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Review article

The influence of family pattern abnormalities in the early stages of life on the course of inflammatory bowel diseases

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ABSTRACT

Crohn's disease (CD) and ulcerative colitis (UC) belong to the group of inflammatory bowel diseases (IBD), chronic immune mediated diseases of the gastrointestinal (GI) tract with significant negative impact on patients' quality of life. CD and UC are related with the development of chronic inflammatory lesions in the GI tract, causing digestive and absorption disorders. Typical symptoms of IBD are: abdominal pain, vomiting, diarrhea, rectal bleeding, and weight loss. In addition, IBD are often associated with the extraintestinal manifestations, including arthritis and dermatoses.

While the cause of IBD is still not fully understood, the psychological aspects are regarded as possible trigger factors. Moreover, most recent studies suggest that family pattern abnormalities associated with stress at the early stages of life may strongly affect health balance. In this paper, the most relevant studies focusing on the association between early life stress and IBD, found in MEDLINE, Cochrane Library and EMBASE are discussed. Possible effects of the early life stress on IBD progression and response to undertaken therapies are analyzed.

Contents

Introduction

Inflammatory bowel diseases (IBD) represent a heterogenic group of idiopathic chronic inflammatory intestinal conditions with exacerbations and remission periods. The two major diseases covered by this term are Crohn's disease (CD) and ulcerative colitis (UC), in which overlapping and distinct clinical and pathological features can be found [1]. Despite the numerous studies the pathogenesis of IBD is not fully understood [2,3]. However, genetic and environmental factors, such as altered luminal bacteria, and an enhanced intestinal permeability are believed to play a major role in the dysregulation of intestinal immunity, leading to gastrointestinal (GI) injury [1,4,5].

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IBD are believed to be associated with industrialization of nations, with the highest incidence rates and prevalence in North America and Europe [6–8]. Recent studies have shown that the prevalence of both UC and CD appear to be increasing over time [9,10]; however, the definitive reasons for the increasing incidence rates of IBD remain still largely unknown [6,11]. As there is no efficient cure, most patients need a life-long drug therapy and many will face surgical intervention [12]. Consequently, IBD are associated with a high economic burden to a society, with hospitalization and surgery accounting for more than half of the healthcare costs [13–15]. Moreover, due to its early onset and chronic character, IBD profoundly affect work productivity leading to significant losses resulting from sick leave and work disability, amounting to almost 50% of the total costs [13,14,16–19].

IBD may significantly affect patient's quality of life [14,20,21]. CD and UC cause chronic inflammation in the GI tract, which is normally responsible for digestion of food, absorption of nutrients, and elimination of waste [22,23]. Inflammation impairs the ability of intestines to function properly, leading to general symptoms, such as abdominal pain, vomiting, diarrhea, fever, weakness, rectal bleeding, and weight loss [24,25].

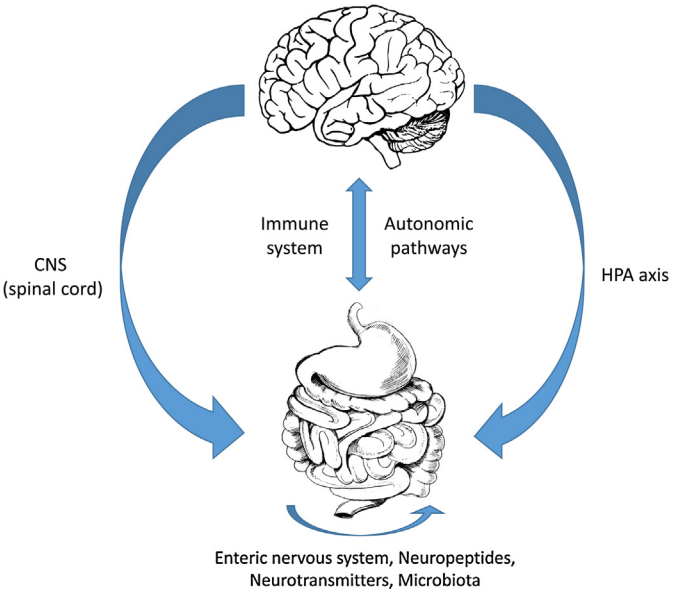

Fig. 1. The bi-directional communication between brain and gut.

Hypotheses on IBD pathogenesis

The development of IBD lesions is thought to be the result of an aberrant immune response to commensal bacteria and luminal antigens in a susceptible host [21,22,26]. Furthermore, genetic and environmental factors may play a role in IBD development, involving changes in innate and adaptive immune function and epithelial barrier function [27,28]. Importantly, epidemiological studies have recognized the family aggregation. First-degree relatives of affected individuals have a fivefold or greater risk of IBD. Of note, the inheritable component seems stronger in CD than in UC [29,30].

Excessive activation of the immune system causes an imbalance between pro- and anti-inflammatory cytokines, which leads to disproportionate adaptive immune responses. It has been hypothesized at first that the clinical manifestations of IBD and inflammatory lesions in the intestinal wall are induced by elevated levels of several pro-inflammatory cytokines, mainly TNF-α [31]. Also, CD has long been considered to be driven by a Th1 response and UC has been associated with a non-conventional Th2 [32,33]. However, the newly conducted studies found that Th17 cells are also involved in the gut inflammatory response in IBD [34]. Th17 cells are the T cell subset characterized by the production of large amounts of interleukin (IL)-17A, IL-17F, IL-21 and IL-22. They are induced by a combination of IL-6 and transforming growth factor (TGF)-β, and their expansion is promoted by IL-23 [35]. The involvement of Th17 cells and, in particular, their signature cytokine IL-17A in intestinal inflammation has been extensively studied [36,37]. However, the true role of Th17 cells in IBD pathogenesis is currently undergoing intense scrutiny.

The brain–gut axis and the psycho-neuro-endocrine-immune modulation

Recent studies revealed that the psycho-neuro-endocrine-immune modulation through the brain–gut axis likely has a key role in the pathogenesis of IBD [38]. The brain–gut axis (BGA) constitutes the central nervous system (CNS), the hypothalamo-pituitary-adrenal (HPA) axis and the enteric nervous system (ENS) and the gut wall in the periphery [39]. The bi-directional communication between the CNS and the gut is based on the neural, endocrine and neuroimmune pathways (Fig. 1). Neuronal pathways include afferent fibers originating in the dorsal root of the ganglia of the thoracic spinal cord (T1–T10) projecting to integrative cortical areas, such as the cerebral, anterior and posterior cingulate, insular, and amygdala cortices and efferent fibers to smooth muscle and glands, originating in the nuclei within the brainstem, as well as S2–S4 spinal levels (parasympathetic) and in the lateral horn of the thoraco-lumbar spinal cord (T1–L3; sympathetic) [40–42]. The major pain signaling pathways in the BGA are the spinothalamic tracts and dorsal columns with descending supraspinal afferents originating from the rostral ventral medulla [40].

In physiological conditions, signals from the GI tract influence the brain, which in turn can exert changes in motility, secretion, and immune function [43]. The axis is therefore an important communication system for healthy regulation of food intake, digestion, gut sensations, and control of the bowel movements. Structural and functional disruptions in the BGA cause changes in perceptual and reflexive responses of the nervous system and may lead to GI disorders, including IBD [44].

The reciprocal relationship between IBD and patients' quality of life

A systematic review of qualitative studies exploring the phenomenon of living with IBD demonstrated a highly negative impact of the disease on the overall quality of life [45]. In the patient survey (n = 5576 participants) conducted by the European Federation of Crohn's and Ulcerative Colitis Associations (EFCCA), 75% of patients reported that symptoms affected their ability to enjoy leisure activities and 69% felt that symptoms affected their ability to perform at work [46]. In a survey of the French association of IBD patients (n = 1663), 12% of IBD patients reported depression and 41% reported anxiety [47]. Other studies showed that as many as 75% of IBD patients believe that stress is a major contributor to the development of their disease and up to 90% of patients believe that stress triggers flares of their disease [48]. In the recent study, 30% of patients (of n = 302) expressed the need for psychological interventions [49] while in another paper it was demonstrated that 60% of IBD patients did not receive adequate help for their psychological problems [50].