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CASE REPORT

Intestinal pseudo-obstruction: An uncommon condition with heterogeneous etiology and unpredictable outcome

Eugen Florin Georgescu, Ion Vasile, Reanina Ionescu

Eugen Florin Georgescu, Reanina Ionescu, Filantropia University Hospital from Craiova, Department of Internal Medicine 2, University of Medicine and Pharmacy of Craiova, Romania
Ion Vasile, Departmental Emergency University Hospital from Craiova, Department of General Surgery 2, University of Medicine and Pharmacy of Craiova, Romania
Correspondence to: Dr. EF Georgescu, Filantropia University Hospital, Department of Internal Medicine 2, Str. Constantin Brancusi nr. 3, Craiova 200136, Romania. efg@usa.net
Telephone: +40-251-420896
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Abstract

Intestinal pseudo-obstruction (IPO) either acute or chronic is a condition including features of intestinal ileus in absence of mechanical obstruction. Our paper presents such a rare case of idiopathic IPO in a 53-year-old male patient with recurrent episodes of pseudo-obstruction, which were successfully resolved by anticholinesterase agents, motilin agonists or colonic decompression. However, the patient finally underwent total colectomy. Huge colonic dilatation was identified intraoperatively, while histology showed a neuropathic variant of chronic intestinal pseudo-obstruction. Etiologic mechanisms and current therapeutic methods are reviewed in this paper, which concludes that IPO is a condition in which conservative treatment usually fails. Total colectomy with ileoanal pouch may be the only solution in these situations.

Key words: Intestinal pseudo-obstruction; Anticholinesterase agents; Motilin receptor agonists; Colonoscopic decompression; Total colectomy with ileoanal pouch

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INTRODUCTION

Intestinal pseudo-obstruction is a condition characterized by intestinal obstruction in the absence of any mechanical obstructing lesion. Pseudo-obstruction can exist in the small bowel or in the colon and can be either acute or chronic. Acute colonic pseudo-obstruction (ACPO), also known as Ogilvie syndrome, is the most common form of intestinal obstruction. It occurs commonly in postoperative period of surgical patients, or as a response to a nonsurgical acute illness. Chronic intestinal pseudo-obstruction (CIP) is a rare and heterogeneous clinical syndrome, with a relapsing and remitting pattern that appears either in idiopathic (as consequence of a primary abnormality of the gut, namely a visceral myopathy or neuropathy) or in other non-intestinal disorders.

Our paper presents a rare case of idiopathic CIP in a 53-year-old Caucasian male showing the neuropathic variant with hypoplasia of ganglionic cells of the rectum, sigmoid and descending colon.

CASE REPORT

The patient complained of abdominal distension, vomiting and no bowel movements for 5-7 d. He had this history three or four years ago, with episodes of progressive abdominal distension and constipation, and was diagnosed as irritable bowel disease. In the last year, these episodes increased in severity and frequency, leading to food abstention and secondary denutrition.

The episodes of bowel movements were more and more severe. However, as mechanical obstruction was systematically ruled out, the patient was discharged after certain symptomatic treatment each time. Finally, after four or five such episodes of "unexplained" pseudo-occlusion, he was admitted to the gastroenterology unit for further investigation.

Physical examination during these obstructive episodes revealed huge abdominal distension with hypoactive bowel, but no abdominal mass or peritoneal signs. The patient had no history of metabolic, neurological, cardiovascular or pulmonary disease, abdominal or pelvic operations, abdominal cancer, intra-abdominal inflammation or abdominal trauma. He did not take other concomitant medication.

Biologic screening showed normal serum electrolyte concentration, hemoglobin, hematocrit, white blood cells, blood glucose, creatinine, and coagulation profile. There was no evidence of metabolic diseases like diabetes, porphyria, amyloidosis. Pulmonary imaging was normal. Abdominal ultrasound did not find any sign of small bowel or colonic mechanical obstruction. Distended

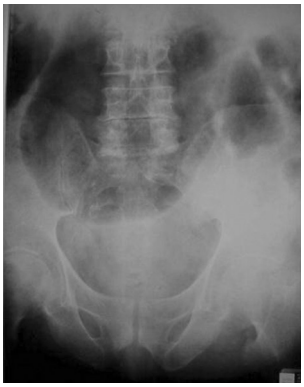

Figure 1 Supine radiograph with no preparation showing massive colonic distention especially the transverse colon, but without air-fluid levels.

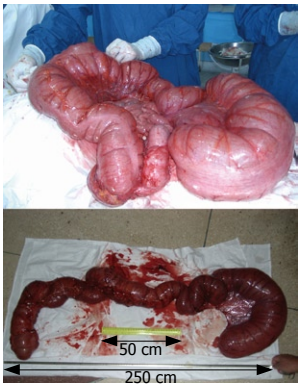

Figure 3 Laparotomy showing massive distension of the whole colon with no perforation or volvulus. Total colectomy removed a completely atonic colon which was 2.5 m in length and 25 cm in diameter. Ileoanal pouch was made subsequently.

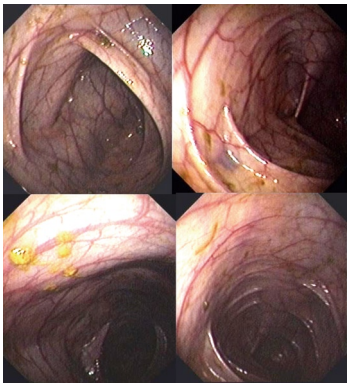

Figure 2 Colonoscopy showing huge colonic distension involving all segments, with a diameter of the rectosigmoid and descending colon greater than 12 cm, and that of the ascending colon and cecum greater than 16-18 cm.

bowel segments were observed, but free peritoneal fluid, pendulating peristalsis, bowel wall edema, or fixed masses of aperistaltic, fluid-filled distended intestinal loops were not observed. Radiographs showed signs of marked colonic dilatation (Figure 1) especially in the cecum and ascending colon, but no air-fluid levels were found in the colon or in the small intestine. Abdominal CT-scan showed nothing apart of bowel distension and aerobilia while the pulmonary and cranial scans were normal.

Colonoscopy showed incredible colonic distension (Figure 2) up to the cecum and decompressed the abdomen. No obstructive, diverticular or mucosal changes were noticed. Randomized multiple mucosal biopsies were also normal. CIP syndrome was strongly suspected, which was enforced by the fact that after intravenous administration of neostigmine (2 mg) rapid evacuation of flatus and stool and significant decrease in abdominal distention were observed.

The patient was discharged and oral neostigmine was administered regularly (15 mg per day). Two weeks after apparent amelioration of bowel habits, the patient had a new pseudo-obstructive accident, which remitted again with colonoscopic decompression and intravenous neostigmine. Oral erythromycin was introduced at discharge, at a dose of 500 mg, three times per day, resulting in fewer episodes of constipation, pain and vomiting and more regular bowel actions, which increased from 1.5 per week to 3 per week for a period of three months. Unfortunately, after this period, recurrence occurred and because of failure in all other conservative therapies (including prokinetics, octreotide, propranolol) the patient finally underwent colectomy.

Intra-operation examination revealed massive colonic distension, the large bowel length was more than 2.6 meters and the cecum diameter was larger than 15 cm (Figure 3). After a total colectomy with ileoanal pouch, the condition was resolved satisfactorily. Full thickness colonic sections were histologically analyzed. No myopathic abnormality was found but ganglionic cells were absent in the last 7 cm of the rectum, and marked depletion of neural plexuses with hypertrophy of the external muscular layer was identified in sigmoid and descending colon (Figure 4), thus diagnosis of neuropathic CIP was established.

No postoperative complication and obstructive episode occurred after colectomy. Prokinetics were discontinued, and the weight of the patient became normal. Apart from some diarrheal stools, which occurred in the first two months after operation, the bowel movements did not exceed 7.5/wk, with no need for antidiarrheal drugs or nutrient supplementation.

DISSCUSION

Megacolon is a descriptive term, without etiologic and pathophysiologic implication. It can be acute or chronic, each category being subdivided in idiopathic and secondary to various disorders. Idiopathic forms are usually assigned to variants that lack decisive elements for diagnosis on routine stains, although specialized immunohistochemical techniques frequently reveal unrecognized disorders, such as primary biochemical disorders of the gut muscle[1]. Toxic megacolon is classically not included in these categories.

When colonic obstruction is acute[2] and associated with a recent, major organic disorder, trauma, or surgical procedure as shown in Table 1, the term of Ogilvie's syndrome is commonly used. Imbalance in the autonomic nervous system is the presumed physiopathologic factor postulated by Sir Heneage Ogilvie when he firstly described ACPO in 1948[3]. In his original work, Ogilvie considered that high parasympathetic tone combined with low sympathetic activity of the colon leads to regional contraction and thus, functional obstruction, but little direct evidence supports this theory. Conversely, many recent observations suggest that parasympathetic deprivation combined with high sympathetic tones is the main factor contributing to pseudoobstruction[4,5]. The

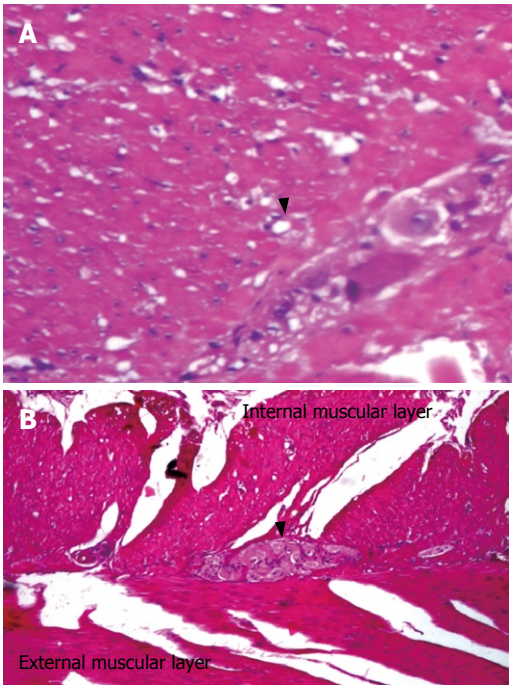

Figure 4 Full-thickness serial biopsies stained with haematoxylin-eosin (× 100) from the removed colon showing no ganglionic cells in the last 7 cm of the rectum. Marked depletion of ganglionic cells (arrow) and hypertrophy of the external muscular layer were identified in sigmoid (**A**) and descending colon (**B**).

efficacy of cholinesterase inhibitors in reversing ACPO[6,7], as well as observations regarding colonic atony similar to Hirschsprung disease after interruption of the sacral parasympathetic nerves suggest that a high sympathetic and/or low parasympathetic activity[8] is more likely to induce ACPO. Some other factors may also contribute, like increase in nitric oxide production[9] or inhibition of motilin receptors to ACPO[10].

Chronic intestinal pseudo-obstruction can be congenital or acquired, both forms can be subdivided into neuropathic and myopathic variants (Table 2).

The most common form of *neuropathic CIP* is Hirschsprung disease, caused by a congenital absence of intramural plexuses that mediate relaxation (aganglionosis), leading to narrowing of a segment of large intestine that impairs progression of colonic content and secondarily generates upstream dilatation. Aganglionosis results from arrest of caudal migration of embryonic cells that will form the myenteric plexus from the neural crest in early embryogenesis, and, consequently this disease is included in a group of disorders called neurocristopathies [11]. The aganglionic segment usually does not exceed 5-15 cm in length, being located in the distal rectum, but in certain cases, it can be longer, extending to the sigmoid or even may exceptionally extend to the entire colon.

Variants of Hirschsprung disease include type Ⅱ (b) multiple endocrine adenomatosis[12] and some other conditions as hypoganglionosis and neuronal intestinal dysplasia. In type Ⅱ multiple endocrine neoplasia (MEN Ⅱ) and Hirschsprung's disease, a mutation of an autosomal dominant gene localized to a 250-kilobase interval containing the RET proto-oncogene is mapped to chromosome 10q11.2[13,14]. The mutation enhances the function of a tyrosine-kinase receptor in MEN Ⅱ, while in Hirschsprung disease it inactivates the protein. Apart from the four variants of this mutation that damages the structure of the tyrosine kinase domain of the RET protein, other mutations have been also recently described[15] in Hirschsprung's disease. In animal models,

Table 1 Major causes for acute intestinal pseudo-obstruction (adapted from 2)

Post-surgery	Abdominal, orthopedic, neurologic, urologic, cardiac interventions, caesarean section, gynecological/pelvic surgery, renal transplantation
Pulmonary diseases	Pneumonia, mechanical ventilation, adult respiratory distress syndrome
Electrolyte disturbances and metabolic disorders	Hyponatremia, hypokalemia, hypocalcaemia or hypocalcaemia, hypomagnesaemia, alcohol abuse, liver and renal failure
Cardiovascular diseases	Myocardial infarction, cerebrovascular accident, congestive heart failure
Malignancy	Retroperitoneal neoplasia, leukaemia, metastatic cancer, pelvic radiotherapy
Infective/inflammatory	Acute cholecystitis, pancreatitis, peritonitis, systemic sepsis, herpes zoster infection, gram-negative infections,
Neurologic	Parkinson's disease, Alzheimer, multiple sclerosis, low spinal cord disease
Traumatic	Pelvic trauma, spinal cord injuries, femoral fracture
Medications	Narcotics, opiates, anticholinergics, clonidine, amphetamines, phenothiazines, steroids

Table 2 Major causes for chronic intestinal pseudo-obstruction (adapted from 11)

	Neuropathic	Myopathic
Idiopathic	-Hirschsprung disease	-Nonfamilial hollow visceral myopathy
Acquired	-Familial visceral neuropathies -von Recklinghausen disease -Infiltrative diseases (amyloidosis) -Metabolic, endocrine and electrolyte diseorders (porphyrias, diabetes mellitus, hypothyroidism, hypokalemia) -Neurologic diseases (brainstem tumors, multiple sclerosis, dysautonomias) -Infectious diseases (trypanosomiasis, cytomegalovirus infections) -Neoplastic diseases (bronchial small cell carcinoma, carcinoids, pheochromocytoma) -Drugs (narcotics, antihypertensives, antidepressants)	-Familial visceral myopathies -Infiltrative diseases (amyloidosis, systemic sclerosis) -Myotonic and other dystrophies

Parisi *et al*[16] investigated the regulation of Hox11L1, a gene expressed by enteric neurons in Hox11L1- transgenic null mice and concluded that expression of the transgene and penetrance of pseudo-obstruction are influenced by one or more modifier genes depending on the genetic background, some of them having a putative role in human disease.

Congenital aganglionosis is associated with other genetic disorders like Down's and Laurence Moon Bardet Biedel syndromes. Type IV Waardenburg-Shah syndrome (WS4) is characterized by association of Waardenburg features (WS, depigmentation and deafness) and absence of enteric ganglia in the distal part of the intestine. Mutations in the genes EDN3, EDNRB and SOX10 have been reported in patients presenting either the classical form of WS4, or chronic intestinal pseudo-obstruction and WS features[17].

Among acquired conditions that generate CIP, Chagas disease is widely known. In this disease, the neurotoxin generated by Trypanosoma cruzii has a deleterious effect on the enteric nervous system. Other infections, like cytomegalovirus can have similar consequences by unknown mechanisms. Metabolic disorders like diabetes mellitus and porphyria, as well as infiltrative diseases (systemic sclerosis, amyloidosis) can also lead to neuropathic variants of CIP. Some drugs (antidepressants, anticholinergics, vincristine) can interfere with myenteric plexus activity. Mechanisms of neuronal damage may be toxic or immune, as in patients treated with buserelin[18], an analogue of gonadotropin-releasing hormone (GnRH) in which formation of buserelin-induced anti-GnRH antibodies can destroy GnRH-producing neurons of the myenteric plexus.

Little is known about the mechanisms generating pseudo-obstruction in neuropathic forms of CIP, either idiopathic or acquired. It seems that lack of normal pacemaker activity, usually generated by the interstitial cells of Cajal (ICC), could account for obstruction[19]. ICC, normally located between the myenteric plexus ganglia, can be stained immunohistochemically with CD117 as well as with CD34, which also stains a population of fibroblasts intimately associated with ICC. In some CIP patients, both CD117 and CD34 are absent or severely reduced, while in controls ICC staining is normal, and moreover, the CD34-positive fibroblasts associated with ICC are absent in these cases[20].

In aganglionosis, the aganglionic segment still exhibits spontaneous phasic contractions that contribute to pseudoobstruction. The mechanism that generates these myogenic contractions and the generation of Ca(2+) waves that underlie contractions of the longitudinal muscle (LM) and circular muscle (CM) was recently studied by Spencer *et al*[21] in a mouse model of Hirschsprung's disease. In control mice, during the intervals between colonic migrating motor complexes (CMMCs), Ca(2+) waves discharged asynchronously between the LM and CM, while a burst of discreet Ca(2+) waves firing simultaneously was noticed in both muscle layers, with an increased propagation velocity of Ca(2+) waves. In aganglionic mice, CMMCs were absent and Ca(2+) waves between the two muscle layers fired asynchronously, despite an increased propagation velocity, resulting in a sporadic and sustained asynchrony in Ca(2+) waves firing between the LM and CM.

Neurotransmitters like nitric oxide (NO) can also play a role in generating pseudo-obstruction. NO is synthesized by the activation of neuronal NO synthase (nNOS) in the myenteric plexus in response to nerve stimulation and determines relaxation of the smooth muscle. Reduction in nNOS expression, associated with impaired local production of NO, may be responsible for some motility disorders including Hirschsprung's and Chagas diseases[9] where it is conceivable that extrinsic denervation may up regulate nNOS expression, resulting in enhanced muscular relaxation and disturbed peristalsis.

Myopathic variants of CIP have been intensively studied, although there are a lot of controversies regarding this inhomogeneous group. Visceral myopathy is a form of CIP characterized by vacuolar degeneration, atrophy and fibrosis of the intestinal muscle layer without inflammatory cells[22]. The familial form occurs in about 30% of cases having a transmission mostly autosomal recessive.

Mitochondrial DNA defects, as well as mitochondrial beta-oxidation disorders can also determine intestinal pseudo-obstruction associated with or not with progressive skeletal myopathy and neuropathy in some cases. Defects in mitochondrial proteins like mitochondrial trifunctional protein[23], an enzyme complex catalyzing the last three steps in the beta-oxidation cycle, causes intestinal pseudo-obstruction by activation of extramitochondrial fatty acid oxidation pathways with generation of excessive reactive oxygen species, leading to visceral myopathy. The muscle biopsies in such cases show intestinal smooth myocytes with bulbous protrusions filled with lateralized mitochondria, while histochemistry can show a decreased reactivity of cytochrome-c oxidase and marked reductions in other mitochondrial enzyme activities like NADH: Q1 and NADH: O2 oxidoreductases. Although considered as causative factors for myopathic CIP, mitochondrial disorders can also determine neuropathic pseudo-obstructions, or at least, can be associated with other neuronal intestinal malformations[24].

Deficiencies of alpha smooth muscle actin (ASMA) expression in intestinal smooth muscle are associated with CIP. Knowles *et al*[25] found that 24% of CIP patients have absent or partial ASMA immunostaining in the circular muscle layer, while smooth muscle alpha-actin staining is preserved in the longitudinal muscle and controls. Other authors[26] also tested the hypothesis that deficient ASMA expression in intestinal smooth muscle is specifically associated with clinical evidence of CIP using primary antibodies to ASMA, smooth muscle myosin heavy chain and desmin. While the staining for the later two antibodies was similar in patients and controls, ASMA expression was absent or minimal in all CIP patients but also in a great number of controls, leading to the conclusion that there is not enough evidence to confirm this theory. In contrast, Silk and his group[27] found that 58% of CIP patients have complete or partial deficiency of alpha-actin epitope staining in the inner circular layer of small intestinal smooth muscle, considering this deficiency as a biomarker of disease rather than a cause of CIP.

Immune disorders can seldom determine CIP. Intestinal pseudo-obstruction has been described in less than 20 cases in association with systemic lupus erythematosus[28] and, in extremely rare situations, autoimmune enteric leiomyositis[29] can determine pseudo-obstruction. It seems that coexisting disorders like autoimmune hepatitis can favor expansion of autoreactive T cells to homologous self-antigens in the muscularis propria, with smooth muscle fibers degenerated but with the myenteric neuronal plexus preserved.

Treatment of CIP is not standardized. Propulsive laxatives, prokinetics, anticholinesterase agents, motilin receptor agonists, and even octreotide, clonidine and propranolol have been tried in small series, but given the rarity of this condition, few controlled trials have been conducted. A number of reports have evaluated the efficacy of a prokinetic agent, cisapride, in the treatment of chronic intestinal pseudo-obstruction[30,31], showing some evidence for short-term improvements, but because of cardiac toxicity, this agent is actually restricted. It has been demonstrated that intravenous administration of neostigmine, 2.5 mg over 2 to 3 min, leads to prompt resolution of acute colonic pseudo-obstruction[32,33] by inhibiting the destruction of acetylcholine by acetylcholinesterase, which facilitates transmission of impulses across the myoneural junction. However, in CIP the results are not so obvious, and the role of neostigmin in treating these patients has not been formally evaluated, except in sporadic case reports[34,35]. Some papers[10] report improvement in gut function with use of erythromycin, given orally or intravenously in a small number of patients with CIP, suggesting that it can be of benefit for preventing and attenuating the episodes of pseudo-obstruction. Erythromycin inhibits the binding of motilin to the receptors on gastrointestinal smooth muscle, and, despite the relative absence of motilin receptors in the lower gut, there is evidence that supports its role in accelerating colonic transit in patients with CIP[36,37].

Colonoscopic decompression[38-40], with or without placement of a decompression tube, is accepted as a standard method to remove air from the colon in CIP, allowing decompression and reducing the risk of perforation. Although this procedure may be hazardous and sometimes difficult to perform because of poor preparation, it is usually efficient and passage of the endoscope to the hepatic flexure always permits decompression of the cecum in most patients. Unfortunately, dilatation usually recurs following decompression.

Surgical treatment is usually reserved to refractory situations, on a case-by-case basis. The options include total abdominal colectomy with ileorectal anastomosis, total proctocolectomy with ileostomy, or with ileoanal anastomosis[41-43] depending on the site of the colon affected.

In conclusion, CIP is a rare disease in which colonic dilatation can be impressive. Its etiology is not obvious, since multiple neuropathic and myopathic abnormalities can account for it. Although conservative treatment with anticholinesterase agents, motilin agonists or colonic decompression is recommended, its long-term efficacy is doubtful and colectomy is sometimes needed.

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