Pediatric Chronic Intestinal Pseudo-obstruction

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The term pseudo-obstruction literally denotes obstruction in the absence of true mechanical occlusion. Intestinal pseudo-obstruction can be either acute or chronic in nature depending on the duration of obstructive symptoms (chronicity defined as symptoms' duration longer than 6 months) [1, 2]. Chronic intestinal pseudo-obstruction (CIPO) was first described in 1958 by Dudley and colleagues to report a series of 13 patients with symptoms suggestive of intestinal occlusion. These patients underwent exploratory laparotomies, which failed to identify a mechanical cause [3]. The existence of this pathological entity, in both the adult and pediatric population, was later substantiated by a number of other clinicians [4–7].

Abnormal antegrade propulsive activity of the gastrointestinal (GI) tract, resulting from processes affecting its neurons, muscles, or interstitial cells of Cajal (ICC), is the pathophysiologic mechanism of CIPO [8]. This functional disability of the gut is responsible for a number of clinical symptoms such as abdominal distention, with or without abdominal pain, nausea, vomiting, and a reduced ability to tolerate oral and/or enteral nutrition [9]. Such symptomatology is, however, non-specific, and the condition can remain undiagnosed for a long period of time during which patients may undergo multiple diagnostic investigations and often repeated surgical explorations in an effort to identify the underlying cause [9].

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Although by definition the small intestine is always involved, any part of the GI tract can be affected in CIPO [1, 2]. Esophageal involvement may lead to dysphagia due to impaired peristalsis, in some cases similar to that seen in achalasia [10]. Involvement of the stomach results in poor feed tolerance due to gastroparesis suggested by the presence of delayed gastric emptying, while involvement of the large bowel and anorectum manifests with constipation (delayed colonic transit) and defecation disorders (sphincteric dysfunction), respectively [1].

This chapter will focus on various aspects of pediatric CIPO and will attempt to address areas of controversy by exploring the most recent advances in the overall approach and management of this clinical entity.

Definition

According to an ESPGHAN/international expert consensus paper on the disorder, CIPO in children has clear distinctions from CIPO in adults with the proposal it be designated pediatric intestinal pseudo-obstruction (PIPO) rather than CIPO and be defined as follows: "Paediatric intestinal pseudo-obstruction is a disorder characterised by the *chronic inability of the gastrointestinal tract to propel its contents mimicking mechanical obstruction, in the absence of any lesion occluding the gut" (*chronic is defined as persistence for 2 months from birth or at least 6 months thereafter). The working group has suggested that the diagnosis of PIPO requires at least two out of four of the following criteria:

1. Objective measure of small intestinal neuromuscular involvement (abnormal validated transit, manometric, and/or histopathology studies)
2. Recurrent and/or persistently dilated loops of small intestine with air-fluid levels
3. Genetic, metabolic, or other abnormalities definitively associated with intestinal pseudo-obstruction

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4. Inability to maintain adequate nutrition and/or growth on normal oral feeding (therefore needing specialized oral and/or enteral nutrition and/or parenteral nutrition support)

For the purposes of this chapter, no distinction will be made between PIPO and CIPO, and the latter will be used to designate chronic intestinal pseudo-obstruction in children.

Epidemiology

CIPO is a rare disease; scanty epidemiological data exist regarding its incidence and prevalence in both adult and pediatric populations. A survey-based study estimated that approximately 100 infants are born in the USA every year with CIPO, suggesting an incidence of approximately 1 per 40,000 live births [11, 12]. A recent nationwide survey for pediatric CIPO performed in Japan revealed that among children younger than 15 years of age, the prevalence of CIPO was 3.7 in one million children, of whom 56.5% developed CIPO in the neonatal period [13]. In another nationwide Japanese survey, 138 cases of CIPO were identified, with an estimated prevalence of 1.0 and 0.8 cases, and incidence of 0.21 and 0.24 cases, per 100,000 males and females, respectively [14]. Adult studies reveal that the disease is more frequent in females [15–17]. Undoubtedly the development of national registries is of paramount importance to delineate the precise epidemiologic characteristics of this orphan disease.

Classification

The classification of CIPO is still challenging. Conditions resulting in CIPO can be classified by whether they primarily affect intestinal nerves (neuropathy), smooth muscle (myopathy), or interstitial cells of Cajal (ICC) (mesenchymopathy). The abovementioned conditions can be further subdivided into primary or secondary, congenital or acquired, and diffuse or segmental depending on the mode of inheritance, presentation, likely etiopathogenesis, or what part of the GI tract is involved. Where classification is not possible, they are defined as idiopathic. In truth, there is a considerable overlap [1, 2].

In primary CIPO the disease is usually localized to the gastrointestinal tract, whereas in secondary cases there is a systemic disorder that directly or indirectly affects GI tract motility. Notably, in some cases of primary CIPO, extragastrointestinal involvement may also be part of the clinical picture; examples include disorders of the urinary tract (e.g., hollow visceral myopathy and megacystis-microcolon-intestinal hypoperistalsis syndrome), the nervous system (e.g., central, peripheral, or autonomic neuropathies), and/or mitochondria [e.g., mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)] [2, 18, 19]. Approximately 50% of CIPO cases qualify as secondary CIPO as presented in Table 24.1 (this is particularly true for adult CIPO patients, whereas in pediatrics the disease is predominantly idiopathic or due to primary causes) [20]. Based on histological findings, both primary and secondary CIPO can be further categorized into neuropathies, myopathies, and mesenchymopathies [21–26]. Although the onset of the disease is used to label whether CIPO is congenital or acquired, in children this area needs further elucidation [2, 8, 27].

Table 24.1 Classification of chronic intestinal pseudo-obstruction

Primary CIPO
• Sporadic or familial forms of hollow visceral myopathy/neuropathy (e.g., megacystis-microcolon-intestinal hypoperistalsis syndrome) [7, 28–45]
• Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) [19, 46–48]
• Hirschsprung disease [49–51]
• Neuropathy associated with multiple endocrine neoplasia type IIB [52–54]
• Malrotation or gastroschisis [55–57]
• Neuropathy post-neonatal necrotizing enterocolitis [58]
Secondary CIPO
• Conditions affecting GI smooth muscle
– Rheumatological conditions (dermatomyositis/polymyositis, scleroderma, systematic lupus erythematosus, Ehlers-Danlos syndrome) [59–70]
– Other (Duchenne muscular dystrophy, myotonic dystrophy, amyloidosis, ceroidosis or alternatively reported as brown bowel syndrome) [71–80]
• Pathologies affecting the enteric nervous system (familial dysautonomia, primary dysfunction of the autonomic nervous system, neurofibromatosis, diabetic neuropathy, fetal alcohol syndrome, post-viral-related CIPO, e.g., CMV, EBV, VZV, JC virus) [81–96]
• Endocrinological disorders (hypothyroidism, diabetes, hypoparathyroidism, pheochromocytoma) [97–101]
• Metabolic conditions (uremia, porphyria, electrolyte imbalances, e.g., potassium, magnesium, calcium) [102–107]
• Other (celiac disease, eosinophilic gastroenteritis, Crohn's disease, radiation injury, Chagas disease, Kawasaki disease, angioedema, mitochondrial disorders, drugs, e.g., opiates, anthraquinone laxatives, calcium channel blockers, antidepressants, antineoplastic agents, e.g., vinca alkaloids, paraneoplastic CIPO, major trauma/surgery, chromosome abnormalities) [108–134]
Idiopathic

Etiology and Pathophysiology

The integrity of gastrointestinal sensorimotor function relies on a precise coordination between the autonomic nervous system, ENS, ICC, and smooth muscle cells. Any noxious stimulus, as depicted in Table 24.1, which affects the GI neuromusculature may lead to impaired peristalsis and the stasis

of luminal contents (1). Neurologic and metabolic disorders may affect the extrinsic GI neurons, whereas neurotropic viruses could evoke an inflammatory process insulting both the ENS and extrinsic nerve pathways [20, 94]. Paraneoplastic syndromes could also target the ENS by initiating an inflammatory process that affects the ganglia of the submucosal and myenteric plexuses via a cellular infiltrate and production of circulating anti-neuronal antibodies [20, 135]. Some pathologies (e.g., muscular dystrophy) target the enteric smooth muscle fibers, whereas entities such as dermatomyositis, scleroderma, Ehlers-Danlos syndrome, and radiation enteritis lead to a mixed neuro-myopathic disorder [12, 136, 137]. Celiac disease, hypothyroidism, hypoparathyroidism, and pheochromocytoma could also lead to CIPO by affecting the GI neuromusculature; however, the exact mechanism is not fully defined.

Genetics

Elucidation of the genetic basis of CIPO has been somewhat disappointing. Some familial cases of CIPO have been recognized, but there appear to be several patterns of inheritance, perhaps reflective of the great heterogeneity of CIPO conditions. Both autosomal dominant and recessive modes of inheritance have been described for neuropathic and myopathic types of CIPO [5, 15, 16, 136, 138]; nonetheless, the majority of CIPO cases are sporadic with no defined or recognizable genetic background.

Genes involved in congenital aganglionosis (i.e., Hirschsprung disease) such as *GDNF* (glial-cell-derived neurotrophic factor), one of its related receptors (*GFRA1*, GDNF receptor-alpha-1), *EDN3* (endothelin 3), and its related receptor (*EDNRB*, endothelin 3 receptor B) have not, as yet, been shown to play a role in CIPO. On the other hand, three patients with a syndromic phenotype of CIPO combined with Waardenburg-Shah features (pigmentary abnormalities and sensorineural deafness) and an underlying "apparently normal" enteric innervation have been demonstrated to carry de novo heterozygous mutations of *SOX10* [139, 140]. Additionally, mutations in the following genes, *filamin A* [141], *actin γ-2* [43], *thymidine phosphorylase (TYMP)* [142], polymerase γ (*POLG1*) [143], and, finally, *RAD21* [144] and *SGOL1* [145], have also been identified in recessive forms of CIPO with an associated syndromic phenotype (Fig. 24.1). Affected families may benefit from genetic counseling.

Specific genetic mutations are associated to complications. Medullary thyroid carcinoma associated with MEN2b and neurogangliomatosis should be searched for by measuring serum calcitonin levels, and early prophylactic thyroidectomy may be considered [146]. In cases with cardiac involvement (SGOL1), a pacemaker is indicated since severe bradycardia may occur [145]. Filamin A gene on chromosome X as well as thymidine phosphorylase mutations are both associated to seizures and impaired neurological development [141].

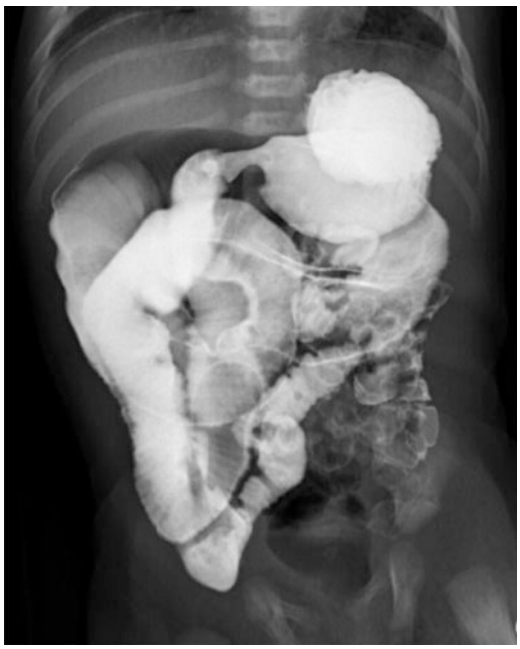

Fig. 24.1 Small bowel follow-through in a 6-month-old boy with an X-linked filamin A mutation-related CIPO. Note the malrotation, narrowed pylorus, and enlarged bowel loops

Histopathology

Studies in adults with CIPO reveal that GI histology can be normal in up to 10% of cases, although in the experience of the authors, this figure is likely to be higher in children. The role of histopathology in the diagnosis of CIPO is crucial; adequate full-thickness bowel biopsy (preferably a circumferential sleeve of at least 1–2 cm) is recommended whenever surgery is being considered [8, 27, 147]. Recent initiatives support a more standardized histological approach for the diagnosis in GI dysmotilities such as CIPO [26, 148, 149] (See Chap. 17).

On the basis of histology, CIPO is classified into neuropathy, myopathy, or mesenchymopathy; mixed forms (e.g., neuromyopathy) are also recognized [26, 150–152].

Neuropathies and myopathies can be further subdivided into inflammatory and degenerative. Inflammatory neuropathies are characterized by an infiltration of T lymphocytes and plasma cells in the myenteric plexuses (myenteric ganglionitis) and neuronal axons (axonopathy); five or more lymphocytes per ganglion are required for the diagnosis of myenteric ganglionitis [26, 153]. Interestingly, patients with lymphocytic infiltration of the myenteric plexus may also develop increased titers of antinuclear antibodies (ANNA-1/anti-Hu, anti-VGKC); the

latter could result in neuronal degeneration and loss via apoptotic and autophagic mechanisms [154–157]. Infiltration of the myenteric ganglia with other cells such as eosinophils and mast cells has also been identified, but their clinicopathological significance is yet to be determined [158–161].

Degenerative neuropathies are defined by a decrease in the number of intramural neurons along with changes in nerve cell bodies and axons [148, 153, 162–164]. It has been postulated that aberrant calcium signaling, mitochondrial disorders, production of free radicals, and abnormalities in the function of glial cells initiate apoptotic mechanisms that are involved in the degenerative process [148, 150, 165, 166].

Myopathies are also categorized as inflammatory and degenerative. Inflammatory myopathy, also termed leiomyositis, is characterized by infiltration of T lymphocytes into both the circular and longitudinal enteric muscle layers and if not treated appropriately with immunosuppressive agents may lead to a severe clinical picture of CIPO [45, 167]. A distinctive presumably acquired degenerative myopathy of unknown etiology, called African degenerative leiomyopathy (ADL), has been described in African populations in southern Africa [168]. The RET gene implicated in Hirschsprung disease appears to confer susceptibility to ADL although the exact mechanism is not known [169].

Histopathology in degenerative myopathies reveals vacuolization and fibrosis of the smooth muscle fibers [170, 171]. In the cases where the longitudinal muscle is more affected compared to the circular muscle layer, diverticula may be identified [172, 173].

Novel techniques in immunohistochemistry, e.g., smooth muscle markers such as smoothelin, smooth muscle myosin heavy chain, and histone deacetylase 8, may reveal subtle histopathologic abnormalities otherwise not detectable with conventional methods [174].

Mesenchymopathies are defined by ICC abnormalities (decreased density of ICC network, intracellular abnormalities) and have been identified in CIPO patients [148, 175]. Despite the fact that adequate data exist regarding the role of ICC in the pathogenesis of diabetic gastroparesis, further research is required to elucidate their involvement in the pathogenesis of other GI dysmotilities [26].

Clinical Picture

Signs and Symptoms

The symptomatology varies according to the age at diagnosis and the part of the GI tract, which is primarily affected. Intestinal malrotation is present in approximately one third of children with congenital CIPO (myopathic and neuropathic) [23]. Cardinal signs and symptoms of CIPO include those of obstruction, namely, abdominal distention (88 %), vomiting (69 %, which can be bilious), and constipation (54 %). Abdominal pain, failure to thrive, and diarrhea may also be part of the clinical picture (Table 24.2, Fig. 24.2) [8, 9, 147].

The diagnosis of CIPO is difficult due to the variable clinical presentation and the lack of a specific diagnostic test. The diagnosis should be suspected in children presenting with signs and symptoms of intestinal obstruction without an occluding lesion. The diagnosis of CIPO should be also considered when there is persistent vomiting after a Ladd's procedure for malrotation [56] when intestinal obstruction is associated with bladder dysmotility or when, in a full-term neonate, there is persistent or recurrent obstruction after exclusion of Hirschsprung disease and hypothyroidism. The differential diagnosis should be carefully considered because establishing a diagnosis of CIPO may be invasive, and the

Table 24.2 Clinical symptoms in children with chronic intestinal pseudo-obstruction

Study	Abdominal distension	Vomiting	Constipation	Failure to thrive	Abdominal pain	Diarrhea	Dysphagia
Faure et al. [176]	100	94	70	64	46	29	9
$n=105$							
Vargas et al. [11]	73	50	51	23	NA	21	2
$n=87$							
Granata et al. [177]	59	31	27	NA	NA	26	NA
$n=59$							
Schuffler et al. [29, 197]	23	19	20	15	NA	16	NA
$n=30$							
Heneyke et al. [22]	31	40	31	NA	NA	–	NA
$n=44$							
Muto et al. [13]	55	33	9	NA	3	2	NA
$n=62$							
Total	341 (88 %)	267 (69 %)	208 (54 %)	102 (31 %)	–	94 (24 %)	11 (3 %)
$n=387$							

NA, not available

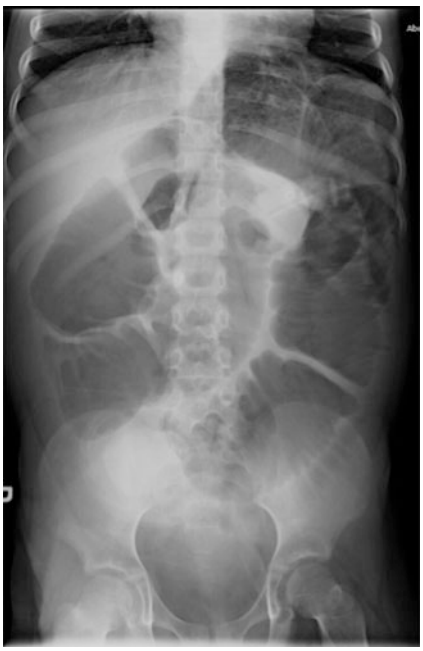

Fig. 24.2 Plain abdominal X-ray in a 7-year-old girl with CIPO. Note the enlarged and hugely dilated small bowel loops

psychological consequences in children and their families are significant.

Dehydration (which can be severe) and malnutrition are often underdiagnosed especially given that weight can be an unreliable measure due to pooling of significant volumes of fluid (third spacing) within distended gut loops. Delayed transit of gut content can also lead to small bowel bacterial overgrowth which can further exacerbate symptoms of diarrhea and abdominal distention [147].

Extraintestinal signs and symptoms may as well be part of the CIPO clinical presentation, e.g., recurrent urinary tract infections or neurologic abnormalities [18, 142]. Furthermore, patients may complain of symptoms indicative of an underlying disorder that accounts for secondary CIPO (e.g., proximal muscle weakness in dermatomyositis) [60].

The clinical course of CIPO is characterized by exacerbations and remissions; the former can be precipitated by various factors such as surgery, general anesthesia, infections, and emotional stress [27]. In the most severe cases, the natural course of the disease leads to significant deterioration of the intestinal function and ultimately in intestinal failure [9, 147].

Prenatal Symptoms

Although the majority of CIPO cases present in the neonatal period or early infancy, in a few cases the diagnosis is supported in utero by ultrasonographic findings of polyhydramnios, abdominal distention, and megacystis [8, 27]. Prenatal signs can be detected in about 20 % of cases [22, 176]. Megacystis is the most frequently reported sign, whereas dilated bowel at this age is quite rare. This has been noted in megacystis-microcolon-intestinal hypoperistalsis syndrome in which an antenatally enlarged bladder is seen by ultrasound in 88 % of cases, hydronephrosis in 53 %, increased volume of amniotic fluid in 34 %, and gastric distension in only 10 % [177]. Although some reports have described the detection of these signs by ultrasound as early as 16 weeks, more often the abnormalities are noted much later in gestation [178]. Antenatally diagnosed non-obstructive megacystis, with neonatal urological symptoms, may precede GI symptoms of pseudo-obstruction by several months.

Clinical Presentation After Birth

Fifty percent to two thirds of patients present within the first month of life and 80 % by 1 year of age. The remainder are detected sporadically throughout the first two decades of life [11, 21, 22, 176]. The clinical presentation is dependent on the age at onset.

Neonatal-Onset Form

In the neonatal form, CIPO presents as severe abdominal distension with bilious vomiting. Although not a universal finding, the abdominal X-ray may show dilated bowel loops with air-fluid levels suggestive of an organic intestinal obstruction. In megacystis-intestinal-hypoperistalsis syndrome, an obstructed urinary system leading to an abdominal distension may be the presenting feature, with symptoms of intestinal obstruction appearing within days to 12 months later. In order to avoid unnecessary surgery, an exploratory laparotomy should be deferred in a neonate with antenatal diagnosis of megacystis. In these neonatal cases, the air-fluid levels on X-ray may be missing. Some affected infants may present with abdominal distension and diarrhea secondary to bacterial overgrowth.

CIPO may be mimicked by immaturity of intestinal motility in preterm infants, and, thus, this diagnosis should be made with caution in this group as the migrating motor complex does not appear in its mature form until a gestational age of 34–35 weeks [179, 180].

Infantile or Late-Onset Form

The symptoms depend on the regions of the gastrointestinal tract primarily involved. Patients present with subacute and/or recurrent episodes of gastric, intestinal, and/or colonic obstruction necessitating frequent drainage and fluid replacement. This picture may be acute or insidious and chronic and persistent or more often intermittent. Exacerbations may be precipitated by a variety of causes including intercurrent infections, fever, vaccines, general anesthesia, and emotional stress. Diarrhea due to bacterial overgrowth is frequent and

may alternate with constipation or episodes of partial obstruction. Stasis of intestinal contents is common in CIPO, and chronic dilatation leads to decompensation and elongation of the bowel, further impairing motility. When fluid and air accumulate in these decompensated loops, torsion caused by mechanical forces is possible. Dehydration (which can be severe) and malnutrition are often underdiagnosed especially given that weight can be an unreliable measure due to pooling of significant volumes of fluid (third spacing) within distended gut loops (147). Mechanical obstruction is normally absent in CIPO patients, but it can however be a complication of CIPO, especially after multiple interventions. Volvulus of the splenic flexure and colonic volvulus have been reported in numerous CIPO cases due to torsion of fluid-filled bowel loops [181–183].

Abdominal pain is often severe enough to lead to feeding difficulties resulting in malnutrition. Notwithstanding frequently detected esophageal involvement by manometry, dysphagia is rarely reported [184]. Recurrent episodes of functional partial bowel obstruction may be very difficult to differentiate from true mechanical obstruction in the child who has undergone a prior laparotomy and who may have adhesions. A change of symptoms such as the new occurrence of abdominal pain may suggest the latter.

Urinary tract involvement occurs in 33–92 % of cases, independent of the type of CIPO [176, 185–187]. Megacystis with a hypo-contractile detrusor, increased bladder capacity, and compliance is the most frequent pattern of urological abnormality (bladder adynamia). Ureterohydronephrosis is seen in 56–68 % of cases, but vesicoureteral reflux occurs in less than 10 % [187]. Urinary tract infections are frequent but may be asymptomatic. The renal prognosis is generally good, provided that careful, active evaluation and management of the poorly dynamic bladder are performed to ensure adequate bladder emptying and to prevent urinary tract infection [187]. Where they are taken, bladder biopsies show nonspecific fibrotic changes in both neuropathic and myopathic forms of CIPO and are thus not useful for subtype classification.

Comorbidities

Malrotation is frequent, especially in neonates (up to 40 % of cases) [21, 22, 176], and has been reported in X-linked familial syndromes associating CIPO, malrotation, and pyloric non-hypertrophic stenosis [141, 188–190] (Fig. 24.1).

The physical examination should encompass a thorough neuromuscular assessment, including testing for pupillary reactions to light and accommodation and external ocular movements to help identify conditions associated with autonomic neuropathy or mitochondrial diseases. Testing for orthostatic stability should be performed in children, especially where postural dizziness, visual disturbances, and sweating abnormalities may suggest the presence of an underlying autonomic neuropathy [41].

External ophthalmoplegia associated with deafness may suggest a mitochondrial defect, namely, mitochondrial neurogastrointestinal encephalopathy (MNGIE). The onset of symptoms (gastrointestinal or ocular or both) generally occurs during adolescence, although very early-onset disease has been reported (5 months of age) [191]. Peripheral neuropathy and diffuse muscle weakness are the predominant manifestations, although almost all patients have indices of leukoencephalopathy on magnetic resonance imaging of the brain [48]. Thymidine phosphorylase activity and plasma thymidine should be measured when suspecting such a diagnosis [192]. Audiological assessment is important to rule out deafness, seen in patients with a *SOX10* gene mutation [139, 140]. The dermatological examination should note signs of connective tissue disease (i.e., scleroderma, dermatomyositis, lupus) including: Raynaud's phenomenon, skin eruption, palmar erythema, telangiectasia, nodules, and scleroderma of the hands, feet, face, and forearms. Digestive symptoms may precede the skin involvement in these disorders [193].

Neural crest-derived tumors and pheochromocytoma should be suspected and ruled out in children and infants with CIPO; appropriate CT imaging and ultrasound studies should be considered to exclude the presence of thoracic or abdominal tumors [194].

Cardiac rhythm and function must be evaluated by ECG and echocardiography, since dysfunction of the cardiac sinus node may be associated to CIPO [195], and abnormal cardiac contraction should lead one to suspect muscular diseases such as desmin myopathies [196].

Diagnosis

Chronic intestinal pseudo-obstruction should be suspected in children with early-onset, chronic, recurrent, or continuous signs of intestinal obstruction especially where imaging or indeed surgery fails to reveal a mechanical obstruction of the gut (e.g., repeated "normal" exploratory laparotomies). Since the symptoms of CIPO are not specific, a careful differential diagnosis is of paramount importance.

The diagnosis of CIPO should be guided by a structured algorithm. A detailed history combined with a meticulous clinical examination and laboratory tests (e.g., serum electrolytes, TSH, lactic acid, specific autoantibodies) may suggest the presence of CIPO and potentially elucidate its cause; however, the establishment of a definitive diagnosis should rely on the use of targeted investigations to (1) exclude mechanical occlusion of the gut lumen, (2) confirm GI dysmotility, and (3) rule out treatable causes.

The diagnostic tests, which exclude luminal obstruction and confirm the presence of impaired GI motility in children, thus ruling in the diagnosis of CIPO, are discussed below.

Imaging

Since small bowel is always involved, plain abdominal radiographs demonstrate a dilated GI tract, with air-fluid levels (Fig. 24.2), while contrast GI series can demonstrate anatomical abnormalities (e.g., malrotation, microcolon) and also exclude the presence of gut occlusive lesions [2, 147, 197, 198] (Fig. 24.3 & 24.4). It needs to be kept in mind that a water-soluble substance should be used instead of barium in order to prevent flocculation and inspissation of the contrast material.

Novel imaging modalities such as multidetector row helical CT and cine-MRI have been recently performed with promising results in adult series, but there is currently limited data regarding their applicability and usefulness in pediatrics [199–201].

Endoscopy

Endoscopy may identify upper or lower bowel mechanical occlusion previously missed on radiology and allows for duodenal biopsies to exclude mucosal inflammation [195]. Novel techniques (e.g., natural orifice transluminal endoscopic surgery—NOTES) may revolutionize the role of endoscopy in the diagnosis of gut motility disorders by providing the ability of full-thickness biopsy sampling in a safe and minimally invasive way [202, 203].

Motility Investigations

These studies are performed in order to assess the GI motility and to define the underlying pathophysiologic process; in pediatrics they form the hallmark of diagnosis. The aforementioned studies include gastrointestinal manometries (esophageal, antroduodenal, colonic, anorectal) (see Chaps. 7, 8, 9, and 10), scintigraphy (e.g., gastric emptying, colonic transit) (see Chap. 14), electrogastrography, and radiopaque marker studies (see Chap. 15). The usefulness of novel technologies, such as SmartPill, remains to be determined [8, 204, 205].

Although in children with CIPO the involvement of the GI tract may be generalized, the small intestine is always affected; thus, antroduodenal manometry remains the most discerning test. It needs to be stressed, though, that the optimal placement of the manometric catheter is of pivotal significance for a *lege artis* execution and precise interpretation of this test [206]. Neuropathic cases manifest with uncoordinated contractions, which are of normal amplitude, whereas in myopathic CIPO motor patterns have normal coordination; however, the amplitude of intestinal contractions is low [184, 207, 208]. Additionally, manometry may facilitate the dynamic assessment of potential pharmacotherapeutic options and feeding strategies (e.g., feasibility of oral or enteral feeds) as well as indicate disease prognosis [209–211]. Antroduodenal manometry features suggestive of CIPO are depicted in Table 24.3 and also described in Chap. 8.

In the most challenging cases, exploratory surgery (laparotomy or laparoscopic-assisted procedures) may be required to definitively exclude mechanical obstruction; however, it should be borne in mind that surgery may precipitate a

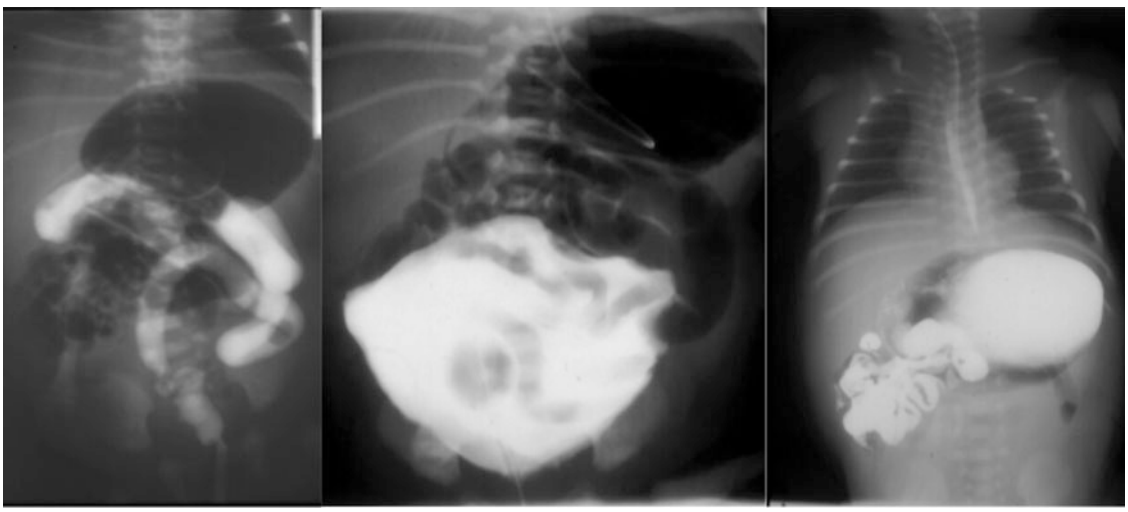

Fig. 24.3 Girl neonate with megacystis, microcolon, and hypoperistalsis syndrome. *Left*: Colonic opacification showing small nonfunctional microcolon. *Middle*: Cystography demonstrating enlarged bladder with "footprints" of digestive loops. *Right*: Small bowel follow-through showing malrotation and nonfunctional small bowel. In neonates, despite the small bowel involvement precluding any enteral feeding, the small bowel loops may not be enlarged converse to older children in whom dilated small bowel is always present

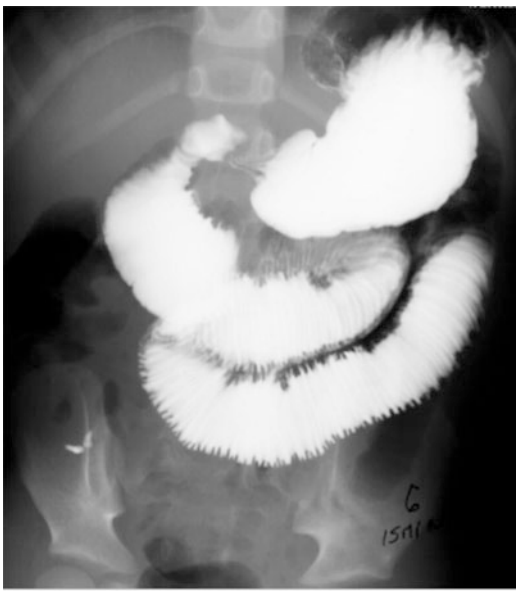

Fig. 24.4 Small bowel follow-through in a 6-year-old boy with CIPO. Note the enlarged and dilated small bowel loops

Table 24.3 Features in antroduodenal manometry associated with CIPO

Interdigestive or fasting period
Absence of phase III
Short intervals between phase III
Abnormal phase III
– Stationary
– Retrograde
Non-migrating burst of contractions[a]
Sustained simultaneous cluster of contractions[b]
Low-amplitude contractions
Postprandial or fed period
Failure to switch to postprandial period
Postprandial hypomotility
– Low frequency of contractions
– Low amplitude of contractions
Non-migrating cluster of contractions

[a]Burst of contractions is defined as sequences of intense irregular pressure waves not satisfying the definition for phase III of MMC
[b]Cluster of contractions is defined as the presence of three to ten pressure waves of slow frequency showing higher amplitude and duration than isolated individual contractions

pseudo-obstructive episode and may also lead to intra-abdominal adhesion formation, which in turn can further complicate future diagnostic or therapeutic procedures as well as lead to secondary mechanical obstruction. Where possible, investigations and then diagnostic/therapeutic surgery should be performed in timeline sequence and in referral centers with relevant expertise in the management of CIPO patients.

Histopathology along with genetics can also be very useful in establishing or confirming the diagnosis of CIPO, highlighting the underlying pathophysiologic process and thus aiding the overall management. Figure 24.5 summarizes the basic steps in the diagnostic evaluation of pediatric patients with suspected CIPO.

Differential Diagnosis

CIPO has to be differentiated from mechanical obstruction of the GI tract; the latter is usually characterized by marked abdominal pain (in keeping with the abdominal distention), specific radiologic signs, and manometric patterns [212, 213]. Acute functional obstruction (e.g., postoperative ileus), functional GI disorders (e.g., rumination syndrome), and pediatric condition falsification should be considered and appropriately investigated and managed [147, 214, 215]. Table 24.4 provides differential diagnoses of CIPO.

Treatment

The therapeutic approach in CIPO is threefold as it aims to (1) preserve growth and development by maintaining adequate nutritional intake; (2) preserve and even promote GI motility with combined medical and surgical interventions; and (3) treat disease-related complications or underlying pathologies in the cases of secondary CIPO.

In spite of the limited effect of the currently applied therapeutic options, refinements and evolution in nutritional, medical, and surgical strategies have considerably improved the overall CIPO management [137, 216]. Acute episodes of pseudo-obstruction are generally treated conservatively by intravenous fluid administration (patients remain nil by mouth) and decompression of the affected bowel with drainage of luminal contents via NG tube or preformed ostomies. Careful attention to fluid and electrolytes' balance is imperative.

Nutrition

The role of nutrition in CIPO is of paramount significance as it is well established that gut motility improves with optimal nutritional support and declines in the face of under- or malnutrition [8]. In the long term, approximately one third of pediatric CIPO patients require either partial or total parenteral nutrition; another third requires a degree of intragastric or enteral feeding, whereas the remaining children are able to tolerate sufficient oral nutrition. Within all of the abovementioned groups, patients able to tolerate feeds may require

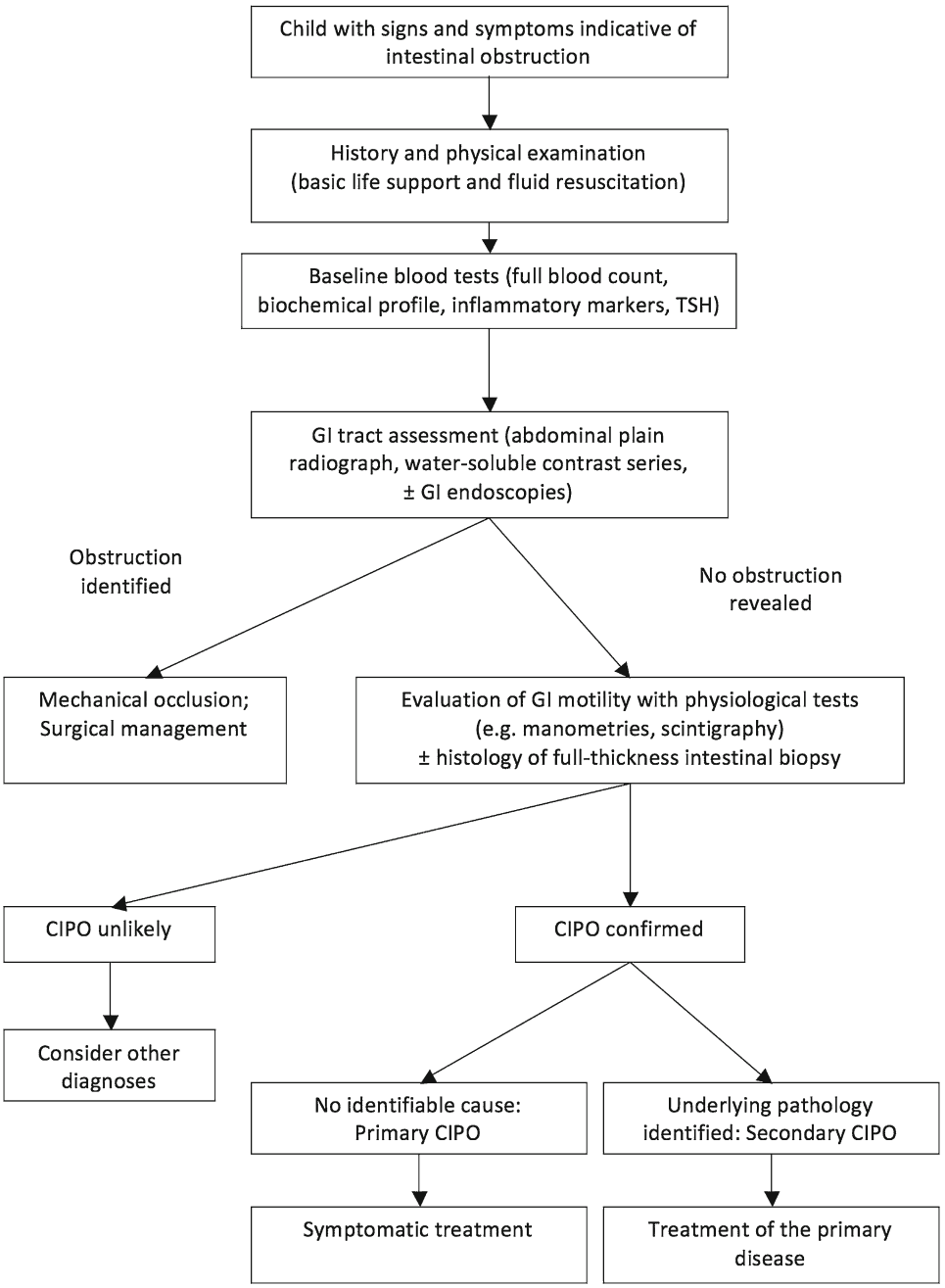

Fig. 24.5 Suggested diagnostic algorithm for childhood chronic intestinal pseudo-obstruction. (Modified from Rudolph CD, Hyman PE, Altschuler SM, Christensen J, Colletti RB, Cucchiara S, et al. Diagnosis and treatment of chronic intestinal pseudo-obstruction in children: report of consensus workshop. J Pediatr Gastroenterol Nutr. 1997;24(1):102–12, with permission)

Table 24.4 Differential diagnosis of CIPO in children

Aerophagia
Gastroparesis
Constipation
Rumination syndrome
Cyclic vomiting syndrome
Severe irritable bowel syndrome
Bacterial overgrowth of various origin (lactase deficiency, disaccharidase deficiency, intestinal duplication)
Aerodigestive fistula
Fabricated or induced illness (Munchausen's syndrome or pediatric falsification disorder)

some dietary modification in order to maintain enteral nutrition and avoid bezoar formation (e.g., low residue feeds, bite and dissolvable food, restriction diets, hydrolyzed formula).

Although parenteral nutrition is lifesaving, it is associated with significant risk of complications, such as central line infections and liver disease; thus, maintaining patients on maximally tolerated enteral nutrition is always strongly encouraged [27]. In the more severe CIPO cases, continuous rather than bolus feeds administered via a gastrostomy or jejunostomy may be better tolerated; the latter is particularly true in those children with impaired gastric motor function [217–219].

Medications

Pharmacotherapy in CIPO patients is mainly confined to the control of intestinal inflammation, suppression of bacterial overgrowth, and promotion of GI motility [210, 219]. In cases of a proven inflammatory process confirmed on full-thickness intestinal biopsies and histology such as lymphocytic or eosinophilic ganglionitis and inflammatory leiomyositis, immunosuppression may be needed.

Prokinetics (e.g., metoclopramide, domperidone, erythromycin, azithromycin, octreotide, neostigmine) and antiemetics (e.g., promethazine, ondansetron) have been used to reduce the severity of nausea and vomiting and improve the GI motor function [220–223]. The use of some of these agents is limited because of their variable efficacy and unacceptable extra-intestinal side effects (e.g., metoclopramide, neostigmine). The best studied and tested prokinetics, i.e., cisapride and tegaserod, have been withdrawn from the market due to safety concerns [224]. Recent data suggests that antibiotics such as co-amoxiclav may have prokinetic effects and induce an increased number of migrating motor complexes during the fasting phase of antroduodenal manometry. The need for novel prokinetics with increased safety profile and efficacy has resulted in the development of new products (e.g., prucalopride, aprepitant, ghrelin), but there is limited data of their use in pediatric CIPO, further impacted on by restricted availability and licensing [225–227]. Undoubtedly, current medical regimens for CIPO are based on limited literature and/or expert opinion (e.g., combined use of octreotide and erythromycin) and are yet to be tested in future in the context of controlled trials [210, 228].

Surgery

Surgery remains a valuable intervention on patients with CIPO as it has a multidimensional role in both the diagnostic (e.g., full-thickness biopsies) and therapeutic processes (e.g., insertion of feeding tubes, formation of decompressing ostomies such as gastrostomy, ileostomy) [219, 229, 230] (See Chap. 50).

Indeed, adequate bowel decompression (e.g., gastrostomy, ileostomy) is crucial not only in providing symptomatic relief by reducing the frequency and the severity of pseudo-obstructive episodes but also in limiting further deterioration of the intestinal motor activity secondary to chronic distention and in enhancing the tolerance of enteral feeding [21, 22, 219, 229, 231–233]. Long decompression enteral tubes and extensive bowel resections are approaches mainly reported in adult CIPO cohorts but remain untested in terms of practicality, efficacy, and safety in pediatrics [234–236]. Moreover, small bowel resections may lead to short gut syndrome and intestinal failure-associated liver disease [229, 237]. One additional concern is that resections of the small intestine may decrease the abdominal domain required for the successful outcome of a potentially necessary future intestinal transplantation [229, 237].

Other surgical procedures aiming in lengthening a dilated intestinal segment (e.g., longitudinal intestinal lengthening and tailoring, serial transverse enteroplasty) have shown promising results in children with intestinal failure including patients with CIPO [238].

Stoma prolapse [239], recurrent pancreatitis [240], diversion colitis [241], and excessive fluid losses with high ileostomy output [242] have been reported in patients with CIPO. In patients with gastric and upper digestive tract involvement, gastric perforation and gastric bezoars may occur [176].

Closure of the decompressive ileostomy and restoration of the gut continuity may be attempted in carefully selected patients who have demonstrated significant and clear improvement post-ileostomy formation, have managed to wean parenteral nutrition, and remain on full enteral and/or oral feeds without experiencing any troublesome symptoms for a period of at least 2 years. In the opinion of the authors, this is most likely to occur in neuropathic cases of CIPO and least in myopathies. In patients that show recovery with an ileostomy in situ, an ileo-rectal Duhamel pull-through has proven to be the most effective approach [22, 176, 236, 243].

The incidence of the enterostomy-associated complications is not insignificant in CIPO patients as these patients do have an increased rate of stomal prolapse along with a high risk of intestinal necrosis [239]. A meticulously constructed ileostomy combined with careful management of the ostomy reduces the probability of stomal prolapse, thus minimizing the risk of additional intestinal resection [22, 239].

Novel surgical methods involve implantation of devices providing electrical pacing of the GI neuromusculature, but data in children are scanty and limited [244]. Significant progress has been made in regenerative medicine especially with neural cell replacement within the bowel. This has not yet reached clinical trials and is hampered by poor disease characterization [245].

Small bowel transplantation still remains today the only definitive cure for CIPO. The outcomes and survival rates in experienced centers have significantly improved (up to 50 % survival rate at 3 years) during the last decade owing to advances in both the surgical approach (e.g., multivisceral transplantation) and the immunosuppressive treatment [238, 246–252] (see Chap. 50).

Natural History, Outcome, and Prognosis

Both pediatric and adult CIPO patients have a severe clinical course, characterized by repetitive relapses and remissions. Regrettably, the low index of suspicion among physicians, along with the lack of well-defined diagnostic criteria and

readily available facilities in performing specialized diagnostic tests (e.g., manometry), often accounts for repetitive unnecessary investigations and surgery as well as delayed diagnosis and thus initiation of appropriate management [15–17, 162].

The majority of the patients complain of symptoms, which progressively worsen and impact upon the tolerance of enteral nutrition consequently increasing reliance on total parenteral nutrition. The latter in conjunction with disease-related adverse events (e.g., central line infections, impairment of the liver function, immunosuppression after small bowel transplantation, surgical procedures) account for high morbidity, poor quality of life, and mortality rates up to 30 % [11, 22, 29, 176, 177, 197, 253, 254].

Despite recent diagnostic and therapeutic advances, CIPO in children remains a serious, life-threatening disease with significant impact on the well-being not only of patients themselves but of their families as well [254].

Outcome

In secondary and acquired forms of CIP, outcome is dependent of the underlying disease responsible for the dysmotility. In cases of destruction of enteric innervation or musculature, deterioration may occur rapidly without specific treatment [255].

Most often viral infection resolves spontaneously [83, 256] but some chronic cases have been reported [257, 258].

In primary forms of CIPO, the prognosis is poor. In one series of 105 patients, two thirds required parenteral nutrition and 41 % could not be enterally fed. More than half of the patients were TPN dependent for periods ranging from 2 months up to 16 years. Eleven patients (10 %) received TPN for more than 10 years. Twenty-four of the 58 patients who underwent bypass surgery were able to eat normally, and 20 of those eventually had their stoma closed [176]. Heneyke and colleagues reported that if TPN is required for more than 6 months, the child will probably be TPN dependent for at least 4 years [22].

Mortality

Progress in the management of parenteral nutrition and the use of bowel decompression have modified the high mortality rate reported in historical series in neonates, for whom up to 90 % of patients died before 1 year of age [57, 177]. In series published more recently, mortality varied from 4.8 % (3/62 patients) [13] to 10 % (10/105) [176] and 25 % (22/85) [21] and in one study just over 30 % (14/44) [22]. Of these, underlying CIPO is rarely the primary cause of death except in cases with MEN2B and medullary carcinoma. In pediatric series reported to date, the high mortality rate is almost always due to iatrogenic complications. Long-term TPN-related complications, including central venous catheter-associated sepsis, liver failure, and thromboembolic events, as well as posttransplantation complications are the major contributing factors to mortality and morbidity in CIP patients [21, 22, 176]. Sudden cardiac arrest has been reported in two patients with chronic intestinal pseudo-obstruction [259].

Prognostic Factors

In the large pediatric series published to date, comparison between patients requiring and those no longer requiring artificial feeding shows significant clinical differences in terms of likelihood of neonatal onset, urinary tract involvement, requirement for surgery during the course of the disease, and myopathic disorders, all features which are more frequent in cases with a poor prognosis [21, 22, 176]. The presence of phase III of the MMC on antroduodenal manometry has been reported by several groups to be a good prognostic indicator for tolerance of enteral feeding [184, 217] response to cisapride [209] and mortality [211]. Malrotation is also a factor associated with worse prognosis [22].

Summary

Pediatric CIPO is an enigmatic disease with poorly defined etiopathogenesis, which is reflected on the limitations encountered in both the diagnostic process and therapeutic management. Clearly multinational initiatives are required to raise awareness, establish stringent diagnostic criteria, and evolve current therapeutic modalities.

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