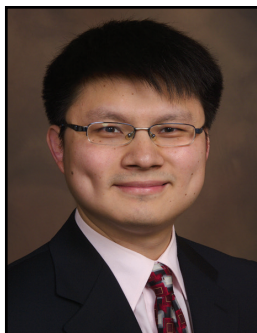


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Gastroesophageal Reflux can be an Explanation for Dysphagia of Otherwise Unknown Etiology



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Dysphagia and gastroesophageal reflux disease (GERD) are common entities in clinical practice. High-resolution manometry (HRM) of the esophagus is a diagnostic test to investigate dysphagia where other esophageal tests and evaluations had not disclosed an etiology. The goals of our study were to investigate the frequency of GERD in patients whose dysphagia cannot be explained by all prior studies, including HRM, and propose that GERD, by inducing esophageal hypersensitivity, could explain this sensation of dysphagia. A retrospective chart review of HRM studies that were performed from 2012-2016 in 167 patients with dysphagia was conducted. Results were categorized based on the Chicago Classifications as follows: achalasia 11%; nutcracker 7%; Jackhammer 2%; scleroderma 4%; diffuse esophageal spasm 1%; elevated integrated relaxation pressure 7%; presbyesophagus 4%; hypertensive LES pressure 3%. In addition, 80 (48 %) had normal and 24 (14%) had minor non-specific HRM findings. Medical records were available for review in 78 of those 104 patients with dysphagia who had normal or minor non-specific HRM findings. We identified Schatzki ring in two and eosinophilic esophagitis in three patients. 73% of the remaining 73 patients had evidence of GERD based on one or more of the following test results: EGD, esophageal biopsy, pH impedance, BRAVO test and barium swallow; while in the other 20 (27%) there was no objective evidence of GERD. 95% were receiving ongoing PPI therapy for symptoms consistent with GERD. In conclusion, when HRM findings are normal or minor non-specific in patients with unexplained dysphagia then evidence for concomitant GERD should be sought since the esophageal hypersensitivity induced by GERD can be one explanation for this dysphagia and can lead to further treatment approaches.

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INTRODUCTION

Patients with gastroesophageal reflux disease (GERD) may present with various symptoms including heartburn, regurgitation, dysphagia, chronic cough, laryngitis, aspiration and even asthma.¹ An etiology of dysphagia in patients with GERD is sometimes unknown and can be further investigated with High-resolution manometry (HRM) of the esophagus.

Prior to referral for HRM, patients often undergo evaluation including esophagogastroduodenoscopy (EGD) and/or barium swallow study to rule out mechanical causes of dysphagia and to exclude eosinophilic esophagitis (with esophageal biopsies). After undergoing HRM, the diagnosis of a motility disorder is made based on the Chicago Classifications; however, many patients who undergo this evaluation for dysphagia with HRM studies have no recognized abnormalities, being regarded as either normal or minor nonspecific findings. At our center, we have observed concomitant GERD in many patients who were referred for HRM to elucidate a suspected esophageal cause of dysphagia but in whom either normal or minor nonspecific abnormalities are found. Patients with GERD may continue to report dysphagia despite being treated with standard anti reflux medications. This sensation of dysphagia in patients with GERD could be secondary to visceral hypersensitivity of the esophagus. Among practicing clinicians there is limited acceptance and appreciation for the term “visceral hypersensitivity” as far as understanding its role in a patient’s symptoms. The concept of visceral hypersensitivity has been described in the literature in functional bowel disorders such as non-cardiac chest pain, non-ulcer dyspepsia and irritable bowel syndrome.²

Aims:

We investigated the frequency of objective evidence for GERD in patients whose dysphagia cannot be explained by all prior studies including HRM. Additionally, we propose that GERD, by inducing esophageal hypersensitivity, could explain this sensation of dysphagia.

Methods:

A retrospective chart review of high resolution manometry studies, performed for various indications, from 2012-2016 in patients referred to a University Motility Center was conducted. The standard technique described for HRM was utilized and a total of 16 wet swallows were employed. Those patients referred for the specific assessment of dysphagia were categorized according to underlying manometric etiologies for dysphagia as recognized in the current as well as the previous Chicago Classifications which overlapped our study years of 2012-16.^{3,4} In patients with no recognized motility disorder on the HRM study, we identified two additional groups: 1) entirely normal

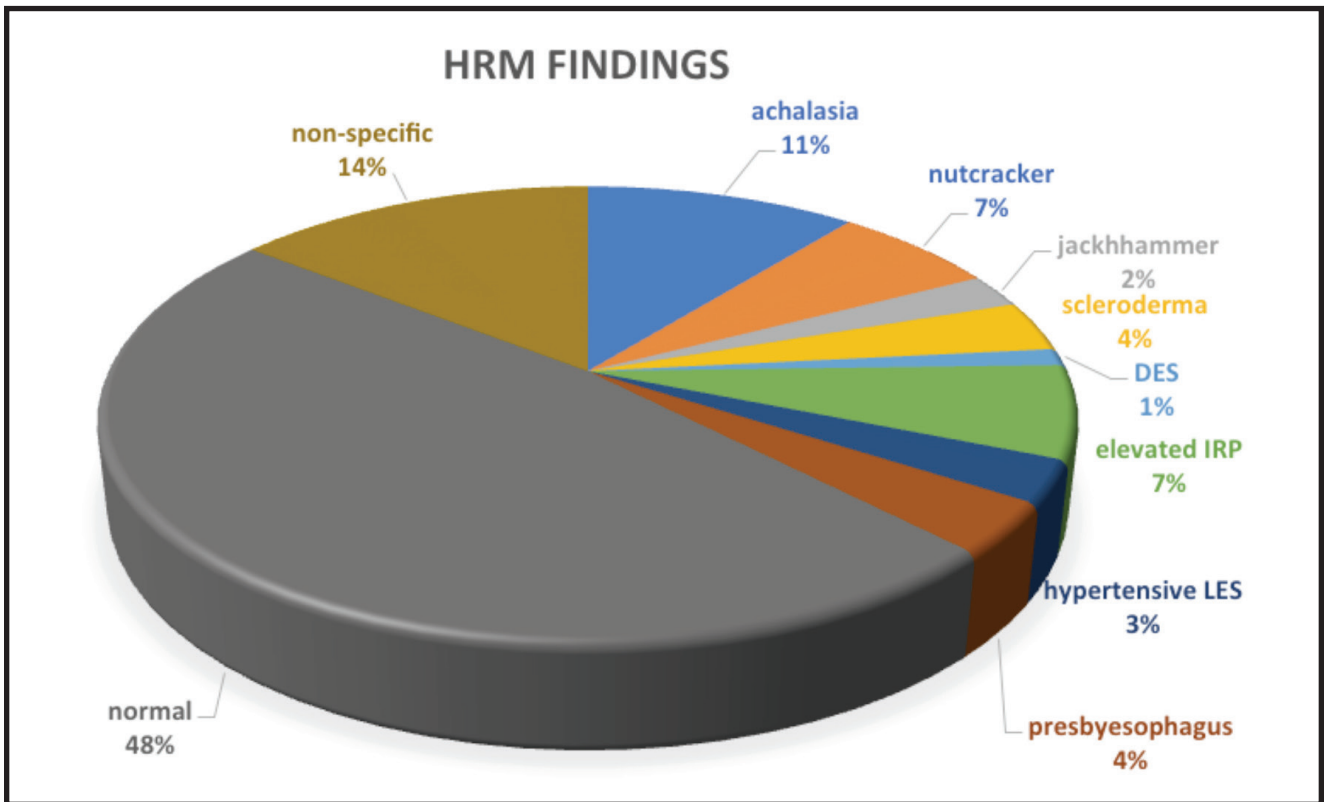
manometric findings and 2) minor, non-specific motility findings. We defined the entity of a minor, nonspecific motility abnormalities as having one or more of the following: 1) a decreased resting lower esophageal sphincter (LES) pressure (< 10 mm Hg); 2) low amplitude contractions defined as < 30 mm Hg in less than 30% of the contractions induced by 16 wet swallows at the level of 3 and 7 cm above the LES; 3) a small percentage loss of peristalsis, < 50% of the sequences following wet swallows, where <30% non-peristalsis is regarded as normal.⁵⁻⁷

Clinical chart reviews were conducted only in patients with dysphagia who had normal or minor nonspecific HRM findings. The aim of the chart review was to identify all the diagnostic testing performed for both confirmatory evidence of GERD as well as excluding other causes of dysphagia. We reviewed EGD reports for evidence of esophagitis as per the Los Angeles classification, and/or Barrett’s esophagus and to identify other etiologies such as strictures, masses, rings and hiatal hernias.⁸ We also examined endoscopic esophageal biopsy reports to identify GERD related changes (basal cell hyperplasia, elongation of connective tissue papillae, infiltration by neutrophils and eosinophils) in patients with an endoscopically normal esophagus as well as to identify other etiologies such as eosinophilic esophagitis.⁹ Barium swallow reports were reviewed to identify mechanical obstruction (including strictures or rings), gastroesophageal reflux and hiatal hernia. BRAVO and 24-hour pH impedance tests were also evaluated where applicable.

Results:

319 patients were referred for HRM testing for all indications from 2012-2016. There were 167 (52.4%) patients that met the criteria of dysphagia. These 167 patients had the following manometric entities based on the definitions of the Chicago classifications (Figure 1): achalasia 18 (11%); high amplitude peristaltic contractions with distal contractile integral (DCI) >5000 but <8000 (nutcracker esophagus) 11 (7%); extremely elevated amplitude but peristaltic contractions with DCI > 8000 (Jackhammer esophagus) 4 (2%); scleroderma 6 (4%); diffuse esophageal spasm in 2 (1%); elevated integrated relaxation pressure in 11 (7%); presbyesophagus 6 (4%); and hypertensive LES pressure (> 40 mm Hg) 5 (3%). In addition, 80 (48 %) were judged as having an entirely normal manometry while there was a subgroup of 24 (14%)

Figure 1. High resolution manometry (HRM) diagnoses based on the previous and current Chicago classifications as well as patients with either normal or minor nonspecific motility abnormalities.



LES: lower esophageal sphincter IRP: integrated relaxation pressure DES: diffuse esophageal spasm

with non-specific minor motility abnormalities (the criteria for which we have previously defined) (Figure 1).

Of those 104 (62%) patients who had either normal or minor non-specific HRM findings, the age range was 15-86 years and 71 (68%) were female. 90% were being managed by a proton pump inhibitor (PPI) for symptomatic GERD at the time of evaluation of dysphagia. Of those 104 patients, 78 had medical chart records available to review results of the diagnostic testing. Based on those studies, Schatzki rings (2 patients) and eosinophilic esophagitis (3 patients) were identified as causes of dysphagia. Fifty-three (73%) of the remaining 73 patients had objective evidence of GERD based on one or more of the following test results: EGD, esophageal biopsy, pH with impedance, BRAVO pH study and barium swallow (Table 1). EGD confirmed esophagitis in 15 patients (LA classification) as well as 4 with Barrett’s epithelial changes confirmed by biopsies. Esophageal biopsies in the patients with normal endoscopic findings were consistent with GERD in 25 patients. Six patients had acid reflux based on

24-hour pH impedance data and one had predominant non-acid reflux. One patient had a positive 48-hour BRAVO study. Barium swallow showed evidences of GE reflux in four patients. Hiatal hernias were observed in one or more of those studies in 16 (30%) patients.

While 73% of the patients had confirmatory objective evidence of GERD, 20 (27%) of 73 patients whose charts were available for review had no objective evidence of GERD but 95% were receiving ongoing PPI therapy for symptoms. In this subset of negative GERD findings, the diagnostic testing was suboptimal in that in the setting of a negative EGD other tests were not routinely pursued for the evaluation of GERD.

Discussions:

Based on HRM classifications, there are well identified manometric disorders that can explain dysphagia. However, 104 (62%) of the patients referred for HRM to evaluate dysphagia at our motility center had a normal or minor nonspecific esophageal motility findings. These findings alone would not explain dysphagia

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without there being other underlying esophageal pathology. Indeed, 73% of our patients with normal or minor nonspecific findings whose medical records were accessible for review had objective evidence of GERD. Therefore, in the setting of either normal or nonspecific HRM findings the presence of GERD could provide evidence for underlying pathology and a possible explanation for their dysphagia.

One of the limitations of our data is that 27% of the patients with normal or non-specific motility findings did not have medical records available for review. This is because they were referred by gastroenterologists in private practice in our city and our access to their medical records was limited. Another limitation of our study is that in the 28% of patients whose medical records were available for review had no objective evidence of GERD and we observed that if their EGD was normal then pH studies and endoscopic esophageal biopsies were usually not pursued. Hence GERD could still have been present. In fact, they were being managed by PPI for symptoms consistent with GERD.

Our findings of esophageal pathology in the form of GERD poses the question of whether GERD related visceral hypersensitivity of esophagus could be an explanation for the sensation of dysphagia. Visceral hypersensitivity is present in other organs and is proposed to be mediated by peripheral, central and psychosocial factors.¹⁰ The sensation of stimuli - chemical, mechanical, thermal etc - in contact with the esophageal mucosa is transmitted to the central nervous system (CNS) via either spinal nerves or vagal nerves (Figure 2).¹⁰ This sensation is thought to be physiologically important to help sense the passage of food or foreign material through the esophagus during swallowing.¹¹ In a hypersensitive esophagus, there is a heightened perception of stimuli, discomfort or pain and this could generate a visceral sensation interpreted by the patient as the symptom of dysphagia.¹²

In reflux esophagitis (RE), there is a break in the esophageal mucosa and noxious stimuli can penetrate and activate nociceptive receptors in deep layers of the mucosa resulting in signals, which then are transmitted to the CNS.¹³ Patients with nonerosive reflux disease (NERD) can have heartburn even though damage to the esophageal mucosa is not observed. Here, microscopic changes based on dilation of the intracellular space have been reported.¹⁴ Based on intra-esophageal acid infusion tests, pain response to acid reflux in patients

Table 1. How objective evidence of gastro-esophageal reflux disease (GERD) was determined in 53 patients whose dysphagia was not explained by high resolution manometry

<p>Upper GI endoscopy and esophageal biopsy findings</p> <ul style="list-style-type: none"> • 17 patients had esophagitis (based on LA classification) and 4 had biopsy proven Barrett's esophagus • 25 patients had biopsy proven GERD in the setting of negative EGD findings
<p>24-hour pH impedance</p> <ul style="list-style-type: none"> • 6 were positive for acid reflux and 1 for non-acid reflux
<p>48-hour BRAVO test</p> <ul style="list-style-type: none"> • was positive for GE reflux
<p>Barium swallow</p> <ul style="list-style-type: none"> • 4 patients were positive for reflux

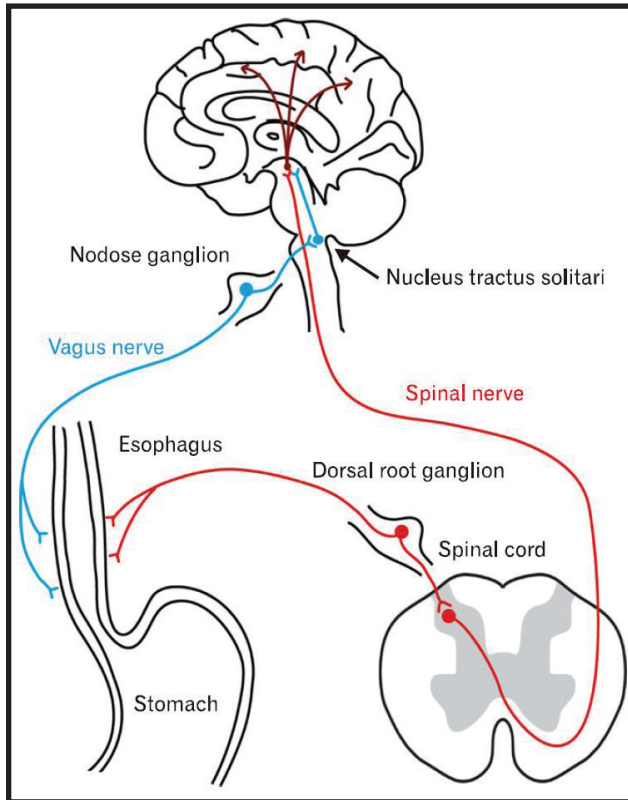
* 5 patients had more than 1 study to confirm GERD

with NERD has been shown to be stronger than in patients with erosive GERD.^{15,16} Miwa and et al. suggested that patients with NERD can have increased mucosal permeability that could permit penetration of the mucosa by noxious stimuli such as gastric acid, bile acids, or pepsin.¹⁵ A symptom of heartburn is not specific to acid reflux into the esophagus and has been reported as a symptom response to mechanical stimuli including esophageal dilation and longitudinal contraction of esophageal smooth muscle.^{17,18} It is conceivable that dysphagia could be perceived as an uncomfortable sensation accompanying swallowing, when there is esophageal mucosa sensitized by chronic GE reflux, in the absence of mechanical obstruction or a motility disorder. Patients with depression, anxiety, somatization disorders, and fibromyalgia tend to have a higher prevalence of esophageal hypersensitivity and this aspect could also be a contributing factor in sensing the symptom of dysphagia.¹⁹

Hypersensitive esophagus has also been investigated by a balloon distension method. Here, a small balloon is distended in the esophagus to assess which volume induces the first perception of symptoms and the degree of discomfort experienced.¹⁹ The implication from the balloon test results are that touching, stretching, or perturbing the esophagus induces a sensation e.g.

Figure 2. Sensory pathway from esophagus to brain. Esophageal nociceptive stimuli are conveyed to the brain via 2 major sensory pathways - a sympathetic pathway and vagal pathway.¹⁰

(*J Neurogastroenterol Motil.* 2010 Oct; 16(4): 353–362.)

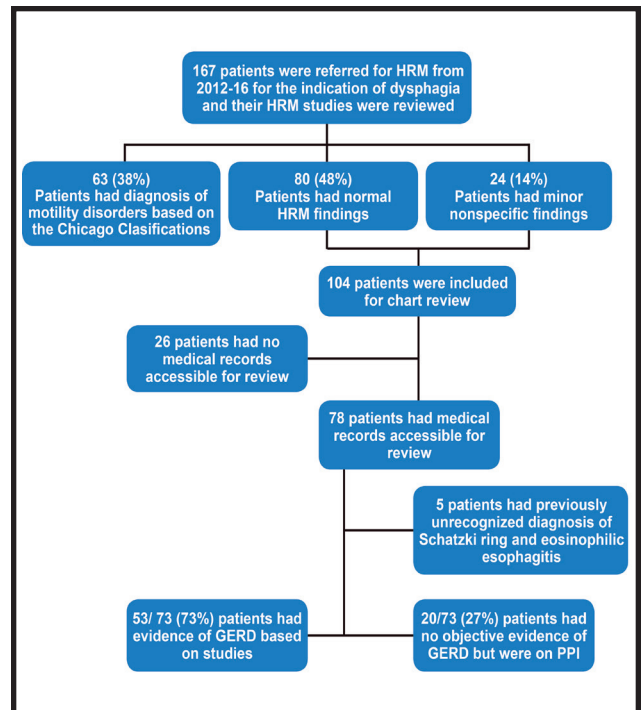


heartburn, chest pain and non-specific discomfort. In the setting of eating where food is stretching the esophageal lumen, the resulting sensation could be interpreted as dysphagia by the patient. This balloon testing was not performed in our patients due to the retrospective nature of the study. However, 90% of patients with unexplained dysphagia were being treated with a PPI for symptomatic GERD at the time of evaluation of

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Diagram 1. Summary of the Methods and Results in this Study



HRM: high resolution manometry GERD: gastroesophageal reflux disease PPI: proton pump inhibitor

dysphagia and 73% patients with available medical records had objective evidence of GERD. In addition, 71% of our patients were females similar to the female dominance in such entities as irritable bowel syndrome and non-ulcer dyspepsia where visceral hypersensitivity is thought to be important in the mediation of the symptoms.

CONCLUSION

In conclusion, in patients with unexplained dysphagia when HRM is normal or only minor non-specific findings are present then evidence for concomitant GERD should be sought. We hypothesize that GERD could induce a hypersensitive state in the esophageal mucosa. This leads to a heightened awareness of esophageal movement and touching during swallowing, which is interpreted by the patient as the symptom of “trouble swallowing” or dysphagia. Our observations should be confirmed in more studies in this specific patient setting of unexplained dysphagia and accompanying GERD where testing for assessing visceral hypersensitivity of the esophagus as well as treatment trials to address this entity are included. ■

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