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REVIEW ARTICLE

Neurologic manifestations in inflammatory bowel diseases: Current knowledge and novel insights

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Abstract

Background: Crohn's disease (CD) and ulcerative colitis (UC), widely known as inflammatory bowel diseases (IBD), are thought to result from an inappropriate activation of the mucosal immune system driven by intestinal bacterial flora.
Methods: Although the extraintestinal manifestations of IBD are well documented, the association of IBD with neurologic and neuromuscular involvement is rare and often controversial, with sporadic and conflicting data on its prevalence and spectrum. In addition, a serious number of the latter manifestations may become life-threatening, playing a very important role in disease morbidity. To define the pattern of neurologic involvement in IBD, the most important manifestations in these patients have been reviewed, exploring also their clinical significance.
Results: There is evidence that UC and CD can manifest both in the PNS and CNS. Thrombotic complications are common in IBD patients, but cerebral vascular involvement is rare.
Conclusions: Neurologic manifestations in IBD patients are more common than previously estimated and may follow a different pattern of involvement in CD and UC. Small numbers of patients currently preclude a better characterization of the clinical spectrum and a better understanding of pathogenesis.

Contents

Abbreviations: IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; PN, peripheral neuropathy; cyA, cyclosporine A; MS, multiple sclerosis; MG, myasthenia Gravis; SEA, spinal epidural abscess; CNS, central nervous system.

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1. Introduction

Inflammatory bowel diseases (IBD), which include Crohn's disease (CD) and ulcerative colitis (UC) have a worldwide distribution and are common causes of gastrointestinal morbidity in Western Europe and Northern America. Recent population based studies suggest that the combined prevalence of these diseases in Western countries approaches 400 per 100,000.[1]

The extraintestinal manifestations of IBD, however, are not of less importance. In some cases they are the first clinical manifestation of the disease and may precede the onset of gastrointestinal symptoms by many years. As multisystemic diseases, IBD, have been correlated with many other organs, including the skin, eyes, joints, bone, blood, kidney, liver and biliary tract. Neurologic and neuromuscular complications have also been reported, but the real incidence of these complications is unknown, with reports varying from 0.25 to 35.7%; the variation could be due to selection bias or to different disease definitions.[2–5]

Although there is increasing evidence that IBD may manifest in the nervous system, a reliable differentiation may clinically not always be possible. More analytically, disorders of the peripheral and central nervous system in association with IBD can be ascribed to at least six different mechanisms, which may be present in isolation or in combination: (i) malabsorption and nutritional, particularly vitamin deficiencies such as B_1, B_{12}, D, E, folic acid and nicotinamide deficiencies (ii) metabolic agents, (iii) infections as a complication of immunosuppression, (iv) side effects of medications (metronidazole, sulfasalazine, steroids, cyclosporine A) or iatrogenic complications of surgery, (v) thromboembolism, (vi) immunological abnormalities. In addition to these — at least theoretically — clearly defined and distinct etiologies, neurologic signs and symptoms may also be due to a so far speculative and not further specified neuronal influence of enteric disease onto the nervous system (and vice versa). Such a hypothesis may be derived from contemporary theories considering the existence of a 'brain-gut axis', and from results of respective functional neuroimaging studies.[6–8] The interactions between the brain and the gut are illustrated by the role of stress in IBD. This interaction has been demonstrated in many animal experiments and in some controlled observations in patients with IBD.[9,10] No longer is stress considered to be an etiological factor in causing the disease, but, rather, stress appears to be a factor contributing to the exacerbation of the disease. Stress is perceived by the central nervous system (CNS) in very specific locations, such as the hypothalamus. The CNS is then able to modulate the degree of inflammation of the bowel through multiple routes including neural and neuroendocrine pathways, the hypothalamic-pituitary-adrenal axis, the release of corticotropin-releasing-factor and its effects on adrenal-corticoid secretion, the autonomic nervous system and systemic stimulation or suppression of immune functions. The multiplicity of pathways by which the brain affects the gut makes it very difficult to study and to modulate the system pharmacologically.[11] In addition, myenteric plexitis seems to have a highly predictive value in IBD recurrence and endoscopic severity.[12]

The paper is a complete and extensive review of the following PubMed key words: neurologic manifestations and IBD, neurologic manifestations and inflammatory bowel diseases, extra-intestinal manifestations in IBD. Table 1a and 1b contains the most commonly reported neurologic and neuromuscular IBD manifestations, even if the level of evidence relies partly on single case reports. Fig. 1 summarizes the pathophysiologic mechanisms for PNS and CNS neuropathy in IBD patients.

1.1. Peripheral neuropathy

Peripheral neuropathy (PN) is one of the most frequently reported neurological complications in IBD patients.[2,5] Several different PN phenotypes have been described in these patients. Paraesthesias due to small fibre involvement (autonomic or sensory) and increased threshold for temperature detection (or axonal sensory findings which could be indicative for early PN) are common in patients with CD who have been treated with metronidazole (21–39%), but also in those who have not received this medication (19%).[13] In a retrospective study of patients with PN and either CD or UC, conducted by Gondim et al.,[14] it was demonstrated that PN symptoms began earlier in the course of CD than in UC ($p<0.05$). In the same study it was shown that men with IBD may be more susceptible to the development of PN than women, but the latter may be more prone to demyelinating neuropathies (chronic inflammatory demyelinating polyneuropathy or multifocal motor neuropathy). Finally, it was concluded that even if axonal neuropathies are more common than demyelinating neuropathies, both can respond well to immunomodulatory therapy. The concept that PN manifesting in IBD is probably autoimmune-induced is strongly supported by further reports, describing recovery after initiation of steroid treatment.[15]

1.2. Drug induced neurotoxicity

Drug induced neuropathy has been ascribed to at least four different medications, commonly used in the treatment of IBD: (i) cyclosporine A (ii) metronidazole, (iii) sulfasalazine (iv) biological agents.