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FUNCTIONAL DISORDER OF UPPER GASTROINTESTINAL TRACT: NONULCER DYSPEPSIA

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Abstract

Background: Nonulcer dyspepsia is a common, but poorly defined symptom complex occurring in the upper gastrointestinal tract. Because of the uncertainty of definition, pathogenesis, and relationship between symptom resolution and treatment, the optimal management strategy has long been controversial. The purpose of the present study was to investigate the incidence, causes, clinical manifestations, and methods of treatment in nonulcer dyspepsia.

Methods: 38 patients aged 19 to 74 years with nonulcer dyspepsia were examined from August 2003 to December 2007. According to complaints, 81.6% of patients were referred to nonspecific dyspepsia; 13.1% of patients were referred to dysmotility-like dyspepsia and 5.3% of patients were referred to ulcer-like dyspepsia.

Results: 30 patients were assessed by Rome II modular questionnaire designed for patients. Two patients after medical therapy had mild pain in midepigastric area, one woman had cyclic vomiting. For one patient there was not any improvement in condition after treatment. The rest of the patients, 86.7%, did not have any clinical sign of nonulcer dyspepsia.

Conclusions: Our study revealed that the main cause of nonulcer dyspepsia was duodenogastric reflux. The empirical therapy is advisable in patients who do not have signs or symptoms of an underlying organic disorder, such as gastric ulcer or cancer.

Keywords: nonulcer dyspepsia, duodenogastrc reflux, gastroparesis, visceral pain, biliary dyskinesia.

Introduction

The term "dyspepsia" derived from the Greek words *dys* ("bad") and *pepsis* ("digestion"), refers to symptoms thought to originate in the upper gastrointestinal tract. Dyspepsia is often used to refer to upper abdominal pain or discomfort but may also encompass symptoms of early satiety, postprandial abdominal bloating or distention, nausea and vomiting. Dyspepsia can be episodic or persistent and is often exacerbated by eating [*McNamara D.. et al., 2000*].

Dyspepsia is a common, but poorly defined symptom complex occurring in the upper gastrointestinal tract and is frequently seen presenting symptom in primary care and gastrointestinal practice. Dyspepsia can be a manifestation of varied and, in some cases, serious diseases; however, in approximately 50% of patients, no organic cause for dyspeptic symptoms is found after a thorough investigation. When this occurs, the symptoms are considered to be functional (or nonulcer) dyspepsia, a condition the underlying pathophysiology of which is poorly understood. There are many possible and, at times, costly investigations that may be used in the investigation of dyspepsia, although clearly these cannot be applied to all cases, given the common prevalence of these symptoms and the minimal yield from exhaustive investigations in most cases. Furthermore, because of the uncertainty surrounding the definition, pathogenesis, and relationship between symptom resolution and treatment, the

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optimal management strategy has long been controversial. For these reasons, various algorithms were developed, recommending different treatment and research approaches that are based on patient characteristics. In understanding the usefulness of these approaches, it is essential to examine the epidemiology and natural history of uninvestigated dyspepsia in the context of the changing epidemiology and natural history of the common underlying organic diseases that cause dyspepsia. Patients with uninvestigated dyspepsia may have any of the organic diseases associated with dyspepsia, but most will have a final diagnosis of functional (or nonulcer) dyspepsia [*Johnson D. et al., 2001*].

The most common organic disorders causing dyspepsia are gastroduodenal ulcer, gastroesophageal reflux disease, and gastric cancer.

Nonulcer dyspepsia is a common condition worldwide; the exact incidence is unknown because most sufferers do not consult a physician. Population-based studies were aimed at screening for dyspepsia using a questionnaire and subsequently investigating positive subjects. Various investigators have shown that the incidence of nonulcer dyspepsia ranges from 7% to 38% among individuals with all types of dyspepsia. About 40% of all cases of nonulcer dyspepsia occur in patients younger than 25 and only 3%–7% of all cases occur in patients older than 60. Nonulcer dyspepsia has been associated with a positive family history of dyspepsia and that of peptic ulcer. The incidence is similar among men and women, but varies regionally [*McNamara D. et al., 2000*].

Diagnostic criteria of nonulcer dyspepsia are as follows: at least 12 weeks, which need not be consecutive, in the preceding 12 months of:

1) persistent or recurrent dyspepsia (pain or discomfort centered in the upper abdomen);

2) no evidence of organic disease (including at upper endoscopy) that is likely to explain the symptoms; and

3) no evidence that dyspepsia is exclusively relieved by defecation or associated with the onset of a change in stool frequency or stool form (i. e., not irritable bowel).

Nonulcer dyspepsia is subcategorized into ulcer-like, dysmotility-like, and nonspecific (unspecified) dyspepsia. Diagnostic criteria of nonulcer dyspepsia subgroups are: *ulcer-like dyspepsia*: pain centered in the upper abdomen is the predominant (most bothersome) symptom; *dysmotility-like* dyspepsia: an unpleasant or troublesome nonpainful sensation (discomfort) in the upper abdomen is the predominant symptom; this latter sensation may be characterized by or associated with upper abdominal fullness, early satiety, bloating, or nausea; *nonspecific (unspecified) dyspepsia:* symptomatic patients whose symptoms do not fulfill the criteria for ulcer-like or dysmotility-like dyspepsia [*Drossman D. et al., 2000a;b; McNamara D. et al., 2000; Talley N., 2001*].

A number of hypotheses have been proposed to explain the pathogenesis of nonulcer dyspepsia. The gastric acid hypothesis suggests that either hypersecretion of gastric acid or increased sensitivity to it is responsible for dyspeptic symptoms. The motor-disorder hypothesis suggests that motor disorders of the upper gastrointestinal tract, such as gastroparesis, small-bowel dysmotility, and biliary dyskinesia, cause dyspeptic symptoms. According to the psychiatric hypothesis, the symptoms of dyspepsia may be due to depression, anxiety, or a somatization disorder. The hypothesis of augmented visceral perception suggests that dyspeptic symptoms are exaggerated responses to physical stimuli such as pressure, distension, and temperature. The food-intolerance hypothesis proposes that certain food may cause dyspeptic symptoms by triggering secretory motor or allergic response [*Fisher R. et al., 1998*].

Despite the use of the term "nonulcer dyspepsia", which suggests an idiopathic functional disorder, a number of motility and nonmotility disorders stated below were identified as potential causes (Table).

In some patients with epigastric pain that occurs after meal and at night and that is relieved with antacids no ulcer is revealed on examination.

Table

Potential Causes of Nonulcer Dyspepsia:

I. Nonmotility disorders
1.Peptic-ulcer diathesis
2. Gastritis
2a. Hypersecretion of gastric acid
2b. Helicobacter pylori infection
2c. Bile (duodenogastric) reflux
2d. Viral infection
3. Duodenitis
4. Maldigestion or malabsorption of carbohydrates
5. Small-intestine parasites
5a. *Giardia lamblia*
5b. *Strongyloides stercoralis*
6. Chronic pancreatitis
7. Psychiatric disorders
8. Augmented perception of visceral pain
II. Motility disorders
1. Idiopathic gastroparesis
2. Nonerosive esophageal reflux disease
3.Small-intestine dysmotility
4.Gallbladder and biliary tract dysmotility

In some patients with dyspeptic symptoms, the duodenal mucosa may appear mottled, hyperemic, or irregular on endoscopy, with duodenitis revealed upon biopsy considered as potential cause of nonulcer dyspepsia [*Fisher R. et al., 1998*].

Some cases of dyspepsia may represent various stages of *Helicobacter pylori* infection and may subsequently progress to ulcer disease. The research of some foreign authorities has shown that almost 50% of patients with nonulcer dyspepsia are positive to *Helicobacter pylori* infection [*Fisher R. et al., 1998; McNamara D. et al., 2000*].

Virus-induced gastritis has been suggested as a cause of unexplained gastrointestinal symptoms, since some patients date the symptoms to a period when they had a viral-like illness. However, there is little objective evidence that any specific virus or viral infection causes dyspeptic symptoms.

Another potential cause of nonulcer dyspepsia is bile reflux into the stomach. A Roux-en-Y diversion of biliary flow has been used successfully in some patients, especially those with bile reflux after surgical treatment for ulcer.

Maldigestion and malabsorption of carbohydrates can be associated with a wide range of clinical signs, including abdominal pain with postprandial nausea and bloating.

Unexplained upper gastrointestinal symptoms, especially in patients who live in or have traveled to parts of the world where parasitic disorders are endemic, may be caused by giardiasis or strongyloidiasis.

The unexplained abdominal pain has been reported in a small number of women in whom the only evidence of chronic pancreatitis (exocrine-pancreatic-function insufficiency) was decreased secretion of bicarbonate into the duodenum. The pain was relieved by treatment with pancreatic-enzyme replacement.

Patients with abdominal pain have higher scores for depression, anxiety, neuroticism, and hypochondriasis than patients without abdominal pain. Exacerbations of nonulcer dyspepsia are often attributed to stressful events.

In recent years, there has been considerable interest in the hypothesis that patients with functional gastrointestinal disorders have an augmented perception of visceral pain. Many patients with nonulcer dyspepsia have an increased sensation of pain from both stomach and small-intestinal distention.

Gallbladder and biliary tract motor dysfunction may also cause nonspecific dyspeptic symptoms. Two types of dysfunction of the sphincter of Oddi cause dyspeptic symptoms, which are referred to as biliary dyskinesia. One type is characterized by an increased resting pressure of the sphincter of Oddi. The second is characterized by incoordination between either bile acid secretion or gallbladder contraction and relaxation of the sphincter of Oddi, resulting in bile-duct distention [*Fisher R. et. al., 1998*].

Gastric motor dysfunction has been reported in 25 to 60 percent of patients with nonulcer dyspepsia [*Stanghellini V. et al., 1996*].

Gastroscopy and ultrasonographic imaging show changes such as erosive prepyloric changes and gastric accommodation abnormalities, respectively, in a high percentage of patients with functional dyspepsia. The gastroscopy may show minor mucosal abnormalities, like "erosive prepyloric changes" [*Berstad A. et al., 1998*].

For treatment of nonulcer dyspepsia proton-pump inhibitors, histamine H_2 - receptors antagonists are administered for gastric acid suppression, and prokinetic agents (metoclopramide, cisapride, domperidone), as well as antibiotics for eradication of *Helicobacter pylori* infection, psychotropic medications (tricyclic antidepressants, anxiolytic agents), antinociceptive agents used to inhibit pain for patients with augmented visceral perception [*Fisher R. et. al., 1998; McNamara D. et al., 2000; Talley N., 200*1].

Antinociceptive agents used to inhibit pain or its perception include low-dose tricyclic antidepressants, kappa opioid agonists (e.g., fedotozine), serotonin-receptor antagonists (e.g., ondansetron and granisetron), and somatostatin analogs (e.g., octreotide) [*Fisher R. et al., 1998*].

There is evidence that symptoms in most patients with *Helicobacter pylori* positive functional dyspepsia do not improve with eradication of the infection [*Xia H. et al., 1998*].

Material and Methods

From August 2003 to December 2007, 38 patients (22 women and 16 men) aged 19 to 74 years with nonulcer dyspepsia were examined (Figure 1). According to complaints, 81.6% (31) of patients were referred to nonspecific dyspepsia; 13.1% (5) of patients were referred to dysmotility-like dyspepsia and 5.3% (2) of patients were referred to ulcer-like dyspepsia.

Research diagnostic questions for functional gastrointestinal disorders (Rome II integrative questionnaire) were used in order to establish diagnosis of nonulcer dyspepsia in our study.

In 24 patients hyperemia of gastric mucous membrane, especially in prepyloric part of stomach and duodenum, as well as reflux of bile from the duodenum into the stomach was found during endoscopic exploration of upper gastrointestinal tract. In one patient there was not any pathological change or evidence during endoscopy. In X-ray examination of upper gastrointestinal tract back flow (reflux) of barium sulfate from the duodenum into the stomach was revealed in two patients, and the delayed stomach emptying was found in 11 patients. Duodenogastric reflux caused nonulcer dyspepsia in 68,4 % of patients, gastroparesis was found as cause of nonulcer dyspepsia for 31.6% of patients.

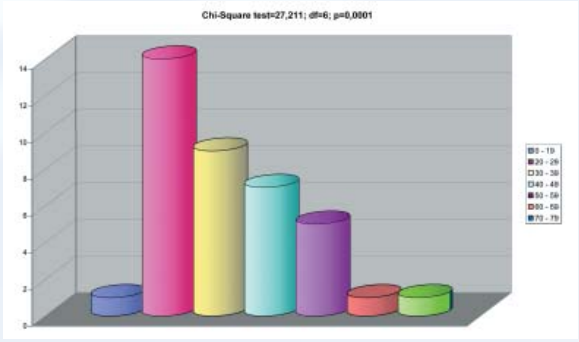

Figure 1 *Relationship between the number of patients and age.*

In a studied cohort 31 (81.6%) patients complained for nausea; 25 (65.8,%) patients vomited, basically, by bile (in 84% of cases); for 28 (73.7%) patients pain in epigastric area was the chief complaint; 11 (28.9%) patients had heartburn (non dominant sign); 14 (36.8%) patients had abdominal distention after meal and 13 (34.2%) patients had early satiety, and abdominal bloating. In 3 cases (7.9%) patients had headache alleviated after vomiting. Patients with nonulcer dyspepsia, 14 (63.6%) women and 4 (25%) men, suffered depression.

Seven patients (6 women and 1 man) with depression had pathological neurological signs like tendinous anisorefelxia, Babinski's sign, asthenia, dystonia. Medical therapy was the main method of treatment for all patients. For treatment of these patients proton-pump inhibitors, histamine H_2 - receptors antagonists were administered, and prokinetic agents, as well as treatment with pancreatic-enzyme replacement. For patients with pronounced depression and presence of pathological neurological signs psychotropic medication like tricyclic antidepressant amitriptyline at low

doses was administered.

The statistical analysis was performed using *Chi Square* - test. Differences with a *p* value less than 0.05 were considered statistically significant.

Results and Discussion

Within 1 to 8 months after treatment initiation 30 patients were assessed by Rome II modular questionnaire designed for patients. Two patients after medical therapy had mild pain in midepigastric area, one woman had cyclic vomiting. For one patient there was not any improvement in condition after treatment. The rest of the patients (86.7%) did not have any clinical sign of nonulcer dyspepsia. Our study revealed that duodenogastric reflux found in 68.4% of cases was the main cause of nonulcer dyspepsia (Figure 2).

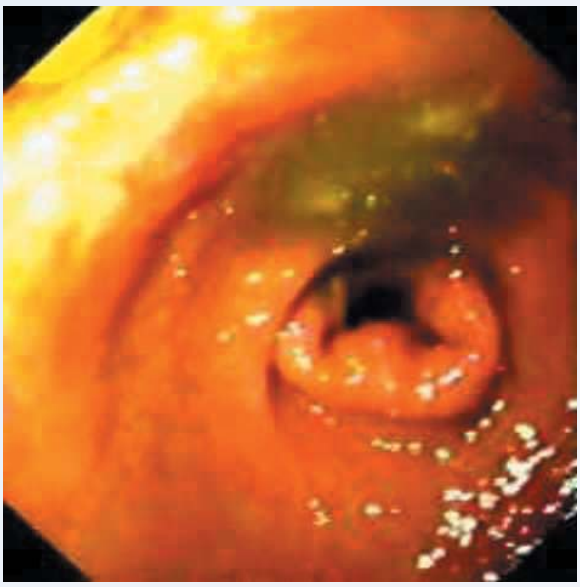

Figure 2. *Reflux of bile into the stomach (endoscopic imaging)*

In patients with documented nonulcer dyspepsia, whose predominant symptoms are ulcer-like, an H2 receptor antagonist or proton pump inhibitor therapy should be tried initially if pharmacologic therapy is considered essential. In those with predominant dysmotility-like symptoms, the choice of therapy is more difficult. A 2- to 4-week trial of a prokinetic agent is reasonable. Domperidone is a peripherally acting dopamine antagonist that is widely used. Likewise metoclopramide, domperidone stimulates esophageal, gastric, and small intestinal motility. Unlike metoclopramide, it does not cross the blood-brain barrier.

Nonulcer dyspepsia is a common disorder with a wide array of symptoms. It is not advisable to perform extensive diagnostic tests such as esophagogastroduodenoscopy, biliary tract ultrasonography, or even abdominal computed tomography in all patients. Whether all patients who present with dyspeptic symptoms should at least undergo initial endoscopy is controversial. Empirical therapy is advisable in patients who do not have signs or symptoms of an underlying organic disorder, such as gastric ulcer or cancer. If empirical therapy is indicated without diagnostic testing, where does one begin? Which approach – prokinetic therapy, acid suppression, eradication of *Helicobacter pylori*, psychotropic therapy, or antinociceptive therapy – is most effective? The answer to this question will be determined by studies of the short- and long-term effects of various therapies on symptoms and quality of life and by cost-benefit analyses.

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