

Distinction between patients with non-erosive reflux disease and functional heartburn

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Abstract

Non-erosive reflux disease (NERD) and functional heartburn (FH) are two different clinical entities and the clear distinction between the two forms is actually possible thanks to the use of impedance-pH monitoring. NERD is the more common manifestation of gastro-esophageal reflux disease (GERD), one of the most widespread chronic gastrointestinal disorders in Western countries. The absence of visible lesions on endoscopy and the presence of troublesome reflux-associated (to acid, weakly acidic or non-acid reflux) symptoms are the two key factors for the definition of NERD. FH is an exclusive diagnosis and is defined by the Rome III criteria as a burning retrosternal discomfort, excluding GERD and esophageal motility disorders as a cause of the symptom. FH does not have any type of reflux underlying symptoms and psychological factors seem to be more expressed in FH patients than in patients with reflux-provoked disturbances. The aim of our review is to report the state-of-the-art knowledge about NERD and FH, to clarify their features and differences and to stimulate new research in this field.

Keywords Non-erosive reflux disease, functional heartburn, gastro-esophageal reflux disease, esophageal impedance-pH monitoring, PPI

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Introduction

Non-erosive reflux disease (NERD) and functional heartburn (FH) have a common predominant symptom, heartburn. The latter is defined as a burning sensation in the retrosternal area [1], and has been reported to occur at least once a week in up to 20% of the general population [2,3].

Traditionally, heartburn has been considered the most specific symptom of gastro-esophageal reflux disease (GERD) [1]. However, in the last decade, different pathophysiological studies carried out in endoscopy negative patients, initially by means of pH-metry [4,5], and more recently by using the modern esophageal impedance-pH monitoring [6], have moved the goalpost in this field.

Indeed, before these investigations, the clinical opinion was that erosive reflux disease (ERD) represented the more common manifestation of GERD. Nowadays, thanks to the application

of esophageal impedance-pH testing with the possibility to detect all kind of refluxes and to correlate symptoms to them, we discovered that GERD is a heterogeneous condition, in which NERD represents about 70% of the GERD umbrella [6,7]. Moreover, this technique was able to narrow down the proportion of patients with FH, an entity that was first defined and differentiated from GERD with the Rome II criteria on functional esophageal disorders [8].

The definition and comprehension of NERD and FH has evolved rapidly through the medical literature in the last decade. Thus, the aim of our review is to report the updated knowledge about NERD and FH, to clarify their features and differences and to stimulate new research in this field.

Methods

We performed a systematic computerized (Medline) and manual literature search for the period up to February 2013, with particular focus on the last decade. The following medical subject heading terms were used: "GERD", "gastro-esophageal reflux disease", "reflux disease", "acid reflux", "weakly acidic reflux", "non-acid reflux", "NERD", "non-erosive reflux disease", "hypersensitive esophagus", "endoscopy-negative reflux", "microscopic esophagitis", "dilatation of intercellular spaces", "functional heartburn", "functional gastrointestinal disease", "Rome criteria", "pH-metry", "impedance-pH testing". These terms were used alone or in combination with the

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following terms: “definition”, “epidemiology”, “pathogenesis”, “pathophysiology”, “management”, “treatment”, “PPIs”, “proton pump inhibitors”, “endoscopic therapy”, “surgical therapy”, “fundoplication”, “H2-blockers”, “alginates”, “antiacids”, “pain modulators”, “antidepressants”.

We critically reviewed all full-text papers and relevant abstracts published in English. The reference lists from the articles identified were searched to identify any additional studies that may have been missed during the process.

Definitions and diagnostic criteria

NERD: According to the Montreal definition, NERD is a condition in which typical reflux symptoms, heartburn and regurgitation, are defined as troublesome in patients with negative endoscopy [1]. As reported above, nowadays we know that this clinical entity is the more common manifestation of GERD, one of the most widespread chronic gastrointestinal diseases in Western countries. The absence of visible lesions on endoscopy and the presence of troublesome reflux-associated (to acid, weakly acidic or non-acid reflux) symptoms are the two key factors for the definition of NERD [6]. This clinical entity requires instrumental diagnostic testing (endoscopy and esophageal impedance-pH testing) for its correct diagnosis (Table 1).

There are studies in the literature reporting that over 50% of patients presenting with reflux symptoms in primary care settings have negative endoscopy (absence of visible mucosal breaks) [9-11]. More recent European investigations showed

that the rate of endoscopy-negative patients with reflux symptoms is as high as 75% [12,13]. However, we cannot exclude that some of these patients were ERD, falsely labeled as NERD, because their esophageal erosions were healed by previous or current proton pump inhibitor (PPI) treatment.

Regarding the second key factor, important improvements in the definition of NERD were established with the advent of esophageal impedance-pH testing; today the state-of-the-art tool for the diagnosis and subclassification of GERD. Using this technique, we now know that stimuli other than acid can evoke typical reflux symptoms [14]. Fass and colleagues were the first to demonstrate that only 45% of NERD patients have an increased esophageal acid exposure, while the remaining 55% do not have an excess of acid in their esophagus. In the latter group, they identified a subgroup of patients with an esophagus hypersensitive to acid reflux and an additional one with an unclear association between heartburn and some kind of non-acid reflux [15]. More recently, our group studied 150 NERD patients off PPI therapy and found that an increased esophageal acid exposure was present only in 42% of cases. The remaining 58% of patients had normal esophageal acid exposure and among them, 32% and 26% respectively, had a positive and negative symptom association probability (SAP) [16]. In this study, we were able to subdivide patients with typical reflux symptoms and normal upper gastrointestinal endoscopy as follows: 1) NERD pH-positive patients with normal endoscopy and abnormal distal esophageal acid exposure; 2) hypersensitive esophagus (HE) patients with normal endoscopy, normal distal esophageal acid exposure and positive symptom association for either acid (acid hypersensitive esophagus) or non-acid reflux (non-acid hypersensitive esophagus); and 3) FH patients - who we will discuss in more detail later in the paper (Table 2).

To conclude, esophageal impedance-pH testing has allowed us to differentiate acid from weakly acid reflux or non-acid reflux (weakly acidic reflux + weakly alkaline reflux) [17-21] and to establish a clear association of symptoms with acid and/or non-acid reflux [22,23]. The new, more recent finding achieved with this technique is the detection of the subset of patients with a hypersensitive esophagus to non-acid reflux and this narrows down the proportion of patients with FH.

FH: According to Rome II criteria, FH was firstly defined as a “burning retrosternal discomfort or pain, presenting for at least for 12 weeks in the preceding 12 months, in the absence of pathologic gastro-esophageal reflux, achalasia, or other motility disorders with a recognized pathologic basis” [8]. This definition has evolved with the Rome III criteria, in which FH is defined as a “retrosternal burning in the absence of GERD that meets other essential criteria for the functional esophageal disorders”. The diagnostic criteria are the “presence for at least 3 months, with onset at least 6 months before diagnosis of: 1) burning retrosternal discomfort or pain; 2) absence of evidence that gastro-esophageal acid reflux is the cause of the symptom; and 3) absence of histopathology-based esophageal motility disorders” [24] (Table 1). A big step forward was taken with the Rome III criteria because the so-called “acid sensitive esophagus”, initially included in the FH group by the Rome II criteria, has been re-qualified as part of the GERD spectrum.

Table 1 Diagnostic criteria of non-erosive reflux disease and the functional heartburn

| Non-erosive reflux disease |
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| Troublesome heartburn and/or regurgitation |
| Normal upper gastrointestinal endoscopy and no eosinophilic esophagitis on biopsies |
| Abnormal impedance-pH monitoring off proton pump inhibitors, with abnormal acid exposure and/or positive symptom association analysis (symptom index >50%, symptom association probability >95%) |
| Functional heartburn |
| Retrosternal burning or discomfort (heartburn) |
| Unsatisfactory or non-response to double dose of proton pump inhibitors (PPIs) after at least 8 weeks of therapy |
| Normal upper gastrointestinal endoscopy and no eosinophilic esophagitis on biopsies |
| Normal esophageal manometry |
| Normal impedance-pH monitoring off PPI, with normal acid exposure and negative symptom association analysis (symptom index <50%, symptom association probability <95%) |

Table 2 Definitions of gastro-esophageal reflux subgroups according to endoscopy and pH-impedance testing with symptom association analysis

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|--|
| Erosive reflux disease (ERD): patients with mucosal breaks at endoscopy |
| Non-erosive reflux disease or true NERD: patients with typical reflux symptoms, negative upper endoscopy and abnormal esophageal acid exposure at impedance-pH monitoring |
| Acid hypersensitive esophagus: patients with negative upper endoscopy, normal esophageal acid exposure and positive symptom association to acid reflux (SI>50%, SAP>95%) at impedance-pH monitoring |
| Non-Acid hypersensitive esophagus: patients with negative upper endoscopy, normal esophageal acid exposure and positive symptom association to non-acid reflux (SI<50%, SAP>95%) at impedance-pH monitoring |
| Functional heartburn: patients with negative upper endoscopy, normal esophageal acid exposure, negative symptom association to any type of reflux (SI<50%, SAP<95%) at impedance-pH monitoring and non-response to PPIs |

SI, Symptom index; SAP, symptom association probability

Acid-sensitive esophagus, better defined as acid hypersensitive esophagus, is characterized by a positive temporal relationship between acid reflux and symptom events despite a normal acid exposure to the esophagus [25,26], while FH does not have any type of reflux underlying its symptoms. It is important to note that the Rome III definition of FH only refers to pH monitoring, but nowadays we should consider the added value of impedance-pH monitoring in distinguishing this clinical entity from NERD. Indeed, it has been clearly shown that when this technique is used to detect acid and non-acid reflux and to assess the temporal relationship of reflux events and symptoms, the proportion of patients with FH decreases [22]. Our group recently conducted a study demonstrating that in the normal-acid exposure population the contribution of impedance-pH increased the number of patients with HE by 10% and reduced the rate of patients with FH by the same factor, highlighting the added diagnostic value of impedance-pH monitoring in the distinction between NERD and FH [27].

It is worth noting that in a large part of medical literature regarding FH, the Rome III criteria are not taken into account and that the definition of NERD is unclear and wrong, issues that make a comparison between studies in this field arduous.

Epidemiology and clinical presentation

Little is known about the epidemiological and clinical features differentiating NERD and FH, mainly because of a lack of standardized definition of the two diseases through the literature, as mentioned above.

Studies using both endoscopy and pH-monitoring indicate that FH ranges from 10% to 40% of heartburn patients presenting to gastroenterologists [15,28], with percentages

that markedly differ between primary care settings and tertiary centers, where impedance-pH monitoring is performed.

Similar to other gastrointestinal functional disorders, a female preponderance in patients with FH as compared to the NERD group has been reported [29-32]. Moreover, our group demonstrated that FH patients have a significantly increased prevalence of dyspeptic symptoms, such as postprandial fullness, early satiety, bloating and nausea compared with the NERD ones [33]; this data was confirmed by Bлага and colleagues [31] and Hershcovici *et al* have hypothesized that FH and functional dyspepsia may constitute a unique functional disorder [34]. Our group also found that symptoms such as epigastric pain and epigastric burning were more frequently encountered in NERD pH-positive patients, thus confirming previous studies showing that the “epigastric pain syndrome” according to Rome III criteria is more prevalent in patients with abnormal pH test [35]. We also showed that FH patients are similar to controls in terms of acid esophageal exposure, BMI values, prevalence of hiatal hernia, esophageal motility and lower esophageal sphincter tone, but differ from NERD, reflux esophagitis and complicated reflux disease [5,36]. Moreover, there are studies showing that irritable bowel symptoms are frequent in GERD patients [37-39].

Like the heartburn symptom of NERD, FH usually occurs during the daytime and may be elicited or exacerbated by certain foods and by lying down or bending over and by doing exercise [1].

A group from Jerusalem showed that in FH patients reflux symptoms severity was inversely related to age and that the opposite was true in case of NERD patients [30]. These authors also demonstrated that gender and esophageal acid exposure time (AET) were not predictors of reflux symptoms severity in both groups when the variables were studied independently, while smoking was independently associated with reflux symptoms severity only in the NERD group [30].

Furthermore, recent studies showed that psychological factors, like stress and anxiety are more common in FH patients than in patients with reflux-provoked symptoms [40,41]. Shapiro and colleagues reported that demographic factors, frequency of hiatal hernia and *Helicobacter pylori* infection were not statistically different between the two groups of patients, but there was an increased report of chest pain, somatization and alteration of autonomic function in the FH patients [41].

From a microscopic point of view, many studies have shown that the presence of dilated intercellular spaces (DIS) by electron microscopy is a common finding in patients with NERD [42-44]. Our group also found this histological alteration by light microscopy in 80% of NERD patients and in 30% of asymptomatic subjects [45,46] and we have recently observed that microscopic esophagitis, including DIS, is represented in 15% of controls, 13% of FH patients, 65% of HE and 77% of increased AET patients [47]. These results have been confirmed by Vela *et al* [48], who showed that only 9% of FH patients had an intercellular distance superior to the normal range, compared to 60% of those with GERD. These findings suggest that the absence of DIS could be used as a simple morphological marker to identify patients with FH,

thus avoiding the use of the invasive and long-lasting 24-h impedance-pH testing in this group of patients.

Pathogenesis of heartburn

Regarding NERD, to date the observation of the presence of DIS in these patients [43-49] supports the “penetration theory” for the pathogenesis of this subgroup of GERD. This theory implies the increased permeability of the epithelial esophageal barrier to noxious agents (acid and/or weakly acidic) refluxing from the stomach [49]. Indeed, it has been hypothesized that noxious agents in the esophagus, thanks to the increased intercellular space between epithelial cells, activate nociceptive receptors more easily, such as the transient receptor potential acid-sensing ion channel (ASIC) or the TRPV1 (vanilloid) receptor. Activation of these receptors generates signals that are transmitted to the central nervous system via either vagal or spinal nerves [50]. Another factor potentially implicated in symptom induction in the NERD group is the proximal migration of refluxate that has been shown to be an important predictor of symptom generation in NERD patients studied both “on” and “off” PPI therapy [22,23]. Moreover, an increased sensitivity of the proximal portion of the esophagus to both mechanical and chemical (acid and weakly acid) stimuli has been described [51,52]. Large drops in esophageal pH, low pH nadir, alterations in clearing time and presence of gas mixed with liquid in refluxate are additional variables involved in the perception of symptoms in NERD patients [53-55]. A recent discovery is the role of weakly acidic reflux in the generation of GERD symptoms, in particular in the HE subgroup [56]. It must be also emphasized that inflammation of the esophageal epithelium can induce an up-regulation of pain transmission and inflammatory products such as bradykinin, histamine and cytokines, thus permitting the firing of nociceptors at reduced thresholds [57,58].

Little is known about the FH pathogenesis. Vela and colleagues showed no significant difference between FH patients and controls regarding intercellular esophageal distance [48]. The authors also demonstrated that the heartburn symptom may be perceived despite the maintenance of the integrity of the mucosa. Farré *et al* also showed that the presence of DIS alone is not sufficient to generate symptoms, at least in healthy subjects in whom esophageal perfusions of acid and bile were performed [59]. Moreover, we recently showed that the number of total acid and weakly acid refluxes does not differ between FH and control subjects and is significantly lower than in the two subsets of NERD (pH-positive and HE). Also the proximal migration of refluxate is similar in FH and controls and significantly lower than in the two subsets of NERD [32]. Finally, patients with FH who report heartburn without any correlation with gastro-esophageal reflux events seem to be more sensitive to mechanical and/or chemical stimuli than NERD patients [49]. Further studies are needed to better clarify the mechanisms of symptom generation in patients with NERD and FH.

Diagnosis and therapy

Patients affected by heartburn are firstly treated with PPIs, such as omeprazole, rabeprazole, pantoprazole, lansoprazole, esomeprazole, that represent not only the best therapy to use in clinical practice but also a diagnostic test in order to easily distinguish patients with GERD from the FH group. If patients with heartburn respond to PPIs and do not have alarm symptoms (e.g. age >50, familiarity for GI cancers, weight loss, recurrent vomiting, dysphagia, bleeding, or anemia) we can consider them as GERD patients and avoid an upper endoscopy. However, despite the documented benefit of standard doses of PPI drugs in healing erosive esophagitis and relieving reflux symptoms [60-63], recent studies found that about 40% of GERD patients have an inadequate response to PPIs and that FH patients have a partial or unsatisfactory response to them [64,65]. The AGA medical position the management of GERD [66] recommends performing an upper endoscopy with biopsies in patients who have not responded to an empirical trial of twice-daily PPI therapy. Biopsies should target any area of suspected metaplasia, dysplasia, or malignancy and, in the absence of visual abnormalities, they are needed to exclude eosinophilic esophagitis. Patients with normal findings on endoscopy and on biopsy specimens are recommended to undergo esophageal manometry and ambulatory impedance-pH or wireless pH monitoring. Esophageal manometry is needed to exclude any primary esophageal motility disorder, such as achalasia and distal esophageal spasm. Ambulatory impedance-pH or wireless pH monitoring permit to carefully analyze the temporal relationship between the occurrence of symptom and the acid and/or non-acid reflux events and the results of this correlation should be expressed using the SAP or the symptom index. This technique allows us to subgroup NERD patients as already reported [16] (Table 2). Nowadays it is not clear whether this test must be performed “on” or “off” PPI therapy. The diagnosis of FH requires discontinuing PPI drugs for at least 7 days before performing the procedure [49]. Moreover, Kahrilas and Smout, in a recent revision of Rome III criteria, suggested a diagnostic algorithm for the evaluation of NERD patients including the use of impedance-pH performed off-PPI therapy as an important step to define these subjects [67].

It is important to keep in mind that FH is an exclusive diagnosis and that this disease should be suspected if a patient refers to a tertiary care center after a long history of troublesome heartburn that has been partially or completely non-responsive to a PPI trial, usually in a double dose regimen taken for several months. Endoscopy with biopsy specimens must show the absence of eosinophilic esophagitis to confirm FH diagnosis (Table 1).

As mentioned above, acid suppression represents the mainstay of GERD medical treatment. Proton pump inhibitors, by inhibiting the H⁺-K⁺-adenosine triphosphatase pump of the parietal cell, markedly reduce gastric acid secretion and due to this mechanism, only patients with an excess of acid in their esophagus (ERD and NERD pH-positive) and those with acid HE can respond satisfactorily to these drugs. On the contrary, non-acid HE and FH patients are likely

to be refractory to PPIs [16,68]. The most proposed long-term modality of PPI administration in NERD patients has been “on demand therapy” [66] since the relapse rate of this condition is high. There are many studies demonstrating a significantly greater reduction in symptoms relapse with PPI administered on demand compared to placebo [69-71]. In case of partial or incomplete response to PPIs, the old antacid or alginate compounds can be used in NERD patients, in whom these drugs are able to relieve typical reflux symptoms very quickly [72-75]. Other type of drugs, aimed to reduce visceral hypersensitivity, like antidepressant agents and selective serotonin re-uptake inhibitors, are reasonable in non-acid HE and FH patients. Clinical evidence showed that these drugs have a therapeutic role in patients with irritable bowel syndrome and functional dyspepsia and given the association of these diseases with FH, also a benefit in FH cannot be excluded [31,49]. However, despite the common use of these drugs to relieve symptoms in FH patients, only few placebo-controlled studies aimed to demonstrate the efficacy of these drugs can be found in medical literature.

Regarding lifestyle modifications to relieve NERD symptoms, the AGA medical position statement recommends to avoid foods that may precipitate reflux (e.g., coffee, alcohol, chocolate, fatty foods), to avoid acidic foods that may precipitate heartburn (e.g., citrus, carbonated drinks, spicy foods), and to adopt behavior that may reduce esophageal acid exposure (weight loss, smoking cessation, raising the head of the bed, and avoiding recumbency for 2-3 h after meals) [66]. Psychological approaches and/or relaxation therapy may be beneficial for patients with FH, but to date no published controlled trials demonstrating the efficacy of these types of intervention are available.

An additional therapeutic option to control chronic heartburn in NERD may be surgery, which must be avoided in FH, because any kind of reflux underlying the symptom is not present in this disorder. In recent years there is growing evidence that fundoplication is the best surgical therapy to control drug refractory symptoms in patients with both acid and weakly acid reflux [76-81]. Broeders *et al* recently showed that patients with positive or negative SAP have the same postoperative outcomes, but all these patients had an abnormal esophageal acid exposure and this excluded the presence of FH patients [82]. Because of the completely different surgical indication between NERD and FH patients, it is of maximum importance to make the correct pre-operative diagnosis with the application of impedance-pH-metry testing.

Conclusions

The advent of impedance-pH monitoring has allowed us to better define and subdivide the heterogeneous subgroups of patients traditionally comprised within the group of NERD. In particular, this technique has clearly separated the subsets of NERD from FH. This clear distinction has markedly improved our management of endoscopy-negative reflux

patients. However, although the pathogenesis, the diagnostic work-up and the management of NERD are clearer than those of FH, further efforts are needed to improve our knowledge of both diseases. The promotion of new studies using well standardized definitions of NERD and FH and acknowledged clinical applications of impedance-pH monitoring (“on” or “off” PPI therapy) are of paramount importance. Moreover, further outcome studies with novel anti-reflux drugs, surgical and endoscopic procedures are mandatory to define the clinical importance of the above-mentioned findings and to clearly define the best therapeutic approach for these patients.

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