REVIEW

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Neurological Manifestations and Psychiatric Disorders in the Course of Inflammatory Bowel Diseases

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ABSTRACT

Inflammatory bowel diseases (IBD) are characterized by cumbersome symptoms with varying severity. However, regardless of the intensity of disease activity the patients may experience extraintestinal manifestations which further deteriorate the patients' quality of life. According to the literature, nearly half of the patients with IBD will develop at least one extraintestinal manifestation in their lifespan. Apart from the most common and often well-surveilled such as articular, ocular, dermatologic or hepatic entities, the neurological and psychiatric ones are often disregarded or not sought. We reviewed the latest literature on the most frequent disorders occurring in patients with IBD covering these two fields.

Key words: inflammatory bowel disease – Crohn's disease – ulcerative colitis – neurological disorders – psychiatric disorders.

Abbreviations: BD: bipolar disorder; CD: Crohn's disease; CIDP: chronic inflammatory demyelinating polyneuropathy; CNS: central nervous system; CVT: cerebral venous thrombosis; FMT: fecal microbiota transplantation; GI: gastrointestinal; IBD: inflammatory bowel diseases; IFN: interferon; LPS: lipopolysaccharide; MG: myasthenia gravis; MRI: magnetic resonance imaging; MS: multiple sclerosis; PN: peripheral neuropathy; TLR: Toll-like receptor; TNF-α: tumor necrosis factor α; UC: ulcerative colitis; VN: vague nerve.

INTRODUCTION

Inflammatory bowel diseases (IBD) are a group of gastrointestinal (GI) tract diseases of multifactorial etiology consisting mainly of Crohn's disease (CD) and ulcerative colitis (UC). Patients with IBD experience the periods of exacerbations and remissions. Several groups of drugs serve as treatment options in patients with IBD, namely 5-aminosalycilic acid derivates, steroids, immunosuppressive agents and biological therapy. Main symptoms including bloody diarrhea and abdominal pain negatively influence the patients' quality of life. Additionally, extraintestinal manifestations from other organs can appear in the course of disease, such as skin, respiratory tract, musculoskeletal system, ocular system. According to the literature, up to 47% of patients with IBD experience at least one extraintestinal manifestation [1]. While arthritis, uveitis or some skin lesions are often observed in patients with IBD, the neurological and psychiatric events are generally neglected by physicians. Several symptoms covering these areas may precede the occurrence of development of severe debilitation disorders (such as demyelinating diseases) or the relapse of disease. In this review we aimed to collectively describe the most common neurological and psychiatric disorders associated with IBD, explain their pathophysiology and treatment options.

NEUROLOGICAL MANIFESTATIONS

The prevalence of neurologic and neuromuscular manifestations of IBD varies between the studies due to diverse inclusion and definition criteria. In a large retrospective register-based study performed by Lossos et al. [2] neurological involvement is reported in 3% of cases of IBD. In another study 67% of patients with CD and 53% of patients with UC had neurologic disorders [3].

The pathogenesis of neurologic disorders associated with IBD is not fully identified and involves several mechanisms. The most common are immunologic abnormalities, but prothrombotic states, malabsorption and nutritional deficiencies, metabolic agents, iatrogenic complications of medical and surgical treatment of IBD as well as the brain-gut axis interactions were also reported [4].

As every extraintestinal manifestation of IBD does,, the neurologic symptoms in IBD may precede the onset of GI signs, appear concurrently or during the course of disease. Moreover, the presence of neurological signs may exacerbate during the flare or evolve independently from intestinal manifestation without responding to the treatment for the underlying disease [3, 5].

It is crucial to separate immune and nonimmune causes directly related to IBD from other mechanisms, such as secondary drug-induced and other approaches in treatment. Moreover, it has to be noted that there is an IBD-independent group of immune-mediated diseases that can coexist with IBD in greater prevalence than patients without IBD. We focused on the IBD-related neurological pathologies. The summary of pathogenetic factors leading to the development of neurological events is shown in Fig. 1.

Polyneuropathy

Peripheral neuropathy (PN) is one of the most common neurological conditions described in both CD and UC and it occurs in higher incidence in IBD than in the normal population [6, 7]. Several types of polyneuropathies have been described in IBD patients. Studies reported demyelinating or axonal involvement of peripheral nerves, including autonomic neuropathy, sensory polyneuropathy, acute and chronic inflammatory demyelinating polyneuropathy (CIDP), mononeuropathy (such as carpal tunnel syndrome), multifocal neuropathy, cranial neuropathy and plexopathy [5]. Its frequency remains indeterminate and its ranges differ between 0.25% and 35.7% in different studies [2, 8]. In the study carried out in Greece [9], out of 45 patients with IBD two patients presented neurological abnormalities: one patient had a history of acute motor sensory polyneuropathy complicating UC and one patient with mild incidental carpal tunnel syndrome.

The pathophysiology underlying the neuropathy in IBD patients remains uncertain and include immunologic anomalies, drug exposure and nutritional deficiencies. Results obtained by Nemati et al. [10] supported immune-based theory by achieving clinical response in patient with CD treated with intravenous immunoglobulin at the dose of 2 g/kg administered twice daily. The clinical response was defined as a relief of all subjective symptoms in response to treatment. Noteworthy, two hallmarks of IBD pathogenesis: intestinal dysbiosis and loss of mucosal integrity in GI tract were found to be implicated in the neuropathy [11]. Although data on microbial-induced neurological disorder in IBD is lacking, Didesch et al. [12] reported that a 71-year-old man with *Clostridioides difficile* infection who underwent the fecal transplantation developed acute demyelinating sensorimotor polyneuropathy, which supports the theory of cross-reaction of pathogenic anti-gut antibodies against neural surface antigens and the molecular mimicry process. Intestinal homeostasis is characterized by a diverse, stable microbiota. The gut receives regulatory signals from the central nervous system (CNS) and vice versa. The term gut-brain axis thus describes an integrative physiology concept that incorporates all, including afferent and efferent neural, endocrine, nutrient and immunological signals between the CNS and GI system [13]. The core feature of this concept is bi-directional interaction with diverse mechanisms guiding each direction of effects.

Other studies that evaluated the IBD patients with axonal as well as demyelinating polyneuropathy showed clinical response to immunotherapy. While T cells are clearly involved in the pathogenesis of demyelinating neuropathies, the relationship between axonal damage and the immune system remains unclear, although supported by the observed clinical improvement with immunomodulatory therapies [14, 15]. In the study carried out in Brazil [15], immunomodulatory therapy was given to treat 33 patients with IBD-related PN, including 18 patients with CD and 15 patients with UC. Different agents such as intravenous immunoglobulin,

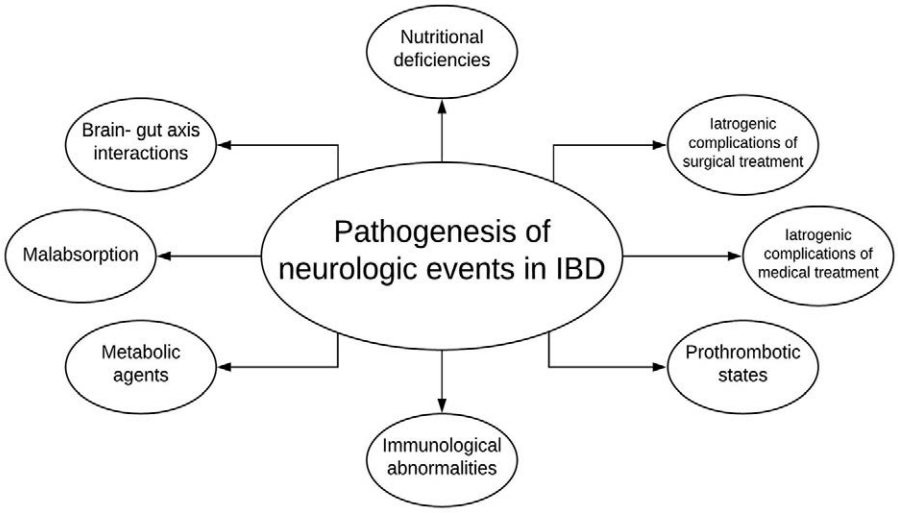

Fig. 1. Summary of pathogenetic factors leading to the development of neurological events in IBD

prednisone, fludarabine, cyclophosphamide, azathioprine, etanercept and/ or plasmapheresis. Immunotherapy of PN led to major improvement in 38%, moderate improvement in 38%, mild improvement in 13% and no response in 13% of patients with CD. Conversely, a major improvement was found in 11%, moderate improvement in 56% and mild improvement in 33% of UC patients with PN [15].

Such discrepancies in achieving the clinical response among different studies may arise from various immune processes involved in neuropathy: primary to IBD, secondary to gut microbiota or coincidence of an autoimmune polyneuropathy. A few cases of chronic inflammatory demyelinating polyneuropathy have been reported, but patients developed their symptoms during the treatment of CD, making it difficult to determine if the cause is primary to CD or secondary iatrogenic complication. Kim et al. [16] described a case of CIDP-like neuropathy in patient who had 3 episodes of motor weakness as the initial presentation of concealed appendiceal CD. Although 3 doses of intravenous immunoglobulin treatment (0.4 g/kg per day for 5 days) influenced the clinical course of the patient, there was only minimal response. The neurological symptoms and abnormal electrophysiologic findings gradually improved after surgical removal of the peri-appendiceal abscess therapy. The appendix is known as an immunological organ, and it may have variable effects on immunologic disease such as IBD and neuropathy.

Cerebrovascular Complications

Studies have shown a clear correlation between IBD and the prothrombotic state [17, 18]. In clinical studies the combined prevalence of arterial and venous thrombosis in IBD population is estimated between 1% and 7.7%, while in autopsy studies it increases to 39% [19, 20]. Schneiderman et al. [20] showed thrombus formation in the small arteries and veins in the pathological examination of the brain tissue of patients with IBD who suffered from a cerebrovascular event. This clinical and pathological observations suggest that in situ thrombosis of arteries and veins is responsible for cerebrovascular occlusion in CD and UC.

The clinical, pathological and hematological findings demonstrate that IBD can be accompanied by a hypercoagulable state that predisposes to stroke [21]. Although, deep vein thrombosis and pulmonary embolism are the most common thromboembolic complications the cerebrovascular disorders also occur, and they are probably underestimated. They may manifest as cerebral venous thrombosis or ischemic arterial stroke.

Cerebral venous thrombosis (CVT) is a fatal extraintestinal manifestation of IBD, that is very rarely reported worldwide and is associated with high morbidity and mortality [22]. The new-onset headache is the most common and sometimes only presenting symptom and has been reported in nearly 90% of patients with CVT. Further increased intracranial hypertension may cause vomiting, diplopia, visual impairment, confusion, decreased level of consciousness and altered mental status. Focal neurological deficit and seizures may suggest the presence of venous infarction and hemorrhagic conversion [23]. These signs can occur from 2 months to 17 years after the first flare of IBD [6]. Cerebral venous thrombosis appears to be more common in UC, but increased risk in those with CD remains [24]. The risk of thrombosis increases during the disease exacerbations [25]. Inflammatory bowel diseases are also a risk factor for recurrent venous thromboembolism [26].

There are no significant differences between IBD-related and non-IBD related CVT in terms of clinical or radiological description, prognosis, or treatment [27]. Imaging studies can confirm the diagnosis of CVT. Defilippis et al. [28] reported six patients presenting with hours to days of headache and were diagnosed with CVT on head computed tomography, magnetic resonance imaging (MRI) or magnetic resonance venography of the brain. Both, MRI and magnetic resonance venography are gold standards for diagnosis of CVT that allow direct visualization of the thrombus. The most common locations for CVT were the sagittal and the transverse sinus [28].

Similarly, to other inflammatory disease, IBD are associated with enhanced pro-coagulative activity including initiation of the coagulation process, reduction of natural anticoagulant mechanisms, impairment of fibrinolysis, thrombocytosis, reactivity and disorder of the endothelium function [29]. Although an active disease is particularly associated with increased risk of complications, some cases of CVT have been described during the remission [30, 31]. The risk of thromboembolism in IBD patients is higher than in other autoimmune diseases without gut involvement, which seems to be a specific feature of IBD [26]. Miehsler et al. [32] estimated the prevalence of thromboembolism in coeliac disease at 1%, rheumatoid arthritis at 3.8%. Meanwhile, in IBD 6.2% patients had a history of radiologically proven thromboembolism.

The search for possible genetic promoters of thrombotic manifestations of IBD including the carriage of factor V Leiden, G20210A prothrombin, methylene tetrahydrofolate reductase mutations has provided negative results [26]. Besides deficiencies of vitamins involved in the proper regulation of coagulation homeostasis, such as vitamin B_6, vitamin B_{12}, folic acid, and hyperhomocysteinemia [33, 34], the alteration of intestinal barrier function may be a cofactor promoting a procoagulative state in IBD [35]. The defective intestinal barrier integrity also was found to be implicated in the development of venous thrombosis through higher circulating levels of lipopolysaccharides (LPS) and increased expression of Toll-like receptor (TLR) 4. In the study, carried out by Pastorelli et al. [35], circulating LPS were measured and found higher concentrations of this bacterial component in the sera of IBD patients. Consistent with the data previously presented by Candia et al. [36] IBD patients also presented higher serum levels of TLR2, as a sign of innate immune activation. High levels of soluble TLR2 may reflect the activation of innate inflammatory responses. Lipopolysaccharides levels correlated with the serum concentrations of TLR4, which is the innate immune receptor deputed to LPS recognition [35]. This may be a sign of an increased expression and activation of TLR4, because of LPS binding. Apart from a modest correlation between LPS and C-reactive protein levels, LPS, TLR2 and TLR4 concentrations did not appear to be influenced by biochemical and clinical disease activity, suggesting that their levels may be influenced majorly by intestinal permeability. Also, both, TLR2 and TLR4 are expressed by platelets and endothelial cells and binding of their respective ligands

causes the procoagulatory activation of these cell populations. TLR2 signaling in platelets leads to a thrombo-inflammatory response, through the activation of phosphoinositide 3-kinase, cyclooxygenase, and purinergic P2Y1 and P2Y12 receptors and alpha-granule release, whereas LPS-TLR4 binding enhances classical agonist-induced platelet aggregation. The TLR2 and TLR4 signaling on endothelial cells strongly activates NF-κB leading to the release of proinflammatory mediators, which can activate the coagulation cascade. Nonetheless, the pathogenesis of atherosclerotic plaques is mediated by the presence of activated macrophages within the plaque, which also respond vigorously to TLR stimulation releasing proinflammatory cytokines [36]. Treatment of CVT in patients with IBD assimilates the standard approach in this thrombotic event. Low molecular weight heparin, intravenous heparin, vitamin K antagonists are the medications of choice. The debate on the use of corticosteroids in patients with CVT or patients who underwent the thrombotic event is still ongoing. Despite the reduction of the procoagulant activity in IBD by ameliorating the inflammation, the intravenous steroids administered intravenously showed to be a risk of thromboembolism [37]. Thus, patients with IBD and high accumulative risk of thrombotic event should be closely monitored while introduced with systemic steroids especially in high doses and might be the candidates for short-term anticoagulant prophylaxis.

Demyelinating Diseases

Demyelinating diseases are rarely encountered in patients with IBD and can be subdivided into those driven by a primary autoimmune process, of which multiple sclerosis (MS) is the most common finding, and treatment-associated demyelinating disorders arising in the context of biologic therapy. The symptoms of MS vary between the patients and can affect any part of the neurological system. The main complaints include fatigue, difficulty walking, vision problems, numbness or tingling in different parts of the body, muscle stiffness and spasms and problems with balance and coordination. The onset of MS may either precede the occurrence of IBD or may appear during the disease [38]. Diagnosis of MS in a patient with IBD can be cumbersome due to the high prevalence of nonspecific white matter changes and other biologic agent-associated demyelinating disorders. Nonspecific T2 white matter changes on MRI are frequently seen in adult patients with IBD [39].

The association between MS and IBD has long been suspected [38, 40]. Studies have demonstrated that the risk of CD was increased by 1.4-fold in the first-degree relatives of MS patients and the risk of MS was increased by 1.7 fold in IBD patients [41]. Coexistence of IBD and MS is highly plausible and recently has gained support from genome-wide association studies. Cotsapas et al. [42] have identified numerous, replicable, genetic associations between common single nucleotide polymorphisms and risk of common autoimmune and inflammatory diseases including MS and CD.

Multiple sclerosis and IBD share similar epidemiology, age of presentation, clinical course and geographic distribution. However, the pathophysiological relationship between these diseases remains unclear. Sheffield et al. [43] reported extensive perivenular demyelination and astrocytosis in monkeys suffering from CD and CU, possibly due to perivenular edema. Additionally, IBD may be classified as a chronic variant of a predemyelinating state that can trigger demyelinating episodes. Inflammatory bowel diseases were also associated with other chronic inflammatory diseases suggesting a common immunologic etiology. Bernstein et al. [44] support the genome scan study, which suggested that chronic immune diseases genetically clustered together [45]. The increased risk for either CD or UC in patients with diagnoses of other inflammatory diseases such as MS support this hypothesis. Treatments that inhibit tumor necrosis α (TNF-α) including infliximab and adalimumab are associated with peripheral and central demyelinating disorders and those therapies are contraindicated for patients with coexistence of IBD and MS [46].

Moreover, it is possible that the association between IBD and MS is mutual. In recent years, the role of microbiome in the pathogenesis of MS has been proposed. Patients with MS showed higher frequency of antibody responses against the GI antigens compared with healthy subjects [47]. It is not clear if high frequency of GI antibodies (against gliadin, tissue transglutaminase, intrinsic factor, parietal cells and *Saccharomyces cerevisiae*) observed in demyelinating diseases is due to shared pathogenesis or coexistence. Whether the increased GI antibody responses are associated with altered microbiota and GI-associated T cell responses needs further investigation. Nevertheless, the high frequency of GI complaints in patients with GI antibodies may also reflect the abnormal functioning of the alimentary tract. Banati et al. [47] also found GI antibodies in MS with a heterogenous immunological background. Active MS lesions show inflammatory changes suggestive of a combined attack by autoreactive T and B lymphocytes against brain white matter. These pathogenic immune cells derive from progenitors that are normal, innocuous components of the healthy immune repertoire but become auto-aggressive upon pathological activation. The stimuli triggering this autoimmune conversion have been commonly attributed to environmental factors, in particular microbial infection. Berer et al. [48] showed that the commensal gut flora, in the absence of pathogenic agents, may result in myelin-specific CD4+ T cells activation that is associated with the relapsing of experimental autoimmune encephalomyelitis.

Treatment of MS in patients with IBD can be challenging due to the necessity of careful choice of drugs. Patients with either disease respond to steroids; however given the increasing number of patients with steroid dependence escalation of the therapy is sometimes needed. TNF-α antibodies generally have no impact in patients with MS, while interferons (IFNs) could even worsen the course of IBD [49]. Natalizumab was found to be very effective in both diseases, however its' utility in patients with IBD is questioned due to the potential of developing leukoencephalopathy [50]. The therapy in patients with both diseases should be personally tailored and adverse events closely monitored.

Epilepsy

Epilepsy is a multifactorial neurological disease, characterized by recurrent spontaneous seizures. The pathogenesis of epilepsy (epileptogenesis) is related to diverse

factors, including genetic predisposition, developmental dysfunction and neurological insult, which contribute to morphological synaptic changes and hyper-excitable neuronal transmission [51]. Although the cellular and molecular pathogenic mechanisms are not clear, it is postulated that focal or systemic unregulated inflammatory processes lead to aberrant neural connectivity and the hyper-excitable neuronal network, which mediate the onset of epilepsy [52-54]. The presence of peripheral inflammation, due to systemic inflammatory diseases such as systemic lupus erythematosus, rheumathoid arthritis or IBD, has the potential capacity to damage the blood-brain barrier and initiate or aggravate epileptogenesis [54]. Accordingly, it was reported that intestinal inflammation in animal epilepsy models lowers seizure threshold, most likely by increasing levels of circulating cytokines and other inflammatory mediators [55, 56]. The link between the intestinal dysbiosis and epilepsy was also found. Medel-Matus et al. [57] showed that fecal microbiota transplantation (FMT) from stressed rats to naïve rats induced pro-epileptic effects while FMT from naïve rats to stressed rats reduced the rate of epileptic events.

Despite those animal models findings, it is commonly accepted, that seizures during IBD are a consequence of metabolic and structural causes, rather than a manifestation of IBD itself [58]. Disorders such as dyselectrolytemia, infection or CVT, as well as medication toxicity are mentioned as triggering factors responsible for epileptic seizures in patients with IBD [59-61].

In the literature, available data on the prevalence of epilepsy among IBD patients is limited. According to different studies, epilepsy occurs in 1.1-5.9% of patients with CD [62, 63] and in 0.9% of patients with UC [58]. A study conducted by Kelleci et al. [64] in a group of 41 patients with CD revealed that electroencephalography (EEG) abnormalities were significantly higher in the CD group (16/41 patients, 39%) (p=0.001) than in the control group of 39 healthy individuals, where no abnormalities were detected. In the CD group epileptiform abnormalities were detected in 3 patients (7.0%), while one patient had a medical history of seizures (2.4%). What is interesting is that patients with EEG abnormalities had no infectious disease nor organic anomalies and did not use any medications that could lower the seizure threshold at the time of EEG examination.

Treatment of epilepsy in patients with IBD follows general rules and guidelines in treating this entity. However, given the significance of the gut microbiota in the pathogenesis of various neurological diseases including epilepsy the modulation of the microbial composition in treating the drug-resistant epileptic patients is being widely studied. Ketogenic diet (KD) covering high proportion of fat and low carbohydrate, use of pro- and prebiotics, antibiotics or even FMT can be future methods of choice in hard-to-treat patients with epilepsy [65, 66]. Nevertheless, utilization of these methods in the treatment of IBD are controversial as the results of studies are sparse and are not recommended in regular treatment. Moreover, vague nerve (VN) stimulation used in the treatment of epilepsy has a potential of being another therapeutical option for patients with IBD as it was shown in mouse model of colitis [67] and in 2 pilot studies [68-70].

Myasthenia Gravis

Myasthenia gravis (MG) is associated with both UC and CD. The connection between IBD and MG seems to be related to the abnormal T-lymphocyte function and production of acetylcholine receptor antibodies, secondary to autoimmune dysregulation [71]. Myasthenia gravis is also associated with other autoimmune disorders including alopecia, lichen planus, vitiligo or systemic lupus erythematosus [71]. The relationship between thymus abnormalities, characteristic for MG, and IBD was also described. The lack of age-related involution of the thymus, observed in patients with MG, seems to be related to UC as well. T-cells obtained from the thymus of patients with MG and UC present similarly reduced ratios of suppressor (CD8+) to helper (CD4+) T- cells, compared with control group [72, 73].

The immunological link between MG and IBD is underlined by case reports of patients undergoing surgical treatment. Finnie et al. [74] reported a case of a female patient, who developed both MG and CD, complicated by perineal abscesses and fistulas, after total colectomy. Due to MG unresponsiveness to pharmacological treatment, a thymectomy was performed, which subsequently improved the course of CD. In contrast, the case of a patient with both MG and UC presented by Gower–Rousseau et al. [75], demonstrated regression of MG symptoms following proctocolectomy.

Myasthenia gravis may occur in its ocular or generalized form, including symptoms such as paresis, dysphagia, dysarthria or fatigability. Foroozan and Sambursky [76] reported a case of a 21-year-old male with a medical history of UC, focal segmental glomerular sclerosis and primary sclerosing cholangitis, who presented ocular symptoms of MG: binocular diplopia and ptosis of the left upper eyelid. Laboratory evaluation revealed a positive acetylcholine receptor antibody. The symptoms resolved one month later after treatment with plasmapheresis, azathioprine, prednisone and pyridostigmine. A case report of two patients with co-morbid MG in a Brazilian cohort of patients with IBD has been published by Gondim et al. [77]. First patient, a 40-year-old man diagnosed with CD developed quadriparesis, bilateral ptosis, dysphagia and dysarthria after total colectomy. The second patient, a 41-year-old woman, diagnosed with UC and primary sclerosing cholangitis, manifested speech impairment and ptosis. In both cases, symptoms quickly progressed in a few weeks. Myasthenia gravis was diagnosed and confirmed by abnormal repetitive nerve stimulation and elevated anti-acetylcholine receptor antibody level. Both patients were successfully treated using pyridostigmine and prednisone.

Although simultaneous occurrence of these two autoimmune diseases is quite uncommon, it is important to notice, that ocular, bulbar or limb symptoms may be the initial manifestation of MG in IBD patients, in particular after changes in the immunosuppressive treatment was made.

PSYCHRIATIC DISORDERS

The increased frequency of certain psychiatric disorders among patients with IBD is observed. The fact that the majority of patients with IBD are young, socially, and professionally active people implies a negative impact on their mental health further deteriorating the quality of the patients' life [78, 79]. The

development of mental problems amid people suffering from IBD is triggered by many factors and interactions between the GI tract, immunological system, and nervous system such as impaired balance of the immune molecules, oxidative stress, innervation of the vague nerve and impairment of the intestinal barrier (Fig. 2). The cascade of abnormal events and disturbances on cellular level add up to each other and effects seem to be similar in most of the chronic diseases, such as CD and UC. Comorbidities may significantly affect the severity of IBD, which induces frequent relapses and increased risk of developing the psychiatric events. Conversely, it was proved that patients with IBD and psychiatric disorders develop exacerbations more often and time between relapses was shorter than patients without these comorbidities [80]. It seems to be a constant and interplaying process. On the other hand, the symptoms of mental disorders among patients with IBD are often neglected and overlooked [81]. The increasing knowledge of triggering factors, mutual relations between the pathophysiology of inflammation and mental disorders may help find the proper way to appropriately evaluate the patients, meet their psychical expectations and prevent them from developing such disorders.

Anxiety and Depression

Anxiety and depression are the most common manifestations of mental disorders diagnosed in patients with IBD [80-82]. Depending on studies, up to 27% of patients with IBD may suffer from depression compared to 12% of healthy controls [83]. The incidence rate of depression after first, third and sixth year of diagnosis is estimated at 2.7%, 5.2%, 8% for CD and 2.6%, 6.6%, 10.8% for UC respectively [84]. In case of anxiety the incidence rate in these timelines was 3.0%, 6.9%, 11.5% for CD and 4.2%, 9.9%, 16.7% for UC, respectively [84]. It was reported that the frequency of anxiety among IBD patients reaches 35% during remission and increases to 80% during flares [81].

Depression is a common and serious mood disorder. It causes severe symptoms that impairs patient's perception and everyday functions such as sleeping, eating, and working [85]. The usual symptoms of depression are lack of energy, anhedonia, low mood, sleep disturbances and a presence of suicide thoughts is sometimes observed [85]. Anxiety is a state of mind characterized by feeling worries and constant tension. Moreover, if symptoms are severe and persistent, The patient may suffer from an anxiety disorder. This term refers to serious psychiatric conditions such as generalized anxiety disorder, panic disorders or attacks, phobias, and social anxiety disorder [86]. The unpredictability of the course of the disease, necessity of complex pharmacological treatment, fear about the possible surgery are only some of the difficulties the IBD patient has to confront during his lifespan [87]. The discrepancies in the

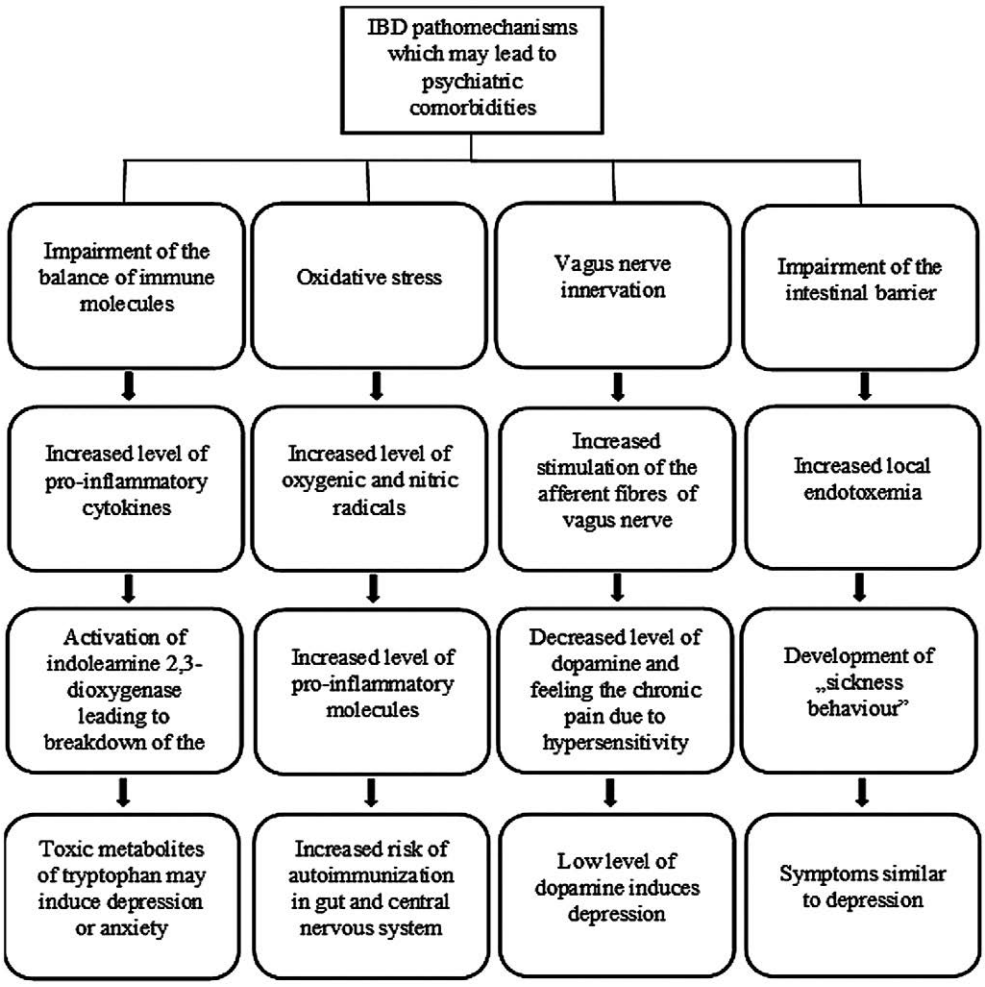

Fig. 2. Scheme depicting the pathomechanisms which may result in the occurrence of psychiatric disorders in IBD

incidence rate observed in studies can emerge from different scales used by investigators or lack off a full, well-conducted psychiatric interview [88]. Routinely, there is no mandatory screening test for mental disorders in patient with IBD.

There are few studies showing the clear connection between anxiety or depression and IBD [79]. The authors observed a higher rate of developing anxiety or depression especially in IBD patients with an aggressive course of the disease. Many patients with CD suffer from ongoing intestinal inflammation, experience fistulizing course of the disease and 2/3 of them require surgery during the lifespan [89]. Accordingly, UC patients with aggressive course of the disease are likely to be operated on in 1/3 of cases, especially those with acute severe colitis [89]. Among these groups, in as many as 16% of patients with CD and 11% of patients with UC the onset of depression or anxiety can occur [89]. Conversely, the depression itself exacerbates symptoms and increases the risk of surgery [78]. It was also proved that depression and anxiety increased the necessity of taking steroids in patients with UC and CD, as well as taking immunomodulators and anti-TNF-α therapy in the latter [78]. Simultaneously, mental disorders decrease the effectiveness of immune treatment and increase the risk of therapeutic failure, which is often the case with infliximab [79]. The fear of living with intestinal stoma and increased risk of cancer during the lifetime burdened psychiatric health even in quiescent disease [89]. Panara et al. [80] also showed that female gender, aggressive course of disease, necessity to receive immunological treatment and age more than 40 were risk factors for developing anxiety or depression. Possible predictive factors for the assessment of the risk of depression and anxiety were high or constantly increasing value of erythrocyte sedimentation rate and a high daily dose of steroids intake [90]. Tendency to suicidal thoughts and suicide also seem to be increased among IBD patient [78]. According to Zhang et al. [88] females with IBD have higher risk of death from suicide than males. In the study performed by Mahadev et al. [91] 13% of 69 patients with CD declared suicidal thoughts or suicidal attempt. Despite the vast knowledge in the field the question whether the depression is directly associated with more severe course of the disease remains unanswered. Recent meta-analysis [92] found no connection between the depression and disease activity in pooled analysis (HR 1.04, 95%CI: 0.97-1.12) and only CD-specific studies exerted this relation. Given the importance of mental health in patients with chronic disorders there is a desperate need for clear elucidation of this phenomenon.

Bipolar Disorder

Bipolar disorder (BD) is a mental disease that causes periods of depression and abnormally elevated moods [93]. Results on BD incidence in IBD patients are confusing. Some studies showed that IBD patients exhibit a lower chance of developing BD than general population [83]. On the contrary, Eaton et al. [94] demonstrated a higher risk of developing BD in patients with IBD. Moreover, CD patients have increased risk of BD in the first four and five years following the diagnosis (1.9%) and also 5 years after diagnosis (1.8%) [94]. Interestingly, antibodies against *Saccharomyces cerevisiae* have been detected in the blood samples of patient with CD and BD [95], which suggests that there is a significant role of immunological response against intestinal antigens, and it may have a role in the pathogenesis of BD [95].

Other Psychiatric Diseases

Patients with IBD are at a higher risk of developing panic generalized anxiety syndrome, panic disorder and obsessive-compulsive disorders than the general population. In the Manitoba IBD cohort study the prevalence rates of these disorders were estimated at 13.4%, 8.0%, 2.8%, respectively [83]. Furthermore, the results of the named study showed that patients suffering from anxiety and mood disorders had earlier onset of IBD [83].

The incidence rate of schizophrenia was higher among patients with immune-based diseases overall, but not in smaller cohorts [96]. Another study based on analysis of 2,419 deaths from UC and 2,399 from CD found that among the UC group 10 patients were diagnosed with schizophrenia and this number was significantly higher than the expected occurrence which was estimated at 2.18 [97]. Ulcerative colitis patient cohorts did not differ from the matched cohort. Interestingly, in older age the prevalence of psychiatric comorbidities is increased, excluding schizophrenia [98]. Another study found no evidence of increased risk of schizophrenia for CD and UC patients [99].

Similarity in the Pathogenesis of IBD and Selected Psychiatric Disorders

It is known that the depression and anxiety are associated with chronic imbalance between the inflammatory triggers and anti-inflammatory cytokines [100]. Significant evidence proves that similar processes co-occur in pathogenesis of depression, anxiety and IBD. It was observed that the level of several interleukins (IL) and cytokines, including IL-1, IL-6, IL-17, IL-22, IL-23, TNF-α, IFN- γ in patients with IBD and patients with depression or anxiety is higher than in the general population [100, 101]. The production of acute-phase proteins, components C3c and C4 of complement system is also increased in depressive patients and IBD patients [78, 82, 101] Both these populations of patients exhibit decreased level of anti-inflammatory cytokines such as transforming growth factor β and IL-10 [101]. Pro-inflammatory cytokines, especially IFN-γ induces the activation of indoleamine 2,3-dioxygenase leading to breakdown of the tryptophan in kynurenine pathway reducing the availability of serotonin. Toxic metabolites of tryptophan such as kynurenine, kynurenic acid and quinolinic acid induce anxiety and depression [102]. Accordingly, patients with IBD have a lower level of tryptophan than normal population due to the increased activity of indoleamine 2,3-dioxygenase which increases the tryptophan catabolism [102]. Moreover, it was observed that the level of tryptophan catabolites positively correlates with disease activity [101, 102]. In conclusion, chronic shortage of tryptophan and overproduction of its metabolites can lead to a relapse of the IBD and increase the risk of depression and anxiety.

The next common pathogenetic factor of depression and IBD is the increased level of free oxygenic and nitric radicals such as lipid peroxidase, hydrogen peroxide. Impairment of the balance between reactive oxygen species and antioxidants produces oxidative stress [101, 103]. Decreased levels of

antioxidative enzymes such as glutathione, superoxide dismutase in blood of IBD patient can lead to impairment of balance of pro-inflammatory molecules in the gut. Similar changes were observed among patients with depression [101, 103]. Presence of the free radicals is also considered as one of the causative factor of autoimmunization found in IBD patients and patients with depression. Free radicals can modify epitopes on cells and provoke auto-aggressive response of the immune system [100].

Recently VN innervation has been also considered as an important factor in maintaining the balanced immunological response [82, 104]. It may play a significant role in immune activation in the GI tract, and it can lead to the chronic process of inflammation. Vague nerve releases acetylcholine which interacts with specific α-7 nicotine receptor [78, 104, 105]. This cholinergic anti-inflammatory pathway weakens the immune cells activation and helps to maintain the homeostasis. The vagotomy impairs the balance, whereas VN stimulation can decrease inflammation and help restore the homeostasis [104]. Chronic irritation of intestines leads to stimulation of the afferent fibers of VN. This process inhibits dopamine system and increase the risk of developing depression [78]. Moreover, another effect of vagal innervation is the exacerbation of pain sensation evoked by visceral hypersensitivity of the intestines also observed during the remission. Visceral hypersensitivity may be caused by impaired interactions between the CNS and the peripheral system [106].

The role of gut microbiota in the modulation of the brain-gut axis is also a very significant pathogenic mechanism of depression. Communication between the gut and the brain is bidirectional. The gut flora produces neuroactive molecules which can affect the nervous system including VN. The central nervous system also produces hormones through hypothalamic-pituitary-adrenal axis and induces changes in intestinal microbiota and the structure of the intestinal barrier during stressful situations [107]. Impairment of the intestinal barrier in patients with IBD play a significant role in the pathogenesis of the depression. Increased permeability leads to infiltration of the bacteria, induction of immunological response and induces dysbiosis. Mucosal biopsy of patient with UC showed an increased level of *Acinetobacteria* and *Proteobacteria* and decreased level of *Bacteroides* compared to their healthy siblings. Patients with UC and CD have also a reduced complexity of phylum *Firmicutes* [101]. Increased permeability in the GI tract can lead to local endotoxemia increased level of LPS and LPS-binding protein. High blood level of LPS in mice leads to development of the "sickness behavior" and even depression. [101,108]. Sickness behavior in animals is also induced by an increased level of TNF-α and IL-1β [108].

Treatment

Diagnostic process and treatment of any mental disorder in a group of IBD patients can be challenging. However, screening of mental disorders should be part of every IBD assessment and recent guidelines have pointed out the importance of screening for depression and anxiety [109]. Usually, the Hospital Anxiety and Depression scale is suggested [109]. It seems to be necessary to explain to the patient the link between depression and anxiety and show them therapeutical options. Studies showed that behavioral therapy is very effective, usually combined with some medication. Among young patient and especially children cognitive behavioral therapy can be useful [109].

As for drugs, selective serotonin reuptake inhibitors (SSRI) have been used with satisfying results, especially in CD patients. After 6 months of antidepressant treatment including SSRI, selective noradrenaline reuptake inhibitors (SNRI) or two of them, patients improved in the symptoms of depression and also in the disease activity of CD [110]. Fluoxetine and citalopram have also proved to help patients with concomitant depression decrease the number of IBD relapses [109, 111]. However, SRRIs and SNRIs have many dose-related side effects. The most frequent adverse effects for SNRI are nausea and vomiting, while diarrhea is more common after SSRI administration [112]. Tricyclic antidepressants reduce the pain and hyperalgesia and decrease the stimulation of afferent fibers of myenteric plexus [82, 112]. Moreover, in some antidepressants the adjuvant anti-inflammatory effect is suspected [113, 114]. Animal studies showed the anti-inflammatory activity of lithium; when administered at the dose of 20 mg/kg intraperitoneally, twice daily for 7 consecutive days soothed the inflammation, decreased the myeloperoxidase activity, and the colonic TNF-α level in the chemically induced mouse model of colitis [114]. Probiotics seem to play significant role in the therapy of IBD as well as depression. Some studies showed that administering the combination of *Lactobacilli*, *Bifidobacteria* and *Streptococcus salivarius* may help prevent relapses of pouchitis. Moreover, *Escherichia coli* Nissle 157 may play a role in maintaining remission in UC patient [115]. Furthermore, administering Lactobacillus *helveticus* R0052 and *Bifidobacterium longum* to healthy adults for 30 days reduced psychological stress and decreased the risk of depression [116]. There is no drug of choice for psychiatric comorbidities in IBD and the influence on the course of the diseases of those substances is still to be verified. Nevertheless, every psychotropic drug can be used if its effectiveness and safety is adequate. Additionally, IBD patients should be provided with psychiatric support.

CONCLUSIONS

In this review we presented the most common neurological and psychiatric entities which may co-exist with IBD. Due to multifactorial pathogenesis of IBD, most of the extraintestinal manifestations share the pathological features with UC and CD. Mild neurological and psychiatric symptoms may occur in the course of IBD. Sometimes they may be a first sign of the development of extraintestinal manifestations. However, the physicians have to stay alert to the possible deleterious effects of used drugs on the organism inducing neurological or psychiatric events. Although they are sometimes disregarded by the physician the basic and psychiatric examination should be a routine management in both the outpatient clinic and in the hospital.

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