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TOPIC HIGHLIGHT

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Structural brain lesions in inflammatory bowel disease

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Abstract

Central nervous system (CNS) complications or manifestations of inflammatory bowel disease deserve particular attention because symptomatic conditions can require early diagnosis and treatment, whereas unexplained manifestations might be linked with pathogenic mechanisms. This review focuses on both symptomatic and asymptomatic brain lesions detectable on imaging studies, as well as their frequency and potential mechanisms. A direct causal relationship between inflammatory bowel disease (IBD) and asymptomatic structural brain changes has not been demonstrated, but several possible explanations, including vasculitis, thromboembolism and malnutrition, have been proposed. IBD is associated with a tendency for thromboembolisms; therefore, cerebrovascular thromboembolism represents the most frequent and grave CNS complication. Vasculitis, demyelinating conditions and CNS infections are among the other CNS manifestations of the disease. Biological agents also represent a risk factor, particularly for demyelination. Identification of the nature and potential mechanisms of brain lesions detectable on imaging studies would shed further light on the disease process and could improve patient care through early diagnosis and treatment.

Key words: Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; Structural lesions; Magnetic resonance imaging; Brain lesions

Core tip: Central nervous system complications or manifestations of inflammatory bowel disease deserve particular attention because symptomatic conditions can require early diagnosis and treatment, whereas unexplained manifestations might be linked to pathogenic mechanisms. This review focuses on both symptomatic and asymptomatic brain lesions detectable on imaging studies, as well as their frequency and potential mechanisms. A direct causal relationship between inflammatory bowel disease and asymptomatic structural brain changes has not been demonstrated, but several possible explanations, including vasculitis, thromboembolism and malnutrition, have been proposed. Identification of the nature and potential mechanisms of

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INTRODUCTION

Inflammatory bowel diseases (IBDs), namely ulcerative colitis (UC) and Crohn's disease (CD), are chronic, debilitating conditions with their onset at relatively young ages. CD is a transmural disease of gastrointestinal mucosa, and it has the potential to affect the entire gastrointestinal tract; in contrast, UC is not a transmural disease, and it affects the colon[1,2]. Both have relapsing and remitting courses. It is estimated that the total (UC plus CD) prevalence of IBD is approximately 0.4% in the Western populations[3].

Because IBD can involve body parts other than the gastrointestinal tract, it can be regarded as a systemic disease. Involvement of the skin, eyes, joints, liver, biliary tract, kidneys, and bone, as well as hematological, and neurological involvement, can occur, preceding, accompanying or following gastrointestinal symptoms. These extraintestinal manifestations are more common in CD patients, although a substantial number of IBD patients can develop these conditions[4-6].

Neurological manifestations are relatively rare but are of clinical importance, particularly in terms of the need for timely diagnosis and management. Several mechanisms, including thromboembolisms, immunologic abnormalities, drug side effects, malabsorption, and infections, have been suggested as pathogeneses[7]. Most central neurological manifestations of IBD can be detected by brain imaging studies because they cause structural alterations of neural structures to some extent. However, lesions of unknown clinical relevance have also been detected in these patients, with significantly higher prevalence than in the normal population.

This review focuses in particular on structural brain lesions with positive findings on imaging studies, including symptomatic conditions and asymptomatic situations with brain lesions as well (Table 1).

ASYMPTOMATIC STRUCTURAL CHANGES ON MAGNETIC RESONANCE IMAGING

To date, a small number of studies have examined the presence of white matter lesions and other structural alterations on imaging studies in patients with IBD. These lesions were asymptomatic with potential associations with IBD, and whether these structural changes represent a unique extraintestinal manifestation of the disease remains unclear. Figure 1 depicts white matter and gray matter (GM) on an magnetic resonance imaging (MRI) scan.

Initial reports examining the associations between IBD and asymptomatic brain lesions were conflicting[8,9]. In a study by Geissler *et al*[8], 72 patients with IBD (48 cases of CD and 24 of UC) and 50 healthy age-matched controls underwent magnetic resonance imaging with gadolinium-enhanced studies. In that series, hyperintense focal white-matter lesions of 2-8 mm in diameter were found in 42% and 46% of patients with CD and UC, respectively, whereas such lesions were only present in 16% of healthy controls, resulting in relative risks of 2.6 for CD (95%CI: 1.3-5.3) and 2.9 for UC (95%CI: 1.3-6.2). A longer duration of disease and older age were associated with an increased tendency for the lesions, and none of the patients had neurological symptoms. In contrast to the study by Geissler *et al*[8], Hart *et al*[9] did not find a significantly increased frequency of asymptomatic brain white matter lesions on the MRIs of IBD patients (n = 40), compared to a control group consisting of 40 age- and sex-matched patients admitted for tension-type headache (12.5% *vs* 5%, P = 0.43). Although the relatively small sample size of the latter study might have prevented the differences from attaining statistical significance, the authors emphasized that such asymptomatic lesions had previously been reported consistently in healthy subjects[10], and they expressed concerns about the clinical relevance of these findings for patients with IBD. However, it should be emphasized that both reports dated from two decades ago. In contrast, a recent study with a relatively small sample size also could not find an increased rate of white matter lesions among patients with IBD, compared to healthy controls[11]. In that study, the frequencies of white matter lesions and other brainstem parenchymal lesions were similar, but among the subjects with white matter lesions, the number of lesions was significantly higher in IBD patients.

Two recent studies compared the frequency of white matter lesions between IBD patients and normal subjects using advanced magnetic resonance imaging techniques and equipment[12,13]. Chen *et al*[12] found a very high prevalence of hyperintense white matter lesions in patients with CD, compared to age-matched controls (75% *vs* 34%, $P < 0.001$). Their study had a relatively large sample size (54 Crohn's patients and 100 age-matched controls). Similarly, Zikou *et al*[13] found a significantly increased frequency of white matter lesions among patients with IBD (Crohn's and UC), compared to controls (66% *vs* 45%, $P < 0.05$). Both studies used fluid-attenuated inversion recovery images to evaluate white matter hyperintensities.

The development of advanced MRI techniques has allowed for better examination of brain structures, including estimation of volume differences and the evaluation of microstructural integrity. Voxel-based morphometry is a technique used to compare the regional

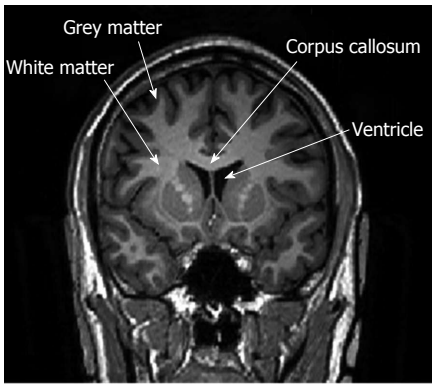

Figure 1 T1-weighted magnetic resonance image of a coronal section through the brain. Gray matter and white matter are indicated, as well as the ventricles.

brain volumes of subjects, and it uses MRI data. Several studies using this technique have found a decreased GM volume among IBD patients, compared to controls. Agostini *et al*[14], in a study of CD patients, found decreased GM volume in parts of the frontal gyrus and in the anterior midcingulate cortex. In addition, negative correlations between disease duration and GM volume in several brain regions were found in the former study. In contrast, a recent study by the same lead author did not identify any decrease in GM volume in UC patients, compared to controls[15]. Zikou *et al*[13], however, found more diffuse GM volume decreases in a sample of IBD patients, consisting of subjects with CD and UC, involving the right and left fusiform gyri, the right and left temporal inferior gyri, the right precentral gyrus, the right superior motor area, the right middle frontal gyrus and the left superior parietal gyrus.

Diffusion tensor imaging (DTI) is an MRI technique that measures molecular diffusion. It is valuable for the identification of axonal injury and can be useful in differentiating between primary and Wallerian degeneration[16]. To date, only a single study has examined the brains of IBD patients using DTI techniques and compared them with age-matched healthy controls[13]. That study found decreased white matter axial diffusivity in the right corticospinal tract and the right superior longitudinal fasciculus in IBD patients (Crohn's and UC) compared to controls, indicating a possible degree of change in neural structures[17-21].

Several possible explanations have been proposed for the increased prevalence of white matter lesions, the decreased GM volume, and the decreased diffusivity in major tracks among patients with IBD. White matter lesions on brain MRI examinations have been associated with many conditions, including migraine headaches, hypertension, diabetes, celiac disease, and cerebrovascular disease, as well as being found in healthy subjects[10,22-26]. The increased frequency of white matter hyperintensities in IBD patients might be due to central nervous system (CNS) vasculitis, likely secondary to coagulation and vessel obstruction[13]. IBD is known to be associated with thromboembolism and hypercoagulability[27-29]. Another possible explanation is malabsorption because such lesions were previously described in celiac disease[26].

Table 1 Structural brain lesions

Asymptomatic structural changes
Symptomatic structural changes
Cerebrovascular lesions
Demyelinating conditions
Cerebral vasculitis
CNS infections

CNS: Central nervous system.

One explanation for decreased GM volume might be excito-toxicity due to chronic pain, which can result in neural atrophy or loss[14,30]. Structural changes of varying types have been observed in pain-related brain regions in other chronic pain syndromes[31-36], with GM decreases in the frontal and cingulate cortices being the most common anomalies[30]. Another possible mechanism might be increased inflammatory cytokines, resulting in astrocyte and oligodendrocyte apoptosis, decreased neurogenesis, and increased oxidative stress, thus leading to GM volume loss[37,38]. Similarly, cerebral small vessel vasculitis and the neurotoxic effects of cytokines could be responsible for the decreased axial diffusivity in major tracts[13].

Although a direct causal relationship between IBD and asymptomatic structural brain changes cannot be established, the available findings and their implications deserve further investigation, particularly in the context of the brain functional changes observed in patients with IBD[39].

CEREBROVASCULAR LESIONS

Patients with IBD have an increased tendency for thrombotic events so that IBD could be considered a prothrombotic condition that increases the risk of cerebral arterial and venous thrombosis[40-44]. A recent meta-analysis found a modestly increased risk of cerebrovascular accidents among patients with IBD (OR = 1.18)[45]. The increased risk was more prominent among female patients and young patients. Venous thrombosis has also been seen in these patients with remarkable frequency[44,46-49]. Cerebrovascular events have been documented in up to 4% of IBD patients[50]. These cases are of particular clinical importance when the consequences of these conditions and the young age of the patient population are considered.

A number of pathological conditions have been linked to IBD in attempts to propose a mechanism for the increased tendency for thromboembolic events, including abnormalities of platelets and coagulation factors, genetic mutations, vitamin B6 deficiency due to hypercatabolism and malabsorption, antiphospholipid antibodies, hyperhomocystinemia, dehydration, and immobilization[4,7,40,49,51-58]. However, to date, the exact mechanism has not been fully understood.

Cerebral arterial thromboembolism can present with headache, paresis, seizures or dysphagia, and it can result in high mortality and morbidity[51]. Large infarcts involving both the anterior and posterior circulation and lacunar infarcts have been reported in IBD[59-63]. In addition, UC has been associated with thrombotic thrombocytopenic purpura and small and large cerebral artery thrombosis risks[64-66]. Infarcts associated with IBD can be identified on computerized tomography and magnetic resonance imaging.

Cerebral venous thrombosis and sinus thrombosis seem to be more frequent in patients with UC than in CD patients[67]. Most often, the superior sagittal sinus and lateral sinuses are involved; however, thrombosis of the cortical venous sinuses has also been reported[68]. Young and male patients seem to be at greater risk[50,69,70]. The most common presenting symptom is headache, usually followed by neurological impairment, and cerebral infarction can develop due to extension of thrombus[71]. A combination of magnetic resonance imaging and magnetic resonance venography could identify venous occlusion[71]. The radiological characteristics, as well as the clinical course and prognosis of IBD-related cerebral venous thrombosis, seem to be similar to those in cases not related to IBD[44,72,73].

DEMYELINATING CONDITIONS

Demyelinating conditions have been reported in the setting of IBD, in association or not with biological treatments.

Multiple sclerosis (MS) or MS-like conditions have long been reported in patients with IBD[74-77]. Such a relationship was first reported by Rang *et al*[74]. A retrospective study found an increased incidence of demyelinating disease among patients with IBD, particularly in UC[77]. Nevertheless, MS has been reported in both UC and CD[78,79]. The findings of a recent meta-analysis supported a relationship between MS and IBD[80]. Both the development of an MS-like syndrome in the setting of IBD and the development of IBD in MS patients have been reported[81-83]. Because the diagnostic criteria for MS have evolved over time, some lesions found in previous studies might not actually be MS; rather, they could represent an MS-like syndrome, which might potentially be linked to IBD. The mechanism of these relationships has not been fully explained, but a role for impairments in functional T-cell subsets has been proposed[4,57].

Anti-tumor necrosis factor (TNF)-alpha drugs and anti-alpha4 integrin drugs (such as natalizumab), which are biological agents used in the treatment of IBD, can have adverse neurological effects[84,85]. Progressive multifocal leukoencephalopathy is the gravest complication, particularly when associated with natalizumab therapy, although few cases have been reported in association with TNF-alpha drugs[85]. Reactivation of John Cunningham virus (JCV) is responsible for the development of PML, and it is associated with visual defects, mental impairment, confusion and personality changes, followed by motor weakness[57]. MRI is helpful in the diagnosis, showing white matter lesions with typical T1 and T2 signals[86]. Diagnosis can be confirmed by polymerase chain reaction for JCV DNA. Despite treatment, PML has a high mortality rate of 60%[87]. In addition, development/exacerbation of MS or demyelination has been reported in association with anti-TNF-alpha therapy[88-90].

CEREBRAL VASCULITIS

Cerebral vasculitis has been reported in patients with UC in a number of studies[91-96]. In addition, a case of cerebral vasculitis was reported in association with CD[97]. Mostly immune-mediated mechanisms have been proposed for the development of vasculitis in UC. Magnetic resonance imaging is abnormal and shows hyperintense lesions[95,96], and magnetic resonance angiography can aid in diagnosis[97]. CNS vasculitis has also been reported in association with anti-TNF therapy[57]. The major symptoms of cerebral vasculitis are stroke, headache and encephalopathy. Other symptoms include seizures, cranial nerve palsies or myelopathies[98]. Cerebral vasculitis mimicking migraine with aura was reported in a case of CD, and the authors stated that migraine with aura can be the only finding in cerebral vasculitis[99]. Cerebral vasculitis resulting in stroke has been rarely reported in UC[61]. Cerebral vasculitis presented with right paresis and unbalanced gait in a 35-year-old woman with UC[93]. Another UC case was complicated by convulsions and was diagnosed as cerebral vasculitis on magnetic resonance imaging[96].

CNS INFECTIONS

Anti-TNF agents can suppress the immune system to such an extent that opportunistic infections develop, including of the CNS, in IBD patients. These patients present with meningeal signs, seizures, symptoms resembling stroke, and encephalopathy[100]; abnormal MRI findings and/or mass lesions are found on imaging studies. Among these opportunistic infections are fungal infections, cerebral tuberculosis, Epstein-Barr virus infection, nocardiosis, toxoplasmosis, herpes simplex virus infection, meningococcal infection, *Campylobacter fetus* infections, and listeria infections[57]. In a severe case of CD with ileocecal involvement, opportunistic meningitis with varicella zoster was reported after adalimumab and prednisone treatment[101]. In a patient with CD, meningococcal meningoencephalitis was reported after certolizumab pegol treatment[102].

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