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Gastrointestinal involvement in Fabry disease

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Abstract

Fabry disease is an X-linked lysosomal storage disorder due to alpha-galactosidase A deficiency. This deficiency results in a progressive accumulation of globotriaosylceramide and related glycosphingolipids, particularly in vascular endothelial cells, renal cells, nerve cells, and cardiomyocytes. Gastrointestinal symptoms are frequent and can be extremely debilitating. It is known that most of the well-characterized gastrointestinal manifestations of Fabry disease are the result of the accumulation of glycosphingolipids, which causes vascular occlusion and malfunction of the peripheral and autonomic nervous system. Although improvement is noted in treating patients with enzyme replacement therapy and migalastat, some continue to experience symptoms after treatment; thus, it remains a significant cause of morbidity, necessitating concurrent adjuvant treatment. Current research is focused on clarifying the underlying dysmotility and further analyzing the correlation between the gut-brain axis, the histologic disease progression, and the clinical symptom presentation.

Keywords: Fabry disease, Fabry gastrointestinal involvement, abdominal pain

INTRODUCTION

Fabry disease (FD) is an X-linked lysosomal storage disorder due to the deficiency of alpha-galactosidase A (α-GalA). As a result of this deficiency, a progressive accumulation of globotriaosylceramide (GL-3) and related glycosphingolipids, particularly in vascular endothelial cells, renal cells, nerve cells, and cardiomyocytes, is present[1]. Fabry disease patients who have very low α-GalA activity exhibit the classic

phenotype and are generally symptomatic in early childhood. In contrast, patients with residual α-GalA activity exhibit milder clinical manifestations and onset occurs later compared to the classic phenotype[2].

CLINICAL MANIFESTATIONS

In the classic phenotype, clinical manifestations are multisystemic, including distal neuropathic pain, acroparesthesia, abdominal cramps, diarrhea, angiokeratoma, anhidrosis, and childhood-onset corneal opacity. As patients age, there is a progression towards major organ involvement in adulthood, marked by proteinuria, impaired renal function, cardiomyopathy, and stroke. In contrast, individuals with the later-onset phenotype retain a notable level of α-GalA activity. However, some male patients may develop either cardiomyopathy or, less frequently, nephropathy, which can be as severe as in the classic phenotype. In nearly every instance, females with late-onset disease have relatively minor kidney involvement[1,2]. Two decades ago, female heterozygotes were erroneously characterized as "carriers of the defective gene" presumed to be more or less safeguarded against developing disease manifestations. However, it has been established that most female heterozygotes do develop symptoms and vital organ involvement including kidneys, heart, and brain a decade later than males[3].

Among classic patients, abdominal pain is the most frequently reported symptom. It manifests as intermittent pain localized in the mid or lower abdomen, accompanied by bloating, cramping, or midabdominal discomfort[4,5]. The aforementioned manifestations may appear during or after meals or may even be triggered by stress. Therefore, it is plausible that many FD patients are unwilling to consume food, potentially leading to lower body weight. Diarrhea ranks as the second most common manifestation, often appearing postprandially and occurring up to a dozen times a day, significantly decreasing the quality of life of affected patients[5,6]. Additional manifestations include nausea, vomiting (both more frequent in children), and constipation, with females experiencing the latter more frequently than males. Mainly in adult patients, the presence of gastritis, hemorrhoids, chronic intestinal pseudo-obstruction, diverticular disease, and bowel ischemia has also been reported[7-11].

The real incidence of gastrointestinal (GI) symptoms among patients with FD is unclear, and underreporting of these non-specific symptoms is a frequent occurrence. However, there has been a notable incidence of GI symptoms reported, particularly among children and female patients[12]. Registry data from patients enrolled in the Fabry Outcome Survey show that 60% of untreated children reported GI symptoms upon enrollment to the Registry[13]. Similarly, 50% of adult female patients exhibited such symptoms[14]. In 2015, Laney published a systematic retrospective analysis of publications and case reports in the pediatric Fabry population symptoms reported before 5 years of age[15]. This group uncovered compelling evidence indicating that symptoms can manifest during early childhood, with cases reported as early as 2 to 3 years of age. They concluded that neuropathic pain, heat sensitivity, especially recurrent abdominal pain and diarrhea, should be monitored during early childhood[15].

The prevalence of GI manifestations in FD should be taken with caution. It is important to consider that these symptoms, which can include recurrent abdominal pain and diarrhea, may not exclusively be attributed to FD, but may also be associated with common functional disorders such as irritable bowel syndrome, particularly in cases of late-onset FD. Reports published over two decades ago indicated a high frequency of GI symptoms in males (69%) and females (58.3%). However, it is crucial to note that the absence of differentiation between phenotypes in these studies could potentially lead to misinterpretation of the results[16,17]. In 2020, Di Toro investigated the pathological basis of FD-related gastropathy, comparing classic and late-onset patients with control cases through gastric endoscopy. All patients experienced long-standing GI disturbances that were poorly managed with medications. In classic FD phenotype,

immunohistochemical study revealed specific immunostaining to GL-3 in various cell types, including endothelial and vascular smooth muscle cells (SMC), pericytes, nerve cells, interstitial mesenchymal cells, and epithelial cells. The ultrastructural study demonstrated the typical lamellar osmiophilic bodies in the cytoplasm of the SMC of the muscularis mucosae, both vascular and non-vascular SMCs, nerve cells, and gastric epithelia. On the contrary, gastric biopsies from late-onset FD patients and control cases did not show GL-3 accumulation. In these patients (both controls and late-onset cases), GI symptoms were attributable to gastric comorbidities[18].

PATHOPHYSIOLOGY

It is known that most of the well-characterized symptoms of FD are the result of the accumulation of GL-3, leading to vascular dysfunction and perturbations in the peripheral and autonomic nervous systems[19]. In a study by Masotti *et al.*, the α-Gal A (–/0) mouse model of FD was used to characterize distinct anatomical, morphological, and molecular features of the colon tract in comparison with the wild type[20]. The authors did not detect any difference based on macroscopic damage parameters, nor did they observe any remarkable sign of inflammatory infiltrate at the mucosal level. These findings are in line with the results of colonoscopies and histological analysis of Fabry patients, which typically exhibit no indications of mucosal damage or inflammation[8,21]. Structural analysis reported a thickening of the muscular layer and the size of ganglia of the myenteric plexus in α-Gal A –/0 colon, by the presence of GL-3 deposits in smooth muscle and neuronal cells. Additionally, α-Gal A –/0 mice exhibited a significant reduction in protein gene product 9.5-positive innervation entering the mucosa, as compared to the control group[20].

Several mechanisms through which FD causes these manifestations in patients are hypothesized to be the result of enteric nervous system dysregulation, impacting gut motility, endothelial GL-3 accumulation leading to vascular compromise, and involvement of visceral hypersensitivity[12]. Autopsy and biopsy studies have shown the presence of GL-3 inclusions in both the submucosal (Meissner's) plexus and the myenteric (Auerbach's) plexus. Anatomopathological records show swelling of ganglion cells and surrounding axons, with intralysosomal GL-3 inclusions characteristic of FD [Figure 1][8,21-23]. Notably, patients and mice models with FD have exhibited an increase in the size of ganglion cells, surpassing twice their normal dimensions[20,21]. The ganglion and axonal autonomic compromise in association with the resulting cellular degeneration leads to focal hyperactivity and lack of coordination of the myogenic activity[7]. Reports on gut motility have reported an overall delay in peristalsis and regional myogenic hyperactivity[24]. It is worth noting that the majority of these reports highlight these spastic contractions occurring predominantly within the small intestine[21,23]. Liquid and solid gastric emptying studies with Tc99 have repeatedly shown gastric dysmotility[10,21,25], confirming this hypothesis. Recently, 48 patients with FD and GI manifestations were studied using a wireless motility capsule (WMC) to measure pan-gut motility[26]. The WMC testing showed a significant correlation between constipation severity and the Bristol stool scale with colonic transit time. The severity of nausea and vomiting displayed an inverse correlation with the motility index of antral and duodenal contractility, indicating that heightened motor activity in the antro-duodenum is associated with less severe nausea and vomiting. Nonetheless, in a symptomatic patient cohort, only about 35% exhibited delayed transit in one section of the gut[26].

Colonic dysmotility can lead some patients to pseudo-obstruction syndrome. As a result, colostomy has been performed in exceptional cases, including children with FD who lack cardiac, renal, or cerebrovascular complications[7,9,11]. Vascular involvement, both of small arteries and large vessels, largely explains the pathophysiology of gastrointestinal alteration. Studies utilizing optical and electron microscopy have demonstrated a narrowing in blood vessel lumen as a result of GL-3 deposits in endothelial cells, pericytes, and vascular smooth muscle cells [Figure 2][21-24,27]. The occlusion of mesenteric vessels resulting in intestinal

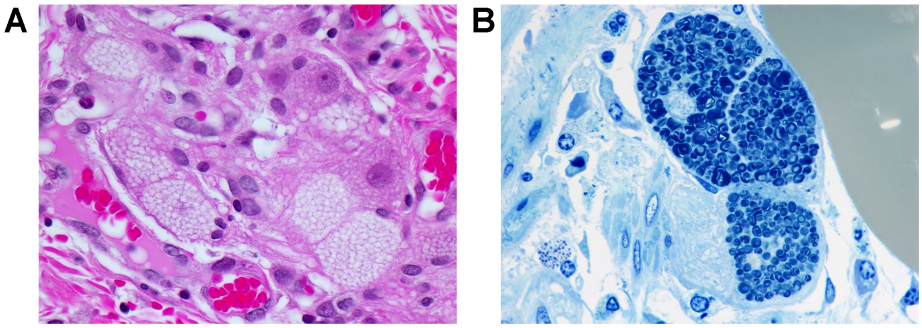

Figure 1. (A) Ganglion cells of Auerbach's plexus: ganglion cells appear markedly foamy due to the accumulation of GL-3. (Paraffin section, H&E, 600x). Photo property of Dr. Politei. Published with permission of Dr. Politei. (B) Ganglion cells of Meissner's plexus: the submucosa of the ileum contains ganglion cells engorged with GL-3 accumulation appearing here in high resolution light microscopy (HRLM) sections as dark blue myelin figures and zebra bodies. (1 micron epoxy resin, 1:1 Richardson's stain, 1,000x). Photo property of Dr. Politei. Published with permission of Dr. Politei.

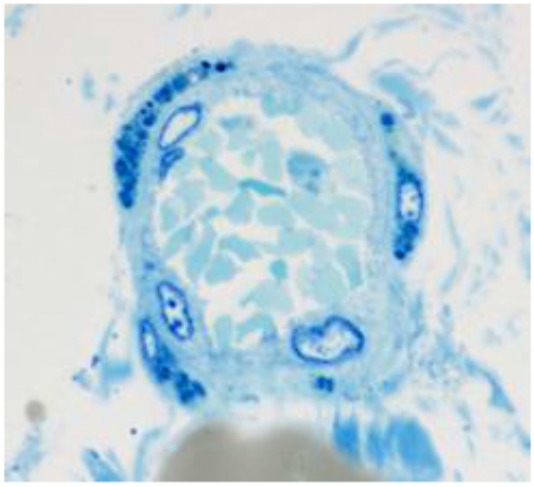

Figure 2. Vascular smooth muscle cells of submucosal arteries contain GL-3. (HRLM, 1 micron epoxy resin, 1:1 Richardson's stain, 1,000x). Photo property of Dr. Politei. Published with permission of Dr. Politei.

necrosis was reported in a Fabry patient at the age of 50 years[24]. The study of tissue obtained after an appendicular resection, examined through electron microscopy, exhibited substrate inclusions within vascular and smooth muscle tissues, consistent with FD involvement[28].

Intestinal perforation secondary to diverticular disease has been repeatedly described in the literature, with diverticula observed in various locations including the duodenal, jejunal, and colonic levels [Figure 3][24,7,8]. Among the reported cases, three reported complications related to diverticular disease, of which two resulted in intestinal perforation. Lysosomal inclusions characteristic of FD were observed in intestinal smooth muscle cells, as well as in ganglion cells of the autonomous nervous system and blood vessels within the intestinal wall[7,21,23]. Areas of muscle wall thickening, coupled with adjacent fibrotic regions near the diverticula, have been reported[7]. The development of diverticula is evident after prolonged periods of dysmotility, generating areas of elevated intraluminal pressure that lead to the protrusion of intestinal mucosa. These smooth muscle fibers, subjected to abnormal motility, are typically compromised by reduced blood flow from small intestinal vessels, stemming from luminal constriction[29]. The focal blood flow

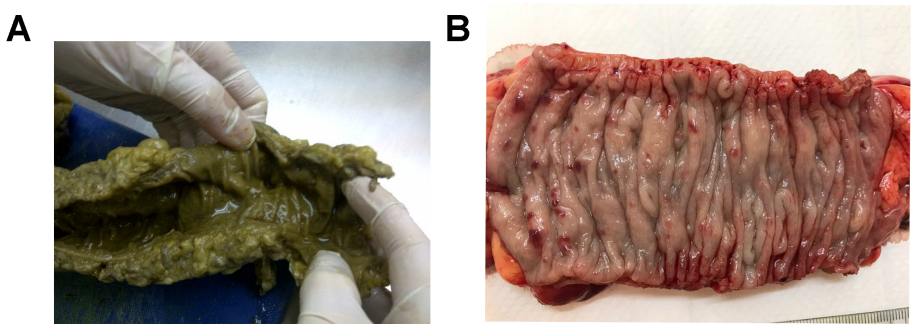

Figure 3. (A) Examination of a hemicolectomy specimen from a female Fabry patient as a result of diverticular perforation. Photo property of Dr. Politei. Published with permission of Dr. Politei. (B) Examination of a colectomy specimen from a male Fabry patient with diverticular disease. Partial sigmoid resection due to multiple episodes of diverticulitis. Photo property of Dr. Politei. Published with permission of Dr. Politei.

reduction has led to the suspicion of "intestinal angina", being the reason for the abdominal cramps after meals.

All these alterations of intestinal motility predispose to bacterial overgrowth and subsequent sustained diarrhea, malabsorption, and diverticula formation[10]. Bile salt breath tests for expiration[24] or aspiration of jejunal content[7] confirm this finding. In addition to bacterial overgrowth, new evidence suggests that globotriaosylsphingosine (lysoGL-3) directly influences microbiotical growth, potentially culminating in dysbiosis and a disproportion of the intestinal microbiota[30]. Dysbiosis is associated with the activation of proinflammatory immune responses due to an abnormal proliferation of immune cells and increases the production of proinflammatory compounds such as lipopolysaccharides[31]. Furthermore, gut dysbiosis compromises the energy supply to the colonic epithelium and elevates epithelial permeability, resulting in a "leaky gut"[4,32]. In this context, lysoGL-3 increases the biofilm-forming capacity of several individual bacteria, including *Bacteroides fragilis*[30]. LysoGL-3 also alters the bacterial conformation of human gut microbiota suspensions, increasing bacterial counts of *B. fragilis*, and influencing the production of short-chain fatty acids, resulting in a notable reduction in butyrate concentration[30]. These results were recently replicated[33], where dysbiotic features imply a disruption of colon homeostasis, leading to accelerated intestinal transit, visceral hypersensitivity, and impaired communication along the gut-brain axis in the mouse model.

DIAGNOSIS OF GASTROINTESTINAL INVOLVEMENT IN FABRY DISEASE

Misinterpretation of gastrointestinal manifestations is commonly reported in patients with FD. The most frequent misdiagnoses are irritable bowel syndrome, chronic inflammatory bowel disease, appendicitis, autoimmune disorders, Whipple's disease, dermatomyositis, or somatoform disorder[34]. Exceptionally, FD may co-occur with other gastrointestinal diseases such as Crohn's disease, coeliac disease, or colon cancer[10]. Previously, the assessment of gastrointestinal signs and symptoms in Fabry patients relied on patient interviews and tools designed for other gastrointestinal disorders, including the Gastrointestinal Symptom Rating Scale (GSRS) and Rome III criteria (now Rome IV)[12]. Evaluating GI symptoms in Fabry patients using questionnaires based on the Rome III criteria, it was found that 16 out of 25 adult and 2 out of 8 pediatric Fabry patients, all experiencing GI symptoms, exhibited a symptom profile resembling that of functional gastrointestinal disorders[35]. The 24-h and 7-day Fabry disease patient-reported outcome-gastrointestinal (FABPRO-GI) assessments represent the first FD-specific Patient-Reported Outcomes (PROs) designed to evaluate GI signs and symptoms in FD patients[36]. Given the paucity of PROs tailored for FD, the 24-h and 7-day FABPRO-GI instruments present an opportunity to gain new insights into Fabry

disease-related GI signs and symptoms. This may prove instrumental in recognizing these manifestations in patients participating in clinical trials, as well as those in real-world clinical settings[36].

Stool studies are useful in the diagnostic assessment for Fabry patients with diarrhea, and the Sitzmarker test serves as a reliable tool for evaluating gut transit time[5]. Radiological studies including Doppler scanning or angiography are instrumental in probing GI motility and blood flow, particularly when vascular compromise is a consideration[5,9]. To assess upper GI symptoms such as nausea, a gastric emptying scan offers insights into motility patterns, while a breath test proves beneficial in identifying bacterial overgrowth secondary to impaired gastric motility and delayed emptying[10]. Additionally, biopsies may be warranted for histological studies aimed at confirming GI involvement. This entails analyzing evidence of GL-3 deposits in enlarged and vacuolated neurons, as well as in endothelial and vascular smooth muscle cells. These biopsies also serve to rule out potential comorbidities[12].

TREATMENT

Specific therapy

Enzyme replacement therapy (ERT) with either agalsidase beta (1 mg/kg every other week) or agalsidase alfa (0.2 mg/kg EOW) has been available for the treatment of Fabry patients since 2001[37,38]. The initial study designed to evaluate the positive impact of ERT on gastrointestinal symptoms was reported by Dehout *et al.*[39]. In total, eleven cases were enrolled and a significant reduction in both the severity and frequency of abdominal pain and diarrhea was obtained. In a study by Wraith *et al.*, encompassing 14 male and 2 female pediatric patients aged 8 to 16, who received agalsidase beta treatment over 48 weeks, patient reports of post-prandial pain, nausea, and vomiting exhibited a consistent decline over time on treatment. By week 24, statistically significant improvements were observed[40]. Additionally, utilizing the Fabry Outcome Survey database, Hoffmann *et al.* observed a reduction in the prevalence of gastrointestinal symptoms following agalsidase alfa at both 12 and 24 months[41].

The Fabry Registry is a multicenter and observational program designed to monitor the natural history and treatment outcomes of patients with FD[42]. In an effort to gain deeper insights into the enduring effects of agalsidase beta treatment on gastrointestinal symptoms, data from the Fabry Registry for the years 2018 and 2020 were analyzed for female and male patients, respectively[43,44]. The outcome measures in 168 females analyzed in the Fabry registry were self-reported gastrointestinal symptoms at both baseline and their last follow-up (with a prerequisite of receiving agalsidase beta treatment for a minimum of 2.5 years). Baseline pre-treatment abdominal pain was reported by 45% of females and diarrhea by 39%. At last follow-up, 31% reported abdominal pain and 27% diarrhea[43]. In males, the Fabry Registry analysis was stratified by phenotype. Classic male patients reported GI symptoms more frequently at baseline *vs.* later-onset phenotype. As compared with baseline, significantly fewer classic patients reported abdominal pain and diarrhea after a median of 4.7 and 5.5 years of follow-up, respectively. While the reduction in reports among males with later-onset phenotypes was statistically non-significant, it still indicated an improvement post-treatment[44]. The results of this Fabry Registry analysis suggest that on sustained treatment with agalsidase beta, both abdominal pain and diarrhea improved in patients with FD.

Furthermore, it is worth noting that the dosage or specific compound utilized may influence the outcome of gastrointestinal (GI) symptoms. Notably, patients who received a reduced dose of agalsidase beta (ranging from 0.3 to 0.5 mg/kg) or those who transitioned from agalsidase beta to agalsidase alfa during the global shortage of agalsidase beta reported an increase in gastrointestinal pain[45]. Unfortunately, in many of these studies, despite documented improvement, some patients continue to experience GI symptoms even after a substantial period of enzyme replacement therapy (ERT) intervention. In certain instances, patients may

even develop new GI symptoms while undergoing ERT, underscoring its continued significance as a source of morbidity[42]. This underscores the necessity for concurrent, targeted, GI-specific treatment.

In addition to ERT, a pharmacological chaperone (oral migalastat 123 mg every other day) is approved for patients (> 12 years old) with an amenable mutation and an estimated glomerular filtration rate (eGFR) ≥ 30 mL/min per 1.73 m^2. In 2019, Germain *et al.* reported that in male patients with classic phenotype previously ERT-untreated, migalastat treatment resulted in a significant reduction of GI symptoms measured by the GSRS, after 24 months[46]. Furthermore, in patients who had previously undergone ERT, migalastat demonstrated an improvement in diarrhea, as evidenced by the Minimum Clinically Important Difference (MCID) score, in comparison to those receiving a placebo[47]. See a summary of treatment option in the flow diagram [Figure 4].

Substrate reduction therapy (SRT) acts on a previous step in the metabolic pathway, by inhibiting the enzymatic conversion of ceramide to glucosylceramide-1 (GL-1)[48]. GL-1 is a key metabolic precursor of more complex glycosphingolipids, including GL-3. MODIFY was the first clinical study in patients with FD to measure the effect of lucerastat on neuropathic pain as a primary endpoint and GI manifestations as a secondary endpoint. Despite the reduction of plasma Gb3, no significant reduction in neuropathic pain was observed after six months of treatment[49].

Venglustat, an investigational orally available compound, serves as a potent, brain-penetrant GL-1 synthase inhibitor, potentially introducing a novel mechanistic avenue for treating FD with potential advantages over current treatment modalities. The outcomes of a Phase II study encompassing a 3-year open-label assessment, examining the safety, pharmacokinetics, pharmacodynamics, and exploratory efficacy of once-daily venglustat administration, have been reported[50]. This study included adult male patients with classic FD who had not previously received disease-specific therapy and displayed no clinically significant organ involvement. At baseline, six out of 11 patients reported gastrointestinal pain based on the IBS GI Questionnaire. By Week 26 (n = 5), the severity of pain decreased in four patients and increased in one patient. At Week 156 (n = 4), all four patients experienced a decrease in pain severity. Additionally, the frequency of GI pain in every 10 days decreased in all patients with available data (n = 5) at Week 26, and in three out of four patients at Week 156[49]. A phase III study is currently underway to evaluate the effect of venglustat tablets on neuropathic and abdominal pain in adult male and female participants with FD (NCT05206773).

Non-specific therapy

Certain adjunctive treatments can offer symptomatic relief for specific gastrointestinal symptoms. For instance, the pro-motility agent metoclopramide has demonstrated some efficacy in improving symptoms in patients with gastroparesis[25]. The use of pancreatic enzymes and bile acids supplementation demonstrated a prospective value for improving diarrhea in FD patients[12]. Other medications used to control manifestations include ondansetron to reduce nausea, proton pump inhibitors (e.g., omeprazole) to relieve upper gastrointestinal symptoms, and antidiarrheal medications (loperamide). Unfortunately, this pharmacological approach rarely results in complete control of symptoms in Fabry patients. Furthermore, it should be highlighted that ondansetron is not suited for continuous and prolonged use[5,12]. The use of gabapentin and carbamazepine showed a beneficial effect in patients with small fiber neuropathies and chronic neuropathic pain[51,52]. Therefore, these "pain killers" can be considered beneficial in the treatment of GI manifestations, justifying their indication as part of the non-specific therapy. Additionally, tetracycline has been explored as a potential treatment for bacterial overgrowth, yielding resolution of diarrhea within two days of treatment in a singular case report[7].

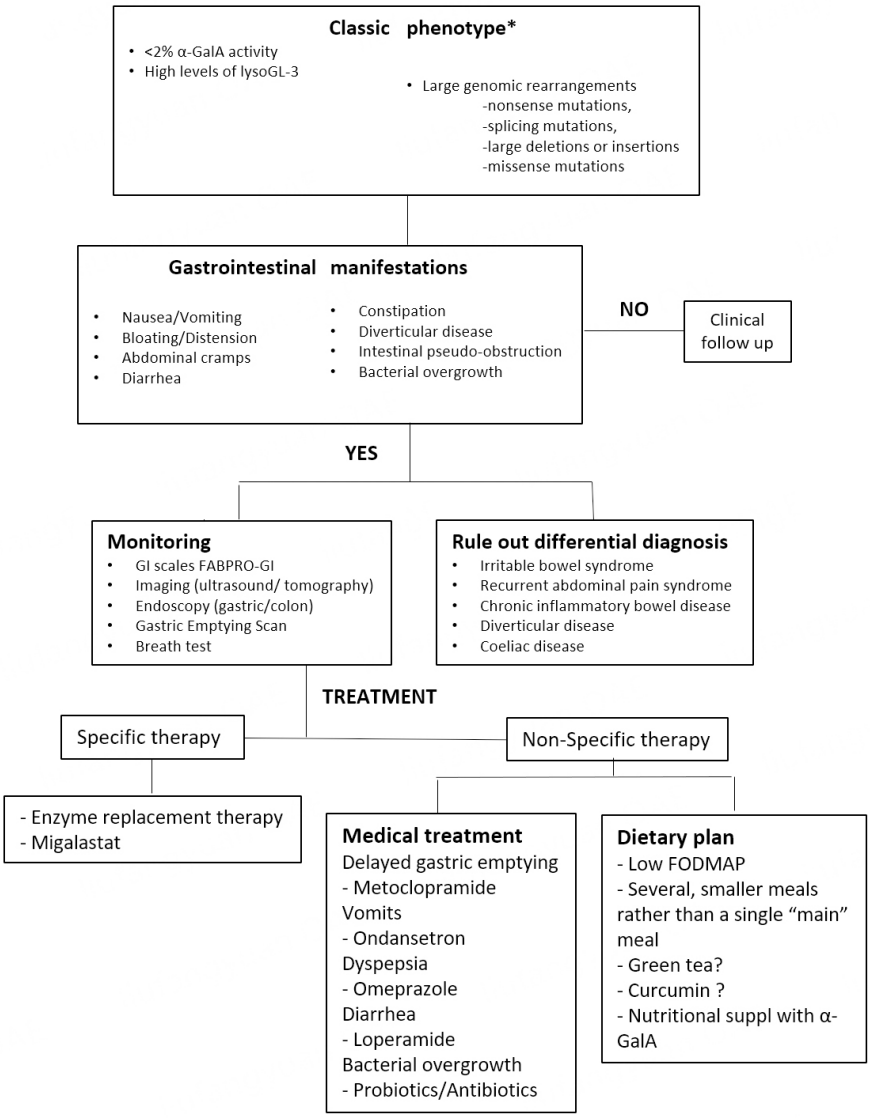

Figure 4. Flow chart for decision making in patients with Fabry disease and gastrointestinal manifestations. *Late-onset Fabry patients do not show GL-3 accumulation in the gastrointestinal system. In these patients, GI symptoms must be attributable to gastric comorbidities.

No specific dietary interventions on FD patients have been reported. Useful non-drug management approaches are dietary modifications such as opting for low-fat meals in cases of pancreatic dysfunction or incorporating pancreatic enzyme supplements. Additionally, consuming several smaller meals throughout the day, as opposed to a single large "main" meal, has shown promise in alleviating upper gastrointestinal (GI) symptoms[5].

Considering that Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyols (FODMAPs) may play a role in GI manifestations and dysbiosis in FD patients, a low-FODMAP diet was explored as a complementary alternative treatment in individuals with FD[53]. Patients were assessed for GI symptoms using IBS severity score and GSRS questionnaires. For symptomatic patients, the low-FODMAP diet involved an initial phase of eliminating fermentable saccharides, followed by a gradual reintroduction of

these components. The implementation of the low-FODMAP diet led to significant improvements in indigestion, diarrhea, and constipation. The authors concluded that a low-FODMAP diet could serve as an effective alternative approach to enhance intestinal manifestations and overall quality of life[52]. These changes in food consumption also allowed patients to adapt the intake of the foods most related to the clinical GI signs (gluten, lactose, and some vegetables).

Lenders *et al.* shared their experience with seven Fabry patients who utilized commercially available oral dietary supplements, providing a daily dose of 1800 U AGAL over a period of 90 to 180 days[54]. Overall, the intensity of abdominal pain notably decreased after 8 weeks and continued to do so after 12 weeks. The frequency of diarrhea also showed a slight decrease from 2.6 days per week to 0.5 days per week. Importantly, none of the patients experienced heightened GI symptoms during the observation period, with all reporting a general improvement in GI symptoms and an enhanced sense of well-being[54].

Monticelli *et al.* reported a co-chaperone role for curcumin in addition to AGAL pharmacological chaperones (1-deoxygalactonojirimycin-DGJ- and galactose) in a cell model[54]. The associated therapy with curcumin and pharmacological chaperones proved beneficial for 4 out of 5 tested mutants and showed fold increases ranging from 1.1 to 2.3 for DGJ and from 1.1 to 2.8 for galactose. In the case of one mutant (L300F), long-term treatment revealed an enhancement in GL-3 clearance and lysosomal markers[55]. In a study exploring early adjunctive antioxidant treatment to mitigate oxidative stress markers, 10 Fabry patients were subjected to adjuvant treatment with green tea[56]. Oxidative stress markers $p22^{phox}$ and MYPT-1 phosphorylation decreased after ERT and significantly further decreased after green tea administration. While ERK 1/2 phosphorylation and MDA levels remained unchanged after ERT, they experienced a significant decrease after green tea. Additionally, Heme oxygenase-1 exhibited a significant increase after ERT, which was further augmented following green tea treatment. These findings underscore an antioxidative effect exerted by ERT, further magnified by the adjunctive antioxidant treatment with green tea[56].

CONCLUSIONS

The recognition of GI manifestations in Fabry disease allows to suspect this condition and achieve a diagnosis in the early stages of the disease, and these symptoms can also justify the initiation of specific treatment in patients with a classic phenotype.

Although published management guidelines suggest studies to evaluate the severity of GI involvement and the prescription of non-specific symptomatic treatments, there is still an unmet need for the design of a consensus that describes in detail which clinical evaluations should be used for routine monitoring, and what adjuvant therapies and dietary plans are most effective in controlling symptoms. Future perspectives in relation to new lines of research seek to elucidate the interactions of the brain-gut axis, as well as the role that the intestinal microbiota plays in pathophysiology.

DECLARATIONS

Author contributions

Conceptualization, writing, revision, conceptualization and validation: Politei JM, Solar B
Writing: Politei JM
Validation: Politei JM
Both authors have read and agreed to the published version of the manuscript.

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Not Applicable

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Both authors declared that there are no conflicts of interest.

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Not applicable.

Consent for publication
Not applicable.

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