Peripheral neuropathy and gastroenterologic disorders: an overview on an underrecognized association

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Summary. *Background and aim of the work:* Although peripheral neuropathies in children are often of genetic origin, acquired causes should be carefully looked for and ruled out also in the pediatric age. Gastroenterological disorders can be complicated by peripheral neuropathy as a result of micronutrients deficiency, drug toxicity or because of shared pathophysiological mechanisms. *Methods:* In this descriptive review we sought to give an overview on the most relevant clinical conditions in which peripheral neuropathies are associated with gastrointestinal disorders or symptoms. *Results:* We describe the clinical, demographic, and electrophysiological features of peripheral neuropathy in three main clinical scenarios: in the context of common gastroenterological disorders (inflammatory bowel and celiac disease), in the context of micronutrients deficiencies arising from malabsorption irrespective of etiology, and in a rare degenerative mitochondrial disorder, mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) disorder. *Conclusions:* The association between gastrointestinal and peripheral nervous system symptoms is probably still underrecognized but has to be actively sought, in order to provide prompt diagnosis resulting in optimal care and long-term management with the aim to improve quality of life and, at least in some conditions, try to impact on prognosis. (www.actabiomedica.it)

Key words: peripheral neuropathy, inflammatory bowel disease, ulcerative colitis, Crohn disease, celiac disease, malabsorption, vitamin deficiency, mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) disease, Guillain-Barré syndromes

Background and aim of the work

Unlike in adult age, pediatric-onset peripheral neuropathies are often of genetic origin. Charcot-Marie-Tooth (CMT), typically presenting with distal weakness and wasting, reduced deep tendon reflexes, contractures and skeletal deformities, is considered the most common neuromuscular disorder (1), and can challenge the clinician with wide range of age of onset (including congenital cases (2)) phenotypic (associated peripheral and central involvement (3), marked sensory or upper limbs involvement, visual/hearing impairment, pyramidal signs (4), intellectual disability) and genetic heterogeneity. Additional genetically-determined peripheral neuropathies, which can be encountered in clinical practice, include hereditary neuropathy with liability to pressure palsy (HNPP) (5), most frequently presenting with acute-onset, non-painful focal sensory and motor mononeuropathy, but also with atypical phenotypes, including chronic cramps and exercise-induced myalgia ((6)) and variable electrophysiological features (5, 7).

Although the presence of an underlying genetic etiology, acquired causes represent a fairly common clinical scenario in children, developing as a consequence of trauma or a complication of a chronic disorder. Toxic effects of medications or a long-term consequence of nutritional deficits also have to be ruled out in the diagnostic work-up.

Gastrointestinal diseases are occasionally associated with neurologic manifestations, including peripheral neuropathies. In most cases, signs and symptoms of peripheral nervous system involvement occur in the setting of a known gastrointestinal disease, but on rarer occasions, neurologic symptoms predate gastrointestinal ones, therefore both the gastroenterologist and the neurologist need to be aware of this potential association. In both cases, a high index of suspicion is crucial for a prompt diagnosis.

We performed a descriptive review with the aim to give an overview of gastroenterological conditions with the higher risk of development of an associated peripheral neuropathy in their natural history.

Methods

We decided to focus our review on two highly prevalent gastroenterological diseases (inflammatory bowel disease and celiac disease) due to their known association with peripheral neuropathy and their frequency in the general population. We also collected data on nutritional deficiencies which could result in peripheral nervous system complications in any gastroenterological condition determining malabsorption. Due to the very high frequency of gastro-enteritis in the pediatric age, we will briefly discuss Guillain-Barré syndrome as a potential complication of gastro-intestinal infections in children. Finally, we reported on a rare, severe mitochondrial disorder, mitochondrial neurogastrointestinal encephalopathy (MNGIE) disorder, as an example of a complex clinical condition for which patients will most probably seek gastroenterological advice, but will have associated neurologic manifestations to be actively sought, especially in the early stages of the disease. We reviewed papers we used the search terms "inflammatory bowel disease" and "peripheral neuropathy", "celiac disease" and "periph-

eral neuropathy", mitochondrial neurogastrointestinal encephalopathy (MNGIE) disorder. We excluded case reports and articles not written in English.

Results

1.1 Inflammatory bowel disease

Inflammatory bowel disease (IBD) includes ulcerative colitis (UC) and Crohn's disease (CD). Neurologic involvement (including peripheral and central nervous system) is rare and has been reported both before and after the onset of intestinal symptoms. The most frequent neurologic complications include inflammatory and axonal neuropathies, cerebrovascular and demyelinating disease (8).

Although peripheral neuropathy (PN) is known to be related to IBD, its real prevalence remains largely unknown. Neuromuscular signs and symptoms are reportedly 3-7 times more prevalent in patients with IBD than in controls, while large-fiber peripheral neuropathy is 5-7 times more prevalent than in controls (9). In a population-based retrospective (1940-2004) cohort of adult patients with newly diagnosed IBD (Figueroa et al.), the neuropathy incidence rate was 72 cases per 100,000 IBD person-years with a cumulative incidence rate of 2.4% after 30 years (10).

Different types of neuropathy have been reported including sensory, motor, autonomic and mixed (axonal and demyelinating), acute and chronic. In a recent retrospective review, more than two-thirds of patients with IBD had axonal neuropathy, with sensory predominance, and only one third developed demyelinating neuropathy (11). Carpal tunnel syndrome seems to be more common in Ulcerative colitis (UC) than in patients with Crohn disease (CD). In UC the most frequent diagnosis is acute inflammatory demyelinating polyradiculoneuropathy, but also mononeuritis multiplex and brachial plexopathy are reported (12). In contrast, patients with CD most commonly demonstrate axonal motor and sensory neuropathy (13). CD patients also present autonomic neuropathy early in their disease course (14).

Interestingly, peripheral neuropathies are not related to disease activity (their onset can occur in peri-

ods of quiescence) and do not respond to treatment of the underlying IBD (15). Demyelinating neuropathies respond better to immunomodulatory therapy than axonal neuropathy (16).

The pathogenesis of peripheral nervous system damage in inflammatory bowel disease is still unclear, although most likely related to immune mechanisms. In addition, it can be iatrogenic or result from micronutrient deficiencies (17).

While T cells are clearly involved in the pathogenesis of demyelinating neuropathies, the relationship between axonal damage and immune system derangements remains unclear, although empirically supported by the observed clinical improvement with immunomodulatory therapies (11).

1.2 Non-drug-induced peripheral neuropathy in IBD

When causes of secondary neuropathy are excluded, the reported frequency of peripheral neuropathy in IBD will vary greatly (0-39%) due to selection bias, use of different definitions, or different population characteristics (18).

1.3 Secondary peripheral neuropathies

In addition to primary causes, patients with IBD may experience severe nutritional and iatrogenic neuropathies which can be more disabling than the bowel disorder (18).

1.3.1 Drug-induced neurologic manifestations of IBD

Biological agents

TNF inhibitors
The proinflammatory cytokine TNF-α plays a main role in the inflammatory cascade in IBD; consequently, anti-TNF-α drugs mitigate this inflammatory process. Many TNF-α inhibitors have been used in IBD therapy, predominantly in severe and moderate cases.

Infliximab was the first TNF inhibitor successfully used in IBD. Additional drugs with demonstrated efficacy include adalimumab and golimumab (humanized monoclonal antibodies), and certolizumab pegol (humanized anti-TNF-α antibody Fab' fragment con-

jugated with a polyethylene glycol molecule) (18).

Cases of neurologic toxicity of infliximab and adalimumab include peripheral neuropathies in 42% of cases. Demyelinating neuropathies, either acute or chronic, compatible with Guillain-Barré syndrome (GBS), Miller Fisher syndrome, Lewis–Sumner syndrome (a rare acquired demyelinating polyneuropathy characterized by asymmetrical distal weakness of the upper or lower extremities and motor dysfunction with adult onset) or chronic inflammatory demyelinating polyneuropathy (CIDP) have been described in IBD patients receiving anti-TNF-α agents (19). GBS cases account for the majority, developing between 6 days and 2 years after initiating anti-TNF-α drugs. In CIDP cases, elevated serum anti-ganglioside antibodies have been described, suggesting an abnormal immune reaction against myelin (19). Moreover, there are case reports of MMN following infliximab treatment; in these cases, patients developed asymmetric progressive weakness and conduction block (20). Finally, axonal sensory neuropathy, mononeuritis multiplex or sensorimotor polyneuropathy was also reported in patients treated with infliximab (21).

The proposed pathogenesis includes a T-cell and humoral immune attack against peripheral nerve myelin, vasculitis-induced nerve ischemia, and inhibition of signaling support for axons (91). Prognosis is usually favorable if treatment is discontinued, which is the first step for the management of these conditions. In patients not achieving clinical recovery, immunomodulatory therapy with steroids or intravenous immunoglobulins should be started (21). Use of TNF inhibitors should be avoided in patients with peripheral neuropathy or multiple sclerosis. Patients with IBD should be examined for neuropathy before initiating anti-TNF-α treatment.

Non-biological agents

Peripheral neuropathy is also a frequent neurologic complication in IBD patients treated with metronidazole, thalidomide, or cyclosporine.

Metronidazole
Metronidazole has been used in IBD for decades but the incidence of PN remains controversial. In one

study, the incidence of PN reached 50% of the IBD patients receiving metronidazole, but diagnosis was clinically based, without neurophysiological confirmation (22). Conversely, in a CD population, no significant differences in PN occurrence were found between patients taking metronidazole (daily dose ≤800 mg) and patients never been treated with metronidazole (23). Metronidazole-induced PN occurs more frequently in patients receiving more than 1.5 g daily of metronidazole for more than 30 days (24).

The genesis of the toxic nerve damage has not been clarified but an increase in free radicals has been hypothesized (25). ENG studies usually demonstrate a pure sensory deficit or autonomic neuropathy, while motor disturbances develop in severe cases. Neuropathy usually resolves completely once metronidazole is discontinued (26), but recovery might be protracted (23).

Thalidomide

Thalidomide is a small molecule with anti-TNF-α, immunomodulatory and antiangiogenic properties. It is used in clinical practice as third line therapy to maintain remission in CD (27). Although used infrequently in the management of pediatric Crohn's disease, it has an important role in treating patients losing response to standard treatment options. The mechanism of action is unclear, but the drug inhibits both angiogenesis and tumor necrosis factor release by leukocytes. A randomized, double-blind controlled trial of thalidomide in pediatric Crohn's disease demonstrated a remission rate of 63% (versus 12% in the placebo group) (28).

Symptomatic PN is frequent, from 20% (29) to approximately 50-55% in pediatric cohorts (30) and even 72.5% (31). Sixteen patients aged 6-24 years received thalidomide for Crohn's disease from 2002 to 2012. Nine subjects had electrophysiologic evidence of sensorimotor axonal polyneuropathy, the vast majority (8/9) with sensory and/or motor symptoms (32).

The underlying mechanisms of nerve damage are still obscure, but most likely involve capillary damage, secondary hypoxemia in nerve fibers and acceleration of neuronal cell death secondary to downregulation of TNF-α.

Given the potential neurotoxicity, patients treated with thalidomide should undergo regular clinical examination and ENG to detect presymptomatic or progressive peripheral neuropathy (33).

Some categories of patients seem to be at increased risk of developing a peripheral neuropathy. There seem to be a dose-dependent effect, as doses > 60 g (32) or >50 g (34) seem to be associated with an increased risk. The risk also increases depending on the mean daily dose. Therapy duration is also a factor, as 4 out of the 5 subjects receiving thalidomide for > 20 months developed polyneuropathy (32). In one study, the median period of treatment before neuropathy developed was 16.5 months; the percentage of neuropathy-free patients was 70% and 35.6% at 12 and 24 months of treatment, respectively. Interestingly, in patients with neuropathy receiving therapy for > 24 months and having ≥3 electromyography studies, the neuropathy severity plateaued (31). Aside from the total administered dose, additional factors might contribute to the risk profile, including pharmacogenetic susceptibility, involving C-hydroxylation and acetylation reactions (35, 36). Single nucleotide polymorphisms in ICAM1 (rs1799969) and SERPINB2 (rs6103) genes were found to be protective against thalidomide-induced PN and favored its resolution, supporting the hypothesis that genetic susceptibility may have a role in the natural history of thalidomide-induced polyneuropathy. ICAM1 gene encodes for an intercellular adhesion molecule playing a role in inflammatory processes (37), involved in nerve repair after traumatic injury (38). SERPINB2 is a serine protease inhibitor with cytoprotective effects whose levels increase during cellular stress (39, 40). Conversely, no risk factor related to IBD characteristics emerged (31). The association between thalidomide and metronidazole does not seem to increase the risk of TiPN (31).

The pathology of thalidomide neuropathy is characterized by loss of large sensory fibers with apparent preservation of small sensory fibers and no apparent demyelination (41); however, 3 among the 7 patients reporting mild sensory symptoms had normal electrophysiological studies, raising the possibility of a small fiber neuropathy, not detectable with routine nerve conduction study.

Children, adolescents, and young adults receiving thalidomide should undergo regular neurophysiological studies to monitor for neuropathy (32). Thalido-

mide-induced PN is generally reversible with dose reduction or drug discontinuation, although irreversible cases have been reported, therefore discontinuation or dose reduction are mandatory. In one study, clinical symptoms resolved in approximately 90% of cases, but nerve conduction studies abnormalities persisted in more than half of the patients for months after drug withdrawal (31).

Cyclosporine

Cyclosporine is a potent immunomodulatory drug, effective in the treatment of IBD, which can also induce peripheral neuropathy, in most cases with mild and reversible symptoms, not necessarily requiring dose reduction (42).

1.4 Clinical approach to peripheral neuropathy in IBD patients

The presence of suspected neuropathic symptoms (weakness, paresthesias) in patients with gastroenterological symptoms should prompt a thorough neurologic evaluation and the execution of neurophysiologic testing. A diagnosis of IBD-associated peripheral neuropathy may be established after exclusion of other causes, including complications of therapy or secondary micronutrients deficiencies. A tentative treatment with immunotherapy should be indicated irrespective of the underlying mechanism of nerve damage. If a secondary peripheral neuropathy is suspected, levels of vitamins and micronutrients (vitamins B1, B12 and E, folate, and copper) should be obtained and a supplementation started in case of documented deficiency. Any drug used for IBD with potential deleterious effects on peripheral nerve should be withdrawn (17).

Nutritional deficiency–induced peripheral neuropathies

Vitamin deficiencies are well-recognized causes of PN in IBD and celiac disease, most commonly vitamin B group deficiency.

Vitamin B12 deficiency

Vitamin B12 and folate deficiencies are common in patients with IBD, particularly in CD (43). The primary function of cobalamin is to provide enzymatic activity for the synthesis of methionine and succinyl coenzyme A, essential for axon formation. The most typical neurologic manifestation of vitamin B12 deficiency is subacute combined degeneration, involving both the posterior columns of the spinal cord and the peripheral nerves, resulting in sensory ataxia and loss of cutaneous sensation (12, 15). ENG studies demonstrate axonal neuropathy, reversible after supplementation (44, 45). Central nervous systems symptoms can also develop.

Other vitamin B group deficiencies

Vitamin B1 deficiency is mainly associated with Wernicke encephalopathy. Peripheral neuropathy, usually axonal, either sensory, motor, or both, has been reported. It may run a rapidly progressive or chronic course (12). It may recover after vitamin supplementation (46, 47).

Folate deficiency can cause axonal neuropathy with slowly progressive course (48, 49).

Vitamin E deficiency

Severe vitamin E deficiency may be genetic (50) or due to malabsorption (gastric and intestinal surgery, biliary and pancreatic diseases, celiac disease, IBD, but also common variable immunodeficiency and cystic fibrosis) (51). Ataxia (from posterior column involvement) is the most common manifestation, along with progressive sensory axonal peripheral neuropathy, especially involving large fibers. Peripheral axonal loss has been demonstrated by both electrodiagnostic and pathologic examinations. Pathologic changes also include degeneration of large myelinated fibers in the posterior columns, sensory roots, and peripheral nerves (52).

Copper deficiency

Bowel surgery in patients with CD has been associated with copper deficiency. Its symptoms are indistinguishable from those of vitamin B12 deficiency (53).

Gluten-related neurologic disorders

Gluten is a product of wheat, rye, and barley. Its breakdown products are responsible for a group of immune-mediated disorders including celiac disease (15).

Celiac disease is a chronic, immune-mediated, inflammatory small bowel enteropathy triggered by the ingestion of gluten by genetically susceptible individuals expressing the HLA class II molecules DQ2 or DQ8. Clinical presentation can vary widely, from typical gastrointestinal manifestations to minimal, unusual or even absent intestinal complaints with extraintestinal manifestations (54). The prevalence of pediatric-onset coeliac disease varies between 0.4% and 1.3% (55). A wide spectrum of associated neurological and psychiatric conditions has been reported (myelopathy, myopathy, brainstem encephalitis, epilepsy, headache), but typically cardinal features are ataxia and peripheral neuropathy. Antibodies associated with the disease occur in 16-57% of individuals with neurological dysfunction (56).

The pathogenesis of neurological manifestations is multifactorial. Some may be secondary to vitamin B12 deficiency (e.g. myelopathy and neuropathy), vitamin D malabsorption (e.g. myopathy), or vitamin E deficiency (e.g. cerebellar ataxia and myopathy), as a consequence of malabsorption (56). However, as neurologic complications are also frequent without malabsorption, other factors (namely humoral mechanisms) likely contribute to the pathogenesis of neurologic deficits. However, antigliadin (AGA), anti-transglutaminase–2 (TG2) and endomysial (EMA) IgA and IgG antibodies can be negative in patients without intestinal manifestations. IgG antibody reactivity to peripheral nerve antigens has been recorded in individuals with celiac disease and peripheral neuropathy (57), while patients with ataxia may have positive antiTG6 antibodies. In individuals with celiac ataxia, antibodies against Purkinje cells and a cross-reactivity between anti-gliadin antibodies and epitopes on Purkinje cells have been demonstrated by some research groups (58). Whether these antibodies are pathogenic or rather represent a non-specific marker is still unclear. Diffuse infiltration of cerebellum and peripheral nervous system by T lymphocytes and perivascular cuffing with inflammatory cells have also been reported (59).

Estimates of the frequency of neurologic manifestations in patients with established celiac disease range from 10% to 22% (60). In one series, 7% of patients with CD presented first with neurologic symptoms (61).

Neuropathy is present in up to 23% of patients with celiac disease. Very few studies have addressed the prevalence of peripheral neuropathy in childhood, and its potential association with celiac disease (54). In one study, 7.4% of children with celiac disease on a gluten-free diet had peripheral polyneuropathy with mixed patterns of axonal motor and sensory polyneuropathy and pure sensory polyneuropathy (including children non-compliant with gluten-free diet) (62).

Most patients present with primarily sensory symptoms and a distal, symmetric neuropathy (12). Peripheral neuropathy may precede, coincide with, or follow gastro-intestinal manifestations (63). Most commonly, it is a slowly progressive, usually slightly asymmetric, distal, painful sensory focal neuropathy with adult onset around the sixth decade, sometimes accompanied by clinical or subclinical autonomic dysfunction (60). Distal large-fiber axonal (and less often, demyelinating) sensory and motor peripheral neuropathy is reported less frequently, followed by multifocal neuropathy, pure motor neuropathy, and sensory neuronopathy (64).

Compared to the general population, celiac disease is associated with a 2.5-fold increased risk of later neuropathy, a 3-fold increased risk of chronic inflammatory demyelinating neuropathy, a 4-fold increased risk of autonomic neuropathy, and 8-fold increased risk of mononeuritis multiplex, but no association with acute inflammatory demyelinating polyneuropathy (65).

Changes consistent with a primarily axonal sensory neuropathy are usually demonstrated by ENG and biopsies. In at least one case, mononeuritis multiplex occurred in the context of vasculitis and responded to corticosteroid therapy (66). According to some authors, clinical improvement is obtained with a gluten-free diet after 1 year (67). The only systematic controlled trial of gluten-free diet in gluten sensitivity-related peripheral neuropathy (in patients with and without enteropathy) outlined a greater benefit if enteropathy was absent and if the duration of symptoms

was shorter (68). Studies on the effect of a gluten-free diet on peripheral neuropathy are conflicting, with some authors reporting clinical improvement while others concluding for a lack of relevant response (69, 70).

The lack of benefit from a gluten-free diet might be explained by inadequate dietary compliance resulting in rekindling of inflammatory response (68), or irreversible damage to peripheral nerves or dorsal root ganglia. Intravenous immunoglobulins have successfully been administered in a few cases of CD and GS-related ataxia and peripheral neuropathy (71). In one study, one female (out of 835 children with coeliac disease, 0.1% (72)) affected by an acute, predominantly motor, demyelinating peripheral neuropathy, experienced relapses upon accidentally reintroducing gluten and remitted on institution of a GFD regimen.

Patients with known celiac disease should be followed-up with an awareness that neurologic manifestations might occur, although uncommonly. Undiagnosed neurologic manifestations compatible with gluten-associated disorders should include gluten sensitivity in the differential diagnosis. This is particularly relevant in patients with appropriate HLA genotype, mild gastrointestinal symptoms, or other known autoimmune diseases, such as type-1 diabetes mellitus, autoimmune thyroid disease, primary biliary cirrhosis, Sjögren's syndrome, or rheumatoid arthritis. In addition, as celiac patients (even in asymptomatic cases) are at risk of refractory iron deficiency, folate deficiency, and osteopenia, the detection of any of these conditions should prompt investigations for celiac disease in neurologic patients.

Campylobacter-associated Guillain-Barré syndrome

Guillain-Barré syndrome (GBS) is an acute inflammatory polyneuropathy with acute onset of progressive ascending symmetric weakness and areflexia, of which two main neurophysiologic subgroups exist: inflammatory demyelinating and acute motor axonal neuropathy. As the pathophysiology is based on an abnormal post-infectious immune response, the onset of symptoms is often preceded by infections, either involving the upper respiratory tract or the gastro-intes-

tinal tract (involved in up to 75% of pediatric cases), with many diverse etiologies being identified (73). *Campylobacter jejuni* is an important epidemiological cause of infectious diarrhea. Typical incubation period is 24-72 hours, but occasionally 1 week or longer. Nonspecific prodromal symptoms include headache, myalgias, chills, and fever, usually lasting approximately 24 hours. The peak of symptoms usually occurs at 24-48 hours before resolving within 1 week. The subtype O:19 has a higher tendency to result in GBS (74). *C. jejuni* infections associated with antibodies against GM1 and GD1b gangliosides tend to be associated with a severe, pure motor form of GBs (75). This group of patients seems to respond better to early treatment with high dose immunoglobulin therapy than to plasma exchange (76).

Mitochondrial neurogastrointestinal encephalopathy ("MNGIE") disease

Mitochondrial neurogastrointestinal encephalopathy (MNGIE) disease is characterized by progressive gastrointestinal symptoms, cachexia, ptosis, ophthalmoplegia/ophtalmoparesis, central and peripheral nervous system involvement (77).

A long history of ill-defined symptoms, such as fatigability, mild gastrointestinal complaints, or thin body habitus can precede the onset of more overt symptoms. To further complicate diagnosis, the order in which symptoms appear is unpredictable, although in a review of 102 patients the first symptoms were gastrointestinal (~57%), ptosis/ophthalmoplegia (~19%), peripheral neuropathy (~14%), and myopathy (~5%) (78). Onset is before 20 years of age in 60% of cases, while the earliest reported onset was at five months (78).

Prevalence is unknown. Parental consanguinity is common, as the disease is transmitted as an autosomal recessive condition.

Progressive gastrointestinal dysmotility, caused by enteric myopathy, occurs in virtually all affected individuals (79) and is carachterized by gastric and small bowel hypomotility resulting in early satiety, nausea, dysphagia, gastroesophageal reflux, postprandial emesis, episodic abdominal pain and/or distention, and

diarrhea. Despite severe GI dysfunction, serum concentrations of micronutrients and vitamins are usually normal.

Rectal biopsy can show eosinophilic cytoplasmic inclusions in the submucosal ganglion cells, corresponding to abnormal mitochondria (80). Duodenal pathology can demonstrate focal muscle atrophy with increased nerve numbers, serosal granulomas, and focal loss of Auerbach's plexus with fibrosis (81). Mitochondrial DNA depletion, mitochondrial proliferation, and smooth cell atrophy are observed in the external layer of the muscularis propria in the stomach and small intestine (79, 82). Loss of the pacemaker cells stimulating gut contraction (interstitial cells of Cajal) is also documented in the small bowel (83).

Neurologic presentation includes ptosis, ophthalmoplegia or ophthalmoparesis, leukoencephalopathy (usually asymptomatic and detected by brain MRI) and demyelinating PN.

All individuals with MNGIE disease develop peripheral neuropathy (84), which is demyelinating in all, with associated axonal neuropathy in half of the cases. In some, the first symptoms are paresthesias (with stocking-glove distribution) and weakness (usually symmetric and distal). The severity of neuropathic symptoms is often fluctuating during the early stages of the disease.

Segmental demyelination is hypothesized to be caused by uneven distribution of mtDNA abnormalities (depletion, single-nucleotide variants, deletions, duplications) along the nerve.

Electrodiagnostic features include decreased motor and sensory nerve conduction velocities, prolonged F-wave latency, and partial conduction block. Myopathic changes are common.

Histologically, demyelination and remyelination are observed, along with loss of large myelinated fibers.

The clinical diagnosis of MNGIE disease is based on the presence of cardinal symptoms, and a family history consistent with autosomal recessive inheritance. The diagnosis can be established by detection of one of the following: (1) biallelic pathogenic variants in *TYMP* (thymidine phosphorylase); (2) markedly reduced levels of thymidine phosphorylase enzyme activity (thymidine phosphorylase enzyme activity in buffy coat <8% of the control mean; less severely re-duced (<18% of the control mean) in late-onset cases (85,86)); or (3) elevated plasma concentrations of thymidine and deoxyuridine (thymidine concentration >3 μmol/L or deoxyuridine concentration >5 μmol/L (86)).

Increased CSF protein (typically ≥60 -100 mg/dL), lactic acidemia and hyperalaninemia are common. Lactic acidosis is unusual (86).

Allogenic stem cells transplantation has been performed in MNGIE patients. It is hampered by a high mortality rate (62.5%) (87). In survivors, an increase in thymidine phosphorylase activity from undetectable to normal levels and an improvement of body mass index, gastrointestinal manifestations, and peripheral neuropathy were reported in patients engrafted and living more than 2 years after transplantation (87). Liver transplantation has been proposed as an alternative treatment (88).

Conclusions

The occurrence of PN in gastro-intestinal diseases is probably under-estimated and still not thoroughly characterized, especially in children. It is sustained by a multifactorial pathogenesis, challenging the clinician in all phases of management of the disease (diagnosis, therapy and follow-up). Promoting a high index of suspicion on frequent associations can result in a potential to significantly impact on patients' quality of life, by initiating the correct treatments or discontinuing neuro-toxic agents. Awareness about the existence of exceedingly rare but severe, degenerative conditions such as MNGIE can result in a reduction of the diagnostic delay and the possibly to address patients to highly specialized centers with the aim to modify their grim outcome or provide the best supportive care.

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