IBS and IBD

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Contributor: Marcin Włodarczyk

Irritable bowel syndrome (IBS) is a functional heterogenous disease with a multifactorial pathogenesis. It is characterized by abdominal pain, discomfort, and alteration in gut motility. The occurrence of similar symptoms was observed in patients in clinical remission of inflammatory bowel diseases (IBD) that is Crohn's disease (CD) and ulcerative colitis (UC), which pathogenesis is also not fully understood.

IBS and IBD seem to be quite separate entities, but still, they do share some similarities. First, their symptoms overlap to some extent: They both may include abdominal pain, bloating, diarrhea, and watery stools, which can make it difficult to distinguish between these disorders. However, pain in IBS results from tension in the intestinal wall and can be relieved by defecation, while in IBD, it is more constant, and it may result from inflammatory cytokines impacting on afferent nerve firing. Moreover, in the case of IBD, there are so-called "alarm symptoms", such as fever, weight and appetite loss, bloody stool, vomiting, or anemia, which are absent in IBS. Second, despite the fact that extracolonic symptoms may appear in the course of both diseases, in IBS, they are more general and include, for example, nausea or dyspepsia, while they seem to be more serious and disabling in IBD—they may affect joints, eyes, skin or liver. Furthermore, the epidemiology is slightly different—IBS may occur at any age and is seen more often in women, while IBD appear mainly in young adults between 15 and 30 years old and remain gender-neutral—as mentioned earlier. Phenotypic differences are also clear—in IBS, visibly normal mucosa is observed. On the contrary, in IBD, inflammation, ulcerations, fibrosis, and structuring can be seen during colonoscopy with the naked eye. The pathogenesis of IBS and IBD is not completely understood; however, it is believed to be multifactorial. In both cases, it may include not only environmental and psychological factors (such as stress, depression, negative life events) but also genetic factors, enduring submucosal inflammation, and other changes involving the gut–brain axis and alteration in gut microbiota.

irritable bowel syndrome | inflammatory bowel diseases | overlapping symptoms

1. Immune System Activation and Increased Permeability

The immune system plays a crucial role in the pathophysiology of IBS and IBD, regardless of the triggering factors [1]. In IBS, the recruitment of immune cells, for example, mast cells (the most common histological finding, responsible for the release of histamine, proteases, and chemokines) and lymphocytes, is observed. That also promotes local edema and increased levels of cytokines, such as IL-6, TNF, IL-1-β, which are currently identified to have a possible relationship with IBS and are also highly linked with depression and anxiety, suggesting the role of the gut in proper brain functioning [2][3][3]. Higher serum levels of IL-6, IL-8, and TNF-α revealed in IBS suggest a role of systemic inflammation in this disorder [4][5]. Moreover, low-grade inflammation reported in IBS can stimulate visceral nerves and induce dysmotility—the most typical symptom of IBS [6]. Interestingly, postinfectious IBS (PI-

IBS, a subtype which is a consequence of past history or history of non-recognized bacterial, viral, or parasite GI infections) is believed to be associated with inflammation and mucosal damage rather than sporadic IBS, and according to Sadeghi et al., its characteristic features are increased macrophages, T lymphocytes, and serum IL-6 [7]. On the other hand, IBD also involves the recruitment of immune cells—mainly lymphocytes, which also release proinflammatory cytokines, such as TNF, IL-23, IL-17A, and IFN-γ [8]. Moreover, the inflammatory environment in IBD promotes the recruitment of monocytes in the immature proinflammatory state, which are believed to intensify chronic inflammation in the gut [9][10]. The best-known immune pathway connected with IBD is the nuclear factor kappa-light-chain enhancer of activated B cells (NF-κB) [11]. It is responsible for hyper-activation in epithelial or immune cells in IBD patients and increased production of other cytokines: IL-6, IL-12, IL-23, IL-1-β, and TNF-α [11][12]. What is more, a study by Langer et al. revealed that the inhibition of IFN-γ (another upregulated cytokine linked with immune modulation in IBD) alleviates experimentally induced colitis in IFN-γ knockout mice [13]. Of note, IL-6 and IL-8, which are elevated in IBD, have also been reported to be increased in IBS, as mentioned above [14][15]. What is more, calprotectin and human beta-defensin 2 (markers of innate immunity activation) can fluctuate in both IBS and IBD: Calprotectin, used mainly for detecting IBD, can also be marginally elevated in IBS patients, and human beta-defensin 2 may be increased even equally to the levels seen in active UC [16][17]. In consequence, despite the fact that each disease engages different elements of the immune system, they share a common consequence—mucosal immune activation and increased intestinal barrier permeability, which may underlie the pathogenesis of both entities [1]. A study by Vivinus-Nebot M. et al. [18] revealed that mucosal permeability in IBD patients with IBS-like symptoms is clearly elevated in comparison to healthy controls and IBD patients without IBS manifestations. Moreover, this abnormality can open the way for other factors to influence the gut, such as bacterial and food antigens [19].

2. Alteration in Gut Microbiota

The intestinal microbiota are responsible for gut development, digestion, metabolism, proper development of the humoral and cellular mucosal immune system, and protection against pathogens [20][21]. Any changes in bacterial number and composition may result in dysregulation between host and microbes known as dysbiosis, which may be triggered by pathogens, inflammatory mediators, or any initiators that can provoke a reaction of the immune system (such as diet, medical treatment, gut transit, redox potential in the gut lumen) [22] and lead to the inappropriate functioning of microbiota [1]. Several studies confirm gut dysbiosis in both IBS and IBS, which may be secondary due to mentioned triggers or may primarily contribute to IBD symptoms themselves [19][22]. However, the results reported are somewhat ambiguous. There is a consensus, based on a meta-analysis of CD-positive patients, that Bacteroidetes and Enterobacteriaceae are highly increased, while Firmicutes are decreased in these patients in comparison to healthy controls [23]. On the other hand, growth of Bacteroidetes was also observed in PI-IBS [24]. At the same time, according to another study [25], the microbiota of patients with CD differ noticeably from IBS patients, especially in the number of Faecalibacterium prausnitzii (F, frequently decreased in CD) and mucosa-associated Escherichia coli (E, often increased in this condition). This study revealed that CD can be distinguished from UC and IBS by a decreased F:E ratio. What is more, according to Porter et al., intercurrent infectious gastroenteritis (IGE, foodborne illnesses caused mainly by Salmonella spp., Campylobacter spp., and others) may

increase IBD risk in IBS patients, suggesting the existence of a complex interaction between these disorders [26]. Interestingly, there are some data about the role of gut microbiota in the regulation and modulation of the immune system in IBD. For example, according to Grainger et al., microbiota are needed for the production of IL-10, which downregulates IFN-γ responses, and according to Longman et al., for proper intestinal barrier repair through innate production of IL-22 [27][28]. Moreover, one study in mice showed that T-reg cells (which are decreased in IBD) contribute to gut homeostasis and are induced by the microbiota [29]. In general, all these features underline the complex relationship between IBS, IBD, microbiota, and the immune system and the necessity for further investigations in this area.

3. Genetic Factors

Recently, investigations on genetic predispositions to IBS and IBD gained more and more interest because of strong evidence that both diseases aggregate in families. One study [30] showed lower concordance of IBS in dizygotic twins and higher in monozygotic twins, suggesting the role of genetics. Another meta-analysis revealed that serotonin transporters (SERT) insertion/deletion was associated with IBS in Asians and Caucasians but only for those with IBS-C [31]. Apart from this, mutations in an ion channel gene TRPM8 and sucraseisomaltase or single nucleotide polymorphisms were found to also play a role in IBS pathogenesis, but this issue needs further research [32][33][34]. Simultaneously, the number of loci responsible for IBD vulnerability continually increases—NOD2, IRGM, ATG16L, and IL23R genes (responsible for detection and response to gut bacteria) can be an example [19].

Of note, there is a possible genetic link between IBS and IBD, i.e., polymorphisms in the TNFSF15 gene (a member of the TNF family, in charge of interferon production)—a risk factor of CD in Europeans and Asians also found in IBS [35][36][37][38]. This can support the theory that excessive immune stimulation plays a role in both IBS and IBD pathogenesis [19]. However, the same study indicated no association between TNFSF15 and 30 other IBD genes, suggesting that IBD occurrence requires other less common factors that are not required for IBS [36].

Summarizing, genetics is highly believed to be linked with the genesis of both entities, and the results of performed investigations are promising. However, there is a long way to the discovery of genes specific for these disorders, mostly due to the small sizes of the samples, lack of reproducibility in large data sets, and variability of the clinical phenotype, which makes many studies easily underpowered [1][19].

4. Gut–Brain Axis

The gut–brain axis is a bidirectional communication system linking the central nervous system (CNS) and the enteric nervous system (ENS) in the intestinal wall, which allows proper GI function (food intake, digestion, adequate bowel movements) [8][39]. Dysregulation of this system due to psychological stressors and emotional responses is believed to be one of the main causes of GI disorders, including IBS [40]. One study [41] proved that 72% of IBS patients had elevated anxiety, 36% depression, and 66% somatization levels. What is more, some studies revealed that anxiety can predict IBS development—this can be proof for its etiological role [42][43].

Experimentally induced anxiety via maternal deprivation or crowding stress in rats may lead to visceral hypersensitivity, increased mast cell count, and gut permeability, which are known as features of IBS [44][45]. Less evidence has been gathered on the role of the gut–brain axis in IBD pathogenesis. However, there are data pointing out that long-lasting stress increases the probability of a relapse in UC [46][47]. Apart from that, animal models of acute stress and anxious phenotype (induced by water avoidance or maternal deprivation) had highly activated innate immunity (also seen in human studies with stressors like academic exams) and reported exacerbation of spontaneous colitis, especially in genetically predisposed mice with IL-2-knockout [48][49][50]. The last one appeared to be connected with mast cells, mainly associated with IBS [19].

As mentioned earlier, psychological factors are considered to be involved in the pathogenesis of both disorders, but it seems that they are more crucial in IBS than in IBD [51]. IBS patients seem to be characterized by higher psychological distress and illness anxiety than patients with IBD, but IBS and active IBD patients have the same anxiety and depression levels. Nevertheless, an important role seems to be played by symptoms activity: Patients with IBS and IBD show little differences in psychological distress or psychological risk factors.

Psychotherapy and behavioral therapy are a part of IBS management as they have a confirmed beneficial effect on unpleasant symptoms. On the contrary, there are limited attempts of psychological interventions in IBD, but so far, they do not show signs of improvement in colitis itself, although they improve the quality of life in both CD and UC [52].

The autonomic nervous system (ANS, consisting of the parasympathetic, sympathetic, and enteric nervous system) also participates in intestinal function control, and its dysregulation is increasingly believed to play a role in initiating and perpetuating IBD; hence its neurons terminate in the gut wall, including the muscularis, mucosal epithelium, enteroendocrine cells, and can be sensitive to chemical mediators of inflammation [53]. Moreover, inflammatory signals from IBD intestinal mucosa can influence peripheral neuronal signaling, resulting in peripheral sensitization with the response of proinflammatory cells. Generally speaking, changes in ANS ganglia and nerve cell bodies' morphology, with modified expression of neurotransmitters, may be responsible for altered communication between ANS and effector intestine cells. ANS imbalance may also play a part in the pathogenesis of IBS, but available data are not clear cut. The results of the ANS investigations vary between the studies and suggest that depending on the IBS subtype parasympathetic/sympathetic, tone, and outflow can be increased or decreased [54]. No morphological changes have been found so far. However, one study [55] confirms that the presence of chronic low-grade inflammation in IBS may influence and change vagal reflexes. Moreover, in another study [56], IBS patients had increased heart rate, which may be an indirect proof for cardiac sympathovagal imbalance. Nevertheless, the role of ANS in IBS pathogenesis requires better study. Changes in ENS will be discussed below.

5. Changes in Enteric Nerves

As mentioned earlier, some changes in ENS have been reported in both IBS and IBD. Analysis involving IBS showed that TRPV-1-immunoreactive fibers and mast cells were related to a higher abdominal pain score,

suggesting their role in visceral hypersensitivity [57]. Whereas, regarding IBD, there are interesting data in this area, especially from the patients suffering from UC. One study showed [58][59] that the more severe UC is, the more substance-P-positive nerves are found in colonic biopsy samples. Increases were also found in nerves co-expressing substance P and TRPV1 nerves with a decrease in somatostatic nerves. As far as TRPV1 nerves are concerned, a research by Akbar A. et al. [60] revealed a strong correlation between the number of TRPV1-positive fibers and pain, suggesting its pain-mediating role. The occurrence of such changes in both IBS and IBD may be proof for common pathways in the pathophysiology of these conditions and, further, a future direction for common pain treatment [19].

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