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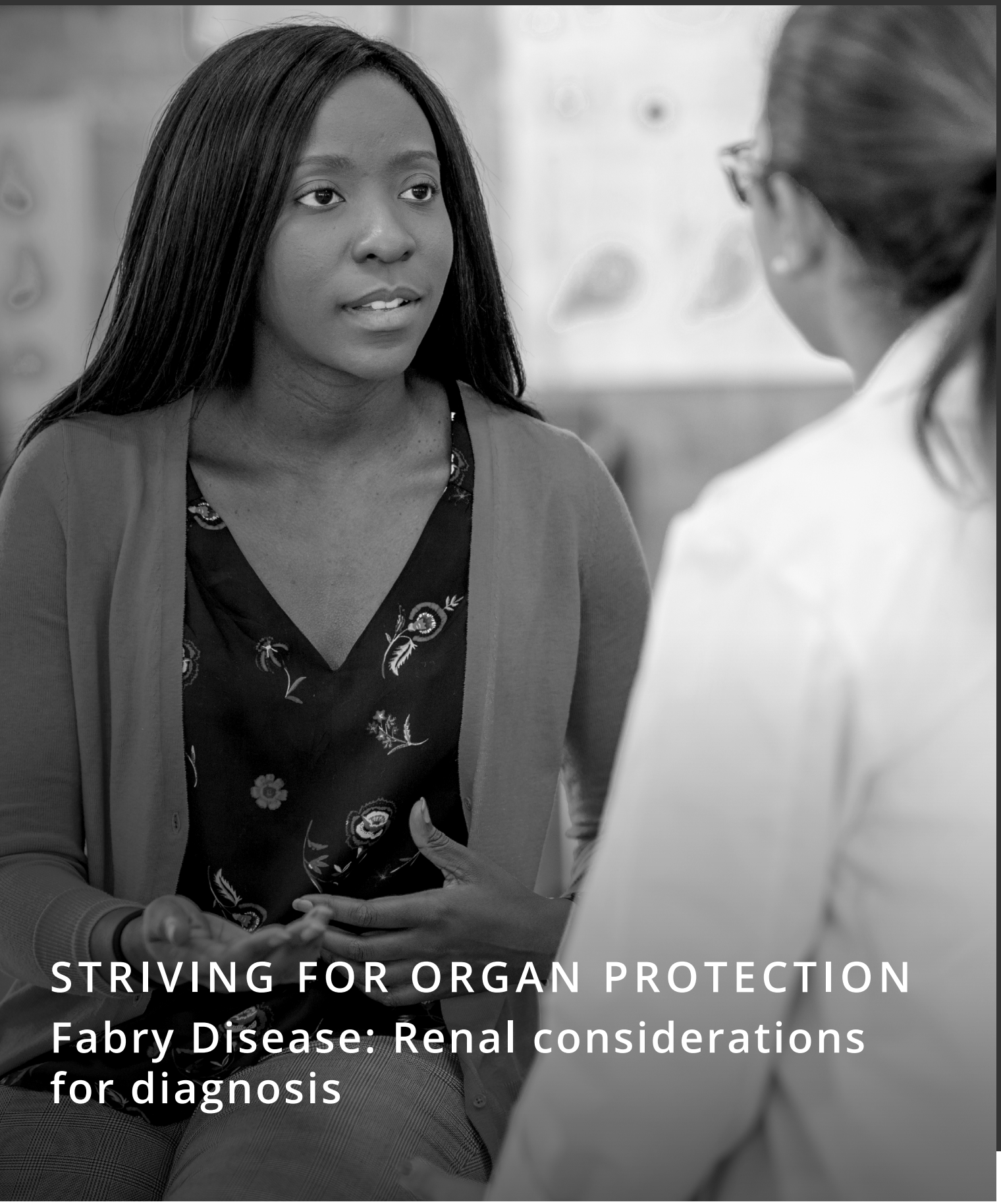

STRIVING FOR ORGAN PROTECTION

Fabry Disease: Renal 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 patients. 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.[5,13]

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, 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 renal and cardiac 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 renal phenotype. These patients do not experience any of the early-onset signs and symptoms of classical Fabry disease and, instead, experience renal complications in early adulthood.[22]
  - Levels of α-Gal A enzyme activity in leukocytes typically range from approximately 1–5% of normal mean values in male patients with the renal variant of Fabry disease.[22] Accumulation of Gb_3 is observed in all glomerular cells in these patients, including within the capillary endothelium.[25]

THE KIDNEYS IN FABRY DISEASE

- Data from December 2007 from 1453 adult patients with Fabry disease (male, n=699; female, n=754) from the FOS indicated that renal symptoms were experienced by 59% of male patients and 38% of female patients with a mean (standard deviation) age at onset of 32.6 (12.7) years and 38.5 (16.2) years, respectively.[13]
- The earliest functional manifestation of renal disease in patients with Fabry disease may be urinary concentration defects, leading to polyuria and nocturia.[26] Referral to a nephrologist is typically initiated upon the development of proteinuria.[27] This symptom may develop during teenage years and become more frequent once patients are aged 20–30 years.[26]
- The renal manifestations of Fabry disease, such as proteinuria or a decreased glomerular filtration rate, occur early in the disease course[27] and are considered 'red flags' for the disease.[28]
- Progression of renal manifestations can lead to chronic kidney disease and end-stage renal disease in almost all male and some female patients with Fabry disease, when they are aged 40–60 years.[22,27]
  - An analysis of kidney function of adults enrolled in the Fabry Registry* in July 2009 revealed that patients with overt proteinuria lose renal function more rapidly compared with those with little or no proteinuria. The results also suggested that proteinuria is the most important predictor of renal disease progression in patients with Fabry disease.[29]

In a study of 23,954 males screened at haemodialysis clinics, the prevalence of variants of the *GLA* gene related to Fabry disease was 0.21%. Similarly, among 2031 screened males receiving a renal transplant, the prevalence of Fabry disease-related *GLA* gene variants was 0.24%.[31]

*The Fabry Registry is an ongoing, international multicentre, observational programme initiated in 2001, and funded and maintained by Sanofi Genzyme, which tracks the routine clinical outcomes for patients with Fabry disease.[30]

CARDIO-RENAL SYNDROME (CRS-5)

- In patients with Fabry disease, clinical manifestations in the kidney and/or heart can lead to acute or chronic organ cross-talk and the development of CRS-5, which comprises simultaneous development of kidney injury and cardiac dysfunction.[32]
- Cross-talk between the kidney and heart may eventually lead to end-stage renal and cardiac involvement. Many patients with Fabry disease and end-stage renal involvement may become dependent on dialysis.[32]
- For patients with Fabry disease and CRS-5, kidney and cardiac dysfunction may develop slowly until a threshold is reached, leading to complete organ decompensation. The sequence of organ involvement and time to development of CRS-5 is dependent upon the acuity and nature of the underlying disease and its influence on renal and cardiac functioning.[32]
- Cardio-renal involvement is a potential disease marker for patients with Fabry disease and is associated with an increased risk of mortality.[33]

THE ROLE OF THE NEPHROLOGIST

- The renal manifestations of Fabry disease, such as proteinuria or a decreased glomerular filtration rate (GFR), occur early in the disease course and affect many patients. End-stage renal disease in patients with Fabry disease can occur due to progression of these symptoms and deterioration of renal function over time.[27]
- Some patients with late-onset Fabry disease may develop chronic kidney disease, which may manifest as persistent albuminuria or proteinuria or estimated GFR <90 mL/min/1.73m^2. In accordance with the European Renal Best Practice guidelines, patients with unexplained chronic kidney disease are recommended to be assessed by a nephrologist and screened for Fabry disease if they[34,35]:
  - Are male, aged <50 years, even in the absence of a family history of Fabry disease
  - Are female, at any age, as Fabry disease onset can occur later in females compared with males
  - Recollect other non-renal signs of Fabry disease such as acroparaesthesia, family history, heat or cold intolerance and hypohidrosis.
- For patients with variants in the *GLA* gene presenting with chronic kidney disease and no other characteristic features of Fabry disease, a kidney biopsy may be necessary to confirm nephropathy related to Fabry disease. For these patients, 'red flags' for Fabry disease include high levels of Gb_3, which may lead to a 'Maltese cross sign' in the urine.[36] In urinalysis, 'Maltese cross signs' are cholesterol-rich fat droplets, which have a cruciform appearance by polarised light, in the urine of patients with Fabry disease due to aggregation of glycosphingolipids.[37]
- Using **electron microscopy imaging** may show the presence of characteristic **lysosomal inclusions** specific to Fabry disease in the kidney biopsy.[38]
  - The lysosomal inclusions, which are known as 'zebra bodies', can be observed in lysosomes of cells, primarily within the glomerular and distal tubule, due to deposition of Gb_3.[35,38]
  - The lysosomal inclusions must be present in the absence of medication use that may induce similar inclusion patterns.[39]

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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