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MINI-REVIEW

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Chronic intestinal pseudo-obstruction: Progress in management?

G. Di Nardo[1,2] | T. B. Karunaratne[3] | S. Frediani[4] | R. De Giorgio[5]

[1]Pediatric Gastroenterology Unit, Santobono-Pausilipon Children's Hospital, Naples, Italy

[2]Pediatric Gastroenterology Unit, International Hospital Salvator Mundi, Rome, Italy

[3]Department of Medical and Surgical Sciences, University of Bologna, Italy

[4]Pediatric Surgery Unit, Sapienza - University of Rome, Italy

[5]Department of Clinical Science, University of Ferrara, Italy

Correspondence
Roberto De Giorgio, Department of Clinical Sciences, Internal Medicine Unit, University of Ferrara, St. Anna Hospital - Cona, Ferrara, Italy.
Emails: deg@aosp.bo.it and dgrrrt@unife.it

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Abstract

Chronic intestinal pseudo-obstruction (CIPO) is a severe form of gastrointestinal dysmotility (often due to derangement of the innervation/smooth muscle/interstitial cells of Cajal) with recurrent episodes of intestinal subocclusion mimicking a mechanical obstruction. Because of its complexity and heterogeneity, CIPO is often misdiagnosed or remains unrecognized until advanced stages. Management is a critical aspect in CIPO patient care. So far, most prokinetic drugs have not proven efficacy in restoring intestinal propulsion, thus nutritional support, fluid/electrolyte replacement, and antibiotics are the mainstay of treatment. In this issue of the journal, Ohkubo et al showed promising data indicating that percutaneous endoscopic gastro-jejunostomy (PEG-J) can be proposed as a measure for intestinal decompression, thereby improving CIPO-associated abdominal symptoms, including pain. In addition to a concise update of clinical and diagnostic features, the present minireview tackles management options, with a major emphasis on PEG-J, for CIPO patients.

KEYWORDS
chronic intestinal pseudo-obstruction, clinical manifestations, diagnosis, intestinal decompression, percutaneous endoscopic gastro-jejunostomy

1 | INTRODUCTION

Chronic intestinal pseudo-obstruction (CIPO) is a rare and debilitating condition affecting about 100 infants per year and with an estimated incidence of 0.2-0.24 per 100 000 adults per year.[1-3] CIPO patients show severe impairment of gastrointestinal (GI) propulsion ensuing symptoms/signs suggestive of partial or complete intestinal obstruction in the absence of any lesion occluding the intestinal lumen.[1-3] Abnormalities in the GI neuromuscular region, including neuropathy (either intrinsic or extrinsic), myopathy and/or interstitial cells of Cajal (ICC) network changes, individually or in combination, contribute to severe dysmotility in CIPO. CIPO is still a challenge for clinicians and surgeons because of several reasons. First, most physicians fail to recognize CIPO patients early due to their limited experience; second, symptoms shown by CIPO patients are non-specific, thus they can be mistaken with other functional GI disorders. This drawback may lead patients to be subjected to inadequate management including ineffective, and potentially dangerous, surgical procedures; third, CIPO is an 'umbrella term' covering a wide heterogeneity of patients, ie, idiopathic, with no apparent cause underlying dysmotility, vs secondary to metabolic/endocrinological, neurological, and paraneoplastic disorders; fourth, the majority of CIPO patients have a sporadic disease, while few have a genetically related background (latter presents with a syndromic phenotype, ie, in addition to the GI tract, other organs, such as heart, brain, and hematopoietic system, can be affected); finally, most CIPO patients show a variable outcome, ie, some cases may remain stable over time, whereas others rapidly worsen to unavoidable parenteral nutrition as a unique measure to prevent severe malnutrition and death. Taken together, these challenges and intrinsic difficulties surrounding CIPO hinder thorough phenotyping of patients, mechanistic studies and, more importantly, patients' management.[4,5] Nonetheless, recent data by Ohkubo et al, in the current issue

of *Neurogastroenterology and Motility*, propose percutaneous endoscopic gastro-jejunostomy (PEG-J) as a method to alleviate symptoms (including pain) and nutritional consequences related to intestinal distension, a key feature of CIPO.[6]

Prompted by the promising results of Ohkubo et al, the purpose of this minireview is to provide the readers with an update on clinical, diagnostic, and management aspects of CIPO patients.

Key Points

- Chronic intestinal pseudo-obstruction (CIPO) is one of the most severe forms of gastrointestinal dysmotility with many debilitating and potentially life-threatening symptoms/manifestations.
- Since most drugs failed to restore gastrointestinal coordinated motility, nutritional support, fluid/electrolyte replacement, and antibiotics are still mandatory as life-saving measures.
- Promising data indicate that percutaneous endoscopic gastro-jejunostomy (PEG-J) can be proposed as a measure for intestinal decompression in CIPO, thereby improving symptoms and preventing malnutrition

2 | CLINICAL FEATURES AND DIAGNOSTIC ASPECTS

Usually CIPO patients show severe symptoms and signs.[7] Abdominal pain and distension are reported/detected in most (80%) cases. Although predominantly chronic in nature, these symptoms worsen during acute subocclusive episodes.[4,5] Nausea and vomiting occur in 75% and 40%-50% of those cases and can be associated with test-proven gastroparesis; constipation occurs in 40%, while diarrhea (rarely steatorrhea) occurs in about 20%-30% of cases.[4,8,9] The latter can be related to small intestinal bacterial overgrowth (SIBO) due to intestinal stasis.[1,4,5] Malnutrition, often requiring parenteral nutrition, is another significant clinical aspect in most CIPO cases.[4,5,7] Esophageal dysmotility has been reported in approximately 70% of CIPO patients.[10] Urinary bladder dysfunction (with or without megacystis and megaureter) often coexists with CIPO, more commonly detectable in children with an underlying myopathic derangement of the GI tract.[1,4,5,8,9] Finally, CIPO patients may develop depression and/or other psychological disorders as a consequence of the disabling nature of this condition as well as of the frustrating ineffectiveness of most prokinetic drugs.[7]

So far, there is no single diagnostic test or pathognomonic finding indicative of this condition. A stepwise diagnostic approach, aimed to rule out mechanical causes of bowel obstruction, identify underlying diseases, and understand the pathophysiological features, is recommended. Evidence of air-fluid levels and dilated bowel loops in a plain radiograph of the abdomen with patients in upright position is mandatory to suspect CIPO. In current clinical practice, computerized tomography (CT) scan of the abdomen is more accurate than conventional radiology to demonstrate air-fluid levels, while ruling out mechanical causes as well as intestinal wall adhesions. Transit time examination with contrast medium has been largely replaced by dedicated enterography with high-resolution CT or magnetic resonance imaging (MRI).[11,12] Cine MRI is an emerging, non-invasive, radiation-free method to assess and monitor GI motility. Using cine-MRI, Fuyuki et al studied 33 patients and showed that the mean luminal diameter and contraction ratio in the CIPO group differed significantly from healthy volunteers. Therefore, cine MRI may be useful in detecting subtle contractile impairment of the gut in patients with CIPO, although further validation vs manometry is necessary.[13] Upper and lower GI endoscopy can contribute to exclude mechanical occlusions and collect routine biopsies. Mucosal sampling in the duodenum can help to rule out those very rare cases in which an underlying celiac disease can be associated with dysmotility, whereas biopsies throughout the upper and lower gut can be useful to unravel an eosinophilic gastroenteropathy.[14] Mucosal biopsies can also be exploited to obtain the submucosal layer with associated neural plexuses.[15] This approach may become of aid to show neural changes in patients with severe dysmotility. Finally, wireless motility and endoscopy capsules have been proposed for evaluating patients with functional bowel disease.[16,17] However, the role of these techniques in the diagnosis of CIPO has not yet been established and their use can be even potentially hazardous if a mechanical obstruction has not been firmly excluded. When imaging and endoscopy fail to show causes of intraluminal or extraluminal mechanical obstruction, secondary causes of potentially treatable pseudo-obstruction should be excluded. Screening tests for diabetes mellitus, neurotropic viruses (eg, 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), and thyroid function should be performed. Other tests include serology for Chagas' disease, urinary catecholamines, and porphyrins to rule out pheochromocytoma and porphyria, respectively, and enteric neuronal autoantibodies (eg, antinuclear neuronal antibodies [ANNA-1] also referred to as anti-Hu antibodies based on molecular target) for paraneoplastic syndrome.[1,5]

Small bowel manometry may provide pathophysiologically relevant information on the mechanisms underlying dysmotility in CIPO patients (eg, neuropathic vs myopathic patterns).[4,5,7,8] In some exceptional cases with an apparently unremarkable imaging, an accurate manometric assessment may reveal a pattern (ie, discrete clustered contractions) suggestive of a recent narrowing of the gut not yet accompanied by bowel loop dilatation above the blockade.[1,4,5,8] Manometric findings do not affect management strategies in CIPO patients, although the evidence of a propulsive pattern (ie, migrating motor complexes) predicts successful adaptation to jejunal feeding in children.[18] Esophageal manometry may predict survival, home parenteral nutrition requirement, and inability to maintain sufficient oral feeding, as emerged by a retrospective, single-center study.[10] Anorectal manometry is indicated when the clinical picture is characterized by intractable constipation and marked colonic distension

in order to exclude Hirschsprung's disease.[5] A manometric assessment of the entire GI tract, including colon, has been deemed helpful as it may provide clues about outcome of isolated or multivisceral intestinal transplantation in carefully selected pediatric CIPO.[1]

Minimally invasive procedures, eg, laparoscopic surgery or endoscopic approaches have contributed to refuel interest for histopathological analysis of full-thickness biopsies.[19] Recently, Valli et al used endoscopic, full-thickness resection (eFTR) with a full-thickness resection device under moderate propofol sedation in 4 CIPO patients with suspected neuromuscular gut disorders. Large colonic full-thickness tissue samples of excellent quality did identify neuromuscular changes in all 4 patients with no adverse events. These data suggest that eFTR allows safe and minimally invasive collection of full-thickness biopsies suitable for histological analysis in patients with neuromuscular gut disorders.[20] Guidelines proposed by an international working group have helped standardizing technical aspects (tissue collection and processing) and histopathological reporting of a variety of gut neuromuscular disorders, including CIPO.[21]

3 | MANAGEMENT

The management of CIPO patients is aimed to avoid unnecessary surgery, restore fluid and electrolyte balance, maintain an adequate caloric intake, promote coordinated intestinal motility, and treat SIBO and associated symptoms (ie, abdominal pain and distension). As experienced in daily practice, current therapeutic approaches are not very effective and this generates frustration in patients and physicians. The following are some indications recommended to improve the management of patients with CIPO.

Patients with adequate intestinal absorption should be encouraged to take small, frequent liquid meals (5-6/day), while avoiding high-fat, residue (delaying gastric emptying), and high-lactose/fructose (evoking bloating/discomfort) foods. Vitamins A, D, E, and K as well as B12 and folic acid should be supplemented when needed. Elemental feedings and dietary supplements with medium-chain triglycerides can be used in combination with aforementioned dietary changes.[1,3,5,14] In cases with inadequate oral intake, enteral nutrition with standard, non-elemental formula should be considered. Before placing a permanent feeding tube, a trial of nasogastric or nasojejunal feeding should be attempted using an enteral formula at a rate sufficient to provide an adequate caloric support. When delayed gastric emptying is present, bypassing the stomach and directing the feeding into the small intestine is recommended. Enteral nutrition starting with a slow infusion and continuous feeding or cyclical feeding (eg, overnight) is preferred to large bolus feedings.[1,5,14,22] In most severe cases, total parenteral nutrition (TPN) is necessary to maintain nutritional support and an adequate level of hydration. Complications of TPN, including liver failure, pancreatitis, glomerulonephritis, thrombosis, and sepsis, are frequent causes of morbidity and mortality in CIPO.[1,5,14,22] Personalized TPN formulations, with minimal intravenous lipid infusion, can help reducing metabolic complications. In any case, a long-term TPN does not seem to be associated with a significant increase in morbidity and mortality in CIPO as compared with other conditions requiring TPN.[23,24]

No evidence indicates that prokinetics restore propulsion; however, these drugs should be one of the most important options for patients with CIPO since they may evoke symptomatic improvement, thereby allowing oral feedings to be tolerated. Unfortunately, due to limited number of trials, most of which based on few patients, the overall efficacy of prokinetics yielded unsatisfactory results.[1,5] Nonetheless, some data should be mentioned as a basis to help clinicians in practice. Erythromycin, a macrolide antibiotic, showed efficacy at a dose of 1.5-2 g/day in adults, or 3-5 mg/kg/day in children, in accelerating gastric emptying and ameliorating symptoms of CIPO.[3,25] Metoclopramide and domperidone are known to exert their prokinetic effects via type 2 dopamine receptor antagonism and by increasing acetylcholine release in the enteric nervous system. Although widely used in most dysmotilities, clinical data for their use in CIPO are lacking. Metoclopramide should be used only for short-term period, as its chronic administration leads to a significant risk of tardive dyskinesia.[26] Octreotide is a long-acting analog of somatostatin that at a dose of 100 mcg subcutaneously/day resulted in a significant beneficial effect by relieving bacterial overgrowth and reducing pain, nausea, and bloating in scleroderma-related CIPO patients.[27] Repeated intravenous use of acetylcholinesterase inhibitor neostigmine (at a dose of 8 mg/day) was successful in an adult patient with chronic colonic pseudo-obstruction.[28] The oral formulation of acetylcholinesterase inhibitor, pyridostigmine (at a starting dose of 20 mg/day), has also been used with success in some adult CIPO patients.[29] Prucalopride, a highly selective 5-hydroxytryptamine-4 (5-HT_4) receptor agonists lacking cardiotoxicity (which caused cisapride to be withdrawn), exerts significant enterokinetic effects. In a recent randomized controlled trial with CIPO patients, prucalopride showed beneficial effects on symptoms.[30] In practice, the association of different prokinetic drugs and/or their rotation may be a strategy useful to increase therapeutic efficacy, while minimizing tachyphylaxis and side effects. Various antibiotic regimens have been recommended for SIBO treatment.[31] Non-absorbable antibiotics, such as rifaximin, can be administered, although broad-spectrum antibiotics, such as amoxicillin and clavulanic acid, gentamicin, and metronidazole, often with an antifungal compounds (eg, nystatin or fluconazole), can be used for 1- to 2-week cycles alternated with antibiotic-free periods.[5,14,31] Recently, amoxicillin-clavulanate has been demonstrated to accelerate intestinal transit in children, thus representing an interesting therapeutic option combining antibiotic and prokinetic effects.[32]

Visceral pain is major concern in patients with CIPO. The ideal treatment would be the use of non-narcotic pain modulators, such as tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and GABA analogs, but these require caution because of their significant side effects, such as constipation and/or drowsiness. Starting with low dose followed by gradual increase is recommended to optimize the beneficial effect. In patients with chronic and unsustainable visceral pain, physicians may carefully consider the use of opiate drugs paying attention to the known antimotility effects of these compounds.[1]

Since bowel distension is commonly associated with pain and other symptoms in CIPO patients, decompression therapy represents one of the key aspects in CIPO management. Apart from neostigmine (mentioned above) proved to be useful in reducing dilatation in patients with acute colonic pseudo-obstruction (also referred to as Ogilvie's syndrome),[33] so far there are no pharmacological remedies to achieve an effective, non-invasive decompression in CIPO. Current therapeutic strategies include conventional methods, ie, intermittent nasogastric suction, rectal tubes or colonoscopic decompression, and surgical procedures, such as feeding/venting gastro-/jejunostomies (or other intestinal 'ostomies'), which overall evoke symptom relief in about half of the patients.[34-38] However, conventional methods are limited by temporary efficacy in GI decompression, whereas surgery shows a high rate of stoma prolapse along with a considerable risk of dehydration due to enteric fluid loss.[37,38] Nonetheless, recent data in this issue of *Neurogastroenterology and Motility* provide new insights into the management of patients with CIPO by using percutaneous endoscopic gastrostomy (PEG), a commonly applied method for long-term home enteral nutrition.[6,39] However, PEG is often associated with aspiration pneumonia, therefore current management suggests a gastro-jejunostomy tube insertion via PEG (hence, PEG-J) as a measure to prevent such a life-threatening complication.[40] Furthermore, both PEG/PEG-J have been exploited to decompress patients with mechanical occlusion of the bowel, such as cases with malignant bowel diseases.[39] Based on this background, Ohkubo and co-workers tested whether PEG-J could be an effective measure for intestinal decompression and symptom improvement in CIPO patients. The authors enrolled 7 CIPO patients with a severe symptom profile/manifestations refractory to any pharmacological treatment. All patients required at least once nasogastric tube or transnasal small intestinal tube insertion for intestinal decompression. PEG tube (24 F caliber) was placed using the introducer method.[6,39] If distended small bowel loops were interposed between the stomach and the abdominal wall, a preceding decompression was obtained via transnasal small intestinal tube. After 7 days of gastropexy, a PEG-J tube (with a caliber of 24 F and length of 60 cm) was inserted through the PEG fistula under fluoroscopy upon removal of the PEG button (Figure 1 A-D). Evaluation of subjective symptoms (number of days without abdominal symptoms in a month) and the assessment of objective nutritional status (body mass index and serum albumin level) were evaluated in each patient before and 3 months after PEG-J. PEG placement and PEG-J tube insertion were performed without major procedure-related complications and both were well-tolerated by all patients. Also, oral intake was well maintained or improved in all patients after the procedure. A significant decrease in the number of days without abdominal symptoms was observed in 6 of 7 patients, along with the improvement of wasting and malnutrition in all patients. Plain abdominal radiographs demonstrated a reduction of abdominal distension, whereas the total volume of the small intestine did not significantly change compared with pre-PEG-J status. One patient developed severe reflux esophagitis, while another had a chemical dermatitis around the PEG-J fistula during follow-up, and in both cases, conservative therapy with proton-pump inhibitors and ointment therapy, respectively, was effective. None of the treated CIPO patients had ulcer formation and perforation due to the tube placement at 1-year follow-up after the procedure. PEG-J is, therefore, suggested as a safe and minimally invasive method to improve abdominal symptoms, including pain, and nutritional status in CIPO.[6] Depending on symptom fluctuation, the use of PEG-J can be modulated (open vs closure intervals) ensuing control of fluid output and avoiding dehydration, a common complication of conventional jejunostomy/ileostomy. Clearly, this study, based on few cases of CIPO, requires further investigation. First, a better characterization of CIPO patients is required. For example, the study by Ohkubo et al does not specify which patient category is more suitable to PEG-J insertion based on underlying pathology (eg, most severe cases—myopathic CIPO—may have a worse outcome than neuropathic CIPO to the procedure). Second, a thorough and better symptom and objective data assessment is highly recommended. Overall, patients with CIPO are unlikely to show a complete remission of symptoms; therefore, new studies using this endoscopic approach should require symptom questionnaire and severity score to determine the actual beneficial effect due to PEG-J. Finally, long-term trials designed on a larger cohort of CIPO patients are necessary to minimize the 'heterogeneity effect' of CIPO, which may hinder the plausible efficacy of PEG-J.

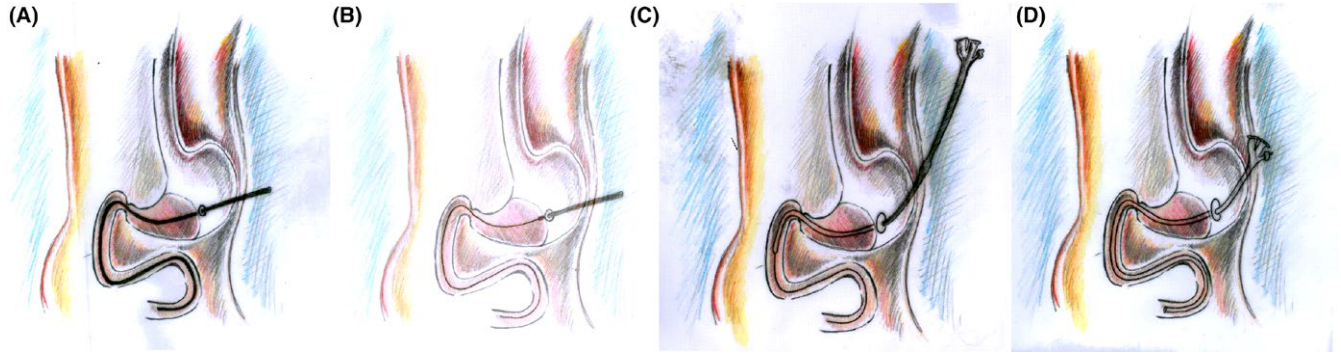

FIGURE 1 Scheme illustrating the methodology used by Ohkubo et al for obtaining intestinal decompression. An ultrathin endoscope is inserted through the percutaneous gastrostomy (PEG) in the jejunum (A). A guidewire is passed through the working channel of the endoscope, which is subsequently removed while retaining the guidewire (B). A jejunal feeding tube is delivered over the guidewire through the PEG (hence PEG-J) under fluoroscopic guidance (C and D)

4 | CONCLUSIONS

CIPO is a label that applies to the most unusual cases falling into a 'gray area' of GI functional disorders. In fact, CIPO is still a challenging condition for clinicians, surgeons, and any healthcare providers because of its complexity, heterogeneity, different natural history, and outcomes. The diagnosis is mainly clinical and largely based on patient's history, physical examination, imaging tests, and laboratory examinations. So far, CIPO treatment has been frustrating because available prokinetic drugs, aimed to restore coordinated motility, showed scarce efficacy. Thus, the main goals of CIPO management remain based on nutritional support, fluid/electrolyte restoration, antibiotics for bacterial overgrowth/infections, and control of particularly bothersome symptoms, eg, abdominal pain and distension. In this respect, PEG-J, as highlighted by Ohkubo et al, has shown promising results in eliciting intestinal decompression with resultant symptom and nutritional improvement, with minimal risk of fluid loss and dehydration. Whether PEG-J will become a safe and relatively easy decompression strategy in CIPO depends on future well-designed studies based on larger series of patients.

DISCLOSURES

No competing interests declared.

AUTHOR CONTRIBUTIONS

All authors equally contributed to this article. All authors approved the final draft of the manuscript.

ORCID

R. De Giorgio http://orcid.org/0000-0003-0867-5873

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