REVIEW

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AGATA MULAK, EWA WASZCZUK, LESZEK PARADOWSKI

Irritable Bowel Syndrome as an Interdisciplinary Clinical Problem

Cierpienie spastyczne jelita grubego jako interdyscyplinarny problem kliniczny

Department of Gastroenterology and Hepatology, Silesian Piasts University of Medicine in Wrocław, Poland

Abstract

Patients with irritable bowel syndrome (IBS) report a wide spectrum of non-gastrointestinal symptoms that require consulting physicians of numerous specialties, which has important impact on increased healthcare costs for IBS. Comorbidity in IBS is related to enhanced medical help, more severe IBS symptoms, higher rates of anxiety and depression, and a greater negative impact on quality of life. Of the broad variety of extra-intestinal comorbidities, fibromyalgia, chronic fatigue syndrome, chronic pelvic pain, and temporomandibular joint disorder are the best documented and appear in up to 65% of patients. Based on the many common features concerning the epidemiology and pathophysiology of IBS and its comorbid disorders as well as their similar response to treatment, the concept of central sensitivity syndromes (CSSs) has been proposed. CSS members share common features, such as chronic pain and/or fatigue, sleep disturbances, absence of structural abnormalities, neuroendocrine dysregulation, especially involving serotonergic transmission and the hypothalamic-pituitary-adrenal axis disturbances, predominance in women, and familial clustering. Excess comorbidity in IBS may also result to some extent from the somatization frequently reported in these patients. The key presenting symptom and the medical specialty to which the patients are refereed seem to determine the final diagnoses strongly. A interdisciplinary approach to IBS is critical to improving the care of these patients. Treatment should be targeted at mechanisms that apply across various disorders, such as impaired stress responsiveness and pain modulation at the central nervous system level, including both pharmacological (antidepressants and CRF_1 receptor antagonists) and non-pharmacological (cognitive behavioral therapy) approaches (**Adv Clin Exp Med 2008, 17, 6, 667–675**).

Key words: irritable bowel syndrome, comorbidity, brain-gut axis, somatization.

Streszczenie

U chorych z cierpieniem spastycznym jelita grubego (IBS) występuje wiele różnych dolegliwości spoza przewodu pokarmowego, które są powodem licznych konsultacji specjalistycznych i znacznie zwiększają koszty opieki zdrowotnej tych pacjentów. Obecność chorób współistniejących istotnie wpływa na poszukiwanie pomocy lekarskiej, nasilenie dolegliwości IBS jest związane z częstszym występowaniem zaburzeń lękowych i depresyjnych oraz pogarsza jakość życia chorych. Spośród wielu chorób towarzyszących, najlepiej jest udokumentowany związek IBS z fibromialgią, zespołem przewlekłego zmęczenia, przewlekłym bólem miednicy mniejszej i dysfunkcją stawu skroniowo-żuchwowego, które mogą występować nawet u 65% pacjentów. Uwzględniając wiele wspólnych cech epidemiologicznych i patofizjologicznych oraz podobną odpowiedź na leczenie w przypadku IBS i chorób współistniejących, stworzono koncepcję „zespołów ośrodkowej sensytyzacji". Zaburzenia zaliczane do tych zespołów charakteryzują się wieloma wspólnymi cechami, takimi jak: występowanie bólu i/lub zmęczenia, zaburzenia snu, brak zmian strukturalnych, zaburzenia neuroendokrynne, w szczególności dotyczące przekaźnictwa serotonergicznego i dysregulacji osi podwzgórzowo-przysadkowo-nadnerczowej, częstsze występowanie u kobiet oraz występowanie rodzinne. Występowanie licznych chorób towarzyszących w przebiegu IBS może także wynikać z somatyzacji często stwierdzanej u tych chorych. Ostateczne rozpoznanie w dużej mierze zależy od charakteru najbardziej nasilonych dolegliwości oraz rodzaju specjalisty, do którego pacjent zwróci się po pomoc. Interdyscyplinarne podejście do problemu IBS warunkuje poprawę opieki nad tymi chorymi. Leczenie powinno uwzględniać podstawowe mechanizmy całego zespołu zaburzeń, takie jak: nieprawidłowa odpowiedź na stres i modulacja bólu na poziomie ośrodkowego układu nerwowego. Dotyczy to zarówno farmakologicznego, jak i niefarmakologicznego postępowania terapeutycznego (odpowiednio leki przeciwdepresyjne i antagoniści receptora CRF_1 lub techniki poznawczo-behawioralne) (**Adv Clin Exp Med 2008, 17, 6, 667–675**).

Słowa kluczowe: zespół jelita nadwrażliwego, choroby współistniejące, oś mózgowo-jelitowa, somatyzacja.

Patients with irritable bowel syndrome (IBS) make two to three times as many visits to consult physicians of various specialties [1]. Levy et al. [2] reported that 78% of the excess visits were for non-gastrointestinal somatic complaints. This has important economic impact on the healthcare system, as 66% of the excess cost for IBS patients are for non-gastrointestinal indications [2]. Patients with one or more comorbid somatic disorders report more sever IBS symptoms, more anxiety and depression, greater impairment in quality of life, and more illness-related absenteeism from work than IBS patients without comorbid disorders. IBS patients very frequently report a wide spectrum of various extraintestinal symptoms, such as headache (23–53% of patients), back pain (28–81%), urinary symptoms (11–61%), fatigue (36–63%), sexual dysfunctions (9–42%), poor sleep (30–50%), and anxiety and depressive disorders (46–60%) [3–4]. There are four specific somatic conditions that seem to be strongly associated with IBS and which share some clinical features: (1) fibromyalgia, occurring in approximately 33% of IBS patients compared with 2% of the general population, (2) chronic pelvic pain, affecting on average 50% of IBS patients, (3) chronic fatigue syndrome, affecting approximately 51% of IBS patients, and (4) temporomandibular joint disorder, which might be present in up to 64% of IBS patients [1]. The wide spectrum of comorbid non-gastrointestinal symptoms causes IBS patients to engage many specialties, such as rheumatology, gynecology, urology, surgery, orthopedics, infectious diseases, allergology, neurology, psychiatry, and stomatology. There is a growing and converging interest across a variety of medical specialties in understanding the development and treatment of patients with multiple chronic symptoms [5].

Functional Somatic Syndrome: One or Many?

The symptom complex in IBS patients is heterogeneous. With a wide spectrum of complaints, the final diagnoses these patients receive are somewhat arbitrary and depend largely on the key presenting symptom and the medical specialty to which the patients are referred. Patients with IBS could be alternatively diagnosed as having fibromyalgia or chronic abdominal pain if the person had sought medical care from a rheumatologist or gynecologist instead of a gastroenterologist. Of the gastrointestinal disorders which overlap with numerous syndromes of different specialties, IBS is the most extensively reported. Moreover, IBS frequently overlaps with functional dyspepsia. In fact, each medical specialty seems to have a specific functional syndrome; for the rheumatologist this is fibromyalgia with prominent muscle pain and tenderness, for the gastroenterologist this is IBS with abdominal pain associated with altered bowel habit, and for infectious-disease specialists this is chronic fatigue syndrome with muscle pain and neurological symptoms.

When the physician can find no objective changes to explain the patient's subjective experience, the symptoms are then frequently referred to as "functional". The differentiation of specific functional syndromes reflects the tendency of specialists to focus on only those symptoms pertinent to their specialty rather than any real differences between patients. Wessely et al. [6] proposed a "one syndrome" hypothesis that suggested all the functional syndromes were in essence part of the same disorder and that the use of multiple diagnostic entities was an artifact of subspecialty medicine. This is in accordance with the concept of central sensitivity syndromes (CSSs) proposed by Dr Muhammad Yunus [7]. He first observed that IBS symptoms and headaches were significantly more common in fibromyalgia syndrome than in normal controls. According to Yunus, these syndromes and several others belong under a common umbrella with overlapping clinical features that as a group were initially called "dysregulation spectrum syndrome" (DSS). In view of current research showing that the central nervous system (CNS), including the spinal cord, is sensitized to pain and other stimuli in these syndromes, Dr Yunus has now collectively named them "central sensitivity syndromes", proposing a new paradigm and group nosology for fibromyalgia and overlapping conditions [7].

CNS sensitivity, either intrinsic or due to CNS neuroplasticity secondary to peripheral stimuli, results in amplified, widespread, and persistent pain. This central sensitivity seems to be the most important aberration among the neuroendocrine dysfunctions. Current research suggests that central sensitivity is present among the CSS members and is likely to be the common biopathophysiological feature that binds them [7]. Members of the central sensitivity syndromes (see Table 1) share common features, such as chronic pain and/or fatigue, sleep disturbances, a high degree of overlapping conditions belonging to CSSs compared with the general population, absence of structural abnormalities, neuroendocrine dysregulation, predominance in women, and familial clustering. There are many common abnormalities believed to be crucial pathophysiological mechanisms observed in IBS, fibromyalgia, and other overlapping conditions belonging to CSSs. The two main

Table 1. Chronic pain syndromes and comorbid functional disorders [7]

Tabela 1. Przewlekłe zespoły bólowe i współistniejące zaburzenia czynnościowe [7]

- Fibromyalgia Syndrome (FMS)
- Chronic Fatigue Syndrome (CFS)
- Myofascial Pain Syndrome (MPS)
- Irritable Bowel Syndrome (IBS)
- Migraine Headaches
- Tension Headaches
- Temporomandibular Joint Disorder (TMD)
- Restless Leg Syndrome (RLS)
- Periodic Limb Movement (PLMS)
- Multiple Chemical Sensitivity Syndrome (MCSS)
- Irritable Bladder
- Primary Dysmenorrhea

disturbances include alterations in serotonergic transmission and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, which is referred to as the body's stress response system. Abnormalities in the levels of various other neurotransmitters (besides serotonin) have also been reported, such as norepinephrine and endocannabinoid deficiency, abnormal dopamine, and increased substance P in the spinal fluid [7, 8]. Sustained activation of the immune system after infection, stress, or other psychological factors also seem to be important [9]. Autonomic nervous system dysregulation and a sensitized CNS as confirmed by neurological tests characterize the conditions comprised in CSSs [8, 9].

Specific Comorbid Somatic Conditions

Fibromyalgia

Fibromyalgia is a complex syndrome characterized by widespread musculoskeletal pain present for at least three months accompanied by multiple areas of tender points (at least 11 of 18 specific anatomical locations) [10]. Secondary diagnostic criteria used in the classification of fibromyalgia are chronic fatigue syndrome, IBS, sleep disturbances, headache, paresthesia, Raynaud's-like symptoms, depression, and anxiety. It affects an estimated 2% of the general population [11]. Fibromyalgia, the most frequently investigated IBS comorbidity, occurs in approximately 32.5% (range: 28–65%) of IBS patients, whereas IBS occurs in an estimated 48% (range: 32–77%) of patients with fibromyalgia [1]. Like in IBS, there is a female predominance of patients with fibromyalgia, and the peak age is 30–50 years [4]. Fibromyalgia, as IBS and other chronic comorbid disorders, is characterized by an increase in symptoms associated with stress. Fibromyalgia can be precipitated by a flu-like viral illness, physical or emotional trauma, and medication, in particular steroid withdrawal. Characteristic alterations in the pattern of sleep and changes in neuroendocrine transmitters such as serotonin, substance P, growth hormone, and cortisol suggest that dysregulation of the autonomic and neuroendocrine system appears to be the basis of the syndrome [12]. While the cause of fibromyalgia remains elusive, substantial findings implicate disturbances in the neuroendocrine axis as central to its etiology. This is particularly true regarding the relationship between the neuroendocrine axis and sleep. The sleep electroencephalograms of patients with fibromyalgia indicate disturbance of the non-REM sleep phase by intrusions of alpha waves with infrequent progression to stage 3 and stage 4 sleep [13]. Moreover, it has been shown that sleep deprivation in healthy volunteers may induce fibromyalgia syndrome, including the development of tender points [14].

Regarding neuroimmunological changes in the course of fibromyalgia, chronic widespread pain is reported to be associated with a lack of anti-inflammatory and analgesic Th_2 cytokine activity (lower serum levels of IL-4 and IL-10) [15]. Other endocrinological and neurological findings in patients with fibromyalgia include elevation of cerebrospinal fluid substance P levels (a neurotransmitter associated with enhanced pain perception) to three times the normal levels and alteration in the HPA axis with low overall production of cortisol [16, 17]. This contrasts with the findings in depression, where a higher-than-normal cortisol level is found. However, over half of patients with fibromyalgia meet criteria for major depression and 44% have a history of depression [18]. Hyperalgesia is present in patients with IBS and in those with fibromyalgia. However, IBS patients demonstrate reduced thresholds for visceral stimuli, whereas fibromyalgia is associated with reduced thresholds for somatic stimuli [1, 4]. Both IBS and fibromyalgia have been associated with an abnormal lactose hydrogene test, suggesting the presence of small intestinal bacterial overgrowth and a link between bacteria in the gut and hyperalgesia [19].

Recently published results of functional brain imaging studies revealing enhanced pain-related activation, similar to the changes observed in IBS, corroborate patients' reports of increased pain [8]. The frequent comorbidity of fibromyalgia with stress-related disorders, such as chronic fatigue syndrome, posttraumatic stress disorder, IBS, and depression, as well as the similarity of many CNS

abnormalities suggest at least a partial common substrate for these disorders. Tricyclic antidepressants such as amitriptyline have been proved to be effective in improving both clinical symptoms and the tender points in fibromyalgia. Based on recently published results of a functional magnetic resonance study preformed in IBS patients during painful rectal distension, amitriptyline is likely to work at the central nervous system level as it reduces brain activation during pain in the anterior cingulated cortex and parietal association cortex [20].

Chronic Fatigue Syndrome

Chronic fatigue syndrome (CFS) is defined as persistent or prolonged fatigue for more than six months causing more than 15% impairment with no medical or psychiatric conditions that account for the symptoms [21]. In addition to fatigue, the International Chronic Fatigue Syndrome Study Group identified eight primary symptoms as minor criteria, i.e. loss of memory or concentration, sore throat, painful and mildly enlarged lymph nodes in neck or armpits, unexplained muscle soreness, pain that moves from one joint to another without swelling or redness, headache of a new type, pattern, or severity, sleep disturbance, and extreme exhaustion after normal exercise. Four of the eight minor criteria must be fulfilled to confirm a diagnosis of CFS. Many CFS patients report additional symptoms that include abdominal pain (often as a symptom of coexisting IBS), chest pain, bloating, diarrhea, dizziness, dry eyes and mouth, irregular heartbeat, jaw pain, morning stiffness, nausea, night sweats, depression, anxiety, and panic attacks. The prevalence of CFS in the general population has been estimated as 0.4%. The presence of IBS in CFS patients ranges from 35–92% (median: 51%), and one study on the prevalence of CFS in IBS patients found that 14% reported a CFS diagnosis [1].

Like IBS, CFS primarily affects middle-class white women between 20 and 50 years of age. The majority of cases start suddenly, triggered by a flu-like virus, a severe infection, another illness, or a period of great physical or emotional stress, which may resemble the pathogenesis of post-infectious IBS. There is a growing body of evidence suggesting an up-regulated gut immune function in patients with IBS, particularly with post-infectious IBS [9]. Inflammation seems to be strongly modulated by stress. The presence of significant life stressors occurring around the time of infection is reported to be one of the risk factors for the development of post-infectious syndromes. A pivotal interaction of the bidirectional communication between the immune and neuroendocrine systems takes place through the HPA axis. In IBS patients, stress may trigger neuroimmune reactions via the brain-gut axis [9].

The etiology of CFS is unknown, but according to some plausible hypotheses, CFS might be described as a constellation of multisystem dysfunctions primarily involving the neurological, endocrine, and immune systems. The possible pathogenic role of viral infection, such as Epstein-Barr or human herpes viruses, has been discussed because antibody titers to EBV, HHV-6, and HHV-7 were found to be higher in the serum of CFS patients than in controls. Reactivation of an HHV-6 infection could be associated with the clinical manifestation of CFS, especially as this virus demonstrates tropism for CD4+ lymphocytes and macrophages, natural killer cells, and glial cells [22]. The immunological abnormalities observed in CFS, as well as in IBS, include cell-mediated immunity disorders and humoral response alterations connected with cytokine over-production, in particular of IL-1 and IL-6 [23].

Recent advances in understanding the pathophysiology of chronic fatigue syndrome continue to demonstrate the involvement of the CNS. A hyperserotonergic state and hypoactivity of the HPA axis constitute other findings, but the question of whether these alterations are a cause or a consequence of CFS remains unanswered. Alterations in serotonin signaling can lead to physiological and behavioral changes.

Chronic Pelvic Pain

Chronic pelvic pain (CPP) is defined as non-menstrual pain lasting six months or more that is severe enough to cause functional disability or require medical or surgical treatment [24]. The source of pain in CPP can be gynecological, urological, gastrointestinal, musculoskeletal, or psychoneurological. More than one cause of pain can be found in the same patient. Four conditions account for most CPP cases: endometriosis, adhesions, interstitial cystitis, and IBS. The management involves treating the underlying condition, the pain itself, or both. A multidisciplinary approach to treatment addressing environmental factors and incorporating physiotherapy and psychotherapy works best. Chronic pelvic pain affects 12–25% of women at any point in time and 33–39% of women during their lifetime [25]. Women with CCP use three times as much medication of any type, have four times more non-gynecological operations, are five times more likely to have a hysterectomy, and have reduced quality of life compared with women without CPP [26].

Among patients with IBS, the rates of abdominal and pelvic surgery are also significantly higher than in controls [26]. For a gastroenterologist, abdominal pain with altered bowel habit is IBS, whereas for a gynecologist the same symptom cluster is labeled CPP. This may raise the question whether IBS and CCP are two separated disease entities with mutually high comorbidity or whether they are the same syndrome with different subgroups which utilize the healthcare system in specific ways [27]. Almost half of the patients who underwent laparoscopy because of CPP and 40% of patients who had an elective hysterectomy had symptoms compatible with a diagnosis of IBS [28]. IBS is a common comorbid condition affecting 29–79% of women with CPP [1, 4, 12]. As was shown in a retrospective study by Williams et al. [25] conducted in a tertiary pelvic pain clinic (987 women included), most gynecologists were unaware of the bowel symptoms so they could not establish the diagnosis and introduce the proper treatment. IBS treatment was not recommended to 67% of the patients with IBS [25]. However, treatment of IBS may reduce the overall abdominal pain of these patients; therefore there is a clear need for greater collaboration among specialists in the fields of gynecology and gastroenterology. Walker et al. [29] found that 35% of IBS patients demonstrated CPP complaints as well. This group showed a significantly higher rate of active disorder, anxiety, somatization disorder, sexual abuse in early childhood, and a history of hysterectomy than patients with IBS symptoms alone.

Dysuria

IBS patients frequently report urinary symptoms such as nocturia, increased frequency or urgency of micturition, and feeling of incomplete bladder emptying [3, 4]. These symptoms are present in up to 50% of IBS patients, independent of psychiatric comorbidities [12]. Conversely, the prevalence of IBS symptoms in patients attending urological clinics is about 30%, significantly higher than in patients attending dermatological or ENT (ear, nose, and throat) clinics [4]. Urodynamic studies in a group of 30 IBS patients demonstrated bladder dysfunction in 50% of them compared with 13% in a control group [3]. Detrusor instability was found in 10 out of 30 patients compared with only one in controls [3]. These findings could support the concept of IBS as part of a generalized disorder of smooth muscles. By analogy, a common underlying disorder of smooth muscles in the bronchial system and in the gastrointestinal tract are discussed, as concomitant occurrence of bronchial hyperreactivity in IBS patients was reported in one uncontrolled trial [12].

Another significant overlap is observed between IBS and interstitial cystitis. Interstitial cystitis (IC) is a chronic heterogeneous syndrome characterized by chronic dysuric complaints such as nocturia, increased frequency of urination, and bladder pain lacking an established etiological or pathogenic model of explanation [12]. Like IBS, IC predominantly affects female patients (90%) and shows significant comorbidity with psychological disorders. About 30–40% of patients with IC report IBS symptoms. Interestingly, by analogy to IBS, an increased number of mast cells have been found in bladder biopsies in IC [30]. Mast cells have been implicated in IBS, IC, and other pain disorders as they can release chemical mediators that may evoke pain by increasing the sensitivity of afferent nerves and increase motor activity.

Recently an animal model of bowel-bladder cross-sensitization was described. Pezzone et al. [31] showed that colorectal distention inhibited urination (colon-to-bladder cross-inhibition) and that colonic motor activity was inhibited during urination (bladder-to-colon cross-inhibition). Acute bladder irritation causes a significant decrease in colorectal sensory thresholds to distention (implying colonic sensitivity as seen in IBS). Likewise, acute colonic irritation led to irritative urination patterns as seen in IC and acute cystitis. Visceral sensitization is thought to occur in the spinal cord via the convergence of both bladder and colon sensory nerves onto spinal interneurons.

Temporomandibular Joint Disorder

Temporomandibular joint disorder (TMD) is characterized by orofacial pain, restricted joint movement, and unpleasant noise in the jaw [32]. Because the disorder transcends the boundaries between several healthcare disciplines, in particular, dentistry, neurology, physical therapy, and psychology, there are a variety of quite different treatment approaches. Temporomandibular joint disorder primarily affects young women. The male-to-female ratio is 1:4. It affects about 21% of the general population, but only 5% seek medical care. Jones et al. [32] found self-reported TMD diagnosis in 16% of 270 IBS patients, whereas Aaron et al. [33] reported that IBS was present in 64% of 25 TMD patients. Although TMD is believed to represent a localized pain syndrome, the relatively high number of tender points suggests that TMD may represent one manifestation of a more global pain sensitivity syndrome. A study by Aaron et al. [35] provided additional evidence that patients with

fibromyalgia, CFS, and TMD share symptoms including generalized pain sensitivity, sleep and concentration difficulties, and bowel complaints. The pathogenesis of TMD remains unclear. The mechanisms of neurogenic inflammation which have been proposed to account for fibromyalgia or multiple chemical sensitivities may occur in TMD as well. For example, a localized injury (e.g. an exogenous agent combined with a chemical irritant) might trigger a sensitization of the CNS to afferent pain signals leading to decreased pain thresholds at other body sites. The onset of the disease is quite often associated with acute or chronic emotionally stressful events which may initiate perturbation in the HPA axis and the autonomic system and result in sensitization of the CNS via neuropeptides, ultimately alternating the processing of nociceptive signals, as has been suggested in other chronic pain disorders.

Migraine Headaches

An association between migraine and functional gastrointestinal disorders has been confirmed by many clinical observations and epidemiological studies. Migraine and IBS often coexist with fibromyalgia and other chronic pain syndromes and functional disorders. In most patients, apart from various neurological and vascular symptoms, gastrointestinal disturbances occur during migraine attacks, including nausea, vomiting, abdominal pain, or diarrhea. Functional gastrointestinal disorders, such as IBS, are reported in patients with migraine between the attacks as well. On the other hand, frequent headaches appear in 23–53% of IBS patients. The presence of headache has been related to the course of abdominal complaints, and headache tends to be associated with a poor outcome of IBS symptoms [4]. Migraine and IBS affect approximately 10–20% of the general population, usually young adults. Both diseases are more prevalent in women; therefore, as in the case of other chronic pain disorders, the role of estrogens in the pathogenesis is discussed. In many female patients, exacerbation of IBS symptoms and migraine headaches correlate with the menstrual cycle. In the search for common pathogenic mechanisms of IBS and migraine, the roles of the brain-gut axis and neuroimmune and neuroendocrine interactions are considered [34]. The influence of stress on symptom occurrence and severity seems to be associated with hyperactivity of the HPA axis. The enteric nervous system, as a source of numerous neurotransmitters and visceral reflexes, is a plausible common pathogenic link between IBS and migraine. In particular, serotonin, the main neurotransmitter of the brain-gut axis, plays a relevant role in the pathogeneses of both IBS and migraine. Serotonin mediates gastrointestinal functions, crucially affects pain perception, influences brain blood vessel dilatation, and, according to the neurovascular theory of migraine, participates in an abnormal inflammatory response in the trigeminovascular system. Agonists and antagonists of serotonergic receptors are now the most efficacious drugs for IBS and migraine therapy [34]. Recently the significance of serotonin transporter gene polymorphism in the pathogeneses of IBS, migraine, and other comorbid disease, including psychiatric disorders, is discussed [35].

Psychiatric Disturbances and IBS

There is a strong overlap between IBS and psychiatric disorders, as from 54% to even 94% of IBS patients meet criteria for at least one primary psychiatric disorder, most notably mood and anxiety disorders [1]. However, it is highly probable that these epidemiological data on comorbidity of IBS and mental disorders are overestimated because most of the studies employ self-reported rating scales that assess only the severity of some psychopathological symptoms, but are not necessarily proper to diagnose a psychiatric disorder itself. A recent study showed a high prevalence of IBS in psychiatric patients who seek treatment, with prevalences of 19% in schizophrenia, 29% in major depression, and 46% in panic disorder, among other disorders [36]. IBS patients with psychiatric diagnoses have significantly more comorbid somatic diagnoses than patients without psychiatric diagnoses [37]. Comorbidity in IBS may also be a consequence of the psychological trait of somatization, which may be defined as a predisposition to experience and report many somatic symptoms that have no pathophysiological explanation, misattribute them to disease, and seek medical attention for them. It is important to distinguish between somatization disorder, which is a psychiatric diagnosis defined by explicit criteria, and the behavioral tendency to report multiple somatic complaints, which is what psychological tests of somatization measure. Comorbid psychiatric disorders and various psychosocial factors do not seem to be directly connected with the occurrence of IBS, but strongly influence how the symptoms are experienced, the individual illness behavior, and ultimately the outcome. When discussing the interdisciplinary character of IBS, it is worth mentioning that IBS appears twice in the current ICD-10 and DSM-IV classifications, as functional gastrointestinal disorder (K58) and somatoform disorder (F45),

respectively. The effective management of IBS requires proper recognition of psychological and psychiatric issues that so often accompany it. Apart from antidepressants, various techniques of psychotherapy or cognitive behavioral therapy are recommended [38].

Hypotheses to Explain Comorbidity in IBS

There are two primary hypotheses. Firstly, comorbidity of IBS with other disorders may be a consequence of shared pathophysiology, i.e. both disorders may have common risk factors or common elements in their etiologies. Secondly, comorbidity in IBS may be a consequence of the psychological trait of somatization, in which case no unique association between IBS and other disorders would be expected [1, 37]. According to the dual-etiology hypothesis there may be a subgroup of subjects among the heterogeneous group of IBS patients whose symptoms result from predominantly biological processes and another subgroup whose IBS symptoms reflect predominantly psychological etiologies [1]. However, these two etiological mechanisms for IBS (biological and psychological) do not act independently of each other. They seem to interact strongly, as described in biopsychosocial models of functional gastrointestinal disorders resulting in the final clinical manifestation of the disease [9]. Regarding the remarkably frequent similarities that can be found between IBS and the most frequent somatic comorbidities (fibromyalgia, CFS, CPP, TMD), a common etiology can be speculated, even though some provocative results have been recently published by Whitehead et al. [37] that IBS does not uniquely overlap with any specific class of disorders, including other "functional" disorders, but has greater comorbidity across all categories of diagnosis, and that excess comorbidity characterizes only a subset of IBS patients. The overall interpretation the authors provide is that the excess comorbidity in IBS is due to hypervigilance in noticing somatic sensations and a lower threshold for consulting a physician [37].

Implications for Treatment

In all of the disorders belonging to the CSSs, symptoms may be aggravated by stress and psychosocial burden and there is an association with enhanced fatigue, sleep disturbances, and psychological comorbidities such as anxiety and depression [12]. All these chronic disorders are associated with central serotonin dysfunction and with hyperactivity of the HPA axis [39]. The female predominance among patients may result from the role of estrogen in modulating serotonergic transmission and the HPA axis. Apart from epidemiological and pathophysiological evidence for linkage among IBS and comorbid disorders, there is also pharmacology that links them. Each disorder in this group has been shown in numerous placebo-controlled and open-label clinical studies to respond to medication affecting central serotonin function [39]. Low-dose amitriptyline seems to be one of the most efficacious treatments in chronic pain syndromes, probably due to its CNS effect. The mechanism of benefit is likely to be through a reduction in the affective component of pain or a reduction in stress-related exacerbation of symptoms [20]. Estrogens may provide an adjunct to treatment with antidepressants for most of these disorders, including depression, fibromyalgia, and migraine, and for perimenopausal women with sexual dysfunction. Other medications that work with serotonergic transmission, such as triptans or serotonin releasers and receptor agonists, also provide pharmacological evidence supporting linkage between the CSSs. The better understanding of the brain-gut axis and neuroimmune interactions within the HPA axis has attracted attention to corticotrophin-releasing factor (CRF) and its receptors as well as to immune modulators [40]. The psychological basis of the disorders support the use of psychotherapy and other psychological treatments.

Therapies should target primarily mechanisms that apply across various disorders, such as stress responsiveness and pain sensitivity. Proper diagnosis, treatment, and outcome depend essentially on the recognition of comorbidity in IBS. This early recognition should prevent unnecessary diagnostic procedures and usually ineffective aggressive treatment aimed at one condition only. A multidisciplinary approach to IBS associated with closer collaboration among various specialties, and at the same time a holistic approach to the individual patient, should result in more effective treatment. Understanding the causes of comorbidity is critical both to improving the care of IBS patients and to reducing the burden on the healthcare system which these patients pose.

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Address for correspondence:

Agata Mulak
Department of Gastroenterology and Hepatology
Silesian Piasts University of Medicine
Borowska 213
50-556 Wrocław
Poland
E-mail: agata.mulak@wp.pl

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