this potential cause. Many algorithms, such as the anatomic diagnostic protocol, are available to help guide the clinician in assessing the patient.<sup>2</sup> Once the most common causes of chronic cough have been ruled out, further inquiry into potential viral illness surrounding the initial presentation of symptoms should be investigated. PVVN is usually associated with an acute onset of cough that persists long after the resolution of the concomitant viral symptoms. The majority of patients presenting with PVVN have previously been misdiagnosed. An average of 83 weeks from onset to diagnosis has been cited; therefore, patients may show significant frustration in the persistence of their symptoms.<sup>3</sup> Many of these patients have been treated with multiple rounds of antibiotics, proton pump inhibitors, and antihistamines well before presenting to the otolaryngologist. Although not all the literature agrees, the majority of recent studies suggest PVVN is more common in women, occurring most often in the fifth and sixth decade of life.<sup>2</sup> The vagus, supplying both the superior laryngeal nerve (SLN) and recurrent laryngeal nerve (RLN), allows for a multitude of presentations, many of which can be classified according to their primary symptoms: motor, sensory, or mixed motor-sensory dysfunction.

### ***Motor Symptoms***

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Acute onset of “breathy dysphonia, vocal fatigue, effortful phonation, odynophagia, cough, globus, or dysphagia lasting long after the resolution of the acute viral illness” may represent the initial presentation of PVVN involving the efferent branches.<sup>3</sup> Whereas routine nasolaryngoscopy can appear both anatomically and functionally normal, videostroboscopy and LEMG may provide the only objective evidence of RLN or SLN dysfunction.<sup>4</sup> With primary motor branch involvement, stroboscopy may reveal reduced diadochokinesis of the vocal folds or axis deviation of the glottis. LEMG may also reveal the presence of polyphasic units, rapid-firing units, and reduced recruitment in the cricothyroid and thyroarytenoid muscles, providing further objective evidence for RLN or SLN paresis.<sup>4</sup>

### ***Sensory Symptoms***

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When the sensory branches are mainly affected, the patient may not necessarily present with sharp pain or the classic burning ache associated with many of the other neuropathies, but may instead describe a tickle, dry patch, or globus most commonly found at the level of the cricoid. This sensation often precipitates a 20- to 30-second coughing spell.<sup>3</sup> Bastian and colleagues<sup>5</sup> describe this phenomenon as a “bogus tickle that leads to uncontrollable coughing.” Excessive throat clearing is another well-recognized symptom within the literature. Tussive-like spells and laryngospasm have been reported, usually following exposure to specific aromatics such as perfume or household cleaning agents.

### ***Viral-induced Laryngopharyngeal Reflux***

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Several studies have recognized symptoms consistent with laryngopharyngeal reflux (LPR) beginning with the onset of a previous viral illness.<sup>6,7,8</sup> Rees and colleagues<sup>7</sup> propose postviral LPR may be secondary to altered esophageal peristalsis and esophageal clearing or alternately an increase in symptoms through altered sensation in the throat due in part to preexisting reflux.

## **TREATMENT OPTIONS**

Whereas several studies have provided objective evidence of vocal fold paresis following a previous viral illness, the majority of cases have been diagnosed through symptomatic presentation and taking a thorough history. At present, there is no standard of care for patients with suspected PVVN, but it has been recently suggested that treatment for PVVN be patient-specific and, therefore, tailored to individual presenting symptoms.<sup>7</sup> The patient’s specific triggers that induce cough should be identified and patients should be educated on avoidance of suspected triggers. Vocal fold paralysis or paresis may be referred to a speech pathologist for vocal therapy and these patients should be counseled concerning their various surgical options, including medialization laryngoplasty and injection augmentation of the vocal folds.

## **PHARMACEUTICALS FOR TREATMENT OF PVVN**

### ***Pregabalin***

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#### ***Method of action***

Pregabalin is a  $\gamma$ -aminobutyric acid (GABA) analog that strongly binds to the alpha(2)-delta site in the central nervous system tissues. Binding to the alpha(2)-delta subunit may be involved in pregabalin’s effects on neuropathic pain. Pregabalin reduces the calcium-dependent release of several neurotransmitters, including glutamate, noradrenaline, and substance P, possibly by modulation of calcium channel function;

however, the exact mechanism of action is unknown. Currently, pregabalin has Food and Drug Administration (FDA) approval in the treatment of neuropathic pain, including postherpetic neuralgia, diabetic peripheral neuropathy, and fibromyalgia. Pregabalin is renally excreted unchanged in the urine, with a half-life of 6.3 hours.<sup>9</sup>

### **Advantages**

Pregabalin shares many of the favorable qualities of gabapentin, including its rapid titration, rapid onset of activity, and minimal drug interactions. Advantages over gabapentin are greater absorption, increased bioavailability, and less dosing frequency.<sup>10</sup> Studies have shown equivalent efficacy to gabapentin at much lower doses of pregabalin in the treatment of neuropathic pain, therefore many believe pregabalin is likely to be associated with fewer dose-related adverse events.<sup>11,12</sup>

### **Disadvantages**

Pregabalin is a pregnancy class C drug. Somnolence is the most common side effect demonstrated in studies, often potentiating the side effects of other sedating drugs. Other common side effects are dry mouth, peripheral edema, weight gain, and blurred vision and dizziness.

### **Dosing schedule**

Patients were started at 75 mg twice a day and were then raised over 4 weeks to 150 mg twice a day if needed for symptomatic relief. In one patient, 150 mg three times a day was needed.

### **Evidence**

Charts were reviewed for 12 consecutive patients prescribed pregabalin for symptoms of LSN. Outcomes were analyzed by reviewing pre- and posttreatment questionnaires.<sup>10</sup>

## **Gabapentin**

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### **Method of action**

Gabapentin does not interact with GABA receptors, is not metabolized to a GABA agonist or to GABA, and does not inhibit GABA uptake or degradation. The mechanism of action is unknown. Gabapentin does, however, prevent pain-related behavior in response to a normally innocuous stimulus and exaggerated response to painful stimuli in animal models. Gabapentin is FDA approved in the treatment of seizure and postherpetic neuralgia, but has secured a long list of off-label uses within the clinical setting. Gabapentin is not metabolized and is entirely excreted renally unchanged with a half-life of 5 to 7 hours.<sup>13</sup>

### **Advantages**

Gabapentin is normally well tolerated and has relatively few drug interactions. It does not change levels of other seizure medications. It is cleared by the kidney, so it does not interact at the level of the liver.

### **Disadvantages**

Gabapentin is slowly absorbed (peak: 3 to 4 hours postdose) and, more importantly, plasma concentrations have been found to have a nonlinear relationship to increasing doses. Other disadvantages of gabapentin include a short half-life that requires a three times daily regimen.

### **Dosing schedule**

Patients were instructed to begin dosing at 100 mg/d and to increase dosage up to 900 mg/d in divided doses over a 4-week period.

**Evidence**

Initially cited in a case report of five patients with suspected PVVN, the empiric use of gabapentin for intractable chronic cough has been accepted as a reasonable first-line treatment in many United States clinics.<sup>4</sup>

**Amitriptyline**

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**Method of action**

Amitriptyline hydrochloride is a tricyclic antidepressant that also exhibits a sedative property. It promotes neuronal activity by blocking the membrane pump mechanism, which is responsible for the absorption of serotonin and norepinephrine in serotonergic and adrenergic neurons. Amitriptyline is FDA approved for the treatment of depression, but has been used off-label for many years for the treatment of headache, irritable bowel syndrome, pain syndromes, and postherpetic neuralgia. Amitriptyline is hepatically metabolized via P450 CYP2D6 and is renally excreted almost entirely in metabolite form. Amitriptyline has a half-life of 10 to 26 hours.<sup>14</sup>

**Advantages**

Amitriptyline is usually well tolerated and is considered to have a less adverse effect profile compared to many of the other tricyclic antidepressants. Amitriptyline is also dosed once daily.

**Disadvantages**

Heavy hepatic metabolism with the major metabolite, nortriptyline, excreted through the urine and feces.

**Dosing schedule**

Patients were treated with 10 mg everyday.

**Evidence**

A prospective randomized controlled study comparing the effectiveness of amitriptyline versus codeine-guaifenesin for select cases of suspected PVVN found that the majority of patients in the amitriptyline arm achieved complete response as defined by the investigators.<sup>3</sup> See the article by Irwin elsewhere in this issue that provides a perspective on the potential limitations of this study.

In a cohort of 12 consecutive patients with suspected PVVN, all patients had at least 40% reduction of self-reported symptoms, with most describing between 75% to 100% short-term relief.<sup>6</sup>

**SUMMARY**

PVNN, while a relatively new clinical diagnosis, has been observed and well described within the literature in recent years. As additional studies are reported, a growing body of anecdotal and empirical evidence suggests PVVN may be a distinct and treatable cause of idiopathic chronic cough. PVVN varies in presentation, but is most commonly seen in adult women with symptoms persisting long after resolution of an acute viral illness. Symptoms are classified according to the vagal branch most affected, either motor, sensory, or both. LPR has also been reported in association with suspected onset of viral neuropathy. At present, there is no standard of care for treating PVVN. This article highlights the efficacy, side effect profiles, and supporting evidence of the currently recommended pharmacological interventions. Future studies are needed to provide greater objective evidence as well as the potential pathophysiologic mechanism behind this elusive disease process.

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