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Review

Gastrointestinal involvement in Fabry disease. So important, yet often neglected

Politei J., Thurberg B.L., Wallace E., Warnock D., Serebrinsky G., Durand C., Schenone A.B.. Gastrointestinal involvement in Fabry disease. So important, yet often neglected.
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Fabry disease is an X-linked metabolic storage disorder due to the deficiency of lysosomal alpha-galactosidase A which causes accumulation of glycosphingolipids, primarily globotriaosylceramide, throughout the body. Gastrointestinal signs and symptoms – abdominal pain, nausea, diarrhea and diverticular disease – are some of the most frequently reported complaints in patients with Fabry disease but are often neglected. Gastrointestinal symptoms are due to intestinal dysmotility as well as impaired autonomic function, vasculopathy and myopathy. Since 2001, enzyme replacement therapy has been a mainstay in treatment of gastrointestinal symptoms of Fabry disease (FD), resulting in reduced gastrointestinal symptoms. Here, we report on four patients with Fabry disease (FD) who manifested early gastrointestinal involvement.

Conflict of interest

J. P. has received speaker honorarium from Genzyme, Shire and Amicus. B. T. is a full-time employee of Genzyme Corporation, a Sanofi company. D. W., E. W., C. D., A. S. and G. S. declare that they have no conflict of interest.

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Fabry disease (FD) is a rare and highly debilitating lysosomal storage disorder that results from a deficiency of α-galactosidase A (α-Gal A) due to mutations in the *GLA* gene located on the X chromosome (1). The deficiency in α-Gal A causes accumulation of globotriaosylceramide (GL-3; also abbreviated Gb3) 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. Many cell types are involved in Fabry disease pathology, including vascular cells (endothelial and smooth muscle cells), cardiac cells, a variety of renal cells (tubular and glomerular cells, and podocytes), and nerve cells (2–5). Gastrointestinal symptoms are some of the most frequently reported symptoms in patients with Fabry disease. The most common complaints – abdominal pain, bloating, diarrhea, constipation, recurrent nausea and vomiting – are probably due to intestinal dysmotility and secondly due to impaired autonomic function, vasculopathy and myopathy (6). Since 2001, enzyme replacement therapy (ERT) with agalsidase alfa and agalsidase beta has been available for the treatment of Fabry disease and several studies have demonstrated its effectiveness in the control of gastrointestinal symptoms (7, 8).

Objective

To describe four cases that illustrates the wide spectrum of gastrointestinal compromise in Fabry disease (Table 1).

Table 1. Demographic data from patients

	Gender	Age at onset of GI symptoms	Age at diagnosis	Abdominal pain	Diarrhea	Vomit	Mutation	ERT	MT[a]	SIFT
1	Female	18	54	++	++	No	L415P	No	Disease	Damaging
2	Male	6	28	+++	+++	+++	T194I	Yes	Disease	Damaging
3	Male	13	17	++	++	+	D264Y	Yes	Disease	Damaging
4	Female	22	59	+	++	No	A292T	Yes	Disease	Damaging

+, mild; ++, moderate; +++, severe; ERT, enzyme replacement therapy; GI, gastrointestinal; MT, Mutation Taster; SIFT, Sorting Intolerant From Tolerant.

[a]Mutation Taster results are disease causing for each mutation.

Patients

Case 1

A 54-year-old female was diagnosed with Fabry disease during a family screening after her son who had chronic kidney disease was identified at the age of 31. On further questioning, the patient complained of neuropathic pain as well as early satiety, bloating and sporadic diarrhea with intermittent abdominal colic pain since the age of 18. At the age of 66, she presented with progressive right faciobrachial hemiparesis of 1 month duration. Radiographic and laboratory examination revealed mild left ventricular hypertrophy (LVH), proteinuria (400 mg/24 h) and estimated glomerular filtration rate (eGFR) 59 ml/min. Brain magnetic resonance imaging (MRI) showed periventricular ischemic silent cerebrovascular lesions and a left frontal solid nodular image compatible with meningioma. Surgical resection was indicated. Two days after surgery, while the patient showing excellent neurological recovery, the patient developed a fever and left, lower-quadrant abdominal pain. Abdominal X-rays showed distended bowel loops. After 4 h, physical exam revealed an absence of abdominal sounds and pain had become progressively worse. Abdominal surgery showed sigmoid colon diverticular perforation and bowel resection with placement of colostomy procedure was performed. Unfortunately, post-operatively, the patient developed multi-organ failure secondary to sepsis and died the day after surgery.

Case 2

A 28-year-old male patient was diagnosed with Fabry disease following a renal biopsy for 2 gm/24 h of proteinuria. He was initiated on ERT with agalsidase alfa 0.2 mg/kg every other week (EOW), but progressed to end stage renal disease (ESRD) requiring hemodialysis at the age of 30. The patient had other classic symptoms of Fabry disease including abdominal pain since the age of 6, acroparesthesias with associated pain crisis in hands and feet associated with fever and exercise. Furthermore, echocardiogram showed mild LVH and brain MRI showed small periventricular ischemic lesions. The ophthalmological exam reported bilateral cornea verticillata, and the dermatological evaluation reported angiokeratomas scattered mainly toward the genital area.

At the age of 32, he presented with a 12 lbs weight loss secondary to worsening abdominal pain, sporadic diarrhea, bloating, postprandial vomiting which had increased in frequency since the time of his diagnosis. Obstructive causes were ruled out, and abdominal computed tomography (CT) scan was normal with the exception of bilaterally small kidneys. Repeated endoscopies showed mild congestion of the antral mucosa, with no other pathologic findings. A magnetic resonance enterography showed severe dilation in the proximal colonic segment and loss of haustral pattern (Fig. 1). Because of the absence of response to the prokinetic agents (metoclopramide, ondansetron, erythromycin and domperidone), an evaluation of nuclear gastric emptying study was performed. A severe delay in gastric emptying was found (400 min, average normal value: 60 min) (Fig. 2). He was counseled on frequent small meals and prescribed octreotide and metoclopramide, with partial improvement in his symptomatology.

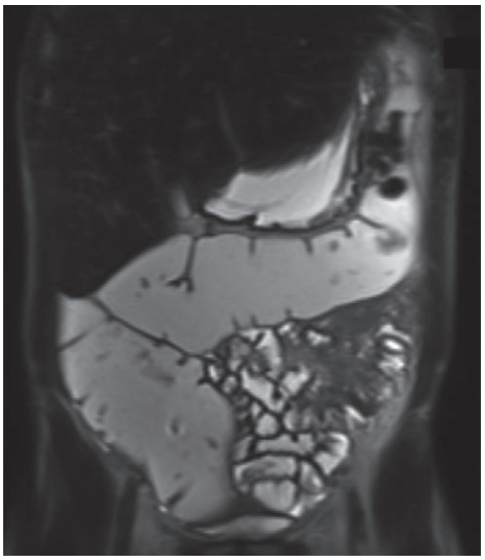

Fig. 1. Magnetic resonance enterography showed severe dilation in the proximal segment of colon and loss of haustral pattern in case 2.

Case 3

A 24-year-old male patient was diagnosed with Fabry disease at 17 years of age following a family screening presented to clinic with sudden onset of abdominal pain. At his initial visit for Fabry disease at diagnosis, 7 years prior to presentation, the patient complained of neuropathic pain in hands and feet since age 12, with pain crises associated with fever and changes in temperature,

Fig. 2. Evaluation of gastric emptying with TC99 shows severe delay in gastric emptying in case 2 in the solid phase.

hypohidrosis, angiokeratomas, cornea verticillata. He also complained of long-standing intermittent abdominal pain associated with diarrhea and rarely with vomiting which began at the age of 13. At the age of 17, he was started on ERT (agalsidase beta 1 mg/kg EOW) with subsequent improvement in neuropathic pain and the complete resolution of diarrhea after 1 year of treatment. The patient reported that sweating returned to normal. The patient consults because of progressive abdominal pain. The location of the pain was described as umbilical and hypogastric. Physical exam revealed fever and decreased bowel sounds. Urgent laparoscopy showed diverticular disease at the jejunal and colonic level, with signs of jejunal microperforation and a 2 cm abscess. Resection and primary anastomosis were performed without incident.

Case 4

A 64-year-old female with Fabry disease on ERT (agalsidase beta 1 mg/kg EOW) for 4 years presented with a 5-day history of abdominal pain. At her initial visit for Fabry disease at the age of 59, the patient described isolated abdominal pain episodes occurring since her youth, sporadic diarrhea. Ophthalmologic exam showed cornea verticillata. She had echocardiographic evidence of LVH and had a history of arrhythmias. Brain MRI showed ischemic periventricular lesions. Laboratory exam showed microalbuminuria with normal eGFR. She consulted because of a 5-day evolution abdominal pain, primarily in the left lower quadrant and associated with intermittent fevers. She did not have any change in bowel patterns during this time. The gynecologic exam was unremarkable. Abdominal CT reported thickening of the sigmoid colon wall, minimum free fluid in adjoining fascias and small regional nodal enlargement compatible with diverticulitis. The decision was made to start intravenous antibiotic therapy. Patient made a full recovery.

Discussion

The impact of gastrointestinal symptomatology as a cause of morbidity in patients with Fabry disease cannot be overstated. The patient first described by Johannes Fabry and William Anderson presented angiokeratoma with multi-organ involvement including gastrointestinal symptoms. However, this manifestation was not considered an important part of the disease for the next 60 years (9, 10). Gastrointestinal symptoms occur in approximately 70% of male patients with Fabry disease (11), but the frequency ranges from 19% to 69% in different series (12, 13). Although heterozygous females were previously considered carriers, almost half of females may experience gastrointestinal symptoms and some of those symptoms, such as constipation, are reported almost twice as often by female patients as by male patients (6). In some cases the gastrointestinal symptoms can dominate the clinical picture, presenting as a so-called 'gastrointestinal phenotype' of Fabry disease (14). It is well known that gastrointestinal involvement can be the first and only manifestation of Fabry disease for years. Recently, one review of early childhood (≤5 years of age) reports, showed gastrointestinal symptoms had been reported in six children from 1.0–4.1 years of age. Specific issues included gastrointestinal pain in four children, as well as additional findings including diarrhea, constipation, nausea, and vomiting (15). Classically, the signs and symptoms more frequently described are abdominal pain and diarrhea. All the patients discussed described this symptomatology at some point in the evolution of their disease. Patients with Fabry disease are frequently misdiagnosed as irritable bowel syndrome, chronic inflammatory bowel disease, appendicitis, autoimmune disorders, Whipple's disease, dermatomyositis, or somatoform disorder (16) Exceptionally, Fabry disease might be associated with other gastrointestinal diseases such as Crohn's disease, coeliac disease, or colon cancer (17–19). Special attention to patients with chronic gastrointestinal complaints without diagnosis should prompt a thorough family history such that the diagnosis of Fabry disease is not delayed in these patients. The pathophysiologic mechanisms by which Fabry disease causes these symptoms are hypothesized to be the result of the dysregulation of the autonomic nervous system responsible for gut motility, vascular compromise from endothelial GL-3 accumulation, and visceral involvement. The ensuing dysmotility can then be associated with bacterial overgrowth. Autopsy and biopsy studies have shown the submucosal (Meissner's) plexus and myenteric (Auerbach's) plexus affected with inclusions. Histopathological descriptions show vacuolization of ganglion cells and surrounding axons, with intracellular glycosphingolipid deposits

typical of Fabry disease (Fig. 3) (20–26). An increase in size of the ganglion cells higher than twice their normal size has also been reported (22). One of the most important functions of the myenteric plexus is the inhibition of local myogenic activity modulating and coordinating the contraction of intestinal smooth muscle cells. The ganglion and axonal autonomic engagement and the ensuing cellular degeneration would result in focal hyperactivity and lack of coordination of the myogenic activity (21). Studies on intestinal transit reported to date show a global decrease of peristalsis and isolated areas of spastic contractions. Some esophageal manometry studies have shown that these abnormalities can occur as proximal as the esophagus (20) However, most reports show these spastic contractions at the level of small intestine level (22, 24). Studies involving liquid and solid gastric emptying with Tc99 have repeatedly shown gastric dysmotility (22, 27) consistent with this hypothesis. Treatment with metoclopramide has proven to be efficient in most cases. The second case discussed had severe delayed gastric emptying for solids as well as for liquids. Large intestine transit study with barium enema shows loss of haustral markings, decrease in peristaltic movement, and colon focal spastic contractions (22, 24, 28, 29). Colonic dysmotility can lead in some patients to the pseudo-obstruction syndrome, simulating intestinal necrosis. That is why up to this date colostomy (14, 21) has been made in exceptional cases, even for children with Fabry disease without cardiological, renal or cerebrovascular compromise. As such, neurologic involvement has been shown to be of primary importance in gastrointestinal manifestations of Fabry disease. Vascular involvement in both capillaries and large vessels also play a role in the abdominal compromise. Optical and electron microscopy studies show decrease in blood vessel caliber due to intracellular deposits in endothelial cells, pericytes and vascular smooth muscle cells (Fig. 3). (21–24, 29). Jardine et al., describe a 50-year-old male patient with intestinal necrosis secondary to superior mesenteric artery infarction (20). One case of appendicitis, with electronic microscopy (EM) showed vascular and smooth muscle Gl3 inclusions consistent with Fabry disease involvement (30).

Other mechanisms of gatrointestinal disturbances are thought to be a result of complications of dysmotility and peristalsis leading to bacterial overgrowth thus predisposing to chronic diarrhea, malabsorption, and diverticula formation. Bile salt breath tests for expiration (20) or aspiration of jejunal content (22) confirm this finding. Also, the use of tetracycline has been used as a potential treatment of bacterial overgrowth leading to resolution of diarrhea after 2 days of treatment in one report (22). The intestinal perforation, secondary to diverticular disease, has been repeatedly described in the literature. The location of diverticula has been described as occurring at duodenal (20), jejunal (21, 25), and colonic (25) level. Three of the reported patients showed diverticular disease complications, and two of those patients reached perforation.

Intestinal smooth muscle cells show typical lysosomal inclusions, in addition to the ganglion cells of the autonomous nervous system and the intestinal wall blood vessels (21, 22, 24). Muscle wall thickening areas associated with fibrotic areas adjoining the diverticula have been described (21). The formation of diverticula may be the result of long periods of dysmotility, which produce high intraluminal pressure areas with protrusion of intestinal mucosa. These smooth muscle fibers, exposed to irregular contractions, are usually affected (weakened) by the hypoflux contributed by the small intestinal vessels, secondary to luminal stenosis (19). The possible local ischemia has led to the suspicion of 'intestinal angina' being the cause for post-prandial abdominal pain in some patients. Malabsorption syndrome has been suspected and described as a possibility in some patients, though to date all reports have described normal results to the xylose (22, 23) test.

Some of the primary symptoms alleviated by ERT are that of gastrointestinal leading to improved quality of life for patients with Fabry disease. The first study to show the beneficial effects of ERT on gastrointestinal symptoms was conducted by Dehout et al. (31). They studied 11 patients and reported a significant decrease in the severity and frequency of abdominal pain and diarrhea. Wraith et al. (32), reported 14 male and 2 female pediatric patients, 8 to 16 years old treated with agalsidase beta during 48 weeks. Patient reports

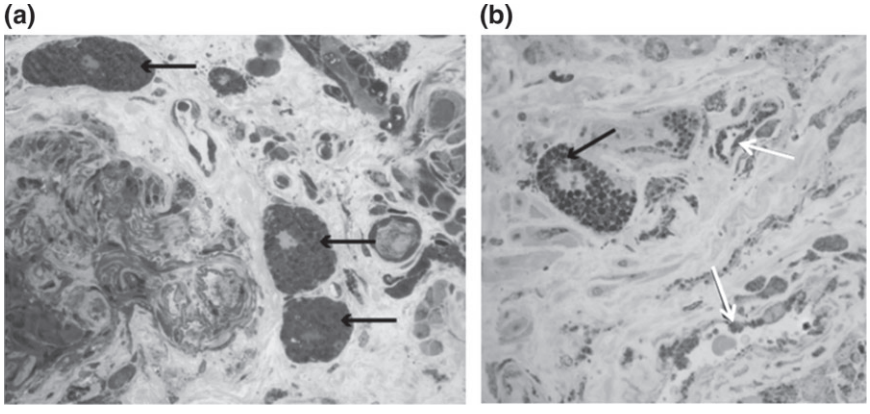

Fig. 3. Gl3 is present in ganglion cells (black arrows) and vascular endothelial cells (white arrows) of the submucosa of the gastrointestinal tract in Fabry patient (high resolution light microscopy, Richardson's stain. Panel A, 600×; panel B, 1000×)

of post-prandial pain, nausea, and vomiting declined steadily with time on treatment, showing statistically significant improvements by week 24. Hoffmann et al., using the Fabry Outcome Survey database, found that the prevalence of gastrointestinal symptoms was reduced following ERT after 12 and 24 months (6). Finally, in four adult patients, after 6–7 months of agalsidase beta therapy, all patients reported 'no or only occasional' abdominal pain or diarrhea and had discontinued their gastrointestinal medications (7). As symptomatic treatment, metoclopramide, pancreatin, antibiotics, and ondansetron together with fractionated meal diet have been used with positive response in most cases (22, 27, 33). There are no validated scales for the Fabry gastrointestinal symptoms follow up before and after treatment indication. In the meantime, validated quality of life scales (like SF-36) and some scales for irritable bowel syndrome evaluation can be used.

Conclusion

Gastrointestinal involvement can be one of the earliest and most significant clinical manifestations of Fabry disease. As a result of the non-specific nature of the presenting symptoms, diagnosis is often delayed for several years. It is therefore important to consider Fabry disease in the differential diagnosis of gastrointestinal disorders and start ERT early when gastrointestinal symptoms are present in order to prevent multiorganic progression.

Acknowledgements

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation of FESEN, Buenos Aires, Argentina and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

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