Laryngopharyngeal reflux: an overview on the disease and diagnostic approach

Asmaa M. Hassan[a], Ashraf M. Osman[a], Mohamed A. A. Ghaliony[a], Emad K. Abd Elhaleem[b], Khaled A. M. Elbeh[c]

[a]Department of Tropical Medicine and Gastroenterology, [b]Department of ENT (Phoniatric Unit), [c]Department of Neurology and Psychiatry, Faculty of Medicine, Assiut University, Assiut, Egypt

Correspondence to Asmaa M. Hassan, MD, Phoniatric Unit, Department of Tropical Medicine and Gastroenterology, Faculty of Medicine, Assiut University, Assiut, Egypt
Tel: 02882414031; Fax: 02882324716; Postal Code: 71515;
e-mail: drasmaamaher83@yahoo.com

Received 12 October 2016
Accepted 30 October 2016

Journal of Current Medical Research and Practice
January-April 2017, 2:67–72

Background
Laryngopharyngeal reflux (LPR) can be defined as chronic symptoms or laryngeal mucosal damage caused by the abnormal reflux of gastric contents into the upper airway. LPR plays an important role in up to 50% of laryngeal complaints that present in the otolaryngeal clinic, and the symptomatology of LPR has more different presentation. LPR is suspected in the presence of symptoms of hoarseness, dysphagia, cough, globus, excessive mucus, throat pain, throat clearing, and laryngospasm. Diagnosis of LPR is confirmed using the following: reflux symptom index (RSI), laryngoscopic examination [reflux finding score (RFS)], and esophagogastroduodenoscopy.

Patients and methods
A cross-sectional study was conducted on 60 patients with typical gastroesophageal reflux disease (GERD) symptoms and laryngeal complaints; these studied patients were recruited from patients who attended the outpatient clinic of Tropical Medicine and Gastroenterology, and Phoniatric Unit, Assiut University Hospital. The symptom questionnaire and the classification proposed by Belafsky and his colleagues (RSI) are used and upper endoscopy is performed for the diagnosis of GERD patients. Nasofibrolaryngoscopy for all these patients was performed to compare the results (RFS). Psychiatric assessment was performed by a psychiatric specialist using symptoms checklist revised 90. Patients with a score more than 60 will be re-evaluated using the following questionnaires: Hamilton checklist of symptoms of depressive illness and Hamilton rating scale for anxiety.

Results
All studied patients showed positive RSI (100%) and diagnostic endoscopy showed GERD in 58 (96.7%) patients, and 32 (53.3%) of them were found to have a positive finding in laryngoscopy; the findings were as follows: vascular congestion and vocal cord hyperemia in 32 (100%) patients, vocal cord edema in 26 (81%), phonatory gap in 13 (40%), subglottic edema in 12 (37%), vocal cord swelling in 10 (31.25%), and contact granuloma in eight (25%). A positive significant correlation was detected between phonasthenia symptoms, mostly lump sensation, hoarseness, throat clearing, and dry mouth (symptoms), and laryngeal finding (RFS), except for difficulty in swallowing saliva. There is a strong association between psychological symptoms and the presence of LPR; the most commonly detected manifestation was anxiety, and there was a positive significant correlation with anxiety and a negative significant correlation between depression and reflux symptoms.

Conclusion
RSI and RFS could be useful for the diagnosis and evaluation of LPR in patients with GERD complaining of laryngeal symptoms. Psychological intervention can improve the general well-being and quality of life of patients with gastrointestinal symptoms.

Keywords:
breast carcinoma, lymphedema, risk factors

J Curr Med Res Pract 2:67–72

2357-0121

Introduction

Laryngopharyngeal reflux (LPR) can be defined as chronic symptoms or damage of the mucosa produced by the abnormal reflux of gastric contents into the upper airway. Although LPR and gastroesophageal reflux disease (GERD) are both caused by reflux of gastric contents, they are distinct clinical entities with differing pathophysiologic mechanisms [1]. LPR has been postulated to play a role in up to 50% of laryngeal complaints that present in an otolaryngological practice [2]. LPR is defined as the backflow of gastric contents into the pharynx, larynx, and upper aerodigestive tract. The main pathological event in LPR is upper esophageal sphincter dysfunction. Upper esophageal sphincter dysfunction is not the sole etiology, as some studies noted a correlation between LPR and the carbonic anhydrase isoenzyme-III depletion in

addition to the presence of pepsin in laryngeal tissues affected by LPR [3]. GERD is diagnosed by the typical symptoms of heartburn and acid regurgitation, and the symptomatology of LPR is more diverse and less pathognomonic [4]. Patients with LPR suffer from phonasthenia symptoms, namely hoarseness, globus, throat discomfort, dysphonia, chronic throat clearing, and dysphagia [5]. Otolaryngological manifestations of acid reflux include a wide range of pharyngeal and laryngeal symptoms, and the constellation of symptoms called LPR. Laryngopharyngeal reflux is a major cause of laryngeal inflammation and presents with symptoms different from classic GERD [6].The combination of direct injury by reflux materials and symptoms such as chronic laryngospasm and throat clearing can lead to vocal cord edema, granulomas, and contact ulcers that cause other LPR-associated symptoms [7]. Various studies evaluated the effect of stress on the gastrointestinal tract (GIT). More recent studies have focused on the relationship between stress and reported symptoms of GERD; increased gastric acid secretion has been seen in patients with a higher tendency toward emotional lability [8]. The goal of this study is to evaluate the criteria for the diagnosis of LPR, estimate the prevalence of LPR in patients with GERD, and to evaluate risk of psychiatric diseases with GERD.

Patients and methods

A cross-sectional study was conducted on 60 patients with typical GERD symptoms and laryngeal complaints; these studied patients were recruited from patients who attended the outpatient clinic of Tropical Medicine and Gastroenterology, Phoniatric Unit, Assiut University Hospital.

The studied patients fulfilled our study criteria and accepted to be enrolled; patients with clinical evidence of medical illness – for example hepatic, pancreatic, cardiac, renal or chronic obstructive airway diseases, pregnant women, smokers (to help us exclude the virgin larynx free from chronic inflammations), and teachers (high vocal demand and voice abuse) were excluded. Studied patients were screened for reflux symptoms, the symptom questionnaire and the classification proposed by Belafsky *et al.* [9] [reflux symptom index (RSI)] were used, and upper endoscopy was performed for the diagnosis GERD patients. Laryngeal examination using nasofibrolaryngoscopy for all these patients was performed to compare the results [reflux finding score (RFS)] [10]. Psychiatric assessment was performed by a psychiatric specialist using symptoms checklist revised 90 (SCL-R 90). Patients with a score more than 60 will be re-evaluated using the following questionnaires [11]: Hamilton checklist of symptoms of depressive illness and Hamilton rating scale for anxiety [12]. The study protocol was approved by the Ethical Committee of Faculty of Medicine, Assiut University Hospital. Written consent was obtained for upper endoscopy, verbal consent was obtained for laryngoscopy, and psychiatric evaluations were obtained from the patients who participated in this study.

Interviewer administered the questionnaire in an attached sheet asking about age, sex, presence, duration, and severity of reflux symptoms and upper GIT symptoms (RSI) [9]. We added two questions – no. 3 and 6 – that have intimate relations to phonasthenic symptoms (items no. 1, 2, 3, 6, 10). The grade of severity ranged from 0 to 5.

RSI score greater than or equal to 13 was positive.

Endoscopic evaluation of GERD for all participants was graded according to the modified Los Angeles classification of GERD [13] as shown in Table 2:

Laryngeal examination using naso fibrolaryngoscopy was done for all studied patients by a single highly experienced phoniatrician using a five-point scale: 0, no and 4, severe; except item 6 – yes or no – RFS is depicted as follows [10]:

(1) Subglottic edema: 0 (absent) and 1 (present)

Table 1 Reflux symptoms index

Within the last months, how did the following problems affect you?						
1. Hoarseness or a problem with your voice	0	1	2	3	4	5
2. Clearing your throat	0	1	2	3	4	5
3. Difficulty in swallowing saliva	0	1	2	3	4	5
4. Excess throat mucous or postnasal drib	0	1	2	3	4	5
5. Difficulty swallowing food, liquid, or pills	0	1	2	3	4	5
6. Sensation of dry throat	0	1	2	3	4	
7. Coughing after you ate or after lying down	0	1	2	3	4	
8. Breathing difficulties or choking episodes	0	1	2	3	4	5
9. Troublesome or annoying cough	0	1	2	3	4	5
10. Sensation of something sticking in your throat or a lump in your mouth	0	1	2	3	4	5
11. Heart burn, chest burn, indigestion, or stomach acid coming up	0	1	2	3	4	5
Total						

Table 2 Modified Los Angeles classification of GERD

Grade	Description
A	One (or more) mucosal break no longer than 5 mm that does not extend between the tops of two mucosal folds
B	One (or more) mucosal break more than 5 mm that does not extend between the tops of two mucosal folds
C	One (or more) mucosal break that is continuous between the tops of two or more mucosal folds but that involves less than 75% of the circumference
D	One (or more) mucosal break that involves at least 75% of the esophageal circumference

(2) Erythema/hyperemia: 0 (none), 2 (arytenoids), and 4 (diffuse)
(3) Vocal fold edema: 0 (none), 1 (mild), 2 (moderate), 3 (severe), and 4 (polypoid)
(4) Diffuse laryngeal edema: 0 (none), 1 (mild), 2 (moderate), 3 (severe), and 4 (obstruct)
(5) Posterior glottis mucosa hypertrophy: 0 (none), 1 (mild), 2 (moderate), 3 (severe), and 4 (obstruct)
(6) Granuloma or granulation: 0 (absent), 2 (present), 3 (unilateral), and 4 (bilateral)
(7) Thick endolaryngeal mucus: 0 (absent) and 2 (present).

The RFS ranged from 0 to 26; scores greater than or equal 7 were positive.

Psychiatric assessment was done by a psychiatric specialist using SCL-R 90 (Abdel Rakeeb Elbehery, 1984). Patient with a score more than 60 will be re-evaluated using the following questionnaires: Hamilton checklist of symptoms of depressive illness [11] and Hamilton rating scale for anxiety [12].

Statistical analysis

The collected data were verified and coded. Analysis of data was performed using SPSS program, versions 16 (Chicago, SPSS Inc). Data were expressed in proportions for categorical variables and mean ± SD for continuous variables. In univariate analysis, Student's *t*-test was used for comparison of means. Spearman's correlation was used to test correlation. χ^2-test was used for comparison of proportions. In multivariate analysis, after adjusting for confounding factors, Cronbach's α is a measure used to assess the reliability or internal consistency of RSI, mostly phonathenia symptoms (way of measuring the strength of that consistency); the logistic regression model identified independent determinants of LPR. The criterion for statistical significance was as follows: *P* greater than 0.05 nonsignificant and *P* less than 0.05 significant.

Results

The mean age was 32.86 ± 7.73 years. Twenty-eight (46.67%) were male, whereas 32 (53.33%) were female. No significant associations were detected between age and sex in relation to symptoms and signs ($P < 0.05$).

Regarding RSI among the studied patients, all were positive. The most common symptoms were heart burn, lump sensation, clearing of throat, hoarseness, and difficulty in swallowing saliva (Table 3).

The frequency of RFS in the studied patient greater than or equal to 7 was considered positive. Out of all patients, 32 (53.33%) were positive (Table 4).

Concerning the evaluation of the reliability of five items from RSI (RSI consist of 11 items), the evaluated five items are concerned with intimate correlation with phonasthenic symptoms. Cronbach's α test was performed, and Cronbach's α was satisfactory, except for difficulty in swallowing saliva (Table 5).

Endoscopic examination is highly diagnostic for GERD symptoms, and association of incompetent cardia is common in studied patients (Table 6).

Table 7 shows the correlation between five items (hoarseness, clearing, saliva, difficulty, and lump) and the presence of RFS, where all of them had positive significant correlation to RFS, except difficulty in swallowing saliva, which had a positive correlation but had no significant statistical difference ($P > 0.05$).

Table 8 shows multi linear regression of different risk factors such as age, sex, cardiac incompetence, degree of GERD, psychiatric manifestations, and reflux symptoms with the presence of RFS, where there is a significant statistical association between laryngoscopic examination finding (RFS) and cardiac incompetency, degree of GERD, psychiatric manifestations, and reflux symptoms, with a *P* value less than 0.05 and the most important risk factor for the presence of RFS being RSI with β-value of 4.8. The significant predictors for RSI were in order: RSI, psychiatric manifestations, degree of GERD, and incompetent cardia. Age and sex were not significant predictors for RSI.

Frequency of psychiatric manifestation among the studied patients was positive if score greater than or equal to 60; the most commonly detected manifestations were anxiety with a score of 44 (73.3%), whereas depression represents a score of 11 (18.33%) (SCL-R 90). Among those patients positive for anxiety, the percentage of those who were positive for RFS was higher than those with

Table 3 Reflux symptom index in the studied patients

Reflux symptom index	Frequency (*n* (%))[a]		Total
	Male	Female	
≥13	28 (46.67)	32 (53.33)	60
<13	0	0	0
Total	28 (46.67)	32 (53.33)	60

[a]Data was expressed in form of frequency (percentage).

Table 4 Reflux finding score among the studied patients

Reflux finding score	Total (*n* (%))
≥7 (positive RFS)	32 (53.33)
<7 (negative RFS)	28 (46.67)
Positive RFS ≥7	*N*=32
1. vascular congestion, vocal cord hyperemia	32 (100)[a]
2. vocal cord edema	26 (81)
3. phonatory gap	13 (40)
4. subglottic edema	12 (37)
5. swelling	10 (31.25)
6. contact granuloma	8 (25)

RFS, reflux finding score. [a]More than one sign detected.

Table 5 Cronbach's α test for the five-items reflux symptom score

Cronbach's α		Number of items
0.9		5
Items	Corrected item total correlation	Cronbach's α if item deleted
Hoarseness	0.75	0.8
Clearing	0.83	0.8
Saliva	0.83	0.8
Difficulty saliva	**0.53**	**0.9**
Lump	0.84	0.8

Bold values: Mean that all have higher cronbach test except for difficulty in swallowing saliva

Table 6 The frequency of gastroesophageal reflux disease among patients by endoscopic examination

GERD (positive RSI)	*N*=60 (*n* (%))
Present (LO classification)	
Grade I	12 (20)
Grade II	26 (43.33)
Grade III	13 (21.67)
Grade IV	7 (11.67)
Absent GERD	2 (3.33)
Incompetent cardia	57 (95)
Competent cardia	3 (5)

GERD, gastroesophageal reflux disease; LO, Los Angeles; RSI, reflux symptom index.

Table 7 Correlation between five items of RSI and RFS

Variables	*r* (*P*)
Hoarseness of voice	0.3 (0.02)
Clearing your throat	0.3 (0.01)
Dry mouth	0.3 (0.01)
Difficulty in swallowing	0.2 (0.23)
Lump sensation	0.3 (0.04)

Table 8 Multlinear regression between different risk factors an presence of RFS

Variables	*β*	*P**
Age	0.28	0.43
Sex	0.83	0.09
Cardiac examination	0.9	0.04
Degree of GERD	2.1	0.00
Psychiatric manifestations	3.6	0.00
Reflux symptom index	4.8	0.00

GERD, gastroesophageal reflux disease. **P* value is considered significant if less than 0.05.

negative RFS; in contrast, for those who were negative for depression the percentage of patients with negative RFS was higher than that for patients who were positive. There was a positive significant correlation between RFS and anxiety; on the other hand, a negative significant correlation was detected between RFS and depression (Figs. 1 and 2).

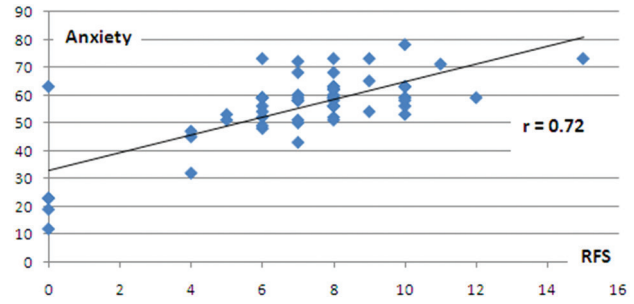
There was a positive significant correlation between RSI and anxiety, whereas negative significant correlation was detected between RSI and depression (Figs. 3 and 4).

Discussion

Diagnosing LPR can be challenging, as symptoms can be nonspecific. A RSI is a questionnaire that can be used to establish the initial diagnosis of LPR and monitor response to treatment. RSI score greater than 13 strongly suggests LPR. The patient can then be referred to phoniatric specialist for a transnasal fiberoptic.

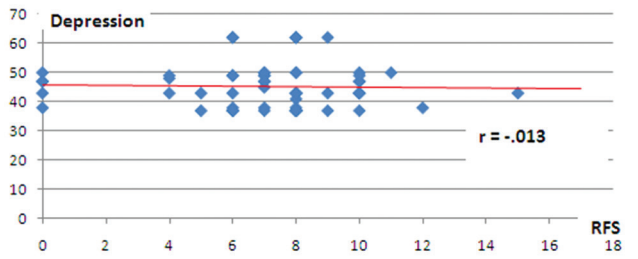
Laryngoscopy is an essential tool in the evaluation of patients with suspected LPR. The laryngeal findings attributable to reflux have been well described and include erythema and vocal cord granuloma, nodules, polyp, and edema of the posterior commissure and arytenoid cartilages [14]. Most presented patients in our study were female, and this is in agreement with results of many authors – for example Jacobson *et al.* [15] and Lin *et al.* [16], who found a higher frequency of symptoms and slightly increased severity of symptoms in women compared with men; however, the clinical importance of this difference is still unclear. Some have suggested that this is the result of different symptom sensitivity due to different patterns of health-seeking behavior between the sexes [17]. This in controversy to the findings of Richter *et al.* [18], who stated that males show more physiologic and pathologic GERD as compared with females. In our study, the mean age was 32.86 ± 7.73 years, which is in controversy to a previous reported study by Becher and Dent [19] that has shown an increase in GERD symptom prevalence with age. Aging is associated with severe patterns of acid reflux and reflux esophagitis; despite this, symptoms associated with GERD become less severe and nonspecific with age. Thus, the real prevalence of GERD may increase with age. Most of the studied patients with GERD symptoms showed positive

Figure 1



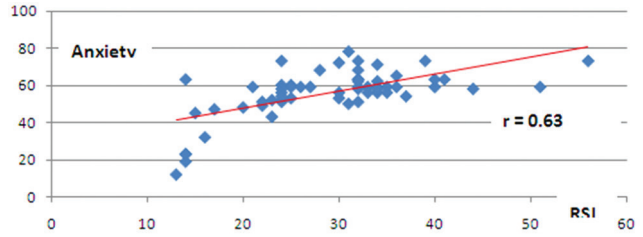
Correlation between reflux finding score and anxiety.

Figure 2



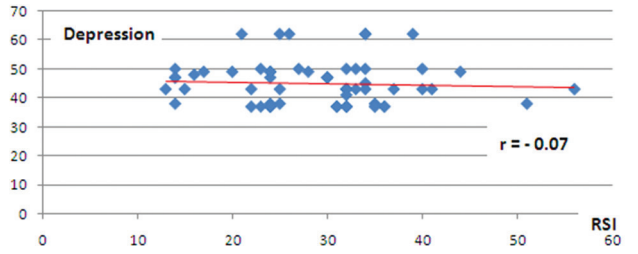
Correlation between reflux finding score and depression.

Figure 3



Correlation between reflux symptom index and Anxiety.

Figure 4



Correlation between reflux symptom index and depression.

endoscopic findings (96.7%); findings were consistent with previous studies reporting that the presence of typical finding of reflux esophagitis was diagnostic of GERD with a specificity as high as 95% Richter JE (2003) [18]. However, in controversy with our result, 50% of patients with reflux symptoms have normal esophageal endoscopic findings Vakil *et al.*, 2006 [20], and another study reported that endoscopic findings were associated with distinct attributes of reflux symptoms. Symptoms are only modestly predictive of findings at endoscopy Lock *et al.*, 2005 [21]. Our results show that through the 23 patients who have positive reflux sign index, the most prominent signs were vascular hyperemia, vocal cord edema, subglottic edema, granuloma, swelling, and phonatory gap. There was a strong positive correlation between RFS and RSI (phonasthena symptoms). These findings go in agreement with Belafsky *et al.* [10], who declared that one or more laryngopharyngeal mucosal signs associated with LPR were identified in 64% of healthy volunteers and in 85% of GERD sufferers (RFS > 7 in 24%). The phonasthenic symptoms could be also found typically in patients with vocal cord abuse/misuse with high vocal demands at their jobs (e.g., teachers, salesmen, etc.). This should be considered for meticulous exclusion of patients having true GERD manifestations from those having phonasthenic symptoms because of their job demands. In the present study, we found that there is a strong association between psychological symptoms and the presence of LPR and GERD symptoms. The most commonly detected manifestations reported were anxiety, and there was a positive significant correlation with anxiety and a negative significant correlation between depression and reflux symptoms, and our result is in accordance with the pervious study Kamolz and Velanovich [22], which reported a strong association between psychological symptoms, mood disorders, anxiety, depression, and GERD-related symptoms in adults. A positive trend was observed when comparing current anxiety disorders and current GERD-related symptoms. However, this was in contrast with the findings of other authors who reported that it is plausible that the presence of GERD-related symptoms can increase feelings of both depression and anxiety. There are many explanations for the association between psychopathology and GERD-related symptoms. As suggested Kamolz and Velanovich [22], the relationship may be contributed to changes in esophageal motility and LOS function in response to stressors. Although little is known about the morphological organization of serotonergic neurons in the esophagus, investigations have indicated that serotonin, the main target of both depression and anxiety treatment, plays a role in esophageal motility [23,24], leading to neurohormonal interaction between the central nervous system and the GI system.

Conclusion and recommendations

Patients with LPR have upper aerodigestive manifestations of reflux disease rather than classic GERD (i.e., esophagitis). The manifestations and

symptoms of LPR are different because the mechanisms and patterns of reflux are different from those of GERD. Our study showed that RSI and RFS could be useful for the diagnosis and evaluation of patients with LPR. The RSI and RFS can easily be included in phonatric unit routine as objective parameters especially in cases having phonasthenic symptoms, with low cost and good practicality. According to the clinical index, it can evaluate the need for further tests. Psychological diagnosis and intervention can improve the general well-being and quality of life of patients with GI symptoms.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1 Orlando RC. Pathogenesis of gastroesophageal reflux disease. Gastroenterol Clin North Am 2002;31(4):S35-44.

2 Koufman JA, Belafsky BC, Bach KK, Daniel E, Postma GN. Prevalence of esophagitis in patients with pH-documented laryngopharyngeal reflux. Laryngoscope 2002;112:1606-9.

3 Johnston N, Knight J, Dettmar PW, Lively MO, Koufman J. Pepsin and carbonic anhydrase isoenzyme III as diagnostic markers for laryngopharyngeal reflux disease. Laryngoscope 2004;114:2129-2134.

4 Jaspersen D, Kulig M, Labenz J, Leodolter A, Lind T, Meyer-Sabellek W, Vieth M, Willich SN, Lindner D, Stolte M, Malfertheiner P. Prevalence of extra oesophageal manifestations in gastro-oesophageal reflux disease: an analysis based on the ProGERD Study. Aliment Pharmacol Ther 2003;18(3):355.

5 Cohen JT, Gil Z, Fliss DM. The reflux symptom index-a clinical tool for the diagnosis of laryngopharyngeal reflux. Harefuah 2005;144:826-829.

6 Ahmad I, Batch AJ. Acid reflux management: ENT perspective. J Laryngolotol 2004;118:25-30.

7 Milstein CF, Charbel S, Hicks DM, Abelson TI, Richter JE, Vaezi MF. Laryngeo-pharyngeal reflux. Laryngoscope 2005;115:2256-2261.

8 Bradley LA, Richter JE, Pulliam TJ, Haile JM, Scarinci IC, Schan CA, Dalton CB, Salley AN. The relationship between stress and symptoms of gastroesophageal reflux: the influence of psychological factors. Am J Gastroenterol 1995;88:11-9.

9 Belafsky PC, Postma GN, Koufman JA. Validity and reliability of reflux symptoms index (RSI). J Voice 2002;16:274-277.

10 Belafsky PC, Postma GN, Koufman JA. The validity and reliability of the reflux finding score (RFS). Laryngoscope 2001;111:1313-1317.

11 Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56-62.

12 Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959;32:50-55.

13 Lundell LR, Dent J, Bennett JR, Blum AL, Armstrong D, Galmiche JP, *et al*. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. Gut 1999;45(2):172-80.

14 Qadeer MA, Phillips CO, Lopez AR, Steward DL, Noordzij JP, Wo JM, *et al*. Proton pump inhibitor therapy for suspected GERD-related chronic laryngitis: a meta-analysis of randomized controlled trials. Am J Gastroenterol 2006;101:2646-2654.

15 Jacobson BC, Somers SC, Fuchs CS, Kelly CP, Camargo CA Jr. Body mass index and symptoms of gastroesophageal reflux in women. N Engl J Med 2006;354:2340-2348.

16 Lin M, Gerson LB, Lascar R, Davila M, Triadafilopoulos G. Features of gastroesophageal reflux disease in women. Am J Gastroenterol 2004;99:1442-1447.

17 Nilsson M, Johnsen R, Ye W, Hveem K, Lagergren J. Prevalence of gastro-oesophageal reflux symptoms and the influence of age and sex. Scand J Gastroenterol 2004; 39:1040-1045.

18 Richter JE. Diagnostic tests for gastroesophageal reflux disease. Am J Med Sci 2003;326:300-8.

19 Becher A, Dent J. Systematic review: ageing and gastro-oesophageal reflux disease symptoms, oesophageal function and reflux oesophagitis. Aliment Pharmacol Ther 2010;33:442-454.

20 Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R. The Montreal definition and classification of gastroesophageal reflux disease: a global evidencebased consensus. Am J Gastroenterol 2006;101:1900-20.

21 Locke GR, Zinsmeister AR, Talley NJ. Can symptoms predict endoscopic findings in GERD? Gastrointest Endosc 2003;58:661-70.

22 Kamolz T, Velanovich V. Psychological and emotional aspects of gastroesophageal reflux disease. Dis Esophagus 2002;15(3):199-203.

23 Pehlivanov N, Sarosiek I, Whitman R, Olyaee M, McCallum R. Effect of cisapride on nocturnal transient lower oesophageal sphincter relaxations and nocturnal gastro-oesophageal reflux in patients with oesophagitis: a double-blind, placebo-controlled study. Aliment Pharmacol Ther 2002;16:743-747.

24 Hempfling C, Neuhuber WL, Worl J. Serotonin-immunoreactive neurons and mast cells in the mouse esophagus suggest involvement of serotonin in both motility control and neuroimmune interactions. Neurogastroenterol Motil 2012;24:67-78.