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Review Article

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

Max J. Hilz[a], Eloisa Arbustini[b], Lorenzo Dagna[c,d], Antonio Gasbarrini[e], Cyril Goizet[f,g], Didier Lacombe[f,g], Rocco Liguori[h,i], Raffaele Manna[j], Juan Politei[k], Marco Spada[l], Alessandro Burlina[m,*]

[a] Department of Neurology, University of Erlangen-Nuremberg, Erlangen, Germany
[b] Center for Inherited Cardiovascular Diseases, IRCCS Foundation Policlinico San Matteo, Pavia, Italy
[c] Unit of Immunology, Rheumatology, Allergy and Rare Diseases (UnIRAR), IRCCS San Raffaele Hospital, Milan, Italy
[d] Vita-Salute San Raffaele University, Milan, Italy
[e] Department of Medical Sciences, Division of Gastroenterology, Catholic University, Rome, Italy
[f] CHU Bordeaux, Department of Medical Genetics, Bordeaux, France
[g] INSERM Unit 1211, Laboratoire MRGM, University of Bordeaux, Bordeaux, France
[h] Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy
[i] IRCCS Institute of Neurological Sciences, Bologna, Italy
[j] Periodic Fever and Rare Diseases Research Centre, Gemelli Foundation, Catholic University of the Sacred Heart, Rome, Italy
[k] Department of Neurology, Fundación para el Estudio de las Enfermedades Neurometabólicas (FESEN), Buenos Aires, Argentina
[l] Department of Pediatrics, University of Torino, Torino, Italy
[m] Neurological Unit, St. Bassiano Hospital, Bassano del Grappa, Italy

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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-

* Corresponding author at: Neurological Unit, St. Bassiano Hospital, Via dei Lotti 40, 36061 Bassano del Grappa, Italy.
E-mail address: alessandro.burlina@aulss7.veneto.it (A. Burlina).

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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-

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