

Symptom Characteristics and Psychosomatic Profiles in Different Spectrum of Gastroesophageal Reflux Disease

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Background/Aims: Gastroesophageal reflux disease (GERD) is diagnosed based on symptoms of heartburn and regurgitation but is a heterogeneous condition which can be subclassified according to endoscopy and esophageal reflux monitoring. The aim of this study was to identify differences in demographic characteristics and reflux symptom patterns among patients with various spectrum of GERD. **Methods:** Patients having weekly heartburn or acid regurgitation were classified into four pathophysiological subgroups according to endoscopy and pH monitoring: reflux esophagitis (RE), endoscopy-negative reflux disease with pathological reflux (PR+), hypersensitive esophagus (HE), and normal acid exposure with negative symptom association (pH-). **Results:** A total of 195 patients were enrolled. The numbers of patients in the subgroups were: RE, 39.0%; PR+, 20.0%; HE, 10.3%; and pH-, 30.8%. Grossly, reflux symptom patterns and relieving/exacerbating factors did not differ between subgroups. Prevalence of extraesophageal syndrome was higher in patients with PR+ than in other groups. Overlapping functional dyspepsia was common in all groups. The SCL-90-R depression score was higher in PR+ patients than in RE patients ($p < 0.05$). **Conclusions:** Demographic characteristics and reflux symptom patterns cannot differentiate pH- group from GERD subtypes. Esophageal pH monitoring could be considered for the initial evaluation of GERD in the tertiary referral setting. (*Gut Liver* 2014;8:165-169)

Key Words: Gastroesophageal reflux; Demographic characteristics; Symptom characteristic; Psychosomatic factor; Esophageal reflux monitoring

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a condition that develops when reflux of stomach contents causes troublesome symptoms and/or complications.¹ GERD is a diagnosis based on the characteristic reflux symptoms of heartburn and regurgitation. However, it contains heterogeneous conditions which can be subclassified according to endoscopy and esophageal reflux monitoring. GERD is classified into reflux esophagitis (RE) and endoscopy-negative reflux disease (ENRD) according to endoscopic findings. It is debated whether the spectrum of GERD is continuous or discontinuous and whether the entities of RE, ENRD, and Barrett esophagus are truly distinct or entities in transition from less severe to more severe forms.^{2,3} Several studies have shown a female preponderance, poorer response to proton pump inhibitors (PPIs), and differences in the psychosomatic profile between ENRD and RE.⁴⁻⁷ Ambulatory esophageal pH monitoring can be used to subclassify ENRD into three groups: ENRD with pathological reflux (PR+), hypersensitive esophagus (HE), and ENRD without pathological reflux (pH-). It is clinically important to distinguish pH- from other subgroups because the overuse of PPIs can be a potential problem in clinical practice. There are limited studies of the three pathophysiological subgroups of ENRD. The aim of this study was to identify differences in demographic characteristics and reflux symptom patterns between patients with various spectrums of GERD.

MATERIALS AND METHODS

1. Patients

Consecutive patients with symptoms suggestive of GERD, typical esophageal symptoms and/or patients with extraesophageal symptoms gastroesophageal reflux symptoms who were referred

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to Seoul St. Mary's Hospital from June 2006 until February 2010 were enrolled in this study. We prospectively collected the reflux questionnaire from the patients for future analysis and the collected data was retrospectively analyzed. This study was approved by the Institutional Review Board after completion of data collection. The patients who were suspected of GERD were screened on whether they had typical gastroesophageal reflux symptoms by using a simple questionnaire including heartburn and acid regurgitation within the recent 6 months with frequency and severity graded with a 6-point Likert scale (0, none; 1, minimal; 2, mild; 3, moderate; 4, severe; 5, very severe). We included patients having typical gastroesophageal reflux symptoms which were defined as at least weekly heartburn or acid regurgitation with moderate, severe, or very severe symptom intensity. The included patients were asked to answer the reflux questionnaire before undergoing upper gastrointestinal endoscopy. Patients with long term acid suppression treatment (more than 12 weeks in recent 1 year), acid suppression treatment within recent 8 weeks, antireflux surgery history, peptic ulcer, malignancy, major abdominal operation history, documented esophageal motility disorder, or systemic disease which causes GERD such as systemic sclerosis were excluded from the study.

2. Endoscopy

Upper gastrointestinal endoscopy was performed to identify RE and other organic abnormality in the esophagus, stomach, and duodenum. The Los Angeles classification was used for the endoscopic assessment of RE.⁸ Los Angeles classification grade from A to D RE in endoscopy was included in the RE group.

3. Ambulatory esophageal pH monitoring

Ambulatory esophageal pH monitoring was performed with Antimony catheter system (Medtronic Inc., Skovlunde, Denmark) or Bravo pH system (Medtronic Inc.) in the patients who had not esophagitis on endoscopy. A monocrystalline antimony pH catheter was placed at 5 cm above the lower esophageal sphincter which was identified by esophageal manometry. In the Bravo pH system, a pH capsule was attached at 6 cm above the gastroesophageal junction which was identified by endoscopy. Patients underwent ambulatory esophageal pH monitoring off-acid suppression treatment within 2 weeks after upper gastrointestinal endoscopy. Ambulatory esophageal pH monitoring data were analyzed with POLYGRAM NETTM.

4. The reflux questionnaire

The reflux questionnaire was comprised of upper gastrointestinal symptoms, reflux symptom patterns including exacerbating/ameliorating factors, ROME-II irritable bowel syndrome (IBS) symptoms, and somatization, depression and depression questionnaire of the Symptom Check List-90-Revision (SCL-90-R).⁹ The questionnaire included demographic characteristics such as height, body weight, past medical history, smoking, alcohol

consumption, and drug history. It also contained detail information of upper gastrointestinal symptoms and extraesophageal syndrome such as heartburn, chest pain, epigastric soreness, epigastric pain, acid regurgitation, globus, dysphagia, hoarseness, cough, epigastric discomfort, early satiety, postprandial fullness, nausea, vomiting, and belching within the recent 6 months with frequency and severity graded with a 6-point Likert scale. Clinically significant symptom was defined as with moderate, severe, or very severe symptom severity scale with more than one episode per week. The SCL-90-R is a 90-item self-report system inventory designed to reflect the psychological symptom patterns of community, medical and psychiatric respondents.¹⁰ The Korean version of SCL-90-R was used and the scores were presented as T-score.¹¹

5. Classification of patients

Endoscopic findings could classify patients into RE and ENRD. Patients with ENRD were further classified into 3 subgroups according to ambulatory pH monitoring results; ENRD with PR+, HE, and pH-. PR+ was defined as having a Demeester Score ≥ 14.72 or % of total period pH below 4 $\geq 4.45\%$ in ambulatory pH monitoring.¹² HE was defined as having normal acid exposure and positive symptom association which was Symptom Index $\geq 50\%$ or Symptom Association Probability $>95\%$.¹³⁻¹⁵ pH- was defined as having normal acid exposure with negative symptom association.

6. Statistical analysis

Patient characteristics, symptom characteristics, accompanying atypical reflux syndrome, accompanying functional gastrointestinal disorder, and psychosomatic factors were compared among the GERD subgroups. The continuous data were analyzed using the unpaired t-test and the discontinuous data were analyzed using chi-square test or Fisher exact test to compare between the groups. All statistical analyses were performed using SAS version 8.2 (SAS Institute, Cary, NC, USA). Differences were considered significant if the p-value was less than 0.05.

RESULTS

A total of 195 patients (mean age, 48 years; 104 women and 91 men) were included in the study. Ambulatory esophageal pH monitoring was performed in 119 patients. Among patients with ENRD, almost half were diagnosed with pH- according to the esophageal pH monitoring. The characteristics of the four groups are summarized in Table 1. The RE group included more men, and the ENRD group included more women. Women comprised a higher percentage of the pH- compared with the RE group ($p < 0.05$). Age, body mass index, and smoking rate did not differ significantly between the four groups.

The characteristics of reflux symptoms are summarized in Table 2. Overeating was the most frequent factor that aggravated

Table 1. Patient Characteristics

Characteristic	RE	ENRD		
		PR+	HE	pH-
Total, n (%)	76 (39.0)	39 (20.0)	20 (10.3)	60 (30.8)
Age, mean (range), yr	47 (24–72)	49 (22–73)	44 (26–74)	49 (19–74)
Female, %	43.4	51.3	65.0	63.3*
Symptom duration, %				
<6 mo	20.3	13.2	5.0	17.9
6 mo–1 yr	6.8	13.2	15.0	17.9
1–2 yr	59.5	44.7	50.0	50.0
>2 yr	13.5	28.9	30.0	14.3
BMI, mean±SD, kg/m ²	23.9±3.4	22.9±2.4	21.9±2.5	22.9±2.8
Obesity (BMI ≥25), %	36.0	19.4	10.5*	21.4
Smoking, %	27.8	12.5	21.1	13.2

RE, reflux esophagitis; ENRD, endoscopy negative reflux disease; PR+, ENRD with pathological reflux; HE, ENRD with hypersensitive esophagus; pH-, ENRD without pathological reflux; BMI, body mass index; SD, standard deviation.
*p<0.05 compared with RE.

Table 2. Characteristics of Reflux Symptoms

Characteristic	RE	ENRD		
		PR+	HE	pH-
Aggravation after meal	34.2	20.0	42.1	34.0
Aggravation in supine or bending position	37.0	51.5	55.0	58.8*
Aggravation after overeating	64.9	66.7	70.0	74.5
Aggravation after fatty food intake	42.3	55.9	50.0	50.0
Aggravation after drinking alcohol	48.5	50.0	55.0	52.3
Relief by antacid, water or milk intake	49.3	55.6 [†]	30.0	31.0

Data are presented as percentage.
RE, reflux esophagitis; ENRD, endoscopy negative reflux disease; PR+, ENRD with pathological reflux; HE, ENRD with hypersensitive esophagus; pH-, ENRD without pathological reflux.
*p<0.05 compared with RE; [†]p<0.05 compared with pH-.

reflux symptoms in all groups. There were no noticeable differences in reflux symptom patterns and relieving and exacerbating factors between the four subgroups except for symptom relief by taking antacid, water, or milk, which was more frequent in the PR+ group than in the pH- (p<0.05).

Extraesophageal symptoms were reported frequently in all subgroups of patients with GERD and pH- (Table 3). The prevalence of extraesophageal syndrome was higher in patients with PR+ than in the other three subgroups. In addition, patients with PR+ had more symptoms of globus and dysphagia compared with patients with RE, but the prevalence of these symptoms did not differ between the ENRD and pH-.

Overlap with functional dyspepsia (FD) was common among the four groups ranging from 78.9% to 84.2% of patients. The

Table 3. Accompanying Extraesophageal Syndrome and Overlapping Symptoms of Functional Gastrointestinal Disorders

Variable	RE	ENRD		
		PR+	HE	pH-
Extraesophageal syndrome	63.2	94.9* [†]	70.0	76.4
Chest pain	32.9	47.4	31.6	35.6
Globus	36.8	69.2*	63.2*	55.9*
Dysphagia	10.5	28.9*	25.0	20.0
Hoarseness	14.5	26.3	33.3	28.3
Cough	25.0	18.4	5.6	25.0
Function dyspepsia	81.3	78.9	84.2	83.1
Epigastric pain syndrome	61.8	57.9	68.4	53.4
Postprandial distress syndrome	70.7	65.8	68.4	71.7
Irritable bowel syndrome	9.1	18.4	30.0*	18.4

Data are presented as percentage.
RE, reflux esophagitis; ENRD, endoscopy negative reflux disease; PR+, ENRD with pathological reflux; HE, ENRD with hypersensitive esophagus; pH-, ENRD without pathological reflux.
*p<0.05 compared with RE; [†]p<0.05 compared with HE; [‡]p<0.05 compared with pH-.

Table 4. T-Score of Somatization, Depression, and Anxiety in SCL-90-R

Variable	RE	ENRD		
		PR+	HE	pH-
Somatization	56.2±12.6 (38–94)	57.8±11.0 (38–83)	59.6±11.7 (44–79)	54.5±12.4 (36–91)
Depression	49.8±13.5 (34–95)	55.7±13.9 (36–86)*	50.0±10.8 (35–73)	53.4±15.0 (33–93)
Anxiety	51.8±14.1 (35–94)	56.5±16.4 (37–96)	52.3±14.2 (37–82)	53.4±17.3 (35–95)

Data are presented mean±SD (range).
RE, reflux esophagitis; ENRD, endoscopy negative reflux disease; PR+, ENRD with pathological reflux; HE, ENRD with hypersensitive esophagus; pH-, ENRD without pathological reflux.
*p<0.05 compared with RE.

prevalence of overlapping IBS symptoms ranged from 9.1% to 30.0%. IBS was more frequent in the HE group than in the RE group. The depression score was higher in patients with PR+ than those with RE. Other scores did not differ between the subgroups (Table 4).

DISCUSSION

Almost half of the patients with ENRD were diagnosed with pH- according to the pH monitoring in this study. The ENRD group included more women and patients with atypical reflux syndrome compared with the RE group. However, overall reflux symptom patterns and the presence of accompanying extraesophageal syndrome, FD, and IBS did not differ significantly

among the subgroups of ENRD. Our findings demonstrate a high prevalence of pH- in patients with classic reflux symptoms, at least in a tertiary referral center. Our data also show that demographic characteristics and reflux symptom patterns cannot differentiate the subgroups of ENRD. Therefore, esophageal pH monitoring could be considered for the initial evaluation of GERD in the tertiary referral setting.

Surprisingly, we found that pH- accounted for about 30% of patients complaining of classic reflux symptoms to gastroenterologists at our tertiary referral center. The PPI responsiveness in patients with nonerosive reflux disease (NERD) is reported to be less than 60%, which is lower than that for patients with RE.⁹ Functional heartburn (FH) is included in NERD and has a poor response to PPI treatment.¹⁶ We assumed that patients with normal acid exposure and negative symptom association had FH. FH patients may not respond to acid suppression because acid reflux is not the cause of symptoms in most of these patients. This raises a potential problem of the overuse of PPIs in clinical practice. Accurate distinction between FH and GERD would be helpful for appropriate management of patients and use of PPI.¹⁷⁻²⁰ However, it is general opinion that patients with positive response to PPI therapy should be included in the GERD population despite their pH or pH+impedance profile. This study could not assess the therapeutic response to PPI. Majority of the patients received other medications including prokinetic agent, antidepressant, anxiolytic agent, or antacid which could influence global responsiveness. Due to the retrospective review of our medical records we could not investigate compounding factors on PPI response. Also, we could not exactly define the PPI responsiveness because estimation of the response to PPI was not systemically recorded and had great interphysician variability in the patients' responsiveness grading. Nevertheless, the high prevalence of pH- in this study suggests that esophageal pH monitoring could be considered for the initial evaluation of GERD in the tertiary referral setting. This strategy may be helpful for appropriate long-term management.

The female preponderance in patients with ENRD compared with RE in this study is consistent with previous studies from Korea and Hong Kong.^{5,7} FH affects more women than men, a finding that is consistent with the diagnosis of FD reported in another Korean study.²¹

There are no evidence-based data to identify the specific symptom features of pH- such as the diurnal characteristics, exacerbating factors, and ameliorating maneuvers. Although symptom relief by taking antacid, water, or milk was more common in patients with PR+ than in those with pH- in this study, there were no noticeable differences in overall reflux symptom patterns and relieving and exacerbating factors between the four subgroups. Therefore, it was difficult to predict pH- by reflux symptom characteristics only. This can be explained partly by the contribution of acid to symptom generation in FH.^{22,23}

Consistent with previous studies,^{5,24-26} in our study, more pa-

tients with ENRD, especially those with PR+, had extraesophageal syndrome than did patients with RE. The patients with pH- also showed a high prevalence of extraesophageal syndrome, but this prevalence did not differ from that of other patients with reflux symptoms.

Our study showed that the prevalence of overlapping symptoms of FD was high and did not differ among various spectrums of GERD. HE patients had higher prevalence of IBS than RE. Previous studies have revealed that GERD, IBS, and FD may frequently overlap.²⁷⁻³⁰ Patients with ENRD or FH had higher prevalence of IBS and FD than RE.^{7,21}

The PR+ group had a higher depression score on the SCL-90-R compared with the RE group in this study. Psychosomatic factors can also affect the perception of reflux symptoms and FD. Previous studies reported that the severity of anxiety and depression was higher in the ENRD subgroup than in the RE subgroup.^{31,32} The scores for somatization, depression, and anxiety might have been high in the patients with RE because the study population included patients referred to a tertiary center.

In conclusion, almost half of the patients with ENRD were diagnosed with pH- according to pH monitoring. pH- could not be predicted by demographic characteristics or reflux symptom patterns. Therefore, esophageal pH monitoring could be considered for the initial evaluation of GERD in the tertiary referral setting.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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