Surgical Endoscopy (2019) 33:4116–4121
https://doi.org/10.1007/s00464-019-06716-y

Minor psychiatric disorders and objective diagnosis of gastroesophageal reflux disease

Rafael Melillo Laurino Neto[1] · Fernando A. M. Herbella[1,2] · Andre Zugman[3] · Vic Velanovich[4] · Beth Montera[4] · Francisco Schlottmann[5] · Marco G. Patti[5]

Received: 18 September 2018 / Accepted: 19 February 2019 / Published online: 27 February 2019

Abstract

Background Symptoms may be unreliable to diagnose gastroesophageal reflux disease (GERD) in patients with minor psychiatric disorders (MPD). This study aims to evaluate the influence of MPD in the diagnosis of GERD.

Methods We prospectively studied 245 patients (based on a sample size calculation) with suspected GERD. All patients underwent manometry and pH monitoring and MPD evaluation based on the Hospital Anxiety and Depression Scale (HADS).

Results Based on the results of the pH monitoring, patients were classified as GERD + ($n = 136$, 55% of the total, mean age 46 years, 47% females) or GERD − ($n = 109$, 45% of the total, mean age 43 years, 60% females). The mean HADS score for GERD + and GERD − for anxiety was 7.8 and 8.5, respectively ($p = 0.8$) and for depression was 5.4 and 6.1, respectively ($p = 0.1$). DeMeester score (DS) did not correlate with total HADS score ($p = 0.08$) or depression domain ($p = 0.9$) but there was a negative correlation between DS and anxiety level ($p < 0.001$). A significant threshold accuracy value for HADS to diagnose GERD was not found on receiver operating characteristics curve analysis.

Conclusion Almost half of the patients evaluated for GERD did not have the disease on objective evaluation. GERD + and GERD − patients had similar levels of MPD. However, the amount of reflux correlated negatively with the severity of anxiety. Symptoms and HADS cannot accurately diagnose or exclude GERD. pH monitoring should be more liberally used especially in patients with high levels of anxiety.

Keywords Gastroesophageal reflux disease · Esophageal pH monitoring · Anxiety · Depression · Surveys and questionnaires

Gastroesophageal reflux disease (GERD) is defined as the clinical condition that occurs due to the retrograde flow of gastroduodenal contents into the esophagus or adjacent organs, causing symptoms and/or mucosal damage [1]. It has a high prevalence in several continents with individuals presenting at least one episode of heartburn from 2 to 8% in Asia and from 18 to 28% in North America [2].

GERD diagnosis based on symptoms only, even with the use of dedicated questionnaires, has a sensitivity lower than 40% [3]. Upper endoscopy has low sensitivity for confirming the diagnosis, as some patients can have a normal endoscopy without mucosal damage [4]. Esophageal ambulatory pH monitoring, on the other side, is an important tool for the objective diagnosis of GERD with specificity around 90% and sensitivity around 95% [5, 6]. GERD symptoms in the absence of pathologic reflux may occur when psychiatric disorders participate as one of the triggering factors [7, 8]. The frequency and duration of GERD symptoms [9, 10] as well as worse outcomes for clinical [10, 11] or surgical [12] therapies for GERD have been linked to the concomitance of MPD, however, there are still few studies on the influence of these diseases in the diagnosis of GERD.

✉ Fernando A. M. Herbella
herbella.dcir@epm.br

1 Department of Surgery, Escola Paulista de Medicina, Rua Diogo de Faria 1087, cj 301, São Paulo, SP 04037-003, Brazil

2 Hospital São Luiz Morumbi, São Paulo, Brazil

3 Department of Psychiatry, Escola Paulista de Medicina, São Paulo, Brazil

4 Department of Surgery, University of South Florida, Tampa, US

5 University of North Carolina at Chapel Hill, Chapel Hill, USA

Although the association between minor psychiatric disorders (MPD) and functional gastrointestinal syndromes is well established, the influence of MPD on the diagnosis of gastroesophageal reflux disease (GERD) remains elusive [7]. As GERD symptoms are not sensitive and specific and there is a considerable overlap with other gastrointestinal disorders [3], diagnosis of GERD based on symptoms only is less reliable when compared to objective evaluation with esophageal manometry to exclude primary motility disorders and pH monitoring to confirm GERD [5].

We hypothesize that symptoms are even more unpredictable to diagnose GERD in patients with MPD. This study aims to evaluate the correlation between MPD and 24 h pH monitoring test.

Methods

Population

We prospectively studied 245 consecutive adult patients [mean age 44.4 ± 12.8 (19–77) years, 133 females—54%] with suspected GERD. Patients with primary esophageal motility disorders; previous upper digestive tract operations; and those who refused to sign the informed consent were excluded.

Symptoms were grouped as esophageal (heartburn, regurgitation, dysphagia) or extra-esophageal (otolaryngologic, pulmonary, chest pain). The most prevalent symptom reported during the pH monitoring study was considered as the main complaint.

Upper endoscopy was available to review in 189 (77%) patients as most of the patients were referred for esophageal function tests only, and not treated in our institution. The presence of endoscopic esophagitis, hiatal hernia or Barrett's esophagus was recorded.

Esophageal function tests

Esophageal tests were performed as previously detailed [13].

All patients underwent an esophageal manometry (Multiplex High Resolution Manometry, water perfused 24 channels, Alacer Biomedica, São Paulo) to determine the correct placement of the pH monitoring catheter and to exclude primary esophageal motility disorders. Patients fasted for at least 8 h before the test, and all medications that may interfere with esophageal motility were discontinued for at least 2 days. Acid-reducing medications were discontinued 3 days (H2 blocking agents) to 7 days before the pH monitoring (proton pump inhibitors).

All patients underwent pH monitoring (Al-3, transnasal antimony catheter, Alacer Biomedica, São Paulo) immediately following manometry [14]. Patients with a composite score (DeMeester score—DS) > 14.7 were considered GERD +.

All esophageal function tests were performed and interpreted by the same investigator.

MPD evaluation

MPD was evaluated based on Hospital Anxiety and Depression Scale (HADS). This self-assessed form has 14 questions and 2 domains, 7 questions are focused on the assessment of anxiety (HADS-A) and 7 of depression (HADS-D). Each question can be scored from 0 to 3, composing a maximum score of 21 points for each domain [15].

Statistical analysis

The number of recruited patients was based on a sample size calculation considering the prevalence of MPD of 20% in the local general population of 20,000,000 inhabitants [16].

All continuous variables are presented as means ± standard variation (range) and categorical variables as percentages.

Fisher, Student's *t* test and Pearson correlation tests were used when appropriate. Receiver operating characteristics (ROC) curve was used to determine accuracy of GERD diagnosis based on HADS.

Results

Population

GERD + comprised 136 patients, 55% of the total, mean age 45.8 ± 13.5 (22–77) years, 64 (47%) females.

GERD − comprised 109 patients, 45% of the total, mean age 42.6 ± 11.8 years, 65 (60%) females. The prevalence of females was higher in GERD − patients as compared to GERD + ($p = 0.05$).

Esophageal symptoms were present in 140 (57%) of the total number of patients. Extra-esophageal symptoms were present in 77 (31%) patients. Twenty-eight patients did not have any GERD symptom (pre-operative evaluation for bariatric surgery).

Upper endoscopy showed esophagitis in 133 (70.4%) patients, hiatal hernia in 59 (31.2%) and Barrett's esophagus in 5 (2.6%) patients.

Esophageal function tests

Mean DS was 43.6 ± 32.0 (15–163) and 6.8 ± 4.0 (0.2–14.1) for GERD + and GERD −, respectively.

Minor psychiatric disorders

HADS scores are depicted in Table 1. There was no difference in HADS scores between groups GERD + and GERD −.

Correlation between DS and HADS

There was no correlation between DS and total HADS score ($r = 0.1$, $p = 0.08$) and between DS and depression HADS score ($r = 0.005$, $p = 0.9$) for the whole population. DS and anxiety HADS score had a negative relationship ($r = -0.2$, $p < 0.001$) (Fig. 1).

Subanalysis of patients with esophageal symptoms showed a negative correlation between DS and HADS anxiety ($r = -0.2$, $p = 0.01$). In patients with extra-esophageal symptoms, there was a negative relationship between DS and HADS anxiety ($r = -0.2$, $p < 0.001$) and a positive relationship between DS and HADS depression ($r = 0.3$, $p < 0.001$). The distribution of females and males according to symptoms was not different ($p = 0.1$).

Subanalysis of correlation between DS and HADS total + domains according to gender, did not show correlation for males (total $r = -0.1$, $p = 0.1$; anxiety $r = -0.1$, $p = 0.1$; depression $r = -0.1$, $p = 0.2$) and females for HADS total ($r = 0.08$, $p = 0.4$) and anxiety ($r = -0.1$, $p = 0.08$). Females had a positive relationship between depression and DS ($r = 0.3$, $p = 0.001$) with equal amount of depression between genders ($p = 0.4$).

ROC curve showed a very low accuracy (inferior 50%) to diagnose GERD based on HADS (Fig. 2).

Discussion

MPD and GERD

Few studies by gastroenterologists and psychiatrists show a higher prevalence of GERD symptoms in depression [17, 18] and a higher incidence of MPD in GERD series [9, 11, 19–21]. There is also evidence suggesting the association between other functional digestive diseases, such as irritable bowel syndrome, and psychiatric diseases [19, 22].

Some authors report that for individuals with anxiety or depression there is a threefold increase in the chance of an individual complaining of reflux symptoms [20] while others do not demonstrate an association of these psychiatric

Table 1 Level of MPD

	Total ($n = 245$)	GERD + ($n = 136$)	GERD − ($n = 109$)	p (95% CI)[a]
HADS total	13.8 ± 6.9 (0–42)	13.1 ± 6.6 (0–36)	14.6 ± 7.1 (1–42)	0.07 (−3.3–0.2)
HADS anxiety	8.1 ± 4.0 (0–21)	7.8 ± 3.7 (1–18)	8.5 ± 4.2 (0–21)	0.8 (−0.2–1.8)
HADS depression	5.7 ± 3.6 (0–21)	5.4 ± 3.5 (0–18)	6.1 ± 3.8 (0–21)	0.1 (−1.6–0.2)

Values presented as means ± standard variation (range)

GERD gastroesophageal reflux disease, *HADS* Hospital Anxiety and Depression Scale, *CI* confidence interval

[a]GERD + versus GERD −

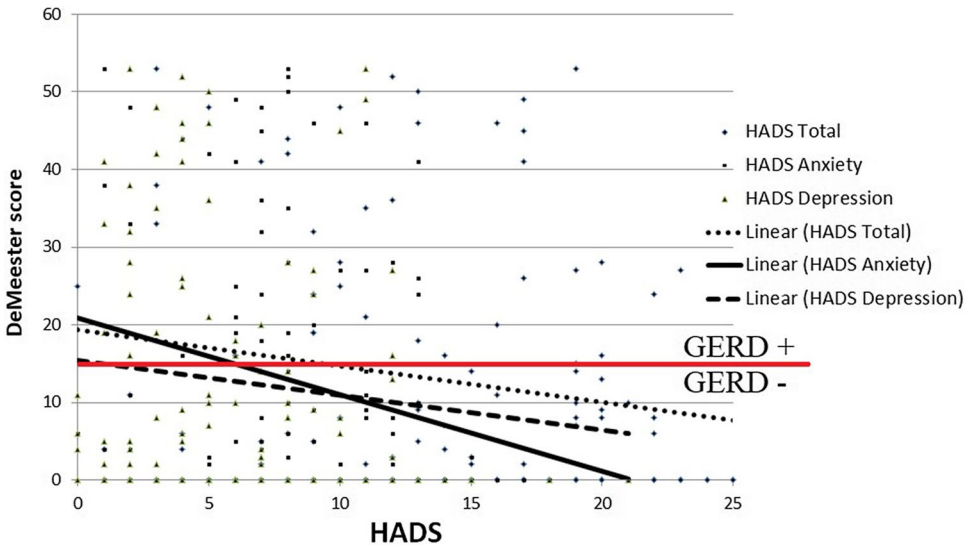

Fig. 1 Correlation between DS and HADS. DS and HADS anxiety had a negative relationship ($r = -0.2$, $p < 0.001$)

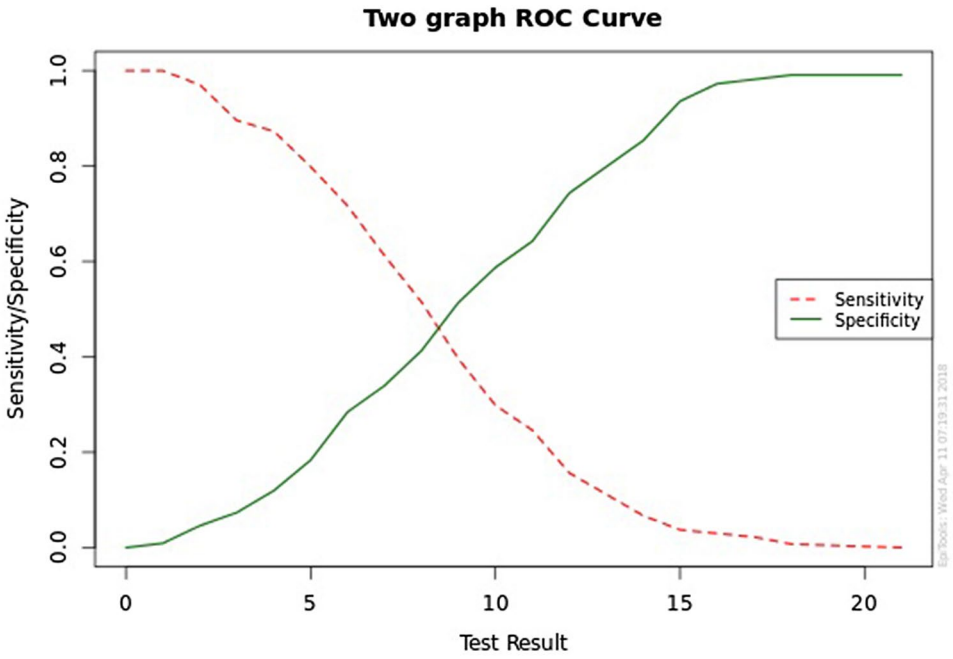

Fig. 2 ROC curve for GERD diagnosis based on HADS

disorders with the number of complaints of daily reflux symptoms [23].

GERD symptoms in the absence of pathologic reflux may be explained by hypersensitivity and hypervigilance both of which may be related to MPD. Hypersensitivity occurs when symptoms are triggered by an amount of reflux that falls within normal pH monitoring values [8]. Daily short-duration episodes of reflux are very common even in healthy volunteers, as such in susceptible individuals this situation may lead to an increased number of reported symptoms [24]. Hypervigilance is closely related to MPD and also leads to an increased number of daily complaints of symptoms since psychiatric factors alter the perception of the physiological changes by the patient [25].

This study evaluated the influence of MPD on the objective diagnosis of GERD. Our hypothesis was that symptoms were unpredictable for this purpose in patients with these psychiatric disorders. However, the degree of MPD was not able to distinguish GERD + from GERD − patients. Moreover, the expectation that a simple questionnaire easy to be applied during the initial evaluation of a patient with suspected GERD would select patients to an objective diagnosis of GERD was not fulfilled. We did find that low levels of reflux are associated with higher levels of anxiety. This fact may denote hypersensitivity and hypervigilance and linked to worse treatment outcomes as previously mentioned. In addition, females had higher levels of depression when higher amounts of reflux are present even though both genders had equal amount of depression levels. Not coincidently, males have more severe reflux as compared to females but female gender is associated with worse outcomes after surgical treatment [26]. Similarly, patients with extra-esophageal symptoms had higher levels of depression when higher amounts of reflux are present.

Study limitations, strengths and comparison to similar studies

Our study had several limitations. HADS was the tool to assess MPD. Although this questionnaire is widely used [15], it is not specific for digestive disorders such as the EHAS [27], which does not include depression analysis. Our preference for this questionnaire was based on free access, easiness to complete, and inclusion of both depression and anxiety. We opted not to use a threshold value to define MPD as other authors did [20, 23, 28]. Instead, we looked for a significant cutoff more linked to GERD that unfortunately we did not find. We did not evaluate quality of life and other functional digestive disorders in the current study. The strengths of the study are the calculated sample size, the prospective design and the collaboration of a psychiatrist.

There are similar previous studies that correlate GERD to MPD [23, 29–33]. GERD was diagnosed by pH monitoring in two studies [23, 30], others used only endoscopy or response to medications. MPD was diagnosed in the majority of the studies by HADS. Kessing et al. [23] found a correlation between increased GERD symptoms for anxiety but not for depression, similar to our findings. Other studies found positive correlation between anxiety and depression according to endoscopic findings [29, 32, 33], non-response to medication [30] or the presence of functional heartburn [31]. Interestingly endoscopic findings and non-response to

medications may correspond to absence of reflux since these studies did not use pH monitoring precluding a comparison with our results. The limited availability of endoscopic data in our study is also a drawback for this analysis.

Conclusions

Our study demonstrated once more that symptoms are unreliable to diagnose GERD as almost half of the patients evaluated for GERD did not have the disease on objective evaluation. We expected that MPD could explain in part the presence of symptoms in the setting of a negative pH monitoring but our results showed that GERD + and GERD − patients have similar levels of MPD. Thus, symptoms and HADS score cannot accurately diagnose or exclude GERD and pH monitoring should be more liberally used.

A subanalysis of the data showed that increased levels of depression in women are associated to increase in GERD severity. On the other side, the amount of reflux correlated negatively with the severity of anxiety showing that patients with severe anxiety must be objectively tested with pH monitoring.

Acknowledgements We are indebted to Dr. Sun Rein Lin to allow his patients to be included in the study; Ms. Eliane Francisco for her invaluable assistance with IRB bureaucracy and Edkerly Noronha, NP and her team for priceless help to perform the esophageal functions tests.

Author contributions RMLN: Protocol/project development; data collection or management; data analysis; manuscript writing/editing. FAMH: Protocol/project development; data collection or management; data analysis; manuscript writing/editing. AZ: Protocol/project development. VV: Protocol/project development; data collection or management; manuscript writing/editing. BM: Data collection or management. FS: Manuscript writing/editing. MGP: Manuscript writing/editing. All authors contributed sufficiently to be named as authors and are responsible for the manuscript. No professional or ghost writer was hired.

Compliance with ethical standards

Disclosures Rafael Melillo Laurino Neto, Fernando A. M. Herbella, Andre Zugman, Vic Velanovich, Beth Montera, Francisco Schlottmann, and Marco G. Patti, MD have no conflicts of interest or financial ties to disclose.

Ethical approval The study protocol was approved by the local Ethics Committee, and written informed consent was obtained from each subject.

References

1. Vakil N et al (2006) The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol 101(8):1900–1920. (**quiz 1943**)
2. El-Serag HB et al (2014) Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut 63(6):871–880
3. Dent J et al (2010) Accuracy of the diagnosis of GORD by questionnaire, physicians and a trial of proton pump inhibitor treatment: the Diamond Study. Gut 59(6):714–721
4. Nasi A et al (2001) Gastroesophageal reflux disease: comparison between patients with and without esophagitis, concerning age, gender and symptoms. Arq Gastroenterol 38(2):109–115
5. Moraes-Filho JP et al (2010) Guidelines for the diagnosis and management of gastroesophageal reflux disease: an evidence-based consensus. Arq Gastroenterol 47(1):99–115
6. Andolfi C et al (2016) Importance of esophageal manometry and pH monitoring in the evaluation of patients with refractory gastroesophageal reflux disease: a multicenter study. J Laparoendosc Adv Surg Tech A 26(7):548–550
7. Olden KW (2008) Psychosocial factors in functional gastrointestinal disorders: an evolving phenomenon. Neurogastroenterol Motil 20(Suppl 1):114–120
8. Aziz Q et al (2016) Functional esophageal disorders. Gastroenterology. https://doi.org/10.1053/j.gastro.2016.02.012
9. Nunez-Rodriguez MH, Miranda A, Sivelo (2008) Psychological factors in gastroesophageal reflux disease measured by scl-90-R questionnaire. Dig Dis Sci 53(12):3071–3075
10. Lee KJ et al (2009) Demographic, clinical, and psychological characteristics of the heartburn groups classified using the Rome III criteria and factors associated with the responsiveness to proton pump inhibitors in the gastroesophageal reflux disease group. Digestion 79(3):131–136
11. Wiklund I et al (2006) Psychological factors as a predictor of treatment response in patients with heartburn: a pooled analysis of clinical trials. Scand J Gastroenterol 41(3):288–293
12. Velanovich V, Karmy-Jones R (2001) Psychiatric disorders affect outcomes of antireflux operations for gastroesophageal reflux disease. Surg Endosc 15(2):171–175
13. Del Grande LM, Herbella FA, Bigatao AM, Abrao H, Jardim JR, Patti MG (2016) Pathophysiology of gastroesophageal reflux in patients with chronic pulmonary obstructive disease is linked to an increased transdiaphragmatic pressure gradient and not to a defective esophagogastric barrier. J Gastrointest Surg 20(1):104–110
14. DeMeester TR et al (1980) Technique, indications, and clinical use of 24 hour esophageal pH monitoring. J Thorac Cardiovasc Surg 79(5):656–670
15. Zigmond AS, Snaith RP (1983) The hospital anxiety and depression scale. Acta Psychiatr Scand 67(6):361–370
16. Andrade LH et al (2012) Mental disorders in megacities: findings from the Sao Paulo megacity mental health survey, Brazil. PLoS ONE 7(2):e31879
17. Avidan B et al (2001) Reflux symptoms are associated with psychiatric disease. Aliment Pharmacol Ther 15(12):1907–1912
18. Martin-Merino E et al (2010) Depression and treatment with antidepressants are associated with the development of gastro-oesophageal reflux disease. Aliment Pharmacol Ther 31(10):1132–1140
19. Hartono JL, Mahadeva S, Goh KL (2012) Anxiety and depression in various functional gastrointestinal disorders: do differences exist? J Dig Dis 13(5):252–257
20. Jansson C et al (2007) Severe gastro-oesophageal reflux symptoms in relation to anxiety, depression and coping in a population-based study. Aliment Pharmacol Ther 26(5):683–691
21. Baker LH, Lieberman D, Oehlke M (1995) Psychological distress in patients with gastroesophageal reflux disease. Am J Gastroenterol 90(10):1797–1803
22. Mykletun A et al (2010) Prevalence of mood and anxiety disorder in self reported irritable bowel syndrome (IBS). An epidemiological population based study of women. BMC Gastroenterol 10:88

23. Kessing BF et al (2015) Effects of anxiety and depression in patients with gastroesophageal reflux disease. Clin Gastroenterol Hepatol 13(6):1089–195.e1
24. Neto SC et al (2014) Ratio between proximal/distal gastroesophageal reflux does not discriminate abnormal proximal reflux. World J Surg 38(4):890–896
25. Oh JH et al (2009) Relationship between psychological factors and quality of life in subtypes of gastroesophageal reflux disease. Gut Liver 3(4):259–265
26. O'Boyle CJ et al (2002) Preoperative prediction of long-term outcome following laparoscopic fundoplication. ANZ J Surg 72(7):471–475
27. Taft TH et al (2018) Validation of the oesophageal hypervigilance and anxiety scale for chronic oesophageal disease. Aliment Pharmacol Ther 47(9):1270–1277
28. Boltin D et al (2013) Psychological distress is not associated with treatment failure in patients with gastroesophageal reflux disease. J Psychosom Res 75(5):462–466
29. Yang XJ et al (2015) Anxiety and depression in patients with gastroesophageal reflux disease and their effect on quality of life. World J Gastroenterol 21(14):4302–4309
30. Kimura Y et al (2016) Persistent reflux symptoms cause anxiety, depression, and mental health and sleep disorders in gastroesophageal reflux disease patients. J Clin Biochem Nutr 59(1):71–77
31. Bilgi MM et al (2017) Prevalence of psychiatric comorbidity in symptomatic gastroesophageal reflux subgroups. Dig Dis Sci 62(4):984–993
32. Okuyama M et al (2017) Associations among gastroesophageal reflux disease, psychological stress, and sleep disturbances in Japanese adults. Scand J Gastroenterol 52(1):44–49
33. Javadi S, Shafikhani AA (2017) Anxiety and depression in patients with gastroesophageal reflux disorder. Electron Physician 9(8):5107–5112