Latest developments in chronic intestinal pseudo-obstruction

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Abstract

Chronic intestinal pseudo-obstruction (CIPO) is a type of intestinal dysfunction presenting as symptoms of intestinal obstruction but without actual mechanical obstruction. An extremely low incidence, non-specific clinical symptoms, strong heterogeneity, and no definitive cause in some patients make CIPO very difficult to diagnose correctly. Imaging and gastrointestinal manometry are commonly used. Most patients have progressive worsening of their symptoms and require intervention, and nutritional assessment and treatment are very important to determine the prognosis. With improvements in surgical techniques, small bowel transplantation is a feasible treatment option for patients with advanced CIPO; however, the long-term prognosis for CIPO patients remains unsatisfactory. Generally, the disease is rare and difficult to diagnose, which leads to clinicians’ lack of understanding of the disease and results in a high rate of misdiagnosis. This review describes the characteristics of CIPO and the latest developments in diagnosis and treatment, in detail. The goal of our review is to improve clinicians’ understanding of CIPO so that the disease is identified quickly and accurately, and treated as early as possible to improve patients’ quality of life.

Key Words: Chronic intestinal pseudo-obstruction; Intestinal obstruction; Enteral nutrition; Parenteral nutrition; Intestinal transplantation

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Core Tip: Chronic intestinal pseudo-obstruction (CIPO) is an intestinal motility disorder caused by neuropathies, myopathies, and mesenchymopathies. CIPO is very difficult to diagnose correctly, leading to most patients experiencing several years from symptom onset to diagnosis. The high misdiagnosis rate relates not only to the characteristics of CIPO itself, but also to the lack of clinicians’ understanding of the disease. Using...
Intestinal pseudo-obstruction, first reported by Dudley in 1950\(^1\), refers to a rare disordered peristalsis characterized by symptoms of intestinal obstruction, but without frank mechanical obstruction\(^3\). The disorder is caused by abnormalities of the enteric neuromusculature and/or its autonomic innervation and represents the most severe form of gastrointestinal dysmotility with debilitating and potentially lethal consequences. Chronic intestinal pseudo-obstruction (CIPO) was proposed by Christensen in 1978 to describe intestinal pseudo-obstruction persisting for more than 6 mo\(^4\). Due to its rarity and non-specific symptoms, the misdiagnosis rate is extremely high, and CIPO is at an advanced and severe level, when the correct diagnosis is established\(^5\). We reviewed the most recent literature on CIPO, and comprehensively summarized the etiology, diagnosis, treatment, and prognosis to improve clinicians’ understanding of the disease.

### Epidemiology

Clinically, CIPO is quite rare, and definitive knowledge regarding its prevalence or incidence is lacking in most countries. According to Vargas, the incidence of pediatric CIPO is estimated at approximately 1 per 40000 live births\(^6\). According to data from the American Pseudo-Obstruction and Hirschsprung’s Disease Society, an estimated 100 infants are born with congenital pseudo-obstruction every year in the United States\(^7\). In 2014, a Japanese survey found that the estimated prevalence was 3.7/100000, and 56.5% of cases had a neonatal onset; 41 (91.1%) had no pathological abnormalities and were considered idiopathic\(^8\). In another survey of 378 institutions belonging to the Japanese Society of Gastroenterology, CIPO prevalence in adult patients was estimated at 1.0 and 0.8 cases per 10000 men and women, respectively. The incidence in the same population was 0.21 and 0.24 cases per 100000 males and females, respectively\(^9\).

### Classification

CIPO is generally divided into congenital, acquired, and idiopathic (no definitive cause) forms\(^10\). Most CIPO cases occur in children, are sporadic, and patients have no clear family history. However, some cases with obvious genetic characteristics suggest that CIPO may involve autosomal dominant-, autosomal recessive-, and sex chromosome-related inheritance. CIPO is a common clinical manifestation in many types of mitochondrial myopathies, such as mitochondrial neurogastrointestinal encephalomyopathy (MNGIE), which is caused by a mutation in the TYMP gene\(^11\). Megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS) caused by a mutation in the ACTG2 gene\(^12\) and chronic atrial and intestinal dysrhythmia syndrome (CAID) caused by mutations in the SGOLI1 gene\(^13\) also belong to this category. CIPO has also been reported in association with Alpers’ disease, which is caused by POLG gene mutations or mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes syndrome\(^14\). Table 1 shows the details of the congenital forms of CIPO. Patients with hereditary degenerative smooth muscle and enteric nervous system diseases, i.e., familial visceral myopathy and neuropathy, also have CIPO manifestations, but the underlying genes have not been identified.
Acquired CIPO is more common in adults and is often secondary to a wide array of diseases, such as systemic neurological, endocrine, and connective tissue diseases, or malignancy. These diseases affect intestinal motility through one or more of the following: autonomic nervous system (stroke, encephalitis, calcification of basal ganglia, orthostatic hypotension, diabetes); intestinal wall nervous system (paraneoplastic syndromes, viral infections, iatrogenic (anthraquinones), diabetes, Hirschsprung’s disease, Chagas’ disease, Von Recklinghausen's disease); intestinal wall muscle layer (myotonic dystrophy, progressive systemic sclerosis); mixed enteric nervous system and smooth muscle layer (scleroderma, dermatomyositis, amyloidosis, Ehlers–Danlos syndrome, jejunal diverticulosis, radiation enteritis); and unknown mechanisms (hypothyroidism, hypoparathyroidism, pheochromocytoma, clonidine, phenothiazines, antidepressants, antiparkinsonian drugs, antineoplastics, bronchodilators). Neurological diseases such as Parkinson’s disease and metabolic diseases such as diabetes affect intestinal function through parasympathetic and/or sympathetic nerves. Paraneoplastic syndromes may cause inflammatory/immune infiltrates of neurons located in submucosal and myenteric ganglia of the enteric nervous system by cellular infiltrates and circulating antineuronal antibodies, resulting in intestinal motility disorders. Myotonic dystrophy or progressive systemic sclerosis mainly damage the enteric smooth muscle cells\(^{[7,15,16]}\). Autoimmune disorders, collagenopathies, jejunal diverticulosis, and radiation enteritis can alter enteric nerves and smooth muscle cells and even the interstitial cells of Cajal, resulting in a combined neuro-myopathy. Other diseases such as hypothyroidism, hypoparathyroidism, and pheochromocytoma are known causes of CIPO, but the pathogenesis remains unknown. Given that healthy controls rarely harbor viral DNA in the myenteric plexus compared with CIPO patients, many different neurotropic viruses\(^{[18]}\) such as herpesviruses\(^{[19]}\), polyomaviruses (JC virus\(^{[20]}\), cytomegalovirus\(^{[21]}\), and Epstein–Barr virus\(^{[22]}\) might play an etiological role in the development of CIPO.

**PATHOLOGY**

Congenital and acquired CIPO both constitute three histological categories: neuropathies, myopathies, and mesenchymopathies. More than one pathological type can occur in the same patient simultaneously. (1) Intestinal neuropathies involve neurodegeneration and dysplasia of the enteric nervous system. Neurodegenerative disorders, such as neuronal intranuclear inclusion disease\(^{[23]}\), are characterized by progressive degeneration and disappearance of ganglion cells, leading to a gradual decrease in the number of nerves. In addition to symptoms related directly to CIPO, symptoms also include neurological abnormalities such as ataxia. Dysplastic disorders of the enteric nervous system constitute mainly aganglionosis in Hirschsprung’s disease\(^{[24]}\), diffuse intestinal ganglioneuromatosis\(^{[25]}\), intestinal hypoganglionosis\(^{[26]}\), and neurogenic intestinal dysplasia\(^{[27]}\), which involve abnormalities in intestinal nerve distribution, development, and quantity. CIPO can also be seen in other diseases, such as intestinal ganglionitis; (2) Intestinal myopathies involve the supernumerary intestinal muscle coat and diffuse abnormalities in muscle layering\(^{[28,29]}\). Portions of the muscularis propria retain the normal bilayered architecture, but malformed regions contain broad fascicles of smooth muscle that course obliquely or perpendicularly in
degenerative leiomyopathy, smooth muscle degenerates, is lost, and is then gradually replaced by fibrous connective tissue; CIPO symptoms appear gradually. Other adverse stimuli, such as inflammation of the intestinal wall, ischemia, drugs, and immune dysfunction, also cause CIPO in intestinal myopathies; and (3) Mesenchymopathies mainly constitute abnormalities of the interstitial cells of Cajal and tendinous collagenous tissues of the muscularis propria.

It must be clarified that Hirschsprung’s disease is caused by dysplastic disorders of the enteric nervous system, and belongs to the category of intestinal neuropathies, which constitute secondary diseases in CIPO.

SYMPTOMS

Approximately 20% of CIPO cases have clinical manifestations before birth, while 50%–70% of patients show symptoms in the first month after birth. Eighty percent of patients have clinical manifestations at the age of 1 year, and the remaining 20% have sporadic onset before 20 years old. CIPO may involve any segment of the gastrointestinal tract, and clinical manifestations are mainly related to the location and extent of the involved gastrointestinal tract. Approximately 70% of CIPO patients have esophageal motility disorders. Generally, the most common symptoms reported by patients are abdominal pain and distension (80%) that is non-colicky, persistent, and aggravated by eating. These symptoms are generally located in the umbilical or upper abdominal regions and gradually spread to involve the whole abdomen. Other symptoms are nausea (75%), vomiting (40%-50%), constipation (40%), and diarrhea (20%-30%). Sub-occlusive episodes can strike in apparently healthy people, but the onset of CIPO is generally insidious, with gastrointestinal symptoms preceding the first acute episode and symptoms worsening significantly during acute episodes, which can last only a few hours. Between acute attacks, patients are asymptomatic or affected by persistent gastrointestinal obstruction. The frequency and severity of acute and intermittent exacerbations are unpredictable, have no detectable cause, and vary widely from patient to patient. Small intestinal bacterial overgrowth (SIBO) may occur in approximately 30% of patients, which can cause mucosal damage, steatorrhea, diarrhea, and intestinal damage, with chronically dilated bowel loops contributing to malabsorption and vitamin deficiency, which then lead to weight loss. Furthermore, intractable constipation may occur when SIBO is treated with antibiotics. The urinary system is the most common organ involved outside the digestive tract, manifesting mainly as bladder and ureteral dilation associated with a microcolon, a phenotype referred to as MMIHS, which is considered the most severe form of CIPO. Onset is antenatal and is detected prenatally by ultrasonography in up to 59% of CIPO cases. Patients with CIPO may develop depression or other psychological disorders due to the long course of the disease and unsatisfactory treatment. Secondary CIPO is common in older people, presenting as the characteristics of the primary disease(s). For example, MNGIE patients not only have intestinal obstruction, but also progressive external ophthalmoplegia, ptosis, and peripheral polyneuropathy.

Due to the non-specific nature of CIPO, even if the identification of CIPO can be improved by clinical features such as extra-intestinal manifestations and malnutrition, it is still easy to confuse CIPO with other diseases with similar symptoms, such as gastroparesis, functional constipation, cyclic vomiting syndrome, drug toxicity, and hypothyroidism. The reasons are as follows: (1) Diagnosis still relies on clinical experience rather than on biomarkers of disease; (2) The clinical presentation (intestinal sub-occlusive crisis mimicking a mechanical sub-occlusion) and clinical complexity (i.e., the presence of comorbidities, such as urinary bladder abnormalities or syndromic forms) are factors; and (3) The wide heterogeneity of mechanisms leading to CIPO and related clinical manifestations are additional factors. The diagnosis of CIPO can only be made after several abdominal explorations to exclude mechanical obstruction. The median time for the final correct diagnosis is 8 years, and 88% of patients undergo an average of three non-therapeutic operations.

DIAGNOSIS

Computed tomography (CT) and plain upright abdominal radiography show non-specific obstruction of the digestive tract. Mechanical obstruction can be eliminated by contrast medium examination, but the risk of retaining contrast medium and the
TREATMENT

Except for a small number (11%) of asymptomatic patients, most patients have progressive worsening of their symptoms and require medical intervention. Increasing gastrointestinal motility, improving nutritional status, and maintaining the stability of the internal environment are the goals of CIPO therapy. For patients with secondary CIPO, the primary disease should be actively treated. It is important to be aware that currently, the overall effects of CIPO treatment are unsatisfactory, and the disease course is long; therefore, patients are prone to depression and other psychological disorders.

Nutritional support
Please refer to the subsection, “nutritional assessment and support”, for details.

Treatment of acute intestinal obstruction
It is crucial to evaluate and maintain the stability of the internal environment. As much as possible, surgical intervention should be minimized because operation can inhibit formation of fecal stones, which aggravate obstruction, are concerns. Currently, contrast-enhanced examination has been gradually replaced by high-resolution CT or magnetic resonance imaging (MRI). CT demonstrates mechanical obstruction, but also provides more information, such as the presence of intestinal adhesions. As a means of assessing and monitoring gastrointestinal motility, cine-MRI can detect subtle contractile impairment of the gut in patients with CIPO, and this method is widely used clinically because of its non-invasive, non-radiation advantages.

Gastrointestinal manometry can effectively evaluate the intensity and coordination of digestive tract contraction, which is significant for diagnosis. Abnormal esophageal pressure occurs in approximately 50% of patients, and measuring gastric antral and duodenal pressure is helpful to evaluate motility in the gastric antrum and proximal small intestine, and colonic pressure can directly reflect colonic motility. Some studies have shown that there is no correlation between the results of gastrointestinal manometry and the pathological types of CIPO and no apparent relationship between the manometric pattern(s) and the type or severity of a patient’s symptoms. However, other studies suggest that antrudodenojejunal manometry may be helpful both in diagnosing CIPO and in indicating the etiology of the condition by showing manometric features suggesting intestinal myogenic or neuropathic processes. Small intestinal manometry is useful not only as an aid in providing pathophysiologically relevant information regarding the mechanisms underlying dysmotility in CIPO patients, but also in predicting outcomes.

Endoscopy can confirm mechanical obstruction caused by space-occupying lesions and stenosis in the digestive tract. Colonoscopy can also play a role in gastrointestinal decompression. Although capsule endoscopy can provide more information on the digestive tract, this method has potential risks, especially without excluding mechanical obstruction. The diagnostic value of capsule endoscopy for CIPO is still unclear, and the technique is not currently recommended.

Genetic testing is useful for the diagnosis of special types of diseases associated with CIPO. These diseases include SOX10/Waardenburg–Shah syndrome, ACTG2/MMIHS, SGOL1/CAID, POLG/Alpers’ disease, TYMP mutation, and POLG/MNGIE. When we encounter these diseases, genetic testing can help make the correct diagnosis quickly.

Due to limitations in our understanding of the nerve and muscular layers of the intestinal wall, it is very difficult to interpret the histopathology of CIPO. It is not uncommon to find no recognizable abnormalities despite a thorough microscopic evaluation of full-thickness bowel biopsies, in children with CIPO. Therefore, full-thickness biopsies of the gastric antrum, small intestine, and colon are of limited value in the diagnosis of CIPO, and this method is not recommended as a routine examination.

Establishing a diagnosis of CIPO is mainly based on clinical manifestations, as well as the presence of extensive intestinal dilatation and multiple gas–liquid levels as imaging findings, and abnormal intestinal manometry, after excluding mechanical obstruction caused by occupying lesions detected by imaging or endoscopy. Diagnostic examination should also identify the pathogenesis of CIPO as clearly as possible, such as with full-thickness biopsies.
intestinal peristalsis, and even induce intestinal failure, which can significantly increase the reoperation rate\[64,65\]. However, CIPO patients with Hirschsprung’s disease are at risk for colonic volvulus, and timely operation is recommended in this situation\[66\].

**Analgesic therapy**

Visceral pain, especially chronic pain, is a primary concern. Due to their inhibition of gastrointestinal peristalsis, opioids are not recommended. Pain can be treated with low-dose tricyclic antidepressants and gabapentin\[67\]; however, as the disease progresses, approximately 25% of patients gradually increase their tolerance to analgesic medications\[68\]. It is suggested that surgeons participate in CIPO pain management with pain specialists and psychologists\[69\].

**Gastrointestinal motility therapy**

Currently, there is no evidence to support gastrointestinal motility drugs\[70,71\]. The most commonly used drug for promoting gastric motility is erythromycin (1.5-2 g qd for adults; 3-5 mg/kg qd for children)\[72,73\]. Drugs promoting intestinal peristalsis are omeprazole (100 mcg/day, subcutaneous injection)\[74,75\] and amoxicillin-clavulanic acid\[76\]. There is still insufficient evidence for the treatment of CIPO with metoclopramide and domperidone, and the former carries the risk of tardive dyskinesia when used long-term\[77\]. Acetylcholinesterase inhibitors (neostigmine, 8 mg/d, intravenous injection)\[78\]; pyridostigmine, 20 mg/d, oral administration\[79\] have also been used in adults with CIPO. Prucalopride, a highly selective 5-hydroxytryptamine-4-receptor agonist lacking cardiotoxicity, exerts significant enterokininetic effects\[80\]. Cisapride and tegaserod are effective, but these drugs have been banned because of related fatal arrhythmias\[81,82\].

**Gastrointestinal decompression**

Enemas (polyethylene glycol, glycerin), nasogastric tubes, small intestinal tubes, digestive endoscopy, and even surgical fistulation are all optional methods. Colonoscopic decompression has been successfully used in the preoperative treatment of pregnant women with CIPO\[83\]. Percutaneous endoscopic gastrojejunostomy fully reduces pressure and relieves abdominal pain, and allows for good nutritional management in patients with CIPO\[84\]. Currently, there is no consensus on the timing of decompression by enterostomies in patients with CIPO\[85\].

**Anti-infection**

SIBO is the most common complication of chronic bowel dilatation, and bacterial concentrations are usually higher than $10^4$-$10^6$ CFU/mL\[86\]. Oral antibiotic therapy is effective, and there are mature antibiotic programs to choose from\[87\], such as amoxicillin-clavulanic acid (500 mg, tid), ciprofloxacin (500 mg, bid), doxycycline (100 mg, bid), metronidazole (250 mg, tid), neomycin (500 mg, bid), rifaximin (550 mg, bid), and tetracycline (250 mg, qid)\[88\]. Antibiotics should be prescribed for 7-10 d each month, with the type of antibiotic changed each month for 5-6 mo\[89\].

**Fecal bacterial transplantation**

Some studies\[90\] have shown that fecal bacterial transplantation significantly alleviates patients’ abdominal distention and abdominal pain, increases their tolerance for enteral nutrition, and prevents and treats SIBO, indicating that fecal bacterial transplantation may be a new direction in CIPO treatment.

**Immunosuppressive therapy**

For CIPO patients with significant inflammation/immune reaction in the myenteric ganglion or neuromuscular tract, immunosuppressive agents may reverse the histopathological signs\[91,92\]. However, due to a lack of evidence-based medical data, this method should be used with caution.

**Allogeneic hematopoietic stem cell transplantation**

This therapy definitely improves clinical symptoms in patients with mitochondrial neurogastrointestinal encephalomyopathy, long-term, but the effect in patients with CIPO with intestinal failure is unsatisfactory\[93\].

**Small intestine/multi-visceral transplantation**

Currently, small bowel transplantation secondary to CIPO accounts for approximately
9% of all small bowel transplants. The 1-, 3-, and 5-year survival rates between small bowel transplantation secondary to intestinal dysfunction and total small bowel transplantation (75% vs 73%, 62% vs 61%, and 57% vs 55%, respectively) are comparable. Additionally, the incidences of infection and opportunistic complications are similar in CIPO and non-CIPO small bowel transplantation. Nakamura et al. found that the overall 3-year survival rate after small bowel transplantation in patients with total intestinal aganglionosis was 66%, and the longest survival time was 12.8 years. Therefore, for CIPO patients with intestinal failure and potentially fatal complications of parenteral nutrition, small bowel transplantation is a feasible treatment option that can improve long-term prognosis.

If other organs are involved, modified multi-visceral transplantation should be performed, such as stomach–duodenum–pancreas–small intestine transplantation, or combined liver and intestine transplantation. A study of 98 patients undergoing multiple organ transplantation from the University of Miami showed that the 5-year survival rates of patients and grafts were 49% and 47%, respectively. Considering that, compared with general transplantation, this type of operation is more difficult, more traumatic, and requires more complex postoperative management, this approach is recommended only in experienced transplantation centers.

**NUTRITIONAL ASSESSMENT AND SUPPORT**

Approximately 2/3 of patients with CIPO have insufficient nutritional intake and may experience significant weight loss. Therefore, strict and systematic nutritional evaluation and selecting appropriate nutritional supports are essential to improve patients’ quality of life and long-term prognosis. However, no evidence-based consensus proposals are available for nutritional management in patients with CIPO.

**Nutritional assessment**

A strict and systematic nutritional assessment of patients with CIPO should be performed by experienced nutritionists. Macro measurements such as weight, body mass index, and eating habits, and laboratory measurements such as serum albumin, prealbumin, lymphocyte count, and C-reactive protein are recommended. Secondary to insufficient intake and/or absorption obstacles in some patients, the concentrations of serum calcium, iron, vitamin B12, folic acid, fat-soluble vitamins, thiamine, and niacinamide may be abnormal; therefore, levels should be measured and corrected, as needed.

**Nutritional support**

**Dietary support**: Nutritionists provide nutritional education and create personalized diet plans for patients. Generally, oral intake is most desirable, and smaller, more frequent meals (5–6 times/day) are recommended. The ideal diet is a liquid formulation containing protein and high fat; high fiber diets should be restricted or even avoided. Patients’ levels of water-soluble vitamins, minerals, and electrolytes should be regularly measured and supplemented, as needed. If SIBO occurs, it must be remembered that the levels of fat-soluble vitamins and vitamin B12 should be measured. If necessary, an elemental diet and dietary supplements rich in medium-chain triglycerides can be used.

**Enteral nutrition**: Enteral nutrition can be considered if oral feeding cannot meet the patient’s nutritional requirements. Standard, non-elemental enteral nutrition can generally meet the nutritional needs of most patients with CIPO. Nasogastric tubes or gastrostomy tubes can be used for continuous and small-dose feeding, if needed. Nasojejunostomy or jejunocecal tubes can work well if gastroparesis occurs. Compared with one-time high-dose feeding, continuous, low-dose, or periodic feeding is more easily accepted by patients.

**Parenteral nutrition**: Approximately 60%–80% of patients rely on parenteral nutritional support to different degrees, and home parenteral nutrition is used by approximately 20% of patients. Approximately 2/3 of children with CIPO rely on parenteral nutrition for sufficient energy intake. If patients are exclusively dependent on parenteral nutrition, total energy intake is calculated as approximately 25 kcal/kg/day, and lipids should supply approximately 30% of total parenteral calories with 1.0–1.5 g/kg/day of protein and the remaining calories provided by...
glucose. Amiot et al. found that parenteral nutrition can effectively maintain patients’ body weight and relieve symptoms. The 1-, 5-, 10-, and 15-year survival rates of patients with CIPO supported by parenteral nutrition were 94%, 78%, 75%, and 68%, respectively, and approximately 2/3 of patients used home parenteral nutrition for 15 years. However, 90% of deaths in patients with CIPO were related to parenteral nutrition-related complications, in one study. Other studies reported that the mortality rate of children with CIPO ranged from 4.7% to 15.2%. Metabolic complications include metabolic bone disease, electrolyte abnormalities, dehydration, and intestinal failure-associated liver disease. Infectious complications include catheter-related blood stream infections, and exit site. Mechanical complications include catheter breaks, catheter occlusions, thrombosis, especially deep vein thrombosis, superior vena cava syndrome, and air embolism. Therefore, maximizing oral intake in patients with CIPO is recommended to minimize or avoid the use of parenteral nutrition.

PROGNOSIS

The long-term prognosis of patients with CIPO is unsatisfactory. Intestinal myopathies, esophageal involvement, inadequate response of the digestive tract to food stimulation, deficiencies in the migrating motor complex during fasting, concurrent urinary retention, and concurrent intestinal malrotation are poor prognostic factors. 10%–25% of children with CIPO die before adulthood. Parenteral nutrition combined with oral feeding can significantly improve patients’ survival rates, and oral feeding is an independent predictor of long-term prognosis.

CONCLUSION

CIPO is a rare disorder of intestinal function characterized by abnormal intestinal peristalsis. The symptoms, signs, and imaging features all indicate mechanical intestinal obstruction, and the misdiagnosis rate is very high. Clinicians should inquire about the history of disease and physically examine patients carefully. Once the possibility of organic obstruction is eliminated, the possibility of CIPO should be considered. Although no studies have evaluated the relationship between early diagnosis and prognosis, a greater awareness of CIPO would indeed help reduce unnecessary surgical procedures, and full thickness biopsies at an early and potentially curable stage of the disease are recommended to evaluate the gut nervous layer, identify pathology, and to provide targeted treatment as quickly as possible.

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