FABRY in Females

Understanding the need for improved diagnosis and management

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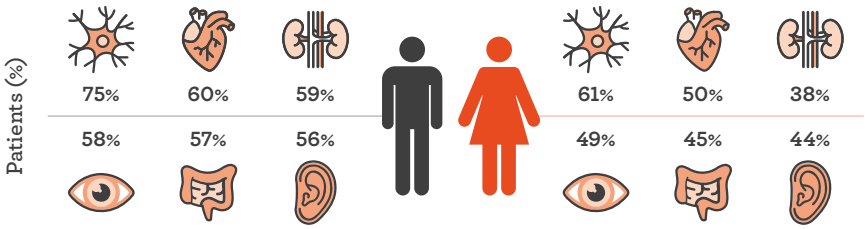
Fabry disease may cause significant symptoms, complications, and quality-of-life impairment in female patients

The course of Fabry disease in females is exceptionally variable

- Once considered only "carriers" of Fabry disease, females are now known to have disease courses ranging from mild to severe, with symptoms similar to those seen in males[1]
- Most are symptomatic, with a high percentage developing complications in vital organs
- Reasons for variability include:[2]
  - The lack of genotype–phenotype correlation, even within families[2,3]
  - The effects of X-chromosome inactivation, including the potential for skewed expression of the mutant *GLA* allele[4]

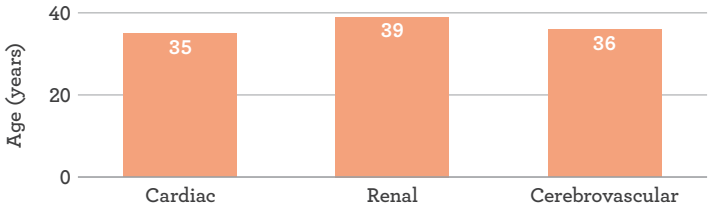
The majority of females with Fabry disease have symptoms in multiple organ systems

ORGAN SYSTEMS MOST FREQUENTLY INVOLVED IN UNTREATED MALES (n=699) AND FEMALES (n=754) WITH FABRY DISEASE[5]



Major organ involvement in females often begins in the 30s[5]

MEAN AGE AT ONSET OF ORGAN INVOLVEMENT IN FEMALES (n=754)[5]



"Females should be followed clinically and evaluated comprehensively to monitor for disease burden and progression." — Wilcox WR, et al, 2008[6]

Fabry disease may have profound psychosocial impacts on females[9-11]

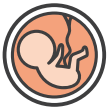
Females with Fabry disease may experience more than physical symptoms

Pain

The most common symptom in females at presentation is neurologic pain at a mean age of 14.2 years. Pain was most often described as burning and was comparable in intensity, location, and frequency between males and females.[6-8]

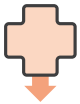
Depression

Depression is frequent and underreported in Fabry disease. In a study, about a third of women living with Fabry disease described feelings of depression, anxiety, fatigue, and frustration.[1-9]



Impact on childbearing

Women often report having negative feelings about passing Fabry disease on to their children. In one study, almost half of women of childbearing age reported being against bearing more children because of the disease.[9,10]

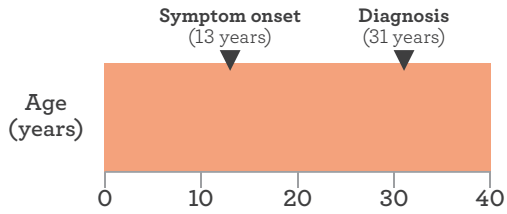


Health-related quality of life (HRQoL)

HRQoL scores in females with Fabry disease were significantly diminished relative to healthy controls in all eight measured domains and more similar to those in females with multiple sclerosis and rheumatoid arthritis.[11]

Diagnosis of Fabry disease in females may be delayed by a decade or more — even with a family history of Fabry disease[6]

MEDIAN AGE AT SYMPTOM ONSET AND DIAGNOSIS IN FEMALE PATIENTS[6]



84% of females in the study had a family history of Fabry disease[7]

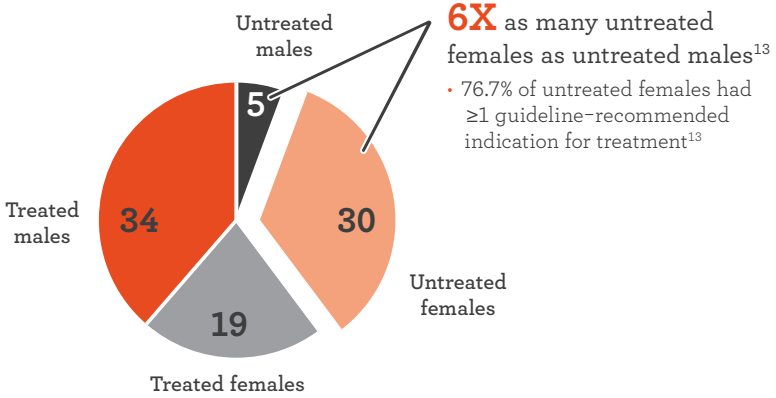
Age at diagnosis was available for 1018 of 1077 total female patients in the study, of whom 581 had data on age of symptom onset. Family history data are a percentage of total female patients in the study (906/1077).[6]

Females with Fabry disease may be undertreated

Females with Fabry disease may be undertreated relative to males despite having indications for Fabry-specific treatment[12]

- In a cohort of untreated Spanish females with Fabry disease[13]:
  - 20/29 (69.0%) considered themselves asymptomatic, even though
  - 22/32 (68.8%) had ≥1 Fabry disease symptom reported by their physicians

TREATMENT STATUS OF 88 MALE AND FEMALE SPANISH PATIENTS WITH FABRY DISEASE[12]



Data from a retrospective analysis of patients from 28 Spanish centers enrolled in a registry study.[12]

- In a retrospective study of 261 adult female patients with genetically confirmed Fabry disease from six centres in Germany, 34% of patients were untreated despite having an indication for Fabry-specific treatment[14]
  - 37 patients with VUS and polymorphisms were excluded from the analysis[14]
- Females with Fabry disease may be disadvantaged as a result of disease rarity, devalued status as "carriers," and gender[15]

"These observations urge the need for a more stringent implementation of the new European FD guidelines for females across centres and reevaluation of untreated females." — Lenders M, et al, 2016[14]

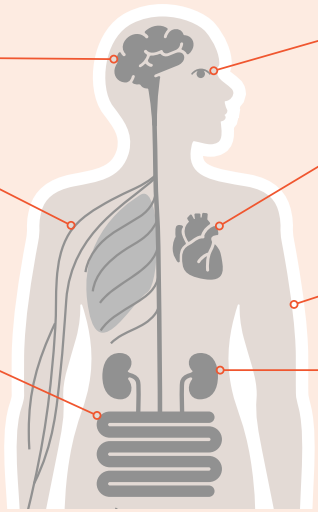
FD, Fabry disease; VUS, variant of unknown significance.

How can you improve diagnosis and management of females with Fabry disease?

Suspect → Test → Refer

Remember, females with Fabry disease may experience signs and symptoms in a wide variety of organ systems:

Suspect



NEUROPSYCHIATRIC[1]
Depression

NEUROLOGIC[1]
Stroke/transient ischaemic attack, pain, especially in hands/feet, chronic neuropathic pain

GASTROINTESTINAL[1]
Nausea, vomiting, diarrhoea, pain/bloating after eating, difficulty gaining weight

OCULAR/AUDITORY[1]
Corneal whirling, cataracts, hearing loss, tinnitus, vertigo

CARDIAC[1]
Arrhythmia, left ventricular hypertrophy, myocardial infarction, heart failure

DERMATOLOGICAL[1]
Angiokeratoma

RENAL[1]
Glomerulosclerosis, proteinuria, decreased renal function, kidney failure

Confirm your suspicion. Fabry testing is accessible and actionable.

Test

Genetic testing is essential in females since they may show α-galactosidase A (α-gal A) activity that is within the normal range

Panels with Fabry disease include:

- R335 Fabry disease
- R131 Hypertrophic cardiomyopathy
- R328 Progressive cardiac conduction disease
- R195 Proteinuric renal disease
- R257 Unexplained early onset ESRD
- R193 Cystic kidney disease

Visit the **National Genomic Test Directory** to find out more.

Positive result? Don't delay

Refer to an Inherited Metabolic Disease (IMD) centre.

Refer

To find your local IMD centre, visit amicuseducation.co.uk or scan the QR code

Fabry-specific treatment is recommended for all females with disease-related symptoms or evidence of organ involvement; treatment should commence when one of the following criteria are met:[16]

RECOMMENDATIONS FOR INITIATION OF FABRY-DISEASE-SPECIFIC TREATMENT IN FEMALES[16]

Organ system	Recommendation
Fabry-related renal disease	CKD stage 3: at least two consistent estimates or measured GFR over a minimum of six months CKD stage 2: at least three consistent estimates or measured GFR over at least 12 months with a GFR slope greater than age-related normal (0.8–1.0mL/year) Persistent proteinuria: if proteinuria is the only presentation, anti-proteinuria medications (ACEi/ARB) should be tried in the first instance for a minimum period of 12 months
Fabry-related cardiac disease	LV wall thickness >12 mm LV mass index by 2D echo / cMRI above normal for age Late gadolinium enhancement on cMRI
General symptoms of Fabry disease	Uncontrolled pain or gastrointestinal symptoms leading to a need to alter lifestyle or which significantly interferes with quality of life

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; CKD, chronic kidney disease; cMRI, cardiac magnetic resonance imaging; GFR, glomerular filtration rate; LV, left ventricle

The clinical hetereogeneity of Fabry disease mandates an individualised approach to patient care that reflects the patient's gender along with other personal, disease, and family characteristics[17]

Clinical vigilance and regular monitoring are vital

Even if no apparent symptoms are present at baseline or at follow-up appointments, complications involving the organs can still occur. Therefore, routine assessments and monitoring are key in Fabry disease management.[17]

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