Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://doi.org/10.21608/zumj.2024.280809.3302 Volume 31, Issue 1.1, JAN. 2025, Supplement Issue
Manuscript id ZUMJ-2403-3302
Doi 10.21608/ZUMJ.2024.280809.3302
REVIEW ARTICLE

Neurological complications in children and adolescent with Inflammatory Bowel diseases

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Submit date 31-03-2024
Revise Date 19-04-2024
Accept date 25-04-2024

Abstract

The two primary distinguishing characteristics of inflammatory bowel diseases (IBD) are ulcerative colitis (UC) and Crohn's disease (CD). IBD is a group of chronic inflammatory illnesses of the gastrointestinal tract. IBD generates extraintestinal symptoms in the central and peripheral nerve systems in addition to gastrointestinal symptoms. Although the exact cause of the neurological symptoms of IBD is still unknown, other possible explanations include immune-mediated etiology, brain-gut axis dysfunction, thromboembolism, poor nutrition, side effects from medication (metronidazole, sulfasalazine, anti-integrin antibodies, steroids), and thromboembolism. Peripheral neuropathy, demyelinating central nervous system illness, and cerebrovascular disease are the most common neurologic occurrences documented in people with CD and UC. It is not appropriate to treat patients with both multiple sclerosis and IBD with anti-TNF-α therapy. Rarely, anti-TNF-α therapy can also result in demyelinating diseases. To avoid significant neurologic morbidity in IBD patients, early suspicion, diagnosis, and treatment of neurological consequences are essential for better outcomes.

Keywords: neurological; inflammatory bowel disease; ulcerative colitis; Crohn's disease.

INTRODUCTION

Most cases of inflammatory bowel diseases (IBDs), which include ulcerative colitis (UC) and Crohn's disease (CD), occur in adolescence and early adulthood. These conditions are chronic inflammatory illnesses of the gastrointestinal system. About 25% of IBD patients first appear before the age of 20. With a peak beginning in adolescence, 4% of children with IBD present before the age of five, and 18% before the age of ten [1]. The hallmark of ulcerative colitis is a widespread, ongoing colonic inflammation that starts close to the rectum. Backwash ileitis is a minor form of ileal inflammation that can occur in patients with diffuse pancolitis and ulcerative colitis. Furthermore, modest upper gastrointestinal tract inflammation is present in 40–70% of UC patients [2]. Any part of the gastrointestinal system, from the mouth to the anus, can be affected by Crohn's disease; however, the terminal ileum and colon are the most frequently affected [2]. Inflammatory, penetrating, stricturing, or mixed phenotypes are possible presentations of the disease. Several organs are included in extraintestinal manifestations (EIMs), which can happen concurrently with or before the start of intestinal symptoms. But a lot of EIMs tend to go in their own direction. 20%–40% of IBD patients have these EIMs, while CD patients have a higher frequency of observation [3–7]. IBD-related neurologic involvement is usually underreported. Nevertheless, as early diagnosis and treatment of neurologic illnesses are essential for averting substantial morbidity, it is vital to evaluate the morbidity burden of clinically significant neurologic consequences in IBD [8,9]. The etiology of neurogenic diseases linked to inflammatory bowel disease (IBD) remains unclear and could stem from various factors. Although prothrombotic conditions, dietary deficiencies (vitamin B12, folate, copper, vitamin E, thiamine), and iatrogenic consequences of medical and surgical care are among the other documented causes, the majority have an

immunological base. Furthermore, the application of tumor
necrosis factor (TNF) inhibitors have been documented as an effective treatment for refractory IBD in recent years [10], despite the fact that anti-TNF-α antibodies seem to predispose certain patients to a variety of problems involving the central and peripheral neurological systems.

We will examine the neurological symptoms in children and adolescents with IBD and biologic-induced neurological events in this narrative review.

Epidemiology

In the US and Canada, there are roughly 10 cases of pediatric IBD for every 100,000 children [11]. IBD is becoming more commonplace worldwide, in both developed and developing nations. An incidence of 0.5 per 100,000 per year and a prevalence of 5 per 100,000 per year were calculated by one investigation on the epidemiology of juvenile onset IBD from Central Saudi Arabia [12]. The prevalence of neurological abnormalities in IBD patients has not been thoroughly studied in much systematic research. Furthermore, these research' outcomes have been erratic, mostly because of variations in the case-finding techniques used. Magnetic resonance imaging was not a component of the usual workup in most of the investigations that were reported. Additionally, some research has included neurological symptoms of iatrogenic origin or symptoms resulting from illnesses associated to malabsorption that are secondary to vitamin deficiencies [13, 14]. Lastly, data on clinical symptoms involving other nervous system components is lacking from the most recent findings on neurologic consequences in IBD disease, which have concentrated on peripheral nervous system (PNS) involvement [15,16,17]. According to Lossos et al. [17] 3% of the 638 patients with UC or CD who were the subject of a thorough retrospective register-based analysis had neurological involvement. On the other hand, neurological or neuropsychiatric problems were reported by 33.2% of patients in a CD sample; however, this percentage dropped to 19.3% when limited to cases where a direct link was present [12]. In another investigation, neurologic abnormalities were present in 67% of patients with CD and 53% of patients with UC; however, the authors did not describe if the neurologic involvement and IBD were coincidental [18]. According to two studies [13,19], peripheral neuropathy is present in 13.4% and 8.8% of people, respectively. In MRI examinations of IBD patients compared to healthy age-matched controls, asymptomatic localized brain white matter lesions were also seen (43.1% versus 16.0%; RR 2.6, 95% CI 1.3–5.3) [20].

Pathophysiology

There are several possible factors that contribute to the pathophysiology of IBD's neurological effects. Many neurological symptoms are immune-mediated, but it's also important to take into account the brain-gut axis, infections, venous and arterial thromboembolism, malnutrition, and side effects from therapeutic drugs and procedures [21–24].

Determining the primary mechanism is essential to avert further brain injury. Sadly, it is frequently impossible to pinpoint the primary pathogenic cause. However, pharmaceutical drugs typically employed in IBD may potentially contribute to the progression of such symptoms, therefore it is important to consider factors other than disease-related mechanisms [25].

Neurological manifestations

1. Cerebrovascular disease

Because IBD causes a hypercoagulability state, thromboembolic consequences are typical in this condition. This is linked to an increase in platelet count and activity, a decrease in natural anticoagulant factors and fibrinolytic activity, and an increase in coagulation factors, thrombin levels, and fibrin formation [26]. According to clinical studies, the incidence of thromboembolism in people with IBD ranges from 1% to 7.7% overall; however, post-mortem investigations can increase this number to 39% [27, 28]. Although the venous and arterial systems may be impacted, the most common thromboembolic consequences in IBD are pulmonary embolism and deep vein thrombosis [27–30].

A 2013 meta-analysis revealed that UC and CD were linked to a higher risk of transient ischemic attack or hemorrhagic or ischemic stroke (OR = 1.28, 95%CI: 1.17-1.41), particularly in young patients and women [31].There is little doubt that the likelihood of thrombotic or thromboembolic events is correlated with disease activity [26, 27].Although the exact cause of the elevated incidence of thromboembolic events in IBD patients is unknown, it is most likely due to the interplay of hereditary and acquired risk factors. Additionally, studies have documented the interplay between the coagulation system and cytokine mediators of chronic inflammation. [32] Genetic variables such as factor Leiden and factor II, methylenetetrahydrofolate reductase gene mutation, plasminogen activator inhibitor type 1

gene mutation, and factor XIII have been suggested as potential promoters of the thrombotic symptoms of IBD. Nevertheless, no research has shown solid evidence that IBD patients are more likely than the general population to have prothrombotic genetic or non-genetic risk factors, such as factor ≤ Leiden mutations, hyperhomocysteinemia, antiphospholipid antibodies, or thrombophilia These findings have led numerous studies to propose that IBD might be a separate risk factor for thromboembolic diseases [10].

2. Demyelinating disorders

Since the early 1980s, there has been a hypothesized link between demyelinating disorders. Multiple sclerosis (MS) was found to be more prevalent in patients with UC, according to Rang et al. [33]. Many writers have since corroborated this conclusion, not just for UC but also for CD [34–36]. A high risk of optic neuritis, for example, was identified by Gupta et al. in CD (odds ratio = 1.54) and UC (odds ratio = 1.75), respectively [33]. According to a recent meta-analysis, individuals with IBD are more likely to experience contemporaneous MS, while individuals with MS are more likely to experience related IBD [34].

There might be a strong connection between IBD and MS. immunological system inhibitors that reduce cell-mediated immunity are useful in the treatment of both MS and IBD, which lends credence to the idea that immunological mechanisms have a role in the pathophysiology of both conditions. A disturbance in antigen-presenting cells and functional T-cell subsets has also been linked. Research indicates that a common route leading to the loss of target tissue in both disorders may involve abnormal pro-inflammatory activity in particular [3-5].

3. Epilepsy

Seizures, either localized or generalized, may sporadically occur in patients with IBD, either CD [11] or UC [10,42]. Most of these seizures are acute symptomatic seizures that result from structural brain lesions, primarily vascular, or from metabolic disruptions [35].

It is unclear how epilepsy and IBD are related to one another. In a cohort of 638 IBD patients, Lossos et al. found a prevalence of 1.9%; however, many of these individuals had a structural and/or metabolic reason that might potentially result in epileptic seizures [17].

4. Peripheral neuropathy

Peripheral neuropathies of various kinds have been linked to both active and inactive IBD. Peripheral nerves in IBD have been shown to be affected by demyelinating or axonal neuropathies, both of which can be acute and chronic [36–39].

PN is a common neurologic consequence seen in individuals with inflammatory bowel disease (IBD) receiving anti-tumor necrosis factor alpha (anti-TNF-α), cyclosporine, thalidomide, and metronidazole medication. Despite decades of use in IBD, metronidazole's correlation with PN is still debatable. 50% of IBD patients on metronidazole developed PN; however, the diagnosis of PN was made only based on neuropathic symptoms; neurophysiological evidence was not obtained [40].

Anti-TNF-α medications reduce inflammation because the pro-inflammatory cytokine TNF-α is a key player in the inflammatory cascade that results in intestinal inflammation in IBD patients. Several TNF-α inhibitors have been utilized in the treatment of IBD, mainly in instances that are moderate to severe. Although the first anti-TNF-α treatment was infliximab, other humanized monoclonal antibodies, such as golimumab and adalimumab, have also been effectively employed [41]. Anti-TNF-α drugs used in clinical settings have been shown to disclose PN among other immune-mediated neurologic side effects. Patients with IBD receiving drugs have been reported to have peripheral demyelinating neuropathies, either acute or chronic, compatible with Guillain Barre syndrome (GBS), Miller Fisher syndrome, Lewis-Sumner syndrome, or chronic inflammatory demyelinating polyneuropathy (CIDP). The majority of GBS cases occur between six days and two years after starting anti-TNF-α medication. Elevated serum anti-ganglioside antibodies have been reported in instances of CIDP, which may indicate a humoral attack on myelin [42]. Additionally, there have been case reports of multifocal motor neuropathy (MMN) after infliximab treatment; in these instances, patients experienced conduction blockages of different motor neurons on NS as well as asymmetric progressive weakening. Lastly, among patients receiving infliximab treatment, reports of small fiber neuropathy (SFN), axonal sensory neuropathy, mononeuritis multiplex, or sensorimotor polyneuropathy were also made [43]. Before starting anti-TNF-α medication, patients with IBD should be evaluated to identify risk factors for developing PN. The initial step in treating individuals with PN caused by anti-TNF is medication cessation. However, further immunomodulatory treatment with steroids or intravenous immunoglobulins should be administered if individuals do not show clinical improvement. TNF-inhibitors should not be used

in patients with PN, according to the evidence presented here [44].

CONCLUSIONS

Patients with IBD may experience a range of neurological symptoms. The pathogenesis is diverse and frequently remains undiagnosed. To avoid significant neurologic morbidity in IBD patients, it is imperative to recognize, identify, and treat neurological problems as soon as possible.

REFERENCES

[1] **Tavakoli, P., Vollmer-Conna, U., Hadzi-Pavlovic, D**, A Review of Inflammatory Bowel Disease: A Model of Microbial, Immune and Neuropsychological Integration. Public Health Rev, 2021 ,42, 160-9.

[2] **Verstockt, B., Bressler, B., Martinez-Lozano, H., et al. Dermot M, Mark S**,. Time to Revisit Disease Classification in Inflammatory Bowel Disease: Is the Current Classification of Inflammatory Bowel Disease Good Enough for Optimal Clinical Management? Gastroenterology, 2022,162, 1370-82.

[3] **Abraham C, Cho JH**. Inflammatory bowel disease. N Engl J Med 2009; 361: 2066-2078 [PMID: 19923578 DOI: 10.1056/ NEJMra0804647]

[4] **Baumgart DC, Sandborn WJ**. Crohn's disease. Lancet 2012; 380: 1590-1605 [PMID: 22914295 DOI: 10.1016/s0140-6736(12)60026-9]

[5] **Ordás I, Eckmann L, Talamini M, Baumgart DC, Sandborn WJ**. Ulcerative colitis. Lancet ,2012; 380: 1606-1619 [PMID: 22914296 DOI: 10.1016/s0140-6736(12)60150-0]

[6] **Bernstein CN, Blanchard JF, Rawsthorne P, Yu N**. The prevalence of extraintestinal diseases in inflammatory bowel disease: a population-based study. Am J Gastroenterol 2001; 96: 1116-1122 [PMID: 11316157 DOI: 10.1111/ j.1572-0241.2001. 03756.x]

[7] **Veloso FT**. Extraintestinal manifestations of inflammatory bowel disease: do they influence treatment and outcome? World J Gastroenterol 2011; 17: 2702-2707 [PMID: 21734777 DOI: 10.3748/wjg. v17.i22.2702]

[8] **Scheid R, and Teich, N**., Neurologic manifestations of ulcerative colitis. European Journal of Neurology, 2007.14(5), pp.483-493.

[9] **Wills, A.J., Tengah, D.P. and Holmes, G.K.,** The neurology of enteric disease. Journal of Neurology, Neurosurgery & Psychiatry, 2006,77(7), pp.805-810.

[10] **Morís G**. Inflammatory bowel disease: an increased risk factor for neurologic complications. World Journal of Gastroenterology: WJG. 2014 Feb 2;20(5):1228.

[11] Zagórowicz**, E., Walkiewicz, D., Kucha, P, Michal M P**, **Paulina W**, Nationwide data on epidemiology of inflammatory bowel disease in Poland between 2009 and 2020. Pol Arch Intern Med, 2022,132, 80-9.

[12] **Alatab, S., Sepanlou, S.G., Ikuta, K,.** The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 19902017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet gastroenterology & hepatology, 2020,5(1), pp.17-30.

[13] **Oliveira, G.R., Teles, B.C.V., Brasil, É.F.,** Peripheral neuropathy and neurological disorders in an unselected Brazilian population-based cohort of IBD patients. Inflammatory bowel diseases, 2008. 14(3), pp.389-395.

[14] **Elsehety, A. and Bertorini, T.E**., Neurologic and neuropsychiatric complications of Crohn's disease. Southern medical journal ،11997, Jun;90(6):606

[15] **De Lau, L.M., de Vries**,. Acute CNS white matter lesions in patients with inflammatory bowel disease. Inflammatory bowel diseases, 200915(4), pp.576-580.

[16] **Shen, T.C.D., Lebwohl, B**, **Himanshu V, Nikhil K**, **Christin T,** Peripheral neuropathic symptoms in celiac disease and inflammatory bowel disease. Journal of Clinical Neuromuscular Disease, 2012.13(3), pp.137-145.

[17] **Lossos A, River, Y., Eliakim, A. Steiner I**, Neurologic aspects of inflammatory bowel disease. Neurology, 1995,45(3), pp.416-421.

[18] **Graham, D. B. & Xavier, R. J**. Pathway paradigms revealed from the genetics of inflammatory bowel disease. Nature, 2020,578, 527-39.

[19] **Samia.B. S, Lamia K, sawassan R** Peripheral neuropathy in inflammatory bowel disease patients: a prospective cohort study, Scand. J. Gastroenterol. 44 (10) (2009) 1268–1269.

[20] **Geissler A, Andus T, Kullman F, Caser R, Held P, Gross V et al**., Focal white-matter lesions in brain of patients with inflammatory bowel disease, Lancet (1995) 345 (8954) 897–898.

[21] **Derbyshire S.W**, A systematic review of neuroimaging data during visceral stimulation, Am. J. Gastroenterol. 98 (1) (2003) 12–20.

[22] **Konturek S.J, Pawlic T**, Brain-gut axis and its role in the control of food intake, J. Physiol. Pharmacol. (2004) 55 (1 Pt 2) 137–154.
[23] **Zois C.D, Konstantinos H , Maria K, Epameinondas V**, Neurologic manifestations in inflammatory bowel diseases: current knowledge and novel insights, J. Crohns. Colitis 4 (2) (2010) 115–124.
[24] **Guan Q.,** A comprehensive review and update on the pathogenesis of inflammatory bowel disease, J Immunol Res 2019 (2019) 7247238.
[25] **Bernstein CN, Eliakim A, Fedail S, Fried M, Gearry R, Goh K-L**, Update. Journal of Clinical Gastroenterology. August 2015;50(10):803-818
[26] **Zezos P, Kouklakis G, Saibil F.** Inflammatory bowel disease and thromboembolism. World Journal of Gastroenterology. 2014;20(38):13863-13878
[27] **Benarroch HS, Acosta AV.** Complicaciones vasculares asociadas a la enfermedad inflamatoria intestinal. Anales de Medicina Interna. 2003; 20:81-84
[28] **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
[29] **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
[30] **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
[31] **Singh S, Singh H, Loftus EV Jr, Pardi DS**. Risk of Cerebrovascular Accidents and Ischemic Heart Disease in Patients with Inflammatory Bowel Disease: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol 2013 Aug 24; Epub ahead of print [PMID: 23978350 DOI: 10.1016/ j.cgh.2013.08.023]
[32] **Danese S, Papa A, Saibeni S, Repici A, Malesci A, Vecchi M**, Inflammation and coagulation in inflammatory bowel disease: The clot thickens. Am J Gastroenterol 2007; 102: 174-186 [PMID: 17100967 DOI: 10.1111/j.1572-0241.2006. 00943.x]
[33] **Gupta G, Gelfand JM, Lewis JD**. Increased risk for demyelinating diseases in patients with inflammatory bowel disease. Gastroenterology. 2005 Sep;129(3):819-826
[34] **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
[35] **Kelleci U.A, Turan C, Abdurrahman S, Zeyneb E, Resul K,Kamil O et al.,** Electroencephalography findings in Crohn's disease, Clin. EEG Neurosci. 50 (2) (2019) 129–133.
[36] **Torre RG, Moris G, Martinez DP, Montes IC**. Guillain–Barre syndrome, tuberculosis and inflammatory bowel disease: a multiple association. Int Arch Med 2010;3: 15. http://dx.doi.org/10.1186/1755-7682-3-15.
[37] **Krystallis CS, Kamberoglou DK, Cheilakos GB, Maltezou MN, Tzias VD**. Guillain–Barre syndrome during a relapse of ulcerative colitis: a case report. Inflamm Bowel Dis 2010; 16:555–6. http://dx.doi.org/10.1002/ibd.21071.
[38] **Rubio-Nazabal E, Alvarez-Perez P, Lema-Facal T, Brage-Varela A**. Guillain–Barre syndrome as extraintestinal manifestation during relapse of ulcerative colitis. Med Clin (Barc) 2014; 142:419–20. http://dx.doi.org/10.1016/j.medcli.2013.04.009.
[39] **Ariatti A, Ficarra G, Girolami F, Pentore R, Galassi G**. Chronic inflammatory demyelinating polyradiculoneuropathy associated with inflammatory bowel diseases: questioning the autoimmunity hypothesis. Int J Colorectal Dis 2009; 24:603–4. http://dx.doi.org/10.1007/s00384-009-0646-x
[40] **Daneman, N., Cheng, Y., Gomes, T., Gun J, Muhhamed M, Farah E**, Metronidazole-associated Neurologic Events: A Nested Case-control Study. Clin Infect Dis, 2021,72, 2095-100.
[41] **Etminan, M., Sodhi, M., Samii, A**, Tumor necrosis factor inhibitors and risk of peripheral neuropathy in patients with rheumatic diseases. Semin Arthritis Rheum, 2019. 48, 1083-6.
[42] **Patwala, K., Crump, N. & De Cruz, P,** Guillain-Barré syndrome in association with antitumour necrosis factor therapy: a case of mistaken identity. BMJ Case Rep, 2017, 480-96
[43] **Papamichael, K., Vajravelu, R. K., Vaughn, B. P,** Proactive Infliximab Monitoring Following Reactive Testing is Associated with Better Clinical Outcomes Than Reactive Testing Alone in Patients with Inflammatory Bowel Disease. J Crohns Colitis, 2018. 12, 804-10.
[44] **Kucharz, E. J. & Kotulska-Kucharz, A**, Tumor necrosis factor alpha inhibitors and demyelinating disease: what is behind it? Reumatologia 2021, 59, 65-7.

Citation

Risha, A., Hammed, M., Abdelhady, E., Abdelmalek Hanna, D., Hassan, Y. Neurological complications in children and adolescent with Inflammatory Bowel diseases. *Zagazig University Medical Journal*, 2025; (346-351): -. doi: 10.21608/zumj.2024.280809.3302