Functional Gastrointestinal Disorders: Recognition of Clinical Features and Progress of Understanding of Pathological Patterns

Short title: Clinical Features and Pathogenesis of FGIDs

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ABSTRACT

Functional gastrointestinal disorders (FGIDs) is almost the most common diseases in the outpatient department of gastroenterology. However, patients with different FGIDs often have different symptoms and severity. Gastroenterologists not only need to distinguish it from other diseases, but also to refine the classification of functional gastrointestinal diseases in order to obtain the greatest therapeutic benefit for the FGIDs patients. The pathophysiology of functional gastrointestinal disorders is sophisticated, which leads to complex clinical manifestations. The latest theoretical hypotheses and research focus on altered brain-gut axis, intestinal microecology, GI mucosal immunity, and GI neuroendocrine, it will help us have a deeper understanding of the pathogenesis and pathophysiology of FDIDs.

Keywords： Functional gastrointestinal diseases, clinical features, subgroups, pathogenesis, brain-gut axis, gut microbe.

INTRODUCTION

Functional gastrointestinal diseases (FGIDs) are very common in digestive clinics. By definition, no structural abnormalities explain FGIDs, but due to its persistent, protracted, overlapping and refractory characteristic, it affects patients' study, work, life, mental health, quality of life and brings major economic effects on health care systems. In a epidemiologic investigation in 33 countries on 6 continents, among the 73,076 adult respondents, diagnostic criteria were met for at least 1 FGID by 40.3% persons.[1] FGIDs can account for 50% to 70% of outpatient visits in gastroenterology clinics. Exampled as functional dyspepsia (FD), among Chinese 15-75 years old adults, the prevalence of FD is 23.5%, more than 1 person in 5 has FD on average. [2] In the past, people have

recognized that FGIDs are caused by non-organic changes in dysfunction. But with the deepening of research, this boundary has gradually become blurred. FGIDs may be organic changes that occur at a more microscopic and complex level.

THE CONCEPTION AND CLINICAL FEATURES OF FGIDS

Functional Gastrointestinal Disorders (FGIDs), better termed as Disorders of Gut-Brain Interaction, though to be prevalent in human society for centuries, have just been studied, categorized and treated scientifically based on well-designed basic medicine or clinical investigations over the past several decades. Our perception of its origins and clinical features has developed from a dualistic and reductive perspective to a more overall biopsychosocial model by Engel[3] and adapted by Drossman[4,5], scientific bases for symptom generation changed from purely being disorders of motility to the more comprehensive disturbances of neurogastroenterology and brain-gut interactions.

Definition

The current diagnosis of functional gastrointestinal diseases is based on the Rome IV criteria established by the Rome Foundation in 2016. [6]It refined the conception of the functional gastrointestinal diseases and identified it with organic gastrointestinal disorders and motility disorder Functional gastrointestinal diseases are recognized by morphologic and physiological abnormalities that often occur in combination including motility disturbance, visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota, and altered central

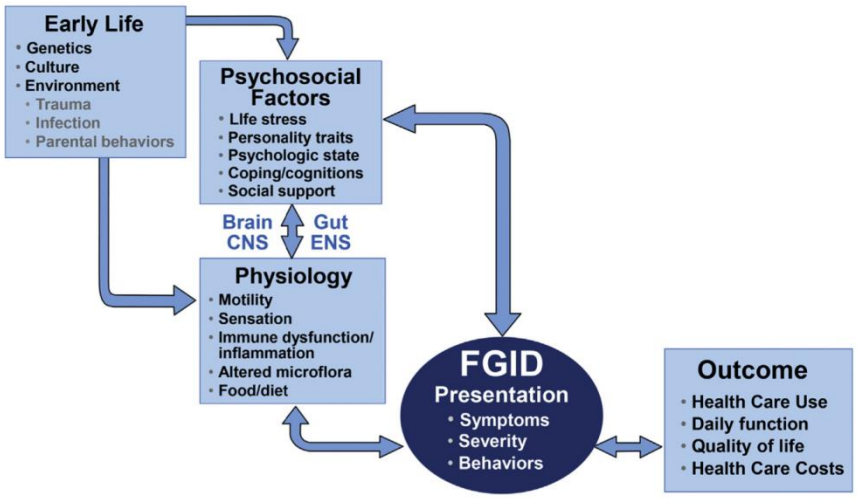

Figure 1. Biopsychosocial conception model

nervous system processing, whereas usually lack of organic pathological changes(Figure1). The understanding and definition of FGIDs varied based on societal perspectives of illness and disease over time, as the development of the biomedical perspective to the overall biopsychosocial model, Rome IV has refined the well shared and agreed definition is as follows: functional GI disorders are disorders of gut–brain interaction. Combined with any of follows: motility disturbance, visceral hypersensitivity, altered mucosal and immune function, altered gut micro- biota, and altered central nervous system (CNS) processing, it can show series of related symptoms and signs.

Subgroups

Rome IV classification of FGIDs is based primarily on symptoms rather than physiological conditions. It favored the clinical utility, because clinically may many patients describe unbearable gastrointestinal symptoms, whereas endoscopy does not report corresponding lesions. The Rome IV criteria divides FGIDs into 3 major groups according to symptom areas and characteristics (Table 1):

1.Functional esophageal diseases, including functional heartburn, functional chest pain of esophageal origin, functional dysphagia, hysteria.

2.Functional gastroduodenal diseases, including functional dyspepsia, belching, nausea and vomiting, ruminant syndrome).

3. Functional bowel diseases, including irritable bowel syndrome, functional abdominal distension, functional constipation, functional diarrhea, non-specific functions Enteropathy)

This classification is generally based on the anatomic regions, premised that the GI symptoms emerge relate to the corresponding organ functional disorders. FGIDs usually begin with classic GI symptoms such as postprandial fullness, belching, decrease of appetite, nausea and vomiting, epigastric pain, and changes in bowel habits or fecal property, it helps physicians to identify the subgroup of FGIDs.

However, symptom localization is not enough, especially painful FGIDs (eg, irritable bowel syndrome, functional dyspepsia, and centrally mediated abdominal pain syndrome) are not as easy to localize and are interfered more by overarching effects resulting from central nervous system–enteric nervous system dysregulation. It is easily proved that no few FGIDs patients often having extra-GI symptoms, such as dyspnea, palpitation, chronic headaches, and depression. Mental disorders are also common, especially those with severe or stubborn symptoms, with an incidence of 42% to 61%.[7] If without timely diagnosis and treatment in time, recurrent episodes may affect patients’ life quality, aggravating the patient's tension and anxiety, thereby further aggravating the physical symptoms.

Table 1. Anatomical cassifications of functional gastrointestinal disorders

Esophageal Disorders	Gastroduodenal Disorders	Bowel Disorders
1. Functional chest pain	1. Functional dyspepsia	1. Irritable bowel syndrome (IBS)
2. Functional heartburn	1a. Postprandial distress syndrome (PDS)	1a. IBS with predominant constipation (IBS-C)
3. Reflux hypersensitivity	1b. Epigastric pain syndrome (EPS)	1b.IBS with predominant diarrhea (IBS-D)
4.Functional dysphagia	Belching disorders	1c. IBS with mixed bowel habits (IBS-M)
5. Globus	2a. Excessive supragastric belching	1d. IBS unclassified (IBS-U)
	2b. Excessive gastric belching	2. Functional constipation
	Nausea and vomiting disorders	3. Functional diarrhea
	3a. Chronic nausea vomiting syndrome (CNVS)	4. Functional abdominal bloating/distension
	3b. Cyclic vomiting syndrome (CVS)	5. Unspecified functional bowel disorder
	3c. Cannabinoid hyperemesis syndrome (CHS)	6. Opioid-induced constipation
	4.Rumination syndrome	

THE PATHOGENESIS OF FGIDS

In recent years, the rapid progress of basic medicine and clinical researches on altered brain-gut axis, intestinal microecology, GI mucosal immunity, and GI neuroendocrine has also contributed to clinicians' knowledge of FGIDs mechanism. Hence, following the advanced hypothesises and studies can help us understand the pathophysiology of FGIDs.

The Altered Brain-Gut Axis in FGIDs

Within the underlying causes and pathogenesis of FGIDs, CNS processing of pain and other gut signals are required for the subjective patient symptoms. This interaction acts through the brain-gut axis. The occurrence of FGIDs caused by brain-gut axis dysfunction has been widely accepted. The brain-gut axis is a complex reflex pathway mediated by neuroendocrine and immune factors that

regulates the cerebral cortex and digestive system. Many studies have shown that brain-gut interaction affects various brain functions, including sensory functions and cognitive functions. [8] These studies emphasize the role of CNS in transmitting visceral signals, and the brain is involved in the process of perceptual function and emotional response[9]. Abnormalities in CNS and interaction between brain and intestine may be one of the factors in the pathogenesis of FGIDs. It is supported by the evidence that there are several areas of abnormal brain activity associated with visceral hyper sensitivity, as well as anxiety and depression, in patients with FGIDs. [10,11] Research on the brain-gut axis of FGIDs is conducive to the development of targeted therapies. For example, irritable bowel syndrome(IBS) treatment not only to control symptoms, but also to carry out early prevention.

Nonetheless, cause and effect cannot be entirely refined from these studies. Further studies of pathophysiology to investigate this process are still needed.

Emerging studies indicate the different gut-brain interaction pathways in patients with FGIDs. Some epidemiological studies found that in 50% of FGIDs cases, courses begin with psychological distress, followed later by GI symptoms, while in another 50% of cases gut dysfunction occurs first, and psychological distress follows later.[12-13] This observation indicates the hypothesis that a subset of patients have a disease process that begins in, and is primarily driven by abnormal regulations between brain and gut, which later induces systemic manifestations, including GI symptoms as an integral part of the FGIDs course. After successful eradication of infection,[14]and following gastroenteritis relative IBS, or functional dyspepsia, could occur and persist,[15,16] although gastroenteritis can be identified as a potential precipitating factor in only a few cases in occurrence,[17,18] it indirectly verifies the important role of brain-gut dysregulation persisting the FGIDs pathological process.

Altered Gut Microbe in FGIDs

There are trillions of intestinal microbes living in the human intestine, which form a huge micro-ecological system. They are involved in host nutrient metabolism, immune development and maturation, intestinal endocrine, nerve signal transduction, resistance to pathogens, cell proliferation and angiogenesis. [19] In view of the multiple functions of the intestinal flora, changes in its composition and metabolic functions are bound to have an important impact on human health. Due to the important role of intestinal flora on brain-gut interaction, it is closely related to the pathophysiological mechanism of FGIDs. The research progress of intestinal microecology is expected to bring new cognition to the pathogenesis of FGIDs.

Many studies showed that IBS patients have different constitutions and abundance of gut microbiota from that of healthy controls. The change of IBS intestinal microflora is usually

manifested as the decrease of Bacteroides and the increase of Firmicutes, that is, the ratio of Firmicutes to Bacteroides is increased. A clinical data suggested that the abundance of bifidobacterium decreases in IBS, such changes as the diversity and stability of the flora of IBS to varying degrees. [20] The latest systematic evaluation study on the changes of IBS intestinal flora pointed out that potentially harmful bacteria associated with IBS include the Enterobacteriaceae bacteria belong to Proteus phylum and the increased abundance of Lactobacillus and Bacteroides bacteria of Bacteroides phylum. The Enterobacteriaceae contains some pathological bacteria including Escherichia coli, Shigella, Campylobacter jejuni and Salmonella. The rise of these pathological bacteria indicated the potential infection that existed before the onset of IBS. In turn, inflammation and abnormal motility can also lead to a decrease in anaerobic bacteria and an increase in facultative anaerobes (such as Enterobacteriaceae). The abundance of intestinal bacteria, including Bifidobacterium and Faebacterium, which are considered to have a protective effect, decreased to varying degrees in IBS.[21] Though the intestinal flora altered in IBS patients has compared with healthy people, the changes in the flora of different subtypes of IBS have different manifestations. Compared with IBS with constipation（IBS-C）, IBS with diarrhea(IBS-D) has a higher abundance of lactobacilli.[22]

Interestingly, not all patients with IBS have a significant imbalance of the intestinal flora, and the IBS patients with severe depression is rather similar to that of healthy people, which seems to contradict our knowledge.[23] Small intestinal bacterial overgrowth (SIBO) is also considered to be related to the symptoms of FGIDs, but the underlying mechanism is still not clear. SIBO may only be the result of dietary preference and has nothing to do with the symptoms of FGIDs, and only a small part of FGIDs patients have intestinal flora imbalance.[24]

Helicobacter pylori（HP） infection is generally thought to be related to the occurrence of functional dyspepsia (FD). A systematic evaluation review of randomized controlled studies showed that HP eradication therapy is the most effective intervene to relief FD symptoms.[25] Indigestion is significantly common in HP infected population, and the symptoms may still persist after the eradication. [26] Although it has not been proven that HP infection is a truly cause of FD, it has gradually come into being a consensus on the correlation between HP infection and FD. Other acute gastrointestinal infections such as Salmonella gastroenteritis are also related to the occurrence of FD. After acute infectious diarrhea caused by bacteria, viruses, and parasitic pathogens, a few patients continue to develop IBS, mainly IBS-D, which is referred to as post-infectious IBS (PI-IBS). While numerous studies have revealed the altered pattern of flora of patients with FGIDs, the

of the role of changes in gut microbiota in the production of FGIDs, that is the underlying mechanism of FGIDs pathogenesis is still not thoroughly.

Underlying Mechanism of FGIDs

Animal model researches verified that intestinal flora dysregulation may increase intestinal permeability and inflammation, visceral hypersensitivity and affect intestinal motility, what's more other pathway, leading to FGIDs.

low-grade mucosal inflammation and immune activation is responsible for the impaired epithelial barrier. A systematic review of 16 studies emphasized the role of mast cells and lymphocytes as the main cellular components of the IBS inflammatory response.[27] Mast cells near the intestinal epithelium can activate the basolateral PAR-2 receptors, leading to the redistribution of the tight junctions and increasing the permeability to macromolecules. Other released mediators such as histamine, chymosin and prostaglandin D2, also regulate the permeability of the intestinal mucosal barrier.[28] The increased permeability of the epithelium leads to the bacterial infiltration and promotes the synthesis and release of pro-inflammatory factors, aggravating the inflammatory response.

The intestinal flora have an impact on a variety of factors related to signaling pathway of pain such as the vagus nerve, the production of cytokines, the secretion of corticosterone, the release of short-chain fatty acids and microbial metabolites. Germ-free mice studies proved that certain symbiotic bacteria are necessary for pain sensitivity. [29-30]Antibiotics regulate the innate mucosal immune of mice and reduce the visceral pain of model mice. However, exposure to antibiotics in early adult rats can also increase visceral sensitivity, which indicates the key time window within which the microbiota could regulate the pain sensitivity.[31] This intersection with visceral hypersensitivity provides a promising target for the treatment of FGIDs-related visceral pain.

The intestinal microbiota and its metabolites can regulate gastrointestinal motility through the brain-gut axis, exampled for targeting intestinal neurons, glial or intestinal myometrial macrophages. GF mice gastric emptying time delays compared to SPF mice. Compared with wild-type mice, sterile mice lacking intestinal flora have increased gastric emptying time and intestinal transit time. Instead, the intestinal transit time restore after accepting the transplantation of normalize the intestinal flora.[32] The fermentative products of bacterial are understood to adjust intestinal motility. The short-chain fatty acids (SCFAs) induce the expression of tryptophan hydroxylase 1 to raise serotonin in the intestine, which modulate the gut motility.[33] The experiment, that transplants IBS intestinal flora mice, proved that imbalance of flora can up-regulate the expression of intestinal serotonin transporter, thereby increasing the uptake and decomposition of intestinal serotonin and inhibiting intestinal movement.[34] In addition, the abundance of specific intestinal microbes directly relates to intestinal motility. For example,

Actinomycetes, Bacteroides, Lactococcus and Rossella increase in intestinal transit time, while Faecalis are inclined to the slowdown the gastric emptying.[35]

CONCLUSION

We have made striking progress over the past decade in investigating the pattern and mechanism of FGIDs, which devoted to striving for the more clinical benefits. The complex symptom subtypes drive us to explore the different potential pathological pattern of FGIDs. In this review, we have tried to provide a summary of our current understanding and outlined steps that can help understand and partly explain the occurrence of FGIDs of a part population, concluding the pathways such as motility disturbance, visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota. We need to more robust designs of human studies, which includes extensive metadata collection and processing , standard processing and analyzing microbiome samples and rigorous statistical testing, and processing to improve data and metadata sharing practices. It can provide a more robust pipeline to more meaningful stratification of patients for therapeutic trials of multi-targets therapeutics.

Conflict of Interest

None declared.

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