Evaluation of Symptom Presentation in Dyspeptic Patients Referred for Upper Gastrointestinal Endoscopy in Estonia

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Aim. To investigate the structure of dyspeptic symptoms and determine the association between dyspeptic symptoms and endoscopic findings in patients referred for upper gastrointestinal endoscopy by family physicians in a country with a high prevalence of Helicobacter pylori infection.

Methods. Consecutive outpatients (n = 172; median 36 years, range 18-75; 85 male; 87 female) were referred to upper gastrointestinal endoscopy. Patient history was recorded prior to upper gastrointestinal endoscopy using the computer-aided Glasgow Diagnostic System for Dyspepsia (GLADYS). Family physicians used open access endoscopy with a short waiting list. Two biopsies, both from the antrum and the corpus, were taken for histological assessment.

Results. Out of the 172 patients studied, 81% (n = 139) were H. pylori positive, 65% (n = 112) were younger than 45 years. The incidence of peptic ulcer was 44% (n = 75). Upper abdominal pain was the predominant complaint in 73% (n = 126) of the patients, as well as the most frequent overall complaint. Hunger pain, night pain, periodical nature of symptoms, and history over 2 years were of independent value in differentiating between peptic ulcer and functional dyspepsia. The symptoms of gastroesophageal reflux disease and irritable bowel syndrome predominated in the minority of patients (11% and 5% respectively) but accompanied other complaints in almost 2/3 of the patients. In 32 out of 75 patients with peptic ulcer, the symptoms of irritable bowel syndrome and in 29 cases the presence of frequent heartburn and regurgitation were noted.

Conclusions. Classical symptoms are valuable in predicting the diagnosis of peptic ulcer. Heartburn and acid regurgitation are present in both gastroesophageal reflux disease and peptic ulcer. Irritable bowel syndrome is common in patients with peptic ulcer.

Key words: dyspepsia; endoscopy; diagnosis, computer-assisted; Helicobacter pylori; peptic ulcer; gastroesophageal reflux; esophagitis

Dyspepsia is a frequent reason for attending primary care consultations (1,2) and it has a great impact on the patient’s quality of life (3). Not every patient in primary care may need investigations. Directing diagnostic tests only to those with a high probability of benefiting from having their diagnosis established (e.g. patients with peptic ulcer or gastric cancer) is valuable. Guidelines for the management of the dyspeptic patient are drawn up regarding the patient’s age and H. pylori status (4-6), as several studies have shown that dyspeptic symptoms are nonspecific for differentiating between diagnoses (7-10). However, the initial management plan in primary care has to be established on clinical grounds. Recent studies suggest that analysis of predominant symptoms and overlapping digestive syndromes can identify dyspepsia subgroups with different underlying pathophysiological features and aid in selecting appropriate treatment, especially in presence of gastro-esophageal reflux disease (11). Also, clinical prediction models of various causes of dyspepsia have been published by several authors (12). These studies are mostly conducted in non-primary care settings of Western countries with a known H. pylori prevalence of less than 50% among the population (13).

Estonia is a country with a high prevalence of H. pylori infection and related diseases: chronic gastritis, peptic ulcer, and gastric cancer (14-17). The risk of having duodenal ulcer is very high among male patients even in young age, but duodenal ulcer was also diagnosed in more than 20% of female patients under the age of 45 years, who had been referred for upper gastrointestinal endoscopy by their family physicians (15). Prevalence of H. pylori infection among dyspeptic patients was similar to that among general population, 81%. Whether the high prevalence of H. pylori infection influences the clinical presentation of the organic diseases of the upper gastrointestinal tract is unknown.

The aim of the study was to investigate the structure of dyspeptic symptoms and to determine an association between existing symptoms and endoscopic
and histological findings in patients referred for upper endoscopy by family physicians in a country with a high prevalence of *H. pylori* infection.

**Material and Methods**

**Patients**

Over a period of 20 months (1995-1997) 172 consecutive outpatients (median age 36 years, range 18-75), among them 85 male (median age 33, range 18-75) and 87 female (median age 38, range 18-73), referred for upper gastrointestinal endoscopy by their family physicians because of dyspepsia, were included in the study. Dyspepsia was defined as persistent or recurrent abdominal pain or abdominal discomfort, centered in the upper abdomen, with duration of at least 3 months. Discomfort was characterized by early satiety, fullness, nausea, retching, upper abdominal bloating, anorexia (18,19). Heartburn and regurgitation, are classified as gastroesophageal reflux disease according to the definition developed by the Rome II working team (18), and were classified as gastroesophageal reflux disease according to the Rome criteria (18,22), as at least 3 months' continuous or recurrent symptoms of abdominal pain which is relieved by defecation, or is associated with a change in stool consistency, or with two of the following symptoms – altered stool frequency, stool form, straining, urgency, incomplete evacuation, passage of mucus, or abdominal bloating (18,22).

**Follow-up of Patients after Upper Gastrointestinal Endoscopy**

To ascertain whether the initial findings at upper gastrointestinal endoscopy could explain dyspeptic symptoms, intercurrent events as well as the results of the investigations performed during the 36-month follow-up period, were recorded by researcher by interviewing the patients and their family physicians and reviewing all available data including medical records.

**Ethics**

The study was carried out in accordance with the Helsinki Declaration and was approved by the Ethics Committee of the University of Tartu.

**Statistical Analysis**

Statistical analysis was done using SPSS 8.0 for Windows (SPSS Inc., Chicago, IL, USA). The value of the criteria distinguishing between the two major diagnostic groups, peptic ulcer and functional dyspepsia, was assessed by comparing the group of functional dyspepsia (n=86) with the group of patients with peptic ulcer (n=75), and the group of *H. pylori* positive functional dyspepsia (n=58) with the group of *H. pylori* negative functional dyspepsia (n=28). All collected demographic and clinical parameters were analyzed. The significance of differences between the groups was tested with Fisher’s exact test or with chi-square test. The interdependence of the symptoms and patient characteristics was studied using logistic regression analysis. Statistical tests utilized the significance level of 0.05.

**Results**

Out of the 172 patients interrogated, 130 attended their first upper gastrointestinal endoscopy, and 42 were referred for a repeat investigation. Among 112 (65%) patients who were younger than 45 years, 49 (44%, 35 male and 14 female) had duodenal ulcer and 3 had (isolated) esophagitis at upper gastrointestinal endoscopy. Gastric cancer was diagnosed in one 36-year-old female patient. The prevalence of *H. pylori* infection among the investigated patients was similar to that recorded among general population, 81% (139 from 172). All patients with peptic ulcer, except for one with duodenal ulcer, were *H. pylori* positive. In 33 cases when histological examination did not reveal the presence of *H. pylori* infection, the gastric mucosa was normal in 29 cases, while 4 persons had signs of atrophy.
The mean follow up time after upper gastrointestinal endoscopy was 30 months (range 2-37 months). Owing to supplementary investigations during follow-up, both colon cancer and ulcerous colitis were diagnosed in one patient. Gallstones were the likely reason for the existing symptoms in 3 cases with “typical” pain attacks. During follow-up repeat upper gastrointestinal endoscopy was done in 6 from 168 patients. One female patient with duodenal erosions at the first endoscopy developed duodenal ulcer by the end of the second follow-up year, otherwise the endoscopic diagnoses had not changed. For the remaining patients, supplementary investigations added secondary or third diagnoses to the primary diagnosis.

Predominant Symptom
Abdominal pain was the predominant or the most bothersome symptom for 73% of the patients thus being the most frequent complaint at all (Table 1). Most of the remaining patients who reported some other principal complaint, had also been suffering from abdominal pain, leaving only a total of 4 patients free of pain. Logistic regression analysis revealed 4 significant predictors for peptic ulcer vs functional dyspepsia: duration of main symptom over 2 years (OR = 3.3; 95% confidence interval (CI) = 1.7-8.1), presence of episodic or seasonal pain (OR = 2.2; 95% CI = 1.3-4.2), presence of frequent night pain (OR = 2.6; 95% CI = 1.1-3.7), and presence of hunger pain (OR = 3.1; 95% CI = 1.2-6.6). The model explained 55% of the overall variance (Nagelkerke R² = 0.55).

Heartburn and Acid Regurgitation. In only 11 cases were heartburn or regurgitation mentioned as the main complaint. However, altogether 119 patients answered positively to the question about heartburn (58 frequent heartburn) and 115 patients complained of acid regurgitation at the time of the present illness, or during earlier similar episodes. Both symptoms coexisted in 90 cases. The endoscopic diagnoses of the patients who often experienced gastroesophageal reflux disease symptoms are presented in Figure 1.

Symptoms of Irritable Bowel. Symptoms characteristic of irritable bowel syndrome were reported by 126 patients (73%). Altogether 68 patients had experienced 3 or more symptoms of irritable bowel syndrome; 58 patients had 1-2 symptoms; 46 patients denied having symptoms of irritable bowel syndrome. Patients with symptoms of irritable bowel syndrome

Table 1. Predominant complaints, endoscopic findings and H. pylori status of 172 patients referred for upper gastrointestinal endoscopy by their family physicians

<table>
<thead>
<tr>
<th>Predominant symptom</th>
<th>Endoscopic findings (No. of patients)</th>
<th>H. pylori status (positive/ negative)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>duodenal ulcer* gastric ulcer† esophagitis gastric cancer normal or minor findings Total (%) negative)</td>
<td>64/1 100/0 3/2 1/0 61/30 139/33 139/33</td>
</tr>
<tr>
<td>Upper abdominal pain</td>
<td>58 10 2 1</td>
<td>55 126 (73) 103/23</td>
</tr>
<tr>
<td>Weight loss/general being unwell</td>
<td>2 0 1 0</td>
<td>11 14 (8) 12/2</td>
</tr>
<tr>
<td>Heartburn/dysphagia/regurgitation</td>
<td>1 0 2 0</td>
<td>8 11 (6) 8/3</td>
</tr>
<tr>
<td>Fullness/bloating</td>
<td>2 0 0 0</td>
<td>9 11 (6) 9/2</td>
</tr>
<tr>
<td>Diarrhea/constipation</td>
<td>1 0 0 0</td>
<td>4 5 (3) 3/2</td>
</tr>
<tr>
<td>Anorexia/vomiting/other</td>
<td>1 0 0 0</td>
<td>4 5 (3) 4/1</td>
</tr>
<tr>
<td>H. pylori positive/negative</td>
<td>64/1 100/0 3/2 1/0 61/30 139/33 139/33</td>
<td></td>
</tr>
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</table>

*Includes 5 cases of concomitant and esophagitis at endoscopy.†Includes 2 cases of concomitant gastric ulcer and duodenal ulcer at endoscopy.
belonged to different diagnostic groups by their findings at upper gastrointestinal endoscopy, including peptic ulcer in 32 cases (Fig. 2). Comparison of the patients with peptic ulcer and those with functional dyspepsia indicates that the pain which is sometimes relieved after defecation is significantly more common among patients with peptic ulcer (p<0.001, Fisher’s exact test). The other symptoms of irritable bowel syndrome did not reach a statistically significant difference between two groups.

Other Dyspeptic Symptoms. Of all patients interrogated, 117 (59 with functional dyspepsia, 49 with peptic ulcer, 94 H. pylori positive, 23 H. pylori negative) mentioned having nausea during their illness. Only 8 patients reported vomiting during the present illness episode. Seventeen patients with functional dyspepsia and 11 patients with peptic ulcer complained of excessive amount of wind in the bowel (flatulence). The above symptoms were not characteristic of either a particular diagnosis or presence of H. pylori infection.

Relationship of Eating and Body Weight to the Diagnosis of Peptic Ulcer and Functional Dyspepsia. Among 86 patients with functional dyspepsia, 47 answered that they lost appetite because of abdominal complaints, 39 had normal appetite despite the illness. The respective figures for patients with peptic ulcer were 42 and 33. In most cases body weight did not change (50 with functional dyspepsia, 46 with peptic ulcer), or increase (23 with functional dyspepsia, 13 with peptic ulcer). Five patients in the functional dyspepsia group and 9 patients in the peptic ulcer group responded that they had lost more than 3 kg during the last 6 months (not due to dieting). There was no significant difference between the functional dyspepsia and the peptic ulcer groups either in the changes in appetite (p = 0.87 Fisher’s exact test) or in the decrease in body weight (p = 0.26).

Previous Medication

Altogether 65 patients with peptic ulcer (among them 41 had been diagnosed with peptic ulcer at earlier upper gastrointestinal endoscopy) and 19 patients with functional dyspepsia had been treated with H2-blockers, mainly cimetidine, before the present or earlier upper gastrointestinal endoscopy. One-third of them (22 patients) did not feel sufficient alleviation of their symptoms. Patients with peptic ulcer had been treated significantly more often with H2-blockers compared with functional dyspepsia patients (p < 0.001, Fisher’s exact test). The same was applied to the 24 patients whose diagnosis of peptic ulcer was first established at the present upper gastrointestinal endoscopy. Antacids were used before the present endoscopy by 73 patients, while a positive effect was reported by 44 patients, among them 14 patients with peptic ulcer.

Dyspeptic Complaints and Presence of Psychological Problems

Almost half (n = 79) of the patients complained of headache; in 36 cases headache was frequent, one or more times per week. Fifty-three patients responded that they suffered or had suffered from psychological disturbance; for 21 of them treatment had been prescribed by the psychiatrist or the family physician. There was no significant difference between the patients with functional dyspepsia and those with peptic ulcer regarding presence of headache (p = 0.08, Fisher’s exact test) or psychological problems (p = 0.11, Fisher’s exact test). In 97 cases the patients replied that their abdominal pain was increasing because of stress or worry (42 with functional dyspepsia, 52 with peptic ulcer). Stress and worry aggravated symptoms more often in peptic ulcer patients (p = 0.01, chi-square), although these symptoms had no independent value for the diagnosis of peptic ulcer.

Smoking and Alcohol Consumption

Out of all patients 69 were non-smokers, 43 were ex-smokers; 52 smoked 1-25 cigarettes per day, 8 were heavy smokers (> 25 cigarettes per day). Most patients (136) reported light alcohol intake (less than 5 liters of beer or 10 shots of whisky or two bottles of wine per week), 2 patients were moderate alcohol consumers (less than 12 liters of beer or 1 bottle of whiskey or 6 bottles of wine), and one patient drank more than moderate, 33 did not drink alcohol at all. Patients with peptic ulcer were more often smokers (p < 0.001, chi-square) than those with functional dyspepsia, but there was no difference between the major diagnostic groups in alcohol intake (p = 0.12, Fisher’s exact test).

H. pylori Infection and Dyspepsia

Comparison of H. pylori positive functional dyspepsia group with H. pylori negative functional dyspepsia group did not reveal specific criteria for distinguishing infected patients. H. pylori positivity was characteristic of organic dyspepsia rather than normal findings at endoscopy (p < 0.001, Fisher’s exact test). No correlation was found between H. pylori infection and dyspeptic symptoms, irrespective of diagnosis.

Discussion

Regardless of numerous studies and trials, dyspepsia still remains a controversial issue. The present study was designed to obtain information about the association between the dyspeptic symptoms and the diagnoses using a novel method of obtaining medical history – a computerized questionnaire. The advantage of the computer based method lies in the unique manner of questioning and registering of answers, avoiding intra/inter-observer variability and mistakes arising from manual data proceeding. It has to be mentioned that the results of the study should be interpreted keeping in mind the limitation of the study: after excluding subjects with possible confounding factors, such as the use of non-steroidal anti-inflammatory drugs, antibiotics, alcohol abuse, etc., the studied cohort was not fully representative of the whole patient population referred for upper gastrointestinal endoscopy by family practitioners. The analysis of the data of the overall patient population remains the subject of future research.

The small proportion of the elderly showed non-correspondence to the inclusion criteria, but also to the tendency to refer relatively few aged patients.
for upper gastrointestinal endoscopy. This circumstance was noticed in another Estonian study (24) and elsewhere (25). One reason for the low referral rate can be the decline in almost all abdominal symptoms with age (1,26). Relatively high proportion of patients younger than 45 years referred to the upper gastrointestinal endoscopy is justified as more than one third of them had an organic disease (mostly duodenal ulcer) diagnosed (15).

One case of gastric cancer in our study group was insufficient for analysis. In another Estonian study (27) the presence of epigastric pain was found in 77% of cases of early and 70% of advanced gastric cancer; the other dyspeptic symptoms were observed in 19% and 39% of cases, respectively. These indicators are not significantly different from those found in dyspeptic patients referred for upper gastrointestinal endoscopy by family practitioners. The only highly significant difference was the decrease in body weight which was recorded in 45% of the patients with early gastric cancer and in only 9% of the patients with peptic ulcer or with functional dyspepsia. Therefore, most guidelines consider significant weight loss an alarming symptom requiring referral for upper gastrointestinal endoscopy.

In recent studies, the focus has been placed on the predominant symptom as a possible indicator of the underlying disorder (9,28) instead of classifying symptoms to reflux-like, ulcer-like, dysmotility-like and unspecified subgroups (29,30). The word “predominant” is an important qualifier to be kept in mind when the symptoms are being evaluated, as it ensures that attention is paid to the symptom of primary concern for the patient. In present study, upper abdominal pain was the most bothersome symptom for 73% and heartburn only for 6% of the subjects. In a randomized study in UK with 708 patients included (31), the predominant symptom was epigastric pain or discomfort in 54% and heartburn or acid reflux in 29% of patients. As no guidelines were followed to exclude patients with predominant reflux symptoms in Estonia at that time, the predominant gastroesophageal reflux disease symptoms and esophageal pathology appeared to be less prevalent in Estonia than in Western countries (32,33). On the other hand, as results of the study indicate, many patients have several complaints simultaneously. Forcing such individuals to decide which complaint is the predominant one at a given moment in time may be both unrealistic and misleading. Half of the patients who mentioned having frequent symptoms of gastroesophageal reflux disease, had peptic ulcer diagnosed, esophagitis was diagnosed in only 7 of them. As biopsies from a visually normal esophagus were not obtained, the cases of endoscopy negative gastroesophageal reflux disease may remain of course, undiagnosed. It is known that the proportion of endoscopy positive gastroesophageal reflux disease accounts for one-third of all cases of gastroesophageal reflux disease (28).

The longer duration of the main symptom in peptic ulcer group in comparison with patients with functional dyspepsia is partly attributed to inadequate treatment of peptic ulcer in Estonia at the time of present study as H2-blockers (mainly cimetidine) appeared on our market first in early nineties, the usage of proton pump inhibitors was very rare, H. pylori eradication was used only for research purposes (34).

The frequent presence of symptoms of irritable bowel syndrome in the study group is in accordance with the finding of symptom overlapping in dyspepsia and irritable bowel syndrome in other studies (22,35-37). Rather unexpected was the coexistence of irritable bowel syndrome and peptic ulcer which could be explained apart from other possible factors, with more detailed interrogation in comparison with a routine physician’s interview.

The relation between psychological problems and dyspepsia, especially functional dyspepsia, has been the matter at issue for decades (38-40). In the present study both, patients with peptic ulcer and with functional dyspepsia suffered from headaches and psychological problems alike. Norwegian investigators have shown that patients with functional dyspepsia had higher scores of negative life events and probably also higher levels of anxiety, depression, and general psychopathology in comparison with healthy controls and patients with duodenal ulcer (39). Among Estonian patients, stress aggravates dyspeptic symptoms in patients with peptic ulcer. The influence of insufficient usage of modern methods of treatment of peptic ulcer in Estonia in the nineties could be speculated as an explanation of the difference of patients of the two countries. There was also a correlation of the incidence of perforated peptic ulcer with suicide rate in Estonia during 1981-2000 (41).

The proportion of smokers among dyspeptic patients was similar to that among Estonian population where approximately 50% of men and 25% of women were regular smokers (42). Though there was no question asked about the reasons of stopping smoking in our study population, the comparatively high number of ex-smokers might be in connection with the overall tendency noticed in Estonia where between 1994-1998 the number of regular smokers decreased by 10% among men and 4% among women. Smoking and H. pylori infection were characteristic of peptic ulcer in studied patients but due to frequent presence of both risk factors in general population, simultaneous presence of them was not predictive to organic dyspepsia as shown elsewhere (43).

A Swedish study using GLADYS found the system performing best in alcohol related dyspepsia cases (20). As patients with known alcohol abuse were excluded in our study no alcohol related dyspepsia could be diagnosed.

The relationship between H. pylori and dyspeptic symptoms, in absence of peptic ulcer, has continued to be a matter of controversy (44,45). Although available evidence indicates the absence of a strong association between H. pylori and dyspepsia, there is yet insufficient evidence to confirm or refute existence of a moderate association. The fact that the prevalence of H. pylori infection among patients with dyspeptic complaints was similar to that in general population rather confirms the absence of the connection between the infection and dyspepsia.
In conclusion, there are slight differences in the structure of dyspeptic complaints and especially in the structure of upper gastrointestinal diseases in the country with high prevalence of *H. pylori* infection in comparison with areas with lower prevalence of the infection. We will need further research to see whether symptoms other than presence of episodic pain, frequent night pain, hunger pain or alleviation from eating food have a value for differentiating organic and functional dyspepsia. Focusing on the predominant symptoms should be done carefully because of frequent overlap of the symptoms of different disease entities.

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