



CASE REPORT

Neurological manifestations related to Crohn's disease: a boon for the workforce

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Abstract

The neurological manifestations of Crohn's disease and its prevalence are not well known. Here, we report five patients of confirmed Crohn's disease with different neurological presentations. The neurological presentations include anterior ischemic optic neuropathy, myelopathy, posterior reversible encephalopathy syndrome, chronic inflammatory demyelinating polyneuropathy, and chronic axonal sensory and motor polyneuropathy. These manifestations should be kept in mind in the assessment of Crohn's disease.

Key words: Crohn's disease; idiopathic inflammatory bowel disease; neurological manifestation

Introduction

Crohn's disease (CD) is an idiopathic inflammatory bowel disease (IBD) associated with various extra-intestinal manifestations, including involvement of skin, joints, liver, vessels and eyes [1,2]. The frequency of neurological manifestations in IBD is not well recognized, varying from 0.2 to 35.7% [3]. This wide range between different reports is mainly due to a lack of reporting and systematic review. The present case series describes five patients with confirmed CD presenting with different neurological symptoms and discusses the probable pathogenesis of these symptoms.

Case presentations

Case 1

A 44-year-old man with CD was referred to a neurologist due to the sudden onset of painless loss of vision in his left eye in June 2013. The patient had been diagnosed with terminal-ileal CD in May 2008. Mesalazine had been administered orally and the disease activity had been controlled according to the clinical status and endoscopic examination, and he had no complaints of abdominal pain, tarry black stool or bloody diarrhea. The patient had no history of surgical intervention of the gastrointestinal tract. He was not taking any medications other than mesalazine

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for CD. He did not have a history of diabetes mellitus, hypertension, hypercholesterolemia or coronary heart disease. Systemic physical examination showed no abnormalities. On neurological examination, left optic disc edema with normal macula and the peripheral retina was observed. Left Marcus Gunn pupil and significant decrement in visual acuity was detected as well. The remaining neurological examinations were normal. The visual evoked potential test showed low-amplitude P100 waveform in the left optic pathway compatible with axonal damage. Fluoroangiography displayed hyperfluorescence of the left optic disc, indicating anterior ischemic optic neuropathy (AION). Work-ups to rule out other causes of papillitis were negative, including anti-nuclear antibody (ANA), rheumatoid factor, anti-phospholipid antibodies, lupus anticoagulant, anti-neutrophil cytoplasmic antibodies (ANCA), Venereal Disease Research Laboratory test (VDRL), erythrocyte sedimentation rates (ESR), and hepatitis B, hepatitis C and HIV serological evaluation. Magnetic resonance imaging of the brain did not show any abnormality. Doppler ultrasound of the carotid arteries and echocardiography were normal. The patient was diagnosed with AION.

Case 2

A 26-year-old male with CD had been admitted to the hospital for recurrent generalized tonic-clonic seizures in October 2010. The patient was diagnosed with ileocolonic, non-stricturing, non-penetrating CD in November 2008. He had a steroid-dependent disease after significant improvement with mesalazine and steroids as conventional treatments. The steroids were gradually tapered when azathioprine added to his medications. Subsequently, azathioprine was used as a maintenance therapy for 18 months. His intestinal disease was inactive and steroids were discontinued several months before the current illness. Two weeks before admission, he had mild diarrhea and abdominal pain, but the GI man refused to switch medication. His condition deteriorated during these 2 weeks and he developed acute headache, nausea and vomiting, visual impairment and altered behavior that was followed by one episode of generalized tonic-clonic seizure. Immediately following stabilization of the patient by emergency medical services, he was transferred to a hospital. His body temperature at the time of arrival at the Emergency Department was 37.9°C. Furthermore, upon monitoring his vital signs, his heart and respiratory rates were found to be 112/min and 30 breaths/min, respectively. The blood pressure (BP) was 130/70 mmHg and arterial oxygen saturation maintaining above 90% of the breathing room air. The physical examination was normal except mild abdominal tenderness in the right lower quadrant. He was irritable and arousable with painful stimuli, but disoriented to place and time for a few hours. The remaining neurological examinations, including meningeal signs, were normal. The primary laboratory studies were as follow: mild leukocytosis (11 500), alkaline phosphatase (380 U/L), bilirubin (1.0 mg/dL), albumin (2.8 g/dL), alanine transaminase (68 U/L), aspartate transaminase (62 U/L), ESR (46 mm/h) and C-reactive protein (35 mg/L). Numerous red and white blood cells were seen on stool examination. Viral and vasculitis antibodies, including hepatitis B and C, ANA and smooth muscle antibody (SMA), were normal. Work-ups to rule out probable infectious causes were normal. The brain computed tomography (CT) scan showed multiple cortical and subcortical hypodense lesions involving bilateral parietal and occipital lobes. Brain magnetic resonance (MR) imaging revealed bilateral parasagittal areas of low T1 signal intensity and high T2 signal intensity without gadolinium

enhancement, involving frontal, parietal and occipital lobes (Figure 1). MR venography showed no evidence of venous thrombosis. These features were suggestive of posterior reversible encephalopathy syndrome (PRES). Seizures were controlled with diazepam and intravenous phenytoin. Follow-up brain MR imaging 3 months after discharge from hospital showed total resolution of abnormal findings previously noted. The endoscopic examination showed a diffuse aphthosis lesion in a limited region of the rectal ampulla and terminal ileum. Ileal and rectal biopsies were suggestive of a diffuse granulomatous inflammation, compatible with CD.

Case 3

A 60-year-old man had a 6-month history of worsening hands and legs paresthesia, dysesthesias, allodynia and lower extremities weakness. He had been diagnosed with CD 5 years ago, and colitis restricted to the ascending colon. Initially, he was treated with sulfasalazine, but prednisolone was added to his medication due to lack of clinical efficacy. He did not report any systemic symptoms and did not have a history of diabetes mellitus, uremia or alcohol consumption. No other extra-intestinal manifestations were found. On neurological examination, mental status and cranial nerves were normal. Muscle power of upper extremities and proximal of lower extremities was normal and he had weakness in dorsi- and plantar-flexion of feet (4/5 on both feet). Mild atrophy at the distal of upper and lower limbs was presented that was more pronounced in the feet. Deep tendon reflexes of upper and lower extremities were decreased and the plantar reflex was mute. Decreased touch and pain sensations in a stocking-glove distribution were observed through the sensory examination. Nerve conduction study showed abnormal findings in favor of chronic axonal sensory and motor polyneuropathy. The amplitudes of the motor nerve action potentials were decreased in the median, ulnar, tibial and peroneal nerves. Additionally, the amplitude of the sensory nerve action potentials was decreased in the median and ulnar nerves, and absent in the sural nerve. An extensive laboratory work-up was unremarkable, including complete blood cell count, renal function tests, urinalysis, thyroid function tests, serum folate and B12 level, ANA and other connective tissue disease markers, tumor markers, serum protein electrophoresis, urine Bence Jones protein, and hepatitis B and C serological evaluation. His ESR was 28 mm/h. A CT scan of the thorax and abdomen was normal, and whole-body scan and skull X-ray were unremarkable. With respect to minimal disability, the patient refused to receive any treatment for polyneuropathy.

Case 4

A 45-year-old male with CD was suffering from slowly worsening paraparesis in both lower extremities beginning 6 months earlier. He was diagnosed as ileocolitis type of CD 4 years previously and initially treated with high-dose mesalamine and then switched to azathioprine after lack of clinical improvement. He was on remission for 4 years. He did not receive any new immunomodulator agent such as infliximab. Systemic examination was normal except for a slight tenderness in the right upper abdomen without palpable masses, organomegaly or any signs of ascites. Neurological examination revealed exaggerated deep tendon reflexes of the lower extremities, increased muscle tone and bilateral extensor plantar responses. Vibration sensation was impaired in the legs. Fasciculation, sensory level and

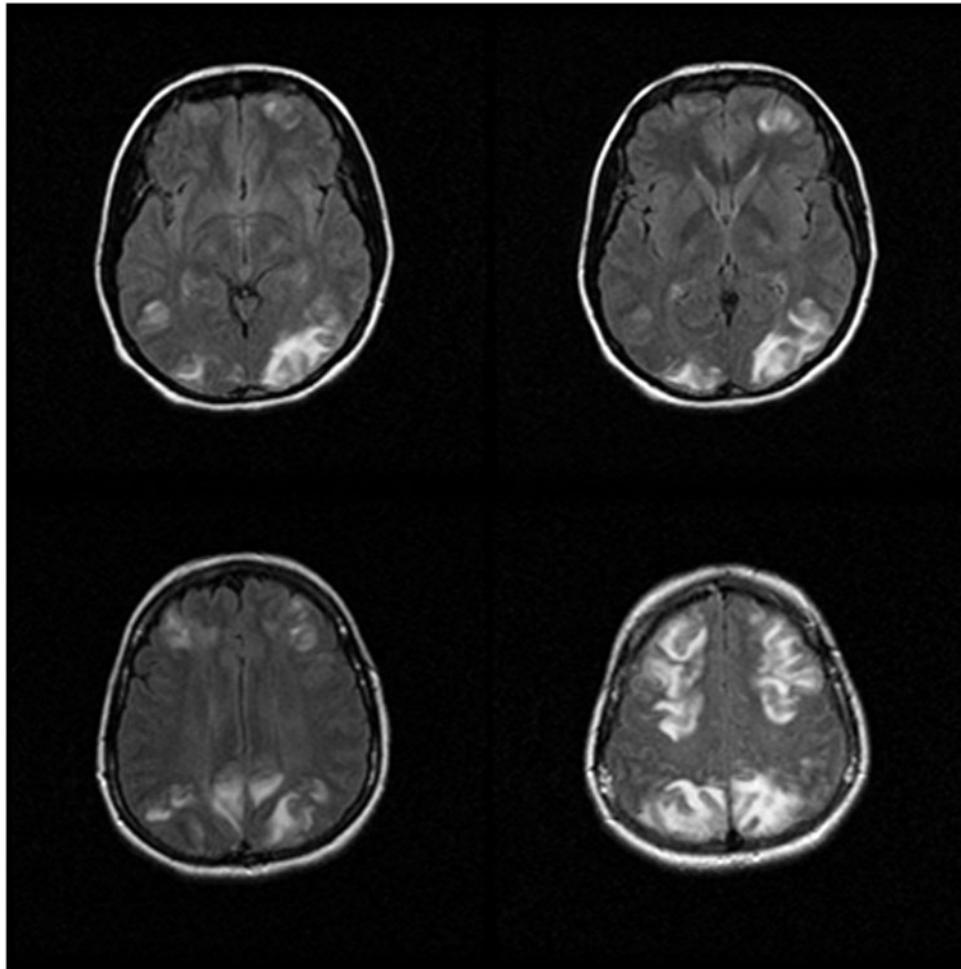


Figure 1. Brain MR imaging (FLAIR sequence) demonstrates moderate vasogenic edema in the subcortical white matter of the frontal, parietal and occipital regions, with some cortical involvement

muscle atrophy did not show upon neurological examinations. Extensive laboratory work-up, including human T-cell lymphotropic virus type-1 and HIV antibody, serum B12 level, serum copper and ceruloplasmin, ANA, VDRL, and anti-Ro and anti-La antibodies, were unremarkable. Brain, cervical and thoracic MR images did not show any significant findings. A nerve conduction study was normal. The clinical findings are suggestive of myelopathy related to CD. Initially, the patient was treated with a high dose of intravenous methylprednisolone (5 g) and showed significant improvement in force and activity, but he developed complications with hypophosphatemia. Therefore, the maintenance treatment was switched to infliximab, which was administered every 2 months.

Case 5

A 28-year-old man had been attending a neurologist's office for the evaluation and treatment of paraparesia and parasthesia, which had started 4 months earlier. The patient had been diagnosed with ileitis type of CD since 2010 with poor follow-up. When initially diagnosed, he was treated with prednisolone and sulfasalazine, but prednisolone therapy was discontinued 5 months after the onset of symptoms. He suffered from two relapses after discontinuing the drug, which were successfully treated with a short-term regimen of oral prednisolone. His

disease was relatively stable before the current visit. His current symptoms began with tingling in the lower extremities, continuing to drag the feet on the ground. He had no history of tobacco, alcohol or drug abuse. Neurological examination showed weakness in dorsi- and plantar-flexion, lack of deep tendon reflexes in both legs and reduced deep tendon reflexes in both hands. A diminished sensation of vibration in the lower extremities was discovered through the sensory examination. Laboratory work-ups for other causes of neuropathy were normal. A nerve conduction study showed decreased compound motor action potential and sensory nerve action potential. Conduction velocities were significantly decreased, and F waves and H reflex latencies of the lower extremities were prolonged. Electromyography was normal. Lumbosacral MR imaging did not show any significant nerve root compression. Lumbar puncture was performed, which showed neither white blood cells nor red blood cells, glucose was 56 mg/dL and protein was 72 mg/dL. The patient was diagnosed with chronic inflammatory demyelinating polyneuropathy (CIDP). He received 2 g/kg intravenous immunoglobulin and his symptoms improved subsequently. He did not have any follow-up for the next 6 months and came back with complaint of lower extremities weakness. He received another bolus of intravenous immunoglobulin. The patient expired due to bowel obstruction and hypovolemic shock 3 weeks later.

Table 1. Clinical studies of peripheral nervous system disorder in IBD

Reference	Study design (no. of patients)	Type of neuropathy	IBD activity	Comorbid or drug	Onset time (years)
Lossos [4]	Retrospective (638; UC & CD)	AIDP: 3 MM: 1 BP: 1 MRS: 1 ASMP: 7	1 active 5 inactive NR	No	1 before (7) 5 after (0.7–12)
Eisehety [8]	Retrospective (253; CD)	CIDP: 7	NR	No	1 before (0.6) 6 after (NR)
Condim [3]	Retrospective	MMN: 2 ASMP: 13 ASP: 5 SFP: 6	13 active 17 inactive 3 NR	No	1 before (11) 32 after (1–50)
Figuerola [9]	Retrospective (772; UC & CD)	BP: 1 LSP: 4 ASMP: 5	2 active (3 episode) inactive 1 NR	4 DM	9 after (1–44)
Babali [10]	Prospective study of subclinical neuropathy (97 CD)	No patient	-	-	-
Kararizou [11]	A clinic-pathological study (700 biopsy-CD)	MSMP: 4	1 active 3 inactive	No	4 after (10.3 ± 2)
Oliveira [12]	Prospective (82; UC & CD)	ASMP: 15 SFP: 15 Others (CTS, mononeuropathy): 9	NR	4 INF 2 MNDZ 9 Low B12 8 DM 1 HT	39 after (NR)
Sassi [13]	Prospective (102; UC & CD)	ASP: 5 ASMP: 1 FNP: 1 CTS: 2	7 active 2 inactive	2 MNDZ 2 DM 1 Low B12 1 Mechanical compression	8 after (0.3–15) 1 NR

UC, ulcerative colitis; CD, Crohn's disease; AIDP, acute inflammatory demyelinating polyneuropathy; MM, mononeuritis multiplex; BP, brachial plexopathy; MRS, Melkersson-Rosenthal syndrome; ASMP, axonal sensory and motor polyneuropathy; CIDP, chronic inflammatory demyelinating polyneuropathy; MMN, multifocal motor neuropathy; ASP, axonal sensory polyneuropathy; LSP, lumbosacral plexopathy; MSMP, mix axonal and demyelinating sensorimotor polyneuropathy; SFP, small fiber polyneuropathy; CTS, carpal tunnel syndrome; FNP, fibular nerve palsy; NR: not reported; DM, diabetes mellitus; INF, infliximab; MNDZ, metronidazole; HT, hypothyroidism.

Discussion

We present five cases of CD with different neurological manifestations, including AION, PRES, myelopathy related to CD, CIDP, and chronic axonal sensory and motor polyneuropathy. In a large retrospective register-based study by Lossos *et al.*, neurological involvement is reported in 3% of cases of IBD [4]. In another study, 67% of patients with CD and 53% of patients with ulcerative colitis (UC) had neurologic disorders [1]. Several mechanisms may explain the peripheral and central nervous systems disorder in patients suffering from IBD: (i) malabsorption, and nutritional and vitamin deficiencies such as vitamins B1, B12, D and E, folic acid and nicotinamide deficiencies; (ii) immunological abnormalities, (iii) infections, (iv) medication side effects (metronidazole, sulfasalazine, steroids, cyclosporine) or iatrogenic complications related to intestinal surgery and (v) precoagulation and thromboembolism [5].

Polyneuropathy

Polyneuropathy is placed among the most frequent neurological complications associated with IBD and frequently reported in previous literature (Table 1). In the two largest retrospective studies, peripheral neuropathy occurred in 0.9–3.6% of patients with IBD [3]. Lossos *et al.* showed incidence of neuropathy in 0.9% of IBD patients, and that the most common type of polyneuropathy was acute inflammatory demyelinating polyneuropathy (AIDP) [4]. It is known that polyneuropathy is an adverse effect of infliximab, sulfasalazine, mesalamine and metronidazole treatment [6,7]. Axonal neuropathies are more frequent than demyelinating neuropathies; however, treatment of both types of IBD with immunomodulatory drugs is promising [5]. Several types of polyneuropathy have been described in IBD patients, including autonomic neuropathy, sensory polyneuropathy, AIDP, CIDP, mononeuropathy (such as carpal tunnel syndrome), multifocal neuropathy, cranial neuropathy and plexopathy [5,6].

The underlying pathophysiology of neuropathy in IBD patients included drug exposure, nutritional deficiency and immune-mediated. The importance of T-cell lymphocytes in demyelinating neuropathies pathogenesis has been shown; however, the role of immune system disturbances in axonal damage is not clear, although clinical response to immunomodulatory agents in patients with axonal neuropathy support this association [1]. Abnormal gut microbial composition and gastrointestinal mucosal integrity that is seen in IBD may have a role in neuropathy [14]. Indeed, both abnormalities may result in a cross-reaction of pathogenic anti-gut antibodies against neural surface antigens and the molecular mimicry process that has an important role in some autoimmune polyneuropathy such as Guillain-Barre syndrome, secondary to *Campylobacter jejuni* infection, a gut commensal species [14]. In support of this theory, Didesch *et al.* reported that a 75-year-old man who underwent fecal transplantation developed acute demyelinating sensorimotor polyneuropathy following *Clostridium difficile* infection [15].

Our two patients did not have contributory risk factors for neuropathy (such as vitamin B12 deficiency and drug exposure) and there seemed to be an immune-based neuropathy that was supported by the clinical response of one of them to treatment with intravenous immunoglobulin. Other studies that evaluated the IBD patients with polyneuropathy, either axonal or demyelinating, showed clinical response to immunotherapy, although the response was different among different studies [3]. This variability may have resulted from different immune processes

Table 2. Clinical studies of myelopathy disorder in inflammatory bowel disease (IBD)

	Reference	Study design	Age (years)	Sex	Type of IBD	IBD activity	Myelopathy course
Abnormal MR	Ray [34]	Case report	32	Female	UC	Inactive	Acute
	De Lau [35]	Case report	57	Female	UC	Inactive	Acute
			28	Male	UC	Inactive	Acute
Normal MR	Lossos [4]	Retrospective	23	Male	CD	Inactive	Chronic progressive
			68	Male	CD	Inactive	Chronic progressive
			50	Female	UC	Inactive	Chronic progressive
			21	Male	CD	Inactive	Chronic progressive
			71	Female	CD	Inactive	Chronic progressive

MR, magnetic resonance; UC, ulcerative colitis; CD, Crohn's disease.

involved in neuropathy: primary to CD, secondary to gut microbiota or coincidence of an autoimmune polyneuropathy.

Posterior reversible encephalopathy syndrome (PRES)

PRES is an acute clinical–radiological syndrome identified by headache, drowsiness, seizures, visual obscuration and altered mental state. The usual MR imaging findings are reversible sub-cortical white matter lesions predominantly involving the posterior cerebral regions, namely the occipital and parietal lobes [16]. PRES has been recognized as a neurological side effect of acute BP rising and treatment with calcineurin [17]. Few cases of PRES are reported in patients with CD and UC following infliximab [17] or mesalamine [18] administration. Our patient developed PRES in the active phase of the disease, and he was not on any medication.

Two possible theories for PRES have been described: first, impaired autoregulation following hypertension resulting in vasogenic edema; another theory suggests that the direct effect of toxins or drugs may result in endothelial and blood–brain barrier dysfunction, and eventually brain edema [19]. Our patient had no history of hypertension or drug exposure. It could be related to another mechanism such as immune activity secondary to IBD which is supported by the association of PRES with the active phase of the disease. Indeed, PRES did not recur in the following 18 months when CD was well controlled. The association of inflammatory disease and PRES has been shown in limited reports. Baizabal-Carvallo *et al.* reported 22 cases of systemic lupus sclerosis with PRES, of which four had no history of hypertension [20]. Kofler *et al.* reported a 75-year-old man with a history of lymphoma who presented with PRES [21]. The brain biopsy of the patient showed endothelial activation, T-cell lymphocyte trafficking and vascular endothelial growth factor expression, which histological finding suggested the role of systemic immune system activation in PRES pathogenesis [20]. Also, the occurrence of PRES following influenza A infection [22] and autoimmune thyroid disease [23] supports the relationship between PRES and inflammatory systemic disease in the absence of hypertension and toxin exposure.

Anterior ischemic optic neuropathy (AION)

AION, an acute infarction of the optic nerve head, occurs following decreased or interrupted blood flow to the optic nerve. Possible risk factors of AION are arteriosclerosis, hypertension, diabetes mellitus, ischemic heart disease, hypercholesterolemia and thrombophilic states. Cerebral and retinal arterial and venous infarction may occur in patients suffering from IBD [2,5]. Falavarjani *et al.* reported a 9-year-old boy with CD who developed central retinal arterial occlusion [24]. In pathological

examination of the brain tissue of a patient with IBD who suffered from a cerebrovascular event, Schneiderman *et al.* showed thrombus formation in the small arteries and veins [25]. In other studies, patients with IBD had higher risk for arterial and venous thromboembolism, including cerebrovascular events, compared with the non-IBD population. The risk of thrombosis increased during disease flare-up [26,27].

Similarly to other inflammatory disease, IBD is associated with enhanced procoagulative activity, including initiation of the coagulation process, reduction of natural anticoagulant mechanisms, impairment of fibrinolysis, thrombocytosis, and reactivity and disorder of the endothelium function [28]. The presence of an active inflammatory process does not explain thromboembolism alone. The risk of thromboembolism in IBD patients is higher than in other autoimmune diseases without gut involvement, such as rheumatoid arthritis [7]. In fact, it has been proposed that some gut-specific mechanisms other than systemic inflammation may be involved [29].

IBD patients display defective intestinal barrier functions. Thus, the molecular patterns associated with pathogens such as lipopolysaccharide, which originates from the intestinal bacteria, may pass from the abnormal gut barrier through the systemic circulation and activate the pattern-recognition receptors in innate immunity onto the endothelial cells and platelets that can lead to a procoagulant state [29,30]. Fialho *et al.* showed that small intestinal bacterial overgrowth, a condition seen in IBD, increases the risk of deep vein thrombosis, as an independent risk factor [30]. Small intestinal bacterial overgrowth may be associated with the release of bacterial compounds such as lipopolysaccharide, which may induce a proinflammatory state that is important in clot formation [30].

A combination of AION and CD in our patient may be a coincidence of two diseases or may be a vascular event related to CD. He did not have a relevant vascular risk factor for AION, so the evidence strengthens the role of CD at the occurrence of AION.

Myelopathy

Few studies have reported myelopathy associated with IBD. Secondary causes of myelopathy, such as drug reaction [31], spinal epidural abscess [32] and malabsorption [33], are seen in patients with IBD. However, myelopathy may occur in IBD without obvious secondary causes as in our patient, and may contribute to the inflammatory process originating from IBD (Table 2) [4,34,35]. Myelopathy following IBD may occur with inflammatory lesion in spinal MR imaging [34,35], although Lossos *et al.* reported five IBD patients with chronic progressive myelopathy who had normal spinal MR imaging [4].

The association of multiple sclerosis (MS) and IBD has been reported by previous studies [36,37]. In a cohort and a cross-sectional study by Gupta *et al.*, the incidence and prevalence of optic neuritis, MS and other demyelination diseases were higher in patients with IBD than the control group [38]. Since the immune mechanism has the main role in the pathogenesis of both diseases, co-occurrence of IBD and MS is feasible. Treatments that inhibits TNF- α including infliximab and adalimumab are associated with peripheral and central demyelinating disorders such as cerebral or spinal demyelinating plaques, optic neuritis and facial palsy [1].

In recent years, the role of microbiome in the pathogenesis of MS has been proposed. Patients with MS showed higher frequency of antibody responses against bacterial antigens of the gastrointestinal tract compared with healthy subjects [39]. Berer *et al.* showed that the commensal gut flora, in the absence of pathogenic agents, may result in myelin-specific CD4(+) T-cells activation that is associated with the relapsing of experimental autoimmune encephalomyelitis [40]. Patients with neuromyelitis optica (NMO) have a higher rate of antibodies against gastrointestinal antigens than healthy controls, which supports the alteration of gut microbiota composition in NMO patients [39]. Aquaporin 4-specific T-cells in NMO patients exhibit cross-reactivity to a protein belonging to *Clostridium perfringens*, a gut commensal species [41]. This finding supports the role of a microbiota-molecular mimicry process in NMO pathogenesis [41].

On the other hand, the IBD subjects have unusual bacterial species, which substitute normal flora of gut and fecal microbiota of these patients, and are different from those seen in healthy subjects [42]. Besides, abnormal gut permeability in CD facilitates the access of immune cells to gut microbiome and the induction of a humoral and cellular immune reaction [14].

Our patient had gradual onset of non-progressive myelopathy but the laboratory and imaging work-up did not show any finding in favor of compressive lesion or nutrient deficiency. We may conclude that the inflammatory process secondary to CD is the probable mechanism in this patient, particularly as his symptoms improved moderately with immunosuppressants such as intravenous immunoglobulin and infliximab.

Conclusion

Idiopathic IBD is a systemic disorder that may involve peripheral and central nervous diseases, and awareness of the probable pathophysiological mechanisms involved in the neurologic manifestation of IBD may be helpful for selecting appropriate treatment. A clinician should keep in mind that the development of a neurological disease in IBD may be coincidental (chance association) or the consequence of the primary disease, each of which may require different treatments.

Conflict of interest

None declared.

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