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TOPIC HIGHLIGHT

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Neurological disorders and inflammatory bowel diseases

Giovanni Casella, Gian Eugenio Tontini, Gabrio Bassotti, Luca Pastorelli, Vincenzo Villanacci, Luisa Spina, Vittorio Baldini, Maurizio Vecchi

Giovanni Casella, Vittorio Baldini, Medical Department, Desio Hospital, 20033 Desio, Italy
Gian Eugenio Tontini, Luca Pastorelli, Luisa Spina, Maurizio Vecchi, Gastroenterology and Gastrointestinal Endoscopy Unit, IRCCS Policlinico San Donato, 20097 San Donato Milanese, Italy
Gabrio Bassotti, Gastroenterology Section, Department of Medicine, University of Perugia Medical School, 06123 Perugia, Italy
Luca Pastorelli, Maurizio Vecchi, Department of Biomedical Sciences for the Health, University of Milan, 20146 Milan, Italy
Vincenzo Villanacci, Institute of Pathology, Spedali Civili, 25123 Brescia, Italy
Author contributions: All authors designed and wrote the current review article.
Correspondence to: Maurizio Vecchi, MD, Gastroenterology and Gastrointestinal Endoscopy Unit, IRCCS Policlinico San Donato, via Morandi 30, 20097 San Donato Milanese, Italy. maurizio.vecchi@unimi.it
Telephone: +39-2-52774655 Fax: +39-2-52774655
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Abstract

Extraintestinal manifestations occur in about one-third of patients living with inflammatory bowel disease (IBD) and may precede the onset of gastrointestinal symptoms by many years. Neurologic disorders associated with IBD are not frequent, being reported in 3% of patients, but they often represent an important cause of morbidity and a relevant diagnostic issue. In addition, the increasing use of immunosuppressant and biological therapies for IBD may also play a pivotal role in the development of neurological disorders of different type and pathogenesis. Hence, we provide a complete and profound review of the main features of neurological complications associated with IBD, with particular reference to those related to drugs and with a specific focus on their clinical presentation and possible pathophysiological mechanisms.

Key words: Inflammatory bowel diseases; Crohn's disease; Ulcerative colitis; Extraintestinal manifestations; Neurological disorders; Multiple sclerosis; Progressive multifocal encephalopathy; Demyelinating neuropathies; Cerebrovascular diseases; Side effects

Core tip: Extraintestinal manifestations occur in about one-third of patients with inflammatory bowel disease (IBD) and may precede the onset of gastrointestinal symptoms by many years. Neurological disorders are uncommon in IBD but they can represent an important cause of morbidity and relevant diagnostic issue. Furthermore, the use of immunosuppressant and biological therapies for IBD may also play a pivotal role in the development of neurological disorders. Hence, we review the main features of neurological complications associated with IBD, with particular reference to those related to drugs, thereby focusing on their clinical presentation and possible pathophysiological mechanisms.

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INTRODUCTION

Inflammatory bowel diseases (IBDs) are common causes of gastrointestinal morbidity in western countries. Extraintestinal manifestations are frequent in the course of IBD and, in some cases, may be the first manifestation of IBD, sometimes preceding the onset of gastrointestinal symptoms by many years[1].

Among the many extraintestinal manifestations af-

fecting various organs, neurological disorders of different type and pathogenesis have been documented[2]. Overall, the occurrence of neurological disorders during the course of IBD is uncommon[3], but they may represent an important cause of morbidity. Neurological complications appear to be more common in men and they usually appear after IBD diagnosis, rarely coinciding with exacerbations of the underlying bowel disease[3]. Only a few systematic studies have investigated their frequency in patients with IBD and the results have been frequently inconsistent due to differences in the methods used for case finding and outcome evaluation[4].

One of the largest studies, performed for this purpose on 638 patients with IBD [either ulcerative colitis (UC) or Crohn's disease (CD)], found neurological disorders in 3%[3], with another study[5] indicating a possible increase in the prevalence of demyelinating diseases, particularly of multiple sclerosis (MS). The increasing use of immunosuppressant and biological therapies may also influence the probability of IBD-associated neurological disorders because these agents, although rarely used, may cause central nervous system (CNS) white matter lesions[6], opportunistic infections[7] with clinical symptoms similar to MS[2], or JC virus (JCV)-mediated progressive multifocal leukoencephalopathy (PML)[7].

On the basis of these considerations, it is obvious that a physician treating IBD/patients should be able to recognize unexplained neurological symptoms, consider their association with IBD, and address a proper diagnostic and therapeutic work-up, possibly with the collaboration of a consultant neurologist.

In this review, we went through the different neurological complications associated with IBD, with particular reference to those related to drugs, with a specific focus on their clinical presentation and their possible pathophysiological mechanisms[8]. We divided the review into the following specific sections: (1) side effects of medications; (2) cerebrovascular diseases; (3) immune-mediated neurological disorders; and (4) miscellaneous.

SIDE EFFECTS OF MEDICATIONS

Biologics

Anti-tumor necrosis factor (TNF)-α drugs such as infliximab, adalimubab, certolizumab, etanercept, onercept[9] and anti-α4 integrin such as natalizumab and MLN020[10], generally referred to as biologic drugs, have all been tested in the treatment of IBD, but etanercept, onercept and MLN020 have not been registered for clinical use, and thus have only had a limited exposure. Although their use has been occasionally associated with the induction or exacerbation of several neurological diseases in IBD patients[11], the diagnosis of a possible causal relationship is usually made on the time-correlation between the use of the drug and the appearance of the neurological manifestation[12]. In a screening study by the Food and Drug Administration on Adverse Event Reporting System (FAERS), Deepak *et al*[13] reported 772 distinct neurological adverse effects secondary to TNF-α inhibitor exposure over a 10-year period. Thus, particular attention should be placed when an IBD patient on biologic therapy develops neurological symptoms, looking for a cause-effect relationship[14]. Conversely, in patients with neurological diseases before the start of biologic therapy, a neurological consultation must be performed and possible alternative therapies, including surgery, should be considered.

PML

Because of its severity and high mortality rate, PML is the most feared neurological complication for patients treated with biologics. Although its occurrence was originally observed in patients treated with natalizumab in combination with β1α interferon for MS, this disease has also been reported in IBD patients treated with natalizumab only and also in very few cases undergoing anti-TNF therapy[7]. PML is a demyelinating disease caused by the reactivation of JCV, a virus with specific tropism for glial cells in the brain[15]. JCV may be reactivated from sites of latency in lymphoid tissues in conditions characterized by reduced immune surveillance[16]. The explanation for the appearance of PML in natalizumab-treated patients is apparently related to both the action of JCV and to a probable increased release of infected lymphocytes from bone marrow determined by the binding of α4β1 integrin with the drug[17].

Yousry *et al*[18], in a review of about 3000 patients treated with natalizumab for MS, CD or rheumatoid arthritis, did not find any case of PML, thus suggesting a risk of PML of < 1 per 1000 patients treated for a mean time of 17.9 mo. The drug, at this moment, is not approved for IBD in Europe, while its use is confined to patients showing no response to anti-TNF agents in the United States. Clinicians should consider PML in the presence of visual defects (45% of all cases) and/or mental impairment (38% of all cases) such as dementia, confusion and personality changes. Indeed, cognitive impairment and behavioral changes frequently are the earliest clinical manifestations of PML[14]. A motor weakness may also be present.

The diagnosis is confirmed by magnetic resonance imaging (MRI), which reveals white matter lesions with typical T2 and T1 signals[18]. Cerebrospinal fluid (CSF) examination is usually normal but polymerase chain reaction (PCR) amplification of the JCV DNA is an important diagnostic tool. It is debated whether patients with IBD, similarly to what happens for MS patients treated with natalizumab, should undergo serial testing for anti-JCV antibodies before and during treatment either with natalizumab or with anti-TNF[18]. Indeed, patients on natalizumab can be risk stratified for the development of PML based on JCV antibody status, history of immunosuppressive drug and duration of natalizumab treatment. Singh *et al*[14] described that all cases of natalizumab-induced PML occurred in patients who were JCV antibody positive. The seroprevalence of JCV-specific IgG in healthy blood donors is estimated to be 50% by 30 years of age and this percentage in-

creases to 60% by 70 years of age[14]. The risk increases with duration of natalizumab therapy, particularly after 24 mo, but some cases have been reported after only 6 mo of therapy[14].

Discontinuation of natalizumab is recommended at the first suspicion of PML[14], and plasmapheresis is the recommended therapy to remove natalizumab, accelerate desaturation of the targeted α4-integrin receptors and restore leukocyte transmigration[14]. When immunosuppression is rapidly reverted in cases of natalizumab-associated PML, an exuberant immune response may occur: this condition has been termed immune reconstitution inflammatory syndrome[14]. The response targeting JCV is evident 2-6 wk later in the CNS and it often results in paradoxical worsening of PML symptoms[14]. High dose corticosteroids are recommended if clinical and radiographic worsening are noted several weeks after immune restoration. Despite these treatments, the clinical outcome of natalizumab-induced PML patients is poor with a reported mortality of 60% in patients with 6 mo follow-up[14].

Posterior reversible encephalopathy syndrome and similar diseases

Zamvar *et al*[19] described a posterior reversible encephalopathy syndrome in a 14-year-old boy affected by CD following infliximab infusion with generalized tonic-clonic seizures and visual disturbances probably caused by occipital lobe involvement. The patient recovered after drug discontinuation by which time he returned to normal.

Brigo *et al*[20] also described a 74-year-old man with CD, without a prior history of seizures, presenting with a seizure after the second infusion of infliximab and caused by a reversible encephalopathy syndrome, an acute form of encephalopathy characterized by headache, seizures and area of increased T2 signal in the posterior quadrants of the brain on MRI[20]. A direct correlation between seizures and infliximab treatment is likely in these cases because a sharp clinical improvement occurred 7 d after infliximab discontinuation.

Faivre *et al*[21] described a 64-year-old woman with CD developing encephalitis associated with acute neuropathy after two infusions of infliximab. The patient had acute anterograde memory deficiency associated with epileptic episodes without infectious, vascular, tumor or toxic causes[21]. MRI showed bilateral hippocampal hypersignals suggestive of limbic encephalitis. The clinical symptoms disappeared after infliximab withdrawal and seizures never relapsed even after discontinuation of antiepileptic drugs.

CNS vasculitis

The most common autoimmune manifestation associated with anti-TNF therapy is the development of antinuclear antibodies and anti ds-DNA autoantibodies without an associated clinical syndrome[22]. A systemic lupus erythematosus (SLE)/lupus-like syndrome occurs in some of these patients and it has been named anti-TNF-induced lupus (ATIL). This syndrome[23] usually shows a high prevalence of anti-dsDNA antibodies (> 90%) and a low prevalence of anti-histone antibodies (57%) in contrast to what is usually seen in drug-related lupus syndromes. As in patients with spontaneous lupus, patients with ATIL may develop vasculitis. This was the case in a 53-year-old woman with ileo-colonic CD in whom adalimubab therapy was complicated by the development of SLE with CNS vasculitis. The patient showed headache, drowsiness, visual defect in her right eye associated with pleural, peritoneal and pericardial effusion 4 mo after initiation of adalimubab therapy at a dose of 40 mg subcutaneously every other week. Brain MRI showed features suggestive of cerebral vasculitis.

Ramos-Casals *et al*[24] found 233 cases of autoimmune diseases possibly induced by TNF-targeted therapies with a prevalence of vasculitis and lupus respectively of 48% and 39%. Among the 92 patients with ATIL, CNS vasculitis was observed only in two patients (1 treated with infliximab for CD and 1 treated with etanercept for rheumatoid arthritis). In the case reported by Vannucchi *et al*[22], the autoantibodies disappeared and the clinical picture returned to normal 6 mo after anti-TNF withdrawal.

MS

The development or exacerbations of MS[25] or CNS demyelination are well-described neurological complications of TNF-α antagonist therapy. TNF-α antagonist might be effective for inflammatory neurological disorders such as MS because elevated levels of TNF-α have been demonstrated in serum or CSF of patients with MS[26].

Microglia and macrophages in the CNS secrete TNF-α with a direct role in the pathogenesis and demyelination of MS[27]. There are two forms of TNF-α: a trans-membrane protein (tmTNF) and a soluble form (sTNF); both interact with two distinct receptors, TNFR1 and TNFR2[28]. In the first stages of MS, TNF-α is involved in demyelination, while in later stages it is fundamental for remyelination[29]. In a double-blind placebo-controlled phase II human study of lenercept, a recombinant TNFR1 fusion protein, more lenercept-treated patients experienced exacerbations compared to placebo patients and these exacerbations occurred early, leading to early study termination[30].

There are several case reports of the development of MS[31] or CNS demyelination during treatment with TNF-α antagonist such as infliximab or adalimubab. The mechanisms of induction or exacerbation of MS and/or CNS demyelination are unknown. One possible hypothesis is that TNF-α has anti-inflammatory effects that may contribute to "off" signals in MS. The "on/off" balance of TNF-mediated signals is relevant to MS and the removal of TNF-α might potentiate the disease[30]. Anti TNF-α drugs, particularly infliximab, do not appear to cross the blood-brain barrier and neutralize local TNF-α-mediated tissue injury. Nevertheless, infliximab causes enhanced permeability of the barrier increasing the activation of myelin-specific peripheral autoreactive T cells[32]. TNFR2 function is important for the enhance-

ment of remyelination and the use of TNF-α antagonists may inhibit the tmTNF-TNFR2 axis[33].

The Mayo Clinic reported one case of MS in 500 CD patients treated with infliximab and another patient has been reported among 651 IBD patients treated with infliximab in the Danish Crohn Colitis database; three further cases of MS were reported in Edinburgh's experience of 620 patients treated with IFX[34]. It is unclear whether these demyelinating events are coincidental or causally associated with the use of TNF-α antagonists because the interval between the administration of anti-TNF-α agents and the appearance of symptoms varies greatly. Most researchers have reported that the average time between the beginning of treatment and the onset of neurological symptoms is about 5 mo[35].

Demyelinating neuropathies

The proposed pathogenesis of anti-TNFα-associated neuropathies encompasses both T cells and humoral immune attacks against peripheral nerve myelin, vasculitis-induced nerve ischemia and inhibition of signaling support for axons[11]. Most of these neuropathies improve over a period of several months after withdrawal of the drug, with or without additional immunomodulating treatment[11].

Guillan-Barré syndrome and its variant Miller-Fisher syndrome

Guillan-Barré syndrome (GBS)[36] and Miller-Fisher syndrome[37] are two types of demyelinating peripheral neuropathies reported during treatment with TNF-α antagonists. GBS is a post-infectious, immune-mediated disease, generally presenting as an acute inflammatory demyelinating polyneuropathy[36] characterized by ascending paralysis with rapid, progressive, symmetric limb weakness and areflexia.

The annual incidence is 1.5 cases/100000 and the mortality rate is about 5%. Approximately 10% of patients are still severely disabled at 1 year after diagnosis. Miller-Fisher syndrome is a rare variant of it and its main manifestation is descending paralysis affecting the eye muscles with the triad ophthalmoplegia, ataxia and areflexia[37]. It is possible that TNF-α antibodies unmask latent infections or cause an increased susceptibility to infections triggering or worsening the autoimmune demyelinating processes[11]. Two-thirds of GBS cases are associated with bacterial or viral infections such as *Campylobacter jejuni*, *Mycoplasma pneumoniae*, *Haemophilus influenzae*, cytomegalovirus (CMV), Epstein-Barr virus (EBV) and varicella zoster virus[37].

It is important to remember that GBS may be an independent extraintestinal manifestation of IBD induced by vasculitis, malnutrition or vitamin deficiencies[37]. Drug withdrawal is always suggested in the management of these patients and, in troublesome cases, cyclophosphamide or intravenous immunoglobulin is needed[37]. Vadikolias *et al*[38] reported a case of a 40-year-old man affected by CD developing autoimmune demyelinating acute paraplegia 4 mo after starting infliximab therapy. Some authors suggest that search subclinical demyelinating processes before initiating anti-TNF-α therapy, particularly in young patients[5], should become a recommended standard practice. Shin *et al*[36] described 15 cases of GBS identified from the postmarketing database of anti-TNF (9 patients on infliximab, 5 on etanercept, and 1 on adalimubab). The symptoms were reported between 6 wk and 2 years after the start of these therapies[36]. Thirteen patients have been subjected to regular follow-up and 12 showed a partial or complete resolution after adequate therapy for GBS[36]. Deepak *et al*[13], in the FAERS about neurological events in patients treated with TNF-α inhibitors, reported 153 cases out of a total of 772 with neurological manifestations related to anti-TNF-α therapy.

Lewis-Summer syndrome

Nancey *et al*[39] reported two cases of Lewis-Summer syndrome (LSS), also called multifocal acquired demyelinating sensory and motor neuropathy, related to the use of infliximab. LSS is a rare, dysimmune, multifocal peripheral nerve disorder described for the first time in 1982 by Lewis *et al*[40], and characterized by asymmetric multifocal and sensory involvement of the nerve roots and trunks of the upper and lower limbs. The disease should be suspected in the presence of distal, asymmetric weakness affecting the upper or lower limbs with initial sensory impairment followed by motor involvement[39]. An electromyographic study showing persistent multifocal conduction blocks allows the diagnosis[39]. LSS involves only peripheral nerves without any damage to central myelin[39].

Multifocal motor neuropathy with conduction block

Barber *et al*[41] reported one case of multifocal motor neuropathy with conduction block (MMNCB) following treatment with infliximab. This is an asymmetric motor neuropathy with diagnostic features including the presence of multifocal partial motor conduction block and the presence of blood anti-GM1 antibodies in 50% of cases. No more than 10 cases of MMNCB associated with anti-TNF therapy have been reported in the international literature. The rate of progression of demyelinating neuropathies is highly variable ranging from a few days to many years and the recovery is not always certain after drug withdrawal[41].

Following suspicion of peripheral neuropathies related to biologic therapy, a consultation with a neurologist should always be suggested for a differential diagnosis between small fiber polyneuropathies and an axonal sensory-motor neuropathies (SM-PNs) characterized by areflexia, sensory ataxia, minor cutaneous sensory deficiency (distal dysesthesia)[41] and variable degree of motor dysfunction.

Ischemia and inhibition of signaling support for axonal transport are the mechanisms proposed for secondary axonal loss. It is conceivable that the adverse effect

of TNF-α antagonists on peripheral nerves is cumulative and, therefore, the severity of neuropathy is proportional to the total dose of the drug received[3]. These data emphasize the importance of long-term vigilance during the course of the treatment with TNF-α antagonists. In most cases, drug withdrawal resolves the complication[3].

Chronic inflammatory demyelinating polyneuropathy

Some cases of Chronic inflammatory demyelinating polyneuropathy (CIDP) have been reported during anti-TNF therapy[42,43], appearing 4-17 mo after initiation of infliximab, with the possible presence of GM2 antibodies in the serum. CIDP is characterized by weakness in the proximal and distal extremity muscle groups associated with bilateral foot drop and a stocking-glove pattern mostly localized in the lower extremities[42]. Electrodiagnostic studies reveal progressive acquired demyelinating sensory and motor peripheral polyneuropathy. Withdrawal of the offending agent does not always reverse the immune process and chronic immunotherapy may be needed to control the inflammatory process and improve clinical outcome[42].

Infections of the nervous system

B-lymphocyte depletion in immunocompromised patients causes meningitis by encapsulated bacterial pathogens, while T-lymphocyte depletion or impaired macrophage function cause the development of infections by intracellular pathogens such as fungi, particularly *Aspergillus* and *Nocardia*, viruses such as herpes simplex virus (HSV), JCV, CMV, human herpes virus 6 and parasites such as *Toxoplasma gondii* (*T. gondii*)[44].

In general, although anti-TNF agents may increase the risk of infections, even at neurological levels, and particularly for intracellular organisms, several observations indicate that the risk of opportunistic infections is greatly increased when patients are treated with more than one immunosuppressant drug. Thus, the main recommendation originating from these observations is to limit multiple immune suppression to the shortest time possible.

Patients with infections of the nervous system may present with many clinical manifestations including meningeal signs, mass lesions, encephalopathy, seizures and stroke-like presentation[44].

CNS fungal infections

CNS infections by *Aspergillus* are usually characterized by mass lesions such as brain abscesses or by cerebral infarction, and more rarely by meningitis[44]. *Cryptococcus neoformans* may show as subacute meningitis with fever and headache without neck stiffness. Mass cerebral lesions usually have a subacute or chronic presentation while meningitis and encephalitis have a more acute presentation. In patients with meningeal signs and/or encephalopathy, a lumbar puncture should be performed with strain culture or serology of CSF[44]. MRI should always be performed in patients with a strong clinical suspicion of encephalopathy. MRI should be performed and tissue biopsy sampling may be always considered[44] in patients with cerebral mass lesions, for a differential diagnosis between tuberculosis, lymphoma and toxoplasmosis. Lumbar puncture should also be always performed in these cases because a positive EBV PCR in the CSF suggests the presence of CNS lymphoma.

Meningococcal meningoencephalitis

Majumder and Kumar[45] described a case of a 51-year-old woman affected by CD showing meningococcal meningitis during treatment with certolizumab in clinical remission for 6 mo. Meningococcal vaccination is safe and it should always be considered in high-risk IBD patients, particularly in those subjected to biologic therapy[46].

Listeria infection

In 2000 Morelli *et al*[47] described for the first time a *Listeria* infection complicating infliximab therapy in a CD patient. *Listeria monocytogenes* (*L. monocytogenes*) is a Gram-positive, rod-shaped, facultative intracellular organism. About 1%-5% of all healthy adults are asymptomatic carriers of *L. monocytogenes*. In the United States, 2500 cases/year are reported and the mortality rate is 15%-30%. Mortality of *Listeria* meningoencephalitis infection, associated with sepsis, is particularly high in pregnant women, neonates and immunocompromised subjects, where it may reach 33% of cases[47]. Listeriosis is a foodborne infection caused by ingestion of soft cheeses, unpasteurized milk, unwashed vegetables, ready-to-eat foods such as hot dogs and cold cuts, and it may be more frequent in populations eating raw food such as those living in Africa and Asia. It is important to wash the hands and to scrub fruits and vegetables[47]. TNF-α, produced by monocytes, macrophages, lymphocytes, and fibroblasts, has a crucial role against *L. monocytogenes* as well as all other intracellular organisms. In fact, TNF-α is crucial in host resistance against intracellular organisms by mediating local inflammation to control infection[47]. Generally, blood culture becomes positive for Gram-positive bacilli after 32 h and lumbar puncture reveals a high percentage of polymorphonuclear leukocytes. Ampicillin and gentamicin is the treatment of choice for listeriosis[47]. On the basis of the above considerations, it is important that patients receiving anti-TNF therapy observe safe food practices and refrain from the above-mentioned food products.

Campylobacter fetus infection

Umehara *et al*[48] described *Campylobacter fetus* (*C. fetus*) meningitis in a CD patient on long-term steroid therapy after only one infusion of infliximab. *C. fetus* is a Gram-negative, mo(b)tile, bacterial species with a typical S-shaped rod morphology and it is particularly present in immunocompromised, pregnant women and neonates in whom it may cause endocarditis, thrombophlebitis, pneumonia, pleurisy and arthritis[49]. The bacterium lives in the intestinal flora of cattle and sheep where it causes

spontaneous abortions[50].

Toxoplasmosis

Young *et al*[51] described a case of cerebral toxoplasmosis during infliximab therapy associated with low doses of prednisone, methotrexate and leflunomide in a 36-year-old woman affected by severe rheumatoid arthritis. The most important neurological symptoms were diffuse headache, slurred speech, weakness in the left arm, and a grand mal seizure. MRI imaging showed two lesions within the right hemisphere and the diagnosis of *T. gondii* infection was obtained by brain biopsy[51]. *T. gondii* is an obligate intracellular parasite infecting up to a third of the world's population[51]. *T. gondii* infection is acquired by ingestion of food or water contaminated with oocysts shed by cats, or by eating undercooked or raw meat containing tissue cysts[52]. Primary infection is usually subclinical but, in some patients, cervical lymphadenopathy, ocular disease, encephalitis, myocarditis and pneumonitis may occur[52]. The disease may be life-threatening in immunocompromised patients, and CNS involvement has been described in AIDS patients[52], and patients receiving corticosteroid[52] and anti-TNF-α[52] therapy. Lassoued *et al*[53] described two cases of chorioretinitis related to *T. gondii* during anti-TNF therapy, with malaise, low-grade fever and visual defects as major complaints[52]. TNF-α has an important role in the protection against *T. gondii* infection, playing a synergic role with interferon γ[54]. Response to treatment for toxoplasmosis occurs early and, in patients with compatible MRI of the brain, empirical treatment should be started[51]; early response to treatment usually confirms toxoplasmosis diagnosis.

Nocardiosis

Wendling *et al*[55] described cerebral nocardiosis during adalimubab and methotrexate therapy for rheumatoid arthritis. A 63-year-old Caucasian man showed the appearance of subcutaneous nodules in the trunk with histological diagnosis of pyogenic granulomas, pulmonary nodules upon chest radiography, and neurological signs such as headache, vertigo, cerebellar dysarthria after 8 mo combined therapy[55]. Brain computed tomography (CT) and MRI showed two lesions with edema and a mass effect in the right parietal region and cerebellum. Surgical biopsies revealed a pyogenic abscess and the presence of *Nocardia farcinica*. Nocardiosis is caused by an opportunistic, aerobic, Gram-positive, filamentous bacterium of the order Actinomycetales. The most common species are *Nocardia asteroides*, *Nocardia brasiliensis*, and *Nocardia otitidis caviatum*. This bacterium has a long incubation period[55]. Modes of contamination include inhalation and direct inoculation through the skin[55]. Systemic nocardiosis is defined by the presence of two or more foci of infection[55]; the lung is the most common primary site of systemic nocardiosis (60%-80% of cases) and cerebral or other locations may occur in 20%-40% of cases. CNS involvement is responsible for the worst prognosis with a 75% rate of mortality, particularly in lupus patients[53]. TNF plays a role in the clearance of *Nocardia* in animal models[55]. However, nocardiosis is rare during anti-TNF-α therapy and only eight cases[55] have been reported among 300000 patients treated with anti-TNF agents in the United States. Anti-TNF-α may accelerate and disseminate previously undiagnosed nocardiosis, particularly when therapy comprises corticosteroids and methotrexate.

Herpes simplex infection

Herpes simplex encephalitis (HSE) has been reported in patients receiving TNF-α antagonist therapy[56]. Also, TNF-α inhibitor therapy appears to be associated with an increased risk of herpes zoster[57]. An increase in the risk of severe HSV infection is related to the use of TNF-α inhibitors because TNF is an important element of the innate immune response to HSV-1 encephalitis, as reported in animal models[58]. About 95% of all cases of HSE are attributed to HSV-1 and, only occasionally, HSV-2 has been described[59]. Bradford *et al*[56] has identified three adults affected by HSE during monoclonal antibody TNF-α inhibitors. The patients clinically showed altered mental status, such depression or reduced affective response, slow mental processing, memory disturbances, fever, meningismus and headache. In patients receiving TNF-α the clinical manifestations may be atypical. Brain MRI shows characteristic temporal lobe involvement, CSF PCR positive for HSV DNA, and the clinical picture significantly improves after acyclovir therapy[56]. More than 90% of adult patients with HSE have temporal lobe abnormalities on brain MRI and a positive HSV PCR at clinical presentation[60]. Weil *et al*[61] reported that these diagnostic tests might be initially negative in 5%-27% of patients if they are performed early in the disease course. Bradford *et al*[56] reported that two of three patients initially had normal brain MRI and negative results for CSF HSV PCR. Recently published guidelines[62] emphasize the need to repeat HSV PCR in 3-7 d if the results are initially negative and the clinical course is highly suggestive for HSE. Bradford *et al*[56] suggest that in patients on anti TNF-α therapy and a clinical presentation suggestive for HSE, empirical acyclovir treatment should be performed until the result of a second PCR. The mortality of HSE at 1 year is 14%-22% and most survivors have residual neurological and cognitive deficits[63].

Lu *et al*[64] reported a case of Bell's palsy caused by HSV in a 43-year-old woman on adalimumab therapy (40 mg biweekly) for CD for 3 years. The patient showed small painful erythematous ulcers on her oral mucosa and lips, fever and right-sided facial palsy suggestive of Bell's palsy secondary to HSV infection. Her symptoms disappeared after 7 d treatment with three 1-g tablets/d valacyclovir, associated with adalimubab withdrawal, but symptoms recurred after rechallenge with adalimubab. Bell's palsy is an idiopathic peripheral facial nerve paralysis and reactivation of HSV may play a major role

through inflammation of the facial nerve[65].

EBV infection

Nozaki *et al*[66] reported one case of Epstein-Barr encephalitis during TNF-α antagonist therapy but the patient also had concurrent HIV infection. Several studies have investigated the possibility of EBV reactivation in patients treated with infliximab but no significant increased risk emerged[67]. Lavagna *et al*[68], in a study of 60 patients with CD treated with infliximab, did not observe any EBV viremia or any clinical manifestations of EBV infection during and after treatment. Serum EBV DNA was never found in a series of EBV-IgG-positive patients treated with TNF-α blockers[69].

Cerebral tuberculosis

Tissot *et al*[70] described a 40-year-old man with CD treated with infliximab monotherapy for 16 mo complicated by the appearance of neurological symptoms such as blurred vision, and motor and sensitive deficiency of the right lower limb. Clinical examination showed a papular erythematous skin lesion localized on the left lateral cervical region and multiple cervical nodes. Cerebral MRI revealed multiple ring-enhancing lesions suggestive of tuberculoma, and chest-abdomen CT showed an upper lobes alveolar syndrome and multiple abdominal lymph nodes suggestive of miliary tuberculosis. This diagnosis was confirmed by skin lesion biopsy with evidence of giant cell granuloma, and PCR for *Mycobacterium tuberculosis* in cultures of bronchial washing lavage. The patient was subjected to classical anti-tuberculosis treatment, with progressive disappearance of all cerebral lesions and complete resolution of neurological symptoms. Therapy for cerebral tuberculosis should comprise four drugs (isoniazid, rifampicin, pyrazinamide and ethambutol) for 2 mo followed by isoniazid and rifampicin for at least 10 mo[70]. Andrisani *et al*[71], in their experience of 92 IBD patients who were candidates for anti-TNF therapy, suggested screening for high-risk latent tuberculosis reactivation during therapy by means of Quantiferon TB-Gold (QFT-G) and tuberculin skin test (TST) because both are useful for identification of high-risk patients.

Ocular nervous disorders

Anterior optic neuropathy[72] and retrobulbar demyelinating optic neuropathy[73] have also been reported as possible complications of infliximab therapy. The clinician should be alert to anterior optic neuropathy when patients, during anti-TNF therapy, develop bilateral simultaneous sudden visual loss with decreased visual acuity, without pain related to eye movements, and swollen optic discs with bilateral inferior arcuate defects upon ophthalmology evaluation. Retrobulbar (posterior) optic neuropathy shows the same symptoms of anterior optic neuropathy, perhaps with monolateral visual loss, and only an ophthalmologist may obtain the diagnosis with specific tests such as visual field and flash visual evoked potentials[73]. Risk factors such as stroke, arterial hypertension, diabetes, atherosclerosis and hypercholesterolemia should always be ruled out[74]. Anterior optic neuropathy generally appears early within the first three infusions of infliximab[74]. In the study of Tissot *et al*[70], three patients with infliximab-related anterior optic neuropathy were described; one had impaired visual loss after rechallenge with infliximab infusion, confirming the association between infliximab and optic nerve damage. To date, four cases of toxic, infliximab-related anterior optic neuropathy and 10 cases of retrobulbar optic neuritis have been described[75]. No patients with toxic anterior optic neuropathy improved after pulsed intravenous infusion of methylprednisolone while all 10 patients with retrobulbar optic neuritis did improve[73]. At this moment, more data are needed to evaluate the exact pathogenic mechanism and dose relationships between these ocular manifestations and infliximab[74]. Deepak *et al*[13], in a FAERS Study about neurological manifestations in patient on anti TNF-α therapy, reported 105 cases of optic neuritis (13.6%) in 772 patients with neurological manifestations during anti TNF-α therapy.

Steroids

Repeated or prolonged exposure to steroids may cause myopathy that needs to be differentiated from predominant involvement of large motor fibers[75]. Steroid therapy may also produce a psychotic condition[76]. Corticosteroid therapy increases the risk of infection in a dose-dependent fashion[77] and corticosteroid-treated patients with intestinal disease have a relative risk of lethal and nonlethal infections of 1.4 (95%CI: 1.1-1.7, $P = 0.02$). Doses of prednisone > 20 mg/d are associated with a twofold increase in overall relative risk of lethal or nonlethal infectious complications compared with controls ($P < 0.004$). *L. monocytogenes* sepsis and meningitis have been described in adult and pediatric patients treated with high doses of steroids with or without azathioprine[78]. The long-term use of steroids may also predispose to the development of *C. fetus* meningitis[78].

Sulfasalazine

Sulfasalazine is still used for both CD and UC because of its low cost/effectiveness ratio. However, its use is mostly hampered by the frequent occurrence of side effects and neurological complications have also been reported.

Severe neurotoxicity leading to drug withdrawal has been reported in < 5% of patients[79]. The neurological toxicity of the drug appears mainly to be related to folate deficiency[80]; a typical adverse result of chronic sulfasalazine intake through different mechanisms: oxidative damage to red cells leading to hemolysis[81]; inhibition of jejunal hydrolysis of pteroylpolyglutamates blocking absorption of dietary folates; and competition with the three enzymes (dehydrofolate reductase, serine transhydroxymethylase and methylene tetrahydrofolate reductase) mainly involved in folate metabolism. Patients with IBD are predisposed to hyperhomocysteinemia[80],

which is considered a risk factor for cardio-cerebrovascular events, and part of this condition might be related to the folate-depleting role of sulfasalazine.

Mechanisms other than folate deficiency appear to be present in patients treated with sulfasalazine who develop neurological disorders but the pathophysiological aspects are currently unknown[81]. Liedorp *et al*[82] described axonal polyneuropathy occurring after 2 years treatment with sulfasalazine without blood folic acid deficiency. Mut *et al*[83] noted a reversible encephalopathy after only 3 wk of sulfasalazine therapy, and the clinical symptoms and MRI lesions resolved completely after drug discontinuation. Gold *et al*[84] have suggested that the drug might also be implicated in the occurrence of MS.

Methotrexate

Methotrexate is an immunosuppressant with anti-folate activity[85]. It is highly ionized with low lipid solubility and it does not readily cross the blood-brain barrier. Methotrexate is a cell-cycle-specific agent that inhibits the enzyme dihydrofolate reductase, preventing the conversion of folic acid to tetrahydrofolic acid and thus inhibiting cell replication[85]. Methotrexate also causes a relative excess of homocysteine determining small-vessel vasculopathy[85]. The risk of neurotoxicity increases with higher doses.

The association between low oral weekly doses of methotrexate and the development of posterior reversible encephalopathy syndrome (PRES) has been described in only a few cases. PRES often shows nonspecific symptoms such as headache, seizures, visual disturbances including cortical blindness, altered mental status, and even coma. Seizures are present in up to 88%, visual disturbances in 60%, and headache with altered mental function in > 50% of patients. In these studies, oral methotrexate had been taken for 3-7 years before the onset of symptoms. The patient described by Hart *et al*[85] was exposed to a total dose of 1560 mg over 4 years. Thus, the association of neurotoxicity with long-term use of methotrexate suggests a cumulative toxic effect on the blood-brain barrier. Neuroimaging, particularly MRI, is essential to obtain a diagnosis: classical lesions are symmetrical and located in the subcortical and cortical areas of the posterior circulation. The frontal lobe, brainstem, basal ganglia, thalamus, and even the spinal cord may also be involved.

Methotrexate-associated neurotoxicity is often termed as leukoencephalopathy (LEP), frequently presenting as transient seizures[85]. Also, headache, confusion and disorientation may be present[86]. LEP is a structural alteration of cerebral white matter in which myelin suffers the most damage. The basic pathophysiological mechanisms leading to methotrexate-induced LEP are unknown but they are multifactorial and include adenosine accumulation, homocysteine elevation, and its excitatory effect on N-methyl-D-aspartate receptor and alteration in biopterin metabolism[85]. The white matter changes are strictly localized to the cerebellum and this selective site may be explained by the involvement of Purkinje cell axons[81]. Only a few methotrexate-induced white matter changes during oral treatment[87] have been reported and most of them appeared to be related to folic acid deficiency. Chronic folic acid supplementation is thus mandatory in patients undergoing methotrexate treatment to avoid, if possible, these neurological side effects.

Metronidazole

Metronidazole is a commonly used antibiotic in the treatment of IBD, particularly in patients affected by CD[88] with perianal involvement. Peripheral neuropathy is a well-documented side effect of the drug, reported in 21-39% of CD patients treated with metronidazole, especially in patients receiving > 1.5 g/d of the drug for > 30 d[89]. Thus, monitoring the neurological state of the patient during metronidazole therapy is strongly encouraged[88]. Both demyelinating and nondemyelinating neuropathies can be observed[89]. Metronidazole-induced neuropathies are characterized by sensory manifestations with occasional ataxic features and generally are transient and resolve completely on discontinuation of medication[14,89]. Peripheral neuropathies are one of the most frequent neurological complications described in IBD patients[78]. The incidence of spontaneous peripheral neuropathy in IBD patients varies from 0.9%[2] to 3.6%[11]. These conditions are also described in other sections of this paper as side effects of biological therapies and in autoimmune nervous system disorders. Indeed, polyneuropathies in IBD may result from multiple interactions between immune-mediated disorders, nutritional imbalances, malabsorption, weight loss, vitamin deficiencies and drug-induced changes[89]. The most important symptoms of peripheral neuropathy are paresthesia and increased threshold for temperature detection (the last sign is indicative of early neuropathy)[88]. Axonal polyneuropathy usually is characterized by sensory loss and dysesthesia in a glove-and-stocking distribution, and decreased or absent ankle jerks with infrequent motor involvement[84]. Small fiber nondemyelinating sensory neuropathy is characterized by subjective numbness and tingling in the absence of demonstrable abnormalities on electromyography and nerve conduction studies[72], and may be misdiagnosed as fibromyalgia upon typically normal electrophysiological testing[14]. IBD patients with restricted sensory involvement are usually younger than those with concomitant involvement of motor and sensory large fibers[90]. Only some of these patients (particularly patients with CD) have been previously treated with metronidazole, and the disease progressed also after drug discontinuation, suggesting its contributory but not causative role[76]. The physician should suspect peripheral neuropathy in cases of sensitive disturbances of the upper and lower extremities, ataxia and/or impairment of walking[84].

Chatzkel *et al*[91] described a 15-year-old girl affected by CD with ataxia and dysmetria 7 d after initiation of

treatment with metronidazole. Cranial MRI revealed bilateral symmetric T2/FLAIR hyperintense lesions of the dentate nuclei without contrast enhancement or restricted diffusion, and the lesions disappeared completely after drug discontinuation[91].

Cyclosporine A

Cyclosporine A is a cyclic polypeptide that interferes with the transcription of cytokines, causing the blocking of activation and maturation of various cell types involved in cell-mediated immunity[92]. This drug has been mostly used in severe refractory UC. Neurotoxicity is one of the major adverse events of this treatment, involving up to 25% of treated patients and including seizures, tremors, paresthesia, ataxia, motor deficits, aphasia, altered consciousness, and various degrees of visual and oculomotor disturbances[92]. The pathogenesis of these neurological side effects is poorly understood. Cyclosporine A may rarely cause accelerated hypertension leading to progressive reversible encephalopathy syndrome[14]; this condition is more frequent in patients with low total serum cholesterol[14].

Irreversible bilateral optic neuropathy has also been described[92] and two possible mechanisms have been proposed: direct toxicity to peripheral nerves, or thromboembolism leading to ischemic optic neuropathy[93].

Cerebellar atrophy[93] caused by cyclosporine A therapy performed despite hypomagnesemia may have its first manifestation in nystagmus. However, cyclosporine-A-induced neurotoxicity has also been described in the absence of known risk factors such as hypocholesterolemia, hypomagnesemia, previous seizure disorders and arterial hypertension[94]. The differences in neurological side effects between oral and intravenous cyclosporine A is another matter of uncertainty[95]. Cyclosporine A is insoluble in water and intravenous formulations are prepared in a polyoxyethilated (POE) castor oil and ethyl alcohol solution[96]. In *in vitro* experiments, 0.1% POE castor oil determines axonal swelling and degeneration while 0.001% POE castor oil may induce demyelination. It has thus been suggested that residues of ethylene or its polymerization products might at least contribute to the neurotoxicity of intravenous cyclosporine A *in vivo*. However, the Cosmetic Ingredient Review Expert Panel has concluded that these cosmetic ingredients (POE castor oil and its derivatives) are safe in practical use[96] and no serious neurotoxicity may be attributable to them.

Azathioprine

This drug has no specific neurotoxicity but it represents a predisposing factor to infection, particularly associated with its prolonged use. Spinal epidural abscess has been described as a complication of azathioprine therapy[97]. Spinal epidural abscess is a rare but known neurological complication of CD[97]; predisposing conditions are immunosuppressive therapy and the presence of intra-abdominal and/or retroperitoneal fistulas[97]. A high index of suspicion should be raised if the patient shows back pain during or immediately after a flare of CD, with or without neurological signs, because this condition is an alarm sign for the presence of inflamed paravertebral and spinal structures[89]. Spinal epidural abscess represents a neurosurgical emergency in the presence of unresponsive back pain or progressive neurological deterioration such as bowel and/or bladder dysfunction. In patients with spinal epidural abscess associated with bowel fistulas and psoas abscesses determined by CD, a combined and highly specialized medical and surgical approach is needed to prevent recurrence[98]. Prolonged antibiotic use is recommended also if cultures are negative.

Murai *et al*[99] reported a myelo-radiculitis determined by *Cryp. neoformans* in a UC patient on immunosuppressive therapy with azathioprine. Robineau *et al*[100] reported a case of HSE related to azathioprine therapy in a 28-year-old woman treated for 4 years[100]. The diagnosis was based on the presence of photophobia, headache, asthenia and nausea associated with nuchal rigidity; lumbar puncture revealed a marked increase of lymphocytes (98%) in cerebral fluid with a detection of HSV-1 DNA determined by PCR. Intravenous acyclovir administration (15 mg/kg every 8 h) for 3 wk completely resolved this complication.

CEREBROVASCULAR DISEASES

In general, the risk of both arterial and venous thrombosis[101], as well as of thromboembolic events, is significantly increased in IBD patients. As a consequence, thromboembolic complications have been reported in various organs, including the brain. Indeed, cerebrovascular disorders have been documented in 0.12%-4% of all IBD patients, and probably they represent the most frequently reported neurological complications[102]. Obviously, cerebrovascular or cardiovascular events and their sequelae may be of particular severity, especially if one considers the usually young age of IBD patients. The relative risk of stroke is higher in young patients, especially women and patients with CD[14]. Thus, a large number of studies addressing the possible underlying causes of this predisposition in IBD and proposing possible prophylactic and therapeutic strategies have been published in recent decades. As a whole, these studies suggest that active disease, even at an outpatient level, appears to be the most important predisposing factor, through many pathogenic factors activated by the ongoing inflammation. Indeed, the intimate inter-relationship between inflammation and coagulation has become clear in recent years with disease clinical and subclinical activity[103] shown to be associated with hypercoagulability related to various factors such as qualitative and quantitative abnormalities of platelets[104] and coagulation factors[94], decreased anticoagulant activity[100], hypofibrinolysis[105], malabsorption and hypercatabolism leading to vitamin B6 deficiency[106], endothelial changes[102] leading also to reduced activation of protein C, dehydration, and corticosteroid therapy[107].

The abundance of the findings showing an association between clinical activity and risk of thrombotic events has led to the introduction of antithrombotic

prophylaxis in the therapeutic guidelines of hospitalized patients with severe relapse.

However, although active disease is particularly associated with an increased risk of these complications, some cases of vascular accidents have been described during remission[101], suggesting that IBD represents a risk factor for thrombosis. The search for a possible genetic association between IBD and carriage of factor V Leiden, G20210A prothrombin and methylene tetrahydrofolate reductase mutations has provided negative results[102], thus suggesting that other, probably acquired although not related to inflammation, factors may indeed play a more important role. One of these factors might be hyperhomocysteinemia[80,81], which may derive from a lack of attention to nutritional status, although in many cases the presence of subclinical inflammation cannot be ruled out. It is important to consider a higher risk in postoperative state associated with the development of arterio-arterial embolism, cardioembolism, and *in situ* cerebral thrombosis[14].

Arterial thromboembolism

An increased risk of these complications is observed in patients with active UC and particularly in those with total colitis[108]; even if active disease is associated with an increased risk, some cases have been described during remission[100]. Men and women are equally affected. The cerebrovascular involvement appears to be more frequent among younger IBD patients, as reported by Houissa *et al*[101] who described four cases of arterial thrombosis in IBD and three of these were younger than 25 years. Intestinal inflammation may lead to increased risk for thrombosis through several pathways: by activating the coagulation cascade; decreasing anticoagulant activity; and inducing hypofibrinolysis, malabsorption and hypercatabolism with vitamin deficiencies that may lead to hyperhomocysteinemia - a well known risk factor for thrombosis[101]. Also dehydration, immobility, sepsis, surgery and corticosteroid therapy may determine cerebral thrombosis in IBD patients[101].

The neurological presentation of cerebral arterial thrombosis may vary from headache (95%), to mono- or bilateral paresis (43%), general or focal seizures (47%), or dysphasia (37%)[104]. The clinical sequelae of cerebral vascular thrombosis can be devastating, especially in young patients with active and complicated IBD, leading to high mortality and disability in about 60% of cases[101]. Conventional CT or MRI identifies the exact site of cerebral affected areas. At present, no guidelines are available for the treatment of cerebral thrombosis and stroke in IBD[108]. Low molecular weight heparin (LMWH) is the most common drug used for the prophylaxis and treatment of vascular thromboembolism.

Given the heightened risk of thromboembolism in patients with IBD, prophylaxis with LMWH is recommended in hospitalized IBD patients, considering exacerbation of the disease[14]. Long-term use of anticoagulant therapy in the treatment of arterial ischemic cerebral lesions is limited, although the presence of a hypercoagulable condition should always be considered an indication for lifelong anticoagulation with warfarin[107]. Thrombolysis with recombinant tissue plasminogen activator, urokinase or streptokinase should also be considered in early cerebral arterial ischemic conditions (within 3 h from development of clinical symptoms) and this procedure, in expert hands, may be considered safe and effective[109]. In selected cases, thrombectomy should also be considered[110]. Rapid evaluation and appropriate multidisciplinary consultation are required for optimal diagnosis and management.

Venous and sinus thrombosis

Cerebral venous and sinus thrombosis is a rare condition and accounts for about 1% of all strokes[111]. Cerebral venous and sinus thrombosis that concurrently develops with UC is rare[111] and they may be associated with abnormalities in the coagulation system[100]. Cerebral venous thrombosis appears to be more common in UC than in CD patients[112], and is more commonly localized in the superior sagittal sinus and lateral sinuses[113], although cortical venous thromboses have also been reported[113].

All patients with UC and cerebral venous thrombosis reported in literature are young, mostly men, without other risk factors[102]. Most patients have a pancolitis suggesting a role for increased endotoxemia and dehydration[102] as culprits for vascular thrombosis. The most frequent symptom is headache occurring in 75%-96% of patients[114]. The headache is often severe and diffuse and it usually precedes the appearance of neurological signs. A combination of focal defects, headache, seizures and altered consciousness is suggestive of cerebral venous thrombosis[114], although the presenting features are variable and the condition should be considered in any IBD patients with neurological symptoms, particularly during an active phase. Cerebral infarction is a dangerous complication and it appears when the thrombosis extends from the superior sagittal sinus to the superficial cerebral veins and their tributaries[114].

MRI studies in combination with MR venography are sensitive in identifying venous sinus occlusion[114]. The use of local endovascular thrombolytic agents may restore the flow more frequently and rapidly than heparin alone; however, there is no evidence of the superiority of this method and the risk of hemorrhage is high[114]. Warfarin is usually continued for at least 6 mo after a first episode of cerebral venous thrombosis, or longer in the presence of persisting predisposing factors[114]. The theoretical risk of intestinal bleeding due to anticoagulant therapy does not appear significant in practice[114]. Given the increased risk of thromboembolism in patients with IBD, aggressive mechanical and pharmacological deep vein thrombosis prophylaxis with LMWH is recommended in hospitalized patients[14].

IMMUNE-MEDIATED NEUROLOGICAL DISORDERS

MS

This topic has been already treated in this paper as a possible complication of biological therapies[25]. However, a possible spontaneous association between MS and IBD has been suspected for decades[115]. Indeed, the estimated prevalence of MS in the general population is about 0.1%, while in IBD patients the prevalence of MS has been reported at up to 0.5%[8,114,115], suggesting a 1.5-5-fold increase in the risk of having MS in IBD patients[30]. In evaluating these data, however, we should bear in mind that all studies involved a limited number of patients, thus yielding low statistical power. Also, results of the studies are greatly influenced by the methods used to look for an associated disease. Indeed, Geissler *et al*[116] observed hyperintensity of the white matter on brain MRI in almost half of the patients with IBD free of neurological symptoms compared to only 16% of healthy age-matched controls. MS has been reported to develop either before or after the clinical onset of IBD[116]. The nature of a possible pathogenic link between IBD and MS has not been identified, but a disturbance in functional T-cell subsets with aberrant proinflammatory activity of T helper 17 subsets has been suggested[2]. Animal studies[117] also suggest a link between the demyelinating lesions suggestive for MS or acute disseminated encephalomyelitis and the prothrombotic state characteristic of UC. Astrocytosis and exstensive perivenular loss of myelin have been described in rhesus monkeys suffering from colitis and cerebral venous thrombosis, and it is possible to speculate that the demyelinating lesions could have been the result of perivenular edema secondary to venous blockade[117]. Indeed, cerebral lesions in the monkey are identical to those observed in confluent leukoencephalitis and perivascular myelosis of the cerebral type; a demyelinating disease of monkeys[118]. Whatever the mechanisms of the underlying possible association between MS and IBD, brain MRI followed by a neurological consultation for further diagnostic work-up should be organized[2] as soon as a patient with a clinical history of UC or CD presents with an unexplained neurological symptom suggestive of MS, such as paresthesia in both arms, fingers, legs and toes, hyperesthesia of the fingertips and hyper-reflexia. Occasional, but clinically important, observations are those reporting that a demyelinating disease may be precipitated or aggravated by the use of infliximab for IBD[119].

Cerebral vasculitis

This topic has already been treated in the chapter on complications of biological therapies[22]. Cerebral vasculitis has been reported in association with UC[120] and can be considered a further cause of stroke. The association between UC and Takayasu's disease, particularly in Japanese patients with an HLA-B52, DR2 haplotype, is strong[121]. The pathogenetic process may be related to common immune-mediated mechanisms such as T-lymphocyte mediated cytotoxicity or immune complex deposition[121], or to a genetic susceptibility determined by patient's HLA status. The association of UC with perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCAs) or atypical ANCAs[122] suggests a common autoimmune etiology, but the existence of different antigenic recognitions by these antibodies in the two diseases is well established. Furthermore, UC-associated ANCAs lack antigenic specificity for proteinase-3 (PR3) or myeloperoxidase (MPO) and do not have the potential for the development of systemic vasculitis or for neutrophil activation[122]. Nevertheless, a p-ANCA (specific for MPO) positive UC patient affected by ischemic lesions in the white matter of the brain has been reported[122].

The clinical manifestations of cerebral vasculitis are hemiparesis, hemianopsia, personality changes, headache, aphasia, seizures, coma and progressive dementia[8]. These clinical manifestations may occur independently of the activity of the underlying bowel disease and, in some cases, they may appear even before the onset of IBD[123]. Cerebral MRI is always abnormal[8]. Nearly half of the reported patients have neurologic signs and symptoms developing during steroid therapy[8].

Necrotizing angiitis may show clinical manifestations similar to the acute hemorrhagic variant of acute disseminated encephalomyelitis (ADEM)[117]. ADEM is suggested to result from a transient autoimmune response directed against myelin or other autoantigens via molecular mimicry[117] caused by a defective epithelial barrier function in UC, leading to uncontrolled uptake of luminal antigens and stimulation of pathologic immune and inflammatory reactions[8]. The presence of lethargy should always suggest a diagnosis of ADEM.

Autoimmune myelopathy

Lossos *et al*[3] reported nine UC patients with neurological disorders and six of these had peripheral nerve disorders considered as acute inflammatory demyelinating polyradiculoneuropathy[3]. This study was limited by the absence of detailed information about CSF features and response to therapy.

Myelopathy, which may present as a slowly progressive systemic spastic paraparesis in the absence of a spinal sensory level, has been associated with UC in some case reports[3]; a link with human T-lymphotropic type 1-associated myelopathy has been proposed[124]. This syndrome may develop without spinal MRI abnormalities[3]; an immune-mediated inflammatory origin has been suggested but a possible association with the use of medications or nutritional deficiencies cannot be ruled out[3]. It is possible to consider this myelopathy or transverse myelitis as a part of a more widespread CNS disorder like MS or a vasculitis process as suggested by Ray *et al*[125].

Also, *Campylobacter jejuni* is linked to exacerbations of IBD and it may contribute to the development of autoimmune inflammatory demyelinating polyneuropathy[121].

It is noteworthy that in the patients with generalized peripheral neuropathy, a demyelinating pattern is present in 30%[125].

Myasthenia gravis

Myasthenia gravis (MG) is a typical immune-mediated disease in which T-lymphocyte function is abnormal, the thymus is enlarged, and circulating acetylcholine receptor antibodies are found[126]. MG is often associated with other autoimmune disorders such as alopecia, lichen planus, vitiligo and SLE[127]; diseases that are also observed in association with IBD. Tsuchiya *et al*[127] described an association between thymic abnormalities and IBD, with the presence of acetylcholine receptor antibodies[128]. Also, the lack of age-related involution of the thymus observed in MG has also been reported in UC[127]. T cells obtained from the thymus of patients with MG and UC have reduced ratios of suppressor ($CD8^+$) to helper ($CD4^+$) T cells compared with control subjects[128].

Diplopia and ptosis of the upper eyelid in IBD patients may be an initial manifestation of MG[129]. For the possible pathogenic association between the two diseases, intriguing observations on their therapeutic management have been reported: Finnie *et al*[126] reported a case of a patient with both MG and CD complicated by perianal disease whose bowel disease improved after thymectomy for severe uncontrolled MG. In contrast, Gower-Rousseau *et al*[130] described a patient with MG and UC in whom MG symptoms improved after proctocolectomy. Foroozan *et al*[129] reported a 21-year-old man with UC and binocular diplopia and ptosis due to MG; both ocular and gastrointestinal symptoms improved after plasmapheresis, azathioprine, prednisone and mestinon[3].

Autoimmune sensorineural hearing loss

Sensorineural hearing loss is probably an immunological manifestation of IBD[131]. The clinical manifestations of the disease are often bilateral and progressive[132]. The hearing level is unstable with periods of deterioration alternating to partial or complete clinical remission[132]. In general, the tendency is for gradual evolution towards permanent hearing loss[132]. Vestibular dysfunction symptoms such as disequilibrium and postural instability may accompany auditory symptoms and these symptoms may have a sudden onset[133].

Hearing loss generally occurs between 2 mo and 17 years after the diagnosis of UC. Hearing loss may appear during both active and remission stages of the disease and it does not have a parallel evolution. Hearing loss, if not treated, is recurrent until leading to complete deafness[133]. A more strict collaboration with ear, nose and throat specialists should be encouraged to research this condition of autoimmune inner ear. Kumar *et al*[134] noted, in a controlled audiometry study, a significant sensorineural hearing loss in UC patients compared with controls. A subclinical sensorineural hearing loss may also be present in CD patients[135].

The clinical response to steroid and immunosuppressive therapy suggests that an autoimmune process causes inner ear impairment[136]. This condition is most frequently bilateral but may also be unilateral. Aggressive treatment should be started as early as possible. At present[134], it is impossible to have detailed information about the beginning and the time-course of hearing loss because this condition is underdiagnosed. Karmody *et al*[133] reported that patients with hearing loss performed their first medical evaluation usually 3 years after the first clinical manifestation.

MISCELLANEOUS

Peripheral neuropathies

Polyneuropathies have previously been dealt as frequent side effects of metronidazole therapy but they may also occur as spontaneous extraintestinal manifestations of IBD. Gondim *et al*[89] identified 33 patients (18 with CD and 15 with UC) affected by polyneuropathies. Male sex was highly predominant (78% in CD and 75% in UC). Neurological symptoms appeared long after the diagnosis of IBD. In 33% of CD patients and 40% of UC patients, the polyneuropathy was correlated with disease activity.

In CD patients, demyelinating neuropathy was present in five patients while a nondemyelinating neuropathy was present in the other 13: small-fiber polyneuropathy (SF-PN) in two and large-fiber axonal neuropathy (LF-AN) in 11. Four patients with UC showed peripheral demyelinating neuropathies. Eleven UC patients showed nondemyelinating neuropathies: four with SF-PN and seven with LF-PN. The diagnosis of SF-PN was obtained by means of skin biopsy[89].

Oliveira *et al*[4] studied 82 IBD patients (31 with CD and 51 with UC). Five CD patients (4 women) (16.1%) had SF-PN and the first symptom was sensory abnormality. Weakness was mild and mostly located in the distal legs. Neurological examination showed decreased or absent ankle jerks, and decreased distal vibration and pinprick. Ten UC patients (19.6%) had mild axonal sensory motor polyneuropathies (SM-PN). Blood B12 levels were < 200 pmol/L in two of these 10 patients, between 200-300 pmol/L in a further two, two patients had diabetes, one was affected by hypothyroidism, and positive blood rheumatoid factor was present in two[4]. Fourteen percent of UC patients were taking steroid therapy[4].

Oliveira *et al*[4] concluded that SM-PN in UC patients was more common in women, in older individuals, in patients developing the disease later in life and in subjects with a body mass index < 18.5. The authors[4] also noted that the association with autoimmune diseases such as diabetes mellitus, hypothyroidism and positive rheumatoid factor was more frequent in UC patients with SF-PN than in CD patients.

Sassi *et al*[137], in a study of 102 consecutive patients with IBD, reported nine patients (8.8%) with peripheral neuropathies. Bernstein *et al*[138], in a large study of administrative healthcare data from the Manitoba County

between 1984 and 2003 on 8072 patients with IBD (3879 with UC and 4193 with CD), reported peripheral neuropathies in 2.4% of UC patients and 2.34 of CD patients compared to 1.35% in the general population. Peripheral neuropathies usually do not respond to treatment of the underlying IBD[14].

Cranial nerve palsies

Cranial nerve palsies can be observed in patients with IBD. The Melkersson-Rosenthal syndrome[139] is defined by recurrent facial nerve palsy, fissuring of the tongue, and noncaseating tissue granulomas, and it has been described in association with CD[140]. The long intracranial course of the sixth nerve predisposes it to injury by a variety of abnormalities[139]. Karajeh *et al*[140] described a 27-year-old female smoker with a 12-d history of diplopia on right lateral gaze associated with retro-orbital pain before the clinical diagnosis of CD. This typical clinical presentation suggests a vascular sixth nerve palsy with a sudden onset of unilateral abduction deficit accompanied by retro-orbital pain and diplopia[140]. It is hypothesized that microvascular ischemic demyelination of a portion of the nerve is the most likely cause of this clinical condition[140]. This area of ischemic demyelination subsequently undergoes remyelination with clinical recovery[140]. Complete recovery within 2-3 mo is generally observed[140].

Optical neuropathy, as outlined above, has a clinical presentation with a bilateral optic disc swelling and it is a rare condition prevalently associated with CD[141]. Romero Aroca *et al*[142] reported a 27-year-old woman affected by UC and optic neuritis that resolved after mesalamine administration. Optic neuropathy may be attributed to peripapillary inflammation, optic disc ischemia, or intracranial hypertension[142].

A local vasculitis process or a general hypercoagulability condition can determine optic nerve ischemia. Modern imaging techniques usually allow one to exclude dural venous sinus thrombosis[113]; a serious cerebrovascular complication of IBD described in another chapter of this paper. Another clinical condition is the severe erosive arthritis of the craniocervical junction that should always be considered in IBD patients with persistent neck pain because a late diagnosis may determine severe neurological defects[143].

Epilepsy

The association between IBD and epilepsy is uncertain[1]. Epileptic seizure in IBD patients may be related to structural or metabolic causes[3]. Seizures may be generalized tonic-clonic complex, simple, partial or even multiple. A MEDLINE search[8] using "epilepsy and ulcerative colitis" as keywords found only five case reports dating back to the early 1970s. According to the literature, epilepsy appears more frequently associated with CD than with UC[1].

Muscle disorders

Granulomatous myositis and myopathies are associated with both CD and UC patients[144]; these manifestations usually appear during exacerbations of IBD[145]. Orbital myositis is a nonspecific, localized orbital inflammatory process in which one or more extraocular muscles are involved[145]. Clinically, orbital myositis is characterized by acute pain exacerbated by eye movements; diplopia, swelling of the eyelid, conjunctival injection, and exophthalmos may also be present[145]. The diagnosis is based on clinical history and imaging[145]. This disease responds to steroid therapy[146]. Orbital myositis is rare in IBD[146]; sarcoidosis, Wegener's granulomatosis, rheumatoid arthritis and Lyme disease should be considered in the differential diagnosis[146].

Nonspecific orbital inflammation includes histological forms that are more difficult to distinguish such as an idiopathic granulomatous and idiopathic sclerosing pseudotumor[147]. Nonspecific orbital inflammation appears to arise from an immune reaction in the orbit secondary to a neighboring zone of inflammation or a distant autoimmune reaction[148]. It has been associated with CD, diabetes, rheumatoid arthritis and Graves' disease[148].

MRI is the method of choice to study the orbital region in orbital myositis because it is able to show the typical diffuse enlargement of extraocular muscles with blurred margins and to rule out other lesions such as tumor/pseudotumor infiltration, apical extension, cavernous sinus involvement and intracranial disease[146]. Orbital myositis most commonly affects the superior recti, the medial recti and oblique muscles.

Classic migraine

The prevalence of migraine in patients with IBD remains unknown[149]. Migraine is associated with systemic endothelial dysfunction[150], which is also proposed as a possible pathogenic factor in IBD[151]. Oliveira *et al*[4] found that headache is the most common neurological complaint reported both in CD and UC patients, in 54.8% and 56.9% of patients, respectively. In most patients headache is not disabling and it is often associated with IBD relapse and treatment[4]. Ford *et al*[149], in a study performed on about 100 IBD patients (77% women and 23% men, 66% with CD and 27% with UC) by an ID-Migraine questionnaire[148], noted a 30% prevalence of migraine in IBD patients. Migraine was more prevalent in CD (36%) than in UC (14.8%). In UC patients, the prevalence of migraine in women did not approach that of the general population (12.5% *vs* 18.2%), whereas the prevalence in men greatly exceeded that of the general population (18% *vs* 6.5%)[152].

Currently, migraine is underdiagnosed in IBD patients, although it causes limited ability to work, study and perform routine activities in a high percentage of IBD patients[146]. It is important to consider that migraine with aura may be an independent risk factor for ischemic stroke in women[153] because they have a 13.7-fold increased risk for silent infarction in the posterior territory and 2.1-fold increased risk for deep white matter lesions[154].

Sleep disturbances, depression and anxiety, chronic fatigue syndrome

Sleep disturbances are recognized reactions to inflamma-

tion[155] and may represent the first response to acute inflammation[156], although they may persist during clinical remission.

Depression and anxiety occur in IBD and they may involve sleep disturbances and asthenia[156]. Assessment of depression and anxiety in IBD is mandatory because these conditions may contribute to the subjective perception of poor quality of life[157]. Anxiety may be associated with more intense disease activity[158].

Fatigue in IBD may be considered as a consequence of the disease and its treatment[157]. Iron deficiency may cause fatigue and sleep disorders in patients with CD[157]. Patients can express fatigue even when bowel disease is inactive[159]. Minderhoud *et al*[160] showed that the fatigue score remains high during disease remission compared with normal control subjects. Lipton *et al*[152], in a study of French IBD patients, found that the scores obtained on the Multidimensional Fatigue Inventory in IBD patients were similar to those affected by cancer. Fatigue may be considered a part of the core symptoms of depression[161] and the use of antidepressants may improve chronic fatigue syndrome. In summary, although chronic fatigue syndrome is frequent in IBD patients, its precise pathogenesis is not clear and this most probably reflects a multifactorial nature of the syndrome.

Restless legs syndrome

Restless legs syndrome (RLS) is a CNS disorder characterized by a compelling urge to move the legs at rest; it contributes to sleep disturbances and impaired quality of life. RLS may be primary (idiopathic and familial) or secondary to many disorders such as pregnancy, end-stage renal failure, iron deficiency anemia, rheumatoid arthritis, diabetes, Parkinson's disease, fibromyalgia, IBD[162], gastric resection, chronic liver disease, and irritable bowel syndrome[163]. The diagnosis of RLS must be made according to the following four criteria established by the International RLS Study Group[164]: (1) an urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs; (2) the urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity; (3) the urge to move or unpleasant sensations are partially relieved by movement at least as long as the activity continues; and (4) the urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night.

Weinstock *et al*[162] reported a prevalence of 30% for RLS in patients with CD and noted that it appeared during or after the onset of CD symptoms, suggesting a link between CD and RLS. This association might at least partly explain the presence of both fatigue and sleep disturbances in CD patients[161]. Patients with iron deficiency anemia are at particularly high risk of developing RLS[165] because low brain iron concentration may play a role in altered dopamine levels, providing a unifying condition for most cases of the syndrome[166]. In fact, inflammatory conditions such as CD cause an increased secretion of proinflammatory cytokines [*i.e.*, interleukin (IL)-6][167] which in turn causes increased hepcidin production[163], leading to iron deficiency in the CNS as a cause of RLS[168]. Small intestinal bacterial overgrowth, which may be observed in CD patients may also cause RLS by an inflammatory state supported by IL-6 and hepcidin as in MS patients[169]; in these cases, antibiotic therapy might be beneficial[169].

Wernicke encephalopathy

Wernicke encephalopathy is a neurological complication determined by vitamin B1 deficiency[170]. Hahn *et al*[170] have reported vitamin B1 deficiency in a young patient with CD receiving total parenteral nutrition without vitamin replacement. Larnaout *et al*[171] reported a CD patient with Wernicke encephalopathy under normal enteral nutrition. This patient died and autopsy revealed the following pathological cerebral lesions: hemorrhagic necrosis around the third and fourth ventricles with vascular proliferation and pericapillary hemorrhages; numerous small hemorrhagic infarctions in the central part of the corpus callosum; marked spongiosis, predominantly in the left cerebellar white matter; slight thickening of leptomeninges with some mononuclear cells; and absence of vascular thrombosis or inflammatory perivascular cuffing in the brain and spinal cord.

Vitamin B12 deficiency

Vitamin B12 deficiency due to terminal ileal disease or surgical resection in CD may cause subacute myelopathy combined with degeneration characterized by bilateral spastic paresis, loss of pressure and vibration sensation due to degeneration of the posterior and lateral columns of the spinal cord[172].

CONCLUSION

Neurological complications of IBD, either related to drug therapy or spontaneously associated with the disease, are relatively frequent and may contribute to a high degree of morbidity and permanent damage. They are also frequently difficult to recognize and diagnose, due to their frequently unclear clinical expression. For these reasons, knowledge of the different presentations as well as of differential diagnosis and therapeutic possibilities is important for the gastroenterologist dealing with IBD patients. This paper is thus aimed at providing interested physicians with an in-depth review of the main features of neurological complications of IBD.

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