Challenges in management and prognosis of pediatric intestinal pseudo-obstruction

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ABSTRACT

Background/Aims: Pediatric intestinal pseudo-obstruction (PIPO) is the most severe form of intestinal dysmotility in children. This study aims to present the cases of PIPO to discuss its diagnosis, management, and prognosis.

Materials and Methods: We retrospectively analyzed the medical records of the patients with PIPO between 2010 and 2018.

Results: A total of 7 patients were included. The admission age was 3 days–10 years. The complaints were abdominal distention and constipation in all the patients. All the patients had passed meconium in the first 48 hours of their life. An upper gastrointestinal (GI) series revealed slow transit in 6 patients and malrotation in 2 patients. Full-thickness rectum biopsies revealed normal ganglion cells. Neurological examination revealed postinfectious pandysautonomy in 1 patient. Furthermore, 2 patients are under follow-up with ileostomy and TPN, 1 patient is with enteral feeding and ileostomy, and 3 patients are stable with pyridostigmine, enemas. Moreover, 1 patient died because of sepsis. The prognosis was not significantly correlated with initial presentation time, lag time, and presence of extraintestinal manifestations ($p>0.05$). The prognosis was significantly better when fewer number of operations were performed ($p=0.029$)

Conclusion: PIPO is a broad-spectrum disease group that is difficult to diagnose and treat. It is mandatory to rule out the secondary causes of diagnosis. Medical and surgical treatments are used to support the nutritional status, prevent sepsis, and restore the intestinal motility. The prognosis was better when the secondary causes were identified and fewer operations were performed.

Keywords: Intestinal obstruction, intestinal pseudo-obstruction, ileus, prognosis, pandysautonomia

INTRODUCTION

Pediatric intestinal dysmotilities cover a wide heterogeneous group of clinical findings, including intestinal pseudo-obstructions (IPO). IPO was first described by Dudley et al. (1, 2) in 1958. They referred to a disease that presented with intestinal obstructive symptoms in the absence of a true mechanical obstructing cause. If the intestinal obstruction symptoms persist longer than 2 months in a newborn or more than 6 months in the late onset ones, the IPO is called chronic IPO (CIPO) (3-5). Since there are important differences between adult and pediatric CIPO, the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) expert group considered CIPO in children as a separate entity and referred to it as pediatric IPO (PIPO) (4).

PIPO is the most severe intestinal motility disorder in children with potentially lethal consequences. PIPO is a very rare disease, and its exact prevalence and incidence are not known. A nationwide survey in the United States revealed that 100 infants were born with PIPO each year (6), while another nationwide study in Japan revealed the prevalence as 3.7 in 1 million (7).

The clinical presentation is mostly abdominal distention and vomiting and less frequently abdominal pain, diarrhea, constipation, and extraintestinal manifestations in children (3, 8). Since all these symptoms are nonspecific, establishing a firm diagnosis is challenging in PIPO (3, 5). The second challenge in PIPO is the need for excessive diagnostic tests; repetitive, ineffective, and potentially dangerous surgical procedures lead to delay in PIPO diagnosis (9). The role of surgery in the management of PIPO is crucial; however, surgery itself is a potential risk factor in the prognosis that may worsen the clinical symptoms (3, 9). A multidisciplinary approach is needed to drive prognosis, which is stated to be poor, especially in neonatal onset PIPO, myopathic involvement, and with multiple

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surgeries (4). Therefore, we conducted a retrospective study to assess all these challenges in our own clinical practice and to increase the awareness on this rare and potentially lethal disease.

MATERIALS AND METHODS

The study was performed in adherence to the Declaration of Helsinki and by approval of the local ethical committee for clinical research of our institution (GO 18/508-07). We carried out a descriptive, retrospective study on patients managed for PIPO in our clinics between 2010 and 2018. In total, 11 patients were referred to our center with IPO. The medical records of 7 patients could be found, and these patients were included in the study.

The presence of one or more clinical intestinal obstruction episodes in the absence of any mechanical obstructive lesion was used as the inclusion criteria for the study. Patients with Hirschsprung's disease or neuronal intestinal dysplasia were excluded.

The demographic features, age at onset of symptoms, symptoms at admission, physical and radiological findings, medicines received, surgical management alternatives, and follow-up data of the patients were recorded.

Statistical Analysis

The Statistical Package for the Social Sciences version 23.0 for Windows (IBM Corp.; Armonk, NY, USA) was used for the analysis of the data. The Fisher exact test was used to compare the 2 independent groups for differences in the categorical variables. Arithmetic mean, standard deviation, median, and minimum-maximum values were given as descriptive statistics for quantitative data. Qualitative data were summarized using frequency and percentages. A p value of less than 0.05 was considered to indicate a statistically significant difference.

RESULTS

The demographic and clinical features of the patients are summarized in Table 1. The medical data of 7 patients with a male to female ratio of 2:5 were included. The age of the patients at initial presentation ranged between 3 days and 10 years. The age of the patients at diagnosis ranged between 2 months and 12 years. Therefore, the average lag time from initial symptom to diagnosis was 10 months (2–24 months). The age of the patients at admission to our center ranged between 2 and 14 years (median: 3 years).

MAIN POINTS

- *Pediatric intestinal pseudo-obstruction (PIPO) presents with non-specific various clinical scenarios.*
- *Diagnostic approach to PIPO should be in stepwise manner.*
- *Prognosis of PIPO is associated with both late diagnosis and high number of unnecessary surgical procedure.*

The family history of all the patients was unremarkable. The initial symptoms in all the patients were constipation and abdominal distention. All the patients had passed meconium in the first 48 hours of their life. In addition, 4 patients had vomiting episodes, 2 had diarrhea, 2 had difficulty in micturition, and 1 had abdominal pain. The percentiles according to the body weight and height of the patients were as follows: below the 10th percentile in 5 patients, 25th percentile in one case (Case 6), and 50th percentile in one case (Case 7). The mean body mass index of the patients was 15.88 (14.04–20.60).

Radiological examinations comprised plain upright abdominal X-ray and fluoroscopic studies, including esophagogastroduodenography, small bowel follow graphy, contrast enema, and voiding cystourethrography. The plain abdominal X-ray revealed dilated bowel loops with air-fluid levels in all the patients. The fluoroscopic studies revealed slow small bowel transit in 6 patients, slow esophageal transit and delayed gastric emptying in 1 patient, malrotation in 2 patients, redundant sigmoid colon in 2 patients, and megacystis in 2 patients.

A full-thickness rectal biopsy was performed in all the patients to exclude Hirschsprung's disease and neuronal intestinal dysplasia. The 7th patient had dysphagia and was examined with a swallowing test and esophageal manometry, which revealed moderate esophageal dysmotility and delayed esophageal clearance. Since the medical history of this patient revealed varicella infection (confirmed with plasma varicella zoster IgM level), he was further evaluated by the neurology department and diagnosed with pandysautonomy secondary to the viral infection. The pediatric neurology department also evaluated all the other patients, and abnormal sympathetic skin reflex was detected, showing possible autonomic nerve system involvement in one of the patients (Case 6) with micturition difficulty. Special examinations for mitochondrial neurogastrointestinal encephalomyopathy syndrome (MNGIE) revealed normal findings in all the patients.

The initial evaluation of all the patients was carried out at another medical center. All but 2 patients were oper-

Table 1. Summary of clinical features and diagnostic workup of the patients.

N	Sex	Age at initial symptom	Lag time	Predominant initial symptom	Extraintestinal manifestations	Fluoroscopic studies
1	F	2 months	18 months	Constipation Abdominal distention Vomiting	-	slow bowel transit
2	F	3 days	2 months	Constipation Abdominal distention Vomiting	-	slow bowel transit malrotation
3	F	5 days	2 months	Constipation Abdominal distention	Micturation difficulty	slow bowel transit, malrotation VCU:Megacystis
4	F	30 months	1 year	Constipation Abdominal distention Vomiting, Diarrhea	-	slow bowel transit
5	F	10 years	2 years	Constipation Abdominal distention Vomiting, Diarrhea	-	slow bowel transit
6	M	3 days	6 months	Constipation Abdominal distention	Micturation difficulty	slow bowel transit, Redundant sigmoid VCU: Megacystis
7	M	5 years	6 months	Abdominal pain Constipation Abdominal distention	Dysphagia Varicella infection	Delayed esophageal clearance Redundant sigmoid

VCU: Voiding cystouretrography

ated upon several times to exclude mechanical obstruction; 2 patients were followed for intestinal obstruction but could not be diagnosed. Therefore, they were referred to our clinics. The summary of the operations is given in Table 2.

Management of the patients was performed with multidisciplinary effort aimed at restoring the fluid and electrolyte balance, increasing caloric intake, and gaining normal or near-normal intestinal motility. For all the patients who could not be fed orally, we ordered PN according to the weight and serum biochemistry results of the patients. We ordered PN for all but 1 patient in this study (Cases 1-6). We usually prefer to order rectal enema for patients with constipation and did for all the patients in this study. Lactobacillus (200–400 million CFU/day) were prescribed for patients with constipation for at least a 4-week duration. Erythromycin (Erythrocin®, ABFAR, Istanbul, Turkey; 3 mg/kg/day; Cases 3-4-7) and pyridostigmine (Mestinon®, MEDA PHARMA, Istanbul, Turkey; 0.25 mg/kg/day; all patients except Case 5) were prescribed to restore the intestinal motility. The duration of the therapy was decided according to the response of each patient. We defined unresponsiveness as the absence of improvement in oral intake and obstructive symptoms after therapy lasting at least 3 weeks. We did not observe improvement in the patients receiving erythromycin therapy. However, we observed partial response in Cases 1, 3, 4, 6, and 7 who received pyridostigmine. The patient with pandysautonomy (Case 7) was fed with hydrolyzed enteral solutions. Antibiotics were used for both treatment of catheter-associated infections and prophylaxis of bacterial overgrowth. One patient (Case 1) developed bacterial overgrowth and died because of sepsis despite wide-spectrum antibiotic therapy, while another patient (case 3) also developed bacterial overgrowth but responded well to the extensive antibiotic therapy.

Although unnecessary operations were avoided, we had to perform laparotomy in 5 patients; 2 of them were for severe intestinal obstruction symptoms that were unresponsive to conservative treatment. We detected malrotation in 2 patients and performed the Ladd procedure. In addition, ileostomy was performed to decompress the dilated bowel loops. The other 3 patients were operated upon for small bowel ileus, adhesive obstruction, and stoma prolapsus (Table 2). None of the patients had gastrostomy or jejunostomy. The total number of operations for CIPO-related indications ranged between 0 and 8 per patient (median: 3).

The median follow-up time of the patients is 4 years (1-5 years). The prognosis was variable in the patients. One of the patients died because of catheter-related infections and sepsis. Moreover, 2 patients are still under follow-up with PN and ileostomy for 2 years; 1 patient is still under

Table 2. Surgical management and prognosis of the patients.

	Procedures before diagnosis		Procedures after diagnosis		
	Procedure	Indication	Procedure	Indication	Prognosis
1	Exploratory laparotomy Bridectomy	Exclude mechanical obstruction Adhesive obstruction	Ileostomy	Decompression	Exitus
2	Exploratory laparotomy (2 times)	Exclude mechanical obstruction	Ileostomy Stoma closure Re-ileostomy	Decompression . Decompression	PN Ileostomy
3	Exploratory laparotomy (2 times)	Exclude mechanical obstruction Adhesive obstruction	Ladd Procedure Ileostomy Stoma closure Re-ileostomy	Malrotation Decompression . Decompression	PN Ileostomy
4	Laparotomy Ileostomy (2) Stoma revision	Exclude mechanical obstruction Intestinal perforation Stoma prolapsus	Ladd Procedure Stoma revision Bridectomy Stoma revision	Malrotation Stoma prolapsus Adhesive ileus Stoma prolapsus	Enteral/PN Ileostomy
5	Exploratory laparotomy	Exclude mechanical obstruction	Ileal resection	Adhesive obstruction	Enteral feeding Medications
6	-	-	-	-	Enteral feeding Medications
7	Appendectomy Bridectomy	Abdominal pain Adhesive obstruction	-	-	Enteral feeding Medications

follow-up with enteral (hydrolyzed enteral solutions according to the daily calorie needs) and parenteral feeding and ileostomy for the last 1 year. In addition, 3 patients are still under follow-up and stable with enteral feeding (hydrolyzed enteral solutions according to the daily calorie needs) and medications including pyridostigmine, enemas, and laxatives for 5 years (Table 2). The prognosis was considered to be good in the patients under follow-up with only enteral feeding and medications. The prognosis was considered to be poor in the patients under follow-up with PN or ileostomy and the exitus case. Then, we compared the initial presentation time, lag time, presence of extraintestinal manifestations, and total operation time with prognosis. The prognosis was not significantly correlated with the initial presentation time, lag time, and presence of extraintestinal manifestations ($p>0.05$). However, the prognosis was significantly correlated with the total operation number. The prognosis was significantly better when fewer number of operations were performed ($p=0.029$) (Table 3).

DISCUSSION

IPOs consist of a variety of problems and challenges because of the following reasons: CIPO causes nonspecific symptoms simulating other gastrointestinal obstructions, clinicians have limited experience on CIPO; misdiagnosis can be seen frequently in CIPO leading to unnecessary, ineffective, and potentially dangerous surgical procedures. The diagnosis and management of CIPO is still challenging for clinicians and surgeons. CIPO in children, namely PIPO, is mostly congenital and the primary type rather than of secondary forms. Most of the patients show symptoms in the neonatal or early infancy period. Intestinal obstruction symptoms predominate, associating with malrotation in 30% of the patients and urological involvement in 40%–100% of the patients (3, 4). Esophageal motility problems have been reported commonly in PIPO and has been stated that presence of esophageal dysmotility is a poor prognostic sign (3, 5, 10-12). Additionally, the ESPGHAN expert group reported that prognosis is poor in the neonatal onset form of PIPO, myopathic involvement, and with multiple surgeries (4).

In this study, only 1 patient showed the secondary form of PIPO, which was caused by pandysautonomy, secondary to varicella infection. Recently, neurotropic viruses, viruses capable of infecting the nerves, are thought to be responsible for the etiopathogenesis of CIPO, although the secondary form of CIPO is extremely rare in childhood (13). The viral infection has a latency period, and

Table 3. Relationship of initial presentation age, lag time, extraintestinal manifestations, and total operation time with prognosis (*: statistically significant).

		Poor prognosis (N)	Good prognosis (N)
Initial presentation	<1 year-old	3	1
	≥1 year-old	1	2
	Fisher's exact test		p: 1.0
Lag time	≤6 months	2	2
	>6 months	2	1
	Fisher's exact test		p: 1.0
Extraintestinal manifestation	Present	1	2
	Absent	3	1
	Fisher's exact test		p: 0.143
Total operation number	0–2	0	3
	≥3	4	0
	Fisher's exact test		p: 0.029 *

subsequent reactivation is occurs under proper conditions, such as immune deficiency (13). In patients with a long latency period, the possibility of viral etiology may be missed in the diagnosis of CIPO. In contrast, that type of IPO progress to severe chronic IPO or may regress with time (13). Therefore, laboratory examinations covering the viral infections should be included in the diagnostic workup of the patients, although the secondary causes are rare in childhood.

The initial symptom was seen at the neonatal or early infancy period in 4 patients and at the early or late childhood in the remaining 3 patients in our study. We could not find a significant correlation between the initial presentation time and prognosis contrary to the literature data. However, the number of patients was small in this study. Therefore, larger clinical series are needed to confirm this result.

Esophageal dysmotility was detected in 1 patient in our study, but the prognosis of this patient was better than other patients, contrary to the literature data. Mauro et al. (11) performed a study with high-resolution manometry investigating the esophageal involvement in CIPO. They concluded that the severity and type of esophageal motility disorder should be defined in detail because the diffuse and severe involvement of the esophagus suggests more severe and widespread motor disorder and poor prognosis in CIPO. We performed conventional esophageal manometry revealing moderate esophageal dysmotility and delayed esophageal clearance. A more detailed examination with high-resolution manometry would be helpful to define the prognosis in this case.

The diagnosis of CIPO is challenging since it depends on the awareness of the clinician. The lag time to diagnosis should be kept to a minimum to prevent the unnecessary diagnostic tests and operations (9). Delayed diagnosis or misdiagnosis is commonly seen in PIPO as in our study. The lag time to diagnosis ranged from 2 to 24 months in this study. There are several reasons for such a long lag time. First, most clinicians cannot recognize PIPO; second, the necessity of excluding the congenital mechanical obstructions in the neonates necessitates in several time-consuming diagnostic tests; and third, nonspecific symptoms may cause unnecessary surgical procedures, which may further worsen and complicate the clinical presentation (9, 12). However, any unnecessary effort to exclude all the congenital diseases or secondary causes should be avoided to shorten the lag time. A careful medical history evaluation and physical examination may exclude some possible causes, such as esophageal dysmotility, micturition difficulty, past infections, or prescribed drugs. Furthermore, the diagnosis should be carried out in a stepwise approach (5, 8).

In this study, the first evaluation of all the patients was carried out at various medical centers. Unfortunately, diagnostic laparotomy was performed in most patients instead of a stepwise approach. The consequences of this "surgery first" approach being followed caused more complicated clinical presentation, delay in diagnosis, increased need for second surgical interventions, and increased complication rates in the following procedures (12, 14, 15). Although the number of patients was limited, the prognosis was significantly poor with higher total number of operations per patient. Sabbagh et al. (14) have stated in their clinical study that frequent reoperation and high number of procedures per patient increases the morbidity and mortality in patients with CIPO (14). Furthermore, the ESPGHAN expert group advised to avoid multiple unnecessary surgeries in CIPO (4).

Once the diagnosis is made, management should be initiated in a multidisciplinary effort. The main goals of the treatment should be to restore the fluid and electrolyte balance, improve the nutritional status, prevent septic

complications, avoid unnecessary surgical procedures, and gain almost normal intestinal motility (3, 4, 10, 12). However, there is no standard treatment protocol, which is definitively effective. We ordered PN in all but 1 patient in this study. The last patient was fed orally with fiber-based formulas. Several types of prokinetic agents were ordered with inconsistent responses. Acetyl cholinesterase inhibitors are also used to enhance the bowel motility per several reports in the literature (16, 17). We ordered long-lasting acetyl cholinesterase inhibitor, pyridostigmine, in 6 patients and obtained a partial response in 4 of them. Antibiotics were administered to all the patients for treatment or prophylaxis of the infectious complications of bacterial overgrowth or central venous lines in this study. Bacterial overgrowth is frequently seen in PIPO, causing acute exacerbation of diarrhea. Probiotic regimens as well as antibiotics are preferred in treatment and prophylaxis of the bacterial overgrowth (12). Central lines or PN complications also worsen the prognosis of patients with PIPO (12, 18). In addition, 4 of our patients (57%) experienced severe PN and central line complications, leading to several line insertion attempts and more complications.

Although unnecessary surgical procedures are to be avoided in the management of PIPO, surgery may have to be performed in different situations. However, there is no definitive indication for surgical procedures in PIPO. Surgery has a crucial role in the placement of central lines, sampling full-thickness biopsy, placement of venting gastrostomy, performing enterostomy to restore the intestinal transit, recurrent laparotomies in intestinal adhesions, and intestinal transplantation (15). In the literature, the closure of enterostomy is advised to postpone until the patient has improved clearly, weaned from PN totally, and recovered without acute exacerbations at least for 2 years (15). However, ileostomy closure had been performed in 3 patients in our study before their admission to our clinics, leading to repeated procedures for performing enterostomy.

Although this study gives several insights to the clinicians on improving new diagnostic approaches to prevent unnecessary surgical procedures in PIPO, it has some limitations. First, the sample size is small because this is a rarely seen disease. Second, the retrospective design of the study may introduce in the interpretation of the decision making in diagnosis and management of the patients with PIPO. Also, the patients were first evaluated at other medical centers, and most of them were operated upon multiple times to rule out the mechanical obstruction. Although future observational studies are needed regarding PIPO management and prognosis, this study may be an inspiration for the clinicians to manage such patients in specialized medical centers.

In conclusion, although this study has a small sample size and a retrospective design, it reflects the challenges in diagnosis of patients with PIPO, especially those who are admitted late after several surgical procedures. Moreover, the authors conclude that the prognosis of PIPO seems to be associated with not only late diagnosis but also increased the number of surgical procedures per patient. Therefore, the awareness of clinicians should be increased to prevent a long lag time to diagnosis and unnecessary surgical procedures. The diagnostic approach should be stepwise manner aiming to exclude the mechanical obstructions and underlying secondary diseases. Although the main goals of management are well defined in PIPO, standard and effective management protocols are needed to improve prognosis.

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