

Chronic Intestinal Pseudo-obstruction: Assessment and Management

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The spectrum of motility disorders ranges from relatively benign conditions such as gastroesophageal reflux and functional dyspepsia to life-threatening illnesses such as chronic intestinal pseudo-obstruction (CIPO). Motility disorders account for up to 15% of pediatric patients with intestinal failure.¹ In other more common causes of intestinal failure, such as short gut syndrome, abnormal motility also plays an important role in determining whether patients will be able to be weaned from parenteral nutrition. Pseudo-obstruction represents the most severe form of motility disorder and may be considered an insufficiency of the intestinal pump, very much like heart failure is caused by an insufficiency of the cardiac pump. Although this review focuses mostly on CIPO, much of the information about pathophysiology and diagnostic and therapeutic approaches is applicable to other less severe forms of motility disorders.

Pseudo-obstruction may be congenital or acquired, primary or secondary (Table 1).² In most pediatric cases, symptoms are present from birth or early infancy.³ Regardless of the underlying cause, 2 main groups can be identified based on histopathology and patterns of motility abnormalities: visceral myopathy and visceral neuropathy. Neuropathic disorders are more common and may be primary (sometimes familial) or secondary (eg, in utero insults such as fetal alcohol syndrome or postnatal injuries such as ischemic events or viral infections). Mitochondrial disorders such as mitochondrial neurogastroencephalopathy also may be complicated by neuropathic pseudo-obstruction,⁴ with the gastrointestinal symptoms often preceding the neurologic dysfunction. Recently, abnormalities of the gastrointestinal pacemaker cells, the interstitial cells of Cajal, have been described in patients with motility disorders.^{5–8} Functionally, these patients may have features of both myopathy and neuropathy. Motility problems also may complicate structural gastrointestinal abnormalities. Patients with a history of malrotation, atresia, enterocolitis, or gastroschisis repair frequently have abnormal motility in the remaining gut, limiting tolerance of enteral feeds even when the length

of residual small bowel apparently is sufficient.³ Animal studies have shown that ischemic insults and exposure to amniotic fluid have additive deleterious effects on gastrointestinal motility, with the potential to cause long-term dysfunction.^{9–12} Damage is progressive throughout gestation.¹⁰ However, in human beings, deliberate premature delivery of fetuses affected by gastroschisis has not been found to be beneficial.¹³

Treatable causes of CIPO are rare but should be considered in every case because of the potential value of specific therapy. In some cases of delayed maturation of the enteric nervous system or of the interstitial cells of Cajal, resolution may be spontaneous.⁸ In other conditions such as celiac disease,¹⁴ hypothyroidism,^{15,16} Kawasaki disease,¹⁷ and cystic fibrosis with meconium ileus or distal intestinal obstruction syndrome, treatment of the underlying disease may improve or reverse severe dysmotility. Pseudo-obstruction has been described in association with DNA viruses such as Herpes simplex, Epstein-Barr virus, and cytomegalovirus.^{18–20} Such cases of dysmotility after specific viral infections theoretically may respond to antiviral therapy, although clinical data are lacking. Rare cases of autoimmune myositis also have been reported with symptoms of pseudo-obstruction improving with corticosteroid therapy.²¹ Similarly, some cases of CIPO in children and young adults appear to be caused by autoimmune lymphocytic destruction of myenteric ganglia.^{22,23} In these cases, anti-Hu (antineuronal nuclear, ANNA-1) antibodies appear to be a useful serologic marker.^{22,23} Cases of eosinophilic myenteric ganglionitis also have been described.²⁴ Although uncommon, these inflammatory and autoimmune cases are important to identify because they may respond to anti-inflammatory medications.^{22–24}

Abbreviations used in this paper: CIPO, chronic intestinal pseudo-obstruction.

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Table 1. Causes of Chronic Intestinal Pseudo-obstruction

Muscle Disorders
Myotonic dystrophy
Duchenne muscular dystrophy
Postoperative
Small bowel ileus
Colonic pseudo-obstruction
Autoimmune
Generalized
SLE
Scleroderma
Dermatomyositis
Polymyositis
Celiac disease
Gastrointestinal
Autoimmune myositis
Autoimmune ganglionitis
Oncology/haematology
Chemotherapy and/or bone marrow/stem cell transplant
Pheochromocytoma
Ganglioneuroblastoma (paraneoplastic syndrome)
Small cell carcinoma (paraneoplastic syndrome)
Multiple myeloma
Sickle cell disease
Infectious/post-infectious
Chagas disease
Cytomegalovirus
Herpes zoster
Epstein Barr virus
Kawasaki disease
Endocrine
Diabetes mellitus
Hypoparathyroidism
Hypothyroidism
Metabolic
Mitochondrial cytopathies
Toxins
Fetal alcohol syndrome
Jellyfish envenomation
Drugs
Diltiazem and nifedipine
Cyclopentolate/phenylephrine eye drops (neonates)
Developmental
Delayed maturation of interstitial cells of Cajal
Miscellaneous
Ehlers Danlos syndrome
Eosinophilic gastroenteritis
Angioedema
Crohn's disease
Radiation injury

Assessment

Radiology

In CIPO, abdominal radiographs may show dilated loops of small bowel and air-fluid levels, except in patients who are not being fed and have venting enterostomies. Contrast radiology should be performed using water-soluble material to avoid the formation of barium concretions in the colon. Upper gastrointestinal series with small-bowel follow-through studies show dilated loops of bowel with very slow transit through a feature-

less intestine (**Figure 1**). Because contrast material often becomes diluted in fluid-filled bowel loops, recognition of mucosal details and detection of partial bowel obstruction may be arduous.

Manometry

Antroduodenal manometry is used to determine the pathophysiology of symptoms in CIPO.²⁵ Antroduodenal manometry assesses contraction amplitude and spatial and temporal organization of phasic contractions. The presence of normal patterns, such as the migrating motor complex in fasting (**Figure 2**), and a change to postprandial motility pattern with a test meal indicate intact enteric neuromuscular function. Manometry is useful to distinguish myopathy, in which contraction amplitude is reduced but spatial and temporal organization is preserved (**Figure 3**), from neuropathy, in which contractions have normal amplitude but are uncoordinated and lack normal physiologic patterns. Intrinsic or visceral neuropathy is characterized by abnormal (**Figure 4**) or even absent phase III of the migrating motor

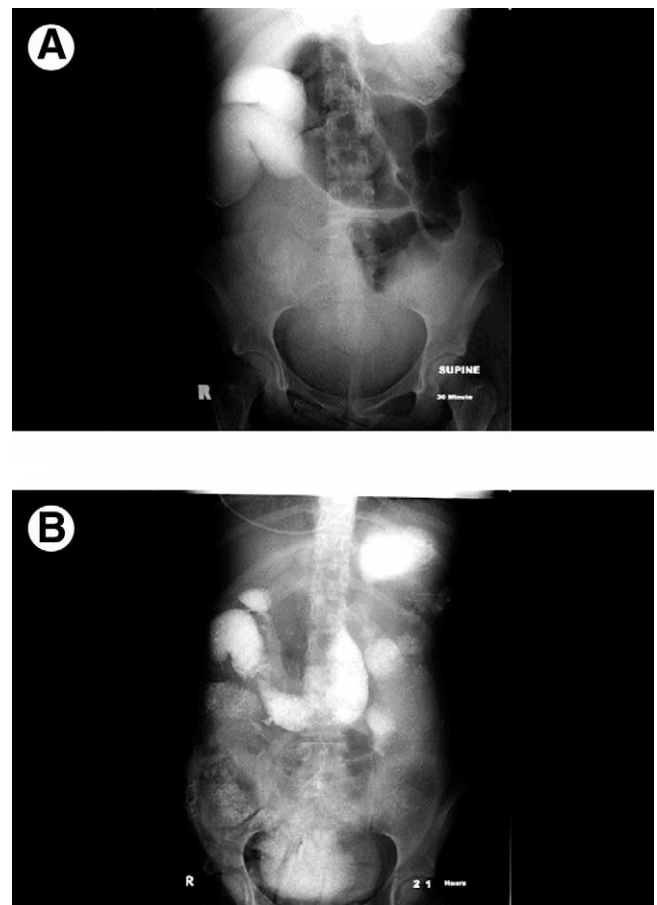


Figure 1. Upper-gastrointestinal series with small-bowel follow-through in a child with CIPO. Note the dilated loops of (A) small bowel and the (B) slow transit with dilution of the contrast material.

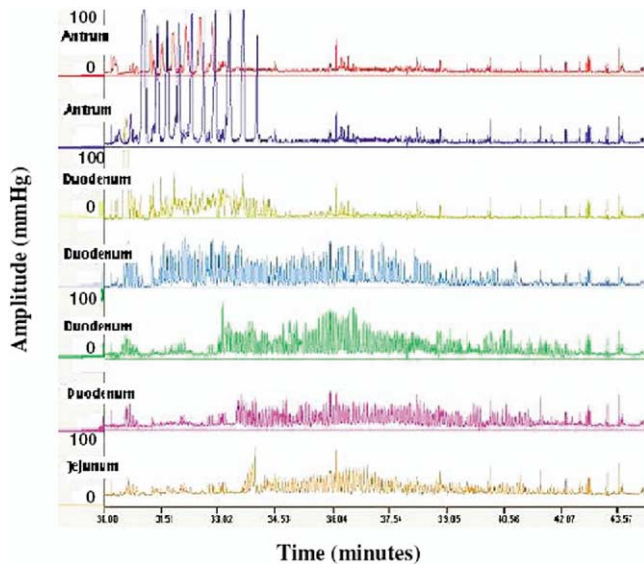


Figure 2. Phase III motor migrating complex originating from the antrum and migrating distally.

complex, the most recognizable motor pattern during fasting. A normal motor response to food is dependent on the integrity of both intrinsic and extrinsic neural control systems, and the gastrointestinal smooth muscle. In the presence of normal amplitude contractions, an impaired or even absent motor response to food may occur in both visceral neuropathy and extrinsic autonomic neuropathy.²⁶ In the presence of severe, long-standing disease with intestinal dilatation, antroduodenal manometry recordings may be nonspecific, with negligible contractile activity detected.

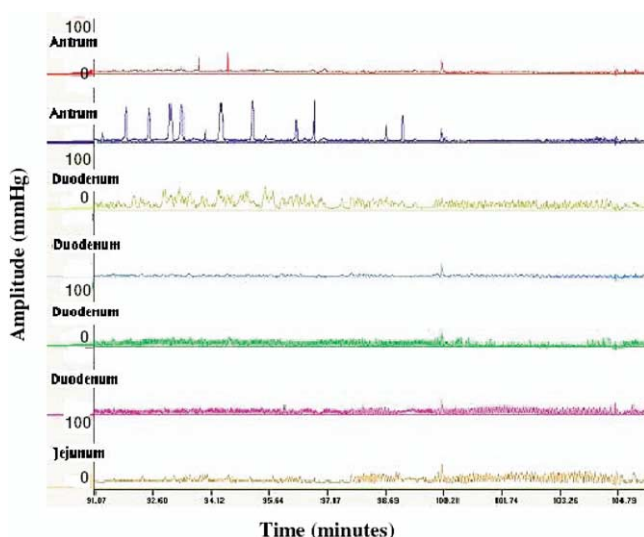


Figure 3. Manometric tracing from a child with hollow visceral myopathy. Amplitude of contractions is less than 50 mm Hg in the antrum and less than 20 mm Hg in the duodenum.

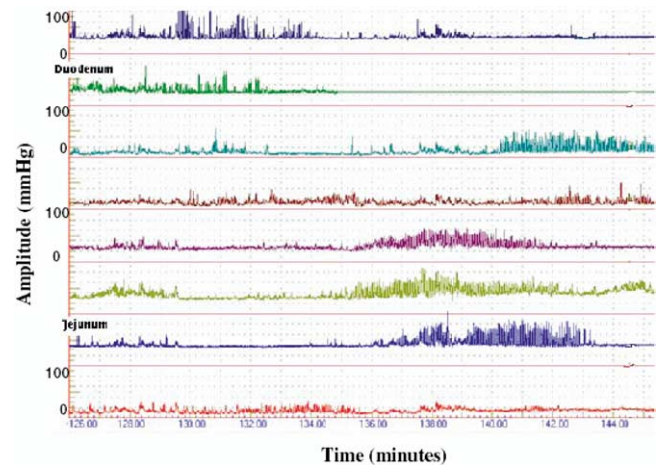


Figure 4. Manometric tracing from a child with visceral neuropathy. There is evidence of abnormal configuration of a phase III motor migrating complex with some retrograde migration (third recording site from above) and lack of propagation (most distal recording site).

Antroduodenal manometry also may be used to suggest prognosis²⁷ and likely response to treatment.²⁸ If the migrating motor complex is present, patients are likely to tolerate enteral feeding.²⁹ Similarly, the presence of phase III of the migrating motor complex is associated with a favorable response to prokinetic therapy with cisapride.²⁸ In patients showing symptoms of intestinal pseudo-obstruction, the presence of normal manometry studies should lead to the consideration of emotional or factitious disorders.^{30,31}

Frequently, the severity of motility dysfunction varies throughout the gastrointestinal tract. Motility studies may identify areas with preserved motility and different feeding strategies then may be devised, bypassing the affected segments. For example, if the stomach is more affected than the small bowel, gastrojejunostomy feedings may be better tolerated.²⁹ Motility studies of the rest of the gut, including colonic manometry and/or radiopaque marker studies, may show distal motility impairment. In such cases, a defunctioning ileostomy may decompress the gut, increasing the ability to receive enteral feeds. When both the upper and lower gastrointestinal tract are diseased, a colectomy is less likely to be beneficial,³² although we believe that abnormal foregut motility is not an absolute contraindication to placement of an ileostomy in CIPO. Esophageal manometry may be abnormal both in children and adults with CIPO.^{33,34}

Transit Studies

Transit studies document prolonged whole-gut transit times in CIPO.³ Radio-opaque marker studies may be useful to identify the site of functional obstruction.

tion in CIPO. In a child with pseudo-obstruction related to neuronal intestinal dysplasia, marker studies indicated a hold-up in the ascending colon. The child did well after defunctioning ileostomy.³⁵ Scintigraphic studies have been used in adults to measure gastric, small-bowel, and colonic transit. Patterns of ileocolonic transfer of solid chyme may suggest the underlying pathophysiology. It was noted that bolus filling of the colon was less frequent in patients with myopathic CIPO whereas it was preserved in patients with neuropathic CIPO.³⁶ Scintigraphic evaluation of small-bowel transit also has been used to characterize subgroups of children with functional dyspepsia.³⁷

Electrogastrography

Electrogastrography was used previously as a screening test for motility abnormalities. However, results are nonspecific, correlate poorly with symptoms, and there is considerable overlap between children with motility abnormalities and controls.³⁸ Therefore, this technique has lost some of its appeal and manometry is now considered a more definitive investigation for pseudo-obstruction.³⁹

Pathology

Increasingly, full-thickness biopsy specimens are obtained to seek a specific pathologic diagnosis. As the range of therapies for CIPO continues to expand, more informative classifications may be necessary to guide management. Biopsy samples should be analyzed in referral laboratories for a wide range of known abnormalities. The biopsy sample should be divided to send some tissue for routine light microscopy (in formalin), some for electron microscopy (in glutaraldehyde), and samples for immunohistochemistry and enzyme histochemistry (snap-frozen).³ Immunoreactivity for c-Kit is a marker for interstitial cells of Cajal and it has been used to show abnormalities in interstitial cells of Cajal distribution in children with CIPO.⁴⁰ Mitochondrial abnormalities may be suggested by megamitochondria in myenteric ganglion cells from rectal suction or full-thickness biopsy specimens⁴ and increased serum lactate, pyruvate, and thymidine levels. Mitochondrial DNA from skeletal muscle confirms the presence of mutations.⁴ If available through research programs, investigations such as in situ hybridization for specific abnormalities may be diagnostic. For example, in situ hybridization on biopsy specimen tissue from patients with megacystis microcolon hyperperistalsis syndrome may show abnormalities of the nicotinic acetylcholine receptor.⁴¹

Therapy

Treatment of patients with CIPO requires a multidisciplinary effort with participation of pediatricians, gastroenterologists, dietitians, surgeons, mental health personnel, occupational therapists, speech pathologists, and other subspecialists based on the presence of comorbidities.

Medical Treatment

Prokinetic therapy with cisapride, erythromycin, octreotide, and tegaserod should be attempted. Cisapride increases the antroduodenal motility index⁴² and may improve tolerance of enteral feeds.²⁸ Unfortunately, the cardiac toxicity of cisapride led to its withdrawal from sale in most countries. Erythromycin mimics the prokinetic hormone, motilin, and induces phase III of the migrating motor complex in patients capable of generating it.^{43,44} It has been used in subantibiotic doses with benefit in CIPO.⁴⁵ Higher doses may be needed in severe cases of gastroparesis. Octreotide is the most potent enterokinetic medication currently available. It stimulates small intestinal motility, inhibits gastric emptying and gallbladder contractility, and has been found to be beneficial in adult patients with CIPO and bacterial overgrowth.⁴⁶ The inhibition of gastric emptying is mitigated by pretreatment with erythromycin⁴⁴ and combination therapy may be beneficial.

Tegaserod, a prokinetic with a similar mode of action to cisapride but no cardiac toxicity, recently has been licensed for use in adults with chronic constipation and may be helpful particularly in patients with colonic involvement. The acetylcholinesterase inhibitor neostigmine is effective therapy for acute colonic pseudo-obstruction in adults and in children.⁴⁷ Recently, repeated use reportedly was successful in an adult patient with chronic symptoms,⁴⁸ although chronic use in children with chronic pseudo-obstruction has not yet been described.

Abnormal motility is associated with bacterial overgrowth,^{49,50} which by itself causes mucosal inflammation, further impairing gastrointestinal motility and creating a vicious cycle.⁵¹ Treatment with antibiotics may improve motility.^{52,53} A variety of antibiotic regimens have been recommended,⁵⁴ although controlled clinical data are few. Most clinicians use 1- to 2-week cycles of broad-spectrum antibiotics such as amoxicillin and clavulanic acid, cotrimoxazole, and metronidazole, often with an antifungal such as nystatin or fluconazole, interspersed by antibiotic-free periods.

Chronic abdominal pain or the fear of pain is a common problem in children with CIPO.⁵⁵ Luminal dilata-

tion, repeated invasive procedures, and mucosal inflammation all may contribute to the development of visceral hyperalgesia with sensitization of peripheral and central pain pathways.^{56–59} The stress of chronic disease also contributes to pain amplification and altered family dynamics, and poor coping skills may play an important role in determining the degree of functional impairment.⁶⁰ The presence of severe pain often triggers adversarial relationships between patients, their families, and physicians. The physicians may aim to avoid the use of narcotics that further impair motility, whereas patients seek immediate symptom relief. Such problems are best approached in the context of a multidisciplinary treatment that includes behavioral or relaxation therapy and the use of nonnarcotic medicines.³¹ The increased understanding of the pathophysiologic disturbances responsible for many functional bowel disorders is now uncovering many putative therapeutic targets for treatment of visceral pain both at the level of the peripheral and central nervous system.⁶¹ These include cholecystokinin A antagonists, several serotonergic agonists and antagonists, selective κ agonists, tachykinin receptor antagonists, somatostatin analogues, cannabinoids, and γ amino butyric acid receptor modulators.⁶¹ Other centrally acting medications, such as gabapentin and tricyclic antidepressants, also may be beneficial when pain constitutes the predominant symptom.^{62–66}

Surgery

Gastrostomy, jejunostomy, or loop enterostomy may be required to shorten the gut and facilitate transit of intraluminal contents. Such interventions reduce distension, reduce vomiting, and improve quality of life in patients with CIPO on total parenteral nutrition (TPN).^{67–70}

The ability to tolerate enteral feedings may improve,^{35,71} and the frequency of hospital admissions for obstructive symptoms is reduced.⁷⁰ In one series of children with CIPO the placement of an ileostomy reduced symptoms in 50%.³ Percutaneous endoscopic colostomy has been successful recently in relieving distension in a group of adult patients with CIPO.⁷² Resection of localized segments of impaired motility may improve symptoms and decrease the need for parenteral nutrition.^{68,73} Most affected segments may be identified by radiologic contrast studies, manometry, or by finding localized massive dilatation at laparotomy.⁷³

Transplantation

Small intestinal transplantation is indicated in TPN-dependent pseudo-obstruction patients with life-

threatening complications of TPN or with dwindling venous access.⁷⁴ Life-threatening complications of TPN include recurrent sepsis and thromboembolic disease. The presence of cholestatic liver disease is also an important indication for early referral for assessment at a transplant center because of the increased mortality rate associated with this condition.⁷⁵ Conversely, patients who are stable on TPN are best managed without transplantation because survival rates are similar to those posttransplantation.⁷⁶ The assessment of candidates before intestinal transplantation should include a thorough investigation of the extent of dysmotility and associated abnormalities. Antroduodenal manometry is useful to evaluate foregut function. In the presence of preserved gastric motility, isolated small-bowel transplant is preferred. However, if stomach motility is impaired severely, multivisceral transplantation is warranted. Other associated conditions such as obstructive uropathy (frequently present in children with gastrointestinal myopathies), cholestatic liver disease, and multiple vascular thromboses require a detailed preoperative assessment to plan appropriate intervention.

Outcomes in series of patients transplanted for CIPO reflect outcomes of other small intestinal transplant recipients in the same epochs.^{77,78} In recent years, children receiving isolated intestinal transplants for intestinal failure have 1-year survival rates of approximately 83%. Small infants fare significantly worse, whereas survival is 90% in children aged 2 years and older.⁷⁴ The presence of abnormal esophageal and bladder function and longstanding visceral pain affecting some patients with CIPO make the postoperative management more challenging in these patients. Early discontinuation of narcotics is particularly important in an attempt to optimize the allograft bowel motility.

Others

A fascinating and promising therapeutic approach to CIPO involves the use of gastric and intestinal pacemakers.⁷⁹ The initial results of gastric electric pacing in adults with different causes of gastroparesis have been encouraging. Gastric pacing involves the use of a high-frequency/low-energy electrical stimulation via electrodes implanted in the muscle wall of the antrum. Insertion of the electrodes is performed either by laparoscopy or laparotomy. The electrodes then are connected to a neurostimulator that is implanted externally or subcutaneously. The use of the pacemaker has been associated with significant improvement in nausea and vomiting.^{80,81} Less impressive has been the effect on gastric emptying, suggesting that the electrical stimulation may stimulate sensory rather than motor neurons.

Recent data also suggest an improvement in pancreatic exocrine function⁸² and nutritional parameters.⁸³ The gastric pacemaker has been approved by the US Food and Drug Administration for use in human beings through the humanitarian device exemption, a category that applies to devices intended to benefit fewer than 4000 patients. Small-bowel pacing is more challenging because of the length of the organ to be stimulated, and it is still in its infancy.

The use of botulinum toxin injection in the pylorus and anus has been used to improve transit through those sphincters.⁸⁴ Hyperbaric oxygenation has been reported to be beneficial in a child with myopathic CIPO who had presented with abdominal distension and obstructive symptoms.⁸⁵

Outcome

Despite ongoing improvements in nutrition, medical, and surgical therapies, children with CIPO are plagued by significant morbidity and mortality. Many are born prematurely, and many others have associated abnormalities such as urologic disorders, dysautonomia, and structural gastrointestinal abnormalities such as malrotation.⁸⁶ Liver disease and sepsis, complications of TPN, are the most common causes of death. A recent study of 85 children with congenital CIPO found a 25% mortality rate at a median follow-up time of 2 years.⁸⁶ In an earlier study, the presence of midgut malrotation, short small intestine, urinary system involvement, onset under 1 year of age, and myopathy on histology were poor prognostic factors (associated with prolonged TPN dependence or death).³ Children with CIPO and their families have a significantly reduced quality of life compared with healthy controls and children with other chronic illnesses.⁸⁷ However, survival and quality of life are improving. With earlier recognition and aggressive nutritional and medical management, survival into adult life and even pregnancy increasingly is achieved.^{88,89}

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