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Clinical Presentation of Gastroesophageal Reflux Disease: A Prospective Study on Symptom Diversity and Modification of Questionnaire Application

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Abstract
Introduction: Symptoms occurring in gastroesophageal reflux disease (GERD) such as heartburn, regurgitation, thoracic pain, epigastric pain, respiratory symptoms, and others can show a broad overlap with symptoms from other foregut disorders. The goal of this study is the accurate assessment of symptom presentation in GERD. ***Methods:*** Patients with foregut symptoms were investigated for symptoms as well as endoscopy and gastrointestinal-functional studies for presence of GERD and symptom evaluation by standardized questionnaire. Questionnaire included a graded evaluation of foregut symptoms documenting severity and frequency of each symptom. The three types of questionnaires include study nurse solicitated, self-reported, and free-form self-reported by the patient. ***Results:*** For this analysis, 1,031 GERD patients (572 males and 459 females) were enrolled. Heartburn was the most frequently reported chief complaint, seen in 61% of patients. Heartburn and regurgitation are the most common (82.4/58.8%, respectively) in overall symptom prevalence. With regard to modification in questionnaire technique, if patients fill in responses without prompting, there is a trend toward more frequent documentation of respiratory symptoms (up to 54.5% [$p < 0.01$]), fullness (up to 93.9%), and gas-related symptoms ($p < 0.001$). Self-reported symptoms are more diverse (e.g., throat-burning [12%], mouth-burning [9%], globus [6%], dyspnea [9%], and fatigue [7%]). ***Conclusions:*** GERD symptoms are commonly heartburn and regurgitation, but overall symptom profile for patients may change depending on the type of questionnaire.

Introduction

Since gastroesophageal reflux disease (GERD) has a prevalence of 20% in industrialized countries, symptoms associated with the disease are common in these populations [1, 2]. In order to define GERD, the authors of the Montreal classification relied heavily on symptoms and their effect on patients: "GERD is a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications" [1]. These

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symptoms can reduce patient's well-being and have a negative influence on the quality of life [3, 4].

In many studies, GERD symptoms are used to define the study populations [5–13]. Other studies, however, have some evidence that symptoms are not always reliable as a guide to the diagnosis of GERD [14–17]. GERD symptoms such as heartburn, regurgitation, thoracic pain, epigastric pain, respiratory symptoms, globus, and others show a broad overlap with symptoms from other esophageal and gastric disorders such as dyspepsia, esophageal motility disorders, functional heartburn, hypersensitive esophagus, irritable stomach and bowel, and somatoform disorders [1, 14–17]. The wide array of symptoms and potential diagnoses make one consider if there is a specific questioning technique or symptom profile that is more highly suggestive of GERD. Klauser et al. [18] have stated that heartburn and regurgitation are the most typical symptoms characterizing GERD, but in clinical practice, a large variety of esophageal and extra-esophageal symptoms can be reported.

Over the last 3 decades, our team had documented symptoms of GERD patients in a large data bank. Initially, the evaluations were standardized and leaned heavily on the early DeMeester symptom score and Gastrointestinal Quality of Life Index [19–22]. Several years later, these questions were validated within the project of creating a symptom questionnaire featuring 53 items to determine somatoform tendencies [17]. With the exception of respiratory symptoms, all items in this current questionnaire differentiated significantly between healthy volunteers and patients with foregut symptoms [17].

The goals of this study are to determine the diversity and most common symptoms of GERD in large patient populations over time. Additionally, we aim to determine if the method of questioning is significant in altering the symptom profile of GERD patients.

Methods

Study Design

Over the course of more than 2 decades, our working group had the opportunity to investigate a large population of patients with GERD in a specialized center for benign esophageal and gastric disorders. All patients with foregut symptoms referred for further exploration of esophageal and/or gastric disease underwent a history and physical examination. The symptoms of the patients were evaluated by a standardized questionnaire over the complete time period from 1995 to 2017. Only the method of application for the questionnaires was changed over time, as described in detail below. All patients received an upper gastrointestinal endoscopy and esophageal manometry. In more recent years, a high-resolution manometry was performed [23]. The presence of pathologic reflux was evaluated by 24-h pH monitoring and later by impedance-pH monitoring.

Varying methods of questionnaire administration were used over the years in different time segments to evaluate the patient's symptoms, as indicated below:

Group 1: (Study period 1995–1999) The study nurse used the standard questionnaire to ask the patients for the symptoms and marked the answers of the patients regarding presence and severity of the symptoms herself.

Group 2: (Study period 2005–2009) The study nurse handed the questionnaire over to the patients and the patients were left alone to fill in the presence and the severity of the symptoms. The patients could ask for assistance to the nurse, if needed.

Group 3a: (Study period 2015–2017) The study nurse handed the questionnaire over to the patients and the patients were left alone to fill in the presence and the severity of the symptoms in the document.

Group 3b: (Study period 2015–2017) Patients (same patients of Group 3a) were asked to document in a free-text version the 3 most important symptoms that limit or reduce the patient's quality of life. Patients were instructed by the study nurse to document their most relevant symptoms as precisely as possible. Additionally, the study nurse also handed the standard questionnaire over to the patients and the patients were left alone to fill in the presence and the severity of the symptoms. It is important to notice that the free formulated description of the symptoms by the patients themselves was always conducted *before* the patients filled in the standardized questionnaire. This order was kept with the aim to avoid influences of the standard questionnaire to the patient formulated free text.

The groups were chosen for different time periods, in which changes of the symptom evaluation was established (solicited, self-reported, and free-form self-reported). The standard symptom questionnaire remained the same over the study duration.

Patient Selection and Inclusion/Exclusion Criteria

The patients were recruited in a tertiary referral center for foregut disorders and its diagnostic functional laboratory and surgery unit. The management of the patients was performed by the same team (same study nurse) over the complete period 1995–2017. The patients were asked to give informed consent to the study evaluation and the diagnostic work-up. The study was approved by our Institutional Review Board.

The data were reviewed in a prospectively maintained databank. Inclusion criteria for this analysis were patients with documented GERD, which required either the presence of esophagitis (esophagitis grading according to Savary-Miller 1–4), pathologic esophageal acid exposure on pH testing, and/or a hiatal hernia with heartburn and/or regurgitation. The hiatal hernia was documented during endoscopy by measuring the vertical extent of the distance between the cardia (beginning of the gastric folds) and the waist of the crurae, best assessed during inspiration (distance >1 cm). Care was taken to measure this length in the beginning of the endoscopy without major air insufflation of the stomach to avoid hernia reduction.

This analysis was not performed in some time periods (2000–2004 and 2010–2014), during which the documentation of symptoms was not rigorously followed due to shortage in personnel for

Table 1. Patients' characteristics for each group

	Group 1 1995–1999	Group 2 2005–2009	Group 3a and b 2015–2017	Statistics, *p* value
Number	481	333	217	
Gender, male/female	275/206	180/115	123/94	ns
Age, years				Group
Mean	48.7	51.9	52.6	1 vs. 2, <0.0014
Median	50	53	55	1 vs. 3, <0.0009
				2 vs. 3, ns
BMI, mean	27.1	27.3	27.2	ns
Esophagitis				Group
Presence, %	76.2	55.1	55.6	1 vs. 2, <0.00001
				1 vs. 3, <0.00001
				2 vs. 3, ns
Hiatal hernia				Group
Presence, %	94.5	86.3	78.8	1 vs. 2, <0.0002
				1 vs. 3, <0.00001
				2 vs. 3, <0.032
GIQLI (normal: 121), mean	92.9	91.1	88.5	ns
LES incompetence				Group
Presence, %	89.4	78.0	85.0	1 vs. 2, <0.0004
				1 vs. 3, ns
				2 vs. 3, ns
Esophageal acid exposure				Group
Mean (normal: <14.7)	53.9	39.0	56.2	1 vs. 2, <0.001
Presence of pathologic acid exposure, %	85.5	70.6	87.0	1 vs. 3, ns
				2 vs. 3, <0.001

ns, nonsignificant; BMI, body mass index; GIQLI, Gastrointestinal Quality of Life Index; LES, lower esophageal sphincter.

administering the questionnaire. In addition, other exclusion criteria were if patients had other diseases such as cancer, inflammatory bowel disease, esophageal spasm, achalasia, or if they had prior operations for GERD.

The Questionnaire

For symptom evaluation, a standardized questionnaire was established and used over 25 years. The questionnaire included a graded evaluation of foregut symptoms: heartburn, regurgitation, retrosternal/thoracic pain, respiratory symptoms (cough/hoarseness), dysphagia, epigastric pain (pain/cramps/burning), nausea/vomiting, fullness (unpleasant fullness, early satiety), and gas-related symptoms (belching/bloating/flatulence). Patients had to document the severity and frequency of each symptom by grading according to the following system: 0 = no symptoms; 1 = symptom occurring rarely; 2 = symptom occurring occasionally; 3 = symptom occurring monthly and/or with mild intensity; 4 = symptom occurring weekly and/or with moderate intensity; 5 = symptoms occurring daily and/or with severe intensity.

Statistical Methods

Symptom results were analyzed according to their documented overall presence in these patients, independent of their severity, as well as by the most frequently reported significant/chief complaints. The mean intensity of the presented symptoms was analyzed. Statistical comparison with a *t* test for unpaired samples was used for the comparison of data from the different samples. A chi-square test was used for comparison of group data.

Results

From 1995 to 2017, over 2,000 patients with symptoms indicative of GERD were seen by our team. Patients with other gastrointestinal diseases that could influence foregut symptoms were excluded from this study. In total, 1,031 met all inclusion criteria as GERD patients and were enrolled from 3 different time segments. Group 1 (1995–1999) included 481 patients, Group 2 (2005–2009) had 333 patients, and Group 3a/3b (2015–2017) had 217 patients. There were 572 males and 459 females. Table 1 demonstrates the characteristics of patients in the different groups. Presence of esophagitis, evidence of lower esophageal sphincter incompetence, esophageal acid exposure, and the level of quality of life showed severity of GERD among the patients in different groups over the years.

Table 2. Overview on the percentage of documented symptoms with intensity 5 (chief complaint) differentiated for each group

Symptom	Group 1, %	*p* value	Group 2, %	*p* value	Group 3a, %
Heartburn	60	ns	61	ns	61.6
Regurgitation	17	ns	13.6	Group 1: 0.03 Group 2: 0.01	36.4
Retrosternal pain/cramps	4.2	ns	6.3	ns	4.0
Respiratory symptoms: cough, hoarseness	1.6	0.001	21.3	Group 2: ns Group 1: 0.001	20.3
Dysphagia	3.6	ns	3.2	ns	2.0
Epigastric pain	13.1	0.01	24.7	Group 2: 0.02 Group 1: ns	12.1
Nausea, vomiting	6.6	ns	9.7	ns	2.0
Fullness	7.0	ns	10.7	ns	7.0
"Gas"-related symptoms: belching, bloating, flatulence	3.3	0.01	27.2	Group 2: ns Group 1: 0.01	22.0

ns, nonsignificant.

Table 3. Overview on the percentage of overall presence of documented symptoms differentiated for each group

Symptom	Group 1, %	*p* value	Group 2, %	*p* value	Group 3a, %
Heartburn	82.4	ns	89.9	Group 2: 0.007 Group 1: ns	78.8
Regurgitation	58.8	ns	54.6	Group 2: 0.001 Group 1: 0.01	73.7
Retrosternal pain/cramps	16.7	ns	14.0	ns	14.1
Respiratory symptoms: cough, hoarseness	11.8	0.03	24.9	0.00001	54.5
Dysphagia	18.7	0.01	31.4	Group 2: 0.04 Group 1: ns	19.2
Epigastric pain	47.2	0.04	58.9	Group 2: 0.0001 Group 1: ns	32.3
Nausea, vomiting	23.6	ns	39.2	ns	32.3
Fullness	11	0.00001	73.2	Group 2: 0.00001 Group 1: 0.00006	93.9
"Gas"-related symptoms: belching, bloating, flatulence	34	0.00001	72.7	Group 2: 0.0001 Group 1: 0.00001	93.9

ns, nonsignificant.

Frequency of Chief Complaints and Overall Presence of Symptoms

Heartburn (retrosternal burning rising from the epigastrium to the chest) was the most frequent chief symptom (intensity: 5), independent of exam technique (Table 2: Group 1: 60%; Group 2: 61%; Group 3a: 61.6%; Group 3b: 48.5%). Table 2 shows the frequency of chief complaints in the different groups. When the questionnaire is filled in by the study nurse (Group 1), the most common symptoms are heartburn and regurgitation (60%, 17%). Additionally in Group 1, other symptoms such as epigastric pain, dysphagia, or gas-related symptoms such as bloating, belching, and flatulence are not often experienced as the primary symptom (frequencies <15%). When comparing between groups, there are significant differences between the reported symptoms (Group 1 vs. Group 2/Group 3a). More often patients self-report respiratory symptoms (1.6% vs. 21.3%/20.2%; $p < 0.001$), epigastric pain (13.1% vs. 24.7%/12.1%), and gas-related problems (2.6% vs. 27.2%/22.0%; $p < 0.01$).

Table 3 provides an overview on the overall presence of symptoms as evaluated in the various time periods.

Table 4. Overview on percentage of symptoms in a free-text version self-assessed symptoms versus documentation in a self-assessed structured questionnaire

Symptoms	Self-assessed chief complaints (intensity 5) in free text, %	Self-assessed chief complaints (intensity 5) in a structured questionnaire, %
Heartburn	31	62
Regurgitation	5	36
Retrosternal pain	8	4
Respiratory symptoms	9	20
Dysphagia	1	2
Epigastric pain	9	12
Nausea/vomiting	5	2
Fullness	1	7
Gas-related symptoms	4	22
Burning in throat	7	–
Burning in mouth	7	–
Globus	2	–
Dyspnea	3	–
Headache	1	–

Heartburn and regurgitation are most frequent in Group 1 (82.4 and 58.8%, respectively). If patients fill in the questionnaire themselves, there are significant differences between groups in the presence of documentation of respiratory symptoms (Group 1: 11.8%; Group 2: 24.9%; Group 3a: 54.5%; $p < 0.01$), fullness (1: 11%; 2: 72.7%; 3: 93.9%; $p < 0.001$), and gas-related symptoms (1: 34%; 2: 72.7%; 3: 93.9%). These differences are even more pronounced in recent years.

Administration of Free-Text Form of Symptom Evaluation

When patients report their symptoms in their own words prior to completing the standard questionnaire (Group 3b), the documented variety of symptoms increases compared to the structured questionnaire alone (Table 4). In Group 3b, heartburn remains the most frequently reported symptom both as chief complaint (31%) and in the overall presence (48.5%). Reported symptoms are much more diversified: burning in the throat (12%), burning in the mouth (9%), globus (6%), headache (1%), dyspnea (9%), and fatigue (7%; Table 4).

Intensity of Symptoms and Their Relation to Objective Functional Data

Data on the intensity of symptoms are summarized in Table 5. The intensity of heartburn is highest in all groups (Group 1: 3.61; Group 2: 3.88; Group 3a: 3.39). The nurse documented the intensity of the symptoms such as regurgitation, retrosternal pain, epigastric pain, and respiratory symptoms higher (Group 1) than the patients themselves (Groups 2 and 3).

The relationship between symptom intensity and the esophageal functional status show only for heartburn a significant rise in intensity for patients with and without lower esophageal sphincter-incompetence. These differences were for Group 1: 3.1 vs. 3.9; for Group 2: 3.2 vs. 3.9; for Group 3: 1.8 vs. 3.4 (all $p < 0.005$). The differences in symptom intensity are also significant for some comparisons with regurgitation; however, all other symptoms have no remarkable differences detected for changes in objective functional status.

Discussion

We show that despite altering modality of questioning and symptom assessment in GERD patients, heartburn is the most frequently reported symptom. The severity and intensity of heartburn were documented to be the highest among all other symptoms through all years of investigation. The reported intensity of heartburn is significantly increased when the functional status of the antireflux barrier deteriorates. On the other hand, the presence/absence and intensity of other symptoms (e.g., regurgitation, respiratory symptoms, bloating) can depend on the concept and details of questioning. Allowing the patients to report free-form selection of symptoms shows a larger variety of documented chief complaints and other gas-related symptoms that may not be appreciated on standardized questionnaire.

Similar to our study, literature review shows that heartburn is reported to be present in patients with pathologic esophageal acid exposure in 72–99% [1, 3, 14, 17, 18, 24–28]. Regurgitation is another important symptom in GERD, with a prevalence of 33–86% [1, 14, 17, 29, 30]. According to some studies, epigastric pain is present in patients with foregut symptoms in 70% and in those with documented pathologic acid reflux in 12–67% [1, 3, 14, 17]. Our study confirms the importance of heartburn as the classic symptom with the highest intensity and the highest frequency as a chief complaint throughout the study. In Group 3b (free-text format), the symptom of heartburn was further delineated as "burning in the throat" or "burning in the mouth" in up to 14%.

Results of the present study show that the documented presence of symptoms can depend on the method of

Table 5. Overview on the mean intensity of symptoms differentiated for each group

Symptom	Group 1, %	*p* value	Group 2, %	*p* value	Group 3a, %
Heartburn	3.6	ns	3.88	0.03	3.4
Regurgitation	3.2	0.0001	1.7	0.001	2.6
Retrosternal pain/cramps	3.3	0.0001	0.5	ns	0.5
Respiratory symptoms: cough, hoarseness	2.4	0.0001	0.99	0.00001	1.8
Dysphagia	2.6	0.0001	0.9	ns	0.5
Epigastric pain	3.2	0.0001	2.2	0.0001	1.1
Nausea, vomiting	1.9	ns	1.4	ns	1.1
Fullness	2.2	ns	2.3	ns	2.5
"Gas"-related symptoms: belching, bloating, flatulence	2.5	ns	2.3	ns	2.4

ns, nonsignificant.

questioning (e.g., whether the symptoms are asked by a study nurse or if the patients are documenting without solicitation). The more the patient is free in her/his answering the questionnaire, symptom variability increases, especially with increased incidence of gas-related and atypical symptoms. The overall presence of heartburn remains independent of questionnaire administration around 80%. Notably, a statistically significant finding of respiratory symptom presence increases from 11 to 50% and the gas-related symptoms from 30 to 90% depending on questionnaire modality of application. All other symptoms have a much lower incidence in our GERD patients, and therefore, functional investigations are helpful to confirm the disease if esophagitis is absent.

There has been a controversial discussion about symptoms as a diagnostic tool for the presence of GERD, initiated by the Montreal definition [1, 14, 18–20]. Our study confirms that there is a significant diversity of foregut symptoms present in GERD patients, as well as numerous extra-esophageal complaints such as cough, hoarseness, burning sensation in pharynx, mouth, and tongue in patients [1, 14–17]. Extra-esophageal symptoms can be respiratory symptoms such as chronic cough, hoarseness, and shortness of breath [31–38]. There may also be symptoms at the level of the head and neck such as globus or burning in the mouth or throat. Recent studies show limitations of measuring acid reflux in the pharynx with current technology [37, 39, 40]. It remains difficult to correlate these symptoms with reflux episodes, even with objective testing.

We show that our validated questionnaire provides adequate assessment of patient symptoms. Allowing free-form reporting of symptoms in addition to a structured questionnaire may provide a more robust symptom profile in reflux disease. There is evidence in literature that structured questionnaires are very helpful and effective for symptom evaluation, and this is confirmed by our study [41–46]. Several instruments have been published, validated, and successfully used in clinical practice [41–46]. Various questionnaires published include the Patient Assessment of Upper Gastrointestinal Symptom Severity Index, the Gastrointestinal Rating Scale, the Chinese GERD Questionnaire, the GERD-Health Related Quality of Life Instrument, the Esophageal Symptoms Questionnaire, and the Reflux Disease Questionnaire [41–43, 47–50]. A systematic review of all the available questionnaires for the assessment of GERD showed that many differ in design, validation, and translation [43]. One should be aware of the strength and shortcomings of each before selecting one for use [43]. All instruments have a self-assessment or self-administered mode of application, usually evaluating severity and/or frequency of GERD symptoms with a median of 15 items (6–30 items) [41–43, 47–50]. The most useful instruments allowed for self-assessment by the patients [43]. However, none of these surveys allow for a free-text version of symptom documentation such as the one tested in this study.

When using the questionnaire over the years we noticed that many patients added remarks in the margin, indicating a possible lack of options or inadequate description. The unprompted free-form clarification of symptoms stimulated the impetus for providing patients more space to document symptoms in this way. None of the available validated questionnaires leaves room for the patient's free text. Variations in patient symptoms such as burning in the mouth, tongue, and throat may be important features to document. In the past, one could only speculate that these symptoms were superficially classified as heartburn or odynophagia. Most of the available structured and validated questionnaires focus on heartburn, epigastric pain, fullness, bloating, regurgitation, and dysphagia. Therefore, it

may be reasonable to add a free-text section to GERD questionnaires for detection of rare but important symptoms restricting the patient's quality of life.

While expanding structured questionnaires to integrate all possible symptoms would be able to register all symptom variations, the more items to be answered lengthen and complicate the questionnaire process, potentially reducing applicability. Recently developed technologies allow patients to record symptoms in an electronic diary using a mobile electronic device. These technologies may be able to integrate self-administered and free text from evaluations to receive a more realistic and clinically valuable assessment.

Limitations of this study include the retrospective character of the analysis and the long duration of data sampling. Additionally, there were periods of time during the study period where documentation was not able to be rigorously completed due to shortage of nurses (2000–2004, 2010–2014), so data from these periods were excluded and sample size reduced as a result. Overall, the size of the patient data sampling performed by one team and one study nurse provides a dependable performance of data sampling and robust data for comparison of the changing techniques of administrating the assessment of GERD symptoms.

GERD remains a disease with a wide variety of symptoms experienced by patients. While heartburn and regurgitation remain mainstays of symptom reporting, there may be a range of symptoms and intensities of symptoms that go unreported if not elicited in a free-text format. The variety of symptoms experienced also shows the importance of a full correlating objective workup with esophagogastro-duodenoscopy, high-resolution manometry, and impedance-pH testing to assist with accurate diagnosis of patients who may need surgical correction of their disease.

Conclusion

GERD symptoms are commonly heartburn, regurgitation, fullness, respiratory, and gas/bloat-related. The most important and frequent symptom is heartburn and its intensity parallels objective functional parameters of the esophagus. The overall symptom profile of patients may vary depending on the modality of questioning: practitioner directed, patient questionnaire, or free-form patient reporting of symptoms. Objective studies should be a key component in determining treatment for GERD due to the wide disparity in presenting symptoms.

Disclosure Statement

The authors have no conflicts of interest to declare.

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