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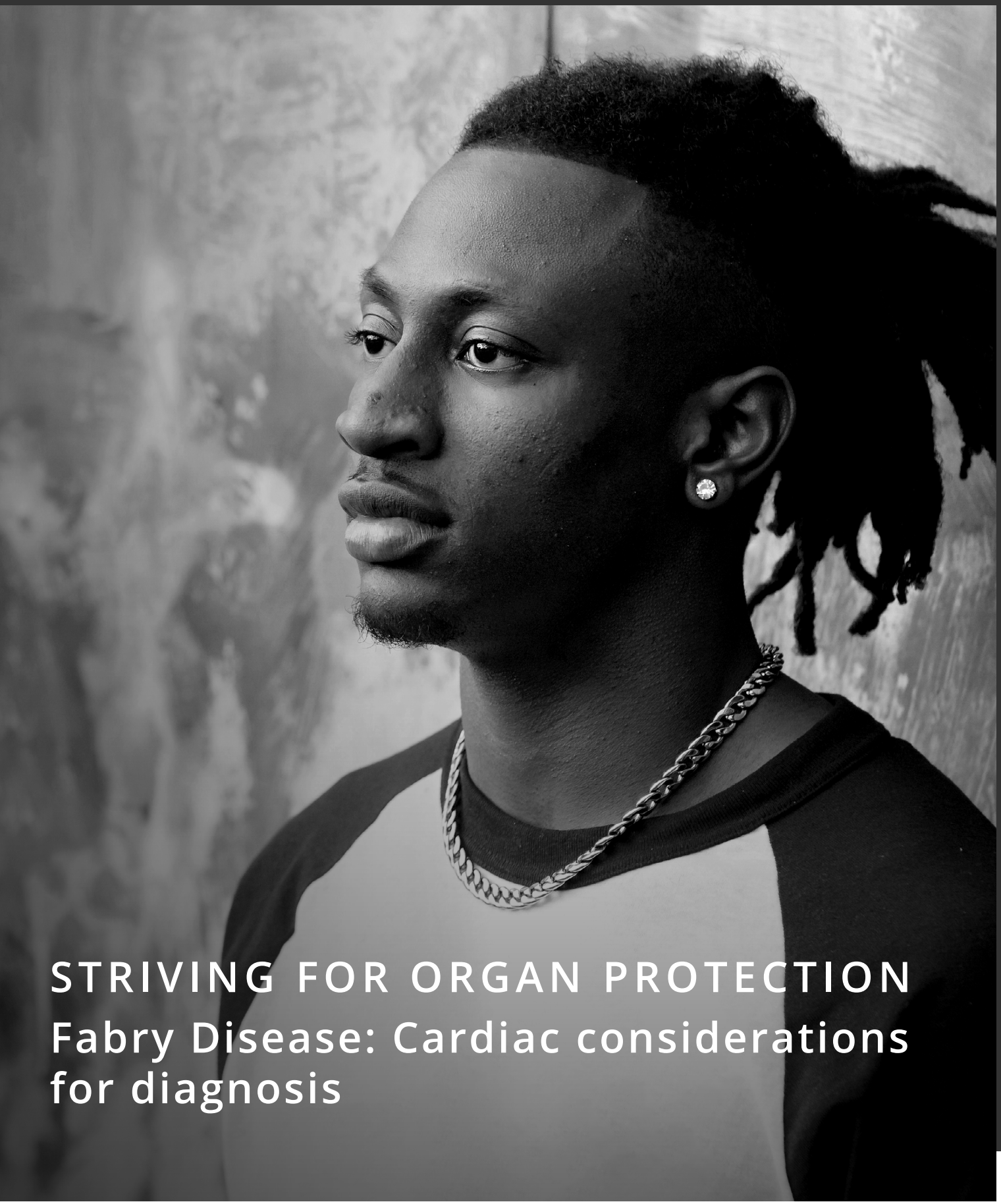

STRIVING FOR ORGAN PROTECTION

Fabry Disease: Cardiac considerations for diagnosis

FABRY DISEASE: A DIAGNOSTIC CHALLENGE

Fabry disease is one of the most common lysosomal storage disorders and is **caused by variants in the *GLA* gene**, which is located on the X chromosome **and encodes the enzyme alpha-galactosidase A (α-Gal A)**.[1-3] The disease is a progressive, potentially life-threatening, multisystemic condition[3,4] whereby the deficiency in the enzymatic activity of α-Gal A leads to accumulation of the glycosphingolipids globotriaosylceramide (Gb_3) and globotriaosylsphingosine (lyso-Gb_3) at a cellular level. Accumulation of these glycosphingolipids causes a wide range of clinical manifestations and can ultimately lead to organ damage.[3-8]

Fabry disease is rare, affecting approximately 1 in 40,000 males[8] and 1 in 20,000 females,[9] and can commonly be misdiagnosed. In an article published in 2004, of 366 patients enrolled in the Fabry Outcome Survey (FOS*), **25% of patients had previously been misdiagnosed**.[4]

The clinical presentation of Fabry disease is phenotypically heterogeneous. Symptoms are non-specific and can range from the classical Fabry disease phenotype, where multiple organs are affected, to involvement of only one organ, as in late-onset Fabry disease.[10,11]

*The FOS is an ongoing patient registry available to patients with Fabry disease, initiated and funded in 2001 by Shire (now part of Takeda) and now continued and funded by Takeda.[12]

PHENOTYPES OF FABRY DISEASE

Fabry disease may present as classical or late-onset disease, with the disease course differing between patients with either phenotype. The prevalence of signs and symptoms, and age at onset of disease manifestations can also vary.[13]

CLASSICAL FABRY DISEASE

- Classical Fabry disease is characterised by **no or little (<1%) α-Gal A enzyme activity** due to variants in the *GLA* gene.[3,14,15]
- The **initial signs** of classical Fabry disease typically manifest in **childhood**.[16]
  - The earliest clinical symptoms include acroparaesthesia, angiokeratomas, heat intolerance, cornea verticillata and gastrointestinal complications.[16]
  - As the disease progresses, complications may include progressive renal failure, hypertrophic cardiomyopathy (HCM), neurological complications and cerebrovascular disease, ultimately leading to reduced life expectancy.[16]

LATE-ONSET FABRY DISEASE

- Late-onset Fabry disease is characterised by **residual (⩾0.5–30%) enzymatic activity levels of α-Gal A** due to variants in the *GLA* gene.[15,17,18]
- Patients may have few or none of the hallmark symptoms associated with classical Fabry disease and **only one or few organs may be affected**.[10,19]
  - Typical cardiac and renal symptoms may only become present later in life (fourth to eighth decade)[15,20-22] whereas cerebrovascular symptoms, such as cryptogenic strokes, present commonly in young adults.[23,24]

Some patients with late-onset Fabry disease may develop a cardiac phenotype. These patients are essentially asymptomatic during most of their lives, and do not develop the early manifestations associated with classical Fabry disease. Most patients are only diagnosed after the onset of cardiac manifestations.[8]

THE HEART IN FABRY DISEASE

Cardiac involvement is common in Fabry disease, and was reported in 69% of 201 male patients and 65% of 165 female patients enrolled in the FOS in 2004.[4] In some cases, such as in patients with late-onset Fabry disease, the manifestations may be limited to the heart.[8,25]

- Cardiac symptoms in Fabry disease may include: atrial fibrillation; bradycardia; cardiac fibrosis; HCM; chronotropic incompetence; heart failure; left ventricular hypertrophy (LVH); reduced exercise tolerance; sudden cardiac death; syncope; and ventricular tachycardia.[15]
- The primary manifestation of cardiac involvement in Fabry disease is the progressive thickening of the heart walls, which may be expressed as HCM.[26]
- Dyspnoea and chest pain, which are clinically important symptoms of cardiac manifestations in patients with Fabry disease, may be related to LVH.[25]

Cardiac involvement is one of the major causes of morbidity and mortality in patients with Fabry disease.[4,25,27] Of 42 patients enrolled in the FOS whose deaths were reported between 2001 and 2007, cardiac disease was the main cause of death (where known) in both male (34%) and female (57%) patients.[13]

TWO KEY CARDIAC FEATURES IN FABRY DISEASE

Hypertrophic cardiomyopathy (HCM)

- HCM is characterised by unexplained LVH in the absence of secondary causes of LVH, such as hypertension and aortic stenosis.[28]
- The disease is a monogenic disorder caused by variants in genes that encode the protein components of the cardiac sarcomere.[29]
- In patients with Fabry disease, accumulation of Gb_3 occurs within many cell types within the heart, and may induce progressive lysosomal and cellular malfunctioning leading to the activation of signalling pathways linked to hypertrophy, apoptosis, necrosis and fibrosis.[25]
- In one study of 151 patients with unexplained HCM, 5.3% were identified as having variants in the *GLA* gene.[30]

Left-ventricular hypertrophy (LVH)

- LVH is an early cardiac abnormality in Fabry disease,[31] and is typically concentric in patients with Fabry disease but can also exhibit asymmetrical shapes on an echocardiogram.[26]
- LVH in Fabry disease is progressive and typically occurs earlier in men than in women.[32]
- Progression of hypertrophy may lead to left-ventricular (LV) dysfunction with localised thinning of the base of the LV posterior wall.[33]
- Of 752 patients enrolled in the FOS between 2001 and 2005, LVH was observed in[34]:
  - 33.1% of 124 untreated males with a mean (standard deviation [SD]) age at onset of 42.0 (14.5) years
  - 21.3 % of 254 untreated females with a mean (SD) age at onset of 50.1 (12.0) years.

In a screening study of 4054 males with HCM or LVH, the prevalence of variants in the *GLA* gene related to Fabry disease was 0.94% (n=38).[35]

THE ROLE OF THE CARDIOLOGIST IN FABRY DISEASE

Due to the high prevalence of cardiac involvement in patients with Fabry disease, cardiologists are vital in the screening and diagnosis of the disease.[36] Cardiologists are recommended to maintain an awareness of Fabry disease.[37]

'Red flags' of Fabry disease for cardiologists may include[38,39]:

- Males aged ⩾30 years and females aged ⩾40 years presenting with unexplained LVH
- Cerebrovascular disease, neurological disease or renal disease
- Gastrointestinal symptoms, chronic fatigue, chronic limb pain, hearing impairment, and eye or skin problems
- **Using an electrocardiogram or 48-hour Holter**: short or prolonged PR interval, intraventricular conduction abnormalities or need for permanent pacemaker, atrioventricular block or decreased heart rate variability, presence of arrhythmias
- **Extracardiac abnormalities**: kidney dysfunction, stroke or transient ischaemic attack, angiokeratomas and corneal verticillata
- **Using echocardiography**: evidence of concentric LVH (13–22 mm), non-obstructive HCM abnormal infero-lateral longitudinal strain, right ventricular hypertrophy or thinning of the basal infero-lateral LV wall
- **Using cardiac magnetic resonance imaging**: evidence of postero-lateral late gadolinium enhancement, reduction in non-contrast T1 signal or elevated T2
- Decreased glomerular filtration rate and evidence of proteinuria or high-sensitivity troponin
- **Family history** of Fabry disease, cryptogenic stroke or severe kidney failure.

If you suspect that your patient has Fabry disease, it is recommended that you:

- Carry out a biochemical or genetic analysis.[17]

If Fabry disease is confirmed in your patient, you may:

- Refer the patient to an appropriate specialist[15]
- Recommend pedigree analysis is performed to determine whether other family members may be affected.[40,41]

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