What is Fabry?

Fabry disease is a rare genetic condition which is estimated to affect around one in 100,000 people. In Fabry, an enzyme called α-galactosidase A (α-Gal A) is missing or there is a reduced amount. This means that the body cannot break down a certain type of fat called globotriaosylceramide (GL-3). GL-3 continues to build-up in body cells causing damage to tissues and organs. Gradually, this leads to a range of physical symptoms and complications, which vary from one person to another.

Study highlights

In our research news, we look at a study that was designed to investigate the accumulation of GL-3 in the GI tract cells of people with different Fabry mutations who all have GI symptoms.

GI tract is the passage for food to travel all the way from the mouth to the anus and includes all of the organs in the digestive system.

In Fabry disease, globotriaosylceramide (GL-3), a type of fat, builds up in tissues and organs causing damage to the kidneys, heart and central nervous system.

For information on inheritance refer to Fabry Findings Issue 1
Symptoms in Fabry

Day to day symptoms in Fabry are known to vary from one person to another.1

**BRAIN AND NERVES**
- Burning in the hands and feet
- Intolerance to heat/cold
- Mini stroke (TIA)/Stroke
- Pain
- Vertigo/feeling dizzy

**HEART**
- Enlarged heart
- Heart attack
- Heart failure
- Irregular heartbeat

**KIDNEYS**
- Decreased kidney function
- Kidney failure
- Protein in urine

**EYES AND EARS**
- Cloudy vision (cataracts)
- Hearing loss (in children)
- Ringing in ears

**SKIN**
- Small dark red/purple spots located between the belly button and the knees
- Sweating less than normal

**OTHER**
- Cough/wheezing
- Shortness of breath
- Tiredness that is not relieved by rest or sleep

**GI SYMPTOMS**
Approximately 52–66% of Fabry patients report GI symptoms.3,4 GI symptoms in Fabry vary from one person to another but often include:5,6,7

- Abdominal pain
- Diarrhoea
- Food intolerance
- Nausea
- Vomiting
- Bloating and frequent gas
- Feeling full before finishing a meal
- Constipation

Abdominal pain and diarrhoea are the most common GI symptoms, affecting around half of the adults with classic Fabry and 60% of children.3

In a study of 25 adult patients, 14 reported feeling full before finishing a regular size meal and 12 feeling bloated.4

Both males and females experience abdominal pain with the same frequency, while diarrhoea affects more males than females.3,4,8

Constipation is also common and it can be twice as frequent in females than in males.3,8

Overall GI symptoms are experienced by more females than males.3
When GL-3 is not completely broken down it builds up within the cells causing progressive damage. Build-up of GL-3 in the intestine leads to interruptions in digestive function and results in many of the different symptoms seen in Fabry disease.\textsuperscript{5,7}
Managing GI symptoms

GI disturbances can have a significant impact on people with Fabry and their quality of life.9

Three key approaches can help improve GI symptoms

Early diagnosis

A Fabry diagnosis is often delayed and can take an average of 14 years in males and 16 years in females from when symptoms first appear.12

If Fabry disease signs and symptoms are recognised promptly, then treatments can start earlier and possibly help delay more serious complications.

Many people with Fabry who experience GI symptoms are incorrectly diagnosed with Crohn’s disease, celiac disease, or irritable bowel syndrome (IBS).5

Diet and lifestyle

People with Fabry have to manage their diets to help improve GI symptoms. Some changes may include:13

- Adjusting meal sizes and patterns towards smaller, more frequent meals.
- Timing of meals, such as avoiding late night eating.
- Eliminating foods from the diet that are not tolerated such as spicy, lactose containing or greasy foods.

Treatment

There is no cure for Fabry disease but current treatments may prevent organ damage and greatly improve the quality of life of patients.

**ORAL CHAPERONE THERAPY**

Chaperones are small molecules that assist enzymes in becoming functional by helping them take the correct shape and stay stable. Chaperone therapy is only suitable for people with amenable mutations of the α-GaL A enzyme. Treatment has shown meaningful reduction in diarrhoea in patients with Fabry disease and amenable mutations.14

**INTRAVENOUS ENZYME REPLACEMENT THERAPY (ERT)**

For people with Fabry, ERT is a long-term therapy whereby the missing or deficient enzyme is given via an intravenous infusion. Recent studies looking at improvements of GI symptoms for patients on ERT have shown a reduction in abdominal pain and diarrhoea in females15 and a reduction in abdominal pain or diarrhoea from weekly occurrences to only occasionally in males who had been on ERT for 6–7 months.16
Research news

‘Pathologic substrate of gastropathy in Anderson-Fabry disease’ was published in *Orphanet Journal of Rare Diseases.*

The study

In 2020, researchers in Italy published a study *investigating the causes of GI symptoms* in six unrelated individuals with Fabry.

Fabry is caused by mutations in a gene known as GLA, which affects the production of the α-Gal A enzyme. The type of mutation of the GLA gene was used in this study to describe the form of the disease: classic Fabry, late-onset Fabry and Fabry-affected.

The researchers were aiming to assess if GL-3 accumulation was seen in the GI tract cells of people with Fabry and how this could help to determine if all GI symptoms are attributable to Fabry.

GI symptoms are usually attributed to Fabry for all forms of the disease.

Study participants

The study included men and women with classic Fabry (mutations GLA p.(Ser401*) and p.(Ala352Asp)), late-onset Fabry (mutation GLA p.(Asn215-Ser)) and Fabry-affected (mutation GLA p.(Asp313Tyr)) individuals.

Study details

All individuals in the study had experienced *long-lasting GI disturbances* that were poorly controlled with medications commonly used to treat GI symptoms.

The two males with classic Fabry disease had experienced *GI symptoms from infancy.*

Individuals with classic Fabry and with late-onset Fabry disease were on ERT treatment.

Fabry-affected individuals were not on ERT treatment.

Gastropathy is the medical term for stomach diseases
‘Pathologic substrate of gastropathy in Anderson-Fabry disease’ was published in *Orphanet Journal of Rare Diseases*.17

GI symptoms that were experienced by individuals in the study:

<table>
<thead>
<tr>
<th>Constipation</th>
<th>Early satiety</th>
<th>Epigastric pain</th>
<th>Heartburn</th>
<th>Intestinal disturbances</th>
<th>Nausea</th>
<th>Vomiting</th>
<th>Weight loss</th>
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<td>22 years Classic Fabry</td>
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<td>51 years Late-onset Fabry</td>
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<td>50 years Fabry-affected</td>
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<td>81 years Fabry-affected</td>
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**Early satiety** is feeling full before the end of a meal. **Epigastric pain** is felt in the upper abdomen, the area that is just below the ribs and above the belly button.

**The assessment**

In the study, researchers assessed the changes in GI cells by using an **endoscope** to look at the lining of the throat, stomach and the first part of the small intestine.

A small sample of the GI tract cells was taken, this is called a **biopsy**. The biopsies were examined under a microscope and the researchers looked for GL-3 accumulation in the cells.

An **endoscope** is a flexible tube with a light and camera at the end that is used to look inside the body. A **biopsy** is a medical procedure that involves taking a small sample of body tissue so it can be examined under a microscope.
Researchers investigated the accumulation of GL-3 in the GI tract cells of six individuals with Fabry.

FABRY GASTROPATHY

- **Fabry gastropathy** was diagnosed in both individuals with classic Fabry.
- Biopsies showed GL-3 was present in GI tract cells of both individuals with classic Fabry.
- **ATTRIBUTED TO FABRY**

GASTRO-OESOPHAGEAL REFLUX DISEASE

- **Gastro-oesophageal reflux disease** is caused by acid reflux from the stomach and inflammation of the oesophagus. It was confirmed in both Fabry-affected individuals and the late-onset Fabry female.
- Biopsies showed GL-3 was absent in GI tract cells of late-onset Fabry and Fabry-affected individuals.
- **NOT ATTRIBUTED TO FABRY**

GI symptoms were present in all six individuals.

**GI symptoms** were present in all six individuals.

**ALL INDIVIDUALS HAD EXPERIENCED LONG-LASTING GI DISTURBANCES**

**CLASSIC FABRY**
- 22 years
- 27 years

**LATE-ONSET FABRY**
- 17 years
- 51 years

**FABRY-AFFECTED**
- 50 years
- 81 years
Further studies may be able to measure how well ERT treatment is working by comparing levels of GL-3 before and throughout ERT treatment.
References
