Nonerosive reflux disease as a presentation of gastro-oesophageal reflux disease

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Abstract

Up to 70% of patients with typical symptoms of gastro-oesophageal reflux disease have neither definite endoscopic oesophageal erosions nor Barrett's oesophagus on upper endoscopy. These patients suffer from nonerosive reflux disease (NERD). There is no gold standard for the diagnosis of NERD, but a well-taken history is usually sufficient to confirm the diagnosis and initiate therapy. A sensitive tool for the diagnosis of NERD is a proton-pump inhibitor (PPI) trial of therapy. The aims of NERD therapy are acute and long-term symptom relief, maintenance of clinical remission and restoration of quality of life. PPIs in full doses are the treatment of choice for NERD patients, who often need long-term therapy for symptom control. For the family physician, identification of the relevant symptoms and initiation of treatment, where alarm symptoms have been excluded, is important in the effective management of NERD.

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Introduction

Gastro-oesophageal reflux disease (GORD) is defined by the American College of Gastroenterology as symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the oesophagus, and by the Montreal Classification as a condition that develops when the reflux of stomach contents causes troublesome symptoms (heartburn and regurgitation) and/or related complications. GORD may present as erosive disease with oesophageal mucosal injury or erosions demonstrated on endoscopy, or as nonerosive disease.[1,2]

Previously it was assumed that patients with GORD symptoms without oesophageal mucosal injury represented a mild form of the disease. In the past they were treated very conservatively. However, it has recently been observed that up to 70% of GORD patients have no evidence of oesophageal mucosal injury. Therapeutic trials have also shown that patients with nonerosive reflux disease (NERD) have a lower symptom response rate to proton-pump inhibitors (PPIs) taken once daily, when compared to patients with erosive oesophagitis. This review will discuss the features of and approach to patients with NERD.

Definition

NERD is defined as a condition with troublesome reflux-related symptoms in the absence of oesophageal mucosal lesions, as demonstrated by conventional endoscopy, and without prior effective acid-suppressive therapy. Classic GORD is typically defined by endoscopic features and an abnormal 24-hour pH study; but in NERD, not only will endoscopy be macroscopically normal, but also between 33% and 50% of patients will demonstrate normal acid exposure over 24 hours. However, there is evidence that abnormalities exist at the microscopic level in NERD patients, including dilated intercellular spaces on electron microscopy.

NERD patients, i.e. patients found to have a normal mucosa endoscopically, have been subclassified into three types on the basis of the results of the 24-hour pH evaluation:[3]

- Type 1: Patients who demonstrate an abnormal acid exposure time in a manner similar to those with erosive oesophagitis.[4]
- Type 2: Patients with a normal acid exposure time but with symptoms and reflux events that are significantly correlated, suggesting acid hypersensitivity; this is also referred to as "the hypersensitive oesophagus."[4-6]
- Type 3: Patients with typical reflux symptoms but normal pH studies and no correlation between symptoms and acid exposure; this is also referred to as "functional heartburn".[7]

Pathophysiology

The main physiological cause of reflux oesophagitis remains exposure of the oesophagus to gastric acid. The majority of patients with erosive reflux oesophagitis can be cured by acid suppression, by means of a PPI. In contrast, only a third of NERD patients are cured with a PPI.

Excessive gastric acid exposure remains the main cause of NERD, but NERD may also be associated with the following factors:

- Incomplete acid suppression
- Oesophageal hypersensitivity to acid
- Oesophageal hypersensitivity to distension
- Reflux of duodenal juice (bile and pancreatic juice)
- Oesophageal motility abnormalities
- Sustained oesophageal contraction
- Psychological factors
- Eosinophilic oesophagitis.

Physiological studies in NERD patients demonstrate a slightly higher rate of failed peristaltic contractions, and a mildly reduced mean lower oesophageal sphincter (LOS) resting pressure and distal amplitude contractions, compared to those with erosive disease.[8] Patients with NERD also demonstrate the lowest oesophageal acid exposure profile, compared to patients with erosive oesophagitis or those with Barrett's oesophagus.[9]

Anatomically, hiatus hernia is a relatively uncommon anatomical finding in NERD patients, compared to patients with erosive oesophagitis or Barrett's oesophagus. Cameron[10] suggests that transient lower oesophageal sphincter relaxation (TLOSR) is the predominant underlying mechanism in patients with NERD.

Clinical features

There are currently no clinical features that can differentiate NERD from erosive oesophagitis or even Barrett's oesophagus. There are also no clinical predictors for patients with functional heartburn, and thus these patients cannot be identified on a clinical basis only. Severity, frequency or intensity of symptoms have been shown consistently to be similar among the different reflux disease phenotypes.[11,12] Furthermore, patients with different degrees of oesophageal acid exposure have similar symptom presentation. Thus the two cardinal symptoms of NERD patients are also heartburn and acid regurgitation.

Heartburn

"Heartburn" is commonly used to describe a burning sensation behind the sternum (breastbone), rising up toward the throat or the neck. It is important to remember that many patients use this term to describe many nonoesophageal causes, such as cardiac chest pain. However, heartburn is exacerbated by certain food products, bending over, and when assuming the supine position and during sleep, and it is temporarily relieved by antacids.[13]

Regurgitation

Regurgitation presents as a bitter or sour taste in the mouth. Regurgitation is less common than heartburn and more difficult to control with anti-reflux treatment. It is exacerbated when bending over or assuming the supine position.

Other symptoms

NERD may also present with coughing, wheezing, sore throat, chest pain, and other extraoesophageal manifestations. Insomnia, dyspeptic symptoms and other functional bowel symptoms may also be reported by patients with NERD.

Furthermore, there are atypical signs that could be found, albeit rare, in NERD, similar to those found in GORD, such as:

- Increased body mass index or obesity
- Submandibular adenopathy (GORD-related pharyngeal involvement)
- Caries and poor oral hygiene (oral involvement)
- Hoarse voice (laryngeal involvement)
- Wheezing (pulmonary involvement).

A careful physical examination should be performed at the first clinical visit and on subsequent visits, as needed. Most patients with NERD do not demonstrate any specific disease-related physical findings.

As with erosive reflux, NERD is a chronic, relapsing disease, with periods of exacerbation and remission.[11] If treatment is discontinued, 75% of patients relapse within six months.[11] As a result, most of the patients with NERD require long-term treatment with anti-reflux medications.

Diagnosis

NERD should be suspected in every patient who presents with typical or extraoesophageal manifestations of GORD. Currently, there are no clinical predictive factors that can help us determine if patients have erosive oesophagitis or Barrett's oesophagus, or lack oesophageal mucosal injury. Regardless, patients presenting with symptoms of heartburn and acid regurgitation, unless alarm symptoms are present, are likely to be, and should be, treated empirically with an anti-reflux medication.[14]

Reported alarm symptoms warrant urgent investigation with an upper endoscopy. These symptoms are the following:

- Dysphagia (difficulty swallowing)
- Odynophagia (painful swallowing)
- Anorexia
- Weight loss (pathological/unintentional)
- Bleeding (haematemesis or melena stools)
- Long-term symptoms (to exclude the presence of Barrett's oesophagus).[15]

Empirical therapy with a PPI once daily is a reasonable approach for patients with typical symptoms, regardless of whether erosive oesophagitis is present or not. A positive response is usually a therapeutic trial to suggest reflux disease, and most patients responding to treatment require long-term maintenance therapy.

Upper endoscopy

Upper endoscopy is indicated when any alarm symptoms (as listed above) are present. As stated in the definition, the diagnosis of NERD depends on the exclusion of erosive disease by endoscopy. In patients (off or on anti-reflux medication) who undergo upper endoscopy, the role of mucosal biopsy to detect histopathological changes consistent with GORD remains an area of controversy. Commonly carried out in clinical practice, biopsy of the distal oesophagus at endoscopy is not usually necessary if no visible abnormality is detected, but it can be useful to exclude specific diagnoses such as eosinophilic oesophagitis.

Oesophageal mucosal biopsy, performed at least 5 cm above the LOS, may demonstrate early changes of oesophagitis, including dilatation of the intercellular spaces.[16] It may also show inflammatory cells (neutrophils and eosinophils), epithelial hyperplasia (basal cell hyperplasia and elongated papillae), and dilated vessels in the papillae.[17] Studies are still questioning the yield of oesophageal mucosal biopsies as a diagnostic tool in NERD patients.[18,19]

A concern has been raised about overdiagnosing NERD during endoscopy because of the common use of anti-reflux medications, and patients already being on such medications (in many cases over-the-counter products).[20] One should not make the diagnosis of NERD in patients with normal endoscopy who are actively consuming or have recently consumed (within three to four weeks) histamine-2-receptor antagonists (H_2RAs) or PPIs. A subset of patients with healed erosive oesophagitis may remain symptomatic and thus should not be considered as having NERD.

In the future, biopsy may become routine if dilated intercellular spaces or other microscopic changes become accepted criteria of NERD.

Twenty-four-hour oesophageal pH monitoring

The pH test is invasive, inconvenient to patients and not readily available. It is currently indicated in NERD patients who are candidates for anti-reflux surgery.[17] Studies have demonstrated that NERD patients with an abnormal pH test are more likely to respond to anti-reflux treatment. There is a close correlation between the extent of oesophageal acid exposure and response to PPIs.[21] The greater the acid exposure, the higher the proportion of patients who achieve complete symptom resolution after four weeks of treatment with a PPI once daily.[22] However, mere abnormal oesophageal acid exposure is an insufficient clinical predictive factor for response to therapy. Many NERD patients with a mildly abnormal pH test demonstrate a limited response to PPI once daily, almost similar to what has been observed in patients with functional heartburn (normal pH test).

The pH test has also demonstrated some clinical value in distinguishing patients with hypersensitive oesophagus (normal pH test but positive symptoms) from those with symptoms that are likely to be caused by nonacid-reflux-related stimuli. The former patients appear to respond favourably, albeit in a limited way, to double-dose PPI.[23]

Performing 24-hour oesophageal pH monitoring for the purpose of subcategorising NERD patients is not practical in clinical practice. However, given the fact that the PPI empirical trial is as sensitive as the pH test in identifying GORD patients, the former is commonly practised by primary care physicians and gastroenterologists alike.[24] Lack of response of a NERD patient to PPI twice daily is suggestive of non-acid reflux-related stimuli that are unlikely to improve with escalating doses of PPI.

Proton-pump inhibitor trial of therapy

The PPI therapeutic trial (or PPI test), which entails using a high dose of PPI over a short period of time, has been found to be an accurate and a cost-effective diagnostic strategy in patients with GORD.[25,26] Patients with NERD demonstrated marked improvement in symptom response rate when the omeprazole test dose (given over seven days) was increased from 40 mg once daily to 40 mg twice daily.[27] Schenk et al evaluated 85 NERD patients with the PPI test (omeprazole 40 mg daily) administered over a period of 14 days, and demonstrated a 66% sensitivity in this group of patients.[25] The PPI test consistently had a low specificity in

GORD patients, specifically in NERD patients. A possible explanation for this phenomenon is the partial response to therapy by patients with functional heartburn, particularly those with a "sensitive oesophagus".

Treatment

The majority of patients with symptomatic reflux are managed by their family physicians. Referral to a specialist is usually reserved for those with alarm symptoms or those who do not achieve an adequate response to the trial of therapy. The goals of treatment in NERD are the following:

- Acute and long-term relief of symptoms.
- Maintenance of clinical remission.
- Restoration of quality of life.

Nonmedicinal/nonsurgical approaches

These measures are aimed at improving LOS function and physically decreasing reflux of gastric acid into the oesophagus. They are identical to those measures used for erosive disease and include the following:

- Eating several smaller meals instead of fewer larger meals.
- Ensuring at least two to three hours between eating and lying down at night.
- Using over-the-counter antacids.
- Avoiding certain acid-increasing foods such as fatty foods, citrus fruits, alcohol and caffeine.
- Weight loss/maintaining a healthy body weight.
- Avoiding tight-fitting clothing around the abdomen.
- Smoking cessation.
- Elevation of the head of the bed at night.
- Avoiding bending over from the waist; instead, bend at the knees and keep you back upright.
- Avoiding straining during bowel movements.

Medical therapy

Proton-pump inhibitors

At present, a PPI-based step-down treatment strategy is suggested for GORD. This thus applies to NERD as well. PPI treatment is the most efficacious therapeutic modality in NERD patients, and it has been reported to be cost effective.

However, it is also true that symptom control is more difficult in NERD compared to that in erosive disease. This is mainly attributed to the functional component in NERD. Thus NERD should not be seen as a milder form of erosive disease, and PPI therapy should not be delayed or avoided and the patient ineffectively treated with H_2RAs or mucosal protectants which show very limited response rates. On-demand therapy is an option for patients, if they remain symptom free, as it is known that the majority of patients with NERD do not progress to erosive disease or Barrett's oesophagus.

Pain modulators

Pain modulators, e.g. tricyclics or selective serotonin reuptake inhibitors, also have a role to play in NERD. They address the functional component of NERD, and are an option in patients where a satisfactory response is not achieved with PPI alone.

Prokinetic therapy

Prokinetic therapies are thought to be effective by reducing the reflux of duodenal juice. Certain prokinetics, e.g. mosapride, also improve oesophageal motility, thereby shortening bolus transit time and enhancing the contraction strength at the LOS.

Surgery

The role of anti-reflux surgery in patients with NERD has scarcely been evaluated. Nissen fundoplication has been shown to reduce the frequency of TLOSR, the main underlying mechanism in NERD. However, patients with NERD and an abnormal pH test had a lower symptom improvement rate, a higher level of dissatisfaction and more reports of postoperative dysphagia than patients with erosive oesophagitis.[28]

Complications

Thus far, clinical evidence is lacking to indicate that patients with NERD are at risk of developing any of the typical complications of GORD, i.e. Barrett's oesophagus or adenocarcinoma of the oesophagus, over time. The main impact of the disease is on patients' perceptions of their quality of life.

Conclusions

NERD is the most common presentation of GORD in community-based patients with moderate to severe symptoms, and causes a significant impairment in quality of life. Therapy with PPIs results in improvement or complete resolution of symptoms in most NERD patients and restores quality of life. The majority of patients with reflux symptoms are effectively managed with empiric PPI therapy prescribed by their family physician, without knowing whether they have erosive or nonerosive disease.

The role of surgery in NERD is currently not well defined and the risk of progression to erosive disease or Barrett's oesophagus is low. That said, NERD should never be seen

as a "milder" form of erosive disease. NERD is shown to have a decreased response rate to PPIs compared to the response rate of erosive disease.

Identification of the relevant symptoms and initiation of a trial of acid suppression, in cases where alarm symptoms have been excluded, is important in the effective management of NERD. Where alarm symptoms are experienced or if there is a non-response to PPI therapy, the patient should, as in the case of GORD, be referred for endoscopic evaluation.

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