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TOPIC HIGHLIGHT

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Functional dyspepsia and irritable bowel syndrome, are they different entities and does it matter?

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Abstract

A high prevalence of overlap between functional dyspepsia and irritable bowel syndrome has been consistently and universally reported. Recent studies demonstrating shared common pathophysiological disturbances including delayed gastric emptying and visceral hypersensitivity involving more than one region, suggest that these patients have a generalised rather than regional, disorder of the gut. Furthermore, a study of the natural history of dyspepsia suggests that with time, a substantial proportion will evolve into IBS. The recognition of IBS in dyspeptic patients has potentially profound therapeutic importance. It could help to reduce the risk of unnecessary cholecystectomy in IBS patients. The ability to appreciate the extent of involvement could allow us to address the disturbances more comprehensively, and thereby achieve greater patient satisfaction with their treatment.

Key words: Functional dyspepsia; Irritable bowel syndrome; Common pathophysiology; Asian; Epidemiology

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INTRODUCTION

Many patients with functional dyspepsia (FD) will also fulfil the criteria for irritable bowel syndrome (IBS). Functional dyspepsia (FD) may coexist with irritable bowel syndrome (IBS) for several reasons. The association may be a chance occurrence simply because both FD and IBS are so common. IBS patients with upper abdominal pain may be mistakenly labelled as FD. Both conditions could share common pathophysiological disturbances.

PREVALENCE OF FD-IBS OVERLAP

In population-based studies, the estimated prevalence of IBS among dyspeptic subjects, ranges between 13% and 29%, while the prevalence of FD among IBS subjects ranges between 29% and 87%[1-3]. These figures are higher than the corresponding figures in the general population, where the prevalence of IBS and FD are estimated to be about 10% and 20% respectively. This would suggest that the overlap is not simply the chance occurrence of two extremely common human conditions. In patient-based series, as opposed to community series, the prevalence of overlap appears to be even higher, with between 26% and 46% of FD patients having concomitant IBS and as many as 87% of IBS patients having concomitant FD[4-8]. This observation would appear to suggest that the coexistence of these two sets of symptoms increases the likelihood of a subject seeking medical attention. There is some support for this from a study by van Bommel *et al* who found in a survey of primary care patients consulting for dyspeptic complaints, that those who had concomitant IBS were most likely to be referred for specialist assessment[9].

In Asia the figures are similar. In a population-based study from Mumbai, India, the prevalence of dyspepsia was 30%, while among subjects with IBS, the prevalence of dyspepsia was 58%[10]. Similarly, the prevalence of IBS among subjects with dyspepsia at 14% was greater than in the general population where it was 7.5%. In a community study from Xi'an in northwest China, Wang *et al*[11]found that significantly more subjects with GERD symptoms also experienced constipation (22%), and diarrhoea (14%) than subjects without GERD symptoms (10%, 5% respectively). In the Guangdong province of south China, Chen *et al* reported that 22% of 473 FD patients attending gastroenterologists had concomitant IBS, whereas the prevalence of IBS in this population was estimated to be 7%[12]. In the Zhejiang province of China, the prevalence of FD among 662 consecutive IBS patients consulting gastroenterologists, was 64%[13].

IBS MISDIAGNOSED AS FD

It is conceivable that IBS patients who present with upper abdominal pain may be mislabelled as FD. Colonic distension studies have clearly demonstrated that in IBS patients, pain from the colon can be referred to the upper abdomen. In a classical experiment, Swarbrick *et al* provoked abdominal pain in 48 IBS patients by using an attached balloon to distend the colon at various regions during colonoscopy[14]. Distension of the mid transverse colon induced pain in the epigastrium in 10 patients.

There are several reasons why doctors may mislabel IBS patients as having dyspepsia and overlook the association with bowel disturbances. Past diagnostic criteria for IBS have tended to focus on the bowel disturbances and lower abdominal pain. Even the Rome II criteria did not consider the association of pain with a meal as a possible symptom of IBS. And yet, a study by Ragnarsson *et al* suggested that about 50% of IBS patients would experience postprandial pain[15]. Foods that are commonly implicated in dyspepsia include spicy foods such as chilli, fatty foods and coffee. In a study of chronic upper abdominal pain, Kang *et al* found that as many IBS patients as FD patients reported precipitation of pain by fatty foods (28%, 19%), chilli (45%, 47%) and coffee (41%, 36%)[16]. A study by Simren *et al* has demonstrated that lipid infusion into the duodenum increased the area of referred pain in IBS patients such that more patients were experiencing pain in the upper abdomen during distension of the sigmoid colon[17].

One important reason for differentiating IBS from dyspeptic symptoms, is to avoid the risks of unnecessary surgery. Several recent studies have highlighted the risks of unnecessary surgery in IBS[18-20]. Based on statistics from studies in the USA population an estimated 8% of IBS patients will undergo unnecessary cholecystectomy in a lifetime[20]. It is possible that in some of these IBS patients undergoing cholecystectomy, their IBS symptoms could have been mislabelled as dyspeptic symptoms. In a study of 22 patients with chronic right upper quadrant pain, their pain was reproduced by distension of the jejunum in 15, ileum in 12 and right colon in 9, and 16 had symptoms consistent with IBS[21]. And yet, prior to their referral these patients had never received a diagnosis of IBS. On the contrary, they had been subjected to an average of 3 pancreatobiliary investigations each, 10 of them had been subjected to cholecystectomy without obvious improvement, even in the 5 who proved to have gallstones. The risk of cholecystectomy could be particularly greater among subjects with FD-IBS. In a community survey Talley *et al* found a cholecystectomy rate of 19% in FD-IBS subjects compared with only 6%-8% for subjects with either FD alone or IBS alone, no different from subjects with neither IBS nor FD[1].

The mislabelling of IBS as dyspepsia is likely to be a greater problem in Asia than in the west. IBS patients in Asia appear to present more commonly with upper abdominal pain[22]. In numerous studies from India, more than half of their patients complained of upper abdominal pain, whereas in western series only about a quarter do so. In a recent study from Taiwan, Lu *et al*[23] looked at 481 patients with FD by Rome criteria, and found more than half had IBS criteria. When they looked at these patients with FD criteria and IBS criteria, they found that in about a third of these patients, their upper abdominal symptoms could be attributed solely to IBS alone. In a study from the same centre in Taiwan, IBS subjects were observed to have twice the rate of cholecystectomy of the non-IBS subjects[24].

In the east, another possible reason for misdiagnosing IBS as dyspepsia could be the milder degree of defecatory and stool disturbances. In a community study from Singapore, more than half of IBS subjects reported pain in the upper abdomen[25]. Despite the fact that 50% fulfilled criteria for chronic constipation and 25% for chronic diarrhoea, when these people were asked to describe their bowel pattern, 77% thought that they had a normal bowel habit.

SHARED COMMON PATHOPHYSIOLGICAL DISTURBANCES

Pathophysiological processes implicated in FD such as altered gastric emptying and visceral hypersensitivity, have also been demonstrated in IBS patients. Post-infectious IBS is a well recognised entity. A recent study suggests that FD could also arise post-infection.

Delayed gastric emptying

Although early studies failed to demonstrate delayed gastric empyting among IBS patients, recent studies employing greater number of patients suggests that it exists in about 30% of IBS patients, particularly in those with constipation-predominant IBS[26-32]. Van Wijk *et al*[29] studied 16 patients with constipation predominant IBS and found slower gastric emptying of solids compared with healthy controls. Evans *et al*[30] studied 44 IBS patients and observed delayed gastric emptying in 9 of 22 (41%) C-IBS and 8 of 22 (36%) D-IBS patients. Caballero-Plasencia *et al*[31] studied 50 IBS (30 C-IBS, 20 D-IBS) patients and found evidence of delayed gastric emptying of both solids and liquids compared with healthy controls. IBS patients with constipation had slower gastric emptying of solids compared with diarrhoea-predominant IBS.

Recently Stanghellini *et al* studied gastric emptying in a large cohort of IBS patients[32]. In 146 IBS patients, majority IBS with constipation, overlapping FD was present in 96 patients (66%). Gastric emptying was delayed in patients with concomitant FD but not in those with IBS alone. In particular, postprandial fullness and nausea were independently associated with delayed gastric emptying. In another large study involving 309 FD patients, Corsetti *et al* using the gastric emptying breath test, found evidence of delayed gastric emptying to solid meal in 23% of patients with FD-IBS and 19% of patients FD alone[8].

Visceral hypersensitivity

In the study by Corsetti *et al*[8] using the gastric barostat, impaired accommodation to a meal was found to be as prevalent in FD-IBS patients (31%) as in FD patients (35%). However, significantly more FD-IBS patients were found to have hypersensitivity to gastric distension than patients

with FD alone (44% *vs* 28%). On the other hand, testing of visceral sensitivity in other regions of the GI tract has not shown any significant differences between FD and IBS subjects. Holtmann *et al* tested sensitivity to distension in the third part of the duodenum and demonstrated hypersensitivity in patients with FD alone, IBS alone and FD-IBS, with no significant differences observed between the groups[33]. Trimble *et al*[34]demonstrated hypersensitivity to distension of the rectum and the oesophagus in both IBS and FD patients compared to healthy controls. However, patients had normal pain thresholds to electrocutaneous stimulus applied to the finger.

Post-infection sensitization

The development of IBS following an episode of acute gastroenteritis has been documented in prospective studies[35-36]. Retrospective studies had previously suggested that FD could also develop post-infection, and that this form of FD was associated with delayed gastric emptying and impaired accommodation[37]. While post-infectious IBS has been largely associated with bacterial infections such as salmonella and campylobacter, post-infectious dyspepsia was presumed to be of viral origin. Recently however, a large prospective study of a well documented single source out-break of salmonella gastroenteritis demonstrated the development not only of IBS, but also for the first time, of dyspepsia[38]. The three most common dyspeptic symptoms were pain, bloating and fullness. Prolonged abdominal pain and vomiting during the acute episode were found to be positive predictors. In patients who developed IBS, there was a 62% overlap with FD at 12 mo post-infection. In patients who developed FD, there was a 46% overlap with IBS.

SYMPTOMATOLOGY OF FD-IBS

The type of symptoms that appear to predominate among FD-IBS subjects, as well as the substantial flux between FD and IBS populations observed in longitudinal studies, lends further support to the hypothesis for a shared common pathophysiology between FD and IBS.

In a Swedish community-based study Agreus *et al* found that the greatest overlap was between IBS and dysmotility-like dyspepsia[3]. In Italy Stanghellini *et al* studied a series of 483 patients with FD, and found that patients with predominantly non-painful symptoms such as post-prandial fullness, nausea and vomiting, were more likely than patients with predominantly epigastric pain to be associated with IBS[6]. Similarly in Singapore, Gwee *et al*[39]studied a consecutive series of 224 patients with FD, and found that 33% had concomitant IBS, with dysmotility type symptoms predominating in the FD-IBS group.

Patients with constipation predominant IBS (IBS-C) appear to be more prone to FD than diarrhoea predominant IBS (IBS-D), and their dyspeptic symptoms appear to be of the dysmotility type. Schmulson *et al*[40] found that IBS-C patients had more upper GI symptoms, in particular early satiety and postprandial fullness, than IBS-D. Similarly, Talley *et al*[7] reported that more patients with IBS-C had upper abdominal pain, and in particular, had significantly more bloating and early satiety than IBS-D. In China, there was a trend for a greater prevalence of FD among IBS-C patients (70%) than IBS-D patients (62%)[13]. A cologastric brake has been proposed by Tjeerdsma *et al* as one mechanism through which constipation could give rise to upper abdominal symptoms[41]. Delayed gastric emptying was recorded in a study of healthy volunteers who had suppressed defecation for 3 d.

The available literature suggests that FD-IBS patients could have more severe symptoms, and it is possible that IBS could be a predictor of consultation seeking behaviour. Talley *et al* reported that community subjects with FD-IBS subjects had made more physician visits for abdominal pain and for disturbed defecation than subjects who had either FD or IBS alone[1]. Furthermore, while the rates of appendicectomy and cholecystectomy among subjects with FD alone or IBS alone were no different from subjects with neither FD nor IBS, the rates were two to three times greater for subjects with FD-IBS. In a study of patients consulting their general practitioners for dyspepsia, it was also found that those who had IBS along with their dyspeptic complaints were most at risk of being referred for specialist assessment[9]. Corsetti *et al*[8] reported that FD-IBS was associated with higher symptom severity scores.

Evolution of Symptoms

In a one year study of symptom turnover by Agreus *et al* 87% of subjects with IBS also fulfilled Rome I criteria for dyspepsia[13]. When these IBS subjects were surveyed one year later, 50% still fulfilled IBS criteria. However, 22% appeared to lose their IBS, but changed their symptom profile to one of dyspepsia. Among subjects who were categorised as dyspepsia, 43% retained this diagnosis, while 16% converted to IBS. By comparison, among subjects who were symptomless at the beginning of the survey, 80% remained asymptomatic, while only 1% developed IBS and 3% developed dyspepsia. When this study was extended to 7 years Agreus *et al*[42] observed that dyspepsia appeared to decrease with advancing age, the prevalence in their cohort declined from an initial 11.7% to 8.1%, whereas IBS increased in prevalence from 8.9% to 13.6%. Of all subjects with dyspepsia on the first survey, only 30% could still be classified as dyspepsia after 7 years, 17% became asymptomatic, while 18% evolved to IBS. With IBS, 55% remained as IBS, 13% became asymptomatic, and only 8% evolved to dyspepsia. Whereas substantial symptom fluctuation and symptom profile flux was observed between IBS and dyspepsia, the prevalence of GERD remained relatively stable, and only a minority (<10%) of GERD evolved to dyspepsia or IBS, or vice-versa. Thus, while patients with GERD appear to form a distinct population from FD or IBS, separation between the latter two blurred with time.

In conclusion, in view of the high degree of symptom overlap it has been suggested that the separation of functional GI disorders into FD and IBS may be inappropriate[3]. Given the shared pathophysiology, some have suggested that patients with FD-IBS have an irritable gut[3,34]. With the substantial flux between FD and IBS, and the observation that a greater proportion of dyspeptic patients

evolved into IBS than the reverse, it is tantalizing to speculate that FD could be a precursor of IBS, and eventually all FD could evolve into IBS. At the end of the day, the key consideration is whether the division of patients into FD and IBS has led to improved treatment outcomes. The experience with sub-classification of FD suggests that this is not the case. Perhaps it is now time to lump again rather than split, and also in our research to return to the old approach of examining combination treatments. After all, combination treatment is the reality of clinical practice.

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