Digestive and Liver Disease 50 (2018) 429–437

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Review Article

Non-specific gastrointestinal features: Could it be Fabry disease?

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ARTICLE INFO

Article history:
Received 11 October 2017
Accepted 19 February 2018
Available online 1 March 2018

Keywords:
Abdominal pain
Diarrhoea
Enzyme replacement therapy
Fabry disease
Lysosomal storage disorders
OMIM #301500
Rare diseases

ABSTRACT

Non-specific gastrointestinal symptoms, including pain, diarrhoea, nausea, and vomiting, can be the first symptoms of Fabry disease. They may suggest more common disorders, e.g. irritable bowel syndrome or inflammatory bowel disease. The confounding clinical presentation and rarity of Fabry disease often cause long diagnostic delays and multiple misdiagnoses. Therefore, specialists involved in the clinical evaluation of non-specific upper and lower gastrointestinal symptoms should recognize Fabry disease as a possible cause of the symptoms, and should consider Fabry disease as a possible differential diagnosis. When symptoms or family history suggest Fabry disease, in men, low alpha-galactosidase A enzyme levels, and in women, specific Fabry mutations confirm the diagnosis. In addition to symptomatic treatments, disease-specific enzyme replacement therapy with recombinant human alpha-galactosidase A enzyme or chaperone therapy (migalastat) in patients with amenable mutations can improve the disease, including gastrointestinal symptoms, and should be initiated as early as possible after Fabry disease has been confirmed; starting enzyme replacement therapy at as young an age as possible after diagnosis improves long-term clinical outcomes. Improved diagnostic tools, such as a modified gastrointestinal symptom rating scale, may facilitate diagnosing Fabry disease in patients with gastrointestinal symptoms of unknown cause and thus assure timely initiation of disease-specific treatment.

1. Introduction

Gastrointestinal (GI) complaints of unknown origin represent a major clinical and diagnostic challenge for general practitioners, internists, paediatricians, surgeons, and gastroenterologists alike. There are many differential diagnoses, ranging from relatively common conditions such as irritable bowel syndrome (IBS) and inflammatory bowel disease, to less common inherited metabolic diseases, including Fabry disease [1]. Fabry disease (Online Mendelian Inheritance in Man [OMIM] #301500) is a potentially life-threatening, X-linked lysosomal storage disorder resulting from mutations in the galactosidase alpha (*GLA*) gene. It has a highly heterogeneous clinical presentation [2] that commonly includes a range of non-specific GI symptoms such as abdominal pain, bloating, constipation, diarrhoea, vomiting, and nausea [3–9].

The exact prevalence of GI symptoms among patients with Fabry disease is unclear, and underreporting of these non-specific symp-

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https://doi.org/10.1016/j.dld.2018.02.011

toms is common, but a high prevalence of GI symptoms has been reported in children and in female patients [3–6,10,11]. Registry data from patients enrolled in the Fabry Outcome Survey, for example, show that 60% of untreated children had GI symptoms on entry to the Registry [3], as did 50% of female adult patients [4,5]. Abdominal pain accounts for about one-third of GI symptoms reported overall in patients with Fabry disease, and for approximately half of the GI symptoms in children [5]. Poor weight gain can also occur in patients with Fabry disease due to malabsorption of nutrients as a consequence of the disease's underlying pathology [1,10]. In children, this primarily occurs in boys, who are underweight and short for their age; girls tend to have normal weight and height [6].

It is important, therefore, that paediatricians, internal medicine specialists, and gastroenterologists are aware of Fabry disease as a possible cause of non-specific GI symptoms, so that appropriate investigations can be carried out to either diagnose or exclude it, and effective disease-modifying treatment can be started as early as possible where appropriate. Enzyme replacement therapy (ERT) with recombinant alpha-galactosidase A is available and has been shown to be effective at improving GI and other Fabry-disease-related symptoms, as well as at delaying or preventing disease progression, organ damage, and Fabry-disease-related mortality [5,12–14]. Notably, response to therapy may vary due to genetic variants in different genes, e.g. those coding for drug absorption, distribution, metabolism and excretion (ADME) proteins [15]. Furthermore, preliminary results from phase III clinical trials have shown that treatment with chaperone therapy for patients with amenable mutations also improved GI symptoms, such as diarrhoea, indigestion, and constipation [16]. Therefore, early treatment, before irreversible organ damage occurs, is key to obtaining the best clinical outcomes [13], but the diagnosis of Fabry disease is challenging, and delays of up to 20 years have been reported due to the unspecific nature of many of the early symptoms [3,10,17,18]. This review describes the GI manifestations, diagnosis, and management of Fabry disease, and aims to facilitate prompt diagnosis, allowing effective early treatment of the disease. It reflects the outcomes of multispecialist discussions that took place during the third Internal Medicine Advisory Board in Rare Diseases, evaluating the role of GI symptoms in Fabry patients, on 10 December 2016, in Rome, Italy.

2. Fabry disease – a brief overview

In Fabry disease, mutations in the *GLA* gene encoding alpha-galactosidase A lead to a lack of – or reduced – alpha-galactosidase A activity, which in turn results in progressive accumulation of globotriaosylceramide (GL-3) and other glycosphingolipids within lysosomes [2,19,20]. Intracellular accumulation of glycosphingolipids results in progressive tissue and end-organ damage [11,21], and leads to a broad range of symptoms and, eventually, fatal complications in a range of organs, including the kidneys, heart, and brain [17,22,23] that compromise life expectancy [10,24]. In the case of the gut, for example, autonomic small fibre damage to the myenteric plexus can develop through glycolipid deposition leading to abnormal smooth muscle activity throughout the GI tract, resulting in symptoms such as diarrhoea and abdominal cramps [1]. Fabry disease has phenotypically heterogeneous presentations ranging from classic severe phenotypes to milder later-onset phenotypes typically seen in heterozygous female patients or patients who have atypical Fabry mutations that are associated with a later onset of disease or disease that is mainly (although not exclusively) confined to a single organ such as the heart [2,25]. Inter- and intra-familial phenotypic variability may be significant [5,26] and is thought to be associated with factors unrelated to *GLA* genetic variants, including other genetic and environmental factors [27]. For example, a recent study showed a link between a number of single nucleotide polymorphisms in ADME-related genes involved in bile acid detoxification, export, and uptake in the liver, and GI symptoms in patients with Fabry disease [26]. The authors hypothesized that genetic heterogeneity in these genes may be linked to susceptibility to GI symptoms in these patients, particularly diarrhoea, via alterations in the enterohepatic circulation of bile acids [26].

In patients with the classic phenotype, symptoms first appear in early childhood, with a median age of onset of 14 years [2,5]. GI symptoms, particularly abdominal pain and diarrhoea, are among the most frequent and often earliest complaints in Fabry patients, affecting around half of the adults (49.8%), and with an even higher incidence in children (60.8%) [5]. Other early symptoms often include neuropathic pain, hypohidrosis, cornea verticillata and lenticular opacity, angiokeratoma, and renal damage leading to proteinuria [2,6,28]. Of interest, Fabry disease can also present with recurrent fever of unexplained origin, which may result in misdiagnoses of familiar diseases such as Mediterranean fever or inflammatory bowel disease [29,30]. In patients with less severe or later-onset disease, non-specific GI symptoms may appear later in life [17], presenting an even greater diagnostic challenge, particularly in patients who do not have a family history of Fabry disease.

3. Gastrointestinal symptoms in Fabry disease

3.1. Types of symptoms

GI symptoms appear early in the disease course; Fabry Registry data indicate that non-specific GI problems are the initial presenting symptom in about 23% of boys (reported at a median age of 5 years) and in about 11% of girls (reported at a median age of 9 years) [6].

Abdominal pain and diarrhoea are the most commonly reported GI symptoms (Fig. 1), followed by constipation, nausea, and vomiting [5,7–9,17]. Registry data from the Fabry Outcome Survey show that abdominal pain affects up to one-third of patients [5], and has been described variously as colic with burning pain in the mid and lower abdomen, superficial abdominal skin tenderness, also bloating and cramping, as well as mid-abdominal discomfort that may increase within minutes of eating, worsen with stress, and be exacerbated by changes in diet or meal plans [10,31]. This relationship between abdominal pain and bloating and food intake can make patients with Fabry disease reluctant to eat, and as such, GI symptoms may have a negative impact on body weight [10]. However, this is not always the case, and registry studies have reported no difference in body mass index in children and adults who have GI complaints and those without [5]. About 20% of patients with GI symptoms in the Fabry Outcome Survey reported having experienced diarrhoea (Fig. 1) [4,5]. This appeared to be more common in male (26%) than female (17%) patients, and was most frequent in children (25%; median age of onset: 15.5 years) [4,5]. Episodes of diarrhoea may be related to meals or food intake, and can be very frequent, with some patients reporting loose or fluid stools, typically free of blood or mucus, up to 12 or more times a day [10,32]. The prevalence of constipation was similar among adults and children with GI symptoms in the Fabry Outcome Survey; the overall rate was 13.5%, but constipation was more frequent in female compared with male patients (16.7% vs 8.6%, respectively) (Fig. 1) [4,5].

Upper GI symptoms include nausea, vomiting, early satiety, and delayed gastric emptying [8,32,33]. Nausea was reported by more children than adults in the Fabry Outcome Survey (15.5% vs 11.4%; Fig. 1), while vomiting was less common (6.7% overall) but was also more common in children than in adults [5]. Other GI disor-

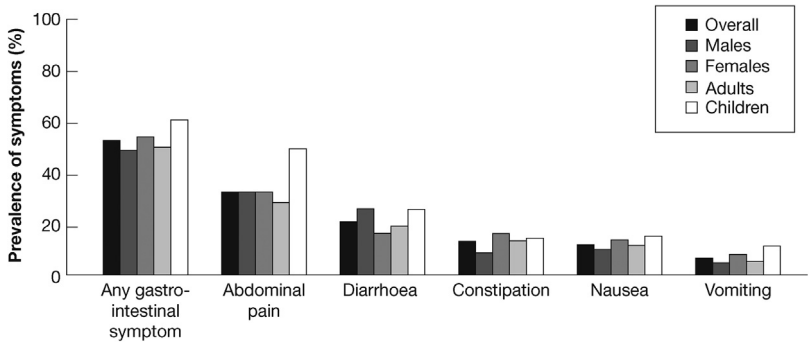

Fig. 1. Prevalence of reported gastrointestinal symptoms in patients with Fabry disease prior to initiation of enzyme replacement therapy ($n = 342$) [5]. Adapted with permission from Hoffmann et al., 2007 [5].

ders include haemorrhoids (adults, not children), gastritis or ulcer and pancreatitis [5]. Chronic intestinal pseudo-obstruction [34,35], diverticular disease [10,36–38], and bowel ischaemia [32,35] have also been reported.

3.2. Impact on quality of life

Patients with Fabry disease commonly report having a reduced health-related quality of life (HR-QoL) [5,6,17,39,40] and depression [39–41]. GI symptoms significantly contribute to the impact of Fabry disease on HR-QoL. For example, adults enrolling in the Fabry Outcome Survey who had GI symptoms reported significantly reduced scores on the EuroQoL five-dimension questionnaire (EQ-5D), a standardized tool for measuring health status ranging from a minimum score of −1 to a maximum score of 1 [5,42]. In Fabry patients with GI symptoms, the mean EQ-5D score at baseline was 0.63 compared with 0.72 in patients without GI symptoms ($p < 0.05$) [5]. Children with GI symptoms also have lower HR-QoL scores compared with healthy children [6], and GI symptoms very likely contribute to the reduced school attendance observed in patients with Fabry disease [43]. GI symptoms are known to be associated with psychological stress, which might augment the pain and discomfort Fabry patients experience from their GI problems, in turn exacerbating their psychological impact – forming a vicious circle – but no evidence supporting this hypothesis has been reported to date.

4. Pathophysiology of gastrointestinal symptoms in Fabry disease

The pathology underlying the GI symptoms of Fabry disease is complex and multifactorial. Dysfunction of the autonomic nervous system responsible for gut motility, vasculopathy affecting GI circulation, and tissue inflammation related to GL-3 accumulation seem to be the three principal mechanisms that are implicated (Fig. 2) [31,34]. Collectively, these pathological processes lead to changes such as a rapid gut transit time, reduced peristalsis, intestinal stasis, bacterial overgrowth, malabsorption of nutrients, pancreatic insufficiency, gastroparesis (delayed emptying), and ischaemic or neuropathic damage, all of which contribute to the GI symptoms associated with Fabry disease [31,34].

Glycosphingolipid-related damage to enteric neurons responsible for controlling gut motility has been suggested as a cause of the abdominal pain, gastroparesis, and abnormal intestinal mobility [1,31,38,44]. Small-calibre, thinly myelinated or unmyelinated nerve fibres – which are associated with thermal and pain perception, autonomic innervation, and with the enteric nervous system – seem to be damaged in patients with Fabry disease [21,45]; this neuropathic damage is likely to contribute to abdominal pain and dysmotility. Evidence from biopsies demonstrated glycosphingolipid accumulation in ganglion cells of the submucosal (Meissner's) plexus and the myenteric (Auerbach) plexus (Fig. 3) [37,38]. This latter finding suggests that GL-3 accumulation in the myenteric plexus contributes to dysmotility. Dysmotility and intestinal stasis may trigger bacterial overgrowth with possible secondary changes in the gut microbiome, which may contribute to diarrhoea [1,31,37,44]. High intraluminal pressure secondary to dysmotility has also been shown to lead to diverticula in the duodenum, jejunum, and colon [37,38,44,45], with severe and potentially fatal consequences. A rapid gut-transit time, malabsorption of nutrients due to glycolipid deposits in muscle and endothelial cells in the microvilli, and pancreatic insufficiency are also associated with diarrhoea in Fabry disease. Parasympathetic dysfunction in the pancreas may cause diarrhoea following the intake of a high-fat meal [28]. In autopsies, GL-3 accumulation in Fabry disease has been observed in autonomic neurons in the thoracic and lumbar segments of the paravertebral sympathetic chain [46] from which the autonomic nervous system that innervates the oesophagus and hindgut originates; this could also affect both gastric emptying and hindgut motility [31].

Intestinal vasculopathy occurs in Fabry disease due to endothelial and/or smooth muscle cell damage caused by deposition of GL-3 and consequent metabolic and pro-inflammatory changes [20,31,37,44,45,47]. Vasculopathy has been proposed as a pathological factor underlying, or contributing to, many of the reported GI symptoms [31]. For example, vasculopathy due to GL-3 accumulation in the small blood vessels of the GI villi could lead to ischaemic changes in the abdominal and mesenteric vasculature and contribute to abdominal pain [31]. Moreover, GL-3 accumulation in small blood vessels that supply the GI villi can compromise villous blood flow and food absorption, and may cause inflammation as well [31]. Further research is needed to explain the various pathophysiological factors contributing to GI symptoms in Fabry patients.

5. Diagnosis and differential diagnosis

5.1. Diagnostic challenges

Fabry disease is rare and patients are not always readily diagnosed, primarily due to the non-specific initial presenting symptoms. GI symptoms are often the first presenting symptoms of the disease [6], and a Fabry diagnosis may be made incidentally either because of physician recognition of the distinctive ocular signs (cornea verticillata) or skin lesions (angiokeratomas) (Fig. 4) [2,10], or as a result of screening of other family members [48,49]. However, the majority of patients experience long diagnostic delays, and misdiagnosis is common [18]. Delays in diagnosis

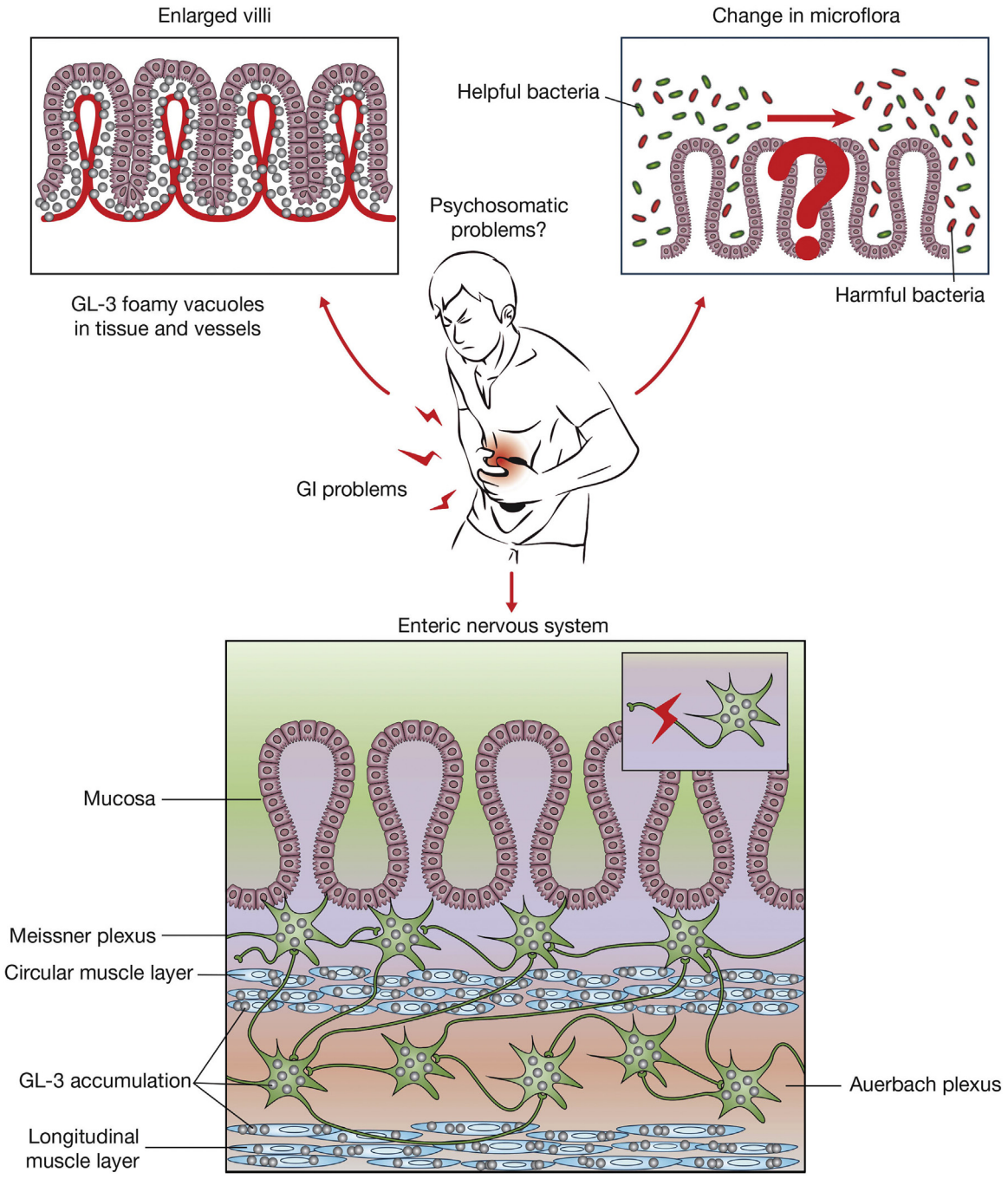

Fig. 2. Hypotheses for the pathophysiology of Fabry-disease-related gastrointestinal symptoms. Globotriaosylceramide (GL-3) accumulates in muscle cells, endothelial cells, and nerve cells. This leads to enlarged villi, vasculopathy, and blocked enteric nerve signal conduction, resulting in disruptions in gastric function, including poor food absorption by the villi and postprandial abdominal pain, early satiety, nausea, and diarrhoea, potentially causing a disturbed gut microflora balance and psychosomatic problems. GI, gastrointestinal.

ranging from 3 to almost 20 years have been reported between onset of the first Fabry-related symptoms and a confirmed diagnosis of Fabry disease [3,10,17,18].

There are numerous possible differential diagnoses for non-specific GI symptoms and the potential for misdiagnosis of GI symptoms is considerable both in patients known to have Fabry disease and in patients who are as yet undiagnosed (Table 1). For example, episodes of diarrhoea alternating with episodes of normal bowel activity or constipation, such as might occur in a patient with Fabry disease, are also suggestive of diarrhoea-predominant IBS, as both conditions can present with diarrhoea, abdominal pain, postprandial bloating, the absence of rectal bleeding, and normal routine blood test results and upper endoscopy/colonoscopy findings [32]. An evaluation of GI symptoms in Fabry patients using validated questionnaires based on the Rome III criteria for functional gastrointestinal disorders (FGID) showed that 16 of 25 adult and 2 of 8 paediatric Fabry patients, who all had GI symptoms, had a symptom profile that mimicked FGID [8]. In a study evaluating diagnostic errors in patients with Fabry disease, 10 patients with Fabry disease who initially presented with abdominal pain were misdiagnosed variously with food poisoning, non-specific pain, gallstones, hepatic insufficiency, dyspepsia, gastro-oesophageal reflux, parasites, and bulimia, and treated accordingly before receiving the correct diagnosis and treatment [18].

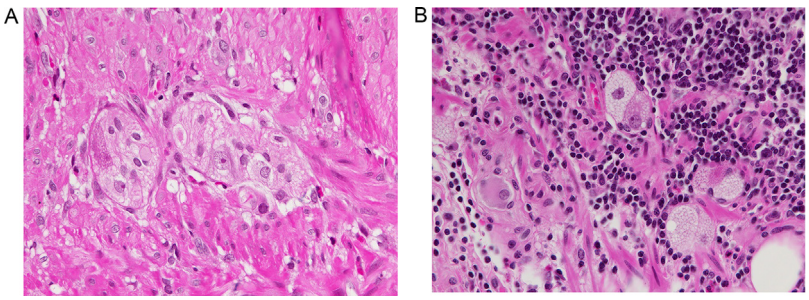

Fig. 3. Globotriaosylceramide accumulation in intestinal biopsy samples. (A) Ganglion cells of the Auerbach plexus appear markedly foamy due to the accumulation of lipids; paraffin section, Haemotoxylin and eosin (H&E), magnification 600×. (B) The submucosa of the ileum contains foamy ganglion cells of the Meissner plexus engorged with lipids; paraffin section, H&E, magnification 400×.
Images courtesy of Dr. Beth Thurberg.

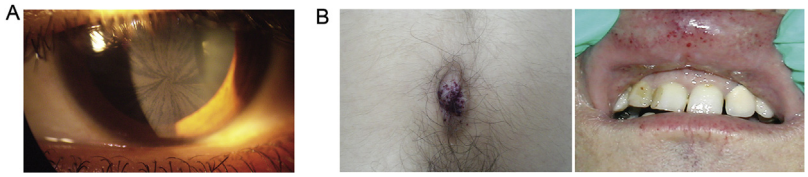

Fig. 4. Clinical findings in Fabry disease. (A) Cornea verticillata: a bilateral, whorl-like corneal pattern of cream coloured lines in a patient with Fabry disease; (B) Angiokeratoma: red-purple, non-blanching vascular skin lesions usually distributed on the buttocks, groin, umbilicus (left figure) and upper thighs (bathing trunk distribution), and occasionally on lips and oral mucosa (right figure).
Reproduced with permission from BMC Neurology: https://bmcneurol.biomedcentral.com/articles/10.1186/1471-2377-11-61 © Burlina et al.; licensee BioMed Central Ltd. 2011 [28].

Table 1
Potential differential diagnoses of adult patients with non-specific gastrointestinal symptoms.

• IBS (particularly diarrhoea-predominant IBS)
• Recurrent abdominal pain syndrome
• Chronic inflammatory bowel disease
• Appendicitis
• Whipple's disease
• Dermatomyositis
• Diverticular disease
• Somatoform disorder
• Crohn's disease
• Coeliac disease
• Colon cancer
• Fabry disease
• Mitochondrial diseases
• Transthyretin-related familial amyloid polyneuropathy

IBS, irritable bowel syndrome.

5.2. Diagnostic evaluation

Patients with unexplained non-specific GI symptoms require a thorough and systematic clinical evaluation based upon their functional GI symptoms and signs in order to identify the potential underlying disorder(s). We find that Fabry disease should be considered as a possible cause of GI problems in patients who present with a long-term history of unexplained GI symptoms such as postprandial abdominal pain, non-inflammatory diarrhoea with frequent urgency, early satiety or gastroparesis, or chronic intestinal pseudo-obstruction [31]. Suspicion should be further raised by the presence of other Fabry-disease-associated symptoms, including neuropathic pain (particularly burning pain in hands and feet), impaired perception of warm and cold, and autonomic nervous system dysfunction (often subtle) such as heat intolerance or abnormal sweating. Finally, clinicians should establish whether there are dermatological, ocular, renal, or cardiac abnormalities, or an extensive family history of such symptoms, or of Fabry disease itself [2,31,50,51].

Tests performed as part of the evaluation of non-specific GI symptoms may help differentiate Fabry disease from other common GI disorders. However, patients with GI disturbances and unclear diagnoses may undergo gastroenterological diagnostic pathways that, in the absence of clinical suspicion, do not include evaluations that are suitable for recognizing Fabry disease. In a survey of patients with GI symptoms and undiagnosed Fabry disease, for example, the patients were found to have undergone various investigations, including gastroscopy, colonoscopy, and barium meal, prior to their diagnosis, which often did not show any abnormalities [10].

Stool studies are useful in the diagnostic work-up of patients with diarrhoea, and gut transit time can be evaluated using the Sitz marker test [31]. Radiological studies such as Doppler scanning or angiography can be used to investigate GI motility and blood flow, particularly if vascular compromise is suspected [1,31]. Upper GI symptoms such as nausea can be evaluated with a gastric emptying scan to study motility, and a breath test can be useful to detect bacterial overgrowth secondary to impaired gastric motility and delayed emptying. Biopsies can be taken for histology studies; typically, patients with Fabry disease have tissue inflammation and normal epithelial/villous structure, with evidence of GL-3 deposits in enlarged and vacuolated neurons (Fig. 3), vascular endothelial cells, and vascular smooth muscle cells [34,38]. Gastric biopsies may reveal positive anti-GL-3 immunostaining results in vascular smooth muscle cells, endothelia, and interstitial cells, in both the classic and non-classic forms of Fabry disease, though some unclassified mutational variants may not react to immunostaining (Fig. 5) [44,45,52].

If clinical findings or diagnostic test results raise a suspicion of Fabry disease, patients should be referred for confirmatory enzymatic and/or genotype testing. A definitive diagnosis is made by measuring alpha-galactosidase A activity in leukocytes, whole blood (dried blood spot), or tissues. While this test is sufficient in males, diagnosis in heterozygous females, who often have low-normal levels of enzyme activity, requires molecular testing [31].

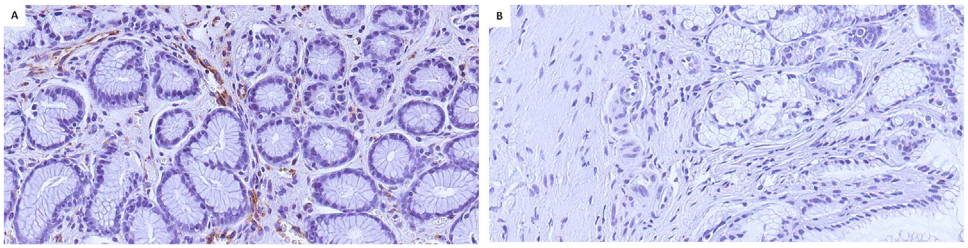

Fig. 5. Globotriaosylceramide (GL-3) accumulation in gastric biopsy samples. Gastric biopsy sample from (A) a male patient diagnosed with classic Fabry disease: biopsy is immunostained with anti-GL-3 antibodies and shows selective reaction in vascular cells; and (B) a female carrier of an unclassified genetic variation in the *GLA* gene: the anti-GL-3 antibodies do not immunoreact with the vascular cells in this biopsy. Magnification (both panels): 40×.
Images courtesy of Prof. Eloisa Arbustini.

Table 2
Examples of questions suitable for prompting consideration of Fabry disease in a patient with non-specific GI symptoms and no family history. We recommend that this type of clinical tool is used alongside a scoring system such as the GSRS.

- How many times (daily/weekly/monthly) do you feel pain in your abdomen?
- Does your pain usually start after a meal or do you experience pain at times other than while/after eating?
- Do you suffer from diarrhoea alternating with constipation?
- Do you often feel nauseous or experience vomiting?
- Do you suffer from unexplained fever (i.e. not related to an infection)?
- Do you experience stomach rumbling or intensive flatulence?
- Are you aware of intolerance to cold/heat?
- Do you have a reduced ability to sweat (particularly as a child)?
- Have you suffered pain attacks triggered by sport, hot weather, stress, or a fever?
- Do you experience excessive burning pain in the extremities, especially in hands and feet? (Or did you experience this during your childhood/teenage years?)
- Do you have a rash of reddish small spots on your skin (known as angiokeratoma), e.g. in the area of your swimsuit?
- Did you undergo examinations/tests for your symptoms? If yes, what were the results?
- Have you had a recent eye (ophthalmic) examination? If yes, did your ophthalmologist mention some "ocular, in particular corneal," abnormality?
- Do you have a history of cardiac disease, arrhythmia, stroke, or renal impairment?
- Do you have any family members who had early kidney disease, heart disease, or stroke?
- Have any of your family members died early or unexpectedly?
- Do you know whether your parents suffered from abdominal pain when they were younger?

GI, gastrointestinal; GRSR, Gastrointestinal Symptom Rating Scale.

Table 3
Example of additional questions for the GSRS questionnaire to include Fabry-disease-specific items. The 15-item GSRS, used as a generalized scoring system for GI symptoms [53], can be expanded with Fabry-disease-specific items to enable possible suspicion of Fabry disease. Similar to the 15 items of the GSRS, the Fabry-disease-specific items 16–18 can be scored 0–3. The Fabry-disease-specific domain of the proposed GFSRS can be analysed as indicated.

16. Presence of limb pain ("glove and socks" – pain in hands and feet)
    0. No pain
    1. Occasional pain in hands and feet
    2. Pain in hands and feet when younger
    3. Pain in hands and feet with unexplained episodes of fever when younger. Pain is still present
17. Sweating
    0. No sweating abnormalities
    1. Less sweating, but increased sweating after sport and in hot environment
    2. Reduced sweating with no change after sport and in hot environment
    3. No sweating
18. Cold perception at distal limbs
    0. Normal cold perception
    1. Usually wearing gloves during the cold season or in a cold environment
    2. Cannot tolerate cold water for long time
    3. Cannot tolerate cold water for long time and cannot touch ice

Evaluation of total score of Fabry-disease-related items (items 16–18)

Score 0	Classic Fabry disease can be excluded
Score 1–3	Likely not classic Fabry disease
Score 4–6	Fabry disease should be explored with questions about/investigations on other organ involvement (heart, kidney, PNS, CNS). Help from Fabry disease experts is needed
Score 7–9	Fabry disease should be investigated with biochemical, genetic, and clinical tests

CNS, central nervous system; GI, gastrointestinal; GRSR, Gastrointestinal Symptom Rating Scale; PNS, peripheral nervous system.

Extensive diagnostic work-ups, such as described above, are costly in terms of time and money. The use of validated patient questionnaires, such as the Questionnaire on Paediatric GI Symptoms (Rome III criteria), has been proposed as a means of specifically characterizing GI symptoms that could lead to more rapid identification of patients who should be evaluated for other Fabry-disease-related symptoms [8]. To take this one step further, we propose that a generic GI symptom rating scale, such as the Gastrointestinal Symptom Rating Scale (GSRS) [53], modified by the inclusion of questions related to Fabry disease symptoms, could serve as a tool for aiding diagnosis in patients with a history of GI symptoms of otherwise unknown cause. Examples of the type of open questions that could be used in conjunction with the GSRS to assist in the identification of patients with Fabry-disease-related GI problems are shown in Table 2.

In addition, an example of how the GSRS can be modified to score for typical Fabry-disease-related symptoms is shown in Table 3. These additions to the GSRS questionnaire (GFSRS), though not yet validated, are tailored for use in patients with the classic form of Fabry disease. Patients with the non-classic later-onset forms of the disease (e.g. cardiac variants) may not be identified by the questionnaire as they may present with organ-confined phenotypes or milder disease phenotypes due to residual enzyme activity.

6. Treatment of gastrointestinal symptoms in Fabry disease

6.1. Symptomatic treatment

Some medical treatments can provide symptomatic relief for specific GI symptoms; for example, the pro-motility agent metoclopramide has been shown to provide some improvement in patients with gastroparesis [33]. Other drugs that have been used for symptom relief include ondansetron for the amelioration of nausea, proton pump inhibitors (e.g. omeprazole) for relief of upper GI symptoms, and anti-diarrhoea medication. However, it has to be stated that these measures rarely work in Fabry patients, and ondansetron is a drug that cannot be used continuously and for a prolonged time. Probiotics and antimicrobial treatments may be useful to prevent or control bacterial overgrowth [31]. Useful non-drug management approaches are dietary modifications (e.g. low-fat meals in case of pancreatic dysfunction, or supple-

Table 4
Proposed guidelines for initiating enzyme replacement therapy in patients with Fabry disease [54–56].

Fabry subpopulation	Initiation of enzyme replacement therapy
Paediatric males	At the time of development of significant symptoms at any age; or if asymptomatic, consider at age 8–10 years [56]
Adult males (>16 years)	At the time of diagnosis of Fabry disease
Females (all ages)	Monitor; initiate if there are significant symptoms or evidence of progression of organ involvement

menting pancreatic enzymes) and the intake of several, smaller meals rather than a single "main" meal to alleviate upper GI symptoms [31]. Rarely, surgical interventions may be necessary where patients have acute complications, such as intestinal perforation or obstruction [38]. However, unless the cause of symptoms is known, symptomatic treatment alone allows the underlying disease to progress beyond the point where organ damage can be prevented by disease-specific treatment. Therefore, it is important to confirm (or rule out) a diagnosis of Fabry disease in patients with non-specific GI symptoms.

6.2. Treatment of Fabry disease

Fabry disease can now be effectively and safely treated with ERT. All symptomatic patients who have a confirmed diagnosis of Fabry disease should be started on ERT with recombinant alpha-galactosidase A, or with a chaperone, provided the patient has an amenable mutation and is therefore eligible for chaperone treatment, to replace the underlying metabolic deficit of Fabry disease and optimize long-term clinical outcomes (Table 4) [54–56]. Two types of ERT are currently available in Europe and many other countries: agalsidase alpha, given at 0.2 mg/kg every other week [57], and agalsidase beta, given at a dose of 1.0 mg/kg every other week [58]. In the USA, only agalsidase beta has licensing approval. Both forms of ERT are given as intravenous infusions, and once initiated, treatment must be maintained for life. Timely initiation of ERT, started as early as possible after diagnosis, has been shown to improve long-term renal and cardiac outcomes, as well as other clinical outcomes, and slow disease progression in patients with Fabry disease [13,14]. In particular, there is evidence that initiating ERT in childhood can reverse early signs of damage to the kidneys [59], which is irreversible by the time clinical signs of renal impairment are evident [25].

ERT has been shown to improve GI symptoms associated with Fabry disease (Supplemental Table 1) [5,7,9,12,38,43,48,60–64]. In a small study, 4 adult male patients with GI symptoms, including postprandial abdominal pain, bloating, frequent diarrhoea, vomiting, food intolerance, and poor weight gain, were treated with agalsidase beta (1.0 mg/kg every other week) [62]. After 6–7 months of treatment, patients reported "no or only occasional" abdominal pain or diarrhoea; they discontinued their GI medications, and gained 3–8 kg in weight. The improvements in GI symptoms in this study persisted over 3 years of ERT [62]. Similar improvements have been reported with agalsidase alpha treatment: a study of 11 adult patients (9 male, 2 female) treated with ERT (agalsidase alpha 0.2 mg/kg every other week) for 6 months found significant and sustained decreases in the severity and frequency of abdominal pain and improvement in the frequency of diarrhoea [60]. In female patients, an analysis of a cohort of 78 female patients from the Fabry Outcome Survey reported that, after 4 years of ERT with 0.2 mg/kg agalsidase alpha every other week, the prevalence of diarrhoea and constipation decreased, while the prevalence of abdominal pain, vomiting, and nausea remained unchanged [7]. However, in a recent large study of 168 female patients in the Fabry Registry, significant improvements in the prevalence of abdominal pain and diarrhoea were reported after 2.5 years of treatment with agalsidase beta, at 1.0 mg/kg every other week [9].

Two studies of children treated with agalsidase beta (1.0 mg/kg every other week) reported improvements in GI symptoms, including postprandial pain, nausea, and vomiting [43], and abdominal pain [64], as well as fewer school absences due to sickness [43]. In a study from the Fabry Outcome Survey, the prevalence of GI symptoms, including abdominal pain, diarrhoea, constipation, and vomiting, were also reduced after 1–2 years of ERT with agalsidase alpha 0.2 mg/kg every other week in a cohort of 64 boys [12]. In another study that analysed Fabry Outcome Survey data from 342 patients (males and females, adults and children), ERT with agalsidase alpha (0.2 mg/kg every other week) resulted in improvement in GI symptoms, including abdominal pain and diarrhoea, particularly in children and male adults after 12 months. An improvement in HR-QoL was also observed after 12 months in male patients who had GI symptoms at baseline [5]. Notably, there were no reports of newly emergent abdominal pain in children on ERT during this study [5].

In addition to ERT with agalsidase alpha or agalsidase beta, migalastat, a novel pharmacological chaperone therapy, has recently been approved in Europe for the treatment of Fabry disease. Migalastat is a small-molecule chaperone that can be orally administered, and is capable of stabilizing and restoring enzyme function in certain mutant forms of alpha-galactosidase A. This chaperone therapy is only suitable for the treatment of patients with certain amenable mutations in *GLA*; currently, clinical experience is still very limited. However, 50 patients with suitable Fabry disease genotypes showed significant GSRS scale reductions in the severity of diarrhoea, reflux, and indigestion in a clinical trial of migalastat, administered at 150 mg twice daily, for 6–24 months, compared with placebo [16].

7. Conclusions

GI symptoms are very common in patients with Fabry disease, and are very often the initial presenting symptoms in children with this disease. Abdominal pain, diarrhoea, bloating, nausea, and vomiting are the most common symptoms and have debilitating effects on patients' lives, leading to reduced quality of life, particularly during childhood. Although GI symptoms of otherwise unknown aetiology, such as abdominal pain, may be the first or only indication that a patient has Fabry disease, these symptoms are often non-specific and similar to those of other GI disorders such as IBS or inflammatory bowel disease. GI specialists involved in the clinical assessment of patients with non-specific upper and lower GI symptoms therefore need to be aware of Fabry disease as a possible cause of non-specific GI symptoms, and Fabry disease should be included in their list of differential diagnoses.

When Fabry disease is suspected on the basis of clinical presentation of a patient with non-specific GI symptoms and/or a family history of the disease, patients should be referred for confirmatory biochemical diagnostic testing, i.e. assessment of alpha-galactosidase A activity for male patients, including genotyping to identify the Fabry mutation. In addition to symptomatic treatments, effective treatment of the underlying disease with ERT and chaperone therapy for eligible patients with an amenable mutation can improve patients' GI symptoms and should be initiated as early as possible after a Fabry diagnosis is confirmed in a symptomatic patient to improve long-term clinical outcomes. Diagnostic tools such as patient-reported GI symptom questionnaires may aid the diagnosis of Fabry disease in patients with GI symptoms of unknown cause. Further studies are required to validate the additions to the GSRS questionnaire, because reducing diagnostic

delays in Fabry disease and diagnosing the disease in patients as young as possible is vital in order to improve clinical outcomes through timely initiation of disease-specific treatment.

Conflict of interest

M.J. Hilz has received research support from Bayer Health Care, Novartis Pharma, and Sanofi Genzyme and has received speaker honoraria and travel support from Sanofi Genzyme.

E. Arbustini has no conflicts of interest.

L. Dagna has received research support from Abbvie, Bristol-Myers Squibb, Mundipharma, Pfizer, and Roche, and has received speaker honoraria and travel support from Sanofi Genzyme, Biotest, and Celltrion.

A. Gasbarrini has received grants or speaker honoraria from Alfasigma, Bristol-Myers Squibb, Janssen, Abbvie, MSD, Gilead, Sofar, Angelini, and Sanofi Genzyme.

C. Goizet has received research support from Sanofi Genzyme, TKT5S, Shire, and Biomarin, and has received consulting fees, speaker honoraria, and travel support from Sanofi Genzyme, TKT5S, Shire, Actelion, Biomarin, Amicus, TEVA, Santhera, and Raptor.

D. Lacombe has received consulting fees, speaker honoraria, and travel support from Sanofi Genzyme, TKT5S, Shire, Actelion, Biomarin, and Amicus.

R. Liguori has received honoraria from Sanofi Genzyme and Biogen for Advisory Board consultancy and has received speaker honoraria from Dynamicom Education and Scientific Press.

R. Manna has received speaker honoraria and travel support from Sanofi Genzyme and Shire.

J. Politei has received honoraria and travel support for lectures on Fabry disease from Genzyme, Shire HGT, Amicus Therapeutics, and Protalix Corp.

M. Spada has received advisory board attendance and speaker honoraria and travel support from Sanofi Genzyme and Shire.

A. Burlina has received speaker honoraria and travel support from Sanofi Genzyme, Amicus, Biomarin, and Nutricia; he is a member of the European Advisory Board of the Fabry Registry, which is sponsored by Sanofi Genzyme.

Funding

The development of this publication and the Internal Medicine Advisory Board in Rare Diseases (10 December 2016, in Rome, Italy) were sponsored by Sanofi Genzyme. The authors received editorial/writing support in the preparation of this manuscript from Rosalie Gadiot, PhD, of Excerpta Medica, which was funded by Sanofi Genzyme. The authors were responsible for all content and editorial decisions and received no honoraria related to the development of this publication.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.dld.2018.02.011.

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