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Overlap of Functional Gastrointestinal Disorders: Common Mechanisms of Pathogenesis as a Key to Rational Therapy

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Aim: to review the common risk factors and links in the pathogenesis of functional gastrointestinal disorders (FGID) to optimize therapy of patients with a combination of multiple FGID.
Key points. FGID occurs in more than 40 % of people globally, mainly affecting the working-age population in young and middle-aged subjects. At the same time, more than 30 % of patients have a combination of 2 or more functional gastrointestinal (GI) disorders, i.e. overlap syndrome. Common links in the pathogenesis of FGID include disorders of gut-brain interaction, visceral hypersensitivity, changes in intestinal microbiota, overproduction of proinflammatory cytokines, impaired epithelial permeability and motor activity of the gastrointestinal tract. The combination of FGID in various gastrointestinal segments is associated with more pronounced clinical symptoms (mutual burden syndrome). Common risk factors and pathogenetic links of the functional disorders enables reducing the number of prescribed medications when several FGIDs overlap in one patient, which also increases adherence to therapy. Treatment of FGID includes adjustment of risk factors and drug therapy. As a pathogenetically justified pharmacotherapy of overlap syndrome, Kolofort, highly diluted antibodies to TNF-α, histamine and brain-specific protein S-100, is of interest.
Conclusion. Kolofort has demonstrated high efficacy and safety including among patients with overlap FGID enabling to consider it as the treatment of choice in these patients.
Keywords: functional dyspepsia, IBS, abdominal pain, overlap syndrome
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Синдром перекреста функциональных гастроинтестинальных расстройств: общие механизмы патогенеза как ключ к рациональной терапии

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Цель исследования: Рассмотрение общих факторов риска и звеньев патогенеза функциональных гастроинтестинальных расстройств (ФГИР) для оптимизации терапии пациента с сочетанием нескольких ФГИР.
Основные положения. ФГИР встречаются более чем у 40 % людей во всем мире, главным образом среди трудоспособного населения – у лиц молодого и среднего возраста. При этом более 30 % пациентов имеют сочетания двух и более функциональных расстройств желудочно-кишечного тракта (ЖКТ) — перекрестный синдром. Среди общих звеньев патогенеза ФГИР выделяют расстройство взаимодействия «головной мозг — кишечник», висцеральную гиперчувствительность, изменение кишечной микробиоты, гиперпродукцию провоспалительных цитокинов, нарушение эпителиальной проницаемости и моторной активности органов ЖКТ. Сочетание у одного пациента ФГИР различных областей ЖКТ связано с более выраженными клиническими симптомами (феномен взаимного отягощения). Наличие общих факторов риска и звеньев патогенеза функциональных расстройств позволяет сократить количество назначаемых лекарств при сочетании у одного пациента нескольких ФГИР, что также увеличивает приверженность терапии. Лечение ФГИР включает коррекцию факторов риска и медикаментозную терапию. В качестве патогенетически обоснованной фармакотерапии перекрестного синдрома интерес представляет препарат Колофорт — технологически очищенные антитела к ФНО-α, гистамину и мозгоспецифическому белку S-100.

Заключение. Колофорт продемонстрировал высокую эффективность и безопасность, в том числе среди больных с синдромом перекреста ФГИР, что позволяет рассматривать его как препарат выбора в данной группе пациентов.
Ключевые слова: функциональная диспепсия, СРК, билиарная боль, перекрестный синдром
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According to Rome IV criteria, functional gastrointestinal disorders (FGID) represent disorders of the interaction between gastrointestinal tract and central nervous system (CNS) in which the existing symptoms cannot be explained by structural or metabolic disorders. FGID occur in more than 40 % of people [1], mainly among young and middle-aged subjects, and they are 2–4 times more common in women than in men. Common risk factors for gastrointestinal functional disorders are thought to include family history, social habits, diet and lifestyle, intestinal infections, social factors (profession, living in megapolis), personal and psychological features and stress. Any FGID significantly reduces the quality of life and requires considerable medical expenses [1]. Meanwhile, more than 30 % of patients have a combination of 2 or more functional gastrointestinal disorders. The greater is the number of FGID of various gastrointestinal segments in a single patient, the more pronounced are the symptoms and the more the quality of life is affected [2].

Common risk factors and pathogenetic links of the functional disorders enables reducing the number of prescribed medications when several FGIDs overlap in one patient. This article considers functional biliary disorder (FBD), functional dyspepsia (FD) and irritable bowel syndrome (IBS), their relationship and approaches to therapy when overlap.

Rome IV Criteria in clinical practice

In 2020, the global prevalence of FGID among the population of 33 countries was assessed. The data were collected via Internet and personal interviews using Rome IV diagnostic questionnaire (Table). Based on the results of the study, overall prevalence of FGID was 40.3 % among Internet respondents and 20.7 % based on personal interviews. Prevalence of FD was 7.2 % vs 4.8 %, IBS — 4.1 % vs 1.5 %, FBD — 0.08 % vs 0.03 %, respectively [1]. In earlier works not compliant with Rome IV criteria for the diagnosis of functional diseases, the values were significantly higher. The prevalence of biliary functional disorders varied from 12 to 58 % [3], while the IBS was 50 % higher compared to the current data [4].

Due to the discrepancy between the Rome IV Criteria and their clinical application, in agreement with the Board of Directors of the Rome Foundation, a modification of the Rome IV Diagnostic Criteria in clinical practice was developed in November 2021. In routine work, the doctor should take into account how painful the symptoms are for the patient ("bothersomeness") and assess the degree of concern of the patient in terms of frequency and severity of the symptoms affecting his/her daily activity. According to the explanations to the Rome IV Criteria, the frequency of complaints should not be regarded as a mandatory criterion for diagnosis, more importantly, the symptoms reduce the quality of life of the patient and disrupt his/her daily activities. Another important factor to be assessed when confirming the diagnosis of FGID is the period during which the symptoms are being assessed: duration of the symptoms is 8 weeks preceding the diagnosis [4]. Recalculation of prevalence of FGID taking into account the modification above has not yet been carried out.

FGID overlap syndrome

Overlap syndrome is a combination of several diseases (organic or functional) of one or more organs with common pathogenetic mechanisms (verified and/or suspected). 30 % of patients with gastrointestinal disorders have two or more FGID [2]. Thus, almost half (49 %) of patients with IBS have impaired biliary motor function and 42–87 % are diagnosed with FD [5]. Among those with dyspepsia, the prevalence of IBS is 8 times higher compared to the population [6], and may vary from 13 % to 46 % [7]. At the same time, severity of the symptoms (e.g. postprandial epigastric fullness) is significantly higher when FD is combined with IBS [8]. Combination of IBS with FBD is also accompanied with more pronounced abdominal pain and more severe autonomic and psychoemotional disorders [9–11]. The researchers called this "mutual burden syndrome": the greater is the number of FGID of various GI segments,

Table. Rome IV Criteria (2016) for diagnosis of FD, IBS, FBD

	Functional dyspepsia	**Irritable bowel syndrome**	**Biliary pain (Functional biliary disorder)**
Diagnostic criteria	1. One or more of the following: ·Bothersome postprandial fullness ·Bothersome early satiation ·Bothersome epigastric pain ·Bothersome epigastric burning	Recurrent abdominal pain on average at least 1 day/week in the last 3 months, associated with two or more of the following criteria: ·Related to defecation ·Associated with a change in frequency of stool ·Associated with a change in form (appearance) of stool	Pain located in the epigastrium and/or right upper quadrant and all of the following: ·Builds up to a steady level and lasts 30 minutes or longer ·Occurring at different intervals (not daily) ·Severe enough to interrupt daily activities or lead to an emergency department visit ·Not significantly (<20 %) related to bowel movements ·Not significantly (<20 %) relieved by postural change or acid suppression
	2. No evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms		
Supportive criteria	Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis		1. Nausea and vomiting
			2. Radiation to the back and/or right infra subscapular region
			3. Waking from sleep

the more pronounced are the symptoms [2, 5]. Simultaneous course of several functional disorders underlies the concept of "overlap syndrome in functional gastrointestinal disorders".

"Overlap" FGID is more common in wealthier countries as well as in young and middle-aged women, characterized by more pronounced abdominal pain syndrome, anxiety and depression, commonly accompanied with "non-gastroenterological" symptoms. The risk factors for overlap syndrome, similar to individual FGID, include smoking, alcohol consumption, eating disorders [12–16].

Let us consider the key links in the pathogenesis of functional diseases.

Common mechanisms of FGID pathogenesis

Disorders of gut-brain interaction

The Rome IV Criteria consider FGID as a disorders of gut-brain interaction. Gut-brain axis includes central nervous system (CNS) with hypothalamic-pituitary-adrenal axis and enteral nervous system. Physiologically, the signals from gastrointestinal tract affect the brain, which, in turn, may cause changes in motility, secretion and immune function of organs. Structural and functional changes in the components of this axis may lead to impaired perception of signals along afferent fibers followed by inadequate response of the nervous system to the received signal [17, 18].

Visceral hypersensitivity

One of the main features of many FGID is pain syndrome. Absence of structural and biochemical changes based on the results of examination in functional GI diseases encouraged investigation of the concept of visceral hypersensitivity — a condition in which normal physiological stimuli are perceived as pathological nociceptive ones. Development of visceral hypersensitivity is mediated by peripheral and central sensitization as well as modulating factors.

A painful (pathological) stimulus promotes release of peripheral inflammatory mediators. These mediators may cause a number of effects including increased pain sensitivity at the site of injury known as primary hyperalgesia as well as recruitment of previously inactive nociceptors. Ion channels, neurotransmitter receptors and trophic factors are involved in these processes. Among the most important ones are type 1 vaniloid receptors — TRPV1. In the gastrointestinal tract TRPV1 are responsible for temperature perception and mechanotransduction (conversion of mechanical stimuli into an intracellular biochemical response), may be activated by exposure to capsaicin and heat,

and hydrogen cations strongly potentiate this interaction. When activated, TRPV1 receptor causes a burning sensation and pain and even neurogenic inflammation when associated with concomitant release of substance P (pain substance P is a neuropeptide from tachykinin family). Animal experiment demonastrated that TRPV1 receptor antagonists reduce visceral hypersensitivity. Evidence is growing for the association between increased TRPV1 expression and visceral hypersensitivity in humans [19]. A study showed increased sensitization of TRPV1 submucosal neurons in patients with IBS compared to the receptors of healthy individuals. This work confirmed potentiating effect of histamine against TRPV1, and prescription of type 1 histamine receptor antagonists decreased visceral hypersensitivity and relieved IBS symptoms [20].

To confirm the mechanism of central sensitization, irritation of the distal part of esophagus with hydrochloric acid was carried out in the experiment demonstrating decreased threshold of pain sensitivity in both distal part of the organ treated with acid and in more proximal intact areas suggesting development of secondary hyperalgesia and central mechanism of sensitization [19].

Changes in intestinal microbiota

Microbiota has been actively investigated as the third component of "gut-brain" axis. Microbiota is considered to be one of the key modulators responsible for the development of visceral hypersensitivity. Microbiota and central nervous system interact in various ways, including through immune system, tryptophan metabolism, vagus nerve and enteral nervous system through microbial metabolites such as short-chain fatty acids, branched-chain amino acids, peptidoglycans etc. [21].

Possible pathogenetic relationship between microbiota condition and FGID is suggested by the development of FD and/or IBS in predisposed individuals after an episode of infectious gastroenteritis. Thus, recent infectious enteritis increases the risk of IBS 4-fold [22]. In this case, pathogenic microorganisms activate innate immune responses of the mucous membranes, thus increasing epithelial permeability (possibly due to damage to the proteins responsible for dense cell junctions), "switch on" nociceptive sensory pathways and disrupt the regulation of the enteral nervous system [23]. Impaired integrity of intestinal barrier promotes migration of bacteria through the intestinal wall and penetration of a pool of bacterial antigens such as peptidoglycans and lipopolysaccharides and pro-inflammatory cytokines into systemic circulation. This in its turn may lead to activation of hypothalamic-pituitary-adrenal system and release of stress hormones which highlights the importance of the role of microbiota in neuroendocrine system. In addition, there is evidence of translocation of peptidoglycans into the brain and their direct impact on the central nervous system. The effect of microflora on central nervous system is also mediated by metabolites of dietary tryptophan produced by commensal bacteria and short-chain fatty acids. Microbiota can control contractile activity of the colon, which peripherally occurs by regulating the synthesis and release of neurotransmitters, e.g. serotonin.

In some studies on patients with IBS, lower levels of serotonin and serotonin reuptake transporter (SERT) in mucosa have been reported. It has also been found that exposure to selective serotonin reuptake inhibitors (SSRIs) in some cases improves the symptoms of IBS associated with accelerated transit and increased colon peristalsis. In addition, antagonists of specific serotonin 5-HT3 receptors expressed in the gut relieves visceral pain, slows down transit through the colon and increases absorption in the small intestine [24].

Epithelial permeability

Increased duodenal permeability is observed in most patients with FD, small and large intestinal permeability did in almost 40 % of patients with IBS. The most pronounced changes are observed in postinfectious IBS with diarrhea. In addition to the infectious process and microbiota disorders, antibacterial drugs and food allergens (gluten) may cause damage to cell junctions. Increased cell permeability in most studies correlates with decreased expression of zonulin-1 and occluding as well as with increased number and activation of mast cells in the mucosa. Severity of morphological changes in this case is commonly consistent with severity of the symptoms [25–32].

Pro-inflammatory cytokines

Significant role in FGID is mediated by pro-inflammatory cytokines, e.g. tumor necrosis factor alpha (TNF-α). Comparison of cytokine profiles revealed that blood level of TNF-α in patients with IBS was significantly increased compared to healthy individuals and patients with inflammatory bowel diseases, while levels of interleukin-6 and interleukin-1β were comparable to those in control group [33]. Another study confirmed significantly higher levels of TNF-α in IBS patients compared to healthy individuals, positive correlation was observed between TNF-α level and the impact of fatigue on daily life in patients with IBS [34]. Noteworthy, TNF-α is involved in the

processes of carcinogenesis including colon cancer and gallbladder cancer [35–38].

Gastrointestinal motility

Regulation of GI motility is a complex multi-level process. Central nervous system is responsible for efferent innervation of smooth muscle cells of organs through autonomic nervous system. Transmission of signals from enteral neurons to smooth muscle cells is carried out by Cajal cells which are pacemakers located in smooth muscles and determining the frequency of peristaltic waves. Where necessary, individual myocytes expressing various specialized receptors (cholinergic, dopamine, serotonin, etc.) may play a role of a pacemaker. Failure at any of these levels may lead to dysregulation of contractile activity of the gastrointestinal tract.

The most common cause underlying impaired motor regulation in FGID is considered to be psychoemotional overstress: social maladaptation, constant stress and fatigue, work, study and rest disturbances. Meanwhile, the symptoms typical for functional disorders of several GI organs causing overlap syndrome are associated with hypo- or hypertonia of different parts of the digestive tract [39].

Biliary and intestinal motor disorders occur in response to certain stimuli, e.g. food and stress [11]. Patients with IBS and tendency to constipation have hyperkinetic biliary markers, while patients with IBS and diarrhea show tendency for hypokinetic markers [40, 41]. Noteworthy, in patients with IBS, gallbladder emptying occurred faster compared to healthy people [42, 43].

FGID overlap therapy

Treatment of FGID should include resolution of the existing risk factors. Quitting smoking, avoiding or limiting alcohol consumption, minimizing the impact of stress are necessary. Where applicable, consultation with a psychologist or psychotherapist may be advised to select the optimal pharmacological therapy (tricyclic antidepressants, selective serotonin reuptake inhibitors, neuroleptics).

Diet is an important factor. It has been established that spicy foods, fatty foods, coffee may trigger IBS. Enhanced chronic upper abdominal pain is observed after fatty meals in 28 % of patients with IBS and in 19 % in those with FD, after chili pepper in 45 % vs 47 %, after coffee intake — in 41 % vs 47 %, respectively [44]. The proposed mechanisms triggering impact of these products include direct effect on mucosal receptors, induction of an immune response, sensitization of mast cells, degranulation of eosinophils in duodenal mucosa, increased epithelial permeability [45, 46]. It was also mentioned earlier that capsaicin (an alkaloid contained in pepper) leads to activation of TRPV1 receptors, which is accompanied by a burning sensation and pain [19]. Patients with FD are advised to follow split meals in small portions, restrict high-fat products and coffee; patients with IBS should be prescribed with individual elimination diet [47–53].

Pharmacological therapy of individual FGID is detailed in the relevant clinical guidelines, however, the treatment of a single functional disorder is often associated with certain difficulties. Thus, in IBS patients efficacy of therapy was reported in only 30 % of cases, while persistent remission is observed in only 10 % of them. In part this may be due to higher predisposition to side effects and, therefore, low adherence to the treatment. On the other hand, the wave-like course of the disease may be associated with persistent risk factors [52, 54].

Treatment of FGID overlap syndrome according to the current clinical guidelines often leads to multidrug regimen which reduces the patient's adherence to the therapy. If there are several FGID, the optimal solution would be to choose a medicine that affects the pathogenetic links of all nosologies included in the overlap syndrome of the patient. Trimebutine for the treatment of IBS and FD overlap is an example [39]. However, a normokinetic agent may not be enough if more than two FGIR overlap.

The option of choice in such situations is Kolofort containing processed purified antibodies to human TNF-α, histamine and brain-specific protein S-100. The first two components produce anti-inflammatory, antispasmodic and analgesic effects. Antibodies to brain-specific protein S-100 promote changes in the functional state of the key neurotransmitter systems, thereby implementing anxiolytic, antidepressant, neuroprotective and vegetative stabilizing activity of the product [55–58].

Efficacy of Kolofort was evaluated in a group of patients with combination of FD and IBS. This study enrolled 14 362 patients. Kolofort was taken in a regimen: 2 tablets twice per day, the treatment duration was 3 months. Severity of gastrointestinal functional disorders was assessed using "7×7" questionnaire (a rating scale assessing 7 main symptoms of IBS and FD in 7 days). The final efficacy analysis included data from 9254 patients (Fig.). Transition to a milder category at the end of the treatment was reported in 93.35 % of patients with FD, 93.80 % with IBS and in 96.17 % with combination of IBS and FD. Overall, 94 adverse events were recorded in 80 patients, i.e. <1 case per 100 patients. All adverse events were mild

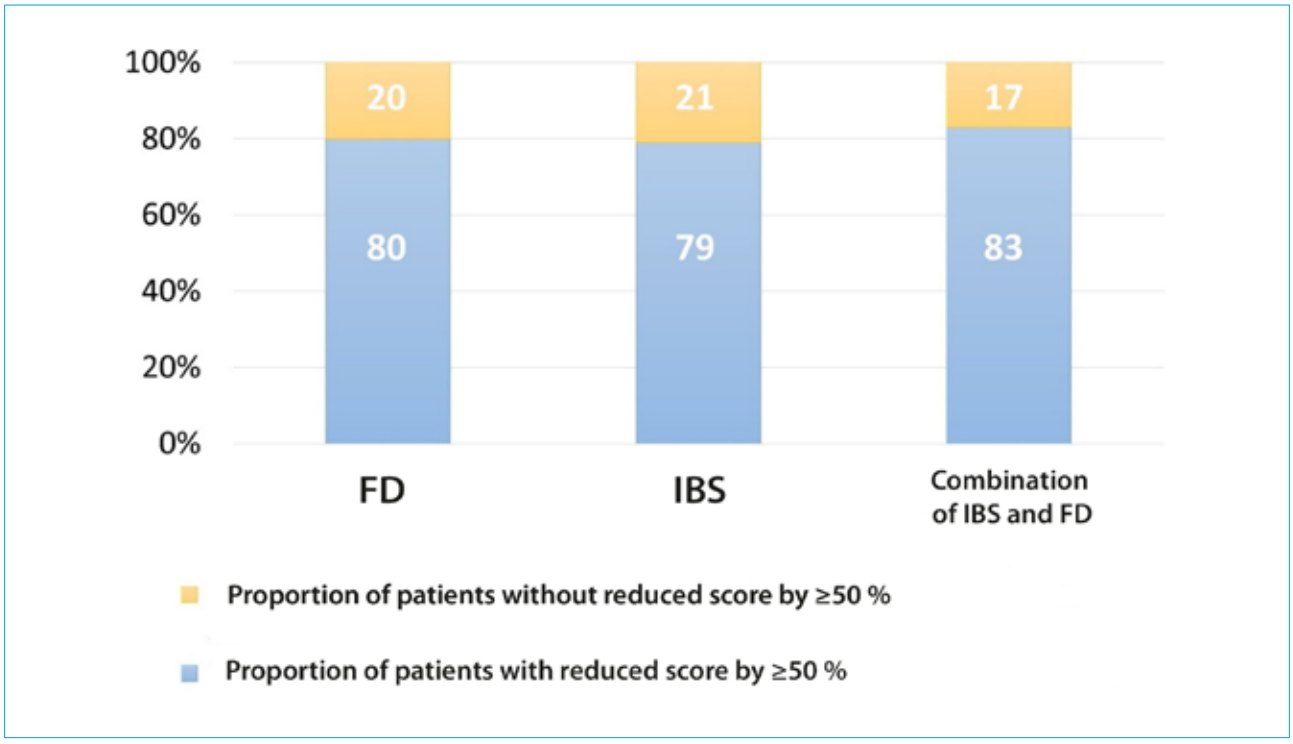

Fig. The proportion of patients who experienced a decrease in scores on the «7×7» questionnaire by 50 % or more after 3 months of treatment with Colofort

to moderate, the most common were nausea, abdominal or headache, urticaria [57].

Efficacy and safety of Kolofort in the treatment of IBS was evaluated in comparison with trimebutine. With comparable tolerability and safety of the products, Kolofort reduced pain syndrome more significantly and was superior to trimebutine in terms of stool normalization according to Bristol scale. Thus, a 12-week course of Kolofort significantly reduced severity of pain (30 % or more) in 95 % of IBS patients, while trimebutine did in 84 % only. In addition, 90 % of patients with IBS and diarrhea and 100 % with IBS and constipation during Kolofort therapy had normal stools by the end of the treatment, while during trimebutine these values were 58 % and 76 %, respectively [58].

Conclusion

Functional gastrointestinal disorders are common among the people of working age, significantly reduce quality of life thus defining their socio-economic significance. Special attention should be paid to cases of overlap syndrome characterized by more pronounced clinical symptoms.

Kolofort affects several key links in the FGID pathogenesis. The product contains processed antibodies to TNF-α (proinflammatory cytokine associated with the symptoms of IBS), to histamine (a mediator of mast cells involved in development of visceral hypersensitivity and increased epithelial permeability), and to brain-specific protein S-100 modulating the function of central nervous system. In the studies Kolofort has demonstrated high efficacy and safety including among patients with overlap FGID enabling to consider it as the treatment of choice in this population.

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