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Globus Pharyngeus: Effectiveness of Treatment With Proton Pump Inhibitors and Gabapentin

Suzanne Kirch, DO; Ryan Gegg, DO; Michael M. Johns, MD; Adam D. Rubin, MD

Objectives: This study was performed to investigate the effectiveness of treatment of globus pharyngeus with proton pump inhibitors, gabapentin, or both.

Methods: The subjects all presented with globus pharyngeus during the years 2006 to 2011. The inclusion criteria included a chief (primary) complaint of globus pharyngeus; a trial of proton pump inhibitor therapy for at least 2 months and/or a trial of gabapentin for at least 2 weeks; and at least 1 follow-up visit. We reviewed 331 charts; 87 patients met the criteria. The response to treatment was graded as none, partial, or complete.

Results: Seventy-seven percent of all patients had improvement. Sixty-seven percent of patients had a partial or complete response from aggressive reflux management. Sixty-six percent of patients who had a trial of gabapentin reported improvement. Eight of 14 patients who did not improve with aggressive reflux management improved with gabapentin.

Conclusions: A majority of patients with globus pharyngeus can be helped by treating reflux or neuralgia. A trial of gabapentin should be considered for patients who do not respond or only partially respond to reflux management.

Key Words: gabapentin, globus pharyngeus, neuropathy, proton pump inhibitor, reflux, throat pain.

INTRODUCTION

Globus pharyngeus is defined as the sensation of a lump or foreign body in the throat. The origin of the term globus comes from the Latin word for ball. It is reported that globus pharyngeus accounts for approximately 4% of new otolaryngology referrals.[1,2] First noted by Hippocrates over 2,000 years ago, globus pharyngeus has many proposed causes. In the 1700s, the term globus hystericus was coined, including the Greek root *hysteria* because of the incorrect assessment that the globus sensation was linked to uterine dysfunction.[3] The first link between globus sensation and gastroesophageal reflux disease was made in the late 1960s, by Malcomson,[4] who noted an association between globus pharyngeus and gastroesophageal reflux on barium studies. Koufman et al[5] coined the term laryngopharyngeal reflux to describe symptoms produced by gastric acid in the larynx and hypopharynx. Today, laryngopharyngeal reflux is widely believed to be one of the most common etiologic factors in globus pharyngeus, despite conflicting reports.[6,7] Other proposed pathophysiologic mechanisms include cricopharyngeal spasm,[7] thyroid enlargement,[8] lingual tonsil hypertrophy,[9] and cervical osteophytes.[7]

Not surprisingly, the exact cause of globus pharyngeus remains unknown, and there is a lack of consensus on how to investigate and treat this common complaint.[10] Often, patients are most concerned about ruling out a malignancy. Efforts to do this may include flexible laryngoscopy, esophagoscopy, rigid endoscopy, and imaging studies. Harar et al[11] suggested that flexible laryngoscopy is sufficient; however, other studies have suggested that esophageal disease can result in symptoms in the throat.[12,13]

It is now recognized that neuralgia can cause cough and other head and neck symptoms.[14-16] Our current practice is to offer a trial of gabapentin to patients with globus pharyngeus in whom aggressive management with proton pump inhibitors (PPIs) fails or in whom other neurologic findings or history suggest a possible neurogenic cause. The main purpose of this study was to review the effectiveness of this strategy in patients presenting with a complaint of globus pharyngeus.

METHODS

Institutional Review Board approval was obtained from St John Providence Hospital and Medical Centers. A retrospective review was performed of consecutive patients who presented with the chief complaint of globus pharyngeus from January 2006

From Lakeshore Professional Voice Center, Lakeshore Ear, Nose and Throat Center, St Clair Shores, Michigan (Kirch, Gegg, Rubin), and Emory Voice Center, Department of Otolaryngology–Head and Neck Surgery, Emory University School of Medicine, Atlanta, Georgia (Johns). Dr Kirch is now at the Department of Otolaryngology, Knox Community Hospital, Mt Vernon, Ohio.

Correspondence: Adam D. Rubin, MD, Lakeshore Ear, Nose and Throat Center, 21000 E 12 Mile Rd, Ste 111, St Clair Shores, MI 48081.

through January 2011. Patients who present with globus pharyngeus and have a history or laryngeal findings suggestive of reflux are given a trial of twice-daily PPIs timed appropriately before meals and are seen in follow-up 2 to 3 months later. Patients who are compliant and fail to respond to PPI therapy are offered a trial of gabapentin (300 mg 3 times daily) and are seen in follow-up 2 to 3 weeks later. Patients who have a history that suggests a neurogenic cause of the globus pharyngeus are started on gabapentin without a PPI trial and are seen in follow-up 2 to 3 weeks later.

The senior author (A.D.R.) always uses the ICD 9 code 784.1 (throat pain) for patients with globus pharyngeus. Subjects were identified by searching for this diagnostic code through the practice billing system. Three hundred thirty-one patients were identified, and their charts were reviewed. To be included in the study, patients had to have a chief (primary) complaint of globus pharyngeus, have tried at least 2 months of PPI therapy and/or 2 weeks of gabapentin therapy, and have at least 1 follow-up appointment. A total of 87 charts met this criteria and were reviewed. The following data were collected: patient age, sex, duration of symptoms, duration of treatment, and response to treatment. The response to treatment was graded as no response, partial response, or complete response. A complete response meant resolution of symptoms, whereas a partial response signified improvement but persistence of symptoms.

RESULTS

A total of 87 patients (32 male, 55 female) met the above criteria (average age, 52 years; range, 18 to 84 years). The average duration of symptoms was 1.26 years (range, 4 days to more than 5 years). Overall, 77% of patients had improvement with treatment using PPIs, gabapentin, or both.

Proton Pump Inhibitor Therapy. Of the 87 patients, 94% (82 of 87) had a trial of a PPI, as described below. Of the 5 patients who were not prescribed PPI therapy, 2 reported prior intolerance to PPIs. The remaining 3 patients were started initially on gabapentin because the senior author suspected that neuralgia was the most likely cause of the globus pharyngeus. One of these patients developed globus pharyngeus after a stroke, and the other 2 developed globus pharyngeus soon after cervical spine surgery. Eighty percent of patients (66 of 82) tried PPI therapy for 2 months or longer, and 49% were treated for 3 months or longer. The average duration of PPI therapy was approximately 4 months. The majority — 94% (77 of 82) — were on twice-daily dosing. Omeprazole was prescribed most frequently (72 of 82; 20 to 40 mg per dose). Overall, 67% (55 of 82) responded to PPI therapy; of these responders, a partial response was seen in 76% (42 of 55) and a complete response in 23% (13 of 55).

Gabapentin Therapy. Thirty-five patients had a trial of gabapentin. Four were lost to follow-up. Of the 31 remaining patients, 21 (68%) responded to gabapentin. (One patient was started on pregabalin [Lyrica] because of poor tolerance of gabapentin and was included in the gabapentin trial group.) Ten patients (32%) had no response.

Of the 31 patients evaluated, 26 had initially tried PPI therapy. Fourteen of these 26 patients had no response to PPI management. Of these 14 patients, 8 (57%) had a response to neuromodulator therapy (5 complete responses and 3 partial responses). Of the remaining 12 patients who responded partially to PPI therapy before their gabapentin trial, 9 had additional improvement with gabapentin (6 complete responses and 3 partial responses). The average length of time patients were treated with PPI therapy before their trial of gabapentin was 5.5 months (range, 6 weeks to 2 years). Four of the 5 patients who never had PPI therapy improved on gabapentin.

DISCUSSION

Our results support the theory of laryngopharyngeal reflux as a leading cause of globus sensation, as more than two thirds of our patients responded to PPI therapy. However, partial responders account for the majority (76%) of responders. A partial response or a lack of response to PPI therapy may be explained by underdosing, an insufficient duration of treatment, incomplete compliance, an inaccurate diagnosis, or a multifactorial cause. The response to gabapentin in this study suggests a potential neurogenic cause for globus pharyngeus. This is not surprising to anyone who has sprayed topical anesthetic into the oropharynx or anesthetized the larynx. Patients will often complain of a globus sensation after application of anesthesia. The two causes are not contradictory, as reflux may irritate nerve endings in the esophagus, pharynx, or larynx. This neurogenic causation could explain why the addition of gabapentin for partial responders may further alleviate symptoms.

In the senior author's experience, many patients who present with globus pharyngeus are concerned they have a serious problem, such as a malignancy. Ruling out a major health issue is always of utmost importance. Although most reports state that globus pharyngeus is rarely caused by a serious medical problem,[17,18] malignancy has been reported as the primary cause of globus sensation.[19] With the improved capability of in-office laryngeal and hypopharyngeal imaging and the advent of transnasal

esophagoscopy, the otolaryngologist can perform a thorough endoscopic evaluation in the office setting and offer the patient reassurance. An improvement of symptoms with medications will likely allay patient fears, and perhaps obviate the need for additional testing. Of course, one might argue that the use of gabapentin may mask symptoms of an underlying malignancy. Clinical acumen is still required.

Gabapentin was approved by the US Food and Drug Administration in 1994 as an adjunctive medication to control partial seizures. Its mechanism of action remains unknown. In 2002, it gained approval for treatment of post-herpetic neuralgia.[20] It is frequently used off-label for other sources of neuropathic pain, migraine headaches, and nystagmus.[21-23] It may cause somnolence and dizziness, but in general is well tolerated. Its serious side effects include leukopenia, thrombocytopenia, ataxia, and withdrawal seizures. Routine monitoring of laboratory levels has been shown to be unnecessary. Discontinuation of the medication should be done gradually over 1 week to prevent withdrawal seizures.[20] Its usefulness for neurogenic cough and hyperirritable larynx syndrome has been reported.[14,16] Other medications may be useful for globus pharyngeus and hyperirritable larynx syndrome, including amitriptyline, nortriptyline, and pregabalin. Amitriptyline and nortriptyline are tricyclic antidepressants. In comparison to gabapentin and pregabalin, they have the advantage of being dosed only once a day. However, they must be used with caution if the patient is taking other antidepressants, to avoid adverse drug interactions.

Laryngeal symptoms from neuralgia have been described previously. Morrison et al[14] described the "irritable larynx syndrome" in 1999, hypothesizing that neural plastic change to brain stem laryngeal control networks can be caused by repetitive stimuli such as acid reflux. Norris and Schweinfurth[15] demonstrated the use of neuromodulator therapy in treating symptoms of cough and laryngospasm after recurrent laryngeal nerve injury. Amin and Koufman[24] theorized that symptoms such as globus pharyngeus and throat pain following an upper respiratory tract infection may be caused by virus-induced injury to the recurrent laryngeal nerve.

Sixty-seven of the 87 patients in this study (77%) responded to medical management consisting of PPIs, gabapentin, or both. Eight of the 14 patients who did not respond to PPI management responded to gabapentin (57%). Nine of the 12 patients who responded partially to PPI management had additional improvement with gabapentin.

Recent studies have suggested some potential negative sequelae to long-term, high-dose PPI management.[25] Recognizing that gabapentin may provide symptom relief of globus pharyngeus may help prevent the use of excessively high doses of PPIs. In addition, the development of transnasal esophagoscopy has made esophageal evaluation and screening for Barrett's esophagus safer and less expensive.[26] In the absence of significant findings of laryngeal or esophageal reflux, long-term treatment with PPIs may be considered less necessary, particularly if symptoms are controlled well with neuromodulator therapy.

Twenty patients in our study did not respond to PPI or neuromodulator treatment. Atypical causes of globus pharyngeus may account for their lack of response, including upper esophageal dysfunction, thyroiditis, malignancy, anxiety, PPI resistance, and muscle tension dysphonia. Additional evaluation for nonresponders could include imaging studies such as computed tomographic scanning or barium swallow study, manometry, thyroid studies, allergy evaluation, or an empiric trial of esophageal dilation or chemical myotomy of the upper esophageal sphincter with botulinum toxin injection. Voice therapy may be useful in some cases.[18,27]

As with all retrospective analyses, there are significant limitations to this study. One of the biggest is that there is no control group. A placebo effect is possible. Of course, for the patients who did not respond to PPI but subsequently did respond to gabapentin, one might argue that a placebo effect is unlikely. Furthermore, there was no use of validated outcome measures (eg, reflux symptom index, reflux finding score) or other objective tests to prove neuralgia or reflux (eg, pH probe testing, laryngeal electromyography, sensory testing). However, we believe that these tests are all controversial, as well as creating additional discomfort and expense for the patient, and that an empiric trial in addition to in-office examination to rule out more sinister occult processes is sufficient in the evaluation and management of patients complaining of globus pharyngeus. One might argue that nonresponders to PPIs might not have been given enough time or a high-enough dose of medication. More objective studies, such as pH probe or impedance testing, might have been useful in this context. There are also some problems with data collection. Some patients could not be included because of inadequate follow-up, and inclusion of these patients might have altered the results.

Last, one might be concerned that gabapentin might mask a malignancy or another process such as reflux. Appropriate in-office endoscopy and follow-up should always be performed. However, an empiric trial of medical treatment for globus pharyngeus and in-office endoscopy may obviate the need for

additional testing or more invasive procedures. A future prospective, placebo-controlled study certainly would be useful. However, this study suggests that a majority of patients presenting with globus pharyngeus can have symptom improvement with reflux and/or neuromodulator therapy.

CONCLUSIONS

Globus sensation can be a source of angst for many patients who present to the otolaryngologist. Although aggressive reflux management helps in a majority of cases, some patients do not respond. A trial of neuromodulator therapy may be useful in patients who do not respond or only partially respond to reflux management. Successful medical treatment of globus pharyngeus in addition to in-office endoscopy may avoid further testing or invasive procedures.

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