

Chronic intestinal pseudo-obstruction

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Abstract

Chronic intestinal pseudo-obstruction (CIPO) is a severe digestive syndrome characterized by derangement of gut propulsive motility which resembles mechanical obstruction, in the absence of any obstructive process. Although uncommon in clinical practice, this syndrome represents one of the main causes of intestinal failure and is characterized by high morbidity and mortality. It may be idiopathic or secondary to a variety of diseases. Most cases are sporadic, even though familial forms with either dominant or recessive autosomal inheritance have been described. Based on histological features intestinal pseudo-obstruction can be classified into three main categories: neuropathies, mesenchymopathies, and myopathies, according on the predominant involvement of enteric neurones, interstitial cells of Cajal or smooth muscle cells, respectively. Treatment of intestinal pseudo-obstruction involves nutritional, pharmacological and surgical therapies, but it is often unsatisfactory and the long-term outcome is generally poor in the majority of cases.

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INTRODUCTION

Chronic intestinal pseudo-obstruction (CIPO) is a rare, severe disease characterized by the failure of the intestinal tract to propel its contents which results in a clinical picture mimicking mechanical obstruction in the absence of any lesion occluding the gut. CIPO is one of the most important causes of chronic intestinal failure both in pediatric (15%) and adult cases (20%)^[1-5], since affected individuals are often unable to maintain normal body weight and/or normal oral nutrition. The severity of clinical picture, generally characterized by disabling digestive symptoms even between sub-occlusive episodes, contributes to deterioration of quality of life of the patients. Furthermore, CIPO often passes unrecognized for long time, so that patients almost invariably undergo repeated, useless and potentially dangerous surgical procedures.

This article is aimed at reviewing the current knowledge on pathophysiology, clinical features and management of patients affected by CIPO.

ETIOLOGY AND PATHOPHYSIOLOGY

CIPO is idiopathic in the majority of cases. In our experience organic, systemic or metabolic causes of the disease were identified in only 4 patients of 77 CIPO patients consecutively referred in our laboratory (5%)^[2]. Nevertheless, it is mandatory to investigate affected individuals by traditional diagnostic procedures (radiology, endoscopy, lab tests, *etc*) in order to exclude every possible cause of secondary CIPO. The main secondary causes of CIPO are specified in Table 1.

In fact, every disease that affects one of the control mechanisms of intestinal functioning, including intrinsic and extrinsic neural supplies as well as muscle cells, can be responsible for secondary and potentially curable forms of CIPO. The extrinsic autonomic nervous system can be affected both centrally (*i.e.* Parkinson syndrome, Shy-Drager syndrome, stroke, encephalitis, neoplasm and any

Table 1 Main causes of secondary chronic idiopathic pseudo-obstruction and relative gut tissue that is predominantly involved

Underlying disease	Main causes
Diseases of central autonomic and enteric nervous systems	Stroke, encephalitis, calcification of basal ganglia, orthostatic hypotension, Von Recklinghausen, Hirschsprung
Immune-mediated and collagen diseases	Paraneoplastic (CNS neoplasms, lung microstoma, bronchial carcinoid, leiomyosarcomas), scleroderma, dermatomyositis, amyloidosis, Ehlers-Danlos, LES
Endocrine and metabolic diseases	Diabetes, hypothyroidism, hypoparathyroidism, pheochromocytoma
Other	Iatrogenic (radiation enteritis, clonidine, phenothiazines, antidepressants, antiparkinsonians, antineoplastics, bronchodilators, anthraquinones) jejunal diverticulosis, chagas

other disease that could affect the encephalic autonomous centres), and peripherally (i.e. diabetic neuropathy, or other neuropathies potentially involving the enteric nervous system including Hirschsprung, Chagas, Von Recklinghausen, as well as non-specific diseases, like paraneoplastic syndromes, autoimmune diseases, viral infections). Enteric smooth muscle cells can be markedly damaged in patients affected by myotonic dystrophy or progressive systemic sclerosis. Collagenosis, Ehlers-Danlos syndrome, jejunal diverticulosis and radiation enteritis can be responsible for both a neuronal and myogenic impairment.

Nonetheless, diseases like hypothyroidism, hypoparathyroidism, and celiac disease have been described to be responsible for some cases of secondary CIPO, even if the underlying mechanism remains undetermined^[1,4].

CIPO is generally sporadic, but familial forms have also been described both with autosomal dominant, autosomal recessive and X-linked transmission^[1,6,7]. Some genes and loci have been identified in syndromic forms of CIPO, including the transcription factor *SOX10* on chromosome 22 (22p12), the DNA polymerase gamma gene (*POLG*) on chromosome 21 (21q17) and a locus on chromosome 8^[7-9]. In terms of X-linked transmission, recently Gargiulo *et al* have identified a 2-base pair deletion in exon 2 of the *filamin A* gene (encoding for a large cytoskeletal protein involved in the modulation of the cellular response to chemical and mechanical environmental factors) that is present at the heterozygous state in the carrier females of a family with syndromic CIPO^[10]. Familial cases are more frequent in mitochondrial neurogastrointestinal encephalomyopathy (MNGIE), which is characterized by subocclusive episodes and lactic acidosis, skeletal muscle abnormalities (i.e. “ragged red fiber”) and specific mitochondrial changes at the ultrastructural level^[11,12]. Mutations of the gene encoding the thymidine phosphorylase gene (*TP* or endothelial cell growth factor-1, *ECGF1*), mapped to locus 22q13.32qter have a pathogenic role and are responsible for MNGIE^[11-15]. The biochemical dysfunctions underlying MNGIE consists of decreased TP activity leading to accumulation of thymidine (dThd) and deoxyuridine (dUrd) in blood and tissues^[16,17].

Toxic levels of dThd and dUrd induce nucleotide pool imbalance that, in turn, leads to mitochondrial DNA abnormalities including point mutations, multiple deletions and depletion^[16,18].

Histopathology and putative pathogenic mechanisms

Examination of full-thickness biopsies of the intestinal

wall may help in establishing a correct diagnosis, revealing pathological abnormalities underlying the neuromuscular impairment. Histopathologic features of CIPO include neuropathic, mesenchymopathic and myopathic forms based on abnormalities affecting the integrity of nerve pathways supplying the gut (either intrinsic or extrinsic), interstitial cells of Cajal (ICC) and smooth muscle cells, respectively. Neuropathic, mesenchymopathic and myopathic changes may contribute to gut dysmotility either individually or in combination (e.g. neuro-myopathies or neuro-ICC alterations) (Table 2)^[1,6,7].

Enteric neuropathies and enteroglia cell abnormalities

Enteric neurodegenerative abnormalities and immune-mediated changes may occur in gut specimens of patients with neuropathic CIPO. Inflammatory neuropathies are characterized by a dense inflammatory infiltrate characterized by CD3 positive (composed of both CD4 and CD8) lymphocytes almost invariably confined to the myenteric plexus (hence the term of *lymphocytic myenteric ganglionitis*)^[7-9,19]. The close apposition of CD3 lymphocytes to myenteric neurons provides the basis to neuro-immune interactions targeting and affecting ganglion cell structure and survival^[20,21]. Indeed, experimental evidence indicates that inflammation/immune activation in the gastrointestinal tract can profoundly affect both morphology and function of the enteric nervous system (ENS).

The evidence that patients with inflammatory neuropathy have circulating anti-neuronal auto-antibodies (e.g. anti-Hu anti-neuronal antibodies) also suggests the role of the immune system in neuronal dysfunction^[19]. Previous results indicated that these autoantibodies alter ascending reflex pathway of peristalsis in *in vitro* preparations^[22] and elicit neuronal hyperexcitability as demonstrated by Ca²⁺-imaging technique^[23]. In addition, anti-HuD neuronal antibodies evoked activation of caspase-3 and apaf-1 along with apoptosis when incubated with primary culture of myenteric neurons^[24]. Taken together, these experimental data suggest that anti-Hu antibodies may exert either a direct pathogenic role or contribute in association with the lymphocytic infiltrate in ENS dysfunction in patients with CIPO related to an inflammatory neuropathy. Although the etiology of inflammatory neuropathies remains undetermined, the demonstration showing herpes virus DNA in the myenteric plexus of patients with CIPO^[25] raises the exciting possibility that infectious agents can be involved in the pathogenic cascade leading to inflammatory damage of the ENS.

Table 2 Immunohistochemical markers to analyze full thickness biopsy of patients with CIPO

Markers	Cell targets and sites	Description
PGP9.5, NSE, MAP-2, NFs, tubulins, Hu C/D	Neurons: Membrane/Cytoplasmic	Identification of the general structure of the ENS
β -S-100, GFAP	Glial cells: Cytoplasmic	Detection of enterogial cells
Kit	Interstitial cells of Cajal: Membrane/Cytoplasmic	Different ICC networks
SP, VIP, PACAP, CGRP, NPY, Galanin, 5-HT, NOS, ChAT, somatostatin, Calbindin, NeuN, NK1, NK2 and NK3	Subclasses of enteric neurons; interstitial cells of Cajal: Membrane/Cytoplasmic	Characterization of neurochemical coding and enteric neuron subclasses; subsets of interstitial cells of Cajal
Bcl-2, TUNEL, Caspase-3, Caspase-8, Apaf-1	Apoptosis and related mechanisms: Nuclear/Cytoplasmic	Assessment of apoptosis and related pathways
Actin, myosin, desmin, smoothelin	Smooth muscle cells: Cytoplasmic	Assessment of smooth muscle integrity
CD3, CD4, CD8, CD79 α , CD68; MIP-1 α , TNF- α , IFN- γ	Immune cells, chemokines and cytokines: Membrane/Cytoplasmic	Evaluation of B (CD79 α) and T-lymphocytes (CD3), T-helper (CD4), T-suppressor (CD8), macrophages (CD68) in enteric ganglionitis; MIP-1 α is a chemokine; TNF- α and IFN- γ are inflammatory cytokines

Bcl-2: B cell lymphoma-2 protein; ChAT: Choline acetyltransferase; CGRP: Calcitonin gene-related peptide; ENS: Enteric nervous system; GFAP: Glial fibrillary acidic protein; Hu C/D: Hu C/D molecular antigen; IFN- γ : Interferon γ ; MAP-2: Microtubule associated protein-2; MIP-1 α : Macrophage inflammatory protein-1 α ; NeuN: Neuronal-specific nuclear protein; NFs: Neurofilaments; NK1, NK2, NK3: Neurokinin1, neurokinin2, neurokinin3; NOS: Nitric oxide synthase; NPY: Neuropeptide Y; NSE: Neuron-specific enolase; PACAP: Pituitary adenylate cyclase activating polypeptide; PGP9.5: Protein gene product 9.5; 5-HT: 5-hydroxytryptamine (serotonin); SP: Substance P; TNF- α : Tumor necrosis factor α ; Tubulins: Cytoskeletal proteins; TUNEL: Terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick-end labeling; VIP: Vasoactive intestinal polypeptide.

Further to lymphocytic ganglionitis, Schappi *et al* have reported on eosinophilic ganglionitis characterized by eosinophils infiltrating the myenteric plexus of pediatric patients with CIPO^[26]. In contrast to lymphocytic, the eosinophilic ganglionitis does not appear to evoke neuronal degeneration and loss and, therefore, gut dysmotility may be interpreted as a functional impairment of the ENS due to the infiltrate *per se* or humoral messengers released by eosinophils. Recently, mast cell predominant ganglionitis has been described in patients with severe gut dysmotility (including CIPO)^[27]. The mast cells detected within myenteric ganglia in these patients were associated with markedly reduced neuronal nitric oxide synthase expression identified at molecular and immunohistochemical level. These findings suggest an impaired enteric inhibitory innervation in these peculiar subsets of CIPO.

Degenerative (or non inflammatory) neuropathies may be regarded as the end result of several putative pathogenic mechanisms, such as altered calcium signaling, mitochondrial dysfunction and production of free radicals, leading to degeneration and loss of the intrinsic neurons of the gut^[28]. Degenerative neuropathies can be familial (related to a genetic background-see above) or sporadic and classified into primary (idiopathic) or secondary forms to a variety of causes, such as radiations, vinka alkaloids, myxedema, diabetes mellitus, muscular dystrophy and amyloidosis. Typical neuropathological findings reported in neurodegenerative CIPO include various qualitative (neuronal swelling, intranuclear inclusions, axonal degeneration and other lesions) and quantitative (especially hypoganglionosis) abnormalities of the ENS. Sporadic cases of visceral neuropathies are associated with two major patterns of alterations: (1) A marked reduction of intramural (especially myenteric) neural cells mainly associated with swollen neural cell bodies and processes, fragmentation and loss of axons and proliferation of glial cells; (2) A loss of the normal staining in subsets of enteric neurons, in the absence of

dendritic swelling or glial proliferation^[6,20,21]. Since no reliable models of degenerative neuropathies exist, the mechanisms through which exogenous noxae or other triggering factors initiate degenerative processes in enteric neurons remain obscure. Enteric neurons of patients with severe forms of idiopathic intrinsic neuropathy display a decreased expression of the protein encoded by *Bcl-2*, a gene related to one of the intracellular pathways leading to programmed cell death^[4,29,30]. Indeed, this finding has been associated with an increased number of neurons displaying TUNEL, a marker of apoptosis^[31].

Abnormalities of enteric glia may also contribute to intrinsic neuropathy either attracting immune cells to the ENS or resulting in insufficient support/trophism to enteric neurons and thus eliciting neurodegenerative events in the absence of inflammation^[32].

Enteric mesenchymopathies

Abnormalities to ICCs have been detected in gut tissues of patients with CIPO. These include decreased ICC density, loss of processes and damaged intracellular cytoskeleton and organelles as revealed by immunohistochemical analysis and electron microscopy^[33-37]. As a result, it has been proposed that the impairment of the major functional subclasses of ICC (i.e. those involved in pacemaker activity and neurotransmission to smooth muscle) may contribute to enteric motility abnormalities detectable in patients with CIPO.

Enteric myopathies

Histopathological analysis of the enteric muscle layer may reveal the existence of muscular abnormalities (i.e. smooth muscle fibrosis and vacuolization) of the circular and longitudinal layers in patients with primary visceral myopathy^[38,39]. A controlled multinational study conducted by Knowles *et al* has proposed that a selective decrease or even absence of α -actin in the circular muscle of the small bowel wall can be regarded as biological markers of

CIPO^[40]. Although exciting, the possibility that a defective expression/localization of α -actin may be a biomarker of a heterogeneous disease such as CIPO awaits solid confirmatory evidence.

The histopathological details concerning other segments of the gut as well as extra-digestive systems (i.e. urinary tract, gall-bladder) is poorly characterized and further studies are awaited to elucidate this important aspect.

CLINICAL FEATURES

Subocclusive episodes can strike in apparently healthy people, but the onset of CIPO is generally insidious, with gastrointestinal symptoms which precede the first acute episode.

The typical clinical manifestation of CIPO is characterized by recurrent episodes of abdominal pain, abdominal distension and inability to defecate (flatus may not be completely suppressed), with or without vomiting, mimicking a mechanical sub-occlusion. During acute episodes radiological evidence of distended bowel loops and air-fluid levels in the upright position is an important diagnostic marker of this pathological condition. Acute episodes can last only a few hours, but in the most severe cases intestinal loops are chronically distended and air-fluid levels are invariably detected. Due to this misleading clinical manifestation, a history of multiple, useless surgeries are typical of the syndrome. Thus, many patients have abdominal adhesions and the concomitant presence of functional and mechanical (secondary to adhesions) obstruction is often impossible to rule out despite extensive investigations.

Between subocclusive episodes patients are very rarely asymptomatic, and almost invariably complain of severe digestive symptoms^[1,2] suggestive of delayed transit in the proximal and/or distal portions of the alimentary canal. Nausea, vomiting and weight loss are predominant symptoms when the functional derangement primarily affects the upper gastrointestinal tract, while diffuse abdominal pain, abdominal distension and constipation are suggestive of a more distal involvement of the gut. Dysphagia is present in a low proportion of CIPO patients although it is relatively frequent in forms secondary to progressive systemic sclerosis.

Diarrhea and steatorrhea often occur as a consequence to small bowel bacterial overgrowth.

This pathologically accelerated transit is often well accepted by patients since it is associated with partial relief of other digestive symptoms, but it contributes to determine intestinal malabsorption and deteriorate nutritional conditions. Indeed, many patients are afflicted by inability to maintain a normal body weight, despite dietary manipulations, both because of the deranged digestive functions and because food ingestion often exacerbates digestive symptoms and consequently patients tend to avoid a normal oral nutrition.

Urinary symptoms, generally associated with evidence of urinary tract distension, are also frequent.

Depression or other psychological disturbances are often secondary to the disabling digestive problems and the disappointing quality of healthcare received.

DIAGNOSTIC PROCEDURES

The diagnosis of CIPO is mainly clinical, supported by radiographic documentation of dilated bowel with air-fluid level, after exclusion of organic lesions occluding the gut lumen, as detected by radiologic and/or endoscopic investigations. Thus, diagnostic tests in patients with suspected CIPO are necessary to exclude mechanical occlusion, identify possible causes of secondary forms, explore underlying pathophysiological mechanisms and disclose possible complications.

Radiology

Radiology is one of the most important examinations in the diagnosis of CIPO. Plain abdominal films identify typical signs of intestinal occlusion such as distended bowel loops with air-fluid levels, the latter obtained with the patients in the upright position (as specified above). Contrast studies are necessary to exclude the presence of organic lesions responsible for the occlusion. Entero-CT scan allows simultaneous internal and external views of the gut wall, abdominal CT and MR scans are important in investigating possible causes of gut compression, while MR angiography may non-invasively identify congenital or acquired vascular abnormalities. Excretory urograms should be performed in patients with urinary symptoms.

Symptoms suggestive of a subocclusive state in the absence of dilated bowel with air fluid levels at radiology have been defined by some authors as a "mild forms of CIPO"^[41]. Nonetheless, this definition has been criticized^[4]. In fact, preliminary studies suggest that patients with extremely severe digestive symptoms and malnutrition, but no radiological evidence of intestinal occlusion, have a significantly reduced probability of undergoing abdominal surgery and present less severe motility disorders^[42].

Endoscopy

The main indication of upper gastrointestinal endoscopy is exclusion of mechanical occlusions in the gastro-jejunal and ileo-colonic regions. It allows to exclusion of false positive radiologic diagnoses of mechanical occlusion in the duodenum and proximal small bowel, as in many cases of the so-called "aorto-mesenteric compression syndrome"^[43]. Mucosal biopsies of the small bowel should be taken to rule out celiac disease. Colonoscopy also has a therapeutic potential, since it can be used to try to decompress the large bowel^[44].

Laboratory tests

Laboratory tests are useful to identify the presence of potentially curable diseases responsible for secondary forms, but also to monitor hydro-electrolyte balance and circulating levels of essential elements in patients on parenteral nutrition or, in general, with a severe malnutrition.

Manometry

Small bowel manometry is invariably abnormal in CIPO patients^[2,3,45]; however, the test is not of diagnostic value due to its low specificity. At best, it can play a supportive role in defining the diagnosis, since it can contribute to differentiate mechanical from functional obstruction and

to recognize the underlying pathophysiological mechanism^[2,3,45].

Describing in detail small bowel manometric abnormalities of CIPO goes beyond the scope of the present review. They can be summarized as follows: uncoordinated bursts of powerful contractions with variable duration are suggestive of an underlying intrinsic neuropathy^[1-4,45-48] conversely, normally coordinated motor patterns with low amplitude have been reported in patients with a myogenic disorder^[1-4,45-48]. Nonetheless, low amplitude contractions may merely reflect the inability of the manometric technique to record non-occlusive contractions, such as in the case of dilated bowel loops^[1-4,45-48].

Unlike what is observed in pseudo-obstruction, the manometric pattern of mechanical occlusion is characterized by giant contractions (prolonged contractions lasting at least 10 s and can be either propagated or non propagated) or clustered contractions (3-10 regular contractions, occurring 1 per 5 s preceded and followed by ≥ 1 min of absent motor activity lasting at least 20 min and can be either propagated or non propagated)^[1-4,45-49].

Esophageal manometry generally adds very little to the diagnostic work-up of CIPO, but it plays an important diagnostic and prognostic role if the disease is secondary to scleroderma. Ano-rectal manometry is important to rule out Hirschsprung's disease, particularly in patients with intractable constipation and a marked distension of the large intestine.

Biopsy and pathologic examination

Full thickness biopsies should be obtained from dilated and non dilated tracts of the alimentary canal in all patients with suspected CIPO who undergo surgery for unexplained occlusive episodes. Biopsies should be processed for in depth pathological evaluation by both traditional staining and immunohistochemistry techniques in dedicated laboratories with a specific interest in this area, as specified above.

NATURAL HISTORY

Even if clinical experience shows that CIPO is a progressive disease that often leads to death, only few studies have precisely described the natural history of this pathology and its symptoms prognostic values, especially in the adult age. Children generally present the first manifestations of CIPO at birth or during the first years of age^[50-53]. The pediatric expression of the disease is often characterized by a particularly severe course, with mortality rates extremely high within the first year of age, mainly due to surgical and parenteral nutrition complications^[52,53]. Several predictors of poor outcome have been identified in children including myopathic forms, malrotation, short bowel syndrome, and urinary tract involvement^[50,51].

In the adult population, the first sub-occlusive episode is often preceded by a long history of non-specific, progressively more severe digestive symptoms. An acute onset of the disease occurs in only one-fourth of the cases^[2].

After diagnosis is established the frequency of sub-

occlusive episodes and, consequently, also of surgical procedures tend to decrease. Nevertheless, the clinical course of CIPO is almost invariably severe^[1,2,52-54] with progressive deterioration of bowel function and digestive symptoms. In order to control both the body weight and the abdominal pain most patients progressively limit oral nutrition and end up on long-term parenteral nutrition.

The main causes of death are TPN-related complications, surgery-related complications, and post-transplantation complication, together with septic shock of GI origin. A variety of clinical, histological and manometric parameters have been found to be predictive of a poor clinical outcome in adult patients, including myopathy and decreased contractile activity^[2,50,52,53,55-60]. MNGIE has a particularly poor prognosis with slowly progressive evolution and death around 40 years of age^[11].

THERAPY

The treatment of CIPO is difficult and often provides unsatisfactory results. Of course, treatment of the underlying disease is mandatory in secondary forms whenever available^[57].

Treatment of the acute phase

During acute phases patients should be treated as those with acute mechanical obstruction. Fluid and electrolytes balance should be maintained *via IV* infusions; abdominal decompression should be attempted by positioning of nasogastric and rectal tubes. The former generally prevents vomiting and *ab ingestis* while the latter is generally ineffective and colonic decompression can be attempted by colonoscopy or cecostomy (see below). In case of prolonged subocclusive episodes systemic or poorly absorbable antibiotics are necessary to prevent bacterial overgrowth. Appropriate caloric support must be provided by *IV* infusion. Erythromycin, somatostatin and neostigmine can be used to promote transit and decrease the duration of acute episodes^[61-63].

Nutritional support

The nutritional status of patients with CIPO is generally poor. Frequent small meals with liquid or homogenized foods, with or without oral nutritional supplements, may help patients with sufficient residual digestive functions. Enteral nutrition is an option for patients whose motility disorder is mainly localized in the stomach and duodenum. It presents fewer complications than parenteral nutrition, but clinical experience suggests that enteral feeding is rarely tolerated by patients. In the most severe cases, when small bowel function is diffusely affected, parenteral nutrition is necessary to satisfy nutritional requirements. The main limitations of this nutritional support include liver insufficiency, pancreatitis, glomerulonephritis and catheter-related complications (i.e. thrombosis and septicemia)^[58,59].

Pharmacological therapy

The pharmacological treatment of CIPO is aimed at controlling symptoms and avoiding complications. Co-

prescription of antiemetics, antisecretory, antispasmodics, laxatives or antidiarrheal and analgesic drugs is often necessary. Prokinetics are often prescribed, with the intention to improve gastrointestinal motility and to control visceral sensitivity^[2,54].

Some prokinetics seem to be more effective than others: metoclopramide, domperidone, bethanechol or neostigmine are often used, but with only limited success, while cisapride, that is currently available only in some parts of the world, has been reported to exert positive effects^[60,64-67]. Two controlled trials including CIPO patients described positive effects of cisapride in accelerating gastric emptying^[60] and improving symptoms^[66]. Erythromycin is a macrolide antibiotic with a specific agonist action on the motilin receptors of the proximal gastrointestinal tract. It increases antral contraction and promotes gastric emptying, while its effects on colonic motility are controversial: at low doses it stimulates intestinal contractions, but doses normally used to enhance gastric emptying decrease motility of the small intestine^[61]. Octreotide is a long-acting somatostatin analog which increases intestinal motor activity and decreases bacterial overgrowth^[62]. Co-prescription of erythromycin and octreotide can be useful to control both the gastric emptying and the intestinal motility^[68]. Anticholinesterase drugs have been described as effective in autoimmune gastrointestinal motor disorders^[69]. Tegaserod, a more recent 5-HT₄ agonist, was also recommended for the treatment of subocclusive episodes in CIPO, but the drug has been withdrawn from the market^[70]. A preliminary open study describes encouraging results exerted gastric electrical stimulation on nausea and vomiting in a small number of CIPO patients^[71].

Opioids are required in patients with intractable pain, but their constipating effect can further deteriorate digestive functions^[72,73].

Antibiotics are often useful to contrast bacterial overgrowth. Poorly absorbable antibiotics such as paramomycin and rifaximine should be preferred, but alternating cycles with metronidazole and tetracycline are necessary to limit resistances^[74].

Steroids or other immunosuppressive treatments are recommended when CIPO is related to an underlying inflammatory neuropathy. These cases have to be selected through tissue analysis or at least suspected by the identification of circulating anti-neuronal antibodies^[6]. Treatment of MNGIE is largely supportive, being based on parenteral nutrition and/or supplementation with coenzyme Q, riboflavin and other vitamins (vitamin C, vitamin K₃, carnitine). Prompt treatment of fever and infections and avoidance of extremes in temperature, over exercise, drugs known to interfere with mitochondrial functions (phenytoin, chloramphenicol, tetracycline, macrolides, and aminoglycosides), are also recommended. Infusion platelets to reduce thymidine level have been reported to exert some positive effect in preliminary study in MNGIE patients^[75].

Surgical therapy

Even if CIPO patients often undergo surgical procedures, this kind of approach has only a limited role in the

management of the disease and has to be considered only in some carefully selected patients. Specifically, since CIPO generally involves the whole alimentary canal, only rare cases can benefit from surgical resections. Indeed surgery can precipitate deterioration of the clinical conditions and should be performed only if strictly necessary. Full thickness biopsies should be obtained whenever possible for pathological examination as stated above. In particular, surgery can be considered in patients having what appears to be localized involvement of the gastrointestinal tract, but CIPO is often a progressive disease and the benefit is likely temporary^[41,76].

Gastrostomies and enterostomies can effectively decrease retching, vomiting and abdominal distension and represent a possible option in patients who can be fed by enteral nutrition. Furthermore, decompression of distended bowel loops can exert a positive effect on the transport capacities of the alimentary canal which, in turn, results in a decreased frequency of further hospital admissions and surgeries.

Small bowel or, when needed, multivisceral transplantation is available only in a few highly specialized centers. The general outcome of this surgical procedure has markedly improved with the use of the immunosuppressive agent tacrolimus associated with steroid and together a number of induction agents such as alemtuzumab, antithymocyte globulins and daclizumab^[77]. However, the need for long-term parenteral nutrition, re-laparotomies, organ rejection and, especially, bacterial infections are frequent complications and the procedure still have mortality rates approaching 50% at 5 years. Predictors of post-transplant complications are: concomitant neuromuscular disorders of the urinary tract, chronic use of opioids and technical problems determined by previous multiple laparotomies and/or the need of gastrectomy for gastroparesis. Nonetheless, transplantation should be considered when all other therapeutic options have failed according to the following indications: chronic intestinal failure with a high risk of mortality, life-threatening complications of parenteral nutrition, lack of venous access, disease-related poor quality of life despite optimal parenteral nutrition^[58].

CONCLUSION

CIPO is a rare and often misdiagnosed pathological condition. Even if the acute phases can be hardly differentiated by mechanical occlusions and the inter-crisis digestive symptoms can mimic other severe functional digestive syndromes, the syndrome should be recognized based on the typical combination of clinical features, natural course and radiological signs. The diagnostic suspicion should be then confirmed by more accurate examinations, in order to identify possible causes of secondary forms and underlying pathophysiological mechanisms.

Management of CIPO remains extremely challenging and often disappointing.

A greater awareness of the clinical features of CIPO would help to limit surgical procedures to a minimum and, even more importantly, to collect full-thickness biopsies

for analysis of the gut neuromuscular layer at an early and potentially curable stage of the disease.

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