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.

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Contents

1. Introduction ......................................................... 116
1.1. Peripheral neuropathy ........................................... 116

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 in isolation or in combination: (i) malabsorption and nutritional, particularly vitamin deficiencies such as B₁, B₂₂, 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. The multiplicity of pathways by which the 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 varies 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 B₁, B₂₂, 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.5,10 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

1.1. Peripheral neuropathy

Peripheral neuropathy (PN) is one of the most frequently reported neurologic 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.
Cyclosporine A (CyA) is a cyclic polypeptide, which interferes with the transcription of cytokines, thus inhibiting the activation and maturation of various cell types involved in cell-mediated immunity. It is mainly used in the treatment of steroid-refractory acute severe UC. Clinical presentation of neurotoxicity, which occurs up to 25% of CyA users, includes seizures, tremors, paraesthesias, ataxias, motor deficits, aphasia, altered consciousness and various degrees of visual and oculomotor disturbances. Pathogenesis of the central nervous system toxicity is poorly understood. CyA-induced visual disturbances such as hallucinations, cortical blindness and oculomotor disturbances, are extremely rare complications that have been well documented before. Porges Y et al. reported a case of CyA-induced optic neuropathy, ophalmoplegia and nystagmus in a patient with CD. The reported patient developed severe visual loss caused by irreversible bilateral optic neuropathy, clinically compatible with ischemic optic neuropathy. Although the pathogenesis of optic neuropathy in the reported patient was not clear, possible mechanisms that have been involved include direct toxicity to peripheral nerves or indirect effect through thromboembolic phenomena leading to ischemic optic neuropathy. Although thromboembolic events during CyA therapy have been detected in branches of the retinal artery, the mechanism

<table>
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<th>Table 1a Neurologic manifestations reported in IBD.</th>
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<td>Manifestation</td>
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<td>Increased reflexes with tremor</td>
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<td>Prolapsed nucleus pulposus</td>
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<td>Cerebellar syndrome or organic brain syndrome</td>
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<td>Classic migraine</td>
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<td>Atypical cerebellar disorders</td>
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<td>Atypical vestibular system disorders(vertigo, loss of equilibrium, etch)</td>
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<td>Acute inflammatory demyelinating neuropathy (antiTNFα)</td>
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<td>CNS tumors</td>
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However, CyA-induced neurotoxicity has been reported during CyA treatment, sometimes with hypomagnesemia. Cerebellar atrophy and toxicity have been described during treatment of CD even in the absence of appendicular and truncal ataxia accompanying by cerebellar atrophy, which was disclosed on MRI examination. The condition reversed on discontinuation of the drug and correction of the associated factors.

The difference between oral and i.v. infusion of CyA is another important issue. Because CyA is insoluble in water, the i.v. preparation is formulated in a polyoxyethylated castor oil and ethyl alcohol. Rat dorsal root ganglion neurons exposed in vitro to the i.v. preparation exhibited axonal swelling and degeneration. No effect of CyA (dissolved directly in serum) was seen on testing individual components of the i.v. solution. However, 0.1% polyoxyethylated castor oil (volume of solute/volume of solvent) produced axonal swelling and degeneration and 0.001% polyoxyethylated castor oil produced demyelination in vitro. Polyoxyethylated castor oil is manufactured by reacting castor oil with ethylene oxide, and it is speculated that residual ethylene oxide or a polymerization product may be responsible for the in vitro neurotoxicity. Although little is known about the pharmacokinetics of polyoxyethylated castor oil, plasma levels of 0.001 to 0.01% polyoxyethylated castor oil (volume of solute/volume of solvent) are probably achieved with therapeutic doses of the i.v. CyA preparation. Overall, the Cosmetic Ingredient Review Expert Panel concluded that these cosmetic ingredients are safe in the practices of use. Therefore, no serious neurotoxicity of CyA could be attributed to them.

Metronidazole is an antibiotic drug commonly used in patients with IBD, especially CD. Peripheral neuropathy is a well-documented side effect of the drug, especially in cases with daily dosages over 800 mg and for long periods of time. In addition, metronidazole-induced neuropathy is characterized by sensory phenomenology (with occasional sensory ataxic features) with or without resolution after discontinuation. The authors underscore the need to closely monitor the neurologic status of patients undergoing chronic treatment with metronidazole.

Sulfasalazine is a widely used and highly effective anti-inflammatory agent in the treatment of CD and UC, also being used with increasing frequency in the treatment of various rheumatological disorders. Severe side effects such as neurotoxicity necessitating discontinuation occur in less than 5% of treated patients. The adverse effect of sulfasalazine in causing folate deficiency has been well documented previously. There are several reasons for this. Firstly, the drug causes oxidative damage to red cells leading to haemolysis and increased folate requirements. Secondly, it can impair folate absorption in a competitive manner, by inhibiting the jejunal hydrolysis of pteroylpolyglutamates and thus the absorption of most dietary folates. In addition, the drug has been shown to competitively inhibit three enzymes involved in the metabolism of folic acid, namely dihydrofolate reductase, serine transhydroxymethylase and methylene tetrahydrofolate reductase.

Recently, monoclonal antibodies against anti-tumor necrosis factor α (infliximab, adalimumab, certolizumab, etanercept, oncept and others) and against α4 integrins (natalizumab, MLN020) have been introduced in the treatment of IBD. However, these therapies carry the risk of severe adverse effects. The induction of lymphoma, opportunistic infections or reactivation of latent infections (e.g. tuberculosis), demyelination and optic neuritis have been reported. The increasing number of neurological complications report on the association between anti-TNF-alpha treatment and various disorders of peripheral nerve such as disconnection and sensory ataxic features.) with or without resolution after discontinuation.23
Guillain–Barré syndrome, Miller–Fisher syndrome, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy with conduction block, mononeuropathy multiplex, and axonal sensorimotor polyneuropathies and the temporal relationship of their occurrence to anti-TNFα treatment support the contention that they are drug induced. The exact mechanism(s) underlying such neurological sequelae remain uncertain. The proposed pathogeneses of TNF-alpha-associated neuropathies include both a T-cell and humoral immune attack against peripheral nerve myelin, vasculitis-induced nerve ischemia, and inhibition of signaling support for axons.

Most neuropathies improve over a period of months by withdrawal of the TNF-alpha antagonist, with or without additional immune-modulating treatment. The proposed pathogeneses of TNF-alpha-associated neuropathies include both a T-cell and humoral immune attack against peripheral nerve myelin, vasculitis-induced nerve ischemia, and inhibition of signaling support for axons. Most neuropathies improve over a period of months by withdrawal of the TNF-alpha antagonist, with or without additional immune-modulating treatment. Even severe cases have been reported, such as the case of a 40-year-old man with CD and acute paraplegia four months after initiation of infliximab.

The advent of progressive multifocal leukoencephalopathy under the treatment with natalizumab is also particularly noteworthy. Since several studies have independently demonstrated an increased prevalence of non-neurologic and neurologic autoimmune disorders amongst IBD, and particularly UC-patients, a heightened awareness of such unforeseen potential drug–disease interactions seems mandatory. Some have advocated a brain MRI to look for silent demyelination before initiating therapies of that kind. This may become the standard in practice in the future.

The most commonly used medications responsible for neurologic manifestations in IBD are summarized in Table 2.

### 1.3. Cranial nerve palsies

Cranial nerve palsies associated with CD have been previously reported in addition to ischemic optic neuropathy and sensori-neural deafness. The Melkerson–Rosenthal syndrome, characterized by recurrent facial nerve palsy, fissuring of the tongue and non-caseating tissue granulomas, has also been described in association with CD. Elsehety et al. in their retrospective review of 263 patients with CD, documented one case of sixth nerve palsy among other neurological complications reported. The long intracranial course of the sixth nerve palsy is compatible with vasculopathic sixth nerve palsy, which typically presents with the sudden onset of a unilateral abduction deficit accompanied by retro-orbital pain and diplopia. Complete recovery is observed and usually occurs within 2–3 months. The microscopic neuroanatomy of the sixth nerve reveals penetration by small nutrient vessels, occlusion of which produces infarction. It is hypothesized that microvascular ischemic demyelination of a portion of the nerve is a most likely cause of vasculopathic sixth nerve palsy. The area of ischemic demyelination subsequently undergoes remyelination over time, precipitating clinical recovery.

Optic neuropathy presenting as bilateral optic disc swelling is a rare complication associated in most cases with CD. However, Romero Arcoa P et al. reported the case of a 27-year-old woman with UC and optic neuritis. The ocular manifestations resolved when systemic mesalamine was initiated. Previously reported cases have been attributed to peripapillary inflammation, optic disc ischaemia or intracranial hypertension. Postulated causes of optic nerve ischaemia include a local vasculitis or general hypercoagulability. The underlying aetiology of intracranial hypertension is often elusive. Modern imaging emphasizes the need to exclude dural venous sinuses thrombosis, a serious cerebro-vascular complication reported in both CD and UC.

IBD can be associated with severe erosive arthritis that affects the craniocervical junction. This process, although infrequent, can result in severe neurological deficit if it is not recognized. The possibility of occultotantal involvement in any inflammatory atlantoaxial subluxation must be considered in the selection of treatment strategies.

### 1.4. Other cerebrovascular conditions

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. 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. It has been shown that especially UC patients have a three to fourfold increased risk of thromboembolism. 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. Autochthonous 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.

The pathophysiology of thrombosis in IBD patients is not fully understood. Associated coagulation problems are thought to be involved. These factors include thrombocytosis, increased levels...
of fibrinogen, fibrinopeptide A, factors V,VIII, antithrombin factor III deficiency and free protein S deficiency. There is a reported case of activated protein C resistance in a child with CD, who developed a thromboembolic event. In many reported cases there has been a link between steroid therapy and the development of thrombogenesis, which is explained on the basis of the antifibrinolytic action of the steroids, which may have augmented the hypercoagulable state in these children. A recent report confirms increases in fibrinogen, prothrombin fragment F1+2, platelets, plasminogen activator inhibitor-1 antigen and soluble thrombomodulin. Many of these levels are higher during the active phase of the disease. Besides these several coagulation abnormalities, attention has recently been focused on antiphospholipid antibodies, including anticardiolipin antibodies and lupus anticoagulant, hyperhomocysteinemia and changes in the lipid spectrum, which have been associated with a tendency to thrombus formation, particularly in cerebral vasculature in young patients. 

**1.5. Association with myopathies and other conditions**

Myasthenia Gravis (MG) has been reported to be associated with both UC and CD. The link between IBD and MG is thought to be related to the production of acetylcholine receptor antibodies. However, autoimmune disorders, including MG, occur more frequently in UC than in CD. MG is also associated with other autoimmune diseases including alopecia, lichen planus, vitiligo and systemic lupus erythematosus. Foroozan R et al. reported the case of a 21-year old male with ocular MG and UC, complaining for binocular diplopia and ptosis of the left upper eyelid. He was hospitalized for plasmapheresis and upon discharge treated with azathioprine, prednisone and mestinon. The symptoms resolved one month later. Based on the few reports with ocular MG in patients with IBD, the mean duration of IBD before the diagnosis of MG was 10 years. Autoimmune dysregulation is the central defect in both MG and IBD. Both IBD and MG may be associated with an elevated carcinoembryonic antigen (CEA) and decreased peripheral lymphocyte counts that subsequently normalise following thymectomy. Some studies have shown abnormal thymic involution and the presence of an abnormal ratio of T suppressor to T helper cells in both MG and UC, while others have noted a decline in suppressor T cells and an increase in immature T cells suggesting migration without normal maturation.

The immunological link between MG and IBD is highlighted by reports of patients undergoing surgical treatment. One report of a patient with both MG and CD documented improvement in perineal and perianal disease following thymectomy for severe uncontrolled MG. Another patient with both MG and UC demonstrated regression of the myasthenia following protocolecotomy.

Granulomatous myositis and myopathy associated not only with CD but also with UC have been reported previously, most of them during an acute exacerbation of the disease. Gilliam et al. described a case of leukocytoclastic vasculitis involving muscle associated with CD colitis. Most cases of polymyositis and pyomyositis have been associated mainly with CD, even if single cases associated with UC have also been reported. Spinal epidural abscess (SEA) is a rare but well-established and serious neurological complication of CD. Both immunosuppressive treatment strategies including chronic steroids and the presence of intra-abdominal or retroperitoneal fistulas represent factors that predispose for the development of SEA. A high index of suspicion is needed, as early diagnosis can lead to a better clinical outcome. Back pain that follows a flare-up of CD with and without obvious neurological signs may be the result of infarmed paravertebral and spinal structures and can serve as an early sign of SEA. SEA is a neurosurgical emergency in the setting of intolerable pain and/or progressive neurologic deterioration, particularly involving bowel or bladder function. Patients with SEA associated with CD often require a combination of medical and surgical therapy, in addition to a workup for and definitive treatment of bowel fistulas and psoas abscesses, hopefully to prevent recurrences. Prolonged use of antibiotics is recommended even if cultures do not yield causative organisms.

In addition, myeloradiculitis caused by Cryptococcus neoformans in a patient with UC has been reported, thus indicating that it should be included in the differential diagnosis of acute onset myeloradiculopathy, especially in cases of immunocompromised hosts. Lymphocytic encephalomyeloneuritis and UC and focal white matter lesions in IBD patients have been described. In patients with CD CNS tumors have also been reported (glioblastoma multiforme, cholesteatoma, spinal meningoia).

Other symptoms such as classic migraine, musculoskeletal headache, tension headache, Parkinson-like syndrome, dystonia, cerebellar syndrome, organic brain syndrome, chronic fatigue syndrome, urinary incontinence, orbital

C.D. Zois et al.
pseudotumor, muscle spasms and chronic back pain have also been reported in patients with IBD.3

Finally, an association of IBD and especially UC with atypical vestibular system disorders such as dizziness, vertigo, nausea and temporary loss of equilibrium has also been described.3 In addition, sensorineural hearing loss, a probable immunologic manifestation of IBD, has been reported in both diseases.105–108 The clinical manifestation of the disease is most often bilateral and progressive. The hearing level often fluctuates, with periods of deterioration alternating with partial or even complete remission. The tendency is for the gradual evolution of permanent hearing loss, which usually stabilizes with some remaining auditory function but occasionally proceeds to complete deafness. Vestibular dysfunction, particularly disequilibrium and postural instability, may accompany the auditory symptoms.

2. Discussion

It seems that neurologic manifestations of IBD consider a major health problem, affecting disease morbidity. There is evidence that UC and CD can manifest both in the PNS and in the CNS. It seems that involvement of the PNS occurs mostly in UC, whereas myopathy and myelopathy characterize CD. Direct extension of inflammatory masses or abscesses into the surrounding tissues is characteristic of CD. MS cannot be definitely ruled out in the patients with myelopathy. Nutritional deficiencies, and medications seem to play an important role in the development of neurological manifestations in patients with IBD.

Thromboembolism is a serious complication of IBD patients that may be sudden and fatal. Thromboses of the lower extremities and pelvic veins are most common, but complications may also present as strokes in young patients without evidence of atherosclerotic disease. Intravascular thrombosis in mucosal blood vessels may play a role in the pathogenesis of IBD. Some studies indicate that heparin may benefit the treatment of IBD.109,110 The risk factors, relationship between disease activity, corticosteroid use and thrombotic events, and incidence of concomitant coagulation disorders on thrombosis in IBD patients are still not completely understood. Nowadays, IBD patients are less frequently hospitalized and immobilized. This may be the reason why the current incidence of thrombotic complications is lower.111

Although the mechanisms involved in the pathogenesis of neurologic manifestations of IBD are not clear, it is probably related to a common dysimmune basis, affecting cell-mediated and humoral immunity and inflammatory mechanisms.5 In addition, infection by microbial agents, namely Campylobacter jejuni, is linked to exacerbations of IBD and may contribute to the development of autoimmune inflammatory demyelinating polyneuropathy.112

It has been known that some neurological manifestations may correlate with several parameters of IBD, such as extent, type and duration of disease. In addition, they usually parallel the activity of intestinal inflammation.

In conclusion, 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. Small numbers currently preclude a better characterization of the clinical spectrum and a better understanding of pathogenesis. A prospective, controlled population-based study is required to further elucidate the interrelationship between IBD and neurologic manifestations.

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