Review Article

NON-SPECIFIC GASTROINTESTINAL FEATURES: COULD IT BE FABRY DISEASE?

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- In Fabry disease, mutations in the *GLA* gene encoding **alpha-galactosidase A** lead to a lack of, or reduced, enzyme activity which results in progressive accumulation of **globotriaosylceramide (GL-3)** and other glycosphingolipids within lysosomes.[1]
- Intracellular accumulation of glycosphingolipids results in progressive tissue and end-organ damage.[1]
- This leads to a broad range of symptoms and, eventually, fatal complications in a range of organs, including the kidneys, heart, and brain that compromise life expectancy.[1]
- In the case of the gastrointestinal (GI) tract, autonomic small fibre damage to the myenteric plexus can develop through glycolipid deposition leading to abnormal smooth muscle activity.[1]
- This frequently results in symptoms such as diarrhoea and abdominal cramps.[1]

Diagnostic challenges

- Fabry disease is rare and patients are not always readily diagnosed, primarily due to the non-specific initial presenting symptoms.[1]
- GI symptoms are often the first presenting symptoms and a Fabry diagnosis may be made incidentally either because of physician recognition of the distinctive ocular signs (cornea verticillata) or skin lesions (angiokeratomas), or as a result of screening of other family members.[1]
- However, the majority of patients experience long diagnostic delays, and misdiagnosis is common.[1] Delays in diagnosis 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.[1]

GI specialists involved in the clinical assessment of patients with non-specific upper and lower GI symptoms need to be aware of Fabry disease as a possible cause of non-specific GI symptoms, and Fabry disease should be included in the differential diagnoses.[1]

Diagnosis

In patients with the classic phenotype, symptoms first appear in early childhood, with a median age of onset of 14 years.[1] 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%).[1]

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:[1]

- Postprandial abdominal pain
- Non-inflammatory diarrhoea with frequent urgency
- Early satiety, or gastroparesis
- Chronic intestinal pseudo-obstruction

Other early symptoms often include neuropathic pain, hypohidrosis, cornea verticillata and lenticular opacity, angiokeratoma, and renal damage leading to proteinuria.[1]

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.[1]

Treatment of GI symptoms in Fabry disease

Some medical treatments can provide symptomatic relief for specific GI symptoms; for example:*[1]

- metoclopramide has been shown to improve gastroparesis
- ondansetron may ameliorate nausea
- proton pump inhibitors may relieve upper GI symptoms.

Useful non-drug management approaches include:[1]

- dietary modifications (e.g. low-fat meals in case of pancreatic dysfunction, or supplementing pancreatic enzymes) and
- the intake of several, smaller meals rather than a single "main" meal to alleviate upper GI symptoms.

However, symptomatic treatment alone allows the underlying disease to progress beyond the point where organ damage can be prevented by disease-specific treatment.[1] Therefore, it is important to confirm (or rule out) a diagnosis of Fabry disease in patients with non-specific GI symptoms.[1]

Fabry disease can now be effectively treated with enzyme replacement therapy (ERT) using recombinant alpha-galactosidase A.[1] ERT can improve patient's 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.[1]

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.[1]

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]

*These measures rarely work in Fabry patients, and odansetron is a drug that cannot be used continuously and for prolonged time.

Reference: 1. Hilz MJ, Arbustini E, Dagna L, *et al.* Non-specific gastrointestinal features: Could it be Fabry disease? *Digestive and Liver Disease* 2018;50:429–437.

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