Fabry Findings

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In this issue we focus on children with Fabry and guidelines produced by an expert group in France for the management of Fabry in children.

What is Fabry?

Fabry is a rare inherited genetic disorder, and it is difficult to give an exact figure for how often it occurs. The current estimate is that 1 in every 80,000 children will be born with Fabry.[1]

Fabry is caused by **mutations** in the **GLA gene**. These mutations lead to a lack or reduced level of an enzyme called α-galactosidase A (α-Gal-A) which is necessary for breaking down certain types of fats in the body, called globotriaosylceramide (Gb3). Without the enzyme, Gb3 builds up in a variety of cells, causing damage to tissues and organs. This results in a range of symptoms and complications, which can vary from one person to another.[2]

The natural course of Fabry leads to a wide spectrum of disease, from a severe form in males (often referred to as classical Fabry) to few or no symptoms occasionally seen in some females.[2]

Fabry in children

For those with more severe forms of Fabry, first symptoms appear in childhood, typically between the ages of 3 and 10 years, and generally a few years later in girls than in boys.[3,4] With age, progressive damage to vital organ systems develops in both genders.[4]

Fabry guidelines

Guidelines for supporting and treating patients with rare diseases are an important way for the medical community to share knowledge and best practice in caring for their patients.

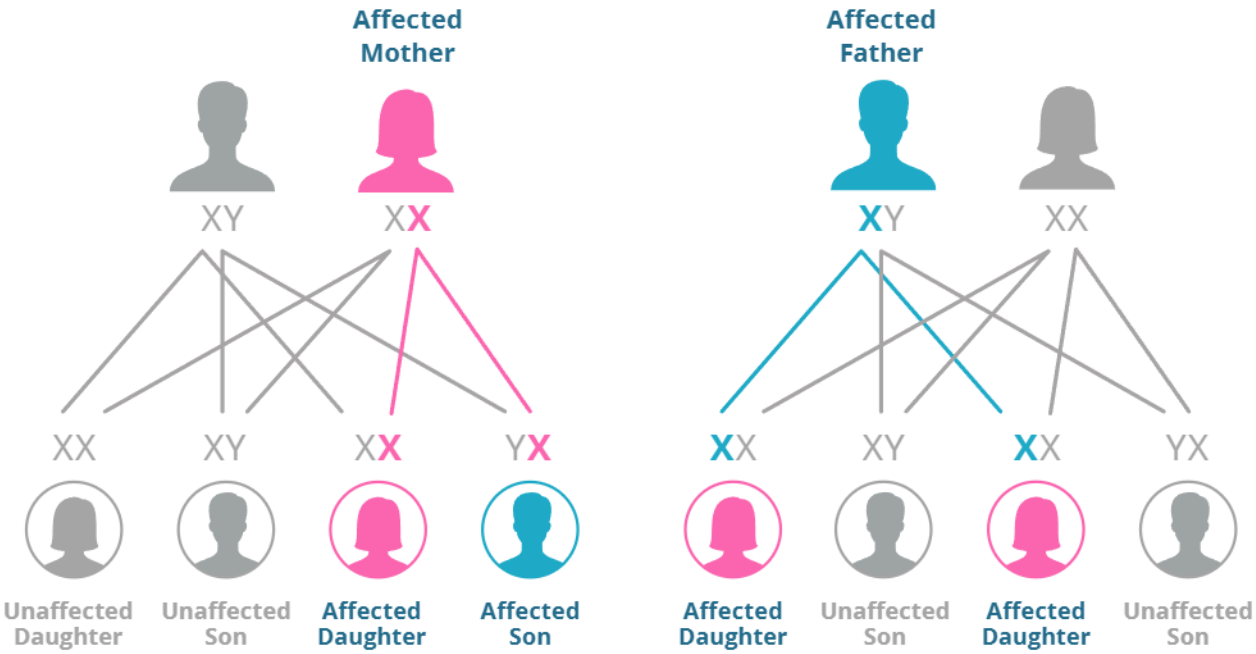
The **GLA gene** provides instructions for the body to make the α-Gal-A enzyme

A **mutation** is a permanent change in a DNA sequence that makes up a gene

Why might Fabry affect boys and girls differently?

The development of Fabry symptoms can be different in boys and girls due to the way that Fabry is inherited. The GLA gene lies on the **X chromosome**, and Fabry is therefore known as an X-linked disease. If only one parent has Fabry, any female children that inherit Fabry will have both a normal X chromosome and an X chromosome that carries the Fabry mutation.[5]

Genes are located on chromosomes. The GLA gene is found on the **X chromosome**, one of the two chromosomes that determine the sex of the individual



As females have two X chromosomes, a natural process known as X-chromosome inactivation occurs before birth to ensure that only one X chromosome is active in the cells of the body. In those who have inherited Fabry, this will lead to some normal X chromosomes being inactivated, and some mutated X chromosomes being inactivated. Differences in the number of mutated X chromosomes that remain active between individuals can therefore lead to differences in the severity of their Fabry.[6]

Symptoms in children

It is difficult to predict which symptoms children will develop and when, as Fabry can vary greatly from person to person. The most frequently reported symptoms in children under 5 years of age are a type of pain known as **acroparesthesia** or **neuropathic pain** and stomach issues.[7]

The information held within a large Fabry registry shows that common symptoms in children included pain, heat intolerance and reduced sweating, stomach and digestive issues, small spots on the skin known as **angiokeratomas**, problems with eyes and ears, tiredness and the detection of **protein in the urine**.[8]

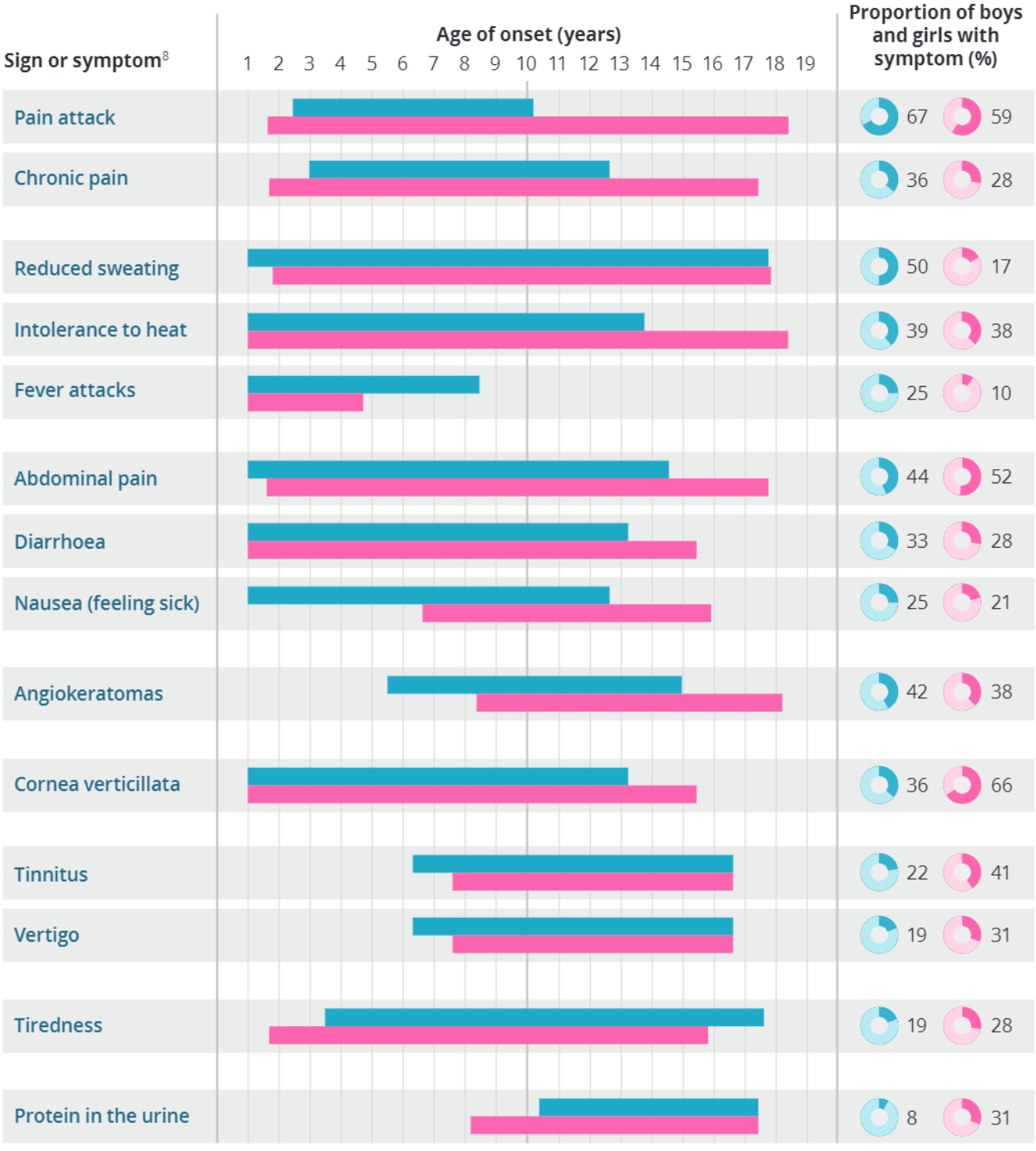
Acroparesthesia refers to tingling, pins-and-needles, burning or numbness or stiffness in the hands and feet, particularly the fingers and toes

Neuropathic pain is pain that originates from damage to the nerves

Angiokeratomas are purple spots on the skin of the lower back, groin, upper thighs and belly button

The presence of **protein in the urine** is an indicator of kidney disease

Information on the symptoms of 36 boys and 29 girls with Fabry was held in the registry.[8] The figure below shows the age when each symptom was first noticed (age of onset) and the proportion of boys and girls who had that symptom. For example, 67% of boys and 59% of girls had pain attacks. In boys, the pain attacks started between the ages of 2.5–10 years and in girls between the ages of 1.5–18.5 years.



Adapted from Ramaswami et al. 2006. More symptoms were reported, only the most common, those reported in one quarter or more of boys or girls, are shown here.

Cornea verticillata are opaque areas on the cornea of the eye

Tinnitus is the sensation of ringing in one or both ears, which is not caused by another sound

Vertigo is the sensation of feeling off balance, and is caused by problems in the inner ear

Research news

'Consensus recommendations for diagnosis, management and treatment of Fabry disease in paediatric patients' was published in 2019 in *Clinical Genetics*.[9]

The publication

As growing experience of enzyme replacement therapy for Fabry has demonstrated that early treatment can prevent organ damage in adulthood, the focus of treatment is moving towards earlier treatment in children to maintain health in later life. With these new developments, the need for updated recommendations for managing Fabry in children was identified.

Between 2016 and 2017, a group of French doctors, including paediatricians and geneticists experienced in treating Fabry, gathered to discuss the management of Fabry in children. Their resulting recommendations are intended to be a practical guide for diagnosis, monitoring and treatment.

Diagnosis

✓ CHILDREN FROM FAMILIES WITH A HISTORY OF FABRY

*Systematic screening of children with at least one **first-degree relative** with Fabry is the simplest and fastest way to improve the rate of diagnosis.*

Diagnosis can be confirmed by a blood test to measure the level of α-GAL-A enzyme and a genetic test to confirm the presence of a Fabry associated gene mutation. While boys will usually have very low enzyme levels, some girls may have almost normal enzyme levels and therefore the genetic test is essential to confirm diagnosis.

✗ CHILDREN WITH NO FAMILY HISTORY OF FABRY

Owing to the lack of specific symptoms, diagnosis of Fabry when there is no family history is usually delayed and rarely occurs during childhood.

The symptoms that should alert paediatricians to the possibility of Fabry include those listed on pages 2 and 3 of this issue. The hallmark sign of classic Fabry in children is neuropathic pain in the hands and feet. However, it can be difficult for doctors to link individual symptoms, such as pain, to Fabry.

Pain in children with Fabry

Fabry-associated pain in children may be misdiagnosed as growing pains. It is vital to distinguish between the two:

- **Pain due to Fabry** is described as burning, followed by stabbing, tingling and shooting pains in the hands and feet and is triggered by physical exercise, heat and fever and occurs during the day, particularly in late morning.[9]
- **Growing pains** are experienced in the hips, legs and feet during late evening and night.[10]

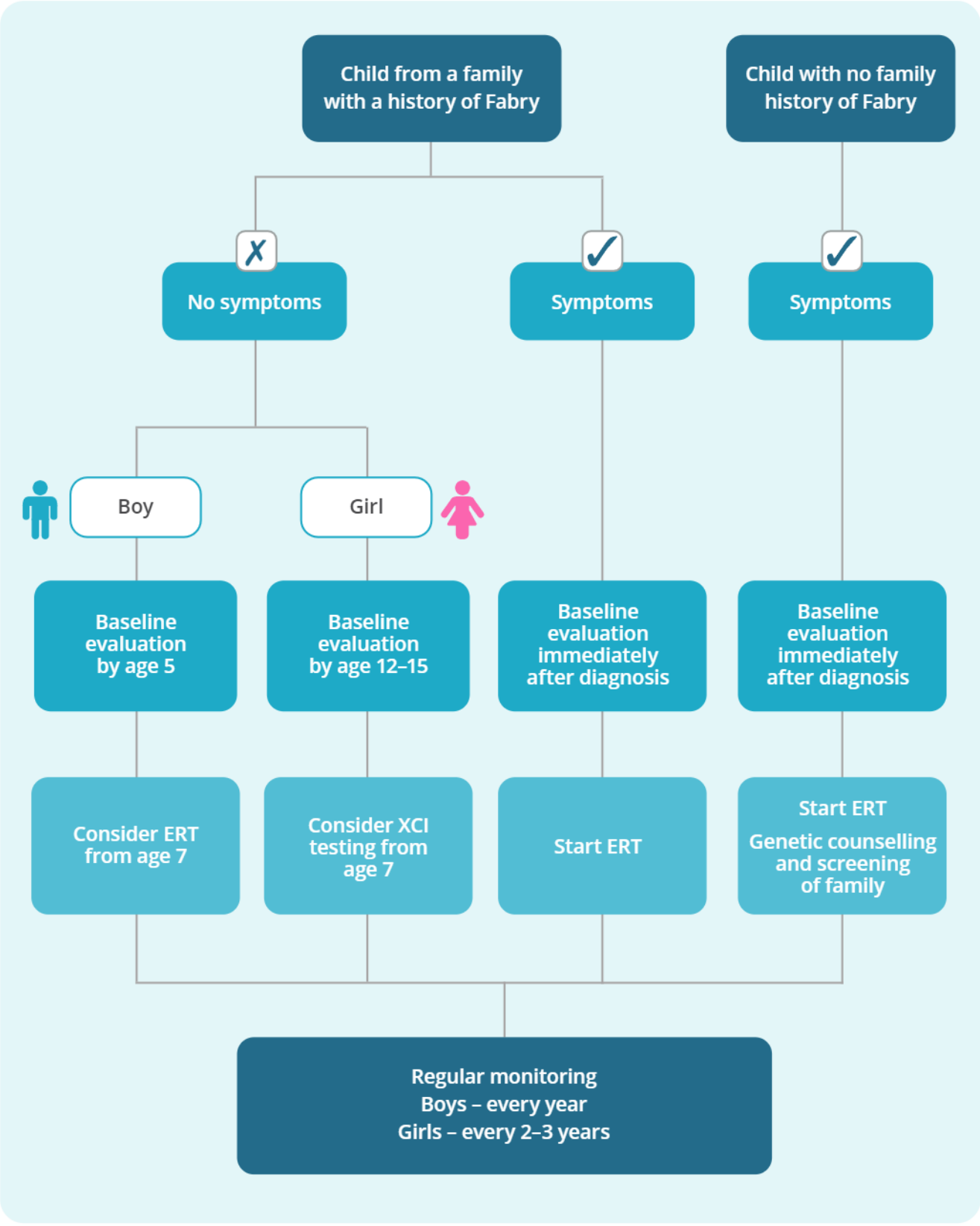
Giving a diagnosis

Once a diagnosis is made, it should be explained to the family, with support given for next steps in treatment and genetic counselling. Family history is investigated to find other cases in the same family.[11]

First-degree relatives include parents, siblings and children

Monitoring and treatment

For children with a confirmed diagnosis of Fabry, the following monitoring and treatment pathway is recommended.

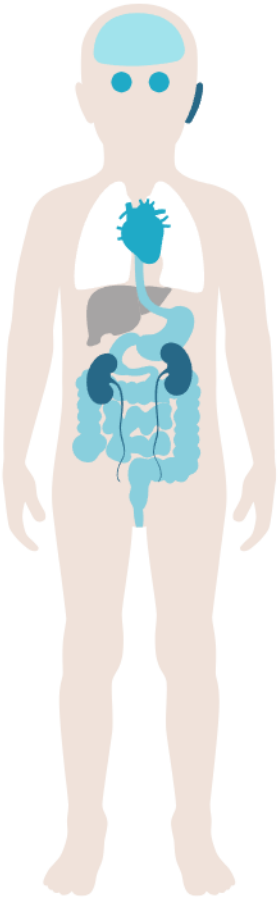


Adapted from Germain et al. 2019[9]

ERT: Enzyme replacement therapy.

XCI: X chromosome inactivation (see explanation on page 2)

A **baseline evaluation** involves the clinical assessment of the patient following diagnosis and before treatment has started



Regular monitoring includes checks on all major organs that may be affected by Fabry.

	Assessment	Baseline	Monitoring
Brain	MRI of the brain	Only if child is experiencing neurological symptoms	
	Consultation with pain specialist	If needed	
Eyes	Eye examination	✓	
Ears	Audiogram	✓ From age 10	If hearing symptoms are present
Heart	ECG (electrocardiogram)	✓	✓
	Ultrasound of the heart	✓	✓
	Holter monitor		Only if symptoms suggest it is necessary
	MRI of the heart	If available and child does not need sedation	
Kidneys	Blood and urine tests	✓	✓
	Ultrasound of kidneys	✓	
Gut	Clinical examination	✓	✓
Skin	Clinical examination of the skin	✓	✓
	Photographs of angiokeratomas	✓	✓
Blood	α-GAL-A enzyme activity	✓	
	$LysoGb_3$ levels	✓ Before starting enzyme replacement therapy	✓
	Anti-agalsidase antibodies	✓ Before starting enzyme replacement therapy	✓
Height	Growth curve	✓	✓
Other	Quality of life assessment and school absenteeism	✓	✓
	X chromosome inactivation assessment	✓ Girls only	
	Vitamin D test	✓	✓

An **audiogram** is a hearing test to see at what frequencies a person can hear sounds

An **electrocardiogram or ECG** is a test to measure the electrical activity of the heart and its rhythm

A **Holter monitor** is a wearable electrocardiogram that monitors the heart over 24 hours or longer

$LysoGb_3$ is a biomarker for Fabry. Its levels in the blood plasma are measured to understand the progress of the condition and treatment effect

Those treated with enzyme replacement therapy may develop an immune response and generate **anti-agalsidase antibodies**

Starting treatment with enzyme replacement therapy

Children with Fabry symptoms

Enzyme replacement therapy should be considered for boys and girls with any of the following symptoms:

- Neuropathic pain
- Evidence of kidney damage
- Severe stomach/ digestive issues and abdominal pain
- Heart involvement

Boys with no Fabry symptoms

Enzyme replacement therapy would usually be started no earlier than the age stated in the product license, as information about its use in younger children is lacking. The authors felt, however, that boys younger than 7 years may benefit from starting treatment if they:

- Have a GLA gene mutation associated with classic Fabry
- Have a family history of Fabry in males
- Have no detectable levels of α-GAL-A enzyme
- Have a high level of lysoGb$_3$ in their blood

Girls with no Fabry symptoms

There is currently no information to support the use of enzyme replacement therapy in girls with no symptoms. The authors however, felt that girls aged 7 years of age and over should be offered X-chromosome inactivation testing, and started on treatment if the test suggests it would be beneficial.

Deciding to start enzyme replacement therapy

The decision to start a patient on treatment should be a joint decision between the paediatrician, geneticist, family and patient, with a careful review of all benefits versus challenges of lifelong bi-weekly infusions. Home infusions may be considered for those who tolerate the infusions in hospital well.[12]

Pain management

Effective pain management is an important step in improving quality of life in Fabry. A strategy that includes medication and education on how to avoid pain triggers such as heat or strenuous exercise is recommended.

Children with pain can be started on pain medication at a low dose, which can be increased slowly according to pain levels. If this does not alleviate pain after several weeks, a different medication can be added.

- Long-term use of pain medication should be avoided due to neurological side effects
- The use of pain medication should not delay the start of enzyme replacement therapy in children with Fabry symptoms

Treating organ involvement

In addition to enzyme replacement therapy, other medications and lifestyle measures can be used to manage the impacts of Fabry on the heart and digestive system.[13]

- Healthy eating
- Managing blood pressure
- Managing blood cholesterol levels, and taking medication to lower this if needed

- Eating small, frequent meals
- Dietary restrictions

Psychological support

A diagnosis of Fabry can be a difficult time for both the child and their family. Children experiencing psychological difficulty should be referred to a psychologist or social worker for support.

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