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Peripheral neuropathy in children and adolescent with Inflammatory Bowel diseases

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Abstract: The inflammatory bowel diseases (IBDs), which are primarily represented by Crohn's disease (CD) and ulcerative colitis (UC), are immune dysregulation-related chronic, relapsing inflammatory disorders of the digestive tract that cause symptoms like diarrhoea, bleeding, and abdominal pain. Because these conditions are systemic, people with IBD frequently have extraintestinal symptoms (EIMs) like arthritis, aphathous stomatitis (AS), and primary sclerosing cholangitis (PSC).Between 25% and nearly 50% of paediatric IBD patients had at least one EIM at the time of diagnosis, based on the scant paediatric data that is currently available,sometimes the term "EIMs" is used to refer to conditions other than the more common ones, such as peripheral neuropathy (PN), pyoderma gangrenosum (PG), arthritis, and growth failure and anaemia. One of the neurological problems that is most commonly mentioned is peripheral polyneuropathy (PN). Numerous PN phenotypes in IBD patients have been documented. In patients with CD who have received metronidazole treatment, paresthesias and an elevation in the threshold for temperature detection are prevalent (21-39%), but they are also observed in patients who have not taken this medication (19%). These findings may indicate early PN.

Keywords: neurological, inflammatory bowel disease, ulcerative colitis, crohn's disease extraintestinal manifestations

Introduction: Idiopathic inflammatory bowel disease (IBD) primarily manifests as Crohn's disease (CD) and ulcerative colitis (UC). Systemic disorders like CD and UC frequently affect organs outside the digestive tract. Extraintestinal manifestations (EIMs) are the term used to describe these inadvertent ailments. In individuals with IBD, the frequency of EIMs varies from 20% to 40% (4). Despite having a significant influence on quality of life, morbidity, and even death in IBD patients, neurologic involvement is one of the most underreported EIMs. For this reason, early detection of neurologic symptoms is essential for treating EIMs

affecting the nerve system. Peripheral neuropathies, cerebrovascular illnesses, and demyelinating disorders are the most common neurologic consequences observed in patients with inflammatory bowel disease (IBD) (5)It is acknowledged that one of the most frequent neurologic side effects of IBD is peripheral neuropathy (PN). Any condition of the peripheral nervous system (PNS) is referred to as PN, Polyneuropathy, on the other hand, describes a generalized rather homogenous process that affects numerous peripheral nerves, with the distal nerves typically being more visibly affected. On the other hand, mononeuropathy pertains to the localised involvement of a solitary nerve, while mononeuropathy multiplex denotes the concurrent involvement of numerous distinct peripheral nerves. The underlying process determines whether peripheral nerve injury is demyelinating or axonal, and this distinction is critical in the diagnostic work-up to determine the cause of the peripheral nerve damage. Classifying a peripheral neuropathy (PN) as either axonal or demyelinating can be aided by neurophysiologic tests (NS), such as nerve conduction studies and electromyography; but, in certain instances, type determination can be quite challenging(6).The involvement of peripheral nerves in CD and UC will be divided into two categories: IBD-associated peripheral nerve involvement, which reviews peripheral nerve involvement related to IBD without taking into account comorbidities, and secondary peripheral nerve involvement, which addresses peripheral nerve involvement resulting from vitamin deficiencies, biological agents, or other IBD management strategies(6)

Inflammatory bowel disease-associated peripheral neuropathy:

1.Guillain–Barré syndrome(GBS).

2.Multifocal motor neuropathy(MMN)

3.Chronic inflammatory demyelinating polyneuropathy(CIDP).

4.Acute motor sensory polyneuropathy.

5.Distal sensory axonal large-fiber polyneuropathy.

6.Distal sensory-motor axonal large-fiber polyneuropathy.

7.Monophasic immune radiculoplexus neuropathy.

8.Mononeuritis multiplex.

9.Autonomic neuropathy.

Pathogenesis of IBD-associated peripheral neuropathies

Uncertainty surrounds the pathophysiology of PN linked to IBD, which could have a variety of reasons, the majority of which have an immunological foundation. There have been reports of a relationship between UC and CD and inflammatory neuropathies; this association is more likely the result of shared etiological variables than a coincidence. One of the most common inflammatory neuropathies is acute and chronic demyelinating polyneuropathies, including Guillain-Barré syndrome (GBS), multifocalmotor neuropathy (MMN), and chronic inflammatory demyelinating polyneuropathy (CIDP), are among the most prevalent inflammatory neuropathies(7) Uncertainty surrounds the pathogenesis of these immunological neuropathies, which involves a number of humoral and cell-mediated processes that are partly similar to those of IBD. Furthermore, infection with Campylobacter jejuni or other bacteria, which is linked to IBD flare-ups, may precede GBS.Immune neuropathies associated with IBD may be largely caused by circulating humoral substances, antibodies, activated B cells, or plasma cells, as seen by the demyelination and nerve conduction block observed in inflammatory PN. Ultimately, T-cells have been linked to the pathophysiology of both IBD and demyelinating neuropathies. Reports have indicated that T-cell malfunction in immunoregulatory T-cells and elevated levels of interleukin-17 are also related to T-cell involvement (7,8). The gastrointestinal and neuropathic symptoms of IBD might be caused by similar immune-mediated pathways. It is commonly known that in a genetically vulnerable host, an improper inflammatory response to intestinal microorganisms causes inflammatory bowel disease (IBD). Disregulation of intestinal CD4+T-cell subsets is implicated in the pathophysiology of both human and mouse inflammatory bowel disease (IBD). The lamina propria has a rise in CD4+ T-cell counts, particularly in proinflammatory T-cell subsets. which release higher quantities of chemokines and cytokines. Though less research has been done on B-cell function in IBD than T-cell function, some studies suggest B-cell reactivity (9) The aetiology of primary axonal involvement in IBD patients' PN cases is still unknown, but clinical improvement in patients treated with immunomodulatory drugs or plasma exchange suggests a connection between immune system dysregulation and axonal neuropathies in IBD patients (10)

Secondary peripheral neuropathies

A.**Drug-induced peripheral neuropathies**

1. Metronidazole therapy;

Patients who receive more than 1.5 g of metronidazole daily for longer than 30 days are more likely to experience metronidazole-induced neuropathy. Although the exact source of the metronidazole-induced toxic nerve injury is unknown, an increase in free radicals has been suggested. Lastly, NS typically exhibit a pure sensory deficiency; nevertheless, in more extreme situations, motor abnormalities may manifest. After stopping the medication, metronidazole induced PN is typically reversible, albeit recovery may take a while (11)).

2. Thalidomide therapy

Although there have been instances of irreparable peripheral nerve injury, Thalidomide-induced peripheral neuropathy is typically reversible with dosage reduction or therapy cessation; hence, therapy withdrawal or dose reduction is required upon the onset of peripheral neuropathy(12)

3. Cyclosporine therapy

Strong immunomodulatory medication cyclosporine is useful in treating inflammatory bowel disease (IBD), which can cause PN. Since most occurrences of neuropathic symptoms are mild and reversible, peripheral neurotoxicity is typically not severe enough to require cyclosporine dose reduction(13)

4.Tumor necrosis factor inhibitor therapy

Anti-TNF-α drugs used in clinical settings have been shown to disclose PN among other immune-mediated neurologic side effects. Although the exact cause of peripheral nerve damage is still unknown, it has been suggested that humoral and T-cell immune responses target the myelin of peripheral nerves. Moreover, it has also been suggested that vasculitis-induced neuronal ischemia or impairment of signalling support for axons (14)

B. Nutritional deficiency-induced peripheral neuropathies

1. Vitamin B12 deficiency

Deficits in vitamin B12 and folate are prevalent in IBD patients, especially in CD patients. Enzymatic activity for the production of succinyl coenzyme A and methionine is cobalamin's principal role. This is a crucial step in the development of axons. Numbness and paraesthesia that starts in the lower limbs and is disseminated symmetrically are neurologic symptoms. For certain patients, gait ataxia may also be the initial complaint. In IBD patients with a vitamin B12 shortage, NS has demonstrated axonal neuropathy; however, following therapy with vitamin B12 supplements, recovery occurred(15)

2. Other vitamin B group deficiencies

There have been reports of PN in certain IBD patients who are deficient in vitamin B1. The most prevalent kind of peripheral neuropathy (PN) is axonal neuropathy, which can heal with vitamin treatment. However, in individuals with IBD, folate insufficiency has also been linked to PN (16). An axonal neuropathy known as folate-deficiency peripheral neuropathy (PN) is characterised by a slowly progressing course, a sensory-dominant pattern of involvement primarily in the lower extremities, and profound sensory loss as opposed to surface sensory loss. (**17**).

3. Vitamin E deficiency

Particularly when it comes to big fibres, a severe vitamin E deficit might cause a gradual sensory axonopathy(18)

4.Copper deficiency

Bowel surgery in people with CD has been linked to copper shortage because copper is absorbed in the stomach and small bowel. The symptoms of copper shortage are identical to those of vitamin B12 deficiency(19)

Conclusion

In patients with CD and UCN, peripheral nerve involvement appears to be common, but because peripheral nerve involvement is hard to diagnose, it goes unreported. PN may be an indication of an immunologic neurologic problem that requires immunomodulatory treatment. Moreover, PN may result from a vitamin shortage or from medicine used to address IBD. As such, internal medicine professionals ought to be particularly aware of this IBD complication.

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