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INFLAMMATORY BOWEL DISEASES AND STROKE.

Neurology

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ABSTRACT

Ulcerative colitis (UC) is a chronic and debilitating disorder that is characterized by an inflammation of the colonic mucosa. The extra-intestinal 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. Cerebrovascular disorders are documented in 0.12% to 4% of IBD patients and apparently constitute the most extensively covered neurologic complication, as they play a very important role in disease morbidity. Physicians should be aware that patients with IBD and focal neurological deficits, even if they resolve automatically, are at an increased risk of stroke, independently of their age.

KEYWORDS

UC (Ulcerative Colitis) Stroke IBD (Inflammatory Bowel Disease) CNS (Central Nervous System)

Introduction:

Ulcerative colitis (UC) is a chronic and debilitating disorder that is characterized by an inflammation of the colonic mucosa. Most often diagnosed in patients aged between 15 and 30 years, it may present at any age. Women and men are equally affected. UC takes a relapsing–remitting course; common symptoms are abdominal pain and bloody diarrhea. Considering the pathogenesis, in addition to a genetic predisposition abnormal and excessive responses to dietary triggers, to unidentified infectious agents, and to the physiologic intestinal flora by an inadequately regulated mucosal immune system are currently being hypothesized [1,2]. 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 [3-6].

Ulcerative colitis:

Ulcerative colitis can affect any part of the colon, but is often restricted to the left side. Rectal involvement is almost always present. In approximately 30% of patients UC extends proximally to the splenic flexure, which is defined as left-sided or distal colitis. Only 15% of patients present with an extensive colitis, i.e. an inflammation extending beyond the splenic flexure. However, subsequent proximal extension eventually occurs in approximately 35% of patients with initial proctitis or left-sided colitis. Medical treatment consists of stepwise oral or topical mesalamine (or its retarded derivative mesalazine), corticosteroids, and immunosuppressants (6-mercaptopurine, azathioprine and cyclosporine). If there is very limited disease activity, probiotics are equally efficacious as mesalamine. In carefully selected patients, leukocyte apheresis or treatment with specific monoclonal antibodies (see below) may be beneficial. Patients with UC probably bear an increased lifetime risk for the development of colorectal cancer. Therefore, proctocolectomy is recommended in any case of intraepithelial neoplasia in an endoscopically non-resectable polyp, or if a high-grade intraepithelial neoplasia is present in flat mucosa [1,2,7].

Effects of IBD on CNS:

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 B1, B12, 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 [8-10].

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]. Fig. 1 summarizes the pathophysiologic mechanisms for PNS and CNS neuropathy in IBD patients [13].

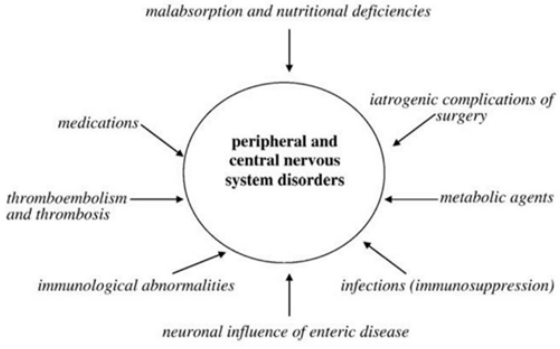

Figure 1: Pathophysiology of neurologic disorders in IBD

IBD and Stroke:

Cerebrovascular disorders are documented in 0.12% to 4% of IBD patients and apparently constitute the most extensively covered neurologic complication, as they play a very important role in disease

morbidity [14]. They occur at any age in both sexes and tend to correlate with disease activity. Cerebral and retinal arterial and venous circulation may be affected by a hypercoagulability related thrombosis, vasculitis and consumption coagulopathy leading to hemorrhagic events [15,16]. It has been shown that especially UC patients have a three to fourfold increased risk of thromboembolism [17]. It is unclear whether primary venous or arterial strokes are more frequent. With respect to the latter, large artery infarctions involving the anterior and posterior circulation, as well as lacunar infarcts have been described. Autochtonous thrombosis, arterio-arterial and paradoxal embolism are possible pathogeneses. Lately, an association of UC and thrombotic cytopenic purpura with its risk for small and large artery thrombosis has also been proposed [13].

As early as in the 1930s arterial and venous thromboses complicating UC have been reported [18]. Reports of ischemic strokes and cerebral venous/sinus thromboses followed [19]. Etiologically, a non-specific hypercoagulable state as well as cerebral vasculitis have been vaguely hypothesized. Meanwhile, it has been shown that UC patients have a three- to fourfold increased risk of thromboembolism (incidence approximately 6.5%), which seems to be independent from the association with classic thrombophilic risk factors such as immobilization, surgery, steroid therapy and others [10]. Keller et al analyzed administrative claims data sourced from the Taiwan National Health Insurance Database. Our study consisted of a study cohort comprising 516 UC patients and a comparison cohort of 2,579 subjects without IBD. Cox proportional hazards regressions were performed to estimate the risk of subsequent stroke during the follow-up period. They also conducted additional analyses investigating the risk of subsequent stroke by age group and gender. As a result, they detected an increased HR for subsequent stroke among Taiwanese UC patients when compared to that among matched comparison patients without IBD [20].

An increased risk of thrombosis is recognised in patients with IBD. The incidence of "thrombo-embolic (TE)" complications ranges between 1–8% [21]. The increased risk of TE complications appears to be unique to IBD when compared to other inflammatory conditions. Mieshler et al [22] demonstrated that IBD patients have a 3.6-fold higher risk of thromboembolism compared with controls. An increased risk was not seen in patients with coeliac disease or rheumatoid arthritis. The majority of TE cases (60%) in patients with IBD occurred during periods of increased disease activity or in the presence of gastrointestinal complications such as fistulae and abscesses [22].

Conclusion:

- There is evidence that UC can manifest both in the PNS and in the CNS.
- The association of neurologic disorders with IBD is probably more common than appreciated and may follow a different pattern of involvement in UC and CD.
- Newer prospective studies of the different aspects of the neurologic manifestations of UC and additional work on its pathogenesis are needed.
- Physicians should be aware that patients with IBD and focal neurological deficits, even if they resolve automatically, are at an increased risk of stroke, independently of their age.

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