



## Case Report

## Chronic intestinal pseudo-obstruction. Did you search for lysosomal storage diseases?

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## ABSTRACT

Chronic intestinal pseudo-obstruction results in clinical manifestations that resemble intestinal obstruction but in the absence of any physical obstructive process. Fabry disease is an X-linked lysosomal storage disease characterized by the dysfunction of multiple systems, including significant gastrointestinal involvement. We report the occurrence of chronic intestinal pseudo-obstruction in two unrelated patients with Fabry disease and the possible explanation of a direct relation of these two disorders. In Fabry disease, gastrointestinal symptoms occur in approximately 70% of male patients, but the frequency ranges from 19% to 69% in different series. In some patients, colonic dysmotility due glycolipid deposition in autonomic plexus and ganglia can lead to the pseudo-obstruction syndrome, simulating intestinal necrosis. That is why up to this date colostomy has been performed in some cases, even for children with FD without cardiac, renal or cerebrovascular compromise. Early treatment with enzyme replacement therapy in asymptomatic or mildly symptomatic patients may be justified in order to prevent disease progression. Several studies have demonstrated that enzyme replacement therapy alleviates GI manifestations. Because of the non-specific nature of the gastrointestinal symptoms, diagnosis of Fabry disease is often delayed for several years. Gastrointestinal involvement is often misdiagnosed or under-reported. It is therefore very important to consider Fabry disease in the differential diagnosis of chronic intestinal pseudo-obstruction.

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## 1. Introduction

Chronic intestinal pseudo-obstruction (CIPO) is a high-morbidity syndrome that develops as a consequence of altered intestinal motility, which results in clinical manifestations that resemble intestinal obstruction but in the absence of any physical obstructive process [1]. CIPO is one of the most important causes of chronic intestinal failure both in pediatric (15%) and adult cases (20%), since affected individuals are often unable to maintain normal body weight and/or normal oral nutrition [2, 3]. The severity of the clinical picture, generally characterized by disabling digestive symptoms even between sub-occlusive episodes, contributes to deterioration of quality of life of the patients. Furthermore, CIPO often passes unrecognized for long periods of time, so that patients almost invariably undergo repeated, unnecessary and potentially invasive surgical procedures [1]. Fabry disease (FD) is an X-linked lysosomal storage disease characterized by the dysfunction of multiple systems, including significant gastrointestinal (GI) involvement such as diarrhea, abdominal pain, early satiety and nausea [4]. The deficiency in

lysosomal  $\alpha$ -Gal A causes accumulation of globotriaosylceramide (GL-3) within the lysosomes of multiple cell types throughout the body. This accumulation results in inflammation, ischemia, hypertrophy, and the development of fibrosis ultimately resulting in cellular damage and progressive organ dysfunction [5,6]. Although FD was thought to be rare, only affecting 1 in 40,000; recent newborn screening data show it to be much more common, affecting up to 1 in 3400–4000 newborns [7].

## 2. Aim

We report the occurrence of CIPO in two unrelated patients with Fabry disease and the possible explanation of a direct relation of these two disorders.

## 3. Cases report

Case 1: 62 years old female with classic phenotype of FD (mutation: A292T). At her initial visit for FD at the age of 59, the patient described isolated bloating and sporadic diarrhea with intermittent abdominal colic pain since the age of 18. Medical records showed at least 4 hospitalizations for intestinal pseudo-obstruction during the last 20 years.

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Ophthalmologic exam showed cornea verticillata. She had echocardiographic evidence of left ventricular hypertrophy (LVH) and had a history of arrhythmias. Brain MRI showed ischemic periventricular lesions. Laboratory exam showed microalbuminuria with normal estimated glomerular filtration rate (eGFR). She presented with a 5-day history of abdominal pain, primarily in the right lower quadrant and associated with intermittent fevers. Abdominal CT reported distended bowel loops, thickening of the proximal colon wall and free fluid in adjoining fascias. The following day, physical exam revealed an absence of abdominal sounds and progressively worsening pain. The patient underwent abdominal surgery with right colonic resection and placement of colostomy due a suspicion of tumoral obstruction. Pathological findings in H&E stained paraffin sections demonstrated enlarged ganglion cells with foamy cytoplasm present within Meissner's plexus of the submucosa present in the ileocecal valve sample. The foamy appearance likely represented the presence of GL-3 accumulation, lost in the paraffin processing. Epoxy resin sections taken from this same area show enlarged ganglion cells filled with zebra bodies, further suggesting the accumulation of GL-3. Ganglion cells of Auerbach's plexus present between the two muscular layers of the muscularis propria were also engorged with GL-3 accumulation (Fig. 1a). Substrate accumulation was also present in the smooth muscle cells of small arteries present in the submucosa (Fig. 1b), and within smooth muscle myocytes of the muscularis propria.

Case 2: 37 years old male patient was diagnosed with classic FD (mutation: D155H) following a renal biopsy for proteinuria study. The patient had other classic symptoms of FD including chronic abdominal pain and episodes of diarrhea during childhood, neuropathic pain in the hands and feet associated with fever and exercise, angiokeratomas and cornea verticillata. Furthermore, echocardiogram showed mild LVH and brain MRI showed small periventricular ischemic lesions. At the age of 32, the patient was hospitalized due abdominal pain and diverticulitis; after 2 days of conservative treatment he made a full recovery. At the age of 38, the patient developed fever and progressive left, lower-quadrant abdominal pain. After 3 days of conservative treatment, physical exam revealed severe abdominal distention, absence of abdominal sounds and progressively worsening pain. Abdominal surgery showed sigmoid colon distention and a delustered appearance; bowel resection with placement of colostomy was performed. Pathological examination of H&E stained paraffin revealed neither obstructive process nor inflammatory infiltration. Enlarged and vacuolated neurons in the Meissner's and Auerbach's plexuses (Fig. 2a) and intracellular inclusions in the smooth muscle cells of small arteries were present in the submucosa. Some vessels were narrowed and a few were occluded at this level (Fig. 2b).

## Discussion

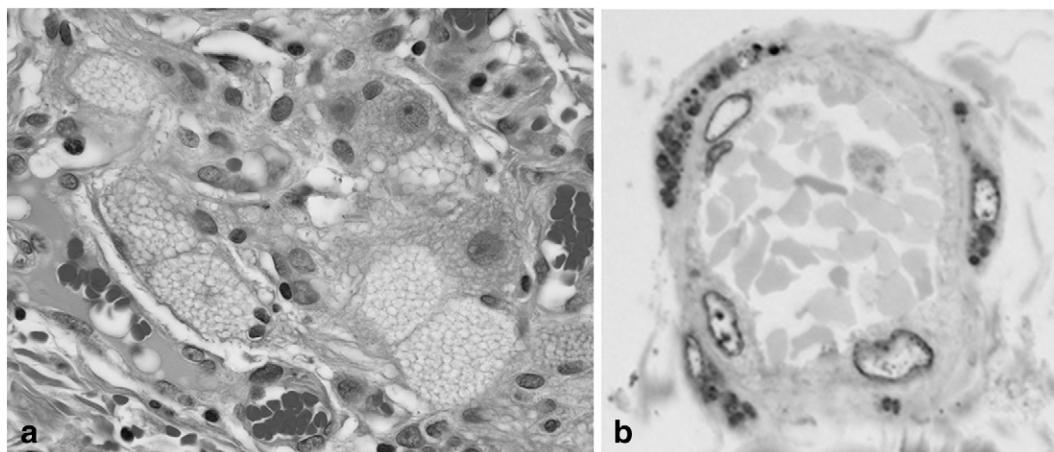
CIPO may be primary, when it exclusively involves intestinal smooth muscle or enteric neural plexus, or secondary to other conditions. The histopathologic presentation of CIPO can be divided in neuropathic, mesenchymopathic and myopathic forms based on abnormalities affecting the integrity of nerve pathways supplying the gut (either intrinsic or extrinsic), interstitial cells of Cajal (ICC) or smooth muscle cells, respectively. Table 1. Neuropathic, mesenchymopathic and myopathic changes may contribute to gut dysmotility either individually or in combination (e.g. neuro-myopathies or neuro-ICC alterations) [8].

In FD, gastrointestinal symptoms occur in approximately 70% of male patients [4,5], but the frequency ranges from 19% to 69% in different series [9,10]. In heterozygous patients (females) almost half of them may experience GI symptoms and some of those symptoms, such as constipation, are reported almost twice as often by female patients as by male patients [11].

Significant GI involvement has also been observed in children and can progress in severity with age. In a systematic review, Laney and colleagues observed that GI symptoms even presented in very young children, aged 1–4 years old, most commonly complaining of abdominal pain [12]. The symptoms present soon after the development of acroparesthesias and can be the initial symptom of FD in up to 20% of patients [13]. Abdominal pain is described as cramping mid-abdominal discomfort, frequently worsened with meals and increased stress. The possible local ischemia due endothelial deposits of GL-3 has led to the suspicion of 'intestinal angina' being the cause for post-prandial abdominal pain in some patients.

The second most common symptom is diarrhea occurring in 20% of patients [14]. The diarrhea can be intake-triggered, frequently associated with significant urgency and frequency, and occurring up to 15 times daily. Some patients report severe urgency leading to routine fecal incontinence. In some patients, colonic dysmotility can lead to the pseudo-obstruction syndrome, simulating intestinal necrosis. That is why up to this date colostomy has been performed in some cases [11,15], even for children with FD without cardiac, renal or cerebrovascular compromise. Intestinal perforation, secondary to diverticular disease, has been repeatedly described in the literature. The location of diverticula has been described as occurring at the duodenal, jejunal, and colonic levels [15–17].

Neuropathic pain (acroparesthesias) and GI involvement may be explained due a multifactorial cascade. Substrate deposits of GL-3 in autonomic ganglia (dorsal root ganglia -DRG- and myenteric and submucosal ganglia) may be the cellular alteration which results in the appearance of symptoms [18–22]. Intestinal ischaemia due



**Fig. 1.** a: Ganglion cells of Auerbach's plexus: Ganglion cells appear markedly foamy due to the accumulation of GL-3 (paraffin section, H&E, 600×). b: Vascular smooth muscle cells of submucosal arteries contain GL-3 (arrow). (HRLM, 1 μm epoxy resin, 1:1 Richardson's stain, 1000×).

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