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# Neurological Manifestations of Inflammatory Bowel Disease

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## Abstract

The inflammatory bowel disease (IBD) is associated with different neurological and psychiatric disorders, which are integrated among the extra-intestinal manifestation of this disease. The physiopathology of neurological manifestations of IBD varies among the different kind of complications. The origin and the significance of these manifestations must be understood by clinicians who manage IBD patients. Some of them are related to therapeutic agents. The present chapter consists of a review of the most prevalent neurological and psychiatric disorders associated with IBD. The physiopathology of those entities will also be discussed, as well as the appropriate management for their prevention and treatment.

**Keywords:** neurological disorders, psychiatric disorders, thrombosis, demyelination, peripheral neuropathy, extra-intestinal manifestations

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## 1. Introduction

Inflammatory bowel disease (IBD) is a chronic disease of the gastrointestinal tract with an unknown etiology, which alternates between periods of symptoms relapse and remission [1, 2]. IBD involves various entities. Crohn's disease (CD) and ulcerative colitis (UC) are the most common, but other inflammatory conditions of the gastrointestinal tract are also included under this term, such as the indeterminate colitis, microscopic colitis and pouchitis [3]. In the present chapter, only CD and UC are discussed.

The incidence of IBD is different depending on its two main forms. CD is diagnosed in 0.5–10.6 patients/100,000 inhabitants/year, while the global incidence of UC is estimated at 0.9–24.3 patients/100,000 inhabitants/year. There is some evidence about the increase of these incidence figures in the past 10 years [2]. On the other hand, the prevalence of CD in European countries ranges from 1.5 to 213 cases per 100,000 people and the prevalence of UC ranges from 2.4 to 294 cases per 100,000 people [2].

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IBD consists of an inflammation of the bowel, with different extension and histological features between CD and UC. However, this disease does not only involve the gastrointestinal tract, but there is also a long list of extraintestinal manifestations that can emerge prior to or during the disease. The most frequent ones are those involving the skin (dermatological), the joints (rheumatological), the eyes (ophthalmological), the liver and/or the biliary tract and the genitourinary area (gynecological and/or urological). The prevalence of at least one extraintestinal manifestation varies from 6.2 to 46.6% [4].

Neurological manifestations of IBD are unusual, but they are potentially harmful, leading to severe and irreversible consequences if they are not detected and managed early and properly. The prevalence of neurological manifestations has not been appropriately established, but some authors have reported a prevalence of 20–30%, although there is a general belief that subclinical or unrecognized neurological impairment may be present in IBD patients [4–6].

The aim of the present chapter is to briefly review the main neurological manifestations associated with IBD, with a special focus on their physiopathological mechanisms.

## **2. General pathophysiological considerations of IBD and its neurological manifestations**

Although a specific etiological agent in the development of IBD has not been established, it is widely accepted that some scenarios may be associated with the development of this disease [4]:

- An inflammatory reaction to a persistent bowel infection.
- The presence of defects in the barrier of the intestinal mucosa to act against certain antigens.
- The presence of disturbances in the immune response to certain antigens.

In this regard, a dysfunction of the immune system and a chronic inflammatory response appear both in the context of a specific environmental situation and in a genetically predisposed patient [1]. However, bearing in mind the physiopathology of neurological manifestations, there are different mechanisms that may specifically be involved in their development [4]:

- Malabsorption and secondary deficit of vitamins (mainly vitamin B12), which are essential for myelin maintenance and regeneration [7].
- Hypercoagulability state, related to a chronic inflammatory response that may lead to ischemic events.
- Formation of metabolic toxic agents in the damaged bowel.
- Immunological disturbances that may lead to autoimmune response against glial-neural components.
- Opportunistic infections secondary to the impairment of the immune system or because of the treatment for IBD.

These mechanisms can lead to neurological damage acting individually or in combination. The identification of the leading mechanism is essential to prevent greater neurological damage. Unfortunately, in many cases, it is not possible to identify the main pathological factor.

Nevertheless, disease-related mechanisms are not the only ones that need to be considered to understand the origin of neurological manifestations. The pharmacological agents usually used in IBD may also lead to the development of such manifestations. The appropriate selection of a therapeutic agent depends on the subtype of disease (CD or UC), location and phenotype of the disease [8].

Some of these treatments try to prevent new relapses of the disease, whereas others try to control the symptoms during a relapse. The vast majority of these therapeutic agents can produce neurological manifestations as an adverse effect (**Table 1**), thus clinicians always have to consider the possibility that neurological manifestations in IBD patients may have a pharmacological rather than a primary IBD-related origin.

| Drug category |                    | High frequency<br>(>1 case per 100 patients)  | Low frequency<br>(>1 case per 1000 patients)   | Rare (>1 case per 10,000 patients)   | Unknown frequency             |
|---------------|--------------------|---|--|--|-------------------------------|
| Steroids      |                    |   |  | Seizures.<br>Development or worsening of psychiatric disorders (euphoria, mood and personality changes, depression and psychosis)            | Dizziness, headache, insomnia |
|               | 5-Aminosalicylates |   |  | Headache, dizziness and peripheral neuropathy  |                               |
| Antibiotics   | Metronidazole      | Seizures, peripheral neuropathy. Others: dizziness, ataxia, incoordination, confusion, irritability depression, weakness, insomnia and encephalopathy |  |  |                               |
|               | Ciprofloxacin      |   | Headache, dizziness, sleep disorders, taste disorders, motor hyperactivity   | Sensitive disturbances, tremor, seizures, migraine, incoordination, olfactory disorders, confusion, anxiety, depression, psychotic reactions | Peripheral neuropathy         |
| Ciclosporin A |                    | Tremor, headache, seizures, paresthesia   | Encephalopathy, confusion, disorientation, decrease level consciousness, anxiety, insomnia, visual disturbances, cortical blindness, comma, paresia and ataxia | Motor polyneuropathy, optic nerve edema  | Migraine                      |

|              |                    |   |  |  |  |
|--------------|--------------------|---|--|--|--|
| Methotrexate |                    | Paresthesia   | Motor weakness, encephalopathy, seizures and headache  | Mood disorders and cognitive disturbances. Motor weakness, aphasia, cranial nerve disturbances               | Intracranial hypertension, neurotoxicity, arachnoiditis, paraplegia, astonishment, ataxia, dementia, dizziness |
| Thiopurines  | Azathioprine       |   |  | Myasthenic crisis, paresia, polyneuritis   | Progressive multifocal leucoencephalopathy when other immunosuppressors are combined                           |
|              | 6-Mercaptopurine   | Not reported  |  |  |  |
| Anti-TNF     | Infliximab         | Headache, dizziness   | Depression, confusion, amnesia, anxiety apathy, drowsiness. Demyelinating disease exacerbation |  |  |
|              | Adalimumab         | Mood changes (depression), anxiety, insomnia. Headache, paresthesias, migraine, radicular compression | Cerebrovascular accident, tremor, neuropathy   | Multiple sclerosis and other myelinating disorders (optic neuritis and Guillain-Barré syndrome)              |  |
|              | Certolizumab pegol |   |  | Demyelinating disease, including multiple sclerosis (onset or exacerbation). Seizures, peripheral neuropathy |  |
|              | Golimumab          | Dizziness, headache, paresthesias. Depression, insomnia   | Instability  | Multiple sclerosis and other demyelinating diseases, dysgeusia   |  |
| Vedolizumab  |                    | Headache, paresthesia   |  |  |  |
| Ustekinumab  |                    | Dizziness, headache   | Depression. Facial palsy   |  |  |

**Table 1.** IBD treatment-related neurological complications with categorization of their frequency.

### 3. Venous and arterial thrombotic and thromboembolic manifestations

Thromboembolic events are common in the context of IBD, secondary to the hypercoagulability state that exists in this disease. This hypercoagulability is associated with an increase of coagulation-associated factors and thrombin levels, as well as fibrin formation; a decrease of natural anticoagulant factors; a decrease in fibrinolytic activity; the presence of endothelial anomalies; and an increase in the count and activity of platelets [9].

Overall, the incidence of thrombotic complications is 1.2–7.5% in clinical studies, but this can rise to 39% when post-mortem studies are considered [10, 11]. Both arterial and venous system may be affected, but deep venous thrombosis and pulmonary thromboembolism are the most common thromboembolic complications in IBD [10–13].

Intracranial thromboembolic events are much less frequent. Cerebral venous thrombosis is more common in CU than in CD, and this may involve superficial or deep cerebral venous systems or even some of the brain venous sinus [11, 14]. The risk of thrombotic or thromboembolic complications in the brain is clearly associated with the activity of the disease. During these periods, IBD patients have a higher risk of cerebral thromboembolic complications than the normal population [9, 10]. These events are rarely reported during periods of non-activity of the disease [9, 10], although some authors have described a higher incidence of thromboembolic events in IBD patients than in healthy controls not only during a relapse of the disease but also during remission periods [15]. Larger cohort and case-control studies are needed to confirm this finding, because if IBD patients suffer more thromboembolic events even during remission periods, anticoagulant therapies might be routinely indicated.

In any case, the increase of thromboembolic events during relapses is clearly related to the inflammatory response whose effect in the coagulation and platelet system has been described above. Nevertheless, the use of steroids, dehydration, the increase of homocysteine and infections (all of which are associated with relapsing periods) may also contribute to the development of thrombotic complications [10–13, 16]. Furthermore, the presence of mutations in Leiden factor V in IBD patients leads to a higher incidence of thrombotic events [17].

Therefore, bearing in mind the high risk of thromboembolic events in IBD patients, mostly during relapses [18, 19], it is essential to rapidly initiate a primary prophylaxis, with an early mobilization, a correct rehydration and vitamin reposition, as well as the use of prophylactic anticoagulants (mainly low molecular weight heparins). All of these measures are proven to be useful in the prevention of venous thromboembolic events [20].

On the other hand, IBD patients also seem to present a higher incidence of arterial thromboembolic events. Indeed, many studies have reported an association between cardiovascular events and other chronic inflammatory diseases, like rheumatoid arthritis, lupus or psoriasis [21–23]. Active IBD is also associated with a higher risk of cardiovascular events (spontaneous or after surgical/invasive procedures), especially in young female patients [9].

When arterial thromboembolic events occur in the brain, they can be classified as ischemic stroke. Although the literature agrees about the high risk of thromboembolic events in IBD

patients, the increase in the incidence of ischemic stroke in IBD patients is a matter of debate [9]. In this regard, Huang et al. [24], in a large retrospective cohort study, analyzed the risk of ischemic stroke in IBD patients of a Taiwanese population. Although the studied groups were not completely comparable in demographical and comorbidity features, the authors reported a higher prevalence of ischemic stroke in IBD patients (mainly in CD patients) than the general population (hazard ratios for UC and CD were 1.01 [95% confidence interval = 0.84–1.21] and 1.15 [95% confidence interval = 1.04–1.28], respectively) [24]. Similar results were reported in a Danish population-based setting (also with a mismatch in comorbidity distribution), showing a relative risk (RR) of 1.15 of suffering ischemic stroke in an IBD population (95% confidence interval 1.04–1.27) of suffering ischemic stroke in an IBD population [25]. Therefore, there is weak evidence of the higher incidence of ischemic stroke in IBD populations. In any case, it seems to be of the utmost importance to manage cardiovascular risk factors in IBD patients [9]. Their combination with the pro-thrombotic situation that may be present in any phase of IBD can play a major role in the development of brain ischemic complications, which are associated with a high level of dependence and an important worsening of quality of life.

However, vascular events may not be only associated with pro-thrombotic conditions. Vasculitis may also contribute to the presence of neurological manifestations. Bearing this in mind, systemic vasculitis is also considered an extra-intestinal manifestation of IBD. Wegener's granulomatosis, Takayasu arteritis, medial temporal arteritis and Cogan's syndrome (among others) have been reported in combination with IBD [4, 26]. For example, Takayasu arteritis is associated with IBD in 9.6% of cases [27], and this frequency seems to be higher in CD patients (9%) [28] than in UC (6.4%) [29]. The pathogenesis of vasculitis associated with IBD is mediated by immune complex deposits and cytotoxic lymphocytes [30]. The vasculitis of IBD patients involves medium and large caliber vessels and may lead to brain ischemic events [4], and some of them can directly affect the central nervous system (CNS) [31]. The global frequency of vasculitis associated with IBD is unknown, but it has been reported that such cases of vasculitis involving the CNS are rare [31]. Furthermore, this manifestation seems to be independent of the activity of the disease in the gastrointestinal tract [30, 32]. A correct diagnosis of CNS vasculitis is essential, because it allows the initiation of the appropriate treatment and the prevention of significant neurological impairment. Thus, when IBD patients present any CNS vascular event, vasculitis must be considered as a possible diagnosis and it has to be appropriately ruled out.

#### 4. Demyelinating diseases

The association of demyelinating diseases has been proposed since the early 1980s. Rang et al. described a higher prevalence of multiple sclerosis (MS) than expected in UC patients [33]. Subsequently, this finding has been confirmed by many reports, but not only for UC but also for CD [34–36]. For instance, Gupta et al. described an increased risk of optic neuritis and other forms of MS in CD (odds ratio = 1.54) and UC (odds ratio = 1.75) [35]. In the same line, a recent meta-analysis concluded that IBD patients present a higher risk of suffering from concomitant MS and vice versa (i.e. MS patients have a higher risk of suffering from associated IBD) [36]. These authors found an increased risk of 50% [36].

However, some authors have proposed that the development of demyelinating diseases in IBD patients is more related to the use of anti-TNF $\alpha$  drugs [37]. In this regard, the Spanish registry

of autoimmune adverse events of biological agents (BIOGEAS Project) reported 12 cases of MS and 25 cases of optic neuritis in IBD patients treated with anti-TNF $\alpha$  [38]. Furthermore, this phenomenon is not exclusive to IBD patients. Arthritis patients treated with anti-TNF $\alpha$  agents may develop MS or demyelinating lesions, with a partial or complete resolution of neurological symptoms after discontinuing the medication [39]. An increased number of new white matter lesions and new relapses have also been reported in MS patients treated with infliximab [40]. On the other hand, the use of Natalizumab, a monoclonal antibody against  $\alpha$ 4-integrin used in some cases of IBD, is associated with progressive multifocal leukoencephalopathy (PML). This disease appears after a reactivation of the JC virus infection, and the use of Natalizumab is clearly associated with this reactivation. PML is associated with a bad prognosis with a mortality rate at 6 months above 60% [37].

Apart from demyelinating diseases associated with IBD, there is strong evidence of a higher prevalence of white matter lesions in neurologically asymptomatic IBD patients than in healthy subjects [5, 41]. Although these lesions are usually asymptomatic, their number and volume tend to increase with age (mostly in CU patients) [41]. In any case, whenever these lesions become symptomatic, their association with other CNS complications (e.g. cerebrovascular complications) has to be identified.

Therefore, in spite of the plausible relationship between MS and IBD, the presence of white matter lesions is not evidence of the coexistence of both diseases. In fact, most of these lesions have no clinical relevance and their presence in IBD patients should not be used to infer active CNS disease [42]. Further research is needed about the origin of these lesions and their neurological and cognitive consequences in IBD patients.

## 5. Epilepsy

The relationship between epilepsy and IBD is uncertain. Lossos et al. reported a prevalence of 1.9% in a cohort of 638 IBD patients, although the majority of these patients had a structural and/or metabolic cause that may lead to epileptic seizures [32]. Other authors have reported an improvement of seizures in CD patients after treatment initiation, suggesting that immunological mechanisms may be associated with the development of this disorder [43]. This finding might also be supported by some case reports [44].

However, the most plausible explanation for the development of epileptic seizures in IBD patients is that other CNS complications (e.g. thromboembolic events or unspecific white matter lesions) or other systemic complications (e.g. dehydration, low levels of magnesium, etc.) may facilitate its development [45, 46]. Because of the above, a correct therapeutic management may help to resolve and/or prevent this condition.

## 6. Peripheral neuropathy

Peripheral neuropathy (PN) is one of the most common neurological complications in IBD patients [32, 43, 47]. Many factors have been associated with the development of PN, such as extraintestinal inflammation, immunological phenomena, nutritional disturbances



(e.g. malabsorption-related vitamin deficit) and adverse effects of IBD therapeutic agents (e.g. metronidazole or anti-TNF agents) [48–50]. Whenever these causes are ruled out, the frequency of PN in IBD patients varies from 0 to 39% [51].

IBD-associated PN may be associated with axonal damage or demyelination and it may have an acute or chronic presentation [47, 51]. Cases of mononeuropathy, plexopathies, multiple mononeuritis, compressive neuropathies and cranial neuropathies have also been reported [50]. Bearing this in mind, IBD-related PNs present great clinical variability, although there is a certain dominance of non-demyelinating vs. myelinating forms [48].

Demyelinating forms have a better prognosis than non-demyelinating forms, because they have a more favorable response to immunotherapy. This situation may be related to the role that T lymphocytes seem to play in demyelinating IBD-associated PNs. On the other hand, the relationship between axonal PNs and immunological disturbances is less clear [47, 48].

## 7. Psychiatric disorders

IBD patients show a high prevalence of psychiatric disorders, with depression and anxiety as the main diagnosis [1, 52, 53]. The prevalence of depression in IBD patients varies from 15 to 30%, but the frequency of anxiety rises to 80%, mainly associated with the relapses of the disease [54, 55]. There is no overall difference in the frequency of psychiatric disorders between UC and CD [52].

Several factors have been associated with IBD-related depression: female gender, active intestinal disease, the presence of fistulas or perianal disease, use of biological treatments and the necessity of surgery because of IBD [55]. On the other hand, IBD patients with IBD seem to present more aggressive phenotypes of the disease, with more relapses and shorter periods of remission [52]. In any case, the prevalence of depression or anxiety is even higher when other psychiatric conditions coexist [1, 52, 53].

Anyway, depression and anxiety are not the only IBD-associated psychiatric disorders. The Manitoba IBD Cohort Study reported a higher prevalence in IBD patients than in general population of panic and obsessive-compulsive disorders [56]. Controversy exists around bipolar disorder. On the one hand, the Manitoba IBD Cohort Study reported a lower prevalence of bipolar disorder in IBD than in the general population. On the other hand, Eaton et al. (2010) reported a higher frequency of this psychiatric condition in IBD patients, more specifically in CD patients [57].

However, it is widely accepted that there is an infra-diagnosis and infra-treatment of psychiatric disorders, with no systematic screening established in clinical guidelines. There is a strong evidence of the presence of a bidirectional relationship between the degree of inflammation in the gastrointestinal tract and the development of depression. This can be explained by the brain-gut axis hypothesis. The brain and the gut are communicated by the autonomic nervous system (sympathetic and parasympathetic systems). The vagus nerve (the main parasympathetic afferent) transmits information to the CNS about luminal osmolarity, carbohydrate levels, mechanical distortion of the mucosa and the presence of bacterial or cytostatic drugs. On the other hand, sympathetic afferents transmit visceral pain [58].

Information sent by the gastrointestinal system reaches the medulla (nucleus tractus solitarius) and travels upstream until it reaches the paraventricular nucleus where it finally modulates the hypothalamic–pituitary–adrenal (HPA) axis [59].

Some authors proposed that an impairment in the gut-brain axis can be induced by stress. In this regard, stressful situations lead to a vagal inhibition and an overactivation of the sympathetic system. These conditions associated with other CNS-mediated responses involving the modulation of the immune system and the HPA axis may be associated with the appearance of a gastrointestinal immunoinflammatory response [58, 60]. For instance, during depression, an elevation of alpha-TNF, IL-1, reactive C protein and haptoglobin and a decrease of IL-10, TGF- $\beta$ , albumin and transferrin are observed [61].

Therefore, there is a notable association between IBD and psychiatric disorders. New studies are necessary to elucidate in which cases the psychiatric condition is the cause or the consequence of IBD. This may help to understand pathophysiological aspects of IBD that are still unknown and ultimately may allow better management of the disease.

## 8. Conclusion

IBD patients may suffer from different neurological manifestations during their disease. The pathophysiological mechanisms involved in these complications are variable and, in many cases, they are still unrecognized. Anyway, clinicians must stay focused on the early identification of IBD neurological complications and to rapidly establish the appropriate management to prevent further impairment.

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