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Psychiatric illnesses in inflammatory bowel diseases – psychiatric comorbidity and biological underpinnings

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Summary

Inflammatory bowel disease is a group of chronic medical conditions comprising Crohn's disease and ulcerative colitis that involves increased frequency of mental disorders. The most common psychiatric disorders in inflammatory bowel disease are depression and anxiety, however, some epidemiologic and biological evidence suggest that other disorders like bipolar disorder occur more often. Biological mechanisms concerning both inflammatory bowel disease and depression or anxiety explain susceptibility to developing mental disorders in inflammatory bowel disease. Interactions of brain gut-axis, immunological disturbances, oxidative stress and vagus nerve dysfunction play a role in pathophysiology of inflammatory bowel disease and mental disorders as well. Significance of these factors was covered in this paper. Psychiatric comorbidity in IBD may affect course of intestinal disease. It can increase frequency and severity of relapses and hinder the treatment so knowledge about relationship between IBD and mental health appears to be vital for proper management of patients with inflammatory bowel disease.

Key words: inflammatory bowel disease, depressive disorders, vagus nerve

Introduction

Crohn's disease (CD) and ulcerative colitis (UC) belong to the group of inflammatory bowel diseases (IBD) which are chronic conditions of unknown etiology. Their relapsing character, debilitating symptoms, such as abdominal pain, diarrhea, bleeding, weight loss or chronic fatigue, and surgical complications can lead to severe disability. There is increased prevalence of certain psychiatric disorders in this group [1] and they

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can worsen the course of intestinal disease in many ways detailed below in this paper. Mental health of IBD patients declines during flares which are more frequent when mental disorder co-occurs [1]. IBDs have peak incidence between late adolescence and early adulthood, so they inevitably affect all spheres of patient's life, profoundly impairing general well-being, social activities, body image and sexual life [2]. Despite increased rates of psychiatric comorbidity, IBD patients are not routinely screened for symptoms of mental disorders and they remain largely undertreated. Unpredictable course of disease, extraintestinal manifestations, need for surgical treatment, including creation of stomas, as well as taking immunosuppressive drugs and complications of such a therapy are main factors burdening IBD sufferers [3]. IBDs entail reduced health-related quality of life, work disability and chronic fatigue [4]. The two last factors occur more frequently with comorbid mood disorder [5]. This review aims to present current knowledge concerning epidemiology of psychiatric disorders in patients with IBD and underlying biological mechanisms.

Psychiatric comorbidity in IBD

Although significant role of psychiatric aspects of IBD were recognized years ago, last two decades brought large-scale studies of mental health in CD and UC. However, many of them, especially the older ones, have poor methodological design, lacking thorough assessment of psychiatric symptoms or being limited by group size [2]. Epidemiological studies confirm that the most common psychiatric problems in patients with IBD are depression and anxiety. According to the Manitoba IBD Cohort Study, for patients with IBD lifetime prevalence of depression is 27% (12% in control group) [6]. Panara et al. estimated the prevalence of 20% [7]. European studies calculations are lower [7] but in general depression prevalence in IBD tends to vary within 15% to 30% [7]. The levels of anxiety are even higher [8], reaching 29–35% in remission up to 80% during exacerbation [9]. Data concerning rates of anxiety in IBD are mostly less precise. Lower rates of depression occurrence in both German and French studies and less accurate estimations of prevalence of anxiety may be caused by the use of the Hospital Anxiety and Depression Scale, which is no longer considered solid instrument to differentiate between depression and anxiety [7]. Analysis of psychiatric comorbidity performed in the Manitoba IBD Cohort Study is one of the most credible because, contrary to the majority of research, structured psychiatric interview was used to assess patients. Unfortunately, treating IBD as one entity, some data concerning differences between CD and UC were lost. It may be assumed that two subtypes of IBD affect mental health in dissimilar manner because of their varied manifestations. Studies regarding those two diseases as separate forms of IBD, however, found no difference in rates of depression or anxiety between the two conditions [1]. Higher frequency of depression and anxiety in patients with IBDs compared to general population is absolutely certain but some controversy still remains, as it may only reflect the fact that these are chronic diseases. So far, rates of depression in IBD

are similar to those in rheumatoid arthritis, diabetes and heart failure [1] but a couple of facts described below indicates that people with CD or UC are especially prone to depression or anxiety.

Several risk factors of developing depression or anxiety in IBD were identified. Even though prevalence of those psychiatric disorders is fairly equal in CD and UC, character of those risk factors and their influence vary in both subtypes of IBD. Female gender, active disease, aggressive character of the disease (defined by Panara et al. as necessity of biological treatment, positive history of fistula, perianal involvement or IBD-related surgery) are independently associated with the diagnosis of depression in IBD patients [7]. Aggressive character of the disease precedes developing of depression in 16% of CD patients and 11% of UC patients in 5-year period. It is relevant, regarding the fact that surgical treatment is needed in up to two-thirds of CD patients and one-third of UC patients [8]. On the other hand, an increase in risk of surgical procedure due to IBD was observed in CD (but not in UC) with pre-existing depression. Furthermore, presence of depression or anxiety increases the risk of corticosteroid therapy requirement in patients with UC and the use of anti-TNF α medications, immunomodulating drugs and corticosteroids in patients with CD [10]. Active disease, thus onset or flare of IBD, are those critical moments when the symptoms of depression or anxiety are most prevalent [11]. In both pediatric and the elderly group of patients with CD, increased disease activity was found to be associated with the presence of depression [12] and erythrocyte sedimentation rate as well as daily steroid dose were proved to be strong predictors of depression [13]. The negative impact of depression on the course of IBD appears to be even greater, given that coexistence of depression is correlated with more aggressive phenotype of the disease, higher risk of relapse and shorter periods of remission [1]. Increase in risk of unsuccessful infliximab treatment (failure to achieve remission and need of retreatment) suggests that depression may also interfere with outcomes of biological treatment of IBD [14].

Although there are solid evidence for negative influence of depression on the course of IBD, influence of depression or anxiety on risk of IBD onset is still unclear. Nevertheless, it cannot be excluded, as one large retrospective study found, that depression as well as anxiety preceded UC (but not CD in this case) significantly more frequently and strength of that association was the greatest up to one year before UC diagnosis (However, according to that study, the association was also present five year prior to it) [15]. Those results are supported by the Manitoba IBD Cohort Study, which reported that IBD diagnosis is made at younger age and gastrointestinal symptoms tend to occur earlier in life in patients with depression or anxiety and that nearly two-third of patients with anxiety and more than a half with depression encounters first episode of mentioned psychiatric disorders up to two years before IBD diagnosis [6]. Despite those observations, further research is needed to determine whether depression or anxiety is a risk factor for developing IBD.

Studies of psychiatric comorbidity in IBD usually focus on depression and anxiety, thus little attention is paid to other mental disorders. In contrast with other research

ignoring differences between clinical entities, the Manitoba IBD Cohort Study screened patients for panic disorder, generalized anxiety disorder and obsessive-compulsive disorder. For lifetime prevalence, rates of the listed disorders were found elevated in patients with IBD, being 8%, 13.4% and 2.8% respectively for panic disorder, generalized anxiety disorder and obsessive-compulsive disorder [6]. Conversely, rates of social anxiety disorder and bipolar disorder (BD) were lower than in the general population [6]. Different results were obtained by Eaton et al. who noted that CD, together with a few other immune-mediated diseases, is associated with an increased risk of bipolar disorder [16]. The co-occurrence of IBD and BD has not been thoroughly discussed yet. Until now, only few case reports documented presence of bipolar disorder in Crohn's disease [17]. Some evidence described later on in this paper show that relationship between those two conditions cannot be completely ruled out.

Depression is well-established risk factor for suicide. Despite the fact that depression is one of two most common psychiatric disorders in IBD, there is scarcity of data covering the question of suicide in this group of patients. Studies found increased rates of suicidal ideation and completion in IBD [18]. 13% of 69 patients with CD inquired in one study confirmed to feel suicidal because of IBD [19].

Biological mechanisms. Brain-gut axis interactions

Although most studies found only statistical associations, being unable to prove clear cause-effect relationship, growing body of evidence suggest bidirectional interactions between depression and gastrointestinal inflammation. CD and UC are currently viewed as multifactorial diseases with complex pathogenesis involving abnormal immune response with chronic pro-inflammatory state and cytokine unbalance with predominance of pro-inflammatory cytokines, including autoimmune phenomena and impairment of anti-inflammatory pathways, interactions with intestinal microbiota, and disturbances in brain-gut axis. Mechanisms leading to the development of depression overlap with those that are key in IBD pathogenesis.

Over the past two decades the role of inflammatory background of depression has been studied intensely. Recent works suggest that depression is associated with chronic inflammation and that it is accompanied by imbalance between anti – and pro-inflammatory factors with the latter prevailing [20]. Elevated levels of numerous pro-inflammatory cytokines, especially TNF-α, IFN-γ, IL-1, IL-1RA, sIL-2, IL-6, sIL-6R, IL-17, IL-22 and IL-23, were observed in depression [21]. Experiments confirm that both TNF-α and IL-1β are responsible for inducing sickness behavior, a set of depressive-like symptoms known to everyone who experienced acute viral or bacterial infection [22]. An ability to produce depression with IFN-α administration is well documented among patients with hepatitis C of which 21% to 58% suffer from broad range of depressive symptoms when treated this way [23]. Decreased levels of anti-inflammatory cytokines, IL-10 and TGF-β, is an additional factor contributing to immune dysregulation in depressed patients [21]. Moreover, greater production of positive acute phase

proteins (APPs), including haptoglobin and CRP, followed by decreased production of negative APPs, such as albumin, transferrin and α(1)-antitrypsin [21, 24] as well as heightened levels of complement component C3c and C4, immunoglobulin M and immunoglobulin G were found in these patients [21]. Similar disturbances in cytokine levels and the same profile of positive and negative APPs are also characteristic of IBD patients [21]. Immune pathologies, that CD and UC inherently involve, create cytokine environment that may promote the development of depression in susceptible individuals. The fact that treatment with anti-TNF-α medications is effective for both gastrointestinal inflammation and depression highlights the crucial role of TNF-α in IBD and concomitant depression [24, 25]. Elevated level of IL-17, a distinctive feature of inflammation in CD [26], was also found in patients after myocardial infarction who later developed depression [27]. Decreased level of zinc, a microelement being another negative APP, is characteristic of both depression [28] and IBD [21]. In case of those gut diseases, hypozincemia can result not only from persistent inflammatory state but also from malnutrition and malabsorption, making IBD patients more prone to depression, as diminished dietary intake of zinc is associated with higher incidence of depression [29]. Impaired intestinal barrier is essential aspect of IBD pathogenesis which may contribute to vulnerability to depression in this group of patients. Increased gut permeability present in IBD lead to periodical endotoxemia resulting in increased lipopolysaccharide (LPS) and LPS-binding protein blood levels [30, 31]. Peripheral as well as central administration of LPS to mice results in elevation of pro-inflammatory cytokines levels, causes sickness behavior and even depressive state when LPS stimulation is prolonged [21, 22]. Abnormal concentrations of LPS along with other markers of bacterial translocation, like raised serum levels of IgA and IgM antibodies against LPS were also detected in patients with depression [21]. Given the suggestion that LPS-dependent pathway with its potential to induce neuroinflammation is involved in the development of depression [32, 33], chronic exposition to gut microbiota antigens occurring in IBD may help explain high prevalence of depression in IBD patients.

Additionally, preliminary evidence support existence of association between gastrointestinal inflammation and bipolar disorder. One of studies found elevated level of marker helpful in making CD diagnosis, anti-*Saccharomyces cerevisiae* antibodies (ASCA), in blood of patients with bipolar disorder [34]. These findings indicate enhanced immune response against antigens of gut origin [34]. It corresponds to results obtained by Eaton et al. who revealed association between CD and increased rates of bipolar disorder [16]. Although the role of brain-gut axis disturbances and hypersensitivity to intestinal antigens in pathogenesis of schizophrenia has been highlighted recently [35], no data suggest higher incidence of schizophrenia in IBD [36].

Another pathological mechanism shared by depression and IBD is generation of oxidative and nitrosative stress (O&NS). Recent evidence shows relationship between O&NS and intestinal pro-inflammatory imbalance [21]. Animal models reveal that anti-oxidizing enzymes deficiency leads to IBD-like symptoms [37]. The supply of oxidizing factors in animals with efficient enzymes can also trigger such symptoms

[37]. These findings are consistent with results of studies which reported decreased levels of antioxidants in the blood of IBD patients [21]. Similar observations were made in case of patients with depression [21]. Taking into account the fact that mood disorders are accompanied by significantly increased O&NS [20, 21, 33], it cannot be ruled out that O&NS, taking part in the development of IBD, eventually facilitate the development of depression. Reactive oxygen and nitrogen species production might bridge autoimmune phenomena reported in both IBD and depression [21], as reactive oxygen species are capable of modifying protein epitopes, being then targets of autoimmune response [20].

Furthermore, IBDs may affect mental health because of impact on serotoninergic system. Pro-inflammatory cytokines, especially IFN-γ, induce indoleamine 2,3-dioxygenase (IDO), a first enzyme degrading tryptophan in kynurenine pathway, leading to build up of metabolites like kynurenine, kynurenic acid and quinolinic acid. Depletion of tryptophan resulting in decreased serotonin availability along with neurotoxic features of tryptophan catabolites can have depressogenic and anxiogenic effects [21, 38]. Overexpression of IDO and high levels of tryptophan metabolites [21] along with reduced plasma levels of tryptophan were found in people with IBD (among all the essential amino acids only the level of tryptophan and histidine was reduced) [39]. In case of CD, concentrations of kynurenine pathway tryptophan metabolites were also correlated with disease activity [21]; studies on animal models provided similar results [17]. Chronic tryptophan deficiency and overproduction of kynurenine and related compounds caused by processes exacerbating IBD may contribute to increased risk of depression and anxiety in IBD patients.

On the other hand, disease flare-ups can be promoted by those mental disturbances through their negative influence on cholinergic tone of vagus nerve [40]. Studies show interactions between depression, vagal tone and bowel disease. Vagal efferent fibers carry impulses of cholinergic anti-inflammatory reflex, thus controlling immune homeostasis of the gut [40]. Animal experiments substantiate potential role of dysfunction of a part of parasympathetic nervous system accompanying depression in IBD. Impaired parasympathetic signaling aggravates symptoms of colitis and makes mice more vulnerable to it [41]. Additionally, induction of depression in mice with quiescent colitis led to reactivation of intestinal inflammation [42]. Ghia's studies showed lack of cholinergic transmission and stimulation of α7 subunit of nicotinic acetylcholine receptor to be responsible for relapse of chronic colitis [42]. Interestingly, those deleterious effects of reduced cholinergic output were ameliorated in mice given tricyclic antidepressants [42]. Diminished vagal tone likewise promotes hyperalgesia in IBD patients [43]. It can explain why some IBD sufferers experience abdominal pain even during remission. Relative efficacy of tricyclic antidepressants in the treatment of those symptoms provides support for this explanation [44]. It was shown that increased stimulation of vagal afferent fibers lead to inhibition of dopamine signaling in the brain, contributing to depressive symptoms in this way [45]. Such overstimulation may result from inflammation in IBD.

Conclusions

Increased prevalence of depression and anxiety in IBD results from complex interactions between bowel inflammation, immune dysregulation and the brain. Although chronic diseases generally involve greater risk of depression and anxiety, interwoven processes including pro-inflammatory factors upregulation, brain-gut axis dysfunction, intestinal microbiota imbalance and oxidative and nitrosative stress make IBD patients especially vulnerable to those mental disorders. As psychiatric disorders significantly influence the course of disease, flare-up rates, treatment outcomes and quality of life, it is essential to encourage cooperation between gastroenterologist and psychiatrists. Screening patients with CD and UC for mental disorders should become element of clinical approach in case of IBD. Achieving psychological remission, next to the remission of somatic symptoms, appears to be a promising endpoint in the treatment of IBD [46].

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