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ORIGINAL ARTICLE

Prospective Study

Incidence and psychological-behavioral characteristics of refractory functional dyspepsia: A large, multi-center, prospective investigation from China

Shu-Man Jiang, Lin Jia, Xiao-Gai Lei, Ming Xu, Sheng-Bing Wang, Jing Liu, Min Song, Wei-Dong Li

Shu-Man Jiang, Lin Jia, Xiao-Gai Lei, Jing Liu, Min Song, Wei-Dong Li, Department of Gastroenterology, Guangzhou First People's Hospital, Guangzhou Medical University, Guangzhou 510180, Guangdong Province, China
Shu-Man Jiang, Lin Jia, Jing Liu, Department of Gastroenterology, Guangzhou Nansha Central Hospital, Guangzhou 510180, Guangdong Province, China
Ming Xu, Department of Gastroenterology, Guangdong Province Second People's Hospital, Guangzhou 510180, Guangdong Province, China
Sheng-Bing Wang, Department of Gastroenterology, Meizhou Municipal People's Hospital, Guangzhou 510180, Guangdong Province, China
Author contributions: Jiang SM, Jia L and Lei XG designed the study; Lei XG, Xu M, Wang SB, Liu J and Song M performed the study; Jiang SM, Jia L and Li WD analyzed the data; Jiang SM and Jia L wrote the paper; Jiang SM and Jia L contributed to the work equally and should be regarded as co-first authors.
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Correspondence to: Lin Jia, MD, Professor, Department of Gastroenterology, Guangzhou First People's Hospital, Guangzhou Medical University, 195 Dongfeng West Road, Guangzhou 510180, Guangdong Province, China. jialin@medmail.com.cn
Telephone: +86-20-81628809
Fax: +86-20-81628809
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Abstract

AIM: To explore the incidence and psychological and behavioral characteristics of refractory functional dyspepsia (RFD) in China.

METHODS: The subjects of this study were 1341 new outpatients with functional dyspepsia (FD) who were diagnosed according to the Rome Ⅲ criteria at four hospitals in Guangdong Province between June and September 2012, and 100 healthy volunteers. All subjects completed questionnaires and scales administered.

RESULTS: Three-hundred and twenty-seven of the 1341 patients with FD had RFD (24.4%). Patients with RFD had a longer disease duration and a more severe form of the disease than patients with non-refractory FD (NRFD). The prevalence of depression and anxiety symptoms was higher in patients with RFD than in patients with NRFD. The prevalence of unhealthy eating behaviors, lack of physical activity, and sleeping disorders was higher in patients with RFD than in patients with NRFD. Patients with RFD sought medical advice on more occasions and spent more money on treatment than patients with NRFD. Finally, patients with RFD had poorer quality of life than patients with NRFD.

CONCLUSION: RFD is not rare in clinical practice and should get attention by patients and doctors because of its long duration, severe symptoms, and associations with abnormal psychology and poor quality of life.

Key words: Refractory functional dyspepsia; Psychological-behavioral characteristics; Depression; Anxiety; Behavior; Quality of life

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Core tip: Functional dyspepsia is the most common functional gastrointestinal disease. Refractory functional dyspepsia (RFD) even makes patients see a doctor repeatedly and aggravates their medical expenses. However, there is rare research concerning the psychological-behavioral characteristics of RFD patients until now. Thus we performed a large, multicenter investigation of RFD in China, and the findings may illustrate the importance of recognition and diagnosis of RFD, and provide a basis for clinical treatment and the relapse prevention of this condition.

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INTRODUCTION

Functional dyspepsia (FD) is one of the most common functional gastrointestinal diseases[1]. Because of differences between Asian and Western countries in diet, lifestyle, environment, and genetic factors, functional gastrointestinal diseases in Asian countries are different from those in Western countries with regard to symptoms, epidemiology, etiology, and pathogenesis[1,2]. Refractory FD (RFD) refers to FD that has continuous symptoms for at least 6 mo that has been unresponsive to at least two medical treatments, such as acid suppressors, proton pump inhibitors, prokinetics, or *Helicobacter pylori* (*H. pylori*) eradication[3]. The failure to respond to treatments is the main reason that RFD patients make repeated visits to a doctor and escalate their medical expenses. However, the pathogenesis of RFD and the reasons this disease fails to respond to treatment are not fully understood. Moreover, there is little research concerning the psychological and behavioral characteristics of patients with RFD.

In this study, we present data from a large, multicenter investigation of RFD in China that were collected as a part of a registered study (ChiCTR-TRC-12001968). The focus of the present study was to quantify the incidence of RFD and to identify the psychological and behavioral characteristics of patients with RFD to illustrate the importance of recognizing and diagnosing RFD, and to provide a basis for clinical treatment and relapse prevention.

MATERIALS AND METHODS

Ethics statement

All participants gave written informed consent. The study was approved by the ethics committees of Guangzhou Nansha Central Hospital, Guangzhou First People's Hospital, Guangdong Province Second People's Hospital, and Meizhou Municipal People's Hospital.

Study subjects

The study involved 9802 patients who visited the digestive department outpatient service of Guangzhou Nansha Central Hospital, Guangzhou First People's Hospital, Guangdong Province Second People's Hospital, or Meizhou Municipal People's Hospital from June to September 2012. FD and the subtype of FD [epigastric pain syndrome (EPS) or postprandial distress syndrome (PDS)] were diagnosed according to the Rome Ⅲ criteria[4]. Patient exclusion criteria were: (1) an endoscopic examination revealed an ulcer, erosion, tumor, another organic disease, or evidence of esophagitis; (2) a history of ulcers, erosion, tumors, other organic diseases, or esophagitis; (3) a laboratory examination, ultrasound, or X-ray revealed an organic disease associated with the liver, gallbladder, pancreas, or intestine; (4) diabetes, connective tissue disease, mental disease, or other systemic diseases; (5) a history of abdominal operations; (6) pregnancy or lactation; and (7) other functional gastrointestinal disorders such as irritable bowel syndrome and gastroesophageal reflux disease. In addition, the FD patients who had to report continuous symptoms for at least 6 mo but failed to respond to at least two medical treatments (such as acid suppressors, proton pump inhibitors, prokinetics, or *H. pylori* eradication) were defined with RFD[3]. All FD patients who did not meet these criteria were classed as non-refractory FD (NRFD) patients.

One hundred healthy volunteers were included as control subjects. Healthy volunteers did not exhibit the following symptoms for 3 mo prior to the study: postprandial fullness, early satiety, epigastric pain, burning epigastric pain, abdominal pain, diarrhea, constipation, and other gastrointestinal symptoms. Healthy volunteers had normal function of the heart, liver, and kidneys, no recent history of drug use, no history of mental disease and no history of surgery.

Data collection

Two unified training doctors obtained data from patients and healthy volunteers in all hospitals. Data collection took place *via* face-to-face interviews in a quiet environment. Consultation time was 20-30 min per subject.

The 25-item Nepean Dyspepsia Index was utilized to evaluate the severity of patients' symptoms. The symptom checklist included frequency, severity and bothersomeness of 15 upper gastrointestinal symptoms, and a higher total score indicates a more severe digestive symptom[5].

The 17-item Hamilton Depression Rating Scale (HAMD) and the 14-item Hamilton Anxiety Rating

Table 1 General characteristics of the study subjects *n* (%)

Feature	RFD (*n* = 327)	NRFD (*n* = 1014)	Healthy volunteers (*n* = 100)	*P* value[1]	*P* value[2]
Gender				0.300	0.470
Male	127 (38.8)	427 (42.1)	45 (45.0)		
Female	200 (61.2)	587 (57.9)	55 (55.0)		
Age group				0.110	0.110
≤ 20 yr	8 (2.4)	39 (3.8)	2 (2.0)		
21-30 yr	54 (16.5)	215 (21.2)	24 (24.0)		
31-40 yr	84 (25.7)	289 (28.5)	28 (28.0)		
41-50 yr	113 (34.6)	294 (29.0)	27 (27.0)		
51-60 yr	52 (15.9)	130 (12.8)	17 (17.0)		
> 60 yr	16 (4.9)	47 (4.6)	2 (2.0)		
Age, yr	41.91 ± 11.30	39.60 ± 11.81	39.83 ± 12.42	0.001	0.780
Subtype					
EPS	120 (36.7)	457 (45.1)	-	0.010	-
PDS	94 (28.7)	280 (27.6)	-	0.690	-
EPS + PDS	113 (34.6)	277 (27.3)	-	0.010	-
Duration of disease, (yr)	6.01 ± 2.87	3.76 ± 1.83	-	0.002	-
Severity of disease					
Mild	101 (30.9)	459 (45.3)	-	0.001	-
Moderate	148 (45.3)	407 (40.1)	-	0.100	-
Severe	78 (23.9)	148 (14.6)	-	0.003	-

[1]Comparison between RFD and NRFD patients; [2]Comparison between all functional dyspepsia patients (RFD and NRFD combined) and healthy volunteers. Continuous data were compared across groups using one-way ANOVA and Student-Newman-Keuls test for multiple comparisons. Count data were compared across groups using a χ^2 test. RFD: Refractory functional dyspepsia; NRFD: Non-refractory functional dyspepsia; EPS: Epigastric pain syndrome; PDS: Postprandial distress syndrome.

Scale (HAMA) were used to evaluate the degrees of depression and anxiety symptoms. Higher scores indicate more severe depressive or anxious conditions. Depression symptoms were classified as severe (HAMD score ≥ 25), moderate (HAMD score 18-24), mild (HAMD score 7-17) or none (HAMD score ≤ 6)[6,7]. Anxiety symptoms were also classified as severe (HAMA score ≥ 24), moderate (HAMA score 15-23), mild (HAMA score 8-14) or none (HAMA score ≤ 7)[8,9].

The unhealthy eating behaviors were investigated including the aspects of skip meals (less than three meals a day), eating late (1 h later than the normal meal time) and eating extra meal (more than three meals a day). The working behaviors included the aspects of working in the day (the time period from 6 am to 6 pm), working at night (the time period from 6 pm to 6 am) and no work, and study was also considered a work. Physical activity was evaluated using the International Physical Questionnaire (IPAQ), and low/moderate/high levels of physical activity were defined according to the guideline for data analysis of IPAQ[10]. Sleeping was also assessed using the Pittsburgh Sleep Quality Index (PSQI). A high PSQI score indicates poor sleep, and patients with a PSQI score > 5 were considered to have a sleep disorder[11]. Quality of life was evaluated using the Short Form 36 Health Survey Questionnaire (SF-36). High SF-36 scores indicate better quality of life[12]. Patients were investigated about the amount of money spent on former treatments (drugs, examination, fee, traffic, *etc*.) when they were diagnosed with FD or RFD. The money was quantified by Chinese Yuan (CNY).

Statistical analysis

Statistical analyses were performed with SPSS 13.0 for Windows. Continuous data are expressed as mean ± SD, and were compared across groups (RFD, NRFD, healthy volunteers) using one-way ANOVA and Student-Newman-Keuls test for multiple comparisons. Count data were compared across groups using a χ^2 test. All tests were two-tailed and $P < 0.05$ was considered statistically significant. Especially, a χ^2 test for independence was used to determine whether severity of disease, depression and anxiety symptoms was related to RFD, and $\chi^2 > 6.635$ was considered statistically significant.

RESULTS

Study sample

Of 1600 patients diagnosed with FD, 390 fulfilled the criteria for RFD. A total of 1341 patients (n = 327 for RFD and n = 1014 for NRFD) completed the questionnaire battery. These patients comprised 554 males and 787 females and were between 18 and 76 years old (mean age = 40.17 ± 11.72 years). The 100 healthy volunteers comprised 45 males and 55 females and were between 18 and 78 years old (mean age = 39.83 ± 12.42 years). Characteristics of healthy volunteers were similar to those of the patients (Table 1).

Incidence and disease characteristics

Of 9802 outpatients, 1600 (16.3%) were diagnosed with FD and 390 (4.0%) were diagnosed with RFD.

Table 2 Psychological and behavioral characteristics and quality of life of the study subjects *n* (%)

Characteristic	RFD (*n* = 327)	NRFD (*n* = 1014)	Healthy volunteers (*n* = 100)	*P* value
Depression symptoms	207 (63.3)[a, c]	212 (20.9)[c]	10 (10.0)	0.002
Mild	112 (34.3)[a, c]	170 (16.8)	10 (10.0)	0.001
Moderate	61 (18.7)[a, c]	34 (3.4)	0 (0)	0.001
Severe	34 (10.4)[a, c]	8 (0.8)	0 (0)	0.004
HAMD score	11.65 ± 6.51[a, c]	7.15 ± 3.34[c]	1.66 ± 2.50	0.003
Anxiety symptoms	201 (61.5)[a, c]	236 (23.3)[c]	10 (10.0)	0.002
Mild	97 (29.7)[a, c]	162 (16)	10 (10.0)	0.001
Moderate	74 (22.6)[a, c]	60 (5.9)[c]	0 (0)	0.003
Severe	30 (9.2)[a, c]	14 (1.4)	0 (0)	0.001
HAMA score	10.84 ± 5.82)[a, c]	6.83 ± 3.53)[c]	2.26 ± 2.68	0.001
Both depression and anxiety symptoms	186 (56.9)[a, c]	171 (16.9)[c]	6 (6.0)	0.001
Eating behavior				
Skip meals	68 (20.8)[a, c]	131 (12.9)[c]	4 (4.0)	0.010
Eating late	92 (28.1)[a, c]	222 (21.9)[c]	6 (6.0)	0.001
Eating extra meal	30 (9.2)[a, c]	55 (5.4)[c]	3 (3.0)	0.010
Physical activity level				
High	98 (30.0)[c]	332 (32.7)[c]	44 (44.0)	0.030
Moderate	156 (47.7)	536 (52.9)	54 (54.0)	0.240
Low	73 (22.3)[a, c]	146 (14.4)[c]	2 (2.0)	0.001
Working time				
Working in the day	160 (48.9)	529 (52.2)	56 (56.0)	0.400
Working at night	22 (6.7)	101 (10.0)[c]	2 (2.0)	0.010
No work	126 (38.5)[b]	333 (32.8)	25 (25.0)	0.030
Sleeping disorder	204 (62.4)[a, c]	334 (32.9)[c]	13 (13.0)	0.001
PSQI score	8.87 ± 5.00[a, c]	5.70 ± 4.12[c]	2.95 ± 2.78	0.001
SF-36 score	61.17 ± 16.77[a, c]	74.96 ± 13.51[c]	88.18 ± 7.30	0.001
Number of times seeking medical advice	13.41 ± 7.66	4.09 ± 2.20	-	0.002
Cost of treatments	3797.28 ± 1406.41	1523.07 ± 665.35	-	0.001

Continuous data are expressed as mean ± SD, and were compared across groups using one-way ANOVA and Student-Newman-Keuls test for multiple comparisons. Count data were compared across groups using a χ^2 test. [a]$P < 0.05$ *vs* NRFD patients; [c]$P < 0.05$ *vs* healthy volunteers. RFD: Refractory functional dyspepsia; NRFD: Non-refractory functional dyspepsia; HAMA: Hamilton Anxiety Scale; HAMD: Hamilton Depression Scale; PSQI: Pittsburgh Sleep Quality Index; SF-36: MOS 36-item Short Form Health Survey.

RFD accounted for 24.4% (390/1600) of all FD diagnoses. Among the 1341 patients who completed the questionnaire, the incidence of RFD was highest in patients that were 41-50 years old. Females were more than males in patients with RFD (61.2% *vs* 38.8%, $P < 0.05$). Incidence of the EPS subtype was lower in patients with RFD than in patients with NRFD (36.7% *vs* 45.1%, $P < 0.05$), whereas incidence of the EPS + PDS subtype was higher in patients with RFD than in patients with NRFD (34.6% *vs* 27.3%, $P < 0.05$; Table 1). Disease duration was longer for patients with RFD than for patients with NRFD (6.01 ± 2.87 years *vs* 3.76 ± 1.83 years, $P < 0.05$; Table 1). RFD was related to severity of disease ($\chi^2 > 6.635$), most patients with RFD or NRFD had moderate symptoms, but the proportion of patients with severe symptoms was higher in RFD than in NRFD (23.9% *vs* 14.6%, $P < 0.05$; Table 1).

Psychological characteristics

The prevalence of depression and anxiety symptoms was higher in patients with RFD (63.3%, 207/327 and 61.5%, 201/327, respectively) than in patients with NRFD (20.9% and 23.3%, respectively) or healthy volunteers (10.0% and 10.0%, respectively; Table 2). Similarly, more patients presented both depression and anxiety symptoms in the RFD group than those in the NRFD group or healthy volunteers group ($P < 0.05$ for all; Table 2). This trend was apparent for all degrees of severity. The prevalence of mild, moderate, and severe depression and anxiety symptoms was higher in patients with RFD than in patients with NRFD ($P < 0.05$ for all; Table 2). Moreover, RFD was measured related to severity of depression and anxiety symptoms ($\chi^2 > 6.635$ for both). The total HAMA and HAMD scores, which represent the severity of depression and anxiety symptoms, respectively, were also higher in patients with RFD than in patients with NRFD and healthy volunteers ($P < 0.05$ for all; Table 2).

Behavioral characteristics

The prevalence of unhealthy eating behaviors, such as skipping meals, eating late, and eating extra meals, was higher in patients with RFD than in patients with NRFD or healthy volunteers ($P < 0.05$ for all; Table 2). Most patients and healthy volunteers reported a moderate level of physical activity, but the proportion of subjects that reported a low level of exercise was higher among patients with RFD than patients with NRFD or healthy volunteers ($P < 0.05$; Table 2). The proportion of subjects without work was higher

among patients with RFD than patients with NRFD or healthy volunteers, but a significant difference only existed between RFD patients and healthy volunteers (Table 2). The proportion of subjects who worked during the day was similar among the three groups. The proportion of subjects who worked at night was higher in patients with NRFD than in patients with RFD or healthy volunteers, but a significant difference only existed between NRFD patients and healthy volunteers (Table 2). The prevalence of sleeping disorders was higher in patients with RFD (62.4%, 204/327) than in patients with NRFD (32.9%, 334/1014, $P < 0.05$) or healthy volunteers (13.0%, 13/100, $P < 0.05$), and PSQI scores, which represent quality of sleep, were higher in patients with RFD than in patients with NRFD or healthy volunteers ($P < 0.05$ for both; Table 2).

Quality of life

The SF-36 score, which indicates quality of life, was lower in patients with RFD than in patients with NRFD or healthy volunteers ($P < 0.05$ for both; Table 2). Furthermore, the numbers of times that subjects had sought medical advice and the amount of money spent on treatment were higher in patients with RFD than in patients with NRFD ($P < 0.05$ for both; Table 2).

DISCUSSION

Estimates of the worldwide prevalence of dyspepsia in the general population range from 7%-40%[13]. With a decline in the incidence of peptic ulcer disease and gastric cancer, the incidence of FD is set to increase. RFD has a poor curative effect[3,14,15], thus it should be taken seriously by the medical community. In 2000, Hamilton *et al*[3] defined chronic FD as FD that had been present for at least half a year and persisted after at least two conventional drug treatments. At present, there is no unified and precise definition of RFD. In this study, RFD was defined according to both the Rome Ⅲ criteria and the criteria of Hamilton *et al*[3], and accounted for 4.0% of all digestive department outpatients and 24.4% of FD cases, indicating that RFD is not rare in clinical practice. RFD was characterized by a long course and high disease severity.

EPS is the main subtype of FD in Western countries, but PDS is the predominant subtype in Japan[16]. Differences in the prevalence of FD subtypes may be uniquely related to differences in dietary habits, customs, the social and cultural environment, and genetic factors. In this study, we found that the prevalence of the EPS + PDS subtype was significantly higher among patients with RFD than among patients with NRFD. This may provide a clue as to the obstinacy of RFD.

The pathogenesis of functional gastrointestinal disorders is complex, and is related to gastrointestinal motility dysfunction, visceral hypersensitivity[17-19], the change between brain-gut axis and gastrointestinal hormones, eating behaviors[20-24], or psychology[25]. Doi *et al*[26] reported that the prevalence of psychological disorders was significantly higher in patients with FD than in the general population. Similarly, the psychological outcomes of our study indicated that the prevalence of depression and anxiety symptoms was higher in patients with RFD than in patients with NRFD or healthy volunteers, and the severity of symptoms associated with depression and anxiety was higher in patients with RFD than in patients with NRFD or healthy individuals.

Some behavioral characteristics were also revealed in this investigation. The prevalence of unhealthy eating behaviors (such as meal skipping, eating late, and eating an extra meal), low levels of physical activity, no work, and sleeping disorders was higher for patients with RFD than for patients with NRFD or healthy volunteers. Sleeping disorders are common for patients with FD, both in China and around the world. Miwa[23] reported that the proportion of subjects who thought they slept enough was significantly lower among patients with FD-irritable bowel syndrome overlap than among control subjects. We believe that sleep disorders in RFD may be the result of other underlying problems, such as depression, anxiety, or other psychological conditions.

Because of the characteristics described above, RFD patients sought medical advice more often and spent more money on treatment than patients with NRFD or healthy volunteers. All of these negative factors combine to reduce quality of life, which was reflected in our SF-36 results.

In summary, the medical community should pay more attention to RFD diagnosis and to the importance of an unhealthy lifestyle, abnormal psychological characteristics, and sleeping disorders in RFD.

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COMMENTS

Background

The incidence of functional dyspepsia (FD) is set to increase nowadays. Refractory functional dyspepsia (RFD) even makes patients see a doctor repeatedly and aggravate their medical expenses. However, the pathogenesis of RFD and the reasons this disease fails to respond to treatment are not fully understood. There is rare research concerning the psychological-behavioral characteristics of RFD patients until now.

Research frontiers

At present, there is no unified and precise definition of RFD. The research about pathogenesis, psychological and behavioral characteristics of RFD is limited.

Innovations and breakthroughs

This study was to quantify the incidence of RFD and to identify the psy-

chological and behavioral characteristics of patients with RFD by a large, multi-center and prospective investigation. The findings revealed that RFD is not rare in clinical practice and should get attention by patients and doctors because of its long duration, severe symptoms, and associations with abnormal psychology and poor quality of life.

Applications

The findings can illustrate the importance of recognizing and diagnosing RFD, and to provide a basis for clinical treatment and relapse prevention.

Terminology

Epigastric pain syndrome or postprandial distress syndrome is one of the subtypes of FD. It is detailedly defined in the Rome Ⅲ criteria.

Peer-review

This is a good and practical study in which the authors analyzed the incidence and psychological-behavioral characteristics of RFD patients. It is believed that the findings can enhance the recognition and diagnosis for RFD, and provide a basis for the further research about RFD.

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