



EVALUATION OF REFRACTORY HEARTBORN ; IS IT “NERD” OR HYPERSENSITIVE ESOPHAGUS

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ABSTRACT

Introduction: Heartburn and non cardiac chest pain is a common symptom. It is known that excessive intraesophageal acid exposure causes the symptoms of retrosternal pain and burning. But many patients with chronic heartburn symptoms have no endoscopically or histologically discernible esophageal mucosal damage and many of them even do not have positive reflux as per 24-h pH monitoring.

Methodology: A retrospective study was carried out from July 2014 to July 2015. A total of 53 eligible study subjects (35 males, 18 females) [range 19 to 62 years] presented to OPD of gastrocare hospital were included. All study subjects who were having symptoms of Gastro Esophageal Reflux Disease, endoscopically negative, were not responding / partially responding to the standard dose of proton pump inhibitor were considered for 24-h esophageal pH monitoring (after off PPI for 7 days). Acid contact time, Demeester score, symptom index and symptom associated probability was recorded.

Results: Out of 53 subjects 73.6% had heartburn and chest pain as their presenting complaints while 26.4 had other symptoms of GERD. 41.5% were having hypersensitive esophagus (HE), 22.6% had Nonerosive Reflux Disease (NERD), 18.9% had NERD with HE and 17% subjects had normal pH monitoring

Conclusion: Unfortunately, not all available drugs (namely 5-HT3 antagonists and opioids), capable of reducing visceral perception in the lower gastrointestinal tract, seem to be effective in the upper gastrointestinal tract. Therefore, reduction of the stimulus intensity (diet and PPI) remains at present the only alternative in clinical practice.

KEYWORDS : Gastroesophageal reflux, Heartburn, Hypersensitivity, Hyposensitivity, Pain receptor

INTRODUCTION

Heartburn and non cardiac chest pain is a common symptom. It is known that excessive intraesophageal acid exposure causes the symptoms of retrosternal pain and burning. But many patients with chronic heartburn symptoms have no endoscopically or histologically discernible esophageal mucosal damage and many of them even do not have positive reflux as per 24-h pH monitoring.

Gastro-esophageal reflux disease (GERD) is one of the most prevalent chronic diseases. Although proton pump inhibitors (PPIs) represent the mainstay of treatment both for healing erosive esophagitis and for symptom relief, several studies have shown that up to 40% of GERD patients reported either partial or complete lack of response of their symptoms to a standard PPI dose once daily. Several mechanisms have been proposed as involved in PPIs resistance, including ineffective control of gastric acid secretion, esophageal hypersensitivity, ultrastructural and functional changes in the esophageal epithelium. The diagnostic evaluation of a refractory GERD patients should include an accurate clinical evaluation, upper endoscopy, esophageal manometry and ambulatory pH-impedance monitoring, which allows to discriminate non-erosive reflux disease patients from those presenting esophageal hypersensitivity or functional heartburn. Treatment has been primarily based on doubling the PPI dose or switching to another PPI. Patients with proven disease, not responding to PPI twice daily, are eligible for anti-reflux surgery.

The criteria for diagnosis rest not only on compatible symptoms but also on exclusion of structural and metabolic disorders that might mimic the functional disorders. Additionally, a functional diagnosis is precluded by the presence of a pathology-based motor disorder or pathological reflux, defined by evidence of reflux esophagitis or abnormal acid exposure time during ambulatory esophageal pH monitoring. Management is largely empirical, although efficacy of

psychopharmacological agents and psychological or behavioral approaches has been established for several of the functional esophageal disorders. As gastroesophageal reflux disease overlaps in presentation with most of these disorders and because symptoms are at least partially provoked by acid reflux events in many patients, antireflux therapy also plays an important role both in diagnosis and management. Further understanding of the fundamental mechanisms responsible for symptoms is a priority for future research efforts, as is the consideration of treatment outcome in a broader sense than reduction in esophageal symptoms alone.

Diagnosis of GERD is usually made on clinical grounds, often supplemented by a therapeutic trial with antisecretory agents. Endoscopy is reserved for patients with alarm symptoms, such as dysphagia, anemia, or weight loss, or to detect Barrett's esophagus. Endoscopy is not useful to exclude the diagnosis of GERD because it will be negative in 70% of cases in primary care. Ambulatory 24-hour esophageal pH monitoring is necessary only when the diagnosis is in doubt, the patient fails medical management, or surgery is contemplated

METHODOLOGY

The present study was conducted in the Department of Gastroenterology ,Gastrocare Hospital Bhopal. After the approval of protocol by the Hospital Ethics Committee and obtaining informed consent from the patient, a total number of 53 patients were included.

Inclusion criteria

1. Age group: 18-60years
2. BMI <35 kg/m²

Exclusion criteria

1. Patients' refusal or inability to give informed consent.

2. pregnancy
3. Cardiorespiratory or cerebrovascular disease
4. Diabetes Mellitus
5. History of allergy to any drug

Study design: Retrospective study

Period of study: The study was carried out from July 2014 to July 2015. [One year]

A total of 53 eligible study subjects (35 males, 18 females) [range 19 to 62 years] presented to OPD of gastrocare hospital were included. All study subjects who were having symptoms of Gastro Esophageal Reflux Disease, endoscopically negative, were not responding / partially responding to the standard dose of proton pump inhibitor were considered for 24-h esophageal pH monitoring (after off PPI for 7 days). Acid contact time, Demeester score, symptom index and symptom associated probability was recorded.

OBSERVATION TABLES

TABLE 1: DISTRIBUTION OF PATIENTS

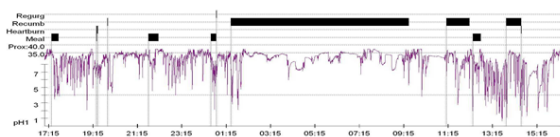
Result	No of Subjects	Percentage (%)
Normal	9	17
Nonerosive Reflux Disease (NERD)	10	18.9
Hypersensitive Esophagus (HE)	22	41.5
NERD with HE	12	22.6
Total	53	100

TABLE 2 PRESENTING SYMPTOMS

Symptom	Normal	Positive	Hypersensitive Esophagus	Positive & Hypersensitive Esophagus
Chest Pain, Heart Burn	4	9	15	11
Other	5	1	7	1
Total	9	10	22	12

TABLE 3 DEEMESTER SCORE, SYMPTOM INDEX (SI) AND SYMPTOM ASSOCIATION PROBABILITY (SAP)

Result	DeeMeste r Score	Symptom index (SI):	Symptom association probability (SAP):
Normal	<14.7	<50%	<95%
Nonerosive Reflux Disease (NERD)	>14.7	<50%	<95%
Hypersensitive Esophagus (HE)	<14.7	>50%	>95%
NERD with HE	>14.7	>50%	>95%
Total			



RESULTS

Out of 53 subjects 73.6% had heartburn and chest pain as their presenting complaints while 26.4 had other symptoms of GERD. 41.5% were having hypersensitive esophagus (HE), 22.6% had Nonerosive Reflux Disease (NERD), 18.9% had NERD with HE and 17% subjects had normal pH monitoring.

Statistical analysis: Statistical analysis was done using Stata 11 software. Demographic characteristics, hemodynamic parameters data was analyzed by simple mathematical analysis.

DISCUSSION

Functional esophageal disorders represent processes accompanied by typical esophageal symptoms (heartburn, chest pain, dysphagia,

globus) that are not explained by structural disorders, histopathology-based motor disturbances, or gastroesophageal reflux disease. Gastroesophageal reflux disease is the preferred diagnosis when reflux esophagitis or excessive esophageal acid exposure is present or when symptoms are closely related to acid reflux events or respond to antireflux therapy. A singular, well-defined pathogenetic mechanism is unavailable for any of these disorders; combinations of sensory and motor abnormalities involving both central and peripheral neural dysfunction have been invoked for some.

Treatments remain empirical, although the efficacy of several interventions has been established in the case of functional chest pain. Management approaches that modulate central symptom perception or amplification often are required once local provoking factors (eg, noxious esophageal stimuli) have been eliminated. Future research directions include further determination of fundamental mechanisms responsible for symptoms, development of novel management strategies, and definition of the most cost-effective diagnostic and treatment approaches.[1]

Many studies are now Available which are done on patients with gastro-oesophageal reflux disease (GORD) who are not responding to proton pump inhibitors (PPIs) given once daily. Various underlying mechanisms have been shown to contribute to the failure of PPI treatment. These include weakly acidic reflux, duodenogastro-oesophageal reflux, residual acid reflux and functional heartburn, as well as others.

In one similar study by Fass R et al Management of heartburn not responding to proton pump inhibitors ,diagnostic evaluation of patients with GORD who have failed PPI treatment , included an upper endoscopy, pH testing and oesophageal impedance with pH monitoring. Commonly, doubling the PPI dose or switching to another PPI was then pursued by the treating physician. They eventually concluded that failure of such a therapeutic strategy may result in the addition of a transient lower oesophageal sphincter reducer or pain modulator. Anti-reflux surgery may be suitable for a subset of carefully studied patients.[2]

Fass R et al in another study on erosive esophagitis and nonerosive reflux disease (NERD), did a comparison of epidemiologic, physiologic, and therapeutic characteristics Nonerosive reflux disease (NERD) and erosive esophagitis are the main presentations of gastroesophageal reflux disease. However, NERD is the most common presentation of gastroesophageal reflux disease in community-based patients. Patients with NERD differ in demographic characteristics from patients with erosive esophagitis, primarily in sex distribution, weight/body mass index, and prevalence of hiatal hernia. Physiologically, patients with NERD tend to have normal lower esophageal sphincter resting pressure, minimal esophageal body motility abnormalities, low esophageal acid exposure profile and minimal nighttime esophageal acid exposure. Patients with NERD have a lower symptom response rate to proton pump inhibitor once daily than patients with erosive esophagitis. Additionally, NERD patients demonstrate a longer lag-time for symptom resolution and lack of difference in symptom response rate between half to full dose proton pump inhibitor as compared with patients with erosive esophagitis.[3]

Miwa H et al did an overview from bench to bedside. They postulated about esophageal sensation and esophageal hypersensitivity- Noxious stimuli in the esophagus activate nociceptive receptors on esophageal mucosa and this generates signals that are transmitted to the central nervous system via either spinal nerves or vagal nerves, resulting in esophageal sensation. Among the noxious stimuli, gastric acid and other gastric contents are clinically most important, causing typical reflux symptoms such as heartburn and regurgitation. Therefore, it may be necessary to approach the causes of heartburn symptoms from a new conceptual framework. Hypersensitivity of the esophagus, like that of other visceral organs, includes peripheral, central and probably

psychosocial factor-mediated hypersensitivity, and is known to play crucial roles in the pathogenesis of nonerosive reflux disease, functional heartburn and non-cardiac chest pain. There also are esophagitis patients who do not perceive typical symptoms. This condition is known as silent gastroesophageal reflux disease. Although the pathogenesis of silent gastroesophageal reflux disease is still not known, hyposensitivity to reflux of acid may possibly explain the condition.[4]

Patients with symptoms suggestive of gastroesophageal reflux disease (GERD), such as chest pain, heartburn, regurgitation, and dysphagia, are typically treated initially with a course of proton pump inhibitors (PPIs). The evaluation of patients who have either not responded at all or partially and inadequately responded to such therapy requires a more detailed history and may involve an endoscopy and esophageal biopsies, followed by esophageal manometry, ambulatory esophageal pH monitoring, and gastric emptying scanning.

To assess the merits of a multimodality 'structural' and 'functional' assessment of the esophagus in patients who have inadequately controlled GERD symptoms despite using empiric PPI, a retrospective cohort study of patients without any response or with poor symptomatic control to empiric PPI (>2 months duration) who were referred to an Esophageal Studies Unit was conducted by Galindo G et al. Patients were studied using symptom questionnaires, endoscopy (+ or - for erosive disease, or Barrett's metaplasia) and multilevel esophageal biopsies (eosinophilia, metaplasia), esophageal motility (aperistalsis, dysmotility), 24-hour ambulatory esophageal pH monitoring (+ if % total time pH < 4 > 5%), and gastric emptying scanning. Cumulative symptom scores for chest pain, heartburn, regurgitation, and dysphagia were similar among the groups (mean range 1.1-1.35 on a 0-3 scale). Similar study was also done by Cicala M, Emerenziani S et al. In their study also multimodality evaluation changed the diagnosis of GERD in 34.5% of cases and led to or guided alternative therapies in 42%. Overlap diagnoses were frequent: 10/15 (67%) of patients with eosinophilic esophagitis, 12/16 (75%) of patients with gastroparesis, and 11/23 (48%) of patients with achalasia or dysmotility had concomitant pathologic acid reflux by pH studies. The authors concluded that patients with persistent GERD symptoms despite empiric PPI therapy benefit from multimodality evaluation that may change the diagnosis and guide therapy in more than one third of such cases. Because symptoms are not specific and overlap diagnoses are frequent and multifaceted, objective evidence-driven therapies should be considered in such patients.[5,6]

Clouse RE, Richter JE et al in their study on functional esophageal disorders stated that the functional esophageal disorders include globus, rumination syndrome, and symptoms that typify esophageal diseases (chest pain, heartburn, and dysphagia). The criteria for diagnosis rest not only on compatible symptoms but also on exclusion of structural and metabolic disorders that might mimic the functional disorders. The authors after extensive study concluded that management is largely empirical, although efficacy of psychopharmacological agents and psychological or behavioral approaches has been established for several of the functional esophageal disorders. As gastroesophageal reflux disease overlaps in presentation with most of these disorders and because symptoms are at least partially provoked by acid reflux events in many patients, antireflux therapy also plays an important role both in diagnosis and management. Likewise, the value of inclusive rather than restrictive diagnostic criteria that encompass other gastrointestinal and non-gastrointestinal symptoms should be examined to improve the accuracy of symptom-based criteria and reduce the dependence on objective testing.[7]

Soll AH, Fass R et al also did a similar study on Gastroesophageal reflux disease and its presentation and assessment. Although gastroesophageal reflux disease (GERD) is frequently referred to as a continuous spectrum, it is more useful to consider GERD as 2 discrete entities with several subsets that differ in pathophysiology,

clinical presentation, natural history, and therapy. One entity is classic severe acid reflux with erosive esophagitis and its complications. Barrett's esophagus is an important subset of this group, with markedly increased acid exposure and an increased risk of adenocarcinoma. The second entity is nonerosive reflux disease (NERD) with minimal or no esophagitis. Patients with NERD do not develop local mucosa complications, like stricture or Barrett's esophagus, but their symptom severity can equal that of erosive esophagitis. Acid is involved in the symptoms of many but not all NERD patients.[8]

This acid dependence is evident either as an increase in esophageal acid reflux or a hypersensitivity to acid, and both generally respond well to proton pump inhibitor (PPI) therapy. NERD patients who are not acid-dependent have what is called functional heartburn; GERD-like symptoms are present, but there is no obvious involvement of refluxed acid. An important subset of GERD is refractory GERD, which consists of patients who fail aggressive PPI therapy. Parallel findings with other refractory syndromes can be anticipated; however, there are indications that psychosocial factors play a major role in refractory GERD, and these patients may benefit more from an integrated biopsychosocial approach.[8]

CONCLUSION

The criteria for diagnosis rest not only on compatible symptoms but also on exclusion of structural and metabolic disorders that might mimic the functional disorders. Management is largely empirical, although efficacy of psychopharmacological agents and psychological or behavioral approaches has been established for several of the functional esophageal disorders. As gastroesophageal reflux disease overlaps in presentation with most of these disorders, antireflux therapy also plays an important role both in diagnosis and management. Further understanding of the fundamental mechanisms responsible for symptoms is a priority for future research efforts, as is the consideration of treatment outcome in a broader sense than reduction in esophageal symptoms alone.

Unfortunately, not all available drugs (namely 5-HT₃ antagonists and opioids), capable of reducing visceral perception in the lower gastrointestinal tract, seem to be effective in the upper gastrointestinal tract. Therefore, reduction of the stimulus intensity (diet and PPI) remains at present the only alternative in clinical practice.

Our study highlights importance of pH monitoring in patients with refractory heartburn. Our finding of hypersensitive esophagus (41.5%) is higher than reported literature and explains why most of these patients are partial/unresponsive to PPI and we have to focus on reducing visceral perception.

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