Case Report

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

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A R T I C L E   I N F O

Article history:
Received 19 March 2017
Accepted 19 March 2017
Available online xxxx

Keywords:
Fabry disease
Lysosomal storage disease
Sphingolipidoses

A B S T R A C T

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 colectomy 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 α-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 colic pain since the age of 18. Medical records showed at least 4 hospitalizations for intestinal pseudo-obstruction during the last 20 years.
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 following a renal biopsy for proteinuria study. 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
myenteric vessel occlusion could also be correlated with the small fiber neuropathy as a result of vasa nervorum obliteration [4]. Animal models with FD showed mechanical hypersensitivity in the von-Frey test and mechanical allodynia when compared with controls [23,24]. The same studies demonstrated that tissue involvement in DRG and small nerve fiber loss are linked with upregulation of sodium channels type 1.8 (Na\(_{\text{V}}\)1.8) and transient receptor potential vanilloid type 1 (TRPV1).

The upregulation of these channels in DRG neurons causes an early depolarization of the resting potential, reduced threshold and increased frequency for evoked firing in these neurons, and increased fraction of DRG neurons that fire spontaneously. The GI manifestations reported by patients with FD might be explained by the effect of the GL-3 deposits on visceral afferents that are known to express Na\(_{\text{V}}\)1.8 and TRPV1 channels [25]. A specific role for Na\(_{\text{V}}\)1.8 in regulating gastrointestinal function is supported by experimental evidence showing that this channel (as well as Na\(_{\text{V}}\)1.9 also) is important for responses to mechanical stimulation and mechanical hypersensitivity of visceral afferents innervating the colon when challenged by an inflammatory mediators or food intake [25]. This hypothesis should be confirmed in further studies.

Enzyme replacement therapy (ERT) should be initiated in all affected patients with FD as soon as clinical signs and symptoms are observed. Early treatment of asymptomatic or mildly symptomatic patients may be justified in order to prevent disease progression [26]. Several studies have demonstrated that ERT alleviates GI manifestations [27–29]. This may be explained by a decrease of GL-3 accumulation in the endothelium of the intestinal vessels and by improved mesenteric circulation. ERT is presently available in the form of agalsidase alfa (Replagal®, Shire HGT, Inc., Cambridge, MA, USA) and agalsidase beta (Fabrazyme®, Sanofi Genzyme, Cambridge, MA, USA) [30,31]. Agalsidase alfa is given at 0.2 mg/kg body weight every other week by intravenous (IV) infusion and is approved in many countries throughout the world, though not by

### Table 1

| Causes of chronic intestinal pseudo-obstruction syndrome. |
|-----------------------------------------------------------|
| **Myopathic**             | **Mitochondrial**             | **Neuropathic**             | **Mesenchymopathic**             |
| Visceral                  | Central:                     | Loss of interstitial cells of Cajal |
| Primary:                  | Diseases from defective genes coding for proteins indirectly related to oxidative phosphorylation |
| • Absence of or selective decrease in smooth-muscle alpha-actin |
| • Familial or sporadic visceral myopathy |
| • Myopathy from abnormal gut morphogenesis |
| • Autoimmune leiomyositis |
| Secondary:                | Diseases from genetically-induced mitochondrial DNA stability disturbance |
| • Lupus, Polymyositis |
| • Amyloidosis Cereoidosis (vitamin E deficiency) |
| • Progressive muscular dystrophy, |
| • Drugs (neuroleptics) |
| | Diseases from defective nuclear genes coding for CRM enzyme complex proteins |
the USA Food and Drug Administration [32]. Agalsidase beta is adminis-
terated at 1.0 mg/kg body weight once every 2 weeks as an IV infusion and is
approved in Europe, the USA and many other countries.

There are no adequately powered head-to-head studies that have
compared the long-term effectiveness of the two enzyme preparations on
clinical outcomes in well-characterized, phenotypically homogenous
populations but evidence suggests that a higher agalsidase dose may be
of clinical benefit in reducing GL-3 accumulation [33,34]. Because of
the shortage of agalsidase-beta in 2009, many patients with FD were treated
with lower doses or were switched from agalsidase beta to agalsidase
alfa. One observational study assessed end-organ damage and clinical
symptoms during dose reduction or switch from agalsidase beta to alfa.
After 1 year, severity score index and frequencies of pain attacks,
chronic pain, gastrointestinal pain, and diarrhea increased significantly in
the dose-reduction and switch groups [35].

Because of the non-specific nature of the GI symptoms, diagnosis of
FD is often delayed for several years. Gastrointestinal involvement is
often misdiagnosed (usually as irritable bowel disease, visceral myopa-
thy or inflammatory bowel disease) or under-reported. It is therefore
very important to consider FD in the differential diagnosis of CIPD.

Conflict of interest statement

Juan Politei has received speaker honorarium from Genzyme, Shire
and Amicus.

Beth Thurberg is an employee of Sanofi Genzyme.

The other authors declare that they have no competing interests in
relation to this work.

This research did not receive any specific grant from funding agen-
cies in the public, commercial, or not-for-profit sectors.

All procedures followed were in accordance with the ethical stan-
dards of the responsible committee on human experimentation of
Laboratorio de Neuroquímica Dr. N. Chamoles, Buenos Aires, Argentina.

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