Gastrointestinal Manifestations and Treatment Options in Fabry Disease Patients. A Systematic Review

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INTRODUCTION

Fabry disease (FD) is an X-linked genetic inherited disease, a lysosomal glycosphingolipid storage disorder triggered by a mutation in the alpha-galactosidase gene (GLA), subsequently leading to a deficit of the acid hydrolase alfa-galactosidase enzyme. As a consequence of this deficit, glycolipid compounds, namely globotriaosylceramides and its metabolites, counting the deacylated derivative globotriaosylsphingosine accumulate in lysosomes and different tissues, including the heart, nervous system, gastrointestinal (GI) tract or the kidneys [1,2], leading to specific symptoms. The accumulation of globotriaosylceramides in neurons of myenteric nerve plexuses and also in the smooth muscle of the bowel, may occur in Fabry patients. Both genders are affected, but generally, females to a less significant extent than males.

There are two phenotypes of this disease, explicitly, patients present with a classic onset of the disease, with symptomatology starting in the childhood or a late-onset group, where manifestations occur after the fourth decade of life [3]. Typical initial symptoms for FD are paresthesia (mostly acroparesthesia) and angiokeratomas [4]. Cardiovascular complications (arrhythmias, valvular defects, fibrosis, left ventricular hypertrophy), neurologic damage and renal failure typically occur later in life [3].
Studies have demonstrated that the GI tract is affected in this disease, and that most patients will present a GI-related symptom, predominantly abdominal pain or changes in bowel movements. The manifestations have a significant impact on the quality of life of these patients, and can even be life-threatening [5], so there is clearly a need for a high level of clinical suspicion in order to properly recognize and manage them. Additionally, GI signs and symptoms may be the first clinical manifestation of this disease, and since they are nonspecific, can ultimately delay diagnosis.

Treatment of FD with enzyme replacement therapy (ERT) or Migalastat (Galafold®), a chaperone, has proven to be beneficial in alleviating some symptoms, but a significant percent of the patients still complain of persistent GI manifestations [5]. Additional studies are needed for better evaluation and treatment of this patients.

We performed a systematic review of the literature regarding GI manifestations and their treatment in FD, in order to help physicians get a clearer understanding and gain knowledge on the complexity of this disease.

METHODS

Our study was completed following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) criteria (Fig. 1). In December 2021, we performed a systematic literature search of the PubMed database and Embase, using the MeSH terms: “Fabry disease”, “gastrointestinal”, “digestive”, “manifestations”, “symptoms”, “clinical”, “treatment”, “therapy” and the supplementary concepts “enzyme replacement”, “chaperone”, “Migalastat”, in different combinations.

Our inclusion criteria were represented by: 1) English written studies; 2) original articles reporting digestive manifestations in FD and their treatment; 3) case-reports or case series of patients with peculiar GI aspects and their treatment; 4) articles including details about general clinical manifestations (of which we selected the digestive ones), diagnostic investigations and treatment, outcome of the patients. Three separate reviewers assessed the studies for eligibility criteria. We proceeded to exclude review articles (apart from the ones that we could not exclude due to the relevance of the information pertained), original articles written in other languages other than English and articles with only an abstract available.

RESULTS

The selection process is detailed in Fig. 1. Initially, 221 studies were identified. After the exclusion of duplicates, a number of 149 articles remained for further analysis. Forty-four studies were excluded based on title and their abstract, leaving 105 to be assessed for eligibility by full text reading. Sixteen articles were also excluded after full text reading, as the content did not bring relevant information for our study. Of the remnant 94 papers, 41 were reviews that were not included in

Fig. 1. PRISMA flow chart for the systematic review
the database of articles selected for our systematic review, but the information offered by some of them was approached in the discussions. The 63 remnant articles were included in this review and, of these, 12 were case reports presenting peculiar clinical manifestations with GI involvement and different types of treatment, with more or less optimistic outcomes. Finally, the date base of articles considered useful for our review contained 51 papers.

Gastrointestinal Involvement in Fabry Disease

Cohort studies revealed that the GI tract may be affected in up to 70% of patients with FD [6]. Different registries mention that the digestive symptoms may be the first clinical manifestation in nearly a fourth of the boys with FD, present at the age of 5 years. They may also be the first symptoms in about a tenth of the girls starting with the age of 9 years. In boys, GI symptoms appear more rapidly than in girls and are more severe [7,8].

The main GI symptoms in FD patients are represented by diarrhea and abdominal pain. A study on 342 patients regarding the prevalence of digestive involvement in FD revealed that aside from abdominal cramps, patients generally complained of both constipation and diarrhea, and also nausea or vomiting (Table I). Large bowel diverticulosis may also be encountered [10-12]. Other less common manifestations were gastritis, gastric ulcer, hemorrhoids, or symptoms suggestive for pancreatitis [5]. Additional possible symptoms are represented by chest pain (of esophageal origin), belching, excessive flatulence and indigestion and gastro-esophageal reflux. The incidence of these symptoms modifies with age and gender, GI involvement being more frequently reported at an earlier age among boys (23.2% at a median age of onset of 5 year) than among girls (11.4% at a median age of onset of 9.5 year) [8]. In female patients, although cardiac, cerebrovascular or renal symptoms are generally milder, the GI symptoms may become quite severe, similar to male patients.

Abdominal discomfort is the most common GI symptom reported [5], ranging from 42.9% to 56% [13, 14] and it was described as a burning pain or as a colic, involving the entire abdomen or the mid and lower part, with tenderness at palpation, that may be triggered by eating or aggravated when there is a diet change. A study from 2020, analyzing 171 male patients with FD, showed a prevalence of 56% for abdominal pain, before treatment [14]. Complaints related to abdominal pain are decreasing with the age of diagnosis, only 6 patients of 48 from the aforementioned study having later-onset (13%) reported abdominal pain. Consistent with these results, Hoffman et al. [5] found that children are reporting abdominal pain in 49.3% of cases, while adults only in 38% [14]. Regarding the relation with gender, in the large cohort of patients analyzed by Hoffman et al. [5], there were no differences between males and females.

Diarrhea is also frequently recounted (41.8-43.4%) [13,15]. A study published in 2020 on 54 patients, reported the presence of postprandial diarrhea accompanied by urgency to defecate in 43,4%, of which 10 patients were female heterozygotes [15]. Another study on 171 male patients, proved that 57% of subjects reported diarrhea. Diarrhea is also age related, patients with later onset, having a lower prevalence of this symptom 11/47 (23%) [14]. It appears to be reported more regularly in males than in females, ranging from 25.9% [5] to 57% male patients with classic phenotype [16] while on 168 female patients with mean age of 43 years, the prevalence of diarrhea was 12-39% [5, 17]. As already mentioned, it is accompanied by abdominal pain and the usual laboratory analyses are in normal range in the early stages of disease (blood cell count, electrolytes, inflammatory parameters). There is no blood in the stool, and endoscopy reveals no pathological findings. The episodes may be related to food intake or not. Regarding the relation with age, diarrhea was more frequently met in children compared to adults (25.4% vs 19.2%) [5].

<table>
<thead>
<tr>
<th>Table I. Gastrointestinal manifestations reported in Fabry disease</th>
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<tr>
<td><strong>Main gastrointestinal symptoms</strong></td>
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<tr>
<td>Abdominal discomfort (42.9-56 %)</td>
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<td>Diarrhea (41.8-57 %)</td>
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<tr>
<td>Constipation (13.5 %)</td>
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<tr>
<td>Nausea (12.3 %), vomiting (6.7 %)</td>
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<tr>
<td><strong>Other gastrointestinal manifestations</strong></td>
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<tr>
<td>Gastritis, peptic ulcer</td>
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<td>Hemorrhoids</td>
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<td>Pancreatitis</td>
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<td>Diverticular bowel disease</td>
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<td>Gastroesophageal reflux</td>
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<td>Achalasia</td>
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<td>Appendicitis</td>
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<td>Chronic bowel pseudo-obstruction</td>
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<td>Post-prandial fullness</td>
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<td>Delayed gastric emptying</td>
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<td>Autoimmune diseases (celiac disease, Crohn’s disease)</td>
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<td>Chest pain, belching, excessive flatulence</td>
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Constipation, on the other hand, was reported to be more common in female patients (reaching twice the prevalence in females) and can sometimes be incapacitating. It was reported (unrelated to age and gender) in 13.5% of patients in the cohort of 342 subjects analyzed by Hoffman et al. [5]. It is met equally in children and adults, with an onset median age of 17.5 years. The alternation of constipation and diarrhea was likewise described [18].

Nausea and vomiting are reported less frequently compared to abdominal pain and stool habits, but still maintaining a high prevalence (12.3% for nausea), with not significant differences depending on gender (13.8% and 10% in favor of men). Vomiting was reported less than other symptoms (6.7%), and mainly for the male gender. Related to age, nausea and vomiting were more prevalent in children (twice more than in adults) [5]. Fabry patients may also present with symptoms of gastroesophageal reflux [10].

Diverticular bowel disease may appear in FD patients and can sometimes lead to life-threatening complications. In a Fabry female patient, whose disease started at 18 years of age, main complaints were bloating, pain in the abdomen, diarrhea and early satiety. Symptoms progressed with time. At the age of 66 years old, she was admitted with right hemiparesis secondary to a meningioma. Investigations showed the presence of left ventricular hypertrophy, proteinuria and a low glomerular filtration rate. During hospitalization, she suffered a colon diverticular perforation, and she died with sepsis after colon resection with colostomy was performed [19].

Regarding rare cases, achalasia and jejunal diverticulosis in FD patients, even ruptured diverticula with bowel perforation were reported in the literature [20]. Politei et al. [21] reported the case of a Fabry male patient, diagnosed at a family screening, at the age of 17, who presented with abdominal pain, diarrhea, vomiting starting at 13 years of age. After initiating ERT at the age of 17, the following year, diarrhea resolved, but the abdominal pains persisted and even increased with time. He was eventually diagnosed with diverticular disease complicated with jejunal perforation; surgical resection followed, with a satisfactory clinical course [21]. A case report of FD involving the ileocecal appendix once again revealed the variability of GI manifestations in this disease. A 24-year-old female patient was admitted for acute abdominal pain, and appendicitis was suspected, so surgery was performed. Histologic examination of the appendix showed only globotriaosylceramides deposits, without any inflammation, adding to the multitude of possible presentations for FD [22]. Other case reports described a chronic pseudo-obstruction syndrome [23]; postprandial fullness [24] or delayed gastric emptying [25]. Autoimmune diseases were described in association with Fabry disease, such as celiac and Crohn's disease [26, 27].

Gastrointestinal symptoms can have an important impact on body mass index, especially in children. Still, data reported by Hoffman et al. [5] showed no differences between subjects with and without digestive symptoms (18.2 vs 18.8 kg/m²), even if former reports were revealing that 47% of patients having GI complaints were considering themselves underweight. Regarding the quality of life, patients with digestive complaints had a significant lower score (EQ-5D) than patients without digestive symptoms [5].

Studies so far demonstrated the variability in manifestations regarding this category of patients; this overload can impact diagnosis and treatment for FD patients. Medical practitioners must be aware that a rare disease can be the cause of common GI symptoms in order to promptly diagnose them.

**Treatment**

**Enzyme Replacement Therapy**

Therapy should be initiated as early as possible to ameliorate symptoms in FD patients. Nowadays there are different treatment options in FD patients, some of them in clinical use, others in trials, others on animal models. The most well-known is ERT with beta or alfa galactosidase. The second modality is the chaperone therapy already present in clinical use. The third modality is the substrate lowering therapy, applicable in some lysosome storage diseases. Other treatments are represented by gene therapy, or a plant base therapy (protalix) [28].

Agalsidase beta is a recombinant form of alfa galactosidase (synthesized in hamster ovary cell cultures). In a regimen of 1 mg/kg iv, every second week, it may clear globotriaosylceramides from the capillary endothelium [6]. Agalsidase beta treatment significantly lowers globotriaosylceramides accumulation in the mesangium and kidney's podocytes. If enzyme treatment is initiated early in the course of disease (before severe proteinuria occurs), FD treated patients suffer less frequently from irreversible advanced stage renal failure [29]. If patients are treated in early phases of disease, accumulation of globotriaosylceramides in the endothelium and podocytes of Bowman capsule may be prevented. With treatment, fewer cases may progress to advanced kidney failure. Treatment may be efficient in relieving some GI symptoms like diarrhea and abdominal pain [14] in a follow up of 4.7 years. In a study conducted by Dehout et al. [3], a significant relief of GI symptoms after 6 months treatment with agalsidase alfa was documented in a group of FD patients. In these patients, abdominal pain decreased in frequency and severity, considerably [30].

New enzyme replacement therapy drugs are actually in advanced clinical human studies. Only FD patients with specific genetic mutations may respond to this therapy. The remission of digestive symptoms is also monitored in these patients. One of them involves the pegunisalidase alfa, which is similar to alfa galactosidase A [31]. In an open label study in FD patients, after one year treatment, renal cerebroside inclusions were significantly reduced (as demonstrated through a kidney biopsy). The pegylated alfa galactosidase has a much longer half-life and is prone to fewer anaphylactoid reactions. Another enzyme replacement drug is moss-a-galactosidase, a new version of alfa-galactosidase. In a phase one, clinical, one month study, after a single administration, globotriaosylceramides were reduced significantly in the patients’ plasma. Additionally, the moss-a-galactosidase administration showed a good patients’ tolerance with no secondary adverse reactions [32].

**Enzyme Replacement Therapy for Gastrointestinal Symptoms**

Currently, there are a limited number of studies that investigated GI symptom relief after FD treatment. Hoffman
et al. [5] reported that treatment with agalsidase alfa led to a decrease in abdominal pain from 49% to 39%, with a significant symptom relief after 12 months of therapy for both males and children. After 24 months of therapy the results were improved, with a more significant reduction of the abdominal pain for the female group. Regarding diarrhea, the group with most benefit was the younger one, with children reporting a decrease in symptomatology from 36% at baseline to 6% after 12 months of therapy. Wilcox et al. [17] reported similar results, with significant reduction of both abdominal pain and diarrhea after agalsidase beta treatment in a cohort of female patients. Hopkin et al. [14] followed a group of male patients undergoing agalsidase beta treatment, for a median of 4.7 years for abdominal pain reports and 5.5 years for diarrhea reports. The study also showed marked improvement in symptoms, like a decrease of abdominal pain from 56% to 41% and for diarrhea, a reduction of prevalence from 57% to 47%, reaching statistical significance. A decrease in symptoms was also met in the group of later-onset patients, with regards to abdominal pain, from 13% to 4% at the last follow-up, and also for diarrhea (from 23% to 13%) [14]. It was shown additionally that a reduction of initial dose of agalsidase beta increased the clinical scores for symptoms, including abdominal pain and diarrhea, while switching to agalsidase alfa was safe related to symptoms, but not to renal function [33]. Therefore, ERT is beneficial for both children and adults, leading to GI symptom relief.

**Symptomatic Therapy for Gastrointestinal Involvement**

Despite the clear benefit and necessity of ERT for FD, an important percentage of patients still complain of GI symptoms, thus, are in need of specific pharmacological therapy. Suggested treatment for the most common complaints are gabapentin and carbamazepine for abdominal pain [34], and probiotics or loperamide for diarrhea [35]. Metoclopramide was shown to improve symptoms in patients with gastroparesis [25]. Ondansetron was proved to ameliorate nausea and vomiting, and tetracycline or rifaximin have a potential use for bacterial overgrowth. The use of pancreatic enzymes demonstrated a prospective value for improving diarrhea in FD patients. Life-threatening complications, such as perforation, can only be treated by surgery [36]. Nutritional changes should also be made for patients with FD, as their symptoms are relatively similar to irritable bowel syndrome, so researchers recommend the same dietary restrictions as with irritable bowel syndrome, like a low fermentable carbohydrates or oligosaccharides, disaccharides, monosaccharides, polyols (FODMAP) diet, as it could improve bloating, cramps and diarrhea [37]. Unfortunately, since FD is a rare disease, it is unclear which of these treatments is beneficial. Further research and larger clinical trials are needed to recommend the best therapeutic schemes for these patients.

**Recent Advances in Fabry Disease Treatment**

**Chaperone Therapy**

Recently, chaperone therapy began to represent a therapeutic option in lysosomal storage diseases. Chaperones are molecules that stick to the involved enzyme, helping its folding, its functioning in the lysosome. N-actyl-beta-valienamine was one of the first chaperones used in GM1 gangliosidosis, a genetic autosomal recessive lysosomal storage disease, affecting the brain and spinal cord. In Gaucher disease, the most often encountered lysosomal storage disease, a mutation of beta glucosidase, is present. In the treatment of Gaucher disease, an iminosugar (N-nonyl deoxynojirimycin) acts like a chaperone molecule. This chaperone augments the enzyme activity of glucocerebrosidase, that is deficient in Gaucher disease. Other chaperone molecules are also investigated in Gaucher disease. Chaperon therapy proved some success in patients with Pompe disease, another lysosomal disease (glycogen storage disease 2), a genetic disorder, characterized by a low activity of intralysosomal acid alpha-glucosidase [38].

In FD, different chaperones are tested, chaperones that inhibit the activity of alpha-galactosidase. An iminosugar, 1-deoxygalactonojirimycin, very active in vitro, augments alpha galactosidase activity in Fabry disease individuals. This chaperone ligates to the enzyme and ameliorates its stability and lysosomal activity. It may also prevent a rapid enzyme metabolism. It is appreciated that about a half of genetic mutations present in Fabry disease may respond to 1-deoxygalactonojirimycin administration, resulting in an increased activity of alpha galactosidase. In vitro cell cultures studies documented that compounds like ambroxol and pioglitazone might augment lysosomal activity of alpha galactosidase in FD [38].

Chaperone therapy was also proved to be successful in improving GI symptoms. Migalastat (Galafold™), a chaperone approved in Europe for FD, has the ability to restore enzyme function and it is only available for patients with certain GLA mutations, so research is limited in this area. However, a clinical trial on 50 patients treated with Migalastat (Galafold™) for 6-24 months, showed a noteworthy decrease in symptoms of reflux, indigestion, or diarrhea [39]. The trial used a validated questionnaire to follow patients after 6 months of therapy; all patients were ERT-naive. The same clinical trial gave some coherent results that were published in 2019, revealing an improvement in GI signs and symptoms, especially with regard to diarrhea [-0.3 change of Gastrointestinal Symptoms Rating Scale Diarrhea subscale (GSRS-D) score after 6 months, and -0.5 change at 24 months] [40]. The results are confirmed by Schiffermann et al. [41], focusing the treatment with Migalastat (Galafold™) in FD on diarrhea [41]. The meaningful improvement in symptomatology suggests that new treatment possibilities are emerging.

**Enzyme Substrate Reduction Treatment**

A third possible and future treatment in FD patients is represented by enzyme substrate reduction. This treatment reduces the production of glycosphingolipids by blocking the enzyme glucosylceramide synthetase. As such FD patients will have less globotriaosylceramides deposits in different organs. This approach already offered promising results in type 1 Gaucher disease, in which enzyme activity, even if low, is still present. Gaucher patients, in which enzyme replacement is not possible, may be treated with N-butyl-deoxynojirimycin, an iminosugar [Migalastat (Galafold™)], which produces substrate deprivation. This iminosugar is of help also in Niemann-Pick type C disease. At present, Fabry patients are treated with a galactose preparation of N-butyl-deoxynojirimycin (lucerastat)
Gene therapy has become a potential new treatment possibility for FD patients. This kind of therapy comprises two methods of gene delivery: viral and nonviral. The viral method utilizes oncoretro- or lentivirus, the lacking gene being introduced into the virus. Two techniques of viral gene therapy are actually in use: ex vivo gene therapy, and in vivo gene therapy. In ex vivo gene therapy, a lentivirus is used as a vector to introduce the α-galactosidase gene into hematopoietic stem cells, cells that are later infused in autologous recipients. Two patients are presently treated as such, with promising results, one of the patients not needing ERT anymore [44]. Animal studies of in vivo gene therapy, consist in delivering the adenosivirus associated gene by intravenous route to the liver. Subsequently, the liver secretes α-galactosidase, in therapeutic levels. These levels were followed by a significant decrease in globotriaosylceramides deposited in different organs [45]. As cardiac involvement in FD is of severe prognosis, recently, a new cardiotoxic variant proved superior gene delivery to cardiac cardiomyocytes [44].

Nonviral gene therapy uses biosynthetic systemic mRNA treatment; mRNA encoding α-galactosidase was injected in Fabry mice and a high α-galactosidase serum activity, with reduced globotriaosylceramides deposits in all tissues, were proved superior gene delivery to cardiac cardiomyocytes [44].

DISCUSSIONS

A systematic review on young patients with FD revealed that the main digestive symptom is abdominal pain, and that GI-related manifestations can occur in patients with 1 to 4 years of age [9]. The prevalence of digestive symptoms ranges between 18% and 69% [5,6]. Besides abdominal discomfort, the second most common symptom described was diarrhea, ranging from 41.8 % to 43.4% of patients. Constipation was also revealed quite often in female patients in up to 13.5% of patients in a study including 342 FD patients [14]. Nausea, vomiting [6], diverticular bowel disease [16], gastroesophageal reflux [11], achalasia [20] or even jejunal diverticulosis with perforation [21] were also described. Rare cases depicted involve the appearance of pancreatitis [5], chronic pseudo-obstruction syndrome [25] or delayed gastric emptying [26] in FD patients. The reason for the appearance of these manifestations is explained by the pathophysiology of the disease, through glycosphingolipid accumulation in various cells and tissues throughout the body.

Globotriaosylceramides accumulation in the ganglion cells of the myenteric (Auerbach) and submucosal (Meissner) plexus which leads to impaired gut motility was confirmed a long time ago [48]. Glycosphingolipid accumulation in the enteric neurons has also been suggested to contribute to the presence of abdominal pain and gastroparesis. The subsequent dysmotility is hypothesized to lead to bacterial overgrowth and the intraluminal pressure created can lead to diverticula formation. Autopsy studies pointed out that globotriaosylceramides deposits were also found in the thoracic segment of the sympathetic chain, thus affecting the autonomous nervous system of the esophagus and stomach [10, 49, 50].

Vasculopathy was also proposed as a pathological process in FD [33, 52], as globotriaosylceramides mounted up in the endothelial and smooth muscle cells; this leaded to vessel wall expansion, vascular remodeling and ultimately ischemia. Moreover, their accumulation in the vessels of the intestinal villi could lead to malabsorption and inflammation. Additionally, glycolipid accumulation was reported to have a prothrombotic and pro-inflammatory effect, contributing to the GI manifestations [52].

Regarding the diagnosis of GI involvement, if a clinical suspicion of FD is present, confirmatory diagnosis is required, based on enzyme and/or genetic testing. Clinicians should be aware of all GI symptoms that could be associated with this disease, for prompt diagnosis.

When dealing with patients already diagnosed with FD who present with GI symptoms, clinical evaluation based on biochemical and imaging tests should be performed based on symptomatology. Blood work is usually normal in FD patients. Anemia may be reported, and the most likely cause is the underlying cardiac or renal involvement, although a GI cause must always be excluded [53].

Imaging methods are useful tools in this setting. Abdominal pain should be evaluated through upper and lower endoscopy and biopsies. Although macroscopically there usually are no findings in FD patients, in some cases, biopsies taken reveal the presence lipid storages in the cytoplasm of the bowel tract neurons [54, 55]. Angiography may be useful in this setting also, for detection of vascular changes [50, 55].

Nausea and early satiety can be evaluated with endoscopy or tests for gastric emptying; a motility capsule can also be useful. Functional tests for the small and large bowel may diagnose decreased kinesis with bacterial growth in the small intestine: studies on FD patients using tests with Tc99 for gastric emptying revealed gastric dysmotility; barium enema for colonic studies showed decrease of peristalsis and loss of hastral markings [57, 58]. Manometry can be performed to reveal esophageal abnormalities. Other tests like lactulose breath test to detect bacterial overgrowth and stool studies to detect malabsorption have been proposed for evaluating patients with diarrhea.

Differential diagnosis is important in FD, especially for patients presenting with unspecific GI symptoms. Investigations are required to exclude more common disorders which can be confused with FD: irritable bowel syndrome, inflammatory bowel disease, diverticular disease, colon cancer,
appendicitis, celiac disease, gastritis, gastro-esophageal reflux. Other rare diseases also need to be considered: Whipple’s disease, mitochondrial diseases or transthyretin-related familial amyloid polyneuropathy [10].

There are no guidelines with recommendations for investigations of the GI tract in FD patients; diagnostic tests should be performed depending on the specifics of each case. Additionally, there are currently no instruments specifically developed for assessing GI symptoms in FD. Shields et al. [59] developed a FD Patient-Reported Outcome-Gastrointestinal (FABRO-GI) questionnaire in order to properly evaluate this category of patients. They established a 24-hour and a 7-day instrument that has a potential benefit in clinical trials and can expedite recognition of patients with FD presenting with GI signs. Hilz et al. [10] also proposed a series of questions that in combination with the Gastrointestinal Symptom Rating Scale could aid clinicians in the prompt recognition of FD. These types of questionnaires are not yet validated, but they should be implemented in clinical practice, seeing as they are easy to use, cost-efficient and potentially lifesaving.

Therapy should be initiated as early as possible to ameliorate symptoms in FD patients. Most used treatment options are ERT (with alfa or beta galactosidase) and chaperone therapy. Enzyme replacement therapy should be initiated in male children, even younger than 18 years, if FD, with all its clinical manifestations, was diagnosed. In male adolescents and adults with FD, ERT therapy is mandatory. In female FD patients presenting clinical symptoms (neurologic, renal, cardiac, GI), ERT therapy must be initiated. The same, in asymptomatic females, but with disease involvement in different organs (pathological renal biopsy, reduced filtration rate, marked proteinuria, silent vascular cerebral accidents, white matter injuries in the brain, cardiomyopathy, rhythm conduction disorders, cardiac fibrosis, GI involvement). In asymptomatic females with no documented organ involvement, ERT therapy may be withheld, but they should be followed-up [60].

Aligalsidase beta was proved to be efficient in alleviating GI symptoms in some studies [14, 30]. Aligalsidase alfa also demonstrated its efficiency in decreasing abdominal pain or diarrhea [5]. New ERT drugs were also reported to improve GI symptoms in FD patients [31]. In regard to chaperone therapy, Migalastat (Galafold™) improved certain symptoms like reflux or diarrhea in this category of patients [39].

Enzyme replacement treatment is also efficient in myocardial mass reduction and may improve myocardium contractility [28, 61]. An early enzyme replacement treatment (before the appearance of myocardial fibrosis) may prevent malignant ventricular arrhythmias and also PR segment prolongation on the EKG. Studies have documented reduced globotriaosylceramides myocardial deposits with enzyme replacement treatment, but there is no convincing evidence that deposits already present in later stages of disease, may be cleared from the myocardium or from the GI tract. Also, if fibrosis is already present, ERT may not remove it [29]. With ERT, serum globotriaosylceramides levels significantly decreased, a fact more obvious in younger individuals. Generation of aligalsidase beta autoantibodies (especially IgG), as a consequence of enzyme long term therapy, may sometimes occur. Although rare, this fact may reduce the efficacy of enzyme replacement. It may be useful to determine serum antibody levels, in FD patients. Besides age, gender and the presence of antibodies, another possibility of a reduced replacement enzyme activity in some patients may be an increased liver enzyme metabolism.

Currently, aside from ERT and Migalastat (Galafold™), there is no other approved treatment for Fabry disease [62]; all other options are still in clinical trials, so their effect on GI symptoms is not yet validated. Gene therapies also give promising new treatment modalities [44], although there is still a long way until clinical implementation. Unfortunately, no curative option is in site for these patients, but steps are made in the right direction, at least for alleviating symptoms and improving their quality of life. Advancements in therapy for FD gives hope for improved outcomes for these patients.

CONCLUSION

Gastrointestinal symptoms in FD can be nonspecific, but can be the first clinical manifestation, and may potentially contribute to delaying proper diagnosis. Close attention to symptomatology, accurate evaluation of motility disorders and biopsies taken, when necessary, could lead to an early and lifesaving diagnosis. Regarding treatment of FD, no curative method is available; ERT and Migalastat (Galafold™) are approved and highly beneficial for improving symptomatology and blocking disease progress, even for GI involvement. Other treatment options are also available, depending on the main complaints. An important number of patients regrettably still remain symptomatic, so larger clinical trials are needed to overcome these barriers and make high grade recommendations for adequate treatment.

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