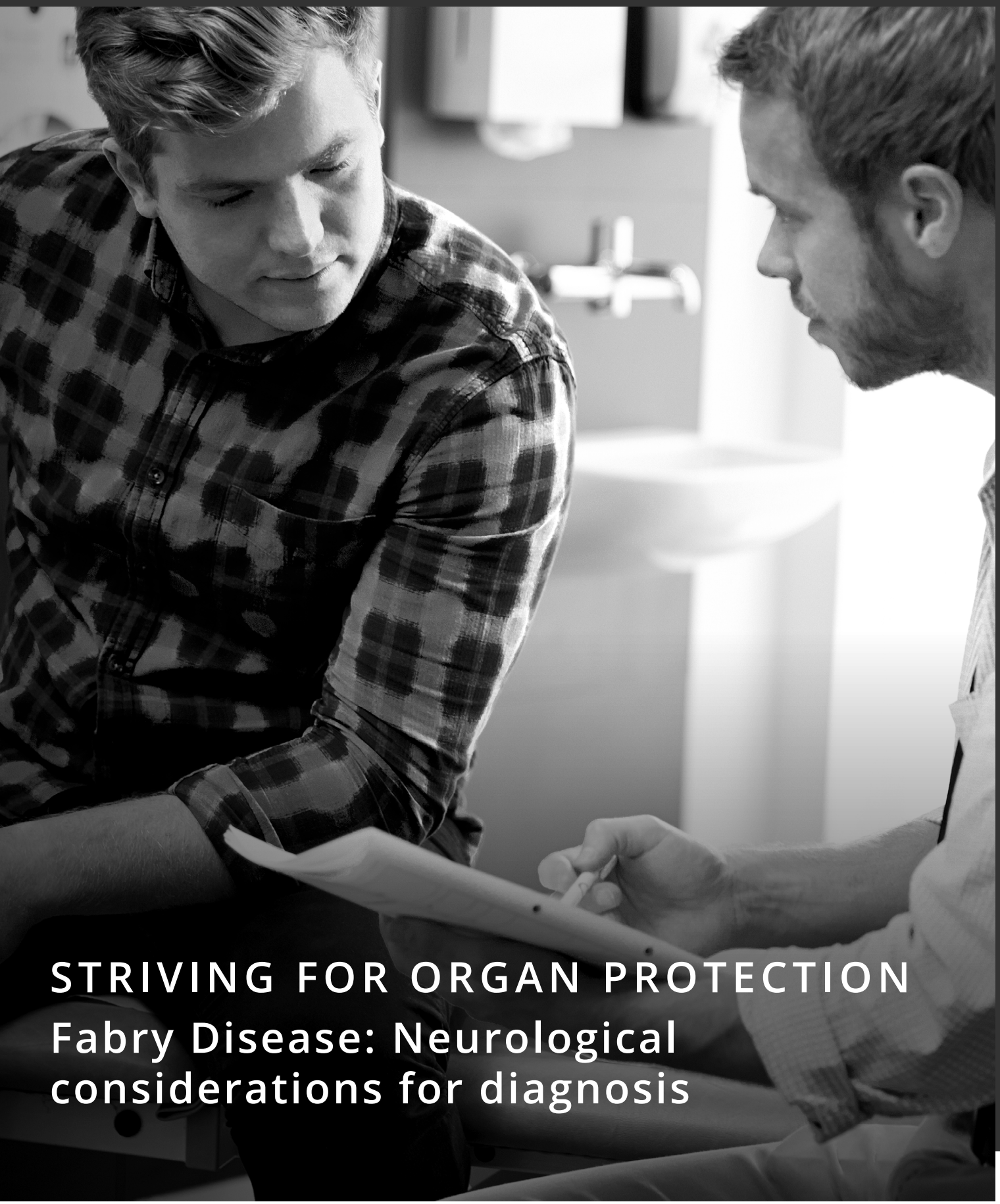
FABRY INSTITUTE
an educational platform developed and funded by Takeda



STRIVING FOR ORGAN PROTECTION

Fabry Disease: Neurological 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.[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 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]
  - Cerebrovascular complications are a major cause of early morbidity and mortality in patients with Fabry disease.[25] Young adults presenting with a cerebrovascular event in association with myocardial infarction and renal dysfunction are recommended to be considered for Fabry disease.[26]
  - In patients with Fabry disease, ischaemic stroke and transient ischaemic attacks (TIAs) are the most prevalent cerebrovascular events and occur at an earlier age than is usual in the general population.[25]

THE CENTRAL NERVOUS SYSTEM IN FABRY DISEASE

- Data from December 2007 from 1453 adult patients with Fabry disease from the FOS indicated that the most common overall clinical manifestations were neurological, experienced by 75% of 699 male patients and 61% of 754 female patients with a mean (standard deviation) age at onset of 15.1 (15.0) years and 20.9 (17.9) years, respectively.[13]
- Neurological signs and symptoms in Fabry disease may include: acroparaesthesia; altered temperature sensitivity[27]; ataxia[23]; brain abnormalities, as shown by magnetic resonance imaging (MRI); cognitive problems; diplopia[28]; dizziness; dysarthria[23]; gastoparesis[29]; generalised pain[27]; hearing loss[28]; hypohidrosis[30]; migraine or recurrent headache[28]; nausea[23]; neuropathic pain[30]; nystagmus[23]; orthostatic intolerance[29]; stroke, typically occurring at an early age[31]; TIA[32]; and vasomotor impairment.[29]
- The neurological manifestations of Fabry disease involve the peripheral and central nervous systems, and are attributed to Gb_3 accumulation within Schwann cells and dorsal root ganglia, and deposition within neurons in the central nervous system. Accumulation of Gb_3 is likely to lead to abnormal control of vessels, secondary to endothelial dysfunction.[30]

STROKE: A KEY NEUROLOGICAL FEATURE IN FABRY DISEASE

- Fabry disease is an important cause of young stroke and cryptogenic stroke, despite its rarity.[33] Cerebral vasculopathy, with an increased incidence of stroke, is one of the key neurological manifestations in patients with Fabry disease.[30]
  - Data from 2005 of 688 patients enrolled in the FOS indicated that 13.2% of patients had experienced an ischaemic stroke or TIA, typically at an early age.[31]
- For many patients with Fabry disease, renal or cardiac disease manifestations are not evident prior to their first stroke, meaning Fabry disease may not be diagnosed until this event.[34]
  - Data from the Fabry Registry* in 2007 indicated that 38.3% of 52 female patients and 50.0% of 86 male patients experienced their first stroke before they were diagnosed with Fabry disease.[34]
- Stroke can be a cause of premature death in patients with Fabry disease, as reported in 45.2% of 42 patients with Fabry disease who died and were enrolled in the FOS in 2007.[13]

Screening of 3904 male patients with primarily cryptogenic or ischaemic strokes revealed a prevalence of *GLA* gene variants related to Fabry disease of 0.13% (n=5).[36]

*The Fabry Registry is an ongoing, international multicentre, observational programme initiated, funded and maintained in 2001 by Sanofi Genzyme, which tracks the routine clinical outcomes for patients with Fabry disease.[35]

THE ROLE OF THE NEUROLOGIST

- Neurologists can aid an early diagnosis of Fabry disease and document neurological involvement associated with the disease.[32]
- It is advised that neurologists be aware that acroparaesthesia could be an early indicator of Fabry disease in children and adolescents.[27,32] Acroparaesthesia or pain crisis is characterised by chronic or episodic burning sensation in the palms of the hands or soles of the feet.[6]
- Fabry disease may also be an underlying cause of TIA or stroke and is recommended to be considered in patients aged 40–50 years.[32] It is advised that neurologists be mindful that these patients may also present with one or more features as angiokeratoma, anhidrosis or hypohidrosis, cornea verticillata, intolerance to extreme temperatures and proteinuria.[32]
- All patients with cryptogenic stroke aged 18–55 years are recommended to be screened for Fabry disease.[23]
- In some cases, Fabry disease can be misdiagnosed as multiple sclerosis (MS), because patients with either disease can present with pain and white matter lesions on an MRI.[37] In one study of data from Fabry disease centres in Germany, 11 of 187 patients (5.9%) initially diagnosed with MS were found to have Fabry disease. Diagnosis of Fabry disease occurred, on average, 8.2 years after diagnosis of MS.[38]
- To aid neurologists' diagnosis of Fabry disease in patients initially diagnosed with MS[37]:
  - Clinical manifestations in different organs including the kidney, heart and eye should be evaluated to support the diagnosis of Fabry disease, particularly in males.
  - Fabry disease should be considered in all cases of presumptive MS with atypical clinical presentation and atypical MRI findings, and in the absence of oligoclonal bands in cerebrospinal fluid.
  - Determining a family history of Fabry disease or its clinical manifestations is recommended, as this is critical in selecting the appropriate treatment.

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.[39,40]

REFERENCES

1. Platt FM, d'Azzo A, Davidson BL, et al. Lysosomal storage diseases. Nat Rev Dis Primers 2018; 4: 27.
2. Meikle PJ, Hopwood JJ, Clague AE, et al. Prevalence of lysosomal storage disorders. JAMA 1999; 281: 249-254.
3. Vardarli I, Rischpler C, Herrmann K, et al. Diagnosis and screening of patients with Fabry disease. Ther Clin Risk Manag 2020; 16: 551-558.
4. Mehta A, Ricci R, Widmer U, et al. Fabry disease defined: baseline clinical manifestations of 366 patients in the Fabry Outcome Survey. Eur J Clin Invest 2004; 34: 236-242.
5. Felis A, Whitlow M, Kraus A, et al. Current and investigational therapeutics for Fabry disease. Kidney Int Rep 2019; 5: 407-413.
6. Schiffmann R, Hughes DA, Linthorst GE, et al. Screening, diagnosis, and management of patients with Fabry disease: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. Kidney Int 2017; 91: 284-293.
7. Desnick RJ, Ioannou YA, Eng CM. α-galactosidase A deficiency: Fabry disease. In: Scriver C, Beaudet A, Sly W, et al., eds. *The Online Metabolic and Molecular Bases of Inherited Disease*. 8th Edition. New York, NY: McGraw-Hill, 2001, Chapter 150, pp3733-3774.
8. Brady RO, Gal AE, Bradley RM, et al. Enzymatic defect in Fabry's disease. Ceramidetrihexosidase deficiency. N Engl J Med 1967; 276: 1163-1167.
9. Laney DA, Fernhoff PM. Diagnosis of Fabry disease via analysis of family history. J Genet Couns 2008; 17: 79-83.
10. Arends M, Wanner C, Hughes D, et al. Characterization of classical and nonclassical Fabry disease: a multicenter study. J Am Soc Nephrol 2017; 28: 1631-1641.
11. Ries M, Gal A. Genotype–phenotype correlation in Fabry disease. In: Mehta A, Beck M, Sunder-Plassmann G, eds. *Fabry Disease: Perspectives from 5 Years of FOS*. Oxford, UK: Oxford PharmaGenesis, 2006, Chapter 34.
12. ClinicalTrials.gov. Fabry Outcome Survey (FOS). Available at: https://clinicaltrials.gov/ct2/show/NCT03289065. Accessed August 2021.
13. Mehta A, Clarke JTR, Giugliani R, et al. Natural course of Fabry disease: changing pattern of causes of death in FOS – Fabry Outcome Survey. J Med Genet 2009; 46: 548-552.
14. Clarke JT. Narrative review: Fabry disease. Ann Intern Med 2007; 146: 425-433.
15. Ortiz A, Germain DP, Desnick RJ, et al. Fabry disease revisited: management and treatment recommendations for adult patients. Mol Genet Metab 2018; 123: 416-427.
16. Ellaway C. Paediatric Fabry disease. Transl Pediatr 2016; 5: 37-42.15.
17. Michaud M, Mauhin W, Belmatoug N, et al. When and how to diagnose Fabry disease in clinical pratice. Am J Med Sci 2020; 360: 641-649.
18. Duro G, Zizzo C, Cammarata G, et al. Mutations in the *GLA* gene and lysoGb$_3$: is it really Anderson-Fabry disease? Int J Mol Sci 2018; 19: 3726.
19. Germain DP. Fabry disease. Orphanet J Rare Dis 2010; 5: 30.
20. Germain DP, Brand E, Burlina A, et al. Phenotypic characteristics of the p.Asn215Ser (p.N215S) *GLA* mutation in male and female patients with Fabry disease: a multicenter Fabry Registry study. Mol Genet Genomic Med 2018; 6: 492-503.
21. Patel V, O'Mahony C, Hughes D, et al. Clinical and genetic predictors of major cardiac events in patients with Anderson-Fabry disease. Heart 2015; 101: 961-966.
22. Oliveira JP, Ferreira S. Multiple phenotypic domains of Fabry disease and their relevance for establishing genotype–phenotype correlations. Appl Clin Genet 2019; 12: 35-50.
23. Rolfs A, Böttcher T, Zschiesche M, et al. Prevalence of Fabry disease in patients with cryptogenic stroke: a prospective study. Lancet 2005; 366: 1794-1796.
24. Bogousslavsky J, Pierre P. Ischemic stroke in patients under age 45. Neurol Clin 1992; 10: 113-124.
25. Kolodny E, Fellgiebel A, Hilz MA, et al. Cerebrovascular involvement in Fabry disease. Stroke 2015; 46: 302-313.
26. Bokhari SRA, Zulfiqar H, Hariz A. Fabry disease. In: Abai B, Abu-Ghosh A, Acharya AB, et al., eds. *StatPearls* [Internet]. Treasure Island, FL: StatPearls Publishing, 2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK435996/.
27. Ramaswami U, Whybra C, Parini R, et al. Clinical manifestations of Fabry disease in children: data from the Fabry Outcome Survey. Acta Paediatr 2006; 95: 86-92.
28. Buechner S, Moretti M, Burlina AP, et al. Central nervous system involvement in Anderson-Fabry disease: a clinical and MRI retrospective study. J Neurol Neurosurg Psychiatry 2008; 79: 1249-1254.
29. Biegstraaten M, van Schaik IN, Wieling W, et al. Autonomic neuropathy in Fabry disease: a prospective study using the Autonomic Symptom Profile and cardiovascular autonomic function tests. BMC Neurol 2010; 10: 38.
30. Schiffmann R, Moore DF. Neurological manifestations of Fabry disease. In: Mehta A, Beck M, Sunder-Plassmann G, eds. *Fabry Disease: Perspectives from 5 Years of FOS*. Oxford, UK: Oxford PharmaGenesis, 2006, Chapter 22.
31. Ginsberg L. Nervous system manifestations of Fabry disease: data from FOS - the Fabry Outcome Survey. In: Mehta A, Beck M, Sunder-Plassmann G, eds. *Fabry Disease: Perspectives from 5 Years of FOS*. Oxford, UK: Oxford PharmaGenesis, 2006, Chapter 23.
32. Salviati A, Burlina AP, Borsini W. Nervous system and Fabry disease, from symptoms to diagnosis: damage evaluation and follow-up in adult patients, enzyme replacement, and support therapy. Neurol Sci 2010; 31: 299-306.
33. Mishra V, Banerjee A, Gandhi AB, et al. Stroke and Fabry disease: a review of literature. Cureus 2020; 12: e12083.
34. Sims K, Politei J, Banikazemi M, et al. Stroke in Fabry disease frequently occurs before diagnosis and in the absence of other clinical events: natural history data from the Fabry Registry. Stroke 2009; 40: 788-794.
35. ClinicalTrials.gov. Fabry Disease Registry & Pregnancy Sub-registry. Available at: https://clinicaltrials.gov/ct2/show/NCT00196742. Accessed August 2021.
36. Doheny D, Srinivasan R, Pagant S, et al. Fabry disease: prevalence of affected males and heterozygotes with pathogenic *GLA* mutations identified by screening renal, cardiac and stroke clinics, 1995–2017. J Med Genet 2018; 55: 261-268.
37. Colomba P, Zizzo C, Alessandro R, et al. Fabry disease and multiple sclerosis misdiagnosis: the role of family history and neurological signs. Oncotarget 2018; 9: 7758-7762.
38. Böttcher T, Rolfs A, Tanislav C, et al. Fabry disease – underestimated in the differential diagnosis of multiple sclerosis? PLoS One 2013; 8: e71894.
39. Laney DA, Bennett RL, Clarke V, et al. Fabry disease practice guidelines: recommendations of the National Society of Genetic Counselors. J Genet Couns 2013; 22: 555-564.
40. Gal A, Hughes DA, Winchester B. Toward a consensus in the laboratory diagnostics of Fabry disease – recommendations of a European expert group. J Inherit Metab Dis 2011; 34: 509-514.

FABRY INSTITUTE
an educational platform developed and funded by Takeda