Distinct Clinical Physiologic Phenotypes of Patients with Laryngeal Symptoms Referred for Reflux Evaluation.
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Discussion Summary

Abstract

One third of adults experience laryngeal symptoms such as throat clearing and chronic cough and 50-80% of adults seeking care of these symptoms are told that laryngopharyngeal reflux (LPR) is the etiology. LPR results from retrograde flow of gastroduodenal contents to the larynx and pharynx; however, treatment of presumed LPR remains challenging with limited evidence-based guidance. This article summarizes the @GIJournal Twitter discussion of Yadlapati et al, “Distinct Clinical Physiologic Phenotypes of Patients with Laryngeal Symptoms Referred for Reflux Evaluation,” originally published in Clinical Gastroenterology and Hepatology. In this study of 302 patients with chronic laryngeal symptoms referred for reflux evaluation, five distinct phenotypic groups were described, and reflux was only present in two of the proposed phenotypes. LPR and GERD with hiatal hernia (group A); mild LPR/GERD (group B); no LPR/no GERD (group C); reflex cough (group D); and mixed/possible obstructive esophagogastric junction (EGJ) (group E). Phenotypic differences can inform targeted clinical trials design and improve outcomes.
Introduction:

Laryngopharyngeal reflux (LPR) is the result of reflux of gastroduodenal contents back to pharynx and larynx and can present with a constellation of heterogeneous symptoms [1]. The refluxed content usually causes laryngeal inflammation causing upper airways symptoms of hoarseness, throat clearing, or chronic cough [2-3]. The lack of gold standard for diagnosis of LPR and the absence of pathologic reflux makes the diagnosis and potential options for treatment challenging. In contrast to gastroesophageal reflux, many patients with presumed LPR do not benefit symptomatically from proton-pump inhibitor therapies (PPI) or anti-reflux surgery [4-7].

The current study by Yadlapati et al. (2022) [8] analyzed a total of 302 adult patients with chronic laryngeal symptoms between January 2018 to October 2020. Discriminant analysis of principal components (DAPC) was applied to 12 clinical and 11 physiologic variables collected in stable condition to derive phenotypic groups, and successfully identified 5 groups, with significant differences across symptoms, hiatal hernia size, and number of reflux events. Group A had the greatest hiatal hernia size and number of reflux events, with frequent cough, laryngeal symptoms, heartburn, and regurgitation. Group B had the highest body mass index and salivary pepsin, with frequent cough, laryngeal symptoms, globus, heartburn, and regurgitation. Group C frequently reported laryngeal symptoms and had the fewest esophageal symptoms and reflux events. Group D commonly reported cough and heartburn. Group E was distinguished by highest integrated relaxation pressure. In conclusion, this study identified five distinct clinical and physiologic phenotypes of patients with laryngeal symptoms referred for reflux evaluation with the aim of helping identify patients who are more likely to have reflux as underlying cause of laryngeal symptoms (groups A, B, and D) and may help guide selecting candidates for upfront testing and reflux therapy.
Discussion:
This article summarizes the August 14th, 2022 @GIJournal Twitter discussion of this multicenter prospective study published in @AGA_CGH by Yadlapati et al. on characterizing clinical physiologic phenotypes in patients with laryngeal symptoms. This includes a lightly edited transcript of discussant and audience questions with answers from a content expert (WC), moderators (ZM), and trainee discussant (YL).

Q1. How do you approach a patient with LPR, do you start with a PPI trial, or do you start with other testing?
WC: Previously, empiric PPI trial was recommended as first line approach to LPR symptoms. However, as shown in our and other studies, many pts with laryngeal symptoms do not have LPR as etiology. Therefore, I have moved away from empiric treatment and towards earlier evaluations. Several large randomized controlled trials found no significant benefit for PPI over placebo for laryngeal symptoms – likely due to heterogeneous causes. Clinical phenotyping and upfront reflux testing may select patients with LPR/GERD who more likely respond to anti-reflux therapy [5].
ZM: Anyone still using PPI trial first, if so why do you do it?
@SalihSamo: If patient has not been on PPI previously, I let them know my preference is to do objective reflux testing but also another option is to try PPI (I let them know the limitation to that). Patients mostly opt for objective reflect testing in my practice.
@ellebelle18: Acutely little to no harm. If they also have some reflux symptoms that improve as many do then reasonable. Longer than 6 months I try weaning all after lifestyle changes and get testing if agreeable in that timeframe.
@JVG_GIMD: I personally go with esomeprazole 40mg bid (go big or go home) unless symptoms very mild or very low likelihood. Also a 2-3 months wait here for EMS/pH-impedance. 1/3 don't want it when I explain the procedure to them. Seeing more ENTs/PCPs referring for EMS/pH-imp directly. Some patients are more convinced by failure of maximum acid suppression for 4-6 weeks than by testing. I don't know if it affects placebo response, but I often say, "I don't think it's going to work but little harm in trying".
@SultanMamoodMD: Can we skip EGD for groups A and B?
WC: EGD may be a part of evaluating for groups A and B - for example presence of large hiatal hernia, high-grade esophagitis, and long-segment Barrett's may also point towards groups A and B phenotypes.
@Laura_targownik: In Canada, it takes 12-18 months to get esophageal pH testing, and therefore it is hard to integrate into clinical decision making for GERD. Can we make a monetary argument for expanding service?
WC: I think you can make that argument - prior cost study showed decreased cost with upfront reflux testing than empiric PPI in these patients. If testing delay is 12-18 months (i.e. prolonged PPI for this duration), the cost saved with upfront testing is likely even more pronounced [9].
@Laura_targownik: What is the evidence that LPR is due to pharyngeal acid exposure?
Some patients with LPR will have abnormal esophageal acid exposure, which predicts response to treatment, but do these patients have pharyngeal acid exposure?
WC: There’s evidence supporting both. Reflux may cause LPR symptoms due to refluxate reaching pharynx (from impedance studies with hypopharyngeal sensors and pepsin studies) (likely group A in our study). Distal reflux may also lead to bronchospasm via reflex pathway causing symptoms (group D)
Q2. Do all patients with LPR need an EGD and a manometry? If not all of them, then how do you select who needs it?
WC: EGD is not sensitive/specific enough to diagnose LPR, but it may help shed lights on potential etiology. Gastric inlet patch is an ectopic gastric mucosa in the proximal esophagus that may secret acid, pepsin etc., thereby potentially contributing to pharyngeal reflux. Conclusive evidence of pathologic reflux can also be found on EGD that may point to a more likely reflux etiology of laryngeal symptoms (LA C+D esophagitis, large hiatal hernia), these would increase the likelihood of group A (LPR/GERD+HH) or B (LPR/mild GERD) phenotypes. Prior studies have previously associated gastric inlet patch (GIP) with increased LPR symptoms. Small case series of eradicating GIP with radiofrequency ablation led to decreased in laryngeal symptoms [10].
@SultanMahmoodMD: I was still not sure about the role of inlet patch in LPR. In your practice do you ablate them?

WC: I don't routinely ablate them. I'd only consider if patient has no other etiologies found for laryngeal symptoms and there is evidence of pharyngeal reflux exposure (e.g., on reflux testing or salivary pepsin). Even then, I'd make it clear to patient the small amount of evidence available.

WC: Esophageal dysmotility may be associated with LPR symptoms (secondary to reflux versus worsens reflux versus no causative relations). Our study of patients with LPR symptoms and HRM found that abnormal findings are common (43%), including 13.4% with EGJOO or a major peristaltic disorder [11]. Impaired esophageal motility may also correlate with worse LPR symptoms. Our other study found that ↑failed swallows on HRM predicted higher RSI and more severe LPR symptoms. Manometry may help identify these patients to help tailor management [12].

Q3. Should all LPR patients get reflux testing? Which testing should they get? On or off therapy?

WC: Reflux testing should be an important (if not necessary) part for diagnosing LPR, given the heterogeneous causes for laryngeal symptoms. Recognizing the burden/challenge in testing everyone, clinical phenotyping as suggested by our study may help identify likelihood candidates. For example, those with features of groups A/B (high BMI, large hernia, esophageal symptoms) are more likely to benefit from testing, while those with clinical features of group C may less likely improve with reflux treatment. Of course, further refinement of these phenotypes is needed. Weakly acidic/non-acidic reflux may also play a role in LPR symptoms. In a study of patients with MII-pH testing, cough-associated reflux episodes have increased proximal extent and longer clearance time, but no difference in nadir pH, pH decrease, or % acidic reflux [13]. Studies using pH-only sensors, even with dual pH sensors, may miss full-column weakly acidic/non-acidic reflux events reaching pharynx, as shown in our study of pts undergoing combined hypopharyngeal-esophageal MII-pH studies [14]. More treatment outcome-based studies evaluating pH-based versus impedance-based testing and catheter characteristics (esophageal only versus combined hypopharyngeal-esophageal sensors), are needed to further optimize and standardize reflux testing protocol for LPR.

ZM: Do you prefer 24 hr pH or Bravo? Or do you like to use restech?

WC: I usually prefer a combined impedance-pH, but also use Bravo study. These should be done off PPI. Pharyngeal pH monitoring (Restech) has not been shown to correlate well with full column reflux on MII-pH or with PPI treatment outcome. Therefore, I generally do not use it.

WC: Optimal reflux testing for LPR is not completely clear. Abnormal indices on pH monitoring (AET, SAP, SI) have been found to associate with better treatment outcomes. Therefore, Bravo study OFF PPI would be a reasonable approach [15].

ZM: Even when they have clear reflux symptoms? Typical GERD symptoms that responded to treatment or esophagitis? For me. in those patients I like to test with 24 hr pH on therapy to see if they have controlled or uncontrolled reflux on therapy.

WC: I use the same approach as suggested by Lyon and Porto consensus - ON PPI for those with high pre-test probability (prior high-grade esophagitis, long-segment...
Barrett's, +pH study etc) and OFF PPI for those with low pre-test probability (which includes extraesophageal symptoms).

Q4. What’s the gold standard for diagnosing LPR? And if you have that diagnosis and a positive reflux test, does that mean the source of LPR is GERD?

WC: The short answer is there is no gold standard for diagnosing LPR. The challenge is that LPR-like symptoms can be due to many causes: vocal cord dysfunction, allergies, other ENT issues, hypersensitivity, etc. Often more than one cause may be at play. A positive reflux test in patients presenting with laryngeal symptoms does NOT necessarily mean that GERD is the main cause of their symptoms. That is why phenotyping considering an aggregate of clinical info may be a more useful approach, rather than relying on one test.

@SultanMahmoodMD: When you see patients for the first time in the clinic referred from ENT for LPR because of changes seen during exam, what numbers do you quote that this is truly LPR?

WC: I quote numbers to let patients know how NOT useful laryngoscopic findings are for LPR. In a study of 105 normal, healthy adults who underwent laryngoscopy, at least one sign attributed to LPR was found in up to 86% of them! [16]

@AllonKahn: This is the Achilles heel of GERD testing in LPR - many people have GERD without LPR symptoms, so causality is tough to establish and predicting treatment outcomes is even harder. Important to step back and look at the whole picture, i.e. phenotype

Q5. I think you led us into this, how do you think the classification system that you proposed will help guide management for these patients?

WC: I think that this classification system may help us identify patients who are more likely to have reflux as underlying cause of laryngeal symptoms. This may help guide selecting candidates for upfront testing and reflux therapy, rather than a one-size-fits-all approach.

ZM: Which patients would you send for anti-reflux surgery? What numbers do you quote them?

WC: I only refer patients to surgery in a very minority of cases - mainly those with group A phenotype + abnormal reflux testing AND no other clear ongoing etiologies of symptoms after comprehensive eval (ENT, allergy, video swallow). I also consider symptom severity and patient HRQOL

Q6. What are some potential therapies for LPR symptoms? Are there ways to predict treatment outcomes?

WC: Therapies for LPR symptoms depend a lot on potential underlying causes. For groups A/B/D pts, anti-reflux therapy would be mainstay: PPI, H2RA, alginate, or even baclofen. Neuromodulators may also be helpful, as hypersensitivity may play a big part in persistent laryngeal symptoms. Voice therapy and other laryngeal or vocal cord dysfunction-targeted treatments may be helpful as well, especially for patients in group C/E whose symptoms are not clearly reflux-related. These may also be useful even in those with evidence of reflux.

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