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Peripheral neuropathy: An underreported neurologic manifestation of inflammatory bowel disease

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ABSTRACT

Background and aims: One of the most frequent neurologic complications reported in inflammatory bowel disease population is peripheral neuropathy; however, clinical aspects of peripheral nerve damage are not well characterized. The aim of the review is to present the existing literature on peripheral neuropathy in inflammatory bowel disease patients.
Methods: A literature search identified the publications reporting on epidemiology, clinical features, underlying mechanisms and management of ulcerative colitis and Crohn's disease patients with peripheral nerve involvement.
Results: The pathogenesis of peripheral nervous system damage in inflammatory bowel disease has yet to be elucidated, although it seems to be related to immune mechanisms; therefore, treatment with immunotherapy is recommended. In addition, peripheral neuropathy may appear as iatrogenic-related disorders associated with several drugs used in controlling inflammatory bowel disease activity; finally, peripheral neuropathy may also be caused by micronutrient deficiencies secondary to malabsorption-related disorders.
Conclusions: Although peripheral nervous nerve damage associated with inflammatory bowel disease is rarely reported, clinicians should be aware of the peripheral neuropathy clinical manifestations in order to recognize it and provide early treatment, which is crucial for preventing major neurologic morbidity. Heightened awareness is necessary for the successful management of these patients.

1. Introduction

The two main forms of idiopathic inflammatory bowel disease (IBD) are Crohn's disease (CD) and ulcerative colitis (UC) [1,2]. CD and UC are systemic diseases that often involve organs other than those of the gastrointestinal tract. These nonintestinal affections are termed extraintestinal manifestations (EIMs). The frequency of the EIMs observed in IBD varies from 20% to 40% of patients depending on the study. It is well-known that CD patients are more susceptible to EIMs than patients with UC [3–5].

Neurologic involvement in IBD patients is one of the most underreported EIMs in spite of having a high impact on quality of life, morbidity and even mortality in these patients; therefore, an early recognition of neurologic symptoms is crucial for treating EIMs affecting the nervous system. According to the available literature, the most frequent neurologic complications reported in patients with IBD are peripheral neuropathies, cerebrovascular diseases and demyelinating diseases [6–9].

Peripheral neuropathy (PN) is recognized as one of the most common neurologic complications observed in IBD. PN is a term that refers to any disorder of the peripheral nervous system (PNS) (Fig. 1). The term polyneuropathy refers to a generalized, relatively homogeneous process affecting many peripheral nerves, with the distal nerves usually affected most prominently. Conversely, mononeuropathy refers to focal involvement of a single nerve and mononeuropathy multiplex refers to simultaneous involvement of different individual peripheral nerves. The differentiation of axonal versus demyelinating PN depends upon the underlying process and it is crucial in the diagnostic work-up to identify the etiology of the peripheral nerve damage. Neurophysiologic studies (NS), including nerve conduction studies and electromyography, can help to classify a PN in axonal or demyelinating type but in some cases it is very difficult to establish the type and a mixed PN should be diagnosed. When a small-fiber neuropathy (SFN) is suspected, skin

Abbreviations: ALFSMN, axonal large-fiber sensorimotor neuropathy; ALFSN, axonal large-fiber sensory neuropathy; AMSP, acute motor sensory polyneuropathy; CD, Crohn's disease; CDSMP, chronic distal sensorimotor polyneuropathy; CIDP, chronic inflammatory demyelinating polyneuropathy; CNS, central nervous system; EIMs, extraintestinal manifestations; EM, entrapment mononeuropathy; IBD, inflammatory bowel disease; LFN, large-fiber neuropathy; MIRPN, monophasic immune radiculoplexus neuropathy; MMN, multifocal motor neuropathy; NS, neurophysiologic studies; PN, peripheral neuropathy; PNS, peripheral nervous system; SFN, small-fiber neuropathy; GBS, Guillain–Barré syndrome; TNF, tumor necrosis factor; UC, ulcerative colitis; VBN, vitamin B12 deficiency-neuropathy.

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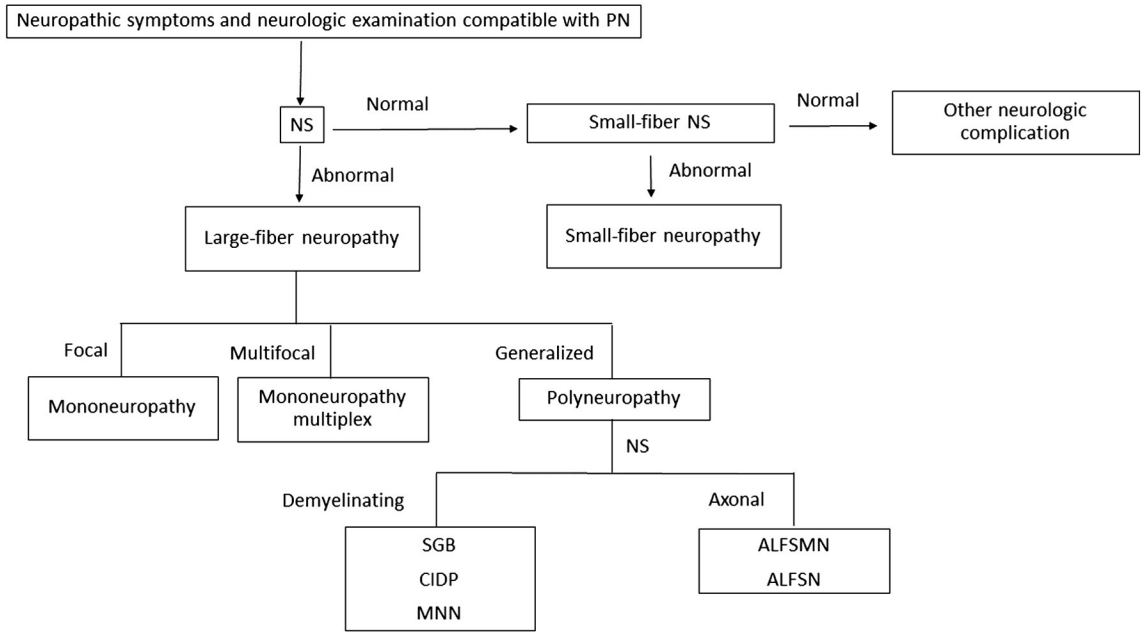

Fig. 1. Algorithm showing the assessment of a peripheral neuropathy in inflammatory bowel disease patients. NS: neurophysiologic studies; GBS: Guillain–Barré syndrome; CIDP: chronic inflammatory demyelinating polyneuropathy; MNN: multifocal motor neuropathy; ALFSMN: axonal large-fiber sensorimotor neuropathy; ALFSN: axonal large-fiber sensory neuropathy.

biopsy with quantification of intraepidermal nerve fibers density is a reliable technique to confirm the diagnosis [10].

Prevalence of PNS involvement in IBD patients is still controversial because few systematic studies have investigated the frequency of peripheral nerve disorders in patients with IBD. The literature review shows case reports and small series; moreover, only a few of the studies have reviewed large groups of IBD patients to identify peripheral nerve symptoms. In addition, most of the recent reviews dealing with UC and CD did not include or only included a brief mention of PNS involvement in IBD [1,3–5,11].

Using the MEDLINE database, we searched the literature from January 1, 1970 to May 31, 2015 in order to update clinical aspects in this topic, including the diagnosis and treatment; possible pathogenic mechanisms are also considered. Papers in languages other than English were also surveyed. The search included the following keywords: Crohn's disease, ulcerative colitis, inflammatory bowel disease, neuropathy, axonal polyneuropathy, demyelinating polyneuropathy, metronidazole, thalidomide, cyclosporine, anti-tumor necrosis factor (TNF)-α, nutritional deficiency, vitamin B, vitamin E, folate, and copper. A search was conducted through the literature cited in articles retrieved and additional papers were identified.

The peripheral nerve involvement in CD and UC will be separated in two categories (Table 1), the first category providing a review of PN associated to IBD without comorbidities associated with PN (IBD-associated PN) and the second category dealing with the PN secondary to vitamin deficiencies and to biological agents or other approaches to IBD management (secondary PN).

2. IBD-associated peripheral neuropathies

2.1. Types of IBD-associated peripheral neuropathies

Various types of peripheral neuropathies have been reported in association with active and quiescent IBD. Studies have described demyelinating or axonal involvement of peripheral nerves in IBD, and both types of neuropathies may be acute or chronic (Table 2) [12–22].

Gondim et al. performed a retrospective study based on computer-guided search for IBD patients in a PN center; after exclusion of secondary PN, 33 patients (18 patients with CD and 15 patients with UC) were found having a PN diagnosis. Demyelinating neuropathies, such as multifocal motor neuropathy (MMN) and chronic inflammatory demyelinating polyneuropathy (CIDP), occurred in 9 patients. Eleven patients had sensory axonal PN (6 patients with small-fiber and 5 patients with large-fiber PN), and large-fiber axonal sensorimotor PN was found in 13 IBD patients [23]. Conversely, Figueroa et al. retrospectively ascertained neuropathy incidence in a population-based cohort of adult

Table 1
Peripheral neuropathy associated with inflammatory bowel disease population.

1. Inflammatory bowel disease-associated peripheral neuropathy:
   - Guillain–Barré syndrome.
   - Multifocal motor neuropathy.
   - Chronic inflammatory demyelinating polyneuropathy.
   - Acute motor sensory polyneuropathy.
   - Distal sensory axonal large-fiber polyneuropathy.
   - Distal sensory-motor axonal large-fiber polyneuropathy.
   - Monophasic immune radiculoplexus neuropathy.
   - Mononeuritis multiplex.
   - Autonomic neuropathy.
2. Secondary peripheral neuropathy:
   - Drug-associated peripheral neuropathy in inflammatory bowel disease:
     - Metronidazole.
       - Sensory polyneuropathy
     - Thalidomide.
     - Cyclosporine.
     - Tumor necrosis factor antagonists.
       - Guillain–Barré syndrome.
       - Multifocal motor neuropathy.
       - Chronic inflammatory demyelinating polyneuropathy.
       - Mononeuritis multiplex.
       - Small-fiber polyneuropathy.
       - Sensory-motor axonal large-fiber polyneuropathy.
   - Vitamin deficiency-associated peripheral neuropathy in inflammatory bowel disease.
     - Vitamin B12 deficiency.
       - Sensory axonal polyneuropathy.
     - Vitamin B1 deficiency.
       - Sensory-motor axonal polyneuropathy.
     - Vitamin E deficiency.
       - Sensory axonal polyneuropathy.
     - Folate deficiency.
       - Sensory axonal polyneuropathy.
       - Copper deficiency.

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