Residência RP Pediátrica
Publicação Oficial da Sociedade Brasileira de Pediatria

Submitted on: 12/11/2017
Approved on: 08/07/2018

ORIGINAL ARTICLE

Pseudo-pediatric chronic intestinal obstruction - A literature review

Phabyana Pereira de Araújo[1] Virgínia Resende Silva Wefford[1], Denise Maria Santos Fernandes Simão[1]

Keywords:
abdominal pain, abdominal wall, radiography, abdominal, intestinal pseudo-obstruction, pediatrics.

Abstract

This article aims to describe pediatric chronic intestinal pseudo-obstruction (POIC) disease by means of a bibliographic review addressing its clinical characteristics, diagnosis and therapeutic options. Chronic intestinal pseudo-obstruction (POIC) represents the most severe form of gastrointestinal dysmotility with debilitating and potentially lethal consequences. The symptoms may not be specific and result in incorrect or late diagnoses resulting in morbidity and even mortality. Although pediatric POIC has recurring clinical features, some specific features can be identified - which sometimes makes it difficult to identify and, consequently, treat the disease. There is no single diagnostic test or pathognomonic finding of POCH, so a phased approach, including radiology, endoscopy, laboratory, manometry and histopathology, should be considered at the diagnostic stage. The treatment of patients with POIC is challenging and requires a multidisciplinary effort with the participation of gastroenterologists, pathologists, dieticians, surgeons, psychologists and other suitably experienced subspecialists based on the presence of comorbidities. Current treatment options invariably involve surgery and specialized nutritional support, especially in children. Medical treatments are mainly aimed at avoiding complications such as sepsis or intestinal bacterial overgrowth and, whenever possible, restoring intestinal propulsion. More effective therapeutic options are eagerly awaited for patients with complications.

[1] Universidade Federal do Triangulo Mineiro (UFTM)|UFTM. Departamento Materno Infantil.

Correspondence to:
Phabyana Pereira de Araújo.
Hospital Escola da UFTM, Secretaria de Pediatria. Rua Getúlio Guaritá, nº 130, Bairro Abadia. Uberaba, MG, Brazil.
Zip Code: 38025-180. E-mail: phisiobr@hotmail.com

Residência Pediátrica 2019;9(2):138-147. DOI: 10.25060/residpediatr-2019.v9n2-10

INTRODUCTION

Chronic intestinal pseudo-obstruction (CIPO) is a rare condition, characterized by severe impairment of gastrointestinal (GI) propulsion, resulting in symptoms suggestive of partial or complete intestinal obstruction in the absence of any lesion that restricts or conceals the intestinal lumen.[1] The prognosis is quite uncertain; therefore variable, but it is in part related to the underlying disease[2], and depends on the location of the process, manifesting with concomitant extradigestive changes.

It is characterized by continuous episodes of intestinal dysfunction, in the absence of an anatomical lesion causing mechanical obstruction, considered the main symptoms and signs of this disease.[3,4] It stems from a reversible or irreversible neuromuscular alteration in the digestive tract.

CIPO pathophysiology can be classified as secondary or primary. In adults it is almost always secondary to systemic diseases such as progressive systemic sclerosis, amyloidosis and Chagas' disease.[5]

In children, the lesions are often primary, where anomalies may be individual or familial, usually congenital, or present at birth. But it can also be acquired later with an illness. They occur in the enteric smooth muscle (visceral myopathy) and in the intrinsic enteric nervous system (visceral neuropathy).[6] This classification is based on the techniques developed by Barbara Smith, based on observation of the histopathological changes that consist, among others, of silver staining.[7,8] When tests show that dysfunction is caused by non-synchronized contractions, the disease is classified as neurogenic (resulting from nerves). If the dysfunction is caused by weak or absent contractions, the disorder is classified as myogenic (resulting from muscles).

It is clinically presented in two types: acute and chronic. It can occur in individuals of all ages, even though it is more frequent in adults.

Chronic intestinal pseudo-obstruction may involve any segment of the GI tract (although the small bowel and colon are primarily affected) and represents the most severe form of GI dysmotility, with potentially lethal consequences.[9] The symptoms may not correspond specifically to CIPO, being mistaken with other diseases and consequently delaying proper diagnosis.[10] The chronicity of severe digestive symptoms, the inability to maintain adequate nutritional status without specialized support, the suboptimal efficacy of medical treatments, and limited knowledge of the syndrome by physicians are some of the major factors contributing to the poor quality of life and the high rate of morbidity and mortality of CIPO patients.[11]

Like other rare diseases with poorly defined diagnostic criteria, CIPO has a widely unknown prevalence and incidence.[12] A national survey in the USA reported that about 100 children are born with CIPO annually.[13] A more recent survey found a prevalence of 3.7 in one million children (1 in 270,000 children younger than 15 years) with the same gender incidence as seen in Japan.[14] These studies probably underestimate the actual number of new cases per year, because they do not include patients who develop CIPO symptoms later in life.

Pathophysiology in children remains poorly understood, and because of this, it is also known as idiopathic intestinal pseudo-obstruction. Most of the time, the diagnosis is difficult and the treatment is palliative.[15] However, it is known that certain factors can be considered as risk, namely: some types of neoplasia, use of certain drugs, pathologies that affect the bowel muscles, bedridden patients and cerebral palsy or other nervous system disorders.

The aim of this paper is to provide a review of CIPO in the pediatric population, specifically highlighting the main clinical aspects, symptoms, diagnosis and treatment options in childhood.

DISEASE SPECTRUM

Intestinal pseudo-obstruction (IPO) is a rare clinical disease[2], debilitating[16] and heterogeneous. This disease was first described by Dudley in 1958[17]. The term "pseudo-obstruction" refers to a group of gastrointestinal diseases with similar characteristics, which may have a variety of causes.

Chronic intestinal pseudo-obstruction (CIPO) is not a single clinical entity, it is a comprehensive term for a number of different diseases, leading to severe motor failure of the bowel. The most severe cases in the CIPO spectrum are those involving pediatric patients with prenatal (in utero) evidence of multivisceral dilatation of the hollow viscera (e.g., digestive and urinary systems), often characterized by inability to tolerate enteral nutrition and bad prognosis.[18] This clinical subset represents the most common group of pediatric patients with diffuse involvement of the GI tract.

In these cases, neuromuscular abnormalities (genetic or acquired) of the GI tract do not prevent birth, but may be severe enough to cause the onset of symptoms in the initial period of the newborn life, with reported mortality rates varying from 10% to 32%.[20]

More rarely, some cases appear to be acquired after birth, being characterized by a variable period of normality, followed by progression to intestinal insufficiency with intestinal dilatation, and often urinary dilatation as well. In some of the more aggressive forms of acquired CIPO, the histopathological analysis can detect a massive (mainly lymphocytic) inflammatory neuromuscular infiltrate, reminiscent of autoimmune pancreatic "insulin" and "insulin dependent diabetes mellitus" in childhood.[20] These CIPO cases may respond to immunosuppressive treatment when the immunity-mediated insult has not completely damaged regulatory cells, i.e., enteric nerves, Cajal interstitial cells (CIC), and smooth muscle.[21]

Other cases of pediatric CIPO may occur in patients with milder, non-specific insidious symptoms (or "irritable bowel syndrome" - such as "dyspepsia"), which may not be at risk of developing severe dysmotility. However, some of these patients progress to a classic CIPO phenotype over time. This is considered the "dark side" of the adult CIPO spectrum, i.e., a number of factors, including altered intestinal microbiota, dysfunction of the intestinal epithelial barrier, immune dysregulation and other poorly defined mechanisms may operate, individually or together, to impair neuromuscular homeostasis.[22] Patients with acute onset CIPO after abdominal surgery, i.e. mimicking a prolonged postoperative ileus, remain a largely unexplained subset of the population. Other impressive examples are the cases that occur after an ileal shunt is created to treat morbid obesity, suggesting that surgical manipulation alone may evoke neuro-myoelectric abnormalities in predisposed feeding pathways.[23]

Table 1 summarizes the CIPO classification in relation to the etiopathogenetic factors.

CLINICAL RESULTS

Chronic intestinal pseudo-obstruction may involve any segment of the GI tract and, therefore, symptoms may vary from patient to patient based on the location and extent of the involved intestinal segment. In addition, extra intestinal manifestations and malnutrition contribute to the clinical characteristics.[24]

Prenatal signs are only detected in about 20% of the cases, while 50-70% of the patients present with perinatal clinical signs (i.e. in the first month of life).

Most patients (80%) present clinical manifestations in their first year of life, while the remaining 20% present sporadic onset during the first two decades of life.[26,27] One study indicated that the median age of symptom onset in adults is 17 years.[28]

Both pediatric and adult CIPO share many clinical features, although distinctive features can be identified. In any age group, the clinical picture tends to be dominated by abdominal pain and distension (80%), which are particularly severe during acute episodes of pseudo-obstruction.[29]

Associated symptoms include nausea and vomiting (75%), constipation (40%) and diarrhea (20%).[30,31] Among acute episodes, patients may be minimally symptomatic or continue to present severe proximal (anorexia, early satiety, nausea and vomiting) and distal digestive symptoms (constipation, diffuse abdominal pain and/or distension)[27].

The prevalence and severity of acute episodes occurring at irregular intervals vary from patient to patient. Malnutrition is another significant clinical aspect in any patient with CIPO. This is due to limited oral intake, because food intake usually aggravates symptoms and intestinal malabsorption related to altered intestinal transit, often associated with dilated intestinal caterpillar sign. In about 30% of patients with CIPO, small bowel microbial overgrowth (SBMO) occurs as a result of intestinal stasis and can cause diarrhea and steatorrhea.[27]

Gastroparesis and urinary bladder dysfunction (with or without megacystis and megaureter) are co-morbidities that share similar pathophysiological mechanisms with those underlying CIPO.[34]

In addition, because of the frustrating ineffectiveness of most therapeutic interventions, patients with CIPO may develop depression or other psychological disorders.[35]

Pediatric CIPO presents a greater risk of large bowel and colonic volvulus, secondary to severe dysmotility and intestinal dilatation, congenital adhesions or simultaneous malrotation.[36]

Urological involvement is commonly identified in patients with familial and congenital forms of CIPO, particularly in the myopathic subgroup, ranging from 36% to 100%.[30] The

Table 1. CIPO etiology and classification

Primary	Secondary	Familial forms
• No demonstrable ethiopathogenic cause	• Neurological disorders	· Dominant Autosomal
	• Medtabolic disorders	· SOX 10 *
	• Paraneoplastic syndromes	· Recessive Autosomal
	• Neurotropic viruses	· RAD21 *
	• Autoimmune diseases	· SGOL1 *
	• Celia disease	· TYMP *
	• Neuromuscular disorders	· POLVO *
	• Radiation enteritis	· X-Linked
	• Endocrine disorders·	· FLNA *
	• Drugs	· L1CAM *

1. * Mutation (s) for the indicated genes.

2. FLNA, filamin; L1CAM, L1 cell adhesion molecule; POLVO, polymerase gama DNA; RAD21, coodine complex component; SGOL1, shugoshin 1-like; SOX10, SRY-BOX 10; TYMP, timidin phosphorilase; CIPO, chronic intestinal pseudo-obstruction.

Source: Nardo et al., 2017.[22] Adapted by the author, from a free translation.

findings include urinary retention secondary to bladder atony, hydronephrosis, vesicoureteral reflux, and recurrent urinary tract infections. Megacystis on prenatal ultrasound has been reported in up to 59% of patients with CIPO, and this finding may require cesarean delivery.[31]

Megacystis may be associated with a microcolon, a phenotype referred to as megacystis-microcolon-intestinal-hypoperistalsis syndrome.[9]

Another syndromic form of CIPO is represented by mitochondrial disorders, which in a large series of adults represent 19% of all CIPO patients. They are characterized by severe intestinal dysmotility, poor nutritional status and neurological manifestations; peripheral neuropathy (with mild to moderate hypoesthesia), proprioceptive ataxia, progressive external ophthalmoplegia with ptosis and hearing loss.[12]

Gastrointestinal manifestations are common upon presentation, and positive family history along with progressive neurological and nutritional deterioration should alert clinicians to search for mitochondrial disorders.[32]

The secondary systemic (i.e., associated with underlying condition) forms of CIPO are more common in adult patients when they occur at a much advanced age.[12]

Proximal muscle weakness may indicate the presence of polymyositis and dermatomyositis. Scleroderma is usually associated with cutaneous abnormalities, while the suspicion of a paraneoplastic syndrome should prompt an investigation for hidden malignancies of the lung, ovary and breast.

Finally, CIPO forms associated with Chagas' disease are common in Latin America and are characterized by a combination of dysphagia and cardiomyopathy.[33]

DIAGNOSIS

CIPO diagnosis is mainly clinical. The diagnosis of children with suspected CIPO has the following objectives: (a) to rule out mechanical causes of intestinal obstruction - this can be achieved by abdominal computed tomography (CT) or simple x-ray; (b) identify any underlying diseases by a precise laboratory workup; (c) assess the possibility of a drug-induced CIPO presentation (e.g., opioids, tricyclic antidepressants, anti-cholinergic agents, anti-Parkinsonian agents, phenothiazines); and (d) understand the pathophysiological characteristics that may direct management or support prognostic information in selected cases (particularly performing GI manometry in cases without intestinal dilation).

Therefore, a step-by-step approach (as described above) is commonly recommended in CIPO cases, and it includes radiology, endoscopy, laboratory, manometry and histopathology.

Radiology

A simple abdominal x-ray usually shows typical signs of bowel obstruction, i.e., air-fluid levels and dilated bowel loops.[12]

Air-fluid levels are best viewed in the upright position, but side views may be useful as well. In symptomatic patients without these radiographic findings, other conditions (eg, chronic constipation, irritable bowel syndrome, and functional dyspepsia) should be considered.

Fluoroscopic studies should be performed using water-soluble contrast solutions to avoid complications related to barium concretions and, concurrently, improve hydration and intestinal content transit.

The upper GI series with small bowel follow-up may reveal dilated bowels (often involving the stomach and duodenum) with very slow transit, although the latter finding may not be detectable in some pediatric cases. Intestinal malrotation can be identified in up to one-third of children with CIPO.[25]

Less common findings include diverticulosis of the small bowel (53% of patients with mitochondrial neurogastrointestinal encephalomyopathy (MNGIE), and 42% of scleroderma) and intestinal pneumatosis.[12]

Mean radiological contrast tests have recently been replaced by dedicated enterography with high resolution CT[34] or MRI, which more accurately detects mechanical obstruction and intestinal adhesions.

Cine-MRI is emerging as a non-invasive and radiation-free method to assess and monitor GI mobility, particularly in the pediatric population.[48]

Excretory urograms should be performed in patients with urinary symptoms, since neuro-myopathies can affect both the GI tract and the urinary system.

A chest CT scan may be needed to rule out small cell lung cancer in adult patients with suspected paraneoplastic CIPO. Finally, brain images may show leukoencephalopathy in CIPO, related to MNGIE.[49]

Endoscopy

Upper GI endoscopy may be useful to rule out a mechanical occlusion of the proximal small bowel and to collect duodenal biopsies in cases where celiac disease or eosinophilic gastroenteropathy are suspected.[50]

Colonoscopy can be used to rule out mechanical obstruction and to decompress the large intestine, although this maneuver rarely offers satisfactory long-term results.[37] The wireless motile capsule measures intraluminal pH, temperature, and pressure; however, the role of this technique in CIPO diagnosis has not yet been established, and its use is possibly dangerous when a mechanical obstruction has not been definitively ruled out.

Laboratory workup

Laboratory tests are aimed at finding secondary causes of CIPO. Blood tests for diabetes mellitus (i.e., hemoglobin A1C and/or postprandial blood glucose concentration), celiac disease (anti-IgA transglutaminase anti-tissue and gliadin peptides antidehyde IgG), connective tissue and skeletal disorders (antinuclear antibody, anti-double strand

DNA and SCL-70, creatine phosphokinase, aldolase) and hypothyroidism.[22]

Other tests include serology for Chagas disease, urinary catecholamines for pheochromocytoma, and enteral neuronal autoantibodies (anti-u-type or anti-neuronal antibodies) in patients with suspected paraneoplastic syndrome.

Urinary porphyrins should be tested in patients with otherwise unexplained severe abdominal pain. A complete count of blood cells, electrolytes, albumin, liver enzymes, vitamin B12, fasting cortisol, inflammatory indexes (C-reactive protein and erythrocyte sedimentation rate) are useful in all cases.[38]

Patients receiving parenteral nutrition (PN) should be closely monitored, with particular attention to fluids, electrolytes and circulating levels of trace elements. In patients with symptoms and signs suggestive of underlying mitochondrial disorder, determination of serum lactate and thymidine phosphorylase should be performed. If thymidine phosphorylase activity is markedly reduced or absent and the nucleosides are increased, then thymidine phosphorylase genetic mutations of (TFGM) and gamma-DNA polymerase (GDP) (in the case of non-toxic sensory neuropathies and disguised and ophthalmoplegia) should be tested.[32]

Manometry

Intestinal manometry may be useful in defining the pathophysiological (neuro-muscular) mechanisms involved in CIPO (e.g., neuropathy or myopathy), although it has a low diagnostic specificity and influences treatment in most pediatric patients. However, intestinal manometry can differentiate the mechanical forms of functional subocclusions, as long as the organic cause is at an early stage. The presence of prolonged and intense postprandial pressure and non-propagated contractions are a pattern suggestive of a recent mechanical obstruction.

A neuropathy is characterized by contractions with normal amplitude, although with uncoordinated patterns[10] (See Figure 1), while coordinated contractions with reduced amplitude are indicative of an enteric myopathy.

However, careful interpretation is mandatory because low-amplitude contractions may be secondary to the inability of the manometric catheter to record non-occlusive contractions when bowel loops are dilated.[12]

The antroduodenal manometry was applied extensively in children to evaluate prognosis, response to treatment and tolerance to oral feeding. In children with chronic symptoms suggestive of CIPO, normal manometry essentially rules out CIPO and should lead to consideration of emotional or fictitious disorders (eg, Munchausen's syndrome by proxy).[39]

Studies have identified abnormal esophageal manometry in PPC cases in children with CIPO.[19] Notably, only esophageal motor disorders had a significantly negative predictive value in terms of survival, need for PN at birth and inability to maintain sufficient oral feeding, suggesting the presence of a more widespread disease[40].

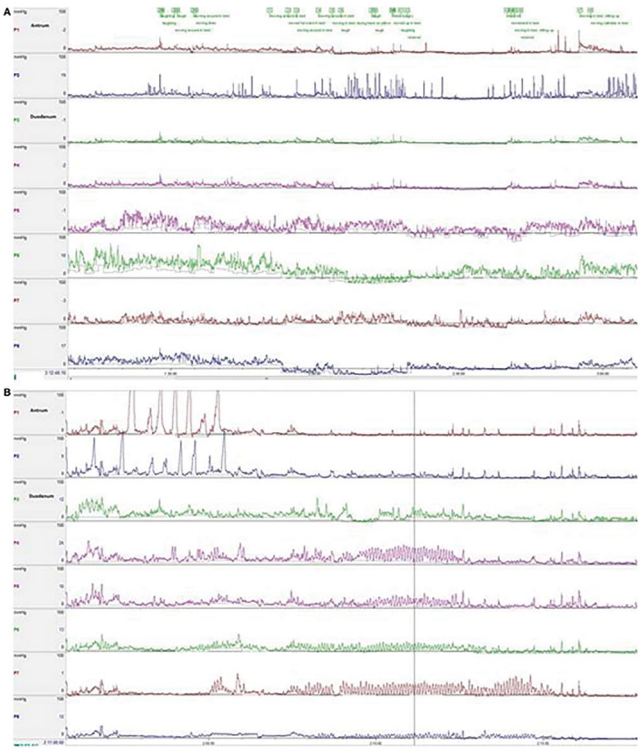


Figure 1. Manometric findings in the POIC. (A) Illustrates a monotonous pattern of phasic and tonic contractions in the small intestine of a 3-year-old boy with a congenital POIC. No migration motor complex (MMC) was detected during a 4-hour fasting study. (B) Shows an abnormal phase 3 migration of MMC with a simultaneous duodenal component in a 7-year-old girl affected by a non-congenital form of POIC.

In addition, esophageal manometry may be diagnostic of CIPO associated with scleroderma. Anorectal manometry is indicated when the clinical picture is characterized by intractable constipation and marked colonic dilation, suggesting Hirschsprung's disease.[12]

Careful gauge evaluation of the entire GI tract, including colon, is considered useful to help plan an isolated or multivisceral transplant in the most severe forms of pediatric CIPO.[13]

Histopathology

Full bowel thickness biopsies aim at providing clinicians with a histopathological correlation that can unravel abnormalities related to: (a) extrinsic and/or intrinsic neurons that control bowel functions; (b) the CCIC networks; and (c) enteric smooth muscle cells.

The changes affecting these cellular systems are closely linked to CIPO pathophysiology, and may have prognostic and sometimes therapeutic implications.[41]

Minimally invasive procedures, e.g. laparoscopic surgery or - very recently - endoscopic approaches (e.g., natural orifice transluminal endoscopic surgery), have shown high diagnostic and safety performance.[42]

In addition, the guidelines proposed by the Gastro International Working Group 2009 have helped to find consensus on technical aspects (including tissue collection and processing) and histopathological results reports on a variety of bowel neuro-muscular disorders, including CIPO.[43]

In the absence of clinical guidelines, it is suggested that ideal CIPO patients who should be referred for laparoscopic surgery for full-thickness biopsies fall into these two main categories: (a) idiopathic cases characterized by a probable acute onset of post- infectious disease; (b) patients with progressive and rapidly evolving forms of CIPO who are not under opioid treatment and do not respond to any therapeutic option.[22]

In contrast, patients with severe pain, not uniquely treated with opioids, should not undergo bowel biopsy. In such cases, it is advisable to decrease the opioids and switch to other non-opioidergic analgesic compound. This measure is designed to avoid unnecessary and often misleading histopathological analyses.[22]

In cases of CIPO with a clear origin (i.e., secondary forms of CIPO), tissue sampling may be clinically less significant, since many systemic diseases affect the neuromuscular layer of the intestine.[22]

TREATMENT

The treatment of CIPO patients is challenging and requires a multidisciplinary effort. Management of CIPO children should be geared towards avoiding unnecessary surgeries, restore fluid and electrolyte balance, maintain adequate caloric intake, promote coordinated bowel mobility, and treat complications such as sepsis, small bowel microbial overgrowth (SBMO) and associated symptoms. In general, current therapeutic approaches are not very effective; however, recent advances in nutritional, pharmacological and surgical treatment have helped to improve the management of patients with CIPO.[12]

Nutritional support

Patients with CIPO are often malnourished due to malabsorption and insufficient food intake. Patients with sufficient intestinal absorption capacity should be encouraged to eat small meals more frequently (5-6 per day), with an emphasis on liquid calories and protein intake, avoiding high-fat, high-residue foods (containing fiber).

Carbohydrate-containing foods rich in lactose and fructose may worsen abdominal bloating and discomfort.[36] Vitamin levels, i.e., A, D, E and K and B12 and folic acid, should be supplemented as necessary. In cases of inadequate oral intake, enteral nutrition with non-elemental standard formula may be considered. In children, elemental and hydrolyzed formulas are often empirically used to facilitate intestinal transit and absorption.[36,38]

Prior to placing a permanent feeding tube, one should make a test with a nasogastric or nasojejunal feeding tube using an enteral formula at a rate sufficient to provide adequate caloric support.[44]

When delayed gastric emptying is present, ignoring the stomach and directing the feeding to the small intestine is generally preferred. Jejunal feeding tubes were tolerated in all patients with manometrically detectable MMC versus 33% of those without.

Enteral nutrition should be initiated with a slow infusion given continuously or preferably cyclically (overnight).[36] In more severe cases, PN is necessary to maintain nutritional support and an adequate level of hydration. If patients depend exclusively on PN, they should receive approximately 25 kcal/kg/day, and the lipids should provide approximately 30% of the total parenteral calories, with 1.0-1.5 g/kg/day of protein and dextrose, covering the remaining caloric needs.[45]

PN complications, including hepatic failure, pancreatitis, glomerulonephritis, thrombosis and sepsis, are frequent causes of morbidity and mortality in any form of pediatric CIPO.[45] Individualized PN formulations with minimal amounts of intravenous lipids may help reduce metabolic complications.

Long-term PN does not appear to be associated with a significant increase in morbidity and mortality in CIPO patients.[45] A retrospective analysis of 51 adult patients who received PN during an average of 8.3 years presented 180 episodes of catheter-related sepsis, 9 of acute pancreatitis, 5 encephalopathies, and 4 patients progressed to cirrhosis.[24]

Oral intake was an important independent factor associated with better survival; thus, patients receiving PN should be allowed and encouraged to maximize oral intake as tolerated.[45]

Pharmacological therapy

The main objective of pharmacological treatment in CIPO patients is to promote GI propulsive activity, thus improving oral feeding, reducing symptom severity and minimizing microbial overgrowth in the small bowel (SMBO).[12]

Efficacy and major drug-related characteristics, such as erythromycin, metoclopramide, domperidone, somatostatin analogues (octreotide and lanreotide), cholinesterase inhibitors (neostigmine and pyridostigmine), serotonergic agents (such as 5-hydroxytryptamine 4-5 receptor agonists -HT4), for example, prucalopride), prostaglandins and analogues of gonadotrophin releasing hormone (leuprolide) have been reported in several pediatric CIPO studies. Erythromycin is a macrolide antibiotic mimicking motile procyanin hormone that induces phase III of MMC. Efficacy (at a dose of 1.5-2 g/day in adults or 3-5 mg/kg/dose in children) was found to accelerate gastric emptying and to improve CIPO symptoms in case reports.[46]

Metoclopramide and domperidone are two orthopramides that exert their prokinetic effects through of dopamine type 2 receptors' antagonism and increase the

release of acetylcholine from the myenteric neurons. Although widely used in patients with functional bowel disorders,[10] there is no clinical data concerning their use in CIPO.

In addition, metoclopramide has a upper-case warning by the Food and Drug Administration because of the risk of late dyskinesia.[47]

Octreotide, a long-acting analogue of somatostatin, is known to evoke phase III of MMC in the small bowel of patients with scleroderma-related CIPO. Subcutaneous octreotide at a dose of 50 µg/day resulted in a significant beneficial effect, reducing bacterial overgrowth in these patients.[48]

Other studies have confirmed its efficacy, showing reduction of nausea, vomiting, abdominal disorders and pain, in a subset of idiopathic CIPO. The acetylcholinesterase inhibitor neostigmine has demonstrated efficacy in colonic decompression in adult and pediatric acute colonic pseudo-obstruction cases.[49]

Repeated use was successful in an adult patient with colonic pseudo-obstruction, although chronic use in children with CIPO has not been reported.[50] Long-acting pyridostigmine has also been used successfully in adult patients with CIPO.[51] Among the newly selected 5-HT4 receptor agonists discovered recently, prucalopride showed high bioavailability and lack of important interactions with other drugs, since it is not metabolized by the P3A4cytochrome.[52]

Prucalopride exerts significant effects of enterokinetics[53], and a recent randomized controlled trial in patients with CIPO (three patients had visceral myopathy, one with visceral neuropathy, all treated with 2-4 mg once daily and followed for 48 weeks) reported beneficial symptomatic effects and less use of analgesic drugs.[54] Although the sample size was very small, the results of this study help future controlled multicenter trials.

Excessive bacterial growth in the small intestine is known to cause mucosal inflammation, which further impairs GI mobility, thus helping cause nausea and abdominal distension.[12] Several antibiotic regimens have been recommended. Treatment of choice usually involves the use of non-absorbable antibiotics, such as rifaximin.[55]

However, most clinicians use 1 to 2-week rotations of broad-spectrum antibiotics, such as amoxicillin and clavulanic acid, gentamicin and metronidazole, often combined with an antifungal compound (e.g., nystatin or fluconazole), followed by periods without antibiotics.[12]

Notably, amoxicillin-clavulanate has been shown to combine antibiotic and enterokinetic properties in children. Non-narcotic pain modulators, such as tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors, should be used with caution in patients with CIPO because of their significant side effects (e.g., constipation and/or drowsiness). It is advisable to start with low doses followed by a gradual increase to optimize the benefit/side effects ratio. Gabapentinoids (gabapentin and pregabalin) and peripheral action µ opioid receptor antagonists may represent promising alternatives to antidepressants; however, there is a lack of studies in CIPO patients.

If visceral pain is not treated, an extremely careful and cautious use of opiates can be attempted. In children with CIPO and significant abdominal pain, transdermal buprenorphine (5 µg/h), an µ partial agonist and κ and δ opioid receptor antagonist, showed adequate pain relief in 3 of 4 patients.[56]

In CIPO characterized by histopathological signs of marked inflammation/immune response in the myenteric ganglia or along the neuromuscular tract, immunosuppressive drugs (e.g., steroids and azathioprine) may be an effective therapeutic option.[57]

Treatment of secondary forms of CIPO is directed primarily to the underlying diseases (e.g., scleroderma, paraneoplastic syndrome, endocrine-related disorders, and many others), as well as targeted bowel therapy such as antibiotics, prokinetics and laxatives.

Endoscopic therapy and surgery

The decomposition of distended GI segments through intermittent nasogastric suction, rectal tubes or endoscopy in adults and children is an important therapeutic target.[12] In some cases, a "ventilation" enterotomy, usually placed endoscopically in the bowel, may be required.

Recently, repetitive colonoscopic decompression was successfully used as bridge therapy prior to surgery in a pregnant woman with CIPO.[58]

In adult patients requiring multiple endoscopic decompression, percutaneous endoscopic colostomy has recently been proposed as a viable therapeutic option as it leads to durable relief of symptoms without the risks of a surgical intervention.[59]

The role of surgery in CIPO has been debated over the years. Although its use may be indicated as a tool for collecting intestinal biopsy specimens for histopathology. The need for surgical therapy is sometimes necessary in emergencies (massive intestinal distention and perforation/ischemia).

Studies in children with CIPO present palliative procedures, such as feeding/ventilation, gastrostomies and jejunostomies mainly used to alleviate symptoms in half of the patients.[60] It is important to keep in mind that when a surgical procedure is performed on a patient with CIPO, full thickness biopsies should be obtained and processed in dedicated centers.

Transplantation

Intestinal (single or multivisceral) transplantation is considered a reasonable therapeutic alternative for patients with CIPO who have severe complications of PN (e.g. liver failure or recurrent sepsis due to a central venous catheter). Other indications for transplantation are the inability to obtain venous access for PN and poor quality of life during PN.[61]

Bowel transplantation is the only possible cure for patients with intestinal failure who develop severe

complications related to prolonged PN use. The patient's overall precocious survival has improved significantly in recent years.[62] "The most recent results show more than 2,000 of these transplants performed in more than 60 centers worldwide, with 50% of the recipients alive and largely independent of TPN."[62] Patients with CIPO represent approximately 9% of total intestinal transplants in adults and children.[63]

Patients with CIPO should be evaluated for urological abnormalities, and antibiotic prophylaxis for urinary tract infections is often required after transplantation in these patients. The development of new immunosuppressive agents, such as tacrolimus and new induction agents (basiliximab, alemtuzumab, daclizumab and anti-lymphocyte globulins) has been associated with an increased overall survival rate and reduced graft rejection.[64]

Complications include acute rejection, opportunistic infections - cytomegalovirus and Epstein-Barr viruses; and surgical morbidity including wound infections, stoma-related complications, graft ischemia, intestinal perforations, delayed gastric emptying, intestinal obstruction and biliary tract dilatation.

In the presence of gastric involvement, the modified multivisceral transplant (stomach-duodenum-pancreas plus small intestine) should be performed, although some reports describe the possibility of overcoming this problem by transplanting the bowel and surgically modifying the stomach to facilitate gastric emptying.

In children, PN-related liver failure is an indication for combined liver and intestinal transplantation, but a complete multivisceral graft (modified multivisceral graft plus liver) is rarely required. Although isolated small intestinal and hepatic-intestinal transplantation have reasonable long-term results, multivisceral transplantation should be performed only in highly selected cases and in experienced centers.

When an underlying treatable disease is not identified, a severe clinical course may be expected for pediatric patients with CIPO.[27] A single center study of 59 adult patients with idiopathic CIPO followed for a long time (13 years) demonstrated that the mean time between the first subocclusive episode and the diagnosis of CIPO was 8 years, with 88% of the patients submitted to a mean of 3 unnecessary surgical procedures.[27]

Studies of idiopathic pediatric CIPO demonstrate that the mean time between the first subocclusive episode and the diagnosis of CIPO was 8 years, with 88% of the patients submitted to an average of 3 unnecessary surgical procedures.[19]

Similar rates of questionable surgery are found in the pediatric setting.[19] Digestive symptoms worsened over time, with abdominal pain becoming intractable or responsive only to stronger analgesics (e.g., opioids - always used parsimoniously and with extreme caution in our own experience) in approximately 25% of cases. Most patients had oral feeding restrictions, while 30-50% of the patients required long-term PN.[24,27,65]

A study by Amiot et al.[24], examined all patients at home with CIPO in parenteral nutrition (PN), showed that lower mortality was associated with the ability to restore oral feeding and the presence of symptoms before 20 years of age, while an increase in mortality was associated with the presence of scleroderma.

Manometric parameters, such as inadequate or absent motor response to meals, absence of migratory motor complex (MMC) during fasting and generalized hypomotility were shown to be predictors of poor outcome in patients with CIPO.[66]

Finally, the detection of esophageal dysmotility in CIPO appears to have negative prognostic implications in terms of mortality and need for home-administered PN.[40] In children with CIPO, a myopathic etiology, coexisting urinary involvement and simultaneous intestinal malrotation are poor prognostic factors.[25]

The risk of death is increased by the absence of a specialized team and in the early stages after the diagnosis of intestinal insufficiency has been established.[44]

CONCLUSION

Chronic intestinal pseudo-obstruction is a rare and serious condition that results in a marked impairment of GI motility with the appearance of a mechanical obstruction without any detectable mechanical cause.

While still a challenge for most clinicians and surgeons, the future of CIPO may be more promising than expected due to a number of important achievements.

First, less invasive diagnostic tests, such as cine-MRI and even endoscopic approaches for full-thickness biopsy sampling, are innovative tools that should facilitate the identification and investigation of patients with CIPO.

The classification of myopathies and enteral neuro-ICC guidelines for tissue processing and analysis represents a trademark for finding new specific therapeutic options.

Mykines - prokinetic agents are in the pharmaceutical pipeline ready to be tested in clinical trials. It is also concluded that intestinal transplantation is improving as confirmed by recently published studies.

Finally, the advances obtained so far and expected in the coming years are likely to educate CIPO patients, their management and related therapeutic options.

ACKNOWLEDGMENTS

First, I thank God for the wisdom I gained in this long journey.

To my family, especially to my husband, who supported me in making this dream come true.

To those who have been with me at all times and to my masters who instructed me to exercise the art of caring for others.

To my Professors, Advisors and assistant advisors, for their dedication to guide me so that this study could be completed.

Thank you all very much!

REFERENCES

1. Connor FL, Di Lorenzo C. Chronic intestinal pseudo-obstruction: assessment and management. Gastroenterology. 2006;130(2 Suppl 1):S29-36.
2. Teixeira C, Lima R, Ferreira H, Recamen M, Martins E, Ramos A, et al. Pseudo-obstrução Intestinal - Caso Clínico. Nascer Crescer. 2006;15(2):91-6.
3. Wyllie R. Chronic intestinal pseudoobstruction. In: Behrman RE, Kliegman RM, Jenson HB, eds. Nelson Textbook of Pediatrics. 17th ed. Philadelphia: WB Saunders; 2003. p. 1138-9.
4. Almeida PS, Penna FJ. Chronic Intestinal Pseudo-obstruction in Childhood. Int Pediatrics. 2000;15(2):83-90.
5. Krishnamurthey S, Schuffler MD. Pathology of neuromuscular disorders of the small intestine and colon. Gastroenterology. 1987;93(3):610-39.
6. Mann SD, Debinski HS, Kamm MA. Clinical characteristics of chronic idiopathic intestinal pseudo-obstruction in adults. Gut. 1997;41(5):675-81.
7. Smith B. Disorders of the myenteric plexus. Gut. 1970;11(3):271-4.
8. Smith B. The neuropathology of pseudo-obstruction of intestine. J Physiol (London). 1978;284:103-9.
9. Yeung AK, Di Lorenzo C. Primary gastrointestinal motility disorders in childhood. Minerva Pediatr. 2012;64(6):567-84.
10. Stanghellini V, Cogliandro RF, de Giorgio R, Barbara G, Salvioli B, Corinaldesi R. Chronic intestinal pseudo-obstruction: manifestations, natural history and management. Neurogastroenterol Motil. 2007;19(6):440-52.
11. Stanghellini V, Camilleri M, Malagelada JR. Chronic idiopathic intestinal pseudoobstruction: clinical and intestinal manometric findings. Gut. 1987;28(1):5-12.
12. De Giorgio R, Cogliandro RF, Barbara G, Corinaldesi R, Stanghellini V. Chronic intestinal pseudo-obstruction: clinical features, diagnosis, and therapy. Gastroenterol Clin North Am. 2011;40(4):787-807.
13. Di Lorenzo C. Pseudo-obstruction: current approaches. Gastroenterology. 1999;116(4):980-7.
14. Muto M, Matsufuji H, Tomomasa T, Nakajima A, Kawahara H, Ida S, et al. Pediatric chronic intestinal pseudo-obstruction is a rare, serious, and intractable disease: a report of a nationwide survey in Japan. J Pediatr Surg. 2014;49(12):1799-803.
15. Almeida OS, Penna FJ. Pseudo-obstrução intestinal crônica na infância - relato de sete casos. J Pediatr. 2000;76(6):453-7.
16. Colin DR, Hyman PE, Altschuler SM, Christensen J, Colletti RB, Cucchiara S, et al. Diagnosis and treatment of chronic intestinal pseudo-obstruction in children: report of consensus workshop. J Pediatr Gastroenterol Nutr. 1997;24(1):102-12.
17. Dudley HA, Sinclair IS, Mclaren IF, McNair TJ, Newsam JE. Intestinal pseudo--obstruction. J R Coll Surg Edinb. 1958;3(3):206-17.
18. Mousa H, Hyman PE, Cocjin J, Flores AF, Di Lorenzo C. Long-term outcome of congenital intestinal pseudoobstruction. Dig Dis Sci. 2002;47(10):2298-305.
19. Faure C, Goulet O, Ategbo S, Breton A, Tounian P, Ginies JL, et al. Chronic intestinal pseudo-obstruction syndrome: clinical analysis, outcome, and prognosis in 105 children. French-Speaking Group of Pediatric Gastroenterology. Dig Dis Sci. 1999;44(5):953-9.
20. De Giorgio R, Guerrini S, Barbara G, Stanghellini V, De Ponti F, Corinaldesi R, et al. Inflammatory neuropathies of the enteric nervous system. Gastroenterology. 2004;126(7):1872-83.
21. Schäppi MG, Smith VV, Milla PJ, Lindley KJ. Eosinophilic myenteric ganglionitis is associated with functional intestinal obstruction. Gut. 2003;52(5):752-5.
22. Di Nardo G, Di Lorenzo C, Lauro A, Stanghellini V, Thapar N, Karunaratne TB, et al. Chronic intestinal pseudo-obstruction in children and adults: diagnosis and therapeutic options. Neurogastroenterol Motil. 2017;29(1):e12945.
23. Weiner P, Shlum H, Ganam R, Plavnick L. Colonic pseudo-obstruction: a late complication of jejunoileal bypass. Isr J Med Sci. 1984;20(5):405-6.
24. Amiot A, Joly F, Alves A, Panis Y, Bouhnik Y, Messing B. Long-term outcome of chronic intestinal pseudo-obstruction adult patients requiring home parenteral nutrition. Am J Gastroenterol. 2009;104(5):1262-70.
25. Heneyke S, Smith VV, Spitz L, Milla PJ. Chronic intestinal pseudo-obstruction: treatment and long term follow-up of 44 patients. Arch Dis Child. 1999;81(1):21-7.
26. Sodhi N, Camilleri M, Camoriano JK, Low PA, Fealey RD, Perry MC. Autonomic function and motility in intestinal pseudo-obstruction caused by paraneoplastic syndrome. Dig Dis Sci. 1989;34(12):1937-42.
27. Stanghellini V, Cogliandro RF, De Giorgio R, Barbara G, Morselli-Labate AM, Cogliandro L, et al. Natural history of chronic idiopathic intestinal pseudo-obstruction in adults: a single center study. Clin Gastroenterol Hepatol. 2005;3(5):449-58.
28. Cogliandro RF, Antonucci A, De Giorgio R, Barbara G, Cremon C, Cogliandro L, et al. Patient-reported outcomes and gut dysmotility in functional gastrointestinal disorders. Neurogastroenterol Motil. 2011;23(12):1084-91.
29. Pini Prato A, Rossi V, Fiore M, Avanzini S, Mattioli G, Sanfilippo F, et al. Megacystis, megacolon, and malrotation: a new syndromic association? Am J Med Genet A. 2011;155A(8):1798-802.
30. Lapointe SP, Rivet C, Goulet O, Fekete CN, Lortat-Jacob S. Urological manifestation associated with chronic intestinal pseudo-obstruction in children. J Urol. 2002;168(4 Pt 2):1768-70.
32. Amiot A, Tchikviladzé M, Joly F, Slama A, Hatem DC, Jardel C, et al. Frequency of mitochondrial defects in patients with chronic intestinal pseudo-obstruction. Gastroenterology. 2009;137(1):101-9.
33. Taverna JA, Babiker HM, Yun S, Bishop MC, Lau-Braunhut S, Meyer PN, et al. The great masquerader of malignancy: chronic intestinal pseudo--obstruction. Biomark Res. 2014;2(1):23.
34. Merlin A, Soyer P, Boudiaf M, Hamzi L, Rymer R. Chronic intestinal pseudo--obstruction in adult patients: multidetector row helical CT features. Eur Radiol. 2008;18(8):1587-95.
35. Menys A, Butt S, Emmanuel A, Plumb AA, Fikree A, Knowles C, et al. Comparative quantitative assessment of global small bowel motility using magnetic resonance imaging in chronic intestinal pseudo-obstruction and healthy controls. Neurogastroenterol Motil. 2016;28(3):376-83.
36. Gabbard SL, Lacy BE. Chronic intestinal pseudo-obstruction. Nutr Clin Pract. 2013;28(3):307-16.
37. Attar A, Kuoch V, Ducreux M, Benamouzig R, Malka D. Simultaneous decompression colonoscopy and radiologic G-tube insertion in a patient with megacolon because of chronic colonic pseudo-obstruction. Gastrointest Endosc. 2005;62(6):975-6.
38. Lyford G, Foxx-Orenstein A. Chronic Intestinal Pseudoobstruction. Curr Treat Options Gastroenterol. 2004;7(4):317-25.
39. Cucchiara S, Borrelli O, Salvia G, Iula VD, Fecarotta S, Gaudiello G, et al. A normal gastrointestinal motility excludes chronic intestinal pseudoobstruction in children. Dig Dis Sci. 2000;45(2):258-64.
40. Amiot A, Joly F, Cazals-Hatem D, Merrouche M, Jouet P, Coffin B, et al. Prognostic yield of esophageal manometry in chronic intestinal pseudo--obstruction: a retrospective cohort of 116 adult patients. Neurogastroenterol Motil. 2012;24(11):1008-e542.
41. Waseem SH, Idrees MT, Croffie JM. Neuroenteric Staining as a Tool in the Evaluation of Pediatric Motility Disorders. Curr Gastroenterol Rep. 2015;17(8):30.
42. Knowles CH, Veress B, Tornblom H, Wallace S, Paraskeva P, Darzi A, et al. Safety and diagnostic yield of laparoscopically assisted full-thickness bowel biopsy. Neurogastroenterol Motil. 2008;20(7):774-9.

43. Giordano C, Sebastiani M, De Giorgio R, Travaglini C, Tancredi A, Valentino ML, et al. Gastrointestinal dysmotility in mitochondrial neurogastrointestinal encephalomyopathy is caused by mitochondrial DNA depletion. Am J Pathol. 2008;173(4):1120-8.
44. Pironi L, Joly F, Forbes A, Colomb V, Lyszkowska M, Baxter J, et al.; Home Artificial Nutrition & Chronic Intestinal Failure Working Group of the European Society for Clinical Nutrition and Metabolism (ESPEN). Long-term follow-up of patients on home parenteral nutrition in Europe: implication for intestinal transplantation. Gut. 2011;60(1):17-25.
45. Pironi L, Arends J, Bozzetti F, Cuerda C, Gillanders L, Jeppesen PB, et al.; Home Artificial Nutrition & Chronic Intestinal Failure Special Interest Group of ESPEN. ESPEN guidelines on chronic intestinal failure in adults. Clin Nutr. 2016;35(2):247-307.
46. Emmanuel AV, Shand AG, Kamm MA. Erythromycin for the treatment of chronic intestinal pseudo-obstruction: description of six cases with a positive response. Aliment Pharmacol Ther. 2004;19(6):687-94.
47. Rao AS, Camilleri M. Review article. Metoclopramide and tardive dyskinesia. Aliment Pharmacol Ther. 2010;31(1):11-9.
48. Soudah HC, Hasler WL, Owyang C. Effect of octreotide on intestinal motility and bacterial overgrowth in scleroderma. N Engl J Med. 1991;325(21):1461-7.
49. Gmora S, Poenaru D, Tsai E. Neostigmine for the treatment of pediatric acute colonic pseudo-obstruction. J Pediatr Surg. 2002;37(10):E28.
50. Calvet X, Martinez JM, Martinez M. Repeated neostigmine dosage as palliative treatment for chronic colonic pseudo-obstruction in a patient with autonomic paraneoplastic neuropathy. Am J Gastroenterol. 2003;98(3):708-9.
51. O'Dea CJ, Brookes JH, Wattchow DA. The efficacy of treatment of patients with severe constipation or recurrent pseudo-obstruction with pyridostigmine. Colorectal Dis. 2010;12(6):540-8.
52. Sanger GJ. Translating 5-HT receptor pharmacology. Neurogastroenterol Motil. 2009;21(12):1235-8.
53. Camilleri M, Deiteren A. Prucalopride for constipation. Expert Opin Pharmacother. 2010;11(3):451-61.
54. Emmanuel AV, Kamm MA, Roy AJ, Kerstens R, Vandeplassche L. Randomised clinical trial: the efficacy of prucalopride in patients with chronic intestinal pseudo-obstruction--a double-blind, placebo-controlled, cross--over, multiple n = 1 study. Aliment Pharmacol Ther. 2012;35(1):48-55.
55. Pimentel M. Review of rifaximin as treatment for SIBO and IBS. Expert Opin Investig Drugs. 2009;18(3):349-58.
56. Prapaitrakool S, Hollmann MW, Wartenberg HC, Preckel B, Brugger S. Use of buprenorphine in children with chronic pseudoobstruction syndrome: case series and review of literature. Clin J Pain. 2012;28(8):722-5.
57. Ooms AH, Verheij J, Hulst JM, Vlot J, van der Starre C, de Ridder L, et al. Eosinophilic myenteric ganglionitis as a cause of chronic intestinal pseudo--obstruction. Virchows Arch. 2012;460(1):123-7.
58. Kim JS, Lee BI, Kim BW, Choi H, Lee YS, Maeng L. Repetitive Colonoscopic Decompression as a Bridge Therapy before Surgery in a Pregnant Patient with Chronic Intestinal Pseudo-Obstruction. Clin Endosc. 2013;46(5):591-4.
59. Küllmer A, Schmidt A, Caca K. Percutaneous endoscopic cecostomy (introducer method) in chronic intestinal pseudo-obstruction: report of two cases and literature review. Dig Endosc. 2016;28(2):210-5.
60. Pakarinen MP, Kurvinen A, Koivusalo AI, Ruuska T, Mäkisalo H, Jalanko H, et al. Surgical treatment and outcomes of severe pediatric intestinal motility disorders requiring parenteral nutrition. J Pediatr Surg. 2013;48(2):333-8.
61. Pironi L, Spinucci G, Paganelli F, Merli C, Masetti M, Miglioli M, et al. Italian guidelines for intestinal transplantation: potential candidates among the adult patients managed by a medical referral center for chronic intestinal failure. Transplant Proc. 2004;36(3):659-61.
62. David AI, Alves FL, D'Albuquerque LAC. Análise da implementação de um programa de transplante intestinal e multivisceral no Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo – Sistema único de Saúde, através da metodologia PMBOK. JBT J Bras Transpl. 2012;15(3):1651-88.
63. Millar AJ, Gupte G, Sharif K. Intestinal transplantation for motility disorders. Semin Pediatr Surg. 2009;18(4):258-62.
64. Sudan DL, Chinnakotla S, Horslen S, Iyer K, Fox I, Shaw B, et al. Basiliximab decreases the incidence of acute rejection after intestinal transplantation. Transplant Proc. 2002;34(3):940-1.
65. Lindberg G, Iwarzon M, Tornblom H. Clinical features and long-term survival in chronic intestinal pseudo-obstruction and enteric dysmotility. Scand J Gastroenterol. 2009;44(6):692-9.
66. Di Lorenzo C, Flores AF, Buie T, Hyams PE. Intestinal motility and jejunal feeding in children with chronic intestinal pseudo-obstruction. Gastroenterology. 1995;108(5):1379-85.