Chronic intestinal pseudo-obstruction: a case report with review of the literature and practical guidance for the clinician

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Abstract

Chronic Intestinal Pseudo-obstruction (CIPO) is a rare but debilitating and severe form of gastrointestinal dysmotility. The diagnosis is often made very late in the disease course due to its rarity and complexity. Treatment is mainly supportive, as there is no definitive cure. Pharmacologic therapy comprises prokinetics, antibiotics for bacterial overgrowth and pain management. Pain can also be alleviated with intestinal decompression in selected cases. Beside the pharmacologic therapy, nutrition and fluid replacement play a key role. Rarely, intestinal transplantation is necessary in patients with CIPO and intestinal failure. In this review, we describe an advanced CIPO case and provide an update of the clinical and diagnostic features and current management strategies. The goal of our review is to raise awareness around CIPO and to give practical guidance for the clinician. (Acta gastroenterol. belg., **2022,** 85, **85-93**).

Keywords: intestinal obstruction, CIPO, management.

Clinical case

A 57-year-old woman was referred to our hospital for a second opinion because of abdominal distention and vomiting. She had a past medical history of a colonic volvulus and small intestinal obstruction for which she underwent a resection of the colon transversum at age 15. The pathology report of the resection specimen suggested a decreased number of neurons in the myenteric plexus without inflammation. When she was 27, an adhesiolysis was performed because of suspected mechanical small bowel obstruction. However, complaints of nausea, abdominal distension and pain persisted. CT abdomen showed an important dilation of the entire small bowel and to a lesser extent also the colon without signs of mechanical obstruction. The diagnosis of Chronic Intestinal Pseudo-Obstruction (CIPO) was made. At age 52, she was hospitalized due to an aggravation of her symptoms and was temporarily treated with a nasogastric tube, IV-fluids and somatostatin analogues. Parenteral nutrition (PN) was started because of malnutrition (BMI 17.8 and limited oral intake) and was continued at home. She developed osteoporotic indentation fractures as a consequence of malnutrition, for which denosumab was started.

Additional testing was performed after referral to our center. Biochemical analysis including anti-neuronal antibodies was normal. Celiac disease was ruled out on duodenal biopsies. A bile acid breath test was compatible with bacterial overgrowth. Small bowel manometry was compatible with a neurogenic pattern without a normal phase III complex. Prokinetics, including prucalopride, and SIBO treatment with antibiotics (doxycycline) were started, with moderate effect. After referral to our center, the home PN was switched to a lipid-free PN formulation due to elevated liver tests for which a workup was started, including a liver biopsy. The pathology confirmed the presence of steatosis without steatohepatitis, suggesting intestinal failure associated liver disease (IFALD) in the absence of alternative causes. Treatment with pyridostigmine was started up to 60mg t.i.d., with initially a good effect on the abdominal distension. However, a few months later, she was hospitalized because of persistent nausea and vomiting several times per day, with impaired quality of life and limited effects of prokinetics, including IV neostigmine. Because of an intrathoracic position of the stomach, no endoscopic nor surgical venting percutaneous endoscopic gastrostomy/jejunostomy (PEG/PEJ) could be placed and surgical intervention was judged as too high risk after multidisciplinary team discussion (Fig 1). She was therefore discharged with a nasogastric tube which

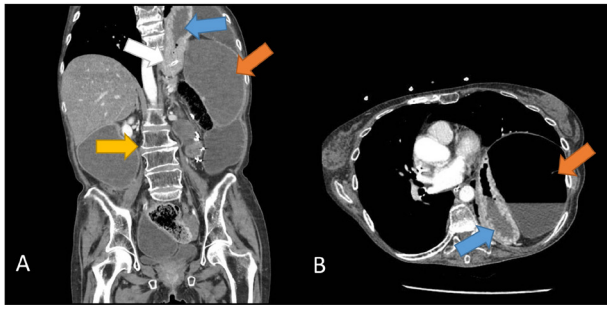

Figure 1. — Computed tomography. A: Coronal plane. B: Transverse plane. Blue arrows: intrathoracic position of the stomach. Red arrows: dilated small bowel loops. White arrow: tip of the nasogastric tube. Yellow arrow: dented vertebra due to osteoporosis.

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was exchanged every 8 weeks. A workup for intestinal transplant was initiated and the patient was eventually listed for a combined liver-intestinal transplant because of the poor quality of life.

In the current review, we aim to raise awareness of CIPO and provide a practical clinical guidance for the clinician.

Methods

A literature search was conducted using the PubMed database using the keywords: chronic intestinal pseudo-obstruction, CIPO, treatment, management, prokinetics, erythromycin, metoclopramide, domperidone, octreotide, prucalopride, intestinal failure, pain relief, immunomodulators, colonic decompression, small-intestinal bacterial overgrowth, SIBO, fecal microbiota transplantation, intestinal and liver transplantation. Only English language papers were included without restricting the period of publication. The bibliographies of relevant papers were searched, including earlier papers.

Definition, Prevalence and Symptoms

Chronic intestinal pseudo-obstruction remains a highly challenging disorder for gastroenterologists. Arguably, it is the most severe form of intestinal dysmotility, which is characterized by the presence of impaired gastrointestinal propulsion of the gut content in the absence of fixed occluding lesions (1,2). The consequence of the impaired motility is intolerance to oral or enteral nutrition resulting in inadequate nutritional intake and malnutrition which is the most important complication (2,3).

The prevalence and incidence of CIPO is largely unknown. According to estimates from pediatric CIPO, approximately 100 infants are born each year in the United States with congenital forms of CIPO, which is most likely an underestimate of the number of new pediatric cases per year and definitely only a tiny proportion of all patients with CIPO (4). Nationwide epidemiologic surveys in Japan have estimated the population prevalence of CIPO to be 3.7 per million in childhood (5) and 8 to 10 per million in general (6). In large published series of adult patients, the prevalence in females is higher than males, with a ratio varying from 2 to 1 up to 5 to 1 (7-9).

The diagnosis is based on symptoms and radiologic features suggestive for obstruction in the absence of an obstructive lesion (1,10). Abdominal pain and distension are the most frequent complaints, followed by nausea, vomiting and constipation. Diarrhea is less frequent but can be seen, often in more advanced cases as a consequence of small intestinal bacterial overgrowth (SIBO) which leads to even more malabsorption and malnutrition. Typically, the complaints are intermittent, with minimally symptomatic periods following acute episodes, although symptoms tend to become more persistent over time (10,11).

Etiology

CIPO can occur in both children and adults. The onset of CIPO can be subdivided in a congenital, pediatric or an adult onset. In pediatric patients, the disease can have a neonatal (from prenatal to 12 months of age) or late onset in sporadic cases (from 1 year to 18 years of age). In adult patients, the median age of onset is between 20 and 40 years (12). When no underlying disorder is found, CIPO is categorized as a primary disorder. This can histologically be further subdivided into 3 categories: neuropathies (when there is damage to the enteric nervous system), myopathies (when there is smooth muscle damage), or mesenchymopathies (when there is damage in the interstitial cells of Cajal), although there may be some overlap (12,13). Primary familial or sporadic visceral neuromuscular disorders are uncommon causes of CIPO (14). CIPO is secondary when it is related to an underlying disease i.e. neurologic, autoimmune and endocrinological disorders, metabolic diseases, paraneoplastic syndromes, neurotropic viruses, auto-immune disorders, celiac disease, neuro-muscular disorders or radiation enteritis. CIPO can also be iatrogenic when it is a consequence of the use of opioids and – less frequently – tricyclic antidepressants, anticholinergic agents, anti-Parkinsonian agents, clonidine, ganglionic blockers, phenothiazines, etc. Secondary forms of CIPO are by far the most frequent. When there is a family history and/or if associated signs and symptoms occur, a genetic syndrome should be excluded (2,11,15). The clinical presentation of primary or secondary CIPO is identical and independent of the underlying disorder. In Table 1, we have summarized the classification of CIPO in relation to etiopathogenic factors.

Diagnosis

The diagnosis of CIPO is a clinical one. When suspecting CIPO, a diagnostic workup needs to be performed.

First, a mechanical cause of bowel obstruction needs to be excluded. Computed tomography (CT) has replaced plain radiography because of its higher sensitivity to demonstrate dilation and air-fluid levels and especially to rule out mechanical obstruction which is not possible on standard X-ray (16). When available, entero-magnetic resonance imaging (E-MRI) is preferred over CT (especially in the pediatric population) because it has the advantage of being a radiation-free method, although there is no benefit in accuracy over CT (1,12). Cine MRI is a recently developed non-invasive and radiation-free method to evaluate gastro-intestinal motility. It may also be useful in predicting a severe clinical course and is superior to CT in detecting early stages of impaired small intestinal contractility (27,28). However, its sensitivity and added value in CIPO remains to be demonstrated.

It is advised to perform an upper and lower endoscopy to exclude mechanical occlusions and collect routine

Table 1. — **Etiology and classification of CIPO**

Primary	Secondary	Familial forms
No demonstrable etiopathologic cause • Neuropathy • Myopathy • Mesenchymopathy	Autoimmune disorders • Celiac disease • Eosinophilic gastroenteritis • Inflammatory bowel disease	Autosomal Dominant • ACTG2 • NF1 • SOX10
	Drugs • Antidepressants • Anticholinergics • Bronchodilators • Clonidine • Narcotics • Parkinson's medication • Phenothiazines • Vincristine	Autosomal recessive • POLG • RAD 21 • SGOL1 • TYMP • 8q23-q24
	Endocrinological disorders • Diabetes mellitus • Hypo- or hyperthyroidism • Hypoparathyroidism	X-linked • FLNA • L1CAM
	Infections	
	• Parasitic infection o Chagas disease • Viruses o California encephalitis virus o Coxsackie o Herpesviridae: Cytomegalovirus, Epstein-Barr virus, Herpes simplex, Varicella-zoster o Echovirus o HIV o Influenza o Japanese encephalitis o Measles o Mumps o Polio o Polyomavirus: JC virus o Rabies o Venezuelan equine encephalitis	
	Jejunal diverticulosis	
	Metabolic disorders • Acute intermittent porphyria • Diabetes mellitus • Fabry's disease • Pheochromocytoma	
	Neurologic disorders • Dysautonomia • Guillain-Barré syndrome • Hirschsprung's disease • Multiple sclerosis • Myasthenia gravis • Parkinson's disease	
	• Neuromuscular disorders • Amyloidosis • Dermatomyositis • Ehlers-Danlos syndrome • Myotonic dystrophy • Progressive or Duchenne muscular dystrophy • Systemic sclerosis • Systemic lupus erythematosus	
	Paraneoplastic syndromes • SCLC • Carcinoid syndrome	
	Radiation enteritis	

ACTG2, actin gamma 2; CIPO, chronic intestinal pseudo-obstruction; FLNA, filamin; JC-virus, John Cunningham virus; L1CAM, L1 cell adhesion molecule; NF1, neurofibromatosis 1; POLG, polymerase DNA gamma; RAD 21, cohesin complex component; SCLC, small cell lung cancer; SGOL1, shugoshin-like 1; SOX10, SRY-BOX 10; TYMP, thymidine phosphorylase.

biopsies. Duodenal biopsies can help to rule out an underlying celiac disease, associated with dysmotility. Random biopsies in the upper and lower gut are useful to detect eosinophilic gastroenteropathy (17). Even if it makes sense to rule out celiac disease and luminal lesions in CIPO, the yield of endoscopy in this setting is unknown and probably low.

When there are no signs of intra- or extraluminal obstruction, secondary causes of potentially treatable pseudo-obstruction should be excluded. This can be done by performing screening tests for diabetes mellitus, neurotropic viruses (such as cytomegalovirus or Epstein-Barr virus), celiac disease, connective tissue and skeletal muscle disorders (antinuclear antibody, anti- double-stranded DNA and SCL- 70, creatine phosphokinase, aldolase). Thyroid function should also be checked. Other tests include serology or PCR for Chagas' disease (American trypanosomiasis) in the right setting (South-American patients with additional symptoms of trypanosomiasis including cardiomyopathy, dysphagia, etc.), urinary catecholamines for pheochromocytoma and enteric neuronal autoantibodies (anti-Hu or type 1 antineuronal nuclear antibodies) in patients with suspicion of paraneoplastic syndrome (14). Urinary porphyrins should be checked in patients with severe, unexplained abdominal pain. In patients where an underlying mitochondrial disorder is suspected, serum lactate and thymidine phosphorylase (TYMP) activities should be performed. If the TYMP activity is markedly reduced and nucleosides are increased, TYMP (in mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)) and polymerase DNA-gamma (POLG) (in sensory ataxic neuropathy dysarthria and ophthalmoparesis) gene mutations should be tested (18,19).

Small bowel manometry may provide pathophysiologically relevant information on the mechanisms involved in CIPO patients (i.e. neuropathic vs myopathic patterns) (4,8,20-23). Its place as a diagnostic test is contested, as it has a low diagnostic specificity and as it will not influence treatment in most patients. It has mainly been advocated as a method to differentiate between a neuropathy and an enteric myopathy. A neuropathy is characterized by contractions with a normal amplitude and uncoordinated contraction patterns whereas an enteric myopathy will have coordinated contractions during fasting and fed state measurements with a reduced amplitude. However, the caveat is that low amplitude contractions could also be due to the inability of the manometric catheter to register non-occlusive contractions when bowel loops are dilated (24). Moreover, a recent study in 38 patients undergoing both full-thickness biopsies and small bowel manometry did not show any correlation between histological and manometric classification of CIPO (25). Finally, manometry can be useful to exclude other causes of small bowel distention and pain, such as a missed mechanical obstruction shown by prolonged or clustered contractions (26).

The place of full-thickness biopsies is still unclear. It has been suggested that this invasive test should be reserved for either idiopathic cases characterized by an acute onset likely of post-infectious origin or patients with rapidly evolving forms of CIPO who are not under treatment with opioids and do not respond to any therapeutic options. In CIPO cases with a clear origin, tissue sampling tends to be less clinically meaningful and can be omitted (11). Of course, besides the opioid-induced or systemic sclerosis related CIPO, this is a small group of patients. Using laparoscopic surgery, full-thickness biopsies can be obtained in a minimal invasive way. An emerging technique is endoscopic full-thickness resection (eFTR), which is a safe and minimally invasive that yields tissue samples of excellent quality (11). The central question remains whether histology changes the clinical management of the patients as the data on immunomodulatory treatment in case of inflammatory conditions are limited (cf. infra).

Treatment

The treatment of CIPO is challenging and often unsatisfactory for both the patient and the physician. The goal of the treatment is to improve or maintain nutritional status, restore fluid and electrolyte balance, promote coordinated intestinal motility and treat complications such as sepsis, SIBO and other associated symptoms (10,11,29).

Nutrition

Malnutrition is a common problem due to malabsorption and insufficient food intake. Therefore, small, frequent protein rich meals should be recommended, preferably in a liquid form (oral supplements), while avoiding high-fat, high-residue and high-lactose foods. Vitamin status should be checked and supplemented when needed (11,17,24).

When oral intake is insufficient, enteral nutrition with standard polymeric formula may be considered. This is preferable to parenteral nutrition as enteral nutrition maintains the normal absorptive function of the gut. A trial with a nasogastric or nasojejunal feeding tube should be performed before placing a percutaneous feeding tube because of the possibility of intolerance to enteral feeding with increased bloating or diarrhea. Continuous, low-dose or periodic feeding appears to be better tolerated than large bolus feedings (11,17,24,30). However, the data on enteral nutrition in CIPO are limited to case reports. Benjamin *et al.* describe a case of a 21-year-old man with CIPO and severe malnutrition (BMI of 11 kg/m^2), who was started on enteral feeding during hospitalization. Nocturnal feeds were started at a rate of 50mL/h and increased to 100mL/h after a fortnight. After 8 months, BMI was normalized (22.3 kg/m^2) (31). However, in regular clinical practice, intolerance to enteral nutrition is often observed in CIPO.

In more advanced cases CIPO can lead to intestinal failure in which case absorption of nutrients fails to supply the needed nutrients, fluids and electrolytes to sustain life (2). In these patients, parenteral nutrition (PN) is necessary to avoid dehydration and malnutrition. Complications of PN and intestinal failure are well known and are frequent causes of morbidity and mortality in CIPO. These comprise metabolic complications such as intestinal failure-associated liver disease (IFALD) and metabolic bone disease, infectious complications such as catheter-related blood stream infections and vascular access complications such as central venous thrombosis, catheter occlusions and breaks (11,17,24,30,32). Personalized PN formulations, with minimal intravenous lipid infusion (max 1g/kg/day) and with a preference for third generation lipid formulations containing fish oil, can help reducing metabolic complications. Maximizing oral or enteral intake in patients with CIPO should be prioritized to minimize or avoid the use of PN (29).

Prokinetics

Although there is no convincing evidence that prokinetics restore propulsion, they are often used empirically in CIPO patients since they can give symptomatic improvement. Unfortunately, there are only a limited number of trials, most of them based on small numbers of patients, to guide our decision.

Metoclopramide, a dopamine-2 receptor antagonist, exerts prokinetic effects by increasing acetylcholine release. Although metoclopramide is often used in clinical practice, evidence supporting its use in CIPO is lacking. In case series, metoclopramide appeared to be poorly effective (33,34). In 2009, the FDA issued a black box warning regarding long-term or high-dose use of this medication because of the risk of tardive dyskinesia (35). Therefore, the use of metoclopramide should be discouraged in CIPO.

The use of *domperidone* (another dopamine-2 receptor antagonist) in CIPO has been described in a limited number of case series and was also not associated with improvement of symptoms (36,37). Moreover, there is a concern of QTc prolongation in older patients or in case of cardiac comorbidity.

Erythromycin, a macrolide antibiotic, acts as an agonist of the motilin receptor and remains one of the most powerful prokinetic drugs. In case reports, it has been shown to accelerate gastric emptying and improve symptoms of CIPO (38,39). Standard dosage is 250 mg t.i.d. per oral or 50 to 100mg intravenous t.i.d. Due to tachyphylaxis secondary to the downregulation of motilin receptors and decreased density of these receptors in the small and large intestine compared with the stomach, there is a limited place for the chronic use of erythromycin in CIPO although it can be used in case of exacerbations of dysmotility. Erythromycin can cause QTc-prolongation, myocardial depression and torsades de pointes. These effects are mostly seen at higher intravenous doses. It is recommended to exclude long QTc before starting erythromycin in clinical practice (17,40,41).

Octreotide, a long-acting analogue of somatostatin, evokes intestinal motor activity in normal subjects. Soudah *et al.* reported a case series of systemic sclerosis associated CIPO, in which the administration of subcutaneous octreotide at a dose of 50 microgram/day reduced bacterial overgrowth and improved abdominal symptoms, probably by inducing phase 3 contractions of the migrating motor complex (MMC) (42). Verne *et al.* reported a prospective case series of idiopathic and systemic sclerosis associated CIPO, where the efficacy of octreotide was confirmed by reducing nausea, vomiting, bloating and abdominal pain (43). In case reports, octreotide has also been described to be successful in paraneoplastic CIPO (44,45).

Calvet *et al.* described the successful repeated use of IV *neostigmine,* an acetylcholinesterase inhibitor enhancing the availability of acetylcholine in the synaptic cleft, at 8 mg/day in a patient with CIPO (46). O'Dea *et al.* reported a case series of 7 patients with CIPO, who had an improvement of symptoms with *pyridostigmine,* an oral formulation of acetylcholinesterase inhibitor (47). Manini *et al.* confirmed its effectiveness in a 18-year old male with CIPO, who reported an improvement in abdominal distension and a substantial reduction of PN (48). The recommended starting dose is 10mg t.i.d., which can be increased up to 60mg t.i.d. if required (47). However, cardiac safety should be monitored and a baseline ECG is necessary to rule out bradycardia or atrioventricular blocks.

Prucalopride, a highly selective 5-hydroxytryptamine-4 (5-HT4) receptor agonist with enterokinetic effects, has shown to be beneficial in 12 patients with CIPO in a randomized controlled trial (RCT) with treatment periods of 12 weeks in an 'n=1' analysis. The main benefit was related to the relief of bloating and abdominal pain, using doses of 2 tot 4mg a day without clear superiority of the higher dose (49).

The association and/or rotation of different prokinetic drugs without overlapping spectrum may be a useful strategy to treat CIPO, while minimizing tachyphylaxis and side effects (10).

Antibiotics

Chronic intestinal pseudo-obstruction can be complicated by bacterial overgrowth in stagnant segments resulting in diarrhea (14,50). Small intestinal bacterial overgrowth (SIBO) is known to cause mucosal inflammation, which further impairs gastro-intestinal motility and contributes to nausea, bloating and abdominal distension in CIPO patients (11). The treatment of choice frequently involves the use of non-absorbable antibiotics, such as rifaximin (51,52). Rifaximin therapy appears to be effective and safe in the treatment of SIBO, although the quality of the available studies is poor. Unfortunately, rifaximin is not reimbursed in Belgium for this indication

and cost is prohibitive. Other non-absorbable antibiotics can also be used, e.g. paromomycin (500mg t.i.d.), but studies are lacking. Even if there is no good evidence, many clinicians use 1- to 2-week rotation of broad-spectrum antibiotics such as amoxicillin/clavulanic acid (125 to 500mg b.i.d.), ciprofloxacin (500mg b.i.d.), doxycycline (100mg b.i.d.), neomycin (500mg b.i.d.) and metronidazole (250mg t.i.d.), followed by antibiotic-free periods (53). By using a rotating schedule, the likelihood of developing antibiotic resistance is suggested to be reduced (14). Amoxicillin/clavulanic acid has been shown to have enterokinetic effects in children, possibly combining prokinetic and antibiotic characteristics (54).

Pain relief

Visceral pain is an important problem in CIPO patients. Ideally, non-narcotic pain modulators, such as tricyclic antidepressants (e.g. amitriptyline), serotonin-norepinephrine reuptake inhibitors (e.g. duloxetine) and GABA analogs (e.g. pregabalin) would be used. Unfortunately, they are associated with significant side effects such as drowsiness, nausea (duloxetine) and sometimes constipation (amitriptyline). Starting with low doses which are gradually increased is the key for a beneficial side effect ratio. Opioids should be avoided as much as possible because of their motility-inhibiting properties, further aggravating CIPO and potentially leading to narcotic bowel syndrome.

Immunomodulators

Immunosuppressive drugs such as steroids and azathioprine, have been proposed as effective therapeutic options in patients with CIPO characterized by histopathologic signs of marked inflammation within myenteric ganglia or throughout the neuromuscular tract (11). However, this has only been described in a few case reports up till now and cannot be generally recommended (55-57). Referral to an expert center is recommended before starting this type of treatment.

The treatment of secondary forms of CIPO should be focused on the underlying diseases (paraneoplastic syndrome, lupus, scleroderma, etc.). Immunosuppressive drugs such as rituximab and cyclophosphamide have been successfully used in case reports of paraneoplastic CIPO (58-60). Xu *et al.* described a retrospective observational study of 51 patients with systemic lupus erythematosus and CIPO, who had a good response on early steroid treatment (61).

Decompression therapy

As bowel distension is frequently associated with pain in CIPO patients, decompression therapy plays a key role in the treatment of CIPO. Current treatment strategies encompass conventional methods such as intermittent nasogastric suction, rectal tubes or colonic decompression and surgical procedures such as feeding and venting gastro-/jejunostomies (62-66). Pakarinen *et al.* found a relief of symptoms after endoscopic or surgical decompressive interventions in half of 8 CIPO patients (62). Surgery should be avoided as much as possible, as it was associated with high postoperative morbidity and mortality rates in a case series of 63 patients described by Sabbagh *et al.* (up to 58% and 7.9% respectively). Post-operative morbidity (Clavien-Dindo score >0) occurred after 107 procedures, leading to an overall morbidity rate of 58.2%. Major morbidity (Clavien-Dindo ≥3) was observed in 20.7% of the procedures. This was related to several cases of emergency re-operation for a refractory post-operative ileus, anastomotic leakage, hemoperitoneum and evisceration. The mortality was due to sudden death in one case and septic shock with multi-organ failure after anastomotic leakage in four. If necessary, surgery should be limited to restricted indications, including diagnostic workup and patients refractory to maximal medical treatment (63). Percutaneous endoscopic gastrostomy (PEG) is a commonly applied method for long-term home enteral nutrition but also gastric venting. Unfortunately, it comes with the risk of aspiration pneumonia, which is why the current recommendation is a gastro-jejunostomy tube insertion via PEG (PEG-J) or even direct jejunostomy (PEJ) as a measure to prevent this (67). Ohkubo *et al.* conducted a pilot cohort study, enrolling 7 CIPO patients who all received PEG-J decompression therapy with concomitant gastric and jejunal decompression. This improved both the abdominal symptoms as the nutritional status. Although sufficient attention should be paid to regurgitation and aspiration, PEG-J can be used as decompression therapy for CIPO at home (68).

Transplantation

a. Fecal microbiota transplantation

Gu *et al.* conducted a prospective, open-label study, in which 9 patients with CIPO were enrolled (69). All patients received fecal microbiota transplantation (FMT) for 6 consecutive days through nasojejunal (NJ) tubes. After 8 weeks of observation following FMT, patients reported significantly less pain and bloating, but there was no effect on vomiting or nausea. Two third of the patients were also able to tolerate enteral nutrition trough a NJ tube. The limitations are the low number of cases, the lack of a comparison group and the short follow-up time. Until further confirmative research is available, FMT should not be advised for CIPO in clinical practice.

b. Intestinal transplantation

Intestinal transplantation (isolated or multivisceral) is a possible treatment strategy for patients with CIPO and intestinal failure who have a life-threatening complication of PN (liver failure, extensive vascular

thrombosis or recurrent sepsis from a central venous catheter), patients in who we cannot obtain a venous access for PN or patients who experience a poor quality of life while on PN, although the latter is a controversial indication and should be carefully evaluated in a multidisciplinary approach in expert centers (70). The number of CIPO patients in intestinal transplantation programs varies between 9 and 19% (71,72). The use of tacrolimus as immunosuppressive agent and induction agents (i.e. basiliximab, alemtuzumab, daclizumab and antilymphocyte globulines) have resulted in an increased overall survival rate and reduced graft rejection rate (73-75). Moreover, we have recently confirmed cost-efficacy of small bowel transplantation in complicated intestinal failure (76). In the case of gastric involvement, modified multivisceral transplantation (stomach, duodenum, pancreas and small bowel) can be considered (11). On the other hand, Lauro *et al.* state that adults with CIPO and irreversible complications of PN would benefit from isolated intestinal transplant with different surgical techniques to empty the native stomach, including the creation of an additional gastro-enterostomy with a Roux-en-Y construction. Longer follow-up in a larger series is needed, as the total study population included only 9 patients (73). In case of intestinal failure-related liver failure, a combined liver-bowel transplant should be performed (77). Multivisceral transplantation on the other hand, is only rarely needed in CIPO patients (72).

c. Allogenic hematopoietic stem cell and liver transplantation

Allogenic hematopoietic stem cell transplantation (AHSCT) has been proposed as a treatment for MNGIE, a rare fatal autosomal recessive disease due to TYMP mutations that result in thymidine phosphorylase deficiency. Halter *et al.* conducted a retrospective analysis of patients suffering from MNGIE who underwent AHSCT between 2005 and 2011. Seven (29%) patients survived more than 2 years after transplantation, in which they saw thymidine phosphorylase activity rise from undetectable to normal levels in all survivors. As mortality is high, AHSCT should only be considered for selected patients with an optimal donor (78). De Giorgio *et al.* described a successful liver transplantation for a patient with MNGIE, suggesting that liver transplantation could act as an alternative treatment for MNGIE, based on data displaying that the liver has high TYMP expression (79). In the future, enzyme replacement therapy also seems a promising treatment strategy (80,81).

Although the treatment in secondary CIPO should also be focused on the underlying disorder (e.g. gluten-free diet in celiac disease, stopping the causal drug in iatrogenic CIPO, etc.), the global treatment strategy in primary or secondary CIPO is the same.

Conclusion

CIPO still remains a challenging condition, both in terms of diagnosis and treatment. A practical guidance for the clinician is provided in Figure 2. Diagnosis is made by combining clinical examination with imaging and selected laboratory tests in the appropriate setting. The current treatment options remain unsatisfactory because of the limited efficacy of the available prokinetics. Standard CIPO management should be based on nutritional support, adequate fluid and electrolyte replacement, intermittent use of antibiotics for SIBO and

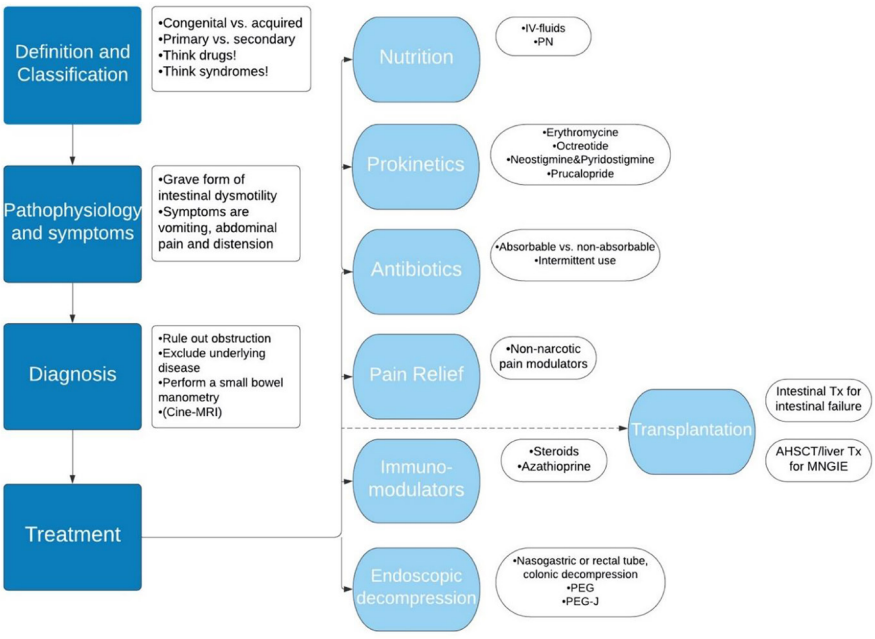

Figure 2. — Flowchart of CIPO management. AHSCT, allogenic hematopoietic stem cell transplantation; liver Tx, liver transplantation; MNGIE, mitochondrial neurogastrointestinal encephalomyopathy; PN, parenteral nutrition.

symptomatic treatment of abdominal pain and distension mainly with prokinetics. PEG or PEG-J can be helpful to obtain gastrointestinal decompression in selected cases. Although CIPO is a rare indication for intestinal transplantation, in some cases the more conservative treatment options are insufficient to maintain an adequate quality of life or avoid malnutrition.

Conflict of interest statement

None.

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