ORIGINAL ARTICLE

TJG
The Turkish Journal of Gastroenterology

Ongoing symptoms after eradication of *Helicobacter pylori:* Psychiatric disorders may accompany!

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Background/aims: *The precise mechanism of functional dyspepsia is yet to be elucidated. Helicobacter pylori infection and psychiatric disorders are implicated in the etiology. We aimed to determine the prevalence of psychiatric co-morbid disorders in patients with Helicobacter pylori-positive functional dyspepsia and the impact of existing psychiatric disorders on symptomatic response following eradication treatment.* ***Material and Methods:*** *Patients with Helicobacter pylori-positive functional dyspepsia and no previous diagnosis of any psychiatric disorder were included in the study. All patients' symptoms were evaluated with a visual analog scale and Likert scale. The Composite International Diagnostic Interview was applied to all patients by an experienced psychiatric nurse.* ***Results:*** *At least one psychiatric disorder was diagnosed in 22 of 54 patients. The most common disorder was depression, found in 13 patients. Symptomatic response to treatment was significantly higher in functional dyspepsia patients with no psychiatric disorder compared to those with at least one psychiatric co-morbid disorder (84% vs. 50%; p=0.007).* ***Conclusion:*** *Psychiatric co-morbid disorders are common in patients with functional dyspepsia and affect symptomatic response to Helicobacter pylori eradication treatment. Psychiatric disorders should be considered in patients who fail to achieve sufficient symptomatic relief after Helicobacter pylori eradication treatment.*

Key words: *Helicobacter pylori,* psychiatric disorders, dyspepsia

Helikobakter pilori eradikasyonu sonrası devam eden semptomlar: Psikiyatrik bozukluk eşlik ediyor olabilir!

Amaç: *Fonksiyonel dispepsi mekanizması henüz tam olarak aydınlatılamamıştır. Etiyolojisinde Helikobakter pilori ve psikiyatrik bozukluklar yer almaktadır. Biz Helikobakter pilori pozitif fonksiyonel dispepsili hastalarda eşlik eden psikiyatrik bozuklukların yaygınlığının belirlenmesini ve eradikasyon tedavisi sonrası mevcut psikiyatrik bozuklukların semptomatik cevaba etkisini belirlemeyi amaçladık.* ***Gereç ve Yöntem:*** *Daha önce herhangi bir psikiyatrik bozukluk tanısı almamış Helikobakter pilori pozitif fonksiyonel dispepsili hastalar çalışmaya dahil edildi. Tüm hastaların semptom ciddiyetleri görsel analog skala ve Likert tipi skala ile eradikasyon öncesi ve sonrası değerlendirildi. Psikiyatrik değerlendirme için uzman psikiyatri hemşiresince uygulanan Composite International Diagnostic Interview kullanıldı.* ***Bulgular:*** *Çalışmaya alınan 54 hastanın 22'sinde en az bir psikiyatrik bozukluk saptandı. En sık saptanan psikiyatrik bozukluk 13 hastada bulunan depresyondu. Tedaviye semptomatik cevap psikiyatrik bozukluk saptanmayan hastalarda daha yüksekti (84%'e, 50%; p=0.007).* ***Sonuç:*** *Fonksiyonel dispepsi hastalarında psikiyatrik bozukluk sıklığı yüksektir ve bu bozukluklar Helikobakter pilori eradikasyonuna semptomatik cevabı etkilemektedir. Eradikasyon tedavisine yeterli semptomatik cevap alınamayan hastalarda psikiyatrik bozukluk olasılığı akla getirilmelidir.*

Anahtar kelimeler: *Helikobakter pilori,* psikiyatrik bozukluklar, dispepsi

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Manuscript received: 21.04.2012 **Accepted:** 12.07.2012

Turk J Gastroenterol 2013; 24 (1): 15-21
doi: 10.4318/tjg.2013.0582

INTRODUCTION

Dyspepsia is one of the most common complaints in patients seeking medical help, but only a small portion of these patients have an organic cause for their symptoms (1). Those patients who have dyspepsia in the absence of any organic cause can be defined as having functional dyspepsia (2). The pathogenesis of functional dyspepsia is poorly understood, and the role of *Helicobacter pylori (H. pylori)* in the pathogenesis of functional dyspepsia is controversial. *H. pylori* plays a major role in the pathogenesis of peptic ulcers, and eradication of *H. pylori* decreases recurrence rates and brings symptomatic relief, so it is possible that *H. pylori* may play a role in the development of symptoms in functional dyspepsia (2-6).

The lack of any detectable organic cause drove the authors to hypothesize whether there could be a link between psychiatric disorders and the pathogenesis of functional dyspepsia. Some studies have reported that psychiatric disorders such as depression, anxiety and neurotic personality traits have been established more frequently among patients with functional dyspepsia in comparison to healthy subjects (7-13). Stress and anxiety disorders are the most common problems detected in symptomatic functional dyspepsia patients who were referred to tertiary medical centers (14). Psychiatric disorders play a major role in the development of dyspeptic symptoms, and influence the response to standard therapy (15,16).

We aimed to determine the prevalence of psychiatric disorders in patients with H. pylori-positive functional dyspepsia and the impact of existing psychiatric disorders on symptomatic amelioration following *H. pylori* eradication treatment.

METHODS

Patients who had displayed dyspeptic symptoms for at least one year and were evaluated in the Gastroenterology Department of Baskent University were enrolled in the study. The study protocol was approved by the Baskent University Ethics Committee.

Dyspepsia was defined as a set of various symptoms originating from the upper gastrointestinal system, such as epigastric pain or discomfort, nausea and or early satiation. All probable organic causes of dyspeptic symptoms were eliminated following a detailed work-up including an upper gastrointestinal system endoscopy and ultrasonographic imaging procedures. All patients included in the study had been diagnosed with functional dyspepsia according to the Rome II criteria.

Patients with a history of peptic ulcer disease; endoscopic findings of peptic ulcer, erosive gastritis, erosive esophagitis, or ulcer scarring; any gallbladder, bile duct or pancreatic pathology by abdominal ultrasonographic imaging; prior history of *H. pylori* eradication treatment; proton pump inhibitor (PPI) treatment during the last month; chronic non-steroidal anti-inflammatory drug (NSAID) use; history of abdominal surgery; pregnancy; prior diagnosis of any kind of psychiatric disorder; or who refused psychiatric evaluation were excluded from the study. Patients who failed eradication therapy for *H. pylori* after first- and second-line treatments were also excluded from the study.

Evaluation of symptoms

The severity of dyspepsia and response to therapy were evaluated by Likert and visual analog scales (VAS) pre- and post-treatment. During evaluation by VAS, patients marked the severity of their symptoms on a scale of 0 to 10 (0 indicating 'I have no complaint', 10 indicating 'The worst pain I have ever had and which also influences my daily life significantly'). The test was repeated by all patients following successful eradication treatment.

Evaluation by the Likert scale performed in two phases (pre- and post-treatment)

Pre-treatment Likert scores consisted of the summation of symptom scores for epigastric burning, epigastric pain, postprandial fullness, belching, bloating, nausea, vomiting, and regurgitation. Each symptom was evaluated for severity on a scale of 1 to 5 (1 indicating no complaint, 5 indicating the most severe). Pre-treatment Likert scores were noted as symptom severity scores.

The evaluation of post-eradication treatment symptom scores consisted of four questions aimed at assessing how the patient felt about his/her dyspeptic symptoms: 1) Do you consider yourself as cured? 2) Do you think that your complaints are totally under control? 3) Do you think there is a decrease in the complaints that significantly affected your daily life? And, 4) In general terms, do you feel well? Every question was evaluated on a scale of 1 to 5 (1 - definitely true; 5 - definitely false). Likert scores gathered after successful eradication treatment were noted as patient satisfaction scores. Patients who scored 8 points or less we-

re classified as good responders, and those who scored more than 8 points were scored as non-responders to treatment.

Psychiatric evaluation

The CIDI (Composite International Diagnostic Interview) questionnaire was conducted by a trained nurse for all patients before eradication treatment. The CIDI is designed as a psychiatric evaluation scale to assist in the diagnosis of psychiatric disorders that are included in the CIDI, Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV and International Classification of Diseases (ICD)-10. The adjustment of CIDI to primary healthcare (World Health Organization, 1991) consists of demographic data, means of access to primary healthcare, somatic disorders and drugs, somatoform disorders, neurasthenia, depression, anxiety disorders, cognitive disorders, and problems related with alcohol use. The interviewer and test–re-test consistency of the CIDI Turkish version has been previously investigated by other authors (17). We performed the parts associated with phobia and other anxiety disorders, depression, and dysthymic disorders and applied the final diagnoses in accordance with the DSM-IV system. After successful eradication treatment, final symptom analysis was performed and patients were diagnosed with depression, anxiety disorder, panic disorder, and social phobia by an expert psychiatrist.

Evaluation of *H. pylori* status

H. pylori positivity was assessed by rapid urease (Pronto-Dry) test and ^{14}C urea breath test in every patient. Patients were enrolled in the study only after determining that both tests were positive. *H. pylori* eradication was tested by ^{14}C urea breath test two months after completion of treatment. Patients who were still positive used a second-line eradication regimen. Two months into the second treatment, patients who were positive for *H. pylori* on the ^{14}C urea breath test were excluded from the study.

Treatment and follow-up

All patients used oral amoxicillin 1 g b.i.d., clarithromycin 500 mg b.i.d., and lansoprazole 30 mg b.i.d. for 14 days. Patients were re-tested by 14C urea breath test two months after completion of treatment. Patients who were H. pylori-negative completed the final symptom evaluation and concluded the study. H. pylori-positive patients were given a second-line regimen consisting of oral tetracycline 250 mg q.i.d., metronidazole 500 mg t.i.d., and ranitidine + bismuth subsalicylate 400 mg b.i.d. for 14 days and were then tested again by ^{14}C urea breath test after two months. *H. pylori*-negative patients were evaluated as successful eradication while H. pylori-positive patients were excluded from the study.

Successful eradication was considered as negative 14C urea breath test two months after completion of treatment.

Statistics

The SPSS 9.0 program was used for statistical analysis utilizing two-way variance analysis, independent t test and chi-square test.

RESULTS

A total of 73 patients were enrolled in the study. Five patients refused psychiatric evaluation, 9 patients failed eradication therapy, 3 patients refused second-line eradication treatment, and 2 patients quit before the follow-up. All of these 19 patients were excluded from the study. Fifty-four patients completed the study. Forty-five (83.3 %) were female and 9 (16.7%) male, with a mean age of 43.5 (20-62)±12 years.

The most common complaints at initial presentation to the gastroenterology outpatient clinic were epigastric burning, epigastric pain and bloating. The distribution of patients' baseline symptoms are summarized in Table 1.

Twenty-two of the 54 patients included in the study had at least one psychiatric co-morbid disorder. Seven patients were diagnosed with multiple co-morbid psychiatric disorders (Table 2).

Visual Analog Scale (VAS)

The patient group with anxiety had the highest pre-treatment mean VAS scores. The pre-treatment VAS score was 10 in one patient with dep-

Table 1. Distribution of patients' complaints upon admission to hospital

Complaint	Number of patients n (%)
Epigastric pain	42 (77.8)
Epigastric burning	44 (81.5)
Belching	39 (72.2)
Nausea	24 (44.4)
Vomiting	6 (11.1)
Postprandial fullness	23 (42.6)
Bloating	42 (77.8)
Regurgitation	23 (42.6)

Table 2. Distribution of psychiatric disorders diagnosed in accordance with CIDI

Psychiatric disorder	Number of patients (n)	Psychiatric disorder	Number of patients (n)
Depression	7	Depression and anxiety disorder	1
Anxiety disorder	4	Depression and panic disorder	3
Social phobia	2	Depression and social phobia	1
Panic disorder	2	Panic disorder and social phobia	1
		Depression, social phobia and panic disorder	1

CIDI: The composite International Diagnostic Interview

Table 3. Distribution of VAS scores before and after treatment according to psychiatric disorders

Disorder	Mean VAS score	Number of patients	SD
None	7.37	32	1.62
Depression	7.42	7	1.90
Anxiety	8.25	4	1.50
Panic disorder	8.00	2	.00
Social phobia	6.00	2	1.41
Depression + Anxiety	10.00	1	.
Depression + Panic disorder	6.66	3	1.52
Depression + Social phobia	8.00	1	.
Panic disorder + Social phobia	5.00	1	.
Depression + Social phobia + Panic disorder	10.00	1	.

VAS: Visual analog scale

Table 4. Distribution of co-morbid psychiatric disorders in relation to symptomatic relief with *H.pylori* eradication therapy

		Pre-treatment VAS	Post-treatment VAS	p
Depression	Yes	7.6	4.7	0.087
	No	7.3	3.1	
Anxiety	Yes	8.6	4.6	0.807
	No	7.3	3.1	
Panic disorder	Yes	7.2	3.7	0.498
	No	7.3	3.1	
Social phobia	Yes	7	4.6	0.117
	No	7.3	3.1	

VAS: Visual analog scale

ression and an anxiety disorder and another patient with depression, social phobia and panic disorder. The lowest pre-treatment VAS score (5) was found in a patient with panic disorder and social phobia (Table 3).

Mean VAS scores before and after eradication treatment were 7.4±1.6 and 3.4±2.1, respectively, and the difference was statistically significant ($p<0.001$). The change in mean pre- and post-treatment VAS scores for any group of psychiatric co-morbid disorder was not statistically different than the change in the patient group with functional dyspepsia without psychiatric disorders (Table 4).

Likert Score

The highest pre-treatment Likert score (32) was determined in a patient with depression and anxiety disorder, while the lowest score (14) was determined in a patient with depression and social phobia (Table 5).

Table 5. The results of multivariate analysis of parameters with a potential impact on symptomatic response to *H.pylori* eradication

Disorder	Mean	N	SD
None	19.74	31	4.17
Depression	20.42	7	6.50
Anxiety disorder	21.75	4	8.65
Panic disorder	17.00	2	2.82
Social phobia	16.00	2	7.07
Depression + Anxiety	32.00	1	.
Depression + Panic disorder	22.66	3	8.50
Depression + Social phobia	14.00	1	.
Panic disorder + Social phobia	18.00	1	.
Depression + Social phobia + Panic disorder	23.00	1	.

Table 6. Comparison of response to treatment in patient groups with or without psychiatric co-morbid disorders

		Response to treatment		Total
		Complete	Inadequate	
Psychiatric Disorder	Yes	11	11	22
	No	27	5	32
				P=0.007

The difference between the pre-treatment Likert scores of patients with *H. pylori*-positive functional dyspepsia without any psychiatric disorder (19.71±4.1), and patients with depression, anxiety disorder, panic disorder, and social phobia (21.53, 23.80, 20.42, 17.40, respectively) showed no statistical significance (p>0.05).

Conversely, there was a statistically significant difference between the mean post-treatment Likert scores of patients with functional dyspepsia without any psychiatric disorder (6.41±3.94) and patients with depression (9.46±3.88 vs. 6.46±3.94, p=0.025). The mean post-treatment Likert scores of patients with panic disorder (9.85±3.9) were likewise significantly different (p=0.046). However, in comparison with patients with functional dyspepsia without any psychiatric disorder (6.46±3.94), patients with anxiety disorders (8.6±2.3, p=0.25) and social phobia (8.20±4.43, p=0.375) showed no difference in terms of mean post-treatment Likert scores.

Complete response to treatment was obtained in 27 of the 32 patients without any psychiatric disorder (84%), while only half of the 22 patients with at least one psychiatric disorder achieved complete response (p=0.007) (Table 6).

In comparison to patients with no psychiatric co-morbid disorder, the rate of complete response to treatment was 46.2% (6/13) in patients with depression (p=0.009), 40% (2/5) in those with anxiety disorders (p=0.025), 28% (2/7) amongst patients with panic disorders (p=0.002), and 60% (3/5) in those with social phobia (p=0.196). In summary, end-treatment response rates in patients with depression, anxiety disorder and panic disorder were significantly lower compared to patients with functional dyspepsia without psychiatric co-morbid disorders.

DISCUSSION

Patients included in the study were all *H. pylori*-positive, and diagnosed with functional dyspepsia according to Rome II criteria. The most common baseline complaint was epigastric discomfort, followed by epigastric pain and bloating.

H. pylori and psychiatric disorders are two major factors indicated in the pathogenesis of functional dyspepsia. Post-eradication treatment, symptomatic improvement ranges between 21-58% in patients with *H. pylori*-positive functional dyspepsia (18,19). These rates, although variable, are significantly higher compared to placebo. *H. pylori* is therefore one, but not the only cause of functional dyspepsia. We achieved symptomatic response in 38 (70%) of the total 54 patients included in the study with successful eradication treatment. This

is a high recovery rate compared to others previously reported. We attribute this to the majority (59%) of our patients having no psychiatric co-morbidity, and the level of trust cultivated in our patients through detailed psychiatric and gastroenterological evaluations. A high level of trust on the patient's part is an important component of treatment in functional disorders of the gastrointestinal system. Jones et al. (15) indicated that the basis of functional dyspepsia is more psychological than physiological. Indeed, the rate of anxiety disorder, depression and somatoform disorder is higher in patients with functional dyspepsia compared to the general population (7,8,10-12). In Turkey, a report published in 1998 determined the prevalence of psychiatric disorders in the general population (20). Upon comparison with these population-based data, the rate of psychiatric co-morbid disorders was significantly higher in our cohort of patients with functional dyspepsia (Table 7). One clinical indication of this finding is that response to antisecretory treatment is lower in patients with functional dyspepsia (21). In a study by Tse et al. (22), the symptoms of patients with functional dyspepsia were evaluated on a Likert scale, and co-morbid psychiatric disorders were found to have a negative impact on quality of life.

We used two different scales to determine the severity of our patients' dyspeptic symptoms and symptomatic response to treatment. One was the VAS assessing the severity of pre- and post-treatment patient complaints on a scale of 1 to 10. This scale sought to answer the query, "How much discomfort was I feeling when I first saw the doctor, and how much did my complaints diminish after treatment?" The Likert type scale aimed to answer the questions "How serious are the patient's complaints?" pre-treatment, and "How satisfied is the patient with treatment?" post-treatment. The CIDI (Composite International Diagnostic Interview) was used in the diagnosis of co-morbid psychiatric disorders. Patients were evaluated in terms of depression, anxiety disorder, social phobia, and panic disorder. The most common psychiatric disorder was depression. Seven patients were diagnosed with multiple psychiatric co-morbid disorders.

We found that mean VAS scores were significantly reduced following eradication treatment. This indicates that eradication treatment is effective in terms of symptomatic relief in patients with *H. pylori*-positive functional dyspepsia. The patient group with the highest pre-treatment VAS score consisted of patients with anxiety disorders. The pre-treatment VAS scores of patients with panic disorder and social phobia were lower than in patients with no psychiatric co-morbidity. In terms of response to treatment, none of the psychiatric co-morbid patient groups demonstrated a significant difference in mean VAS scores compared with patients without psychiatric disorders. Thus, the presence of anxiety disorder causes symptoms to be felt with more severity. However, neither anxiety disorder nor other psychiatric co-morbid disorders produce any difference in terms of response to treatment compared with patients with functional dyspepsia without psychiatric disorders.

Pre-treatment mean Likert scores indicated physician-evaluated severity of patient complaints. There was no statistically significant difference in the pre-treatment Likert scores of patients with depression, anxiety disorder, panic disorder, and social phobia in comparison with patients without psychiatric co-morbid disorders. Accordingly, the presence of psychiatric co-morbid disorders or the type of psychiatric co-morbidity has no impact on the pre-treatment symptom severity of patients with *H. pylori*-positive functional dyspepsia.

Patient satisfaction with treatment was evaluated by the post-treatment Likert scores. When compared with patients with no psychiatric co-morbid disorder, post-treatment satisfaction was significantly lower in patients with depression and panic disorder. Social phobia or anxiety disorder seemed to have no impact on the patients' level of satisfaction in comparison with patients without co-morbid psychiatric disorders.

With post-treatment Likert scores of 8 or less indicating complete response, patients with no psychiatric co-morbid disorders were found to achieve significantly higher rates of response to treatment compared to patients with at least one co-morbid psychiatric disorder. Upon comparison of patient

Table 7. Comparison of our study group with the Turkish population in terms of psychiatric disorders (20)

	Depression	Anxiety disorder	Social phobia	Panic disorder
Our study group (%)	15.5	7.1	2.8	2.8
Overall Turkish data (%)	5.6	0.7	1.8	0.4

groups in terms of response to treatment, all patient groups with psychiatric co-morbid disorders, excluding those with social phobia, showed significantly inadequate response rates.

The small number of patients can be construed as a limitation of this study. The study size is defined by the limited number of patients that present to a tertiary clinic with functional dyspepsia who have not received prior *H. pylori* eradication treatment, the negative outlook of patients regarding psychiatric evaluation, and the fact that psychiatric evaluation with high sensitivity is time-consuming.

In conclusion, the establishment of effective therapy for a disorder with high prevalence and low patient satisfaction such as functional dyspepsia will benefit patients, physicians and national economics in terms of health expenditures. The early diagnosis and accurate, timely management of psychiatric co-morbid conditions that influence patient satisfaction with treatment is thus imperative in functional dyspepsia. We believe that our study, despite its limitations, will provide guidance to clinicians regarding the development of more appropriate patient care for those presenting with functional dyspepsia.

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