Medical Education Needs to Improve Diagnosis of Fabry Disease in the UK

Stuart Gaffney, Kamran Iqbal, Phil Dawson, Thomas Kenny

Chiesi Global Rare Diseases, Medical Affairs, Chiesi Limited, Manchester, UK

BACKGROUND

- Fabry disease is a rare X-linked lysosomal disease caused by mutations in the GLA gene resulting in deficient activity of the α-galactosidase A (α-Gal A) enzyme.[1] The reduced enzyme activity leads to the progressive accumulation of globotriaosylceramide (Gb3) in lysosomes throughout the body causing multisystemic organ damage.[2,3] The estimated prevalence is 1–5/10,000 births.[4]
- The rarity, clinical heterogeneity and presentation of non-specific symptoms may limit awareness of early signs among healthcare professionals (HCPs) to be able to identify and diagnose Fabry.

OBJECTIVES

To understand the patient journey to diagnosis and to identify the unmet medical education needs of UK primary and specialty HCPs that encounter undiagnosed Fabry patients.

METHODS

Patient journey to diagnosis:
Online survey with Fabry patients/caregivers (Oct 2022–Feb 2023)

- Link to survey distributed by UK MPS Society and Fabry specialist nurses by email and social media
- Hosted on the on-line Qualtrics^{XM} platform
- Participant Information and Informed Consent were displayed at the start of the survey
- 38 questions: multiple choice and open text

Nurses' experience and support needed:
Semi-structured interviews with four Fabry specialist nurses (Oct–Dec 2022)

- Recruited through UK MPS Society contacts
- Treating patients with Fabry at four UK specialist centres

Metabolic clinicians
Online meeting with two expert clinicians (Jul 2023)

- Clinicians were involved in the diagnosis, management and treatment of patients with Fabry

Analysis:

- **Quantitative analysis:** Descriptive statistics
- **Qualitative analysis:** Free text responses and discussions analysed using an inductive thematic approach[5]

Patient inclusion criteria: Patients not diagnosed from family screening and diagnosed after 2012

SURVEY RESULTS

Patient demographics

20 survey respondents (65% females) were included in the final analysis (17 patients with Fabry and 3 caregivers).

Median age of symptom presentation:
13.0 years
(mean 25.7 ± 24.0, range 0–70.2)

Median age at diagnosis:
44.0 years
(mean 41.5 ± 21.4, range 4.7–70.2)

Median age at the time of the survey:
52.4 years
(mean 47.1 ± 21.8, range 4.7–75.8)

- For some patients, symptoms presented within their first decade of life but were referred to a specialist in their 20s–40s (Figure 1a)
- For most, the age at which they were referred to the first specialist coincided with the age of diagnosis (Figure 1b)

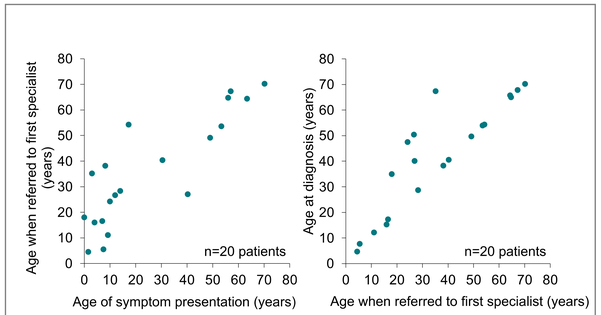

Figure 1. *(a) Age of symptom presentation vs age of referral to first specialist and (b) age of referral to first specialist vs age of diagnosis.*

First symptoms of Fabry

- Neuropathic pain was the most reported first symptom
- Cardiovascular issues were the first severe indication
- First symptoms also included Fabry crisis, heat intolerance, severe fatigue, vertigo, chest pains, gastrointestinal issues, hearing difficulties, transient ischaemic attack (TIA), Fabry appearance, autism spectrum disorder (ASD)-like traits and developmental delay

Diagnostic pathway

PRIMARY CARE

- Patients first sought medical attention from primary care physicians or from emergency departments following a cardiac event
- Patients visited primary care HCPs multiple times for years before action was taken to manage symptoms, identify their cause or refer to a specialist

> *"I saw many GPs [General Practitioner] and specialists for GI symptoms and migraines and vertigo over the years, my mum took me backwards and forwards to the GP as a child for stomach problems."* ***Female patient***
>
> *"I would often go to see my GP but each time they told my mum it was growing pains."* ***Female patient***

SPECIALISTS

- Patients saw many specialists before a diagnosis (Figure 2)
- 45% (9/20) of patients were first referred to a cardiologist (Figure 2) but action was not always taken to investigate heart issues such as chest pain, particularly in young patients
- Cardiologists identified Fabry in 55% (11/20) of patients (9 after a cardiac event) and ophthalmologists in 20% (4/20) (3 after being referred by a high street optician who identified *cornea verticillata*)
- Other specialists suspecting Fabry were a geneticist (n=1), a nephrologist (n=1), and metabolic specialists (n=2)

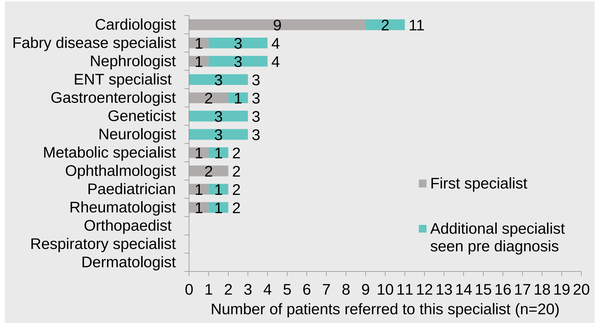

Figure 2. *Specialists patients were referred to before reaching a Fabry diagnosis*

MISDIAGNOSIS

45% (9/20) of patients were misdiagnosed before receiving a Fabry diagnosis (Table 1).

> *"Specialists were good at treating rheumatoid arthritis but this was the wrong diagnosis. Urology never followed up after tests even when they suspected an underlying condition."* ***Male patient***

Misdiagnosis had negative impacts on patients' emotional wellbeing, mental health, self-esteem, and ability to socialise or work, while some patients became distrusting of HCPs.

> *"It was very isolating and made me doubt my symptoms and start to wonder if it was all in my head, many start to see you as a hypochondriac or believe you're lying about being unwell."* ***Female patient***

Table 1. *Misdiagnoses reported by patients (n=9)*

Neurology	Gastroenterology	Cardiology	ENT
Neuropathy Growing pains Migraines TIA	Gastric ulcer IBS	Ischaemic heart disease LVH	Deafness Vestibular neuronitis

Rheumatology	Cognitive/psychology	Other
Rheumatoid arthritis	Anxiety ASD RSD Global development delay	Anaphylaxis Chronic fatigue syndrome Raynaud's Fibromyalgia

ASD: autism spectrum disorder; ENT: ear, nose, and throat doctor (otorhinolaryngologists); IBS: irritable bowel syndrome; LVH: left ventricular hypertrophy; RSD: rejection sensitive dysphoria; TIA: transient ischaemic attack

Unmet educational needs in diagnosis identified by experts

PRIMARY CARE

Experts felt medical education is needed for primary care physicians who are the first point of contact with patients' first symptoms. Diagnosis would improve with appropriate and timely referrals by primary care physicians to a specialist with more knowledge when they are not able to identify a cause for a symptom.

CHALLENGES:

- Non-specific symptoms with common causes are unlikely to prompt further investigation and primary care physicians will optimise management of symptoms within practice before considering referral to a specialist
- Many patients are not referred until symptoms become severe, they experience a clinical event or Fabry-related organ damage has occurred

SPECIALISTS

Awareness of Fabry has improved in recent years which has led to an increase in referrals to Fabry specialist centres. Study participants identified pain clinics, pathologists and nephrologists lacked awareness about symptoms.

CHALLENGES:

- Some specialties may not have the knowledge of Fabry disease required to make a diagnosis

KEY MEDICAL EDUCATION OPPORTUNITIES SUGGESTED BY EXPERTS

Educational seminars targeting primary care delivered by specialists and metabolic experts who have clinical experience with Fabry patients, raising awareness of **specific manifestations** related to their specialist field to better identify Fabry. Existing relationships between specialist departments and local primary care could facilitate training.

Education to be **tailored to individual specialties** (Table 2) focusing on signs and symptoms of Fabry encountered by each specialty and delivered through:

- **specialty-specific symposia**
- **web-based asynchronous teaching** to allow for wider dissemination of information
- **the medical curriculum**: medical students are more motivated to learn and have time for personal development
- **frequent updates** to include emerging research and best practice, and to be regularly repeated due to staff turnover. Integrated with education of other relevant conditions

Publication of **articles and case studies** related to specific symptoms of Fabry in journals with wide coverage would allow further reach to the whole medical community.

Table 2. *HCPs identified by participants to be targeted for medical education*

Primary care	Promote awareness of key or non-specific symptoms and provide training on recognising health patterns of rare disease
Pain clinics	Many Fabry patients are referred to pain clinics before diagnosis: promote awareness to ensure Fabry is considered as a possible cause for unexplained pain
Nephrologists	Information needed to support earlier diagnosis and treatment to prevent organ damage in patients experiencing milder renal issues
Pathologists	Promote awareness of histological indicators of Fabry in biopsy samples
Cardiologists	Reinforce LVH as a significant indication of Fabry and encourage cardiologists to identify a possible cause
Geneticists	Training on Fabry variants and how to accurately inform patients of their prognosis at diagnosis to avoid distress

Experts suggested content for medical education should include:

- **Key principles to learn about Fabry:**
  - Fabry is treatable
  - Women can suffer from Fabry
  - Patients may only experience one symptom
  - Referrals should be made for patients of any age and those without family history
- Tools to **educate HCPs to recognize patterns** suggesting a rare disorder: familial pattern, multiple common symptoms, common symptoms but uncommon for the patient's age, patients under the care of multiple specialists and information about what action to take when patterns have been identified
- **Educate on a holistic approach** to a patient's symptoms particularly when presentation is multisystemic

CONCLUSIONS

- **An early diagnosis can give patients more time to adjust to the challenges of living with a chronic condition, would allow treatment of early symptoms and the early diagnosis of family members.**
- **A multi-disciplinary medical education programme is needed to increase disease awareness and improve overall diagnosis in Fabry disease.**

References: 1. Germain DP. Fabry disease. *Orphanet J Rare Dis.* 2010;5:30. 2. Li X, et al. Fabry disease: Mechanism and therapeutics strategies. *Front Pharmacol.* 2022;13:1025740. 3. Besekar SM, et al. Fabry Disease and Its Management: A Literature Analysis. *Cureus.* 2023; 15(4):e37048. 4. Germain DP. Fabry disease. *Orphanet encyclopedia*, updated March, 2022. 5. Braun V, Clarke V. Reflecting on reflexive thematic analysis. *Qual Res Sport Exerc Health.* 2019; 11(4):589–97.

Acknowledgements: Chiesi Ltd. provided funding for Rare Disease Research Partners' (RDRP) support with data collection, analysis and medical writing for this poster. **Declaration:** This research was conducted in accordance with the British Healthcare Business Intelligence Association's Legal & Ethical Guidelines for Market Research. The survey study was non-interventional and all participants signed a consent form. XI-RD-2400001 Date of Preparation January 2024.