ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

Section Editor: Stephen B. Hanauer, MD

Neurologic Manifestations of Inflammatory Bowel Disease

Jose M. Ferro, MD, PhD
Professor and Chairman of Neurology
Santa Maria Hospital
University of Lisbon
Lisbon, Portugal

G&H Can inflammatory bowel disease cause neurologic complications?

JF Yes. Neurologic complications of inflammatory bowel disease (IBD) are not very common, but they are one of the nongastrointestinal manifestations of the disease. These complications are not widely recognized and are underreported.

G&H What types of neurologic complications can IBD cause?

JF Neurologic manifestations of IBD have not been investigated in a population-based study, so there are few evidence-based details. However, we know that IBD can cause peripheral neurologic complications as well as central nervous system complications. These complications can be acute or chronic. Cranial neuropathies associated with IBD include Melkersson-Rosenthal syndrome, optic neuritis, and sensorineural hearing loss.

Within the central nervous system, there are 2 main types of manifestations: cerebrovascular complications and demyelinating complications. Stroke following arterial thromboembolism may occur, as might thrombosis of the dural sinus and cerebral veins. Patients with IBD have an approximately 3-fold higher risk of venous cerebral thrombosis compared with the general population. Several case reports have linked multiple sclerosis (MS) to IBD, and up to 50% of patients present with asymptomatic white-matter lesions. Some patients experience slowly progressive myelopathy. Other central nervous system manifestations include epidural and subdural spinal empyema following fistulous extension from the rectum, seizures, and encephalopathy.

G&H What other cerebrovascular complications are associated with IBD?

JF Some patients experience vasculitis, which appears to be an immune-mediated complication of IBD. Relatively few cases have been confirmed, and there is some overdiagnosis of vasculitis, in part because it appears as small white-matter changes on magnetic resonance imaging (MRI), and vasculitis is difficult to confirm. Only 5 cases have been diagnosed through biopsies. Advancements in MRI technology are allowing us to improve these diagnoses because we can obtain clearer images of blood vessel walls.

G&H Are some of the neurologic complications due to treatments for IBD?

JF Yes. Peripheral neuropathy, the most common neurologic issue stemming from IBD, can occur as a side effect to anti–tumor necrosis factor-α (anti-TNF) therapy or treatment with the antibiotic metronidazole.

Demyelinating disease, including MS or central demyelination that mimics MS, is also a side effect of anti-TNF therapy, and this therapy can also worsen preexisting demyelinating disease. Several case studies have reported this association. In a recent case series published in *Neurology* that presented clinical and MRI results from patients treated with adalimumab (Humira, AbbVie; n=2), etanercept (Enbrel, Amgen; n=2), or infliximab (Remicade, Janssen; n=2) who were followed for 1 to 4 years, most patients experienced a single clinical neurologic event. Although there are no clinical trial data conclusively linking anti-TNF agents with MS, clinicians need to be very careful when using these drugs in IBD patients who have a history of MS or another demyelinating disease.

In addition, natalizumab (Tysabri, Biogen Idec) has been associated with severe multifocal leukoencephalopathy because the drug can reactivate JC virus; however, this side effect is more common among patients with serologic evidence of previous JC virus infection.

G&H Can the disease itself also have neurologic manifestations unrelated to treatment?

JF Neurologic manifestations unrelated to treatment are possible, although the pathogenesis of neurologic involvement in IBD has not been fully elucidated. Polyneuropathies may be related to micronutrient deficiencies, which may, in turn, be caused by diarrhea. Other polyneuropathies may be related to immune system changes that produce peripheral demyelination.

G&H Are neurologic complications treatable?

JF Yes. Because these manifestations have their own clinical course, they require their own specific treatment. For neurologic manifestations caused by the disease itself, medications used for treating IBD will not necessarily treat the neurologic manifestations of IBD.

G&H How are drug-induced neurologic manifestations treated?

JF The polyneuropathy caused by metronidazole is reversible by stopping the medication. Demyelinating neuropathies respond to immunomodulatory therapy; thus, immunoglobulin or steroid therapy can be used to treat these conditions. The demyelinating disease caused by anti-TNF therapy is treated with steroids. It is important for gastroenterologists to work closely with neurologists to ensure that any neurologic manifestations of IBD are treated properly.

G&H What is the association between MS and IBD?

JF MS is not more common with IBD than with other gastrointestinal disorders. People with MS do have an increased risk of IBD, but it is rare to find a person with both diseases.

G&H Could you further discuss the large percentage of white-matter lesions at the time of IBD diagnosis?

JF When patients diagnosed with IBD undergo a brain MRI, many present with white-matter lesions. These lesions usually appear as white spots in T2 or fluid attenuation inversion recovery sequences on MRI. These spots are different from those found in MS and are more common among IBD patients than control patients. Some case-control studies have found that these white-matter changes are not more common among IBD patients than among controls, so the significance of these lesions in IBD is still uncertain.

G&H Do such lesions impact treatment decisions?

JF These lesions do not typically affect treatment decisions. Treatment-related considerations would be warranted only if a lesion is very suggestive of MS by its shape, distribution, and other features.

G&H Are there any hypotheses about why IBD might be associated with white-matter lesions?

JF As previously noted, the connection between IBD and these lesions is frail; there are no long-term studies showing whether lesions increase with time or are related to the severity of IBD. More studies are needed, particularly longitudinal studies to determine whether these lesions are progressive.

G&H Are there any ongoing studies being conducted to better understand the connection between IBD and neurologic manifestations?

JF There is basic research ongoing to understand the association between neurologic conditions and IBD along with other diseases. Other immunologic diseases, such as lupus, can also cause neurologic changes.

Dr Ferro has no relevant conflicts of interest to disclose.

Suggested Reading

Cognat E, Crassard I, Denier C, Vahedi K, Bousser MG. Cerebral venous thrombosis in inflammatory bowel diseases: eight cases and literature review. *Int J Stroke*. 2011;6(6):487-492.

Cohen M, Baldin B, Thomas P, Lebrun C. Neurological adverse events under anti-TNF alpha therapy [in French]. *Rev Neurol (Paris)*. 2012;168(1):33-39.

Ferro JM, Oliveira SN, Correia L. Neurologic manifestations of inflammatory bowel diseases. *Handb Clin Neurol*. 2014;120:595-605.

Freeman HJ, Flak B. Demyelination-like syndrome in Crohn's disease after infliximab therapy. *Can J Gastroenterol*. 2005;19(5):313-316.

Gondim FA, Brannagan TH III, Sander HW, Chin RL, Latov N. Peripheral neuropathy in patients with inflammatory bowel disease. *Brain*. 2005;128(pt 4):867-879.

Katsanos AH, Katsanos KH, Kosmidou M, Giannopoulos S, Kyritsis AP, Tsianos EV. Cerebral sinus venous thrombosis in inflammatory bowel diseases. *QJM*. 2013;106(5):401-413.

Singh S, Kumar N, Loftus EV Jr, Kane SV. Neurologic complications in patients with inflammatory bowel disease: increasing relevance in the era of biologics. *Inflamm Bowel Dis*. 2013;19(4):864-872.

Thomas CW Jr, Weinshenker BG, Sandborn WJ. Demyelination during anti-tumor necrosis factor alpha therapy with infliximab for Crohn's disease. *Inflamm Bowel Dis*. 2004;10(1):28-31.

Van Assche G, Van Ranst M, Sciot R, et al. Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease. *N Engl J Med*. 2005;353(4):362-368.

Williamson E, Javed A. Demyelinating syndromes associated with anti-TNF alpha agents: case series. *Neurology*. 2012;78(Meeting Abstracts 1):P06.182.