

Causes and prognosis of chronic intestinal pseudo-obstruction in 48 subjects

A 10-year retrospective case series

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Abstract

The aim of the study was to evaluate the prognosis and survival of pediatric subjects with chronic intestinal pseudo-obstruction (CIPO) and investigate the independent risk factors affecting their prognosis.

This was a retrospective case series of all pediatric subjects suffering from CIPO and treated at the Pediatric Surgical ward of Xinhua Hospital between January 2006 and January 2016.

The overall mortality was 19/48 (39.6%). Because of delayed CIPO diagnosis, many subjects underwent a variety of surgical procedures. The rate of additional surgical procedures was high (35/48, 72.9%), but the number of surgical procedures, parenteral nutrition, and megacystis did not affect mortality. Mycotic infection was significantly associated with mortality, while onset at <1 year and hypoganglionosis showed a tendency to be associated with mortality.

Mycotic infection was associated with mortality of children with CIPO. Despite improving treatment approaches, the overall prognosis of CIPO remains poor. The choice of the surgical intervention could be based on standard criteria.

Abbreviations: CIPO = chronic intestinal pseudo-obstruction, CT = computed tomography, EN = enteral nutrition, MCT = medium-chain triglycerides, MMIHS = megacystic microcolon and intestinal hypoperistalsis syndrome, PN = parenteral nutrition, SBS = short bowel syndrome, α -SMA = α -smooth muscle actin.

Keywords: chronic intestinal pseudo-obstruction, hypoganglionosis, management, prognosis, risk factors

1. Introduction

Chronic intestinal pseudo-obstruction (CIPO) is a rare disease characterized by compromised intestinal peristalsis without mechanical occlusion, leading to impaired food transport along the gut.^[1] The diagnosis can be made if the symptoms persist for 2 months in the case of neonatal onset or for 6 months afterwards.^[1] Nevertheless, there is no gold standard for the diagnosis of CIPO and primary CIPO is considered in the absence of another primary disease.^[1] Diagnosis is based on symptoms,

radiologic findings (dilated bowels), endoscopic examination to rule out mechanical obstruction, and bowel manometry.^[2]

Only a few studies examined the incidence of CIPO, suggesting that the annual incidence of CIPO is about 100 neonates in the United States^[3] and of 3.7 per million children under 15 years of age.^[4] In adults, the etiology is mostly neuropathic and death occurs because of severe myopathic compromise.^[2,5] Compared with its adult counterpart, pediatric CIPO has a more severe course and even poorer prognosis. The etiology is congenital in most pediatric subjects,^[6] but the underlying mechanisms remain unclear despite the identification of pathogenic genes in some subtypes.^[7-9]

Because of etiologic heterogeneity, nonspecific manifestations, and low clinical awareness, the diagnosis of CIPO is likely to be delayed and the subjects may suffer from multiple unnecessary surgical procedures, leading to high morbidity and mortality. Therefore, the aim of the present retrospective study was to evaluate the prognosis and survival of pediatric subjects with CIPO and investigate the independent risk factors affecting their prognosis.

2. Methods

2.1. Study design and subjects

This was a 10-year retrospective case series. All pediatric subjects suffering from enteric dysmotility and treated at the Pediatric Surgical ward of Xinhua Hospital between January 2006 and January 2016 were included. The subjects had to fulfill the following criteria to be diagnosed with primary CIPO^[1,2,10] and included in the present study: recurrent or continuous symptoms of bowel obstruction in the absence of mechanical obstruction;

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and symptoms sustained for 2 months in case of neonatal onset or for 6 months afterwards. Common symptoms include delayed meconium exclusion, constipation, abdominal distention, and bilious vomiting. The subjects with any primary disease possibly affecting enteric motility (such as diabetes mellitus, sclerosis, or Hirschsprung disease) were excluded. The study was approved by the Institutional Review Board of Xin Hua Hospital, School of Medicine, Shanghai Jiao Tong University. The need for individual consent was waived because of the retrospective nature of the study.

2.2. Follow-up

All subjects were followed up for at least 3 months. The last follow-up visit of the last included subject was performed in April 2016.

2.3. Data collection

Age at onset, prenatal history, delivery history, symptoms at presentation, physical examination, imaging (plain X-rays, upper and lower gastrointestinal contrast studies, abdominal computer tomography [CT], endoscopy, and/or anorectal manometry), drug history, surgical history, and pathologic diagnosis were collected from the charts. Data regarding mycotic infections were extracted from the medical charts.

2.4. Nutrition

Total parenteral nutrition (PN) was performed for subjects who could not be fed orally. The exact PN protocol was tailored to each specific subject. Nasogastric or nasojejunal feeding tube was performed after stoma formation. If the subject could tolerate continuous infusion, the infusion was switched to slow infusion for 2 hours, with intervals of 1 hour, and then every 3 hours. According to the amount of enteral nutrition (EN), the PN was reduced gradually. The aim was to establish EN and stop PN. EN was lactose-free and contained amino acids or deeply hydrolyzed proteins, and medium-chain triglycerides (MCT). Due to complications (mainly liver dysfunction) and variable disease conditions, the course of nourishment had to be tailored to each subject. Liver dysfunction was defined as 2 consecutive direct bilirubin measurements $>2\text{ mg/dL}$ in the absence of any other cause of liver dysfunction.

2.5. Histopathology

All cases were reviewed by 3 pathologists, including 1 chief clinician and 1 associate research fellow. The slides were reviewed independently. Hematoxylin and eosin (H&E) staining (Shanghai Mingbo Co, Ltd, Shanghai, China) was performed routinely using 4- μm paraffin-embedded sections from the original surgical specimens (kept in the tissue repository of the Pathology Department) from the 48 subjects to confirm the diagnosis of CIPO. Among them, there were 43 ileal specimens and 31 colon specimens. Any disagreement was discussed with a 4th reviewer (the 1st author). Immunohistochemistry and transmission electron microscopy results were retrieved from the medical charts for 21 subjects with available results.

Hypoganglionosis was defined according to a consensus statement by Schappi et al^[11] as <1 ganglia per 10 mm with a mean number of <2 neurons per ganglion. Type B intestinal ganglion cell dysplasia was defined as submucosal ganglions

containing more than 8 neurons. Degenerative neuropathy was defined as cellular degenerative changes. Inflammatory neuropathy was defined as lymphocytic infiltration in or around the ganglion. Structural changes in muscularis propria were defined as lack of muscular layer or excessive muscular structures. Myofibrillar protein abnormalities were defined as the lack of α smooth muscle actin expression in the circular muscular layer. Inflammatory smooth muscle disease was defined as lymphocyte infiltration in the muscular layer. Smooth muscle degenerative disease was defined as degenerative changes of muscle cells and significant proliferation of muscle fibers.

2.6. Statistical analysis

Continuous data were presented as mean \pm standard deviation or median (range or IQR) and analyzed using the Student *t* test or the Mann–Whitney *U* test, as appropriate. Categorical data were described as proportions and analyzed using the Chi-squared test or the Fisher exact test, as appropriate. Survival was evaluated using the Kaplan–Meier method and the log-rank test. SPSS 16.0 for Windows (IBM, Armonk, NY) was used for statistical analysis. Two-sided *P*-values $<.05$ were considered statistically significant.

3. Results

3.1. Characteristics of the subjects

Table 1 presents the characteristics of the subjects. CIPO was diagnosed in 28 males and 20 females. No subject was diagnosed with CIPO before the first surgical procedure. Except 1 pair of monozygotic twins both being affected and 1 mother who had a stillbirth in the third trimester, no family history was reported.

Eleven subjects were premature, among whom 2 were delivered earlier than the 32nd gestational week. There were 2 postterm births. Birth weight was $>3\text{ kg}$ in 34 subjects. Most subjects ($n=26$) developed their symptoms during the neonatal period, soon after birth. About 5 and 7 had onset of illness in infancy and childhood, respectively.

There were 11 subjects with associated anomalies: the urinary tract was involved in 5 subjects, 4 had mild congenital heart disease, 1 had an omphalo-enteric fistula, and 1 had hallux valgus. Abdominal plain X-ray was performed in all children. Upper gastrointestinal contrast studies were performed in 32 children and lower gastrointestinal tract contrast studies in 22. Seven subjects underwent abdominal CT, 4 received endoscopy, and 10 were assessed by anorectal manometry. Plain X-ray showed dilated guts with fluid in the abdomen. Contrast studies

Table 1
Characteristics of the 48 subjects with chronic intestinal pseudo-obstruction.

	All	Survivor	Death	<i>P</i>
Gender, male/female	28/20	15/14	13/6	.251
Birth weight, g	3098 \pm 662	3034 \pm 667	3196 \pm 661	.415
Number of surgical procedures	2.3 \pm 1.4	2.5 \pm 1.4	2.0 \pm 1.2	.155
Parenteral nutrition duration, mo	1 (1, 4)	1 (1, 3)	1 (1, 5)	.800
Cause of death				
Severe infection			15	
Aspiration			2	
DIC			2	
Follow-up, mo	30 (3, 120)			

Table 2**Details of the surgical procedures in the children with chronic intestinal pseudo-obstruction.**

	1st surgical procedure		2nd surgical procedure		3rd surgical procedure		4th surgical procedure		5th surgical procedure		6th surgical procedure						
	DT	RO	DT	RO	DT	RO	DT	RO	DT	RO	DT	RO					
Colostomy	7 (16)	0	6 (86)	3 (9)	1 (33)	2 (67)	1 (5)	1 (100)	0	0	0	0					
Ileostomy	20 (42)	4 (20)	14 (70)	12 (34)	3 (25)	7 (58)	7 (32)	4 (57)	3 (43)	0	0	2 (50)	0	1 (50)	0	0	
Colorectal pull-through	5 (10)	0	4 (80)	3 (9)	1 (33)	1 (33)	1 (5)	0	0	1 (17)	0	1 (100)	0	0	0	0	
Ileectomy	0	0	0	0	0	0	0	0	0	0	0	1 (25)	0	0	0	0	
Colectomy	2 (4)	0	2 (100)	1 (3)	0	0	3 (146)	0	0	0	0	0	0	0	0	0	
Rectal biopsy	4 (8)	2 (50)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Stoma closure	0	0	0	5 (14)	0	4 (80)	4 (18)	0	0	1 (17)	0	0	0	0	1 (100)	0	
Adhesiolysis	5 (10)	0	4 (80)	10 (29)	2 (20)	8 (80)	4 (18)	0	1 (25)	3 (50)	0	2 (67)	1 (25)	1 (100)	1	0	
Colostomy+ ileostomy	1 (2)	0	1 (100)	1 (3)	0	0	0	0	0	0	0	0	0	0	0	0	
Colectomy + ileostomy	2 (4)	0	2 (100)	0	0	0	0	0	0	0	0	0	0	0	0	0	
Colectomy + Colostomy	1 (2)	0	1 (100)	0	0	0	2 (9)	0	2 (100)	0	0	0	0	0	0	0	
Ileectomy + ileostomy	1 (2)	0	1 (100)	0	0	0	0	0	0	1 (17)	0	1 (100.0)	0	0	0	0	
N	48	6 (13)	35 (73)	35	7 (20)	22 (63)	22	5 (23)	6 (27)	6	0	4 (67)	4	1 (25)	1 (25)	1	0

All data shown as n (%), indicating the number of subjects who underwent a specific type of surgical procedure as the 10th surgical procedure.

DT = death toll among the subjects who underwent the type of surgical procedure, RO = additional surgical procedure among the subjects who underwent the type of surgical procedure.

and endoscopic investigation did not show evidence of mechanical occlusion. Among the 48 subjects, 44 underwent a surgical procedure.

3.2. Nutritional support

All subjects received PN and/or EN. Eight children needed total PN support for more than 6 months, and 5 of them required regular PN afterwards. Thirty-five subjects required PN for a shorter period, but only 19 of them were successfully weaned off PN and 14 died. Five subjects received a nasojunal feeding tube and 1 received a gastrostomy jejunal tube after 2012; all 6 achieved optimal outcomes.

3.3. Medication

Prokinetics were administered to 14 children (domperidone, n=7; erythromycin, n=6; Chinese traditional medicine with ventral massage, n=4; itopride, n=2; and mosapride, n=1). Only itopride and Chinese traditional medicine temporarily relieved abdominal distension in 1 subject.

3.4. Surgical management

Only 4 subjects underwent rectal mucosa biopsy without any other surgical management: 2 died before further treatment and the parents of the other 2 children refused surgery despite sustained symptoms. Nine subjects only had 1 surgical procedure during their disease course. Ileostomies were performed on 6 children with neonatal onset and severe abdominal distension; 4 of them died and 2 needed long-term PN support. One colostomy was performed on 1 subject who developed severe and intractable constipation, but the child still suffered from obstruction. Two children whose symptoms (mild) appeared later in childhood only laparotomy, and they achieved stoma closure and oral nutrition with postoperative conservative therapy.

The primary procedure (ileostomy, n=24; colostomy, n=9; pull-through, n=5; and colectomy, n=5) did not improve the

symptoms in the remaining 35 children and they required multiple surgical procedures. Table 2 presents the numbers and types of surgical procedures in the 48 subjects.

Because they were not diagnosed with CIPO at first, 5 subjects underwent pull-through as their first surgical procedure, although it is not standard procedure for CIPO and is controversial. Among the 10 children who received colorectal pull-through, 6 needed stoma formation after the surgical procedure and 2 died after the procedure. Colectomies were conducted as first surgical procedures in 5 subjects, which all ended in the need for stoma, while 6 children received colectomy as later surgical procedure and had better outcomes. Two of the 3 children who received ileectomy died, and only an 11-year boy survived with intermittent intestinal occlusion. Most surgeons selected ileostomy or colostomy to release the symptoms, especially in younger subjects with a critical condition. There were 47 ileostomies and 16 colostomies, but 11 and 2 children died after these procedures, respectively. Twenty-seven ileostomies and 10 colostomies had to be refashioned.

3.5. Outcomes

Among the 48 subjects who were followed up, mortality was 19 (39.6%) as of May 31, 2016. All deaths occurred within 2 years of age, except one girl who died at 4 years of age. Eighteen subjects died after the 3rd surgical procedure and one 10-month boy died after the 5th surgical procedure. Among the 29 survivors (aged of 2–26 years on May 31, 2016), 15 children in whom the stoma was eventually closed could receive EN without obvious manifestation of intestinal occlusion. Five relapsed with mild bloating.

Mycotic infection occurred in 10 subjects. Other common complications included liver dysfunction (n=13), secondary hypothyroidism (n=4), diabetes insipidus (n=2), and vesical calculus (n=1). Perforation occurred in 3 children and was the actual primary manifestation in 2. Univariate analyses of factors associated with death are shown in Table 3. Mycotic infection was significantly associated with mortality, while onset at <1

Table 3**Univariate analysis for predictors of mortality among subjects with chronic intestinal pseudo-obstruction.**

	Dead	Survivors	P
Birth weight (≥ 3 / < 3 kg)	15/4	19/10	.317
Preterm/term	4/15	7/22	1.00
Onset age (≤ 1 / > 1 y)	19/0	22/7	.058
Megacystis (yes/no)	17/2	26/3	1.00
PN usage (≤ 3 / > 3 mo)	13/6	22/7	.571
Mycotic infection (no/yes)	11/8	26/3	.027
Liver dysfunction (no/yes)	12/7	23/6	.218
Number of surgical procedures (≤ 2 / > 2)	14/5	15/14	.128
Hypoganglionosis (no/yes)	10/9	23/6	.051

year and hypoganglionosis showed a tendency to be associated with mortality. Figure 1 shows the Kaplan–Meier analysis of survival according to hypoganglionosis; no relationship was observed ($P = .273$).

3.6. Typical cases

Figures 2 and 3 present typical histopathologic findings in 2 children with CIPO.

4. Discussion

The CIPO has various etiology and nonspecific manifestations. In addition, physicians' awareness of the disease is low and the prognostic factors are unclear. The present study suggests that mycotic infections were associated with a poor prognosis of children with CIPO. Furthermore, the overall prognosis was poor because gastrointestinal decompression and enema could only temporarily alleviate the symptoms. In addition, all subjects received a delayed diagnosis of CIPO, the surgical management is very heterogeneous and many subjects were nonoptimally managed until CIPO was diagnosed.

Consistent with a previous study,^[4] most subjects in the present series developed their symptoms during their 1st year of life and had severe condition and high mortality. Except 1 pair of twins and 1 suspect stillborn history, all subjects seemed to be sporadic cases of CIPO. Unlike another study,^[12] the present cases were not associated with midgut malrotation or congenital short bowel syndrome. Associated congenital heart diseases were mild atrial or ventricular septal defect other than cardiomyopathy. Subjects with megacystis developed dilated gut loops and bladder prenatally, which unfortunately were overlooked and were treated as separate diseases. A study on this subtype of CIPO (known as megacystis microcolon and intestinal hypoperistalsis syndromes [MMIHSs]) suggested that a prenatal finding of unexplained fetal megacystis associated with gastrointestinal abnormalities should be considered as important implications for diagnosis and family consultation.^[13] Furthermore, recent genetic research showed an association between variants of ACTG2 and MMIHS, which provides another possible diagnostic method.^[14] Small bowel manometry is recommended in both adult and pediatric subjects, but it is not routinely performed in pediatric centers in China.^[15]

The aim of treatment should be to improve the nutritional status, prevent bacteria overgrowth and other complications, and improve the quality of life.^[16] Pediatric subjects are in a critical growth stage which needs comprehensive nutritional support to maintain the growth rate. With the help of PN and EN, only 13 cases of mild to moderate liver dysfunctions were observed and reversed under treatment. In addition, nasojejunal or gastrostomy jejunal tube improved the tolerance to EN. Prokinetics have low success in pediatric subjects except cisapride,^[17] but it was withdrawn in many countries due to cardiac risks. In the present study, itopride and Chinese traditional medicine achieved temporary improvements in a few children only.

Bacteria overgrowth was expected in all subjects. Therefore, they were treated with antibiotics according to drug sensitivity results or practical experience during an acute stage. The most commonly used antibiotics were 3rd-generation cephalosporin plus metronidazole, upgraded to carbapenem and vancomycin

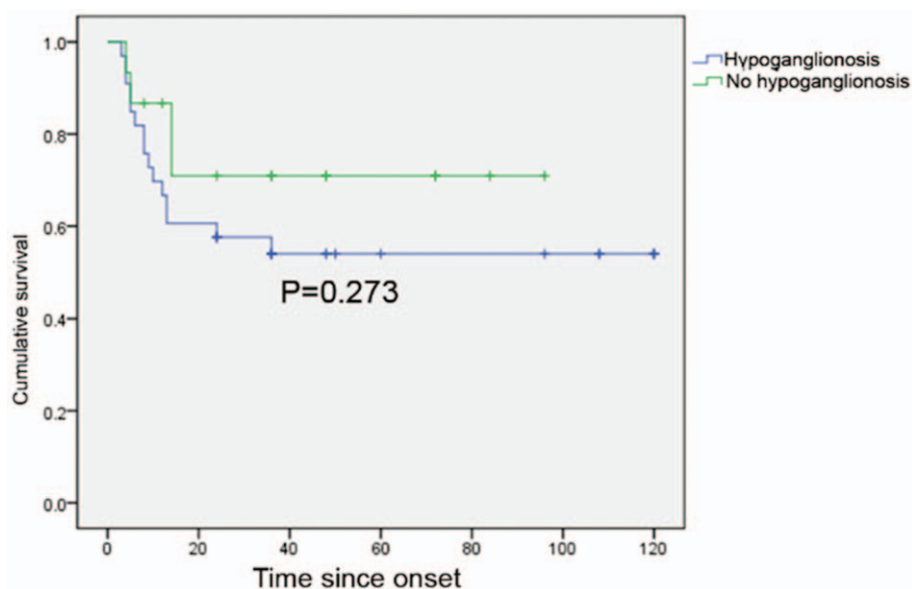


Figure 1. Kaplan–Meier curves of the survival of subjects with chronic intestinal pseudo-obstruction according to the presence of hypoganglionosis. Blue: hypoganglionosis (n = 15). Green: no hypoganglionosis (n = 33). $P = .273$ between the 2 groups.

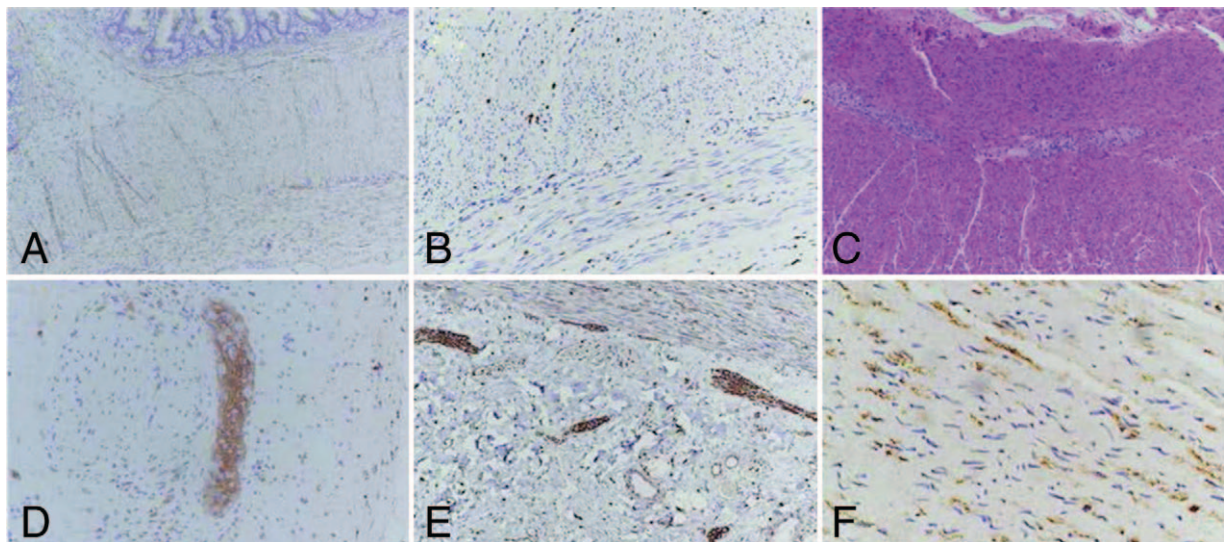


Figure 2. (A) Hypoganglionosis in 1 chronic intestinal pseudo-obstruction (CIPO) subject, TUJ1, $\times 10$. (B) CD3+ lymphocytes infiltrated around and within the myenteric ganglion and smooth muscle in 1 CIPO subject, CD3, $\times 20$. (C) Degenerative neuropathy, hematoxylin and eosin, $\times 20$. (D) Hyperganglionosis in myenteric ganglion in one CIPO subject, TUJ1, $\times 20$. (E) Hyperganglionosis in submucosal plexus in an unaffected segment, TUJ1, $\times 20$. (F) The density of the interstitial cells of Cajal was normal in an unaffected segment, CD117, $\times 20$.

when necessary. When the condition stabilized, neomycin was administered orally until the symptoms were alleviated. In China, bacterial resistance is an aggravating problem, especially for critically ill subjects whose drug sensitivity test often demonstrate extensive antibiotics resistance. Therefore, we administered broad-spectrum antibiotics plus metronidazole by intravenous infusion for both prophylactic and therapeutic use. We attempted in some cases to downgrade to narrower spectrum antibiotics, but failed to control bacterial overgrowth and sepsis. After stabilization, neomycin, which is poorly absorbed, was provided orally over the long term. Although some authors suggested an alternating cycle of different

antibiotics,^[18,19] the choice of drugs for pediatric subjects is limited due to regulatory issues in China. Mycotic infection is a pernicious complication after long-term broad-spectrum antibiotics treatment and occurred in 10 subjects; they were treated with fluconazole or caspofungin. In the present study, mycotic infection was the only factor significantly associated with mortality of CIPO, which had not been identified in any previous study.

The role of surgical procedures for subjects with CIPO is controversial. A study in adult subjects showed an association between surgical procedure and high postoperative morbidity, mortality, and frequent need for an additional surgical

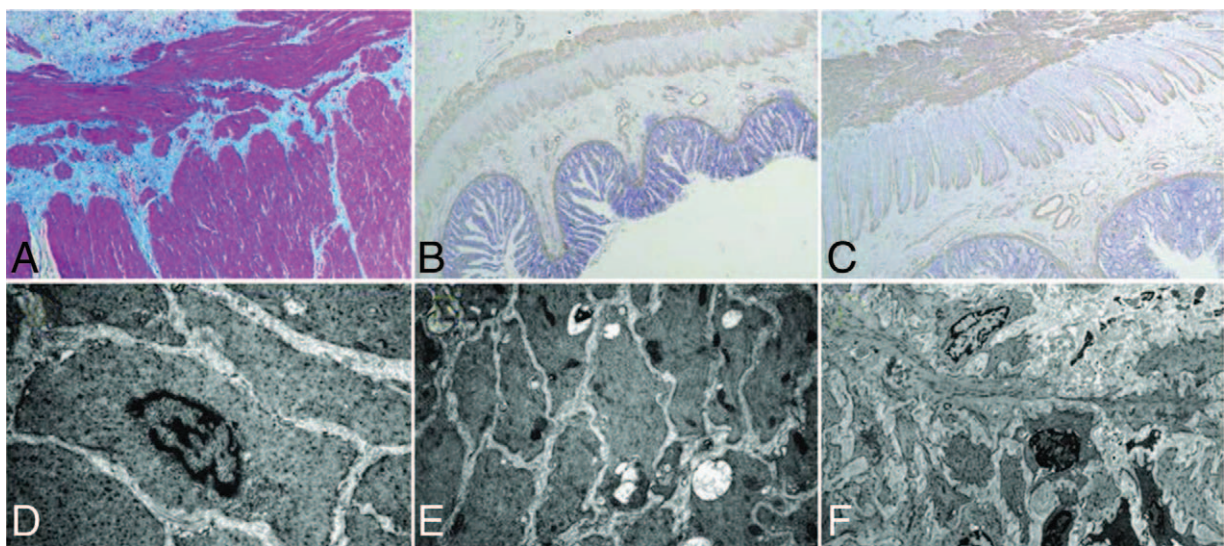


Figure 3. (A) Fibrosis in one subject with chronic intestinal pseudo-obstruction (CIPO), Masson, $\times 10$. α -Actin deficiency seen in both CIPO (B) and unaffected tissues (C), smooth muscle actin (SMA) staining, $\times 4$. Transmission electron microscopy images from an unaffected segment (D, $\times 13,500$) and an affected segment (E, F). In 1 subject, there were multiple vacuoles in the small intestine smooth muscle cells (E, $\times 13,500$), while the smooth muscle cells were atrophic with fibrosis (F, $\times 7400$).

procedure, and it was suggested to avoid a surgical procedure when possible.^[20] Nevertheless, most pediatric subjects developed aggravating symptoms soon after birth and inevitable emergency laparotomy had to be performed before a diagnosis could be given. Studies on pediatric CIPO subjects suggested that palliative ostomies could provide biopsy, feeding pathway, and decompression of the intestines to relieve the obstruction symptoms,^[21] while small intestinal resection should be avoided.^[22] One study suggested that ileo-rectal Duhamel pull-through achieved good outcomes.^[12] In the present series, the number of surgical procedures did not influence mortality, but the selection of the procedures depended on the experience and awareness of the surgeons, without any unified standard. One-stage surgical procedure such as resection and pull-through seemed to have high postoperative morbidity and mortality in young children, while achieved good outcome in older subjects. Stoma formation reduced the symptoms, but in some subjects, the effect was temporary. Postoperative mortality was the highest after ileostomy, which was conducted on more severe subjects only. Most subjects died before being 2 years old, and survivors' intestinal motility improved with time. For terminal stage children, transplantation should be considered in strictly selected cases,^[23] but there was no case of intestinal transplantation. The diagnosis should be based on the medical history and the pathologic results that could exclude other diseases such as Hirschsprung disease. The treatment of CIPO has been largely confused by misdiagnosis, relying solely on the surgeon's experience. Many surgeons at our institution did not thought at first about a more generalized syndrome and performed local treatment only. If no obvious lesions could be observed, ostomy was conducted in the region of the most dilated proximal end. Therefore, the optimal management of pediatric subjects with CIPO needs further study considering the different subtypes and confounding factors.

Alternative therapeutic measures such as gastric pacemaker, Botox, and herbal medicine are only marginally effective at best.^[24] Stem or progenitor cells transplantation seems promising,^[25] but there are still many steps between animal studies and application in humans.

Enteric smooth muscle contractions are orchestrated by the smooth muscles, enteric nervous system, and mesenchymal cells (Cajal cell).^[26] CIPO is a heterogeneous disorder caused by different mechanisms including neuropathy, myopathy, mesenchymopathy, and dysfunction in other cells such as immune cells^[2] and connective tissues.^[27] Full-thickness biopsies of the intestinal wall could help to make a correct diagnosis and select the most appropriate surgical procedure.^[28] Nevertheless, diagnostic criteria and associations between histologic findings and clinical entities are either absent or controversial.^[29] In 2010, an international working group published a classification of gastrointestinal neuromuscular pathologies that elaborated histopathologic phenotypes of possible etiology of congenital CIPO and associated changes.^[30] In the present study, histopathologic examination relied on H&E staining, which revealed 19 cases of hypoganglionosis among the 48 subjects. Hypoganglionosis was reported to be mostly associated with HD, while isolated hypoganglionosis is rare, with symptoms ranging from constipation to severe CIPO.^[31] Congenital hypoganglionosis often have a neonatal onset, high severity, and no improvement overtime.^[32] Pathologic diagnosis often relies on the pathologist's subjective impression and might be influenced by many factors such as specimen preparation.^[11] Furthermore, inter-observer variability is inevitable even when applying the same rigorous

criteria.^[33] Therefore, clinical centers should establish definite criteria applied by experienced specialists.

The present study is not without limitations. The study was retrospective, with all the inherent limitations. The sample size was small and from a single center. Subgroups were too small to perform any reliable multivariate analysis that could have identified independent prognosis factors. Finally, the follow-up was short. Additional studies are necessary to understand CIPO.

In conclusion, mycotic infections were associated with an increased mortality of children with CIPO. Despite evolving treatment approaches, the overall prognosis of CIPO remains poor. The choice of the surgical intervention should be based on standard criteria.

Author contributions

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