Neurological Manifestations of Inflammatory Bowel Disease

Julio Plata-Bello and Silvia Acosta-López

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.73017

Abstract

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

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

1. Introduction

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

The incidence of IBD is different depending on its two main forms. CD is diagnosed in 0.5–10.6 patients/100,000 inhabitants/year, while the global incidence of UC is estimated at 0.9–24.3 patients/100,000 inhabitants/year. There is some evidence about the increase of these incidence figures in the past 10 years [2]. On the other hand, the prevalence of CD in European countries ranges from 1.5 to 213 cases per 100,000 people and the prevalence of UC ranges from 2.4 to 294 cases per 100,000 people [2].
IBD consists of an inflammation of the bowel, with different extension and histological features between CD and UC. However, this disease does not only involve the gastrointestinal tract, but there is also a long list of extraintestinal manifestations that can emerge prior to or during the disease. The most frequent ones are those involving the skin (dermatological), the joints (rheumatological), the eyes (ophthalmological), the liver and/or the biliary tract and the genitourinary area (gynecological and/or urological). The prevalence of at least one extraintestinal manifestation varies from 6.2 to 46.6% [4].

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

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

2. General pathophysiological considerations of IBD and its neurological manifestations

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

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

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

- Malabsorption and secondary deficit of vitamins (mainly vitamin B12), which are essential for myelin maintenance and regeneration [7].
- Hypercoagulability state, related to a chronic inflammatory response that may lead to ischemic events.
- Formation of metabolic toxic agents in the damaged bowel.
- Immunological disturbances that may lead to autoimmune response against glial-neural components.
- Opportunistic infections secondary to the impairment of the immune system or because of the treatment for IBD.
These mechanisms can lead to neurological damage acting individually or in combination. The identification of the leading mechanism is essential to prevent greater neurological damage. Unfortunately, in many cases, it is not possible to identify the main pathological factor.

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

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

| Drug category | High frequency (>1 case per 100 patients) | Low frequency (>1 case per 1000 patients) | Rare (>1 case per 10,000 patients) | Unknown frequency |
|---------------|------------------------------------------|------------------------------------------|-----------------------------------|------------------|
| Steroids      | Development or worsening of psychiatric disorders: euphoria, mood and personality changes, depression and psychosis | Seizures | Dizziness, headache, insomnia |
| 5-Aminosalicilates | Headache, dizziness and peripheral neuropathy | | |
| Antibiotics   | Metronidazole: Seizures, peripheral neuropathy. Others: dizziness, ataxia, incoordination, confusion, irritability, depression, weakness, insomnia and encephalopathy | Headache, dizziness, sleep disorders, taste disorders, motor hyperactivity | Sensitive disturbances, tremor, seizures, migraine, incoordination, olfactory disorders, confusion, anxiety, depression, psychotic reactions | Peripheral neuropathy |
| Ciprofloxacin | | | Motor polyneuropathy, optic nerve edema | |
| Ciclosporin A | Tremor, headache, seizures, paresthesia | Encephalopathy, confusion, disorientation, decrease level consciousness, anxiety, insomnia, visual disturbances, cortical blindness, coma, paresia and ataxia | Motor polyneuropathy, optic nerve edema | Migraine |
| Drug                | Neurological Complication 1 | Neurological Complication 2 | Neurological Complication 3 | Neurological Complication 4 |
|---------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Methotrexate        | Paresthesia                 | Motor weakness, encephalopathy, seizures and headache | Mood disorders and cognitive disturbances | Intracranial hypertension, neurotoxicity, arachnoiditis, paraplegia, astonishment, ataxia, dementia, dizziness |
| Thiopurines Azathioprine | Depression, confusion, anxiety, amnesia, apathy, drowsiness. Demyelinating disease exacerbation | Multiple sclerosis and other demyelinating disorders (optic neuritis and Guillain-Barre syndrome) | Demyelinating disease, including multiple sclerosis (onset or exacerbation). Seizures, peripheral neuropathy | Progressive multifocal leukoencephalopathy when other immunosuppressors are combined |
| 6-Mercaptopurine    | Not reported                |                             |                             |                             |
| Anti-TNF Infliximab | Headache, dizziness         |                             |                             |                             |
| Adalimumab          | Mood changes (depression), anxiety, insomnia. Headache, paresthesias, migraine, radicular compression | Cerebrovascular accident, tremor, neuropathy | Multiple sclerosis and other demyelinating diseases (optic neuritis and Guillain-Barre syndrome) | |
| Certolizumab pegol |                             |                             | Demyelinating disease, including multiple sclerosis (onset or exacerbation). Seizures, peripheral neuropathy |                             |
| Golimumab           | Dizziness, headache, paresthesias. Depression, insomnia | Instability | Multiple sclerosis and other demyelinating diseases, dysgeusia |                             |
| Vedolizumab         | Headache, paresthesia       |                             |                             |                             |
| Ustekinumab         | Dizziness, headache         | Depression. Facial palsy |                             |                             |

Table 1. IBD treatment-related neurological complications with categorization of their frequency.
3. Venous and arterial thrombotic and thromboembolic manifestations

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

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

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

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

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

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

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

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

4. Demyelinating diseases

The association of demyelinating diseases has been proposed since the early 1980s. Rang et al. described a higher prevalence of multiple sclerosis (MS) than expected in UC patients [33]. Subsequently, this finding has been confirmed by many reports, but not only for UC but also for CD [34–36]. For instance, Gupta et al. described an increased risk of optic neuritis and other forms of MS in CD (odds ratio = 1.54) and UC (odds ratio = 1.75) [35]. In the same line, a recent meta-analysis concluded that IBD patients present a higher risk of suffering from concomitant MS and vice versa (i.e. MS patients have a higher risk of suffering from associated IBD) [36]. These authors found an increased risk of 50% [36]. However, some authors have proposed that the development of demyelinating diseases in IBD patients is more related to the use of anti-TNFα drugs [37]. In this regard, the Spanish registry
of autoimmune adverse events of biological agents (BIOGEAS Project) reported 12 cases of MS and 25 cases of optic neuritis in IBD patients treated with anti-TNFα [38]. Furthermore, this phenomenon is not exclusive to IBD patients. Arthritis patients treated with anti-TNFα agents may develop MS or demyelinating lesions, with a partial or complete resolution of neurological symptoms after discontinuing the medication [39]. An increased number of new white matter lesions and new relapses have also been reported in MS patients treated with infliximab [40]. On the other hand, the use of Natalizumab, a monoclonal antibody against α4-integrin used in some cases of IBD, is associated with progressive multifocal leukoencephalopathy (PML). This disease appears after a reactivation of the JC virus infection, and the use of Natalizumab is clearly associated with this reactivation. PML is associated with a bad prognosis with a mortality rate at 6 months above 60% [37].

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

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

5. Epilepsy

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

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

6. Peripheral neuropathy

Peripheral neuropathy (PN) is one of the most common neurological complications in IBD patients [32, 43, 47]. Many factors have been associated with the development of PN, such as extraintestinal inflammation, immunological phenomena, nutritional disturbances
(e.g. malabsorption-related vitamin deficit) and adverse effects of IBD therapeutic agents (e.g. metronidazole or anti-TNF agents) [48–50]. Whenever these causes are ruled out, the frequency of PN in IBD patients varies from 0 to 39% [51]. IBD-associated PN may be associated with axonal damage or demyelination and it may have an acute or chronic presentation [47, 51]. Cases of mononeuropathy, plexopathies, multiple mononeuritis, compressive neuropathies and cranial neuropathies have also been reported [50]. Bearing this in mind, IBD-related PNs present great clinical variability, although there is a certain dominance of non-demyelinating vs. myelinating forms [48].

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

7. Psychiatric disorders

IBD patients show a high prevalence of psychiatric disorders, with depression and anxiety as the main diagnosis [1, 52, 53]. The prevalence of depression in IBD patients varies from 15 to 30%, but the frequency of anxiety rises to 80%, mainly associated with the relapses of the disease [54, 55]. There is no overall difference in the frequency of psychiatric disorders between UC and CD [52]. Several factors have been associated with IBD-related depression: female gender, active intestinal disease, the presence of fistulas or perianal disease, use of biological treatments and the necessity of surgery because of IBD [55]. On the other hand, IBD patients with IBD seem to present more aggressive phenotypes of the disease, with more relapses and shorter periods of remission [52]. In any case, the prevalence of depression or anxiety is even higher when other psychiatric conditions coexist [1, 52, 53].

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

However, it is widely accepted that there is an infra-diagnosis and infra-treatment of psychiatric disorders, with no systematic screening established in clinical guidelines. There is a strong evidence of the presence of a bidirectional relationship between the degree of inflammation in the gastrointestinal tract and the development of depression. This can be explained by the brain-gut axis hypothesis. The brain and the gut are communicated by the autonomic nervous system (sympathetic and parasympathetic systems). The vagus nerve (the main parasympathetic afferent) transmits information to the CNS about luminal osmolarity, carbohydrate levels, mechanical distortion of the mucosa and the presence of bacterial or cytostatic drugs. On the other hand, sympathetic afferents transmit visceral pain [58].
Information sent by the gastrointestinal system reaches the medulla (nucleus tractus solitarius) and travels upstream until it reaches the paraventricular nucleus where it finally modulates the hypothalamic–pituitary–adrenal (HPA) axis [59].

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

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

8. Conclusion

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

Author details

Julio Plata-Bello* and Silvia Acosta-López2

*Address all correspondence to: jplata5@hotmail.com

1 Department of Neurosurgery, Hospital Universitario de Canarias, S/C de Tenerife, Spain
2 Department of Gastroenterology and Hepatology, Hospital Universitario Nuestra Señora de La Candelaria, S/C de Tenerife, Spain

References

[1] Abautret-Daly Á, Dempsey E, Parra-Blanco A, Medina C, Harkin A. Gut–brain actions underlying comorbid anxiety and depression associated with inflammatory bowel disease. Acta Neuropsychiatrica. 2017;8:1-22

[2] Burisch J, Jess T, Martinato M, Lakatos PL. The burden of inflammatory bowel disease in Europe. Journal of Crohn’s and Colitis. 2013;7(4):322-337
[3] Montoro MA, García Pagán JC. Enfermedad inflamatoria intestinal. Enfermedad de Crohn. In: Gastroenterología y Hepatología Problemas comunes en la práctica clínica. 2nd ed. Madrid: Jarpyo Editores; 2012. pp. 443-458

[4] Bermejo PE, Burgos A. Complicaciones neurológicas de la enfermedad inflamatoria intestinal. Medicina Clínica (Barcelona). 2008;130(17):666-675

[5] Geissler A, Andus T, Roth M, Kullmann F, Caesar I, Held P, et al. Focal white-matter lesions in brain of patients with inflammatory bowel disease. Lancet (London, England). 1995 Apr;345(8954):897-898

[6] Lindgren S, Lilja B, Rosén I, Sundkvist G. Disturbed autonomic nerve function in patients with Crohn’s disease. Scandinavian Journal of Gastroenterology. 1991 Apr;26(4):361-366

[7] Mariño Suárez JE, Monedero Recuerdo I, Peláez Laguno C. Deficiencia de vitamina B12 y tratamiento por vía oral. Una opción tan eficaz como (todavía) poco utilizada. Atención Primaria. 2003;32(6):382-387

[8] Bernstein CN, Eliakim A, Fedail S, Fried M, Gearry R, Goh K-L, et al. Update. Journal of Clinical Gastroenterology. August 2015;50(10):803-818

[9] Zezos P, Kouklakis G, Saibil F. Inflammatory bowel disease and thromboembolism. World Journal of Gastroenterology. 2014;20(38):13863-13878

[10] Benarroch HS, Acosta AV. Complicaciones vasculares asociadas a la enfermedad inflamatoria intestinal. Anales de Medicina Interna. 2003;20:81-84

[11] Ashrafi MR, Hosseini F, Alizadeh H. Case report pseudotumor cerebri in a case of ulcerative colitis with sagittal sinus thrombosis case presentation. Iranian Journal of Pediatrics. 2013;23(1):109-112

[12] Lloyd-Still JD, Tomasi L. Neurovascular and thromboembolic complications of inflammatory bowel disease in childhood. Journal of Pediatric Gastroenterology and Nutrition. 1989 Nov;9(4):461-466

[13] Papa A, Gerardi V, Marzo M, Felice C, Rapaccini GL, Gasbarrini A. Venous thromboembolism in patients with inflammatory bowel disease: Focus on prevention and treatment. World Journal of Gastroenterology. 2014;20(12):3173-3179

[14] Cho Y, Chae MK, Cha JM, Il LJ, Joo KR, Shin HP, et al. Cerebral venous thrombosis in a patient with Crohn’s disease. Intestinal Research. 2016;14(1):96-101

[15] Grainge MJ, West J, Card TR. Venous thromboembolism during active disease and remission in inflammatory bowel disease: A cohort study. Lancet. 2010;375(9715):657-663

[16] Twig G, Zandman-Goddard G, Szyper-Kravitz M, Shoenfeld Y. Systemic thromboembolism in inflammatory bowel disease: Mechanisms and clinical applications. Annals of the New York Academy of Sciences. 2005 Jun;1051:166-173
[17] Liebman HA, Kashani N, Sutherland D, McGehee W, Kam AL. The factor V Leiden mutation increases the risk of venous thrombosis in patients with inflammatory bowel disease. Gastroenterology. 1998 Oct;115(4):830-834

[18] Van Assche G, Dignass A, Reinisch W, van der Woude CJ, Sturm A, De Vos M, et al. The second European evidence-based consensus on the diagnosis and management of Crohn’s disease: Special situations. Journal of Crohn’s & Colitis. 2010 Feb;4(1):63-101

[19] Van Assche G, Dignass A, Bokemeyer B, Danese S, Gionchetti P, Moser G, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 3: Special situations. Journal of Crohn’s & Colitis. 2013 Feb;7(1):1-33

[20] Dentali F, Douketis JD, Gianni M, Lim W, Crowther MA. Meta-analysis: Anticoagulant prophylaxis to prevent symptomatic venous thromboembolism in hospitalized medical patients. Annals of Internal Medicine. 2007 Feb;146(4):278-288

[21] Ahlehoff O, Gislason GH, Charlot M, Jørgensen CH, Lindhardsen J, Olesen JB, et al. Psoriasis is associated with clinically significant cardiovascular risk: A Danish nationwide cohort study. Journal of Internal Medicine. 2011 Aug;270(2):147-157

[22] Meune C, Touzé E, Trinquart L, Allanore Y. Trends in cardiovascular mortality in patients with rheumatoid arthritis over 50 years: A systematic review and meta-analysis of cohort studies. Rheumatology (Oxford, England). 2009 Oct;48(10):1309-1313

[23] Svenungsson E, Jensen-Urstad K, Heimbürger M, Silveira A, Hamsten A, de Faire U, et al. Risk factors for cardiovascular disease in systemic lupus erythematosus. Circulation. 2001 Oct;104(16):1887-1893

[24] Huang WS, Tseng CH, Chen PC, Tsai CH, Lin CL, Sung FC, et al. Inflammatory bowel diseases increase future ischemic stroke risk: A Taiwanese population-based retrospective cohort study. European Journal of Internal Medicine. 2014;25(6):561-565

[25] Kristensen SL, Ahlehoff O, Lindhardsen J, Erichsen R, Jensen GV, Torp-Pedersen C, et al. Disease activity in inflammatory bowel disease is associated with increased risk of myocardial infarction, stroke and cardiovascular death—A Danish nationwide cohort study. PLoS One. 2013;8(2):e56944

[26] Sy A, Khalidi N, Dehghan N, Barra L, Carette S, Cuthbertson D, et al. Vasculitis in patients with inflammatory bowel diseases: A study of 32 patients and systematic review of the literature. Seminars in Arthritis and Rheumatism. 2016 Feb;45(4):475-482

[27] Akiyama S, Fujii T, Matsuoka K, Yusuke E, Nega M, Takenaka K, et al. Endoscopic features and genetic background of inflammatory bowel disease complicated with Takayasu arteritis. Journal of Gastroenterology and Hepatology. 2017 May;32(5):1011-1017

[28] Reny J-L, Paul J-F, Lefèvre C, Champion K, Emmerich J, Blétry O, et al. Association of Takayasu’s arteritis and Crohn’s disease. Results of a study on 44 Takayasu patients and review of the literature. Annales de Medecine Interne. 2003 Mar;154(2):85-90
[29] Terao C, Matsumura T, Yoshifuji H, Kirino Y, Maejima Y, Nakaoka Y, et al. Takayasu arteritis and ulcerative colitis: high rate of co-occurrence and genetic overlap. Arthritis & Rheumatology (Hoboken, NJ). 2015 May;67(8):2226-2232

[30] Scheid R, Teich N. Neurologic manifestations of ulcerative colitis. European Journal of Neurology. 2007 May;14(5):483-493

[31] Raj N, Arkebauer M, Waters B, Dickinson B. A case of cerebral vasculitis associated with ulcerative colitis. Case Reports in Rheumatology. 2015;2015:598273

[32] Lossos A, River Y, Eliakim A, Steiner I. Neurologic aspects of inflammatory bowel disease. Neurology. 1995 Mar;45(3 Pt 1):416-421

[33] Rang EH, Brooke BN, Hermon-Taylor J. Association of ulcerative colitis with multiple sclerosis. Lancet (London, England). 1982 Sep;2(8297):555

[34] Marrie RA, Reider N, Cohen J, Stuve O, Sorensen PS, Cutter G, et al. A systematic review of the incidence and prevalence of autoimmune disease in multiple sclerosis. Multiple Sclerosis. 2015 Mar;21(3):282-293

[35] Gupta G, Gelfand JM, Lewis JD. Increased risk for demyelinating diseases in patients with inflammatory bowel disease. Gastroenterology. 2005 Sep;129(3):819-826

[36] Kosmidou M, Katsanos AH, Katsanos KH, Kyritsis AP, Tsivgoulis G, Christodoulou D, et al. Multiple sclerosis and inflammatory bowel diseases: A systematic review and meta-analysis. Journal of Neurology. 2017 Feb;264(2):254-259

[37] Singh S, Kumar N, Loftus EV, Kane SV. Neurologic complications in patients with inflammatory bowel disease: increasing relevance in the era of biologics. Inflammatory Bowel Disease. 2013;19(4):864-872

[38] Ramos-Casals M, Roberto-Perez-Alvarez, Diaz-Lagares C, Cuadrado M-J, Khamashta MA, BIOGEAS Study Group. Autoimmune diseases induced by biological agents: A double-edged sword? Autoimmunity Reviews. 2010 Jan;9(3):188-93

[39] Mohan N, Edwards ET, Cupps TR, Oliverio PJ, Sandberg G, Crayton H, et al. Demyelination occurring during anti-tumor necrosis factor alpha therapy for inflammatory arthritides. Arthritis and Rheumatism. 2001 Dec;44(12):2862-2869

[40] van Oosten BW, Barkhof F, Truyen L, Boringa JB, Bertelsmann FW, von Blomberg BM, et al. Increased MRI activity and immune activation in two multiple sclerosis patients treated with the monoclonal anti-tumor necrosis factor antibody cA2. Neurology. 1996 Dec;47(6):1531-1534

[41] Dolapcioglu C, Guleryuzlu Y, Uygur-Bayramicli O, Ahishali E, Dabak R. Asymptomatic brain lesions on cranial magnetic resonance imaging in inflammatory bowel disease. Gut Liver. 2013 Mar;7(2):169-174

[42] Hart PE, Gould SR, MacSweeney JE, Clifton A, Schon F. Brain white-matter lesions in inflammatory bowel disease. Lancet (London, England). 1998 May;351(9115):1558
[43] Elsehety A, Bertorini TE. Neurologic and neuropsychiatric complications of Crohn’s disease. Southern Medical Journal. 1997 Jun;90(6):606-610

[44] Masaki T, Muto T, Shinozaki M, Kuroda T. Unusual cerebral complication associated with ulcerative colitis. Journal of Gastroenterology. 1997 Apr;32(2):251-254

[45] Fagan C, Phelan D. Severe convulsant hypomagnesaemia and short bowel syndrome. Anaesthesia and Intensive Care. 2001 Jun;29(3):281-283

[46] Shorvon S, Andermann F, Guerrini R. The causes of epilepsy. In 2011. pp. 590-1

[47] Benavente L, Morís G. Neurologic disorders associated with inflammatory bowel disease. European Journal of Neurology. 2011;18(1):138-143

[48] Gondim FAA, Grannagan TH, Sander HW, Chin RL, Latov N. Peripheral neuropathy in patients with inflammatory bowel disease. Brain. 2005;128(4):867-879

[49] Deepak P, Stobaugh DJ, Sherid M, Sifuentes H, Ehrenpreis ED. Neurological events with tumour necrosis factor alpha inhibitors reported to the Food and Drug Administration adverse event reporting system. Alimentary Pharmacology & Therapeutics. 2013 Aug;38(4):388-396

[50] Pfeiffer RF. Gastroenterology and neurology. Continuum (Minneap Minn). 2017;23(3, Neurology of Systemic Disease):744-61

[51] Morís G. Inflammatory bowel disease: An increased risk factor for neurologic complications. World Journal of Gastroenterology. 2014;20(5):1228-1237

[52] Graff LA, Walker JR, Bernstein CN. Depression and anxiety in inflammatory bowel disease: A review of comorbidity and management. Inflammatory Bowel Diseases. 2009 Jul;15(7):1105-1118

[53] Nowakowski J, Chrobak AA, Dudek D. Psychiatric illnesses in inflammatory bowel diseases—Psychiatric comorbidity and biological underpinnings. Psychiatria Polska. 2016;50(6):1157-1166

[54] Bannaga AS, Selinger CP. Inflammatory bowel disease and anxiety: Links, risks, and challenges faced. Clinical and Experimental Gastroenterology. 2015;8:111-117

[55] Panara AJ, Yarur AJ, Rieders B, Proksell S, Deshpande AR, Abreu MT, et al. The incidence and risk factors for developing depression after being diagnosed with inflammatory bowel disease: A cohort study. Alimentary Pharmacology & Therapeutics. 2014 Apr;39(8):802-810

[56] Walker JR, Ediger JP, Graff LA, Greenfeld JM, Clara I, Lix L, et al. The Manitoba IBD cohort study: A population-based study of the prevalence of lifetime and 12-month anxiety and mood disorders. The American Journal of Gastroenterology. 2008 Aug;103(8):1989-1997

[57] Eaton WW, Pedersen MG, Nielsen PR, Mortensen PB. Autoimmune diseases, bipolar disorder, and non-affective psychosis. Bipolar Disorders. 2010 Sep;12(6):638-646
[58] Bonaz BL, Bernstein CN. Brain-gut interactions in inflammatory bowel disease. Gastroenterology. 2013 Jan;144(1):36-49

[59] Benarroch EE. The central autonomic network: Functional organization, dysfunction, and perspective. Mayo Clinic Proceedings. 1993 Oct;68(10):988-1001

[60] Ghia J-E, Blennerhassett P, Deng Y, Verdu EF, Khan WI, Collins SM. Reactivation of inflammatory bowel disease in a mouse model of depression. Gastroenterology. 2009 Jun;136(7):2280-8.e1-4

[61] Martin-Subero M, Anderson G, Kanchanatawan B, Berk M, Maes M. Comorbidity between depression and inflammatory bowel disease explained by immune-inflammatory, oxidative, and nitrosative stress; tryptophan catabolite; and gut-brain pathways. CNS Spectrums. 2016 Apr;21(2):184-198