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Functional dyspepsia – A multicausal disease and its therapy

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Abstract

Functional dyspepsia is a common chronic disorder with non-specific upper abdominal symptoms which can not be explained by organic or biochemical abnormalities. The dyspeptic symptoms are very compromising and bothersome and result in a substantial reduction of quality of life. The substantial direct and indirect medical and economical costs induce a high socioeconomic interest in the pathogenesis and the treatment options of this disease. Over the past 30 years several theories about the etiology of the symptoms in functional dyspepsia patients have been put forward. These include disorders of gastrointestinal motility, acid secretion, visceral hypersensitivity, adaptation and accommodation, Hp-infection, mucosal inflammation and finally genetic predisposition. There is increasing evidence that functional dyspepsia is a multi-causal disorder, which leads to altered processing of afferent information from the gastrointestinal tract to the CNS. Autonomic hypersensitivity and altered central processing could be a common phenomenon whereas motility changes, inflammation or altered secretion could increase neural afferent inputs. Treatment of this complex disorder could and should involve these different levels of symptom generation. Thus different approaches with anti-secretory, spasmolytic, prokinetic and anti-inflammatory effects and most preferably reduction of visceral hypersensitivity seem logical. This could explain the variety of drugs which show a positive symptomatic response. This could also offer the conclusion, whether a combination of these drugs could be clinically superior which remains to be proven. And this could offer a logical approach for the use of substances with a multi-target action, e.g. STW 5.

Keywords: Dyspepsia; Autonomic hypersensitivity; Motility disorder; Prokinetics; Antiacids; H2 receptor antagonists; PPI; Phytotherapy; STW 5; Iberogast; Iberis amara

Introduction

Functional dyspepsia is a very common cause of upper gastrointestinal symptoms and discomfort. These „dyspeptic" symptoms include postprandial fullness, early satiety, epigastric or localized pain, nausea, belching, bloating (Talley et al. 1987). Uninvestigated dyspeptic symptoms can be caused by organic disorders such as peptic ulcer, cholelithiasis, reflux disease or malignant disease. In a population with un-investigated dyspepsia about one third to half of the patients has an organic disease. However, in the majority of the patients with dyspeptic symptoms the routine clinical diagnostic procedures reveal no reasonable explanation for their "dyspeptic" symptoms. If these symptoms persist for a longer time period (more than 3 month) these patients are categorized as having functional dyspepsia. There are some frequent findings in the upper endoscopy (chronic gastritis, duodenitis) or in functional gastrointestinal tests (e.g. lactose deficiency), which are often

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Table 1. Definition of functional dyspepsia according to Rome II criteria (Talley et al. 1999c)

At least 12 weeks, which need not be consecutive, within the preceding 12 months of:
(1) Persistent or recurrent dyspepsia (pain or discomfort centered in the upper abdomen); and
(2) No evidence of organic disease (including 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).

taken as a possible explanations for the etiology of the symptoms (Allescher et al. 1999). It has been emphasized in guidelines that only those lesions or biochemical abnormalities will rule out functional dyspepsia which (a) reproducibly explain the generation of the symptoms an (b) lead to disappearance of the symptoms upon treatment (Malfertheiner et al. 2001).

Most importantly, patients with the leading or sole symptom of heart burn or acid regurgitation are no longer regarded as having functional dyspepsia. These patients are believed to have non erosive reflux disease (NERD) and are diagnosed and treated similar to reflux patients (Klauser et al. 1990; Talley and Vakil 2005).

Functional dyspepsia leads to a substantial reduction of quality of life in the range of or higher than peptic ulcer disease, severe reflux disease or gastrointestinal cancer (Table 1).

Un-investigated dyspepsia is one of the most common reasons for medical consultation in western countries. Up to 25% of the population have occasional upper gastrointestinal symptoms, however only a subgroup of these patients will actually consult a doctor (Malfertheiner et al. 2001; Mearin et al. 1991). These patients usually have more severe or more frequent abdominal symptoms and additional extra-intestinal symptoms (Holtmann et al. 1994).

The diagnosis and initial management of patients with un-investigated dyspepsia und with functional dyspepsia have been summarized and outlined in several national and international guidelines and the reader is referred to these recent publications (Malfertheiner et al. 2001; Talley et al. 1998, 1999b; Vakil 2005).

Etiology

The etiology of functional dyspepsia is still unclear. Several factors and mechanisms have been postulated as underlying cause of this disorder and most of these factors seem to play a role in the development of the symptomatology (Table 2).

Table 2. Postulated disorders and mechanisms for the development of dyspeptic symptoms in functional dyspepsia

- Visceral hypersensitivity
  - Increased perception of distention
  - Impaired or altered perception of acid
  - Visceral hypersensitivity as a consequence of chronic inflammation
- Motility disorders
  - Postprandial antral hypomotility
  - Reduced relaxation of the gastric fundus
  - Decreased or impaired gastric emptying
  - Changes of the gastric electric rhythm
  - Gastro-ösophagealer reflux
  - Duodeno-gastric reflux
- Changes in acid secretion
  - Hyperacidity
- *Helicobacter pylori* infection
- Stress
- Psychological disorders and abnormalities
- Genetic predisposition

Visceral hypersensitivity is currently the most likely candidate as a possible underlying cause leading to increased perception and processing of gastrointestinal neural inputs (Mearin et al. 1991). A majority of patients with functional dyspepsia responds to a lower threshold of distention as matched healthy volunteers. If this phenomenon also applies to other modalities, it could also explain why changes in motility, acid secretion and distention show similar symptomatic responses. It is still unclear whether this hypersensitivity only affects a circum-script region of the GI-tract or whether the hypersensitivity affects the whole gastrointestinal tract. Despite changes of the sensibility of the GI-tract there is no change of distention induced pressure (e.g. compliance). This implies that even physiological conditions and normal activities of the stomach and small bowl could lead to symptoms in patients with functional dyspepsia.

The cause of the hypersensitivity is still a matter of debate. There is some evidence that there is up-regulation of afferent mechanisms in the peripheral (intestinal) level, the pre-vertebral and spinal level. This up-regulation could be due to chronic irritation or inflammation or to an initiating process which caused the up-regulation still in a physiological process and now cannot be reversed. In the large bowel recent evidence draws some attention to a possible role of specific Ig G antibodies to certain food allergens. An elimination diet in these patients with irritable bowl syndrome leads to some symptomatic improvement