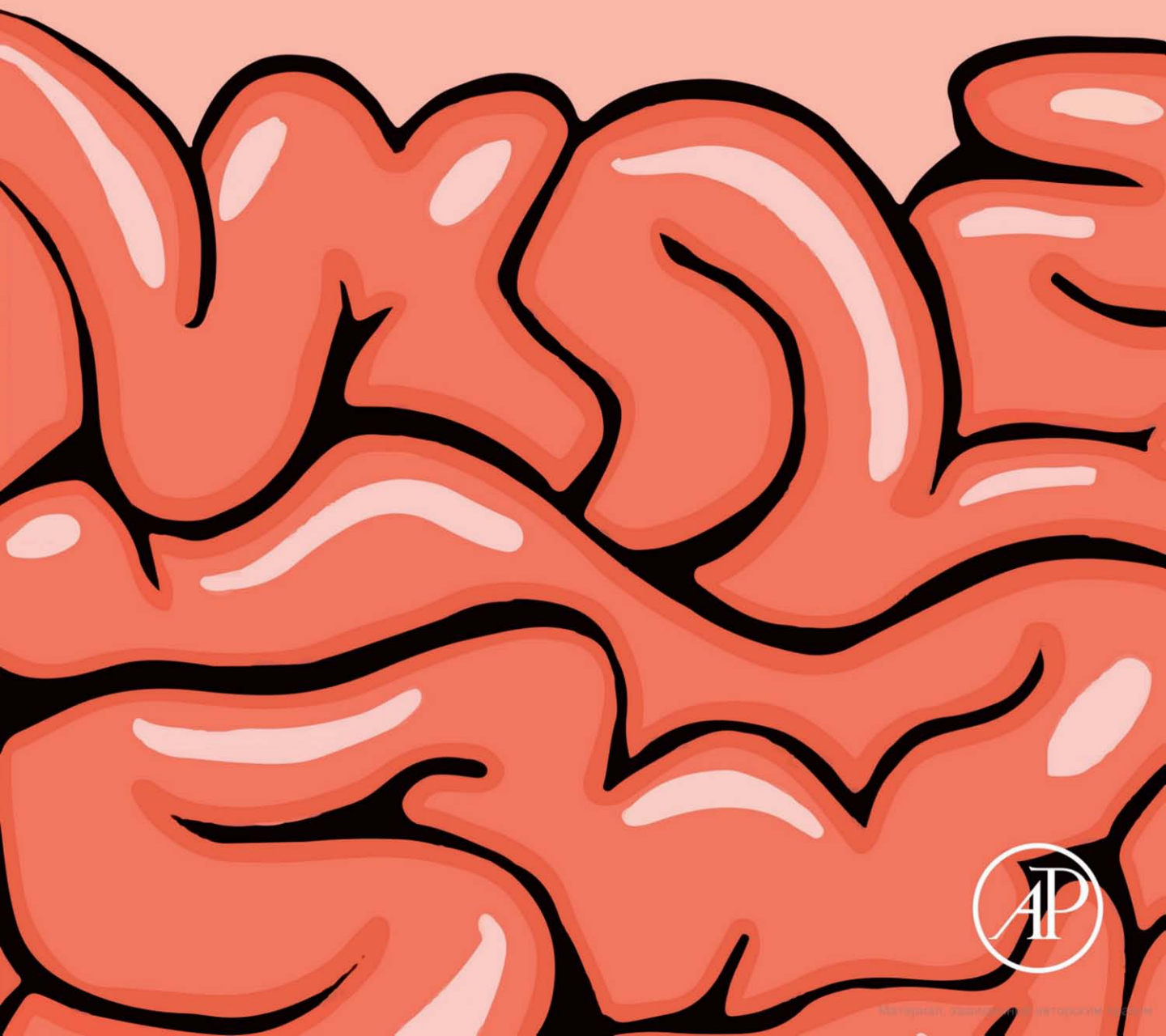
Edited by **Jakub Fichna**

A Comprehensive Overview of Irritable Bowel Syndrome

Clinical and Basic Science Aspects



A COMPREHENSIVE OVERVIEW OF IRRITABLE BOWEL SYNDROME

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Preface

Rich or poor, young or old… Nearly 15% of our population suffer from irritable bowel syndrome (IBS) and only very few are taken good care of. In the era of "westernization" of our lifestyles and increasing environmental pollution, but also in the times when infections spread across the world, there will only be more IBS cases in the coming years. Proper IBS diagnosis and efficient therapy are needed, and they are needed now.

This book summarizes current knowledge on IBS and points to new directions in basic and clinical studies. The book may be read in its entity, but also by single chapters, depending if one is a scientist, a clinician, or a patient. I do hope that it will become a helpful guide for all through IBS causes, symptoms, and treatment.

1

Introduction to irritable bowel syndrome: General overview and epidemiology

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Abstract

Irritable bowel syndrome (IBS) is a functional gastrointestinal condition characterized by the disruption of the bowel movement and abdominal pain. There is no single factor known to cause IBS, hence its diagnosis and treatment are troublesome. Yet, due to increasing incidence, IBS has become a serious global issue.
In this chapter, the incidence and prevalence of IBS are discussed. Also, epidemiology in different corners of the world is compared to elucidate whether there is any association with geographical location or socioeconomical status. Finally, age and gender are briefly discussed in an attempt to draw a picture of an IBS sufferer.

Keywords

Irritable bowel syndrome, Epidemiology, Incidence, Prevalence

List of abbreviations

IBS	irritable bowel syndrome
IBS-C	constipation-predominant irritable bowel syndrome
IBS-D	diarrhea-predominant irritable bowel syndrome
IBS-M	mixed irritable bowel syndrome

Irritable bowel syndrome (IBS) is a functional gastrointestinal condition, to which both internal and external factors contribute. There is no single (in)organic causative agent identified so far, hence several hypotheses were formed to what extent genetic,

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neuronal, microbial, immunological or environmental factors promote the development of IBS. Typical symptoms: abdominal pain and changes in stool frequency or consistency, leading to constipation and/or diarrhea are debilitating to an extent where IBS is a major cause for visits in general practitioners office. Together with a significant impact on patients quality of life due to physical suffering, work absenteeism and economic non-productivity, but also psychological co-morbidity (increased risk of depression and suicidal ideation), IBS constitutes a major socioeconomic issue worldwide [1–3]. Nellesen et al. [4] report that the direct annual cost of diagnosing and treating IBS in the United States alone is estimated between $1.7 and $10 billion, while Chatila et al. [5] evaluate that the indirect costs in terms of absenteeism, workdays lost, disability will double that figure.

As there are no diagnostic or monitoring biological markers, IBS diagnosis bases on well-established criteria (currently Rome IV) in which patient's symptom reporting is crucial [6]. However, as the guidelines are constantly being updated, studies on incidence and prevalence based on Rome I, Rome II, Rome III and Manning criteria need also to be taken into consideration. Worth mentioning, as noticed by Canavan et al. [7], the Manning criteria account for the highest reported prevalence [8, 9] whilst the Rome iterations are associated with lower estimates of prevalence [8]. Consequently, different figures regarding IBS epidemiology are obtained, which can be additionally influenced by the fact that not in all the countries criteria regarding IBS have been defined. Moreover, factors like survey methods and the study instrument could also affect the estimates. This has been best illustrated by Endo et al. [10]: the prevalence of IBS in Iranian adults based on the modified Rome III criteria was established at 21.5% [11] and only 9.0% (95% CI, 6.0–13.0) based on the Rome II criteria [12].

In terms of incidence, Canavan et al. [7] reported two US studies, of which one conducted two population cohort surveys 1 year apart [13] and the other defined cases as first diagnosis by a physician [14]. In the former, 9% of subjects had developed symptoms over the year, an incidence rate of 67 per 1000 person-years. A significantly lower estimate based on the latter, with around two per 1000 person years was provided.

In 2012, based on a systematic review and meta-analysis of 260,960 subjects from 80 studies the global pooled prevalence of IBS was estimated at 11.2% [12], but later the data were questioned due to significant heterogeneity between the studies [6]. Major geographical differences have been observed: in 2012 IBS rates in the Western countries ranged from 10% to 20% [15] compared to 1% to 10% in the Asian countries [16]; the lowest reported rates were in Southeast Asia (7.0%) while the highest (21.0%) were

in South America. However, these estimates change rapidly over time: a rise in IBS rates in Asian countries is observed, and more developed nations, such as Japan and Singapore, already report prevalence comparable to that in the Western countries [17].

In terms of IBS subtypes, Lovell and Ford [12] point to diarrhea-predominant IBS (IBS-D) as the most prevalent (40.0%), followed by constipation-predominant (IBS-C, 35.0%) and mixed (IBS-M, 23.0%). A small study by Kibune-Nagasako et al. [18] on Brazilian population stays in line with these statistics: the most frequent IBS subtype was IBS-D (46%), followed by IBS-C (32%) and IBS-M (22%). However, other studies cited by these authors report opposite results: for example IBS-M was the largest bowel habit subgroup in population-based studies performed in United Kingdom and the United States [19, 20], while IBS-C was the most frequent among Iranian adults [11]. It is thus hypothesized that the increased prevalence of a given IBS subtype depends primarily—but not exclusively—on the severity of symptoms in a given subtype and on who provides the epidemiological data. Consequently, IBS-D—which may demand a more complex investigation in a gastrointestinal outpatient clinic—will rather be reported by GI specialists; general practitioners may be more confident in the management of IBS-C.

There are several demographic parameters that need to be mentioned in relation to IBS epidemiology, including sex, age, and socioeconomical status. Canavan et al. [7] report that in most populations the IBS rates in women are approximately 1.5- to 3-fold higher than those seen in men [21–23] and internationally, the overall prevalence of IBS in women is 67% higher than in men (odds ratio 1.67 [95% CI 1.53–1.82]). These data may also be presented as outnumbering males by females by the ratio of 2:1 in the Western countries, and by 3:2 in United States [24]. On the other hand, in South Asia, South America, and Africa, the rates of IBS in men are almost equal to those of women, and in some cases even higher [12]. For example, Pimparkar et al. report a reversed females to males IBS ratio in India compared to the Western countries, i.e. 1:3, with the prevalence of IBS in general population of India at 15% [25]. This may result from disparities in the access to health care, but also sex-related motivation to seek consulting.

IBS is reported in all age groups, with no difference in the frequency of subtypes by age [7, 26]. However, the disease is more prevalent among adolescents and declines with age [12]. In line, Canavan et al. point to the fact that 50% of patients with IBS report having first symptoms before the age of 35 years, and that prevalence is 25% lower in those aged over 50 years than in those who are younger [7, 12, 27].

Whether IBS is in relation to the socioeconomic status, it remains to be elucidated. Canavan et al. [7] reported two studies with opposing outcomes: Drossman et al. [28] suggested that IBS was associated with lower socioeconomic status (as lower income pairs with poorer health care outcomes, lower overall quality of life, and increased life stressors), while others prove that being in a higher socioeconomic group during childhood or being exposed to the higher level of stress when working in professional and managerial roles is associated with higher prevalence of IBS [29, 30]. In line with the latter, the higher income brings greater access to health care and tendency to seek help and hence receive a diagnosis [31].

Chatila et al. [5] list several lifestyle factors such as smoking, alcohol consumption [32–35] and physical activity [36, 37] being linked to IBS. However, this may differ depending on a study and population examined: for example Nagaonkar et al. [25] found no such correlation between alcohol abuse and IBS in the Urban Slum Community in Mumbai. Higher prevalence of IBS associates with psychological factors such as stress and anxiety [10, 16, 38], and is seen among psychiatric patients (up to 39.7%, which is twice the general population) [39]. Genetics factors may also play a role in IBS pathogenesis and nearly 33% of patients with IBS report a positive family history [40].

Noteworthy, there is no increase in mortality rates in IBS patients compared with healthy controls. Canavan et al. [7] proves this by citing data from a large study conducted in the United States of over 4000 patients, followed for a total of 30,000 patient-years, in which no increased mortality compared with the general population was observed (hazard rate 1.06 [95% CI 0.86–1.32]) [41]. These results were in line with a smaller study from the People's Republic of China which followed 263 patients over 5 years [42].

In conclusion, on average IBS is first diagnosed in 30–50-year-old women; however, the symptoms may already occur in childhood and in both genders, which proves the inaccuracy of reporting techniques as well as unequal access to healthcare and/or regional gender and age-related differences in seeking professional medical aid. Nevertheless, IBS has become a major global issue that needs general attention. Consequently, as proposed by Masudur Rahman et al. [1] based on available guidelines [43, 44] a good care of the IBS patient must be introduced, which should rely on the development of a good doctor patient relationship, identification of contributing factors, and critical appraisal of the efficacies of various drugs according to the subtype of IBS.

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2

Pathogenesis of irritable bowel syndrome

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Abstract

Irritable bowel syndrome (IBS) is a heterogenous, chronic disease with a complex and multifactorial pathogenesis. Multiple studies have provided many well explored mechanisms involved in the pathophysiology of IBS. Possible factors such as genetic predisposition, diet, changes in gut-brain axis, gut microbiota, mucosal inflammation, stress and anxiety have been identified and linked with IBS. However, pathogenesis of this condition is still not fully understood and further investigation is necessary in order to provide more useful information which could help develop specific treatment.

In this chapter, the current knowledge about pathogenesis of IBS will be discussed.

Keywords

Irritable bowel syndrome, Pathogenesis, Diet, Genetics, Microbiota, Serotonin, Brain-gut axis, Peptide YY, Mucosal inflammation

List of abbreviations

5HT	5-hydroxy-tryptamine
CNS	central nervous system
ECs	enterochromaffin cells
ENS	enteric nervous system
FODMAPs	fermentable oligosaccharides, disaccharides, monosaccharides and polyols
GI	gastrointestinal
IBS	irritable bowel syndrome
IFN-γ	interferon-gamma
MCs	mast cells
NCGS	non-celiac gluten sensitivity
NPY	neuropeptide Y
PBMCs	peripheral blood mononuclear cells
PI-IBS	post-infectious irritable bowel syndrome

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PYY	peptide YY
SCFAs	short chain fatty acids
TPH	tryptophan hydroxylase
VH	visceral hypersensitivity

Irritable bowel syndrome (IBS) has been considered a disorder without a clear pathological or biochemical explanation. At first, studies regarding IBS focused on the alteration of gastrointestinal (GI) motility and visceral sensory function. However, while these were the fundamentals of IBS, the pathogenesis remained uncertain. Further search for these abnormalities revealed many well explored mechanisms. According to current research, it is believed that IBS is a condition connected with many factors such as genetic predisposition, stress, anxiety, food intolerance, changes in gut-brain axis and GI impairments which overall make it a heterogenous disorder. The latter also involve alternation in gut microbiota (dysbiosis), changes in gut motility and permeability, low-grade mucosal inflammation and immune activation [1, 2]. Analyses confirm a striking cumulative effect of these factors on the overall IBS somatic symptoms, and also on the patients' quality of life, indicating the importance of considering and evaluating variations of pathophysiologic factors in IBS [3].

Fundamentals—Impaired gut motility and visceral hypersensitivity in IBS

Alteration in gut motility

IBS, sometimes also called "spastic colon," implies heterogenous motility disorders, with various underlying disease mechanisms and subtypes categorized by the predominant stool pattern: diarrhea in IBS-D, constipation in IBS-C or both in IBS-M [4]. Impaired motility from abnormal gut contractions results in symptoms described as abdominal pain and discomfort. Studies have shown that in IBS patients multiple stimuli like diet or stress may implicate exaggerated physiological response and therefore various gastrointestinal (GI) motor disturbances [5]. However lack of consistent motor patterns changes among IBS patients makes it difficult to interpret and understand underlying pathogenesis. Multiple studies proposed a plurality of possible disease mechanisms, acting on different levels along the brain-gut axis or intestines itself [6, 7].

Visceral hypersensitivity

Altered and increased sensation (including pain) of physiological stimuli is defined as visceral hypersensitivity (VH). VH comprises of two major components, which are allodynia and hyperalgesia. Hyperalgesia refers to an intensified pain sensation in response to a certain stimulus, whereas allodynia is defined as painful sensation in response to normal stimulus, which was previously not perceived as being painful. Studies revealed that VH develops from alterations in the peripheral sensory pathway and/or central nervous system (CNS). It is suggested that VH is considered as a pivotal biological hallmark of IBS [8, 9].

According to epidemiological studies prevalence of VH in IBS patients varies from 33% to 90%. VH mainly occurs in IBS-D patients with increased intestinal permeability and affects, apart from rectum and sigmoid colon, also small bowel, stomach and esophagus indicating decreased thresholds of nociceptive sensation all over the GI tract [10].

In fact, VH as a multifactorial condition may occur both within the peripheral nervous system and at the level of CNS. Several factors, including intestinal microbiota, genetics, psychological factors, inflammation and immunological factors, brain-gut axis, diet, are involved in the VH process among IBS patients [10].

Factors and mechanisms in IBS pathology

Brain-gut axis

Anxiety and depression are among the most frequent IBS symptoms which do not relate to the GI tract that are commonly found in outpatient and community samples [7, 11]. Observations as such made many look at IBS as a primary disorder of gut-brain function or somatization, with the brain being responsible for the gut abnormalities and fatigue, among many others. Nevertheless, three recent studies show that in approximately half of the patients the mood disorders are preceded by symptoms of GI nature [12]. These results suggest that in a patients' subgroup mood disorder might be caused by an initial gut disorder. Moreover, structured interviews conducted in an independent study of psychiatric disorders and IBS showed that in 40% of patients with a mood disorder and in 23% of patients suffering from anxiety those disorders were diagnosed after the development of IBS [13]. Additionally, studies regarding cytokine response, intestinal inflammation and gut microbiome provided evidence that gut precipitates brain alterations in IBS [14, 15]. If those implications

are proved to be factual, with a reversal of GI dysfunction, alleviation of inflammation and bringing back proper microbiota balance—which happens to be feasible, as the brain is by far less accessible than the gut—there is a chance to reverse or at least improve gut and mood dysfunction.

Serotonin and its metabolism

Serotonin (5-hydroxy-tryptamine, 5HT) is a monoamine neurotransmitter primarily found in the enteric nervous system (ENS) located in the GI system and the central nervous system (CNS). However, serotonin located in enterochromaffin cells (ECs) of GI system makes up the majority—almost 90%—of total 5HT stores [16]. Serotonin plays a remarkable role in regulation of GI motility and changes in this neurotransmitter levels were observed in patients with IBS: patients with IBS-D have increased serotonin levels while in IBS-C these levels are reduced [16, 17]. There is a theory that those suffering from IBS-D have decreased 5HT reuptake, while IBS-C patients have decreased 5HT release [18]. Additionally, patients with post-infectious IBS have constant increases in ECs and increased 5HT levels after meals, while IBS-C patients have decreased 5HT release [19, 20]. The fact that 5HT receptor ligands (especially 5-HT_3 receptor antagonists and 5-HT_4 receptor agonists) had positive effects on IBS symptoms (such as reducing perception of visceral distension and colonic hypersensitivity in women with IBS-D, improving stool pattern and abdominal pain) is yet another proof of importance of the serotonin's role in the IBS pathogenesis [21].

Polymorphisms in 5HT receptors, 5HT transporters—SERT (especially 5HTTLPR) and in tryptophan hydroxylase (TPH), which is an enzyme responsible for restricting 5HT synthesis have been studied and described in patients with IBS but, unfortunately, the results of the studies are unconvincing [16]. However, according to a meta-analysis from 2014 the LL genotype of 5HTTLPR seemed to be a risk factor for IBS-C in East Asia [22]. Studies have also noted that microRNA expression increases in the colonic samples from IBS patients. It has been proven that microRNAs, such as miR-510 or miR-16, can promote epigenetic and genetic changes through modulating intestinal pathways such as 5HT signaling, which result in intestinal permeability and somatic hypersensitivity in IBS patients [23, 24].

According to few studies there seems to be a connection between 5HT metabolism and immune activation, inflammation of the mucosa as well as intestinal barrier function [16]. A study on colon biopsies from IBS patients versus healthy controls performed in 2011 revealed elevated numbers of EC cells rich in 5HT with the advantage in IBS-D over IBS-C [25]. Moreover, this

study proved that mucosal 5HT was substantially raised in patients with IBS and that it was connected with increased number of mast cells and severity of pain. Another study showed intriguing association between proinflammatory interferon-gamma (IFN-γ) protein and SERT expression [26]. This investigation showed that IFN-γ levels were augmented in IBS patients' mucosa and SERT expression was decreased, what consequently affected the amount of 5HT in gut. These results are in line with knowledge that inflammation lowers SERT expression, what may be another clue to understanding the pathogenesis of IBS.

Possible role of peptide YY

Peptide YY (PYY) which belongs to the neuropeptide Y (NPY) family is synthesized in endocrine cells (PYY cells) located between the epithelial cells of the human ileum, colon and rectum [27]. PYY plays an important role in proper functioning of the GI system: it regulates appetite and food intake, slows emptying of the stomach, inhibits gastric and pancreatic secretion and induces absorption of water and electrolytes [28, 29]. What is more, PYY is considered to have an impact on modulating 5HT excretion from colonic ECs through NK2/NK3 cascade system [30]. As discussed earlier, 5HT modulates visceral sensitivity and accelerates GI motility and secretion [31].

Abnormalities in PYY in IBS patients were a topic of many investigations which led to a conclusion that IBS patients and healthy subjects have the same density of PYY cells in the ileum, but suffer from a decreased density of these cells and concentration of PYY itself in the colon compared with healthy subjects [32, 33]. The same is observed in the rectum. All things considered, it is probable that low density of PYY cells and PYY concentration in the gut may lead to low release of PYY, which consequently contributes to abnormal motility observed in IBS patients. Moreover, the impact of PYY on 5HT release may contribute to visceral hypersensitivity which is crucial in the pathophysiology of IBS.

Histamine and mast cells

Another molecule apart from 5HT, which may be connected with the pathogenesis of IBS is histamine [34]. Histamine is a short-acting endogenous amine involved in inflammatory response that functions as a neurotransmitter in the human body. This compound is mainly produced by mast cells (MCs) using the enzyme histidine decarboxylase, and also by basophils, gastric enterochromaffin-like cells, and histaminergic neurons but in

lower amounts [35, 36]. However, only MCs and basophils store large amounts of histamine, while other cells synthesize it and secrete immediately without storage. Histamine can fulfill its functions by binding to four subtypes of receptors: H_1R-H_4R, of which each has a specific location and role. In the GI system histamine is believed to modulate motility, increase production of gastric acid and modify mucosal ion secretion [37, 38].

There are some studies in which the role of histamine in IBS patients was investigated. One such study revealed that 58% IBS patients experienced GI symptoms due to a histamine-releasing food intake (milk, wine, beer) and food rich in biogenic amines (wine, beer, cheese) [39]. In another study, high levels of histamine were found in supernatants from IBS colonic samples [40]. Moreover, there is proof of increased expression of H_1R (proinflammatory signaling) and H_2R (anti-inflammatory signaling) in IBS patients [41, 42]. Apart from that, H_4R are believed to involve visceral sensory signaling and GI contractility [43].

Mast cells cannot be underestimated in understanding the pathophysiology of IBS. These cells store not only histamine but also tryptase and nerve growth factors, which can activate and sensitize enteric nerves and influence the integrity of the epithelial barrier [44]. A range of investigations prove that IBS patients have elevated number of MCs in almost all intestinal mucosa including rectum, rectosigmoid, descending and ascending colon, cecum, jejunum and duodenum [40, 45–48]. What is more, activation, level of degranulation and, consequently, release of modulators of these cells is also increased.

It is also worth mentioning that mast cells through degranulation might also influence proteins responsible for forming cell junctions, such as zonula occludens-1, claudin-1 and other adhesional molecules, causing their lower expression in both upper and lower GI tract. This is probably connected with tryptase release after exposure to food antigens [48–50].

Gut microbiota

It is commonly known that gut is the richest in microorganisms part of the human body. The intestinal microbiota is composed of 17 families, 50 genera and more than 1000 species of bacteria of which only one third have been identified so far [51]. Gut microbiota include not only bacteria but also viruses, fungi and protozoa which live in symbiosis under normal circumstances and are responsible for gut development, digestion and metabolism, proper development of humoral and cellular mucosal immune system and protection against pathogens [52, 53].

Gut microbiota develops from the day of birth to the adulthood and undergoes wide variety of changes during life due to genetic and environmental factors, dietary habits, stress, invasive medical procedures or use of medications, especially antibiotics [52]. *Firmicutes* (which form approximately 64% of gut microbes; e.g., *Lactobacillus*), *Bacteroidetes* (23%; e.g., *Bacteroides fragilis*), *Proteobacteria* (8%; e.g., *Eschericha coli, Salmonella, Shigella*) and *Actinobacteria* (3%; e.g., *Bifidobacteria*) are four dominating bacterial phyla in human intestines [51, 54, 55]. Methanogens and halophilic archae were also identified as highly associated with gut (e.g., *Methanobrevibacter smithii*) [53].

Any changes in bacterial number and composition may result in dysregulation of interactions between host and microbes. This state is called dysbiosis and might be triggered by pathogens, inflammatory mediators or any initiators that can provoke reaction of the immune system and lead to loss of beneficial influence of microbiota, affecting the intestinal environment. Hence, it is believed that disruptions in the microbiome may play an important role in pathogenesis of IBS by changing integrity of the gut and its immunological properties, and lead to dysregulation of gut-brain axis homeostasis [51, 53].

According to a study from 2015 performed in Sweden, Norway, Denmark and Spain involving patients between 17 and 76 years old, gut dysbiosis was observed in 73% of IBS patients [52]. Although many detailed investigations of bacterial composition of intestines in IBS patients were performed, the results differ between study groups and still are not univocal. Nevertheless, the majority of studies confirm that there are some changes in microbiota of IBS patients in comparison to healthy ones. Some observations show that IBS-positive patients present downregulation of *Methanobacteriales, Prevotella, Bifidobacteria, Lactobacillus* and *Bacteroides* species (the latter two are particularly perceived as beneficial bacteria) and increased number of pathogenic bacteria such as *Streptococcus* spp. [56–58]. A different investigation confirms lower numbers of *Methanobacteriales, Lactobacilli* and *Bifidobacteria*, but indicates that the number of *Bacteroides* was higher in IBS patients (even 12 times according to the 2014 study) [58–60]. Another study, however, showed higher numbers of *Proteobacteria* and *Firmicutes* (including *Lactobacillus*) [61]. In IBS-D subtype significant decrease of *Lactobacillus* and *Bifidobacterium* population was observed contrary to healthy controls and IBS-C patients.

Microbes of the intestine generate gases (hydrogen, methane) and short chain fatty acids (SCFAs) as by-products which could affect bowel passage and permeability [62]. Studies

revealed lower methane production among IBS-D patients and higher in IBS-C, which may explain changes in stool pattern in these patients [63]. Methane production may also have anti-inflammatory effects in the colon, so its lower amount in the state of dysbiosis can be a part of improper functioning of gut immune system. A smaller number of the archaea which convert H_2 to CH_4 in IBS patients may contribute to a lower rate of hydrogen removal, what can lead to abdominal distension observed in these people.

Furthermore, gut microbiota affect also serotonergic regulation through stimulation of EC cells by production of SCFAs and therefore increasing 5HT levels [57].

Summarizing, disturbances in the intestinal microbiota may play a key role in IBS pathogenesis. Additional aspect is that some antibiotics and probiotics have beneficial effect on relief of IBS symptoms. However, many issues still need further investigation to examine which microbes are IBS contributors and which ones only adapt and survive in changed conditions.

Genetics

It has been reported by some that IBS seemingly aggregates in families. Conducted twin studies have shown lower concordance of IBS in dizygotic twins and higher in monozygotic twins, what suggest that genetics might indeed be involved [64]. Some investigators focus on the role of specific genes in IBS predisposition, while others try broader approach by using large population-based cohort studies for gene-hunting efforts. One of the most studied genetic aspects in IBS is its correlation with 5HT transporters—SERT. A recent meta-analysis based on a total of 27 studies including 7039 subjects concluded that the SERT insertion/deletion polymorphism was associated with IBS in both Asians and Caucasians but only for those with IBS-C [22]. Other reports mention multiple genes that might play role in pathophysiology of IBS, such as ion channel gene TRPM8, sucrase-isomaltase mutations or single nucleotide polymorphisms [65–67]. Results are promising, however a wide range of studies were hindered by a small size of the sample, where genetic association of selected candidate genes in IBS had less than 2000 patients enrolled with the largest to date containing just about 7000 patients, compared to 30,000–40,000 in certain inflammatory bowel disease cohorts. In addition a lack of reproducibility in large data sets, together with the variability of the clinical

phenotype have engendered a cautious approach to the interpretation of these findings.

Low-grade mucosal inflammation and immune activation

According to many recent studies, pathogenesis of IBS is believed to be connected with low-grade mucosal inflammation and overactivity of the immune system [1]. Abnormal function of immune responses may be a result of impaired epithelial barrier, dysbiosis and altered stress levels [68–70].

Mucosal inflammation may also be a consequence of past history or history of non-recognized GI infections caused by bacteria, parasites or viruses—this IBS subtype is called PI-IBS (post-infectious IBS) [71]. Consequently, young women with high anxiety, suffering from depression and with history of long initial infection with fever are more prone to PI-IBS [72]. Investigations of biopsies of mucosa from PI-IBS patients revealed an increased number of immune cells such as mast cells (especially near enteric nerve fibers in gut mucosa of IBS patients) and lymphocytes, and elevated cytokine production in peripheral blood mononuclear cells (PBMCs) and intestinal mucosa [60, 73]. A study from 2016 shows that 25% patients with *Clostridium difficile* gastroenteritis developed IBS 6 months or more after infection [74]. What is more, the microbiota of PI-IBS patients differed significantly from other IBS subtypes and healthy controls, and also a correlation between large number of CD8, CD4RA+ cells and depressive mood was observed [75]. Apart from that, in some patients with dysbiosis some studies showed increased levels of C-reactive protein, IL-6, and IL-8 (inflammatory mediators and cytokines) and higher expression of TLR-4 and TLR-5 (which recognize bacterial structures) [76, 77].

Apart from that, many patients with IBS symptoms suffer from innate inflammatory diseases such as celiac disease, inflammatory bowel disease or severe acute gastroenteritis [78, 79]. This may be a proof for a connection between abnormal activity of the immune system and IBS development, however the exact pathophysiological explanation for this relationship is still not clear enough. A possible one is that gut permeability is changed due to inflammatory response that causes infiltration of immune cells which promote local edema and produce large amounts of cytokines [80].

Currently, only a few cytokines are accurately identified to have a possible relationship with IBS. According to a study from 2007 elevated proinflammatory cytokines in PBMCs of IBS-D patients are IL-6, TNF-alfa and IL-1beta, all of which are also highly linked with depression and anxiety, suggesting the role of gut in proper brain functioning [14]. Another study emphasized the association of IL-17 and TNF-alfa with IBS symptoms and quality of life in different subtypes of IBS [81]. Yet another abnormality in patients with IBS is a decreased level of beta-endorphin from PBMCs with consequence of their reduced inhibitory effects in comparison to IBS negative controls [74].

The role of diet in IBS

Dietary influence cannot be omitted in understanding the pathophysiology of IBS. Food and its components can affect proper bowel functioning in terms of gut motility and permeability, GI immune system, microbiota and the gut-brain axis [82].

Some products are more prone to cause or exacerbate IBS symptoms—especially these rich in fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) such as legumes, vegetables, fatty foods, artificial sweeteners, stone fruits and lactose-containing foods [83]. Gut microbiota is responsible for FODMAPs breakdown to gases (methane and hydrogen) [84]. According to investigations weak absorption of these gases is believed to cause bloating symptoms and abdominal discomfort in about 70% of IBS patients [85, 86]. What is more, FODMAPs due to increasing osmotic pressure may be responsible for GI distension and alternation in gut motility [1]. They also have impact on the GI endocrine cells which adjust GI motility and processes of secretion and absorption due to 5HT release [87].

Gluten is another diet component which is believed to cause changes in the gut physiology. Investigations revealed that consuming products with gluten caused symptoms such as abdominal pain in IBS patients diagnosed negatively for celiac disease. This condition is called “non-celiac gluten sensitivity” (NCGS) and may be the reason for IBS-like symptoms development [88]. Another proof of association between gluten and IBS symptoms was provided by the study in which mucosal permeability occurred to be elevated in IBS-D patients on gluten containing diet, contrary to a part of group on gluten-free diet [89].

Although diet clearly seems to be connected with IBS symptoms genesis, it may also be used for managing IBS, for example through low-FODMAP content. These aspects will be discussed specifically in further chapters.

Conclusions

All things considered, it seems clear that IBS is a condition connected with many factors such as genetic predisposition, stress, anxiety, food intolerance, changes in gut-brain axis and GI impairments which overall make it a heterogenous disorder. Pathogenesis also involves alternation in gut microbiota (dysbiosis), changes in gut motility and permeability, low-grade mucosal inflammation and immune activation. Highlighting a specific factor as a main and leading aspect in IBS pathophysiology is troublesome and questionable. Moreover, mentioned factors require further investigation in order to provide more useful information on the origin of IBS and to identify potential triggers of the disease, so that specific treatment could be designed and used to help patients dealing with this disorder.

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