Know Fabry Disease

Silently Progressive.

Increasingly Debilitating.

Often Life-Threatening.

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Know Fabry Disease

Fabry disease is a multisystemic genetic disorder that ultimately results in irreversible, potentially life-threatening disease of the kidney, heart, and brain.

Affects Men, Women, and Children

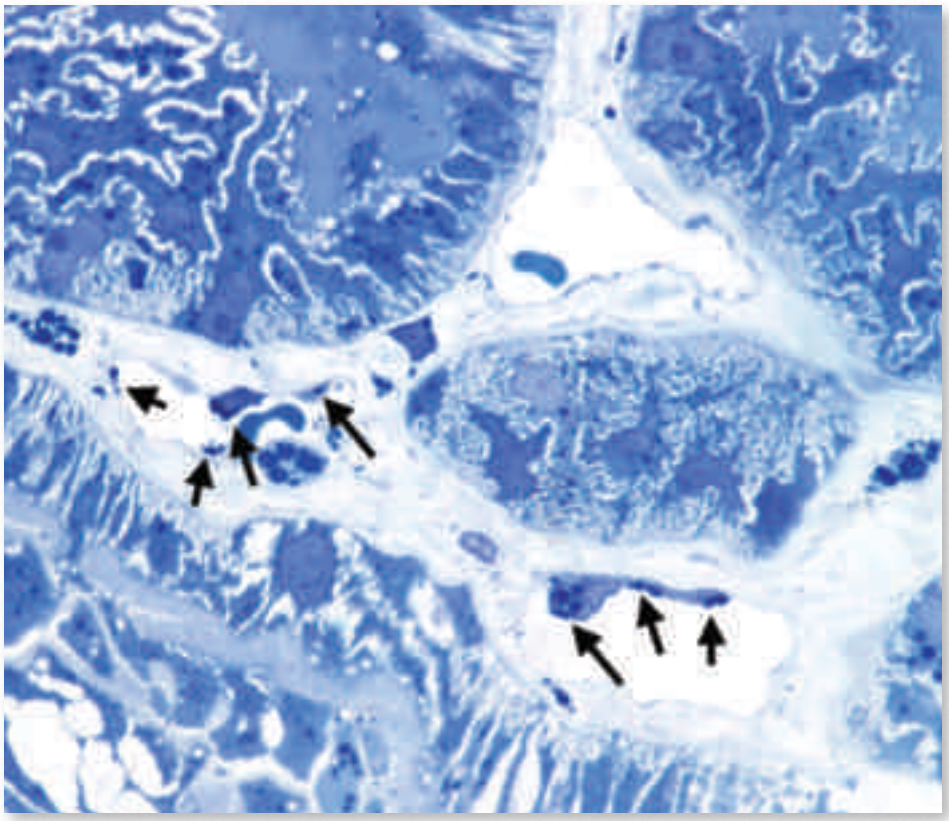
- Fabry disease affects both males and females of all ethnicities and ages.
- Women, in particular, can experience significant organ damage in the absence of overt symptomatology.

Substrate Accumulation and Resulting Organ Dysfunction

Fabry disease is characterized by the progressive and unrelenting cellular accumulation of a lipid substrate called globotriaosylceramide (or GL-3).

- Caused by deficiency of the lysosomal enzyme alpha-galactosidase A (or α-GAL), which usually metabolizes GL-3 and keeps it from accumulating.
- Without enough of this essential enzyme, GL-3, accumulates in the lysosomes of most cell types.

Pervasive accumulation of GL-3 eventually causes tissue ischemia and fibrosis.



GL-3 inclusions (arrows) in the renal capillary endothelium.

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Pathology at a Glance

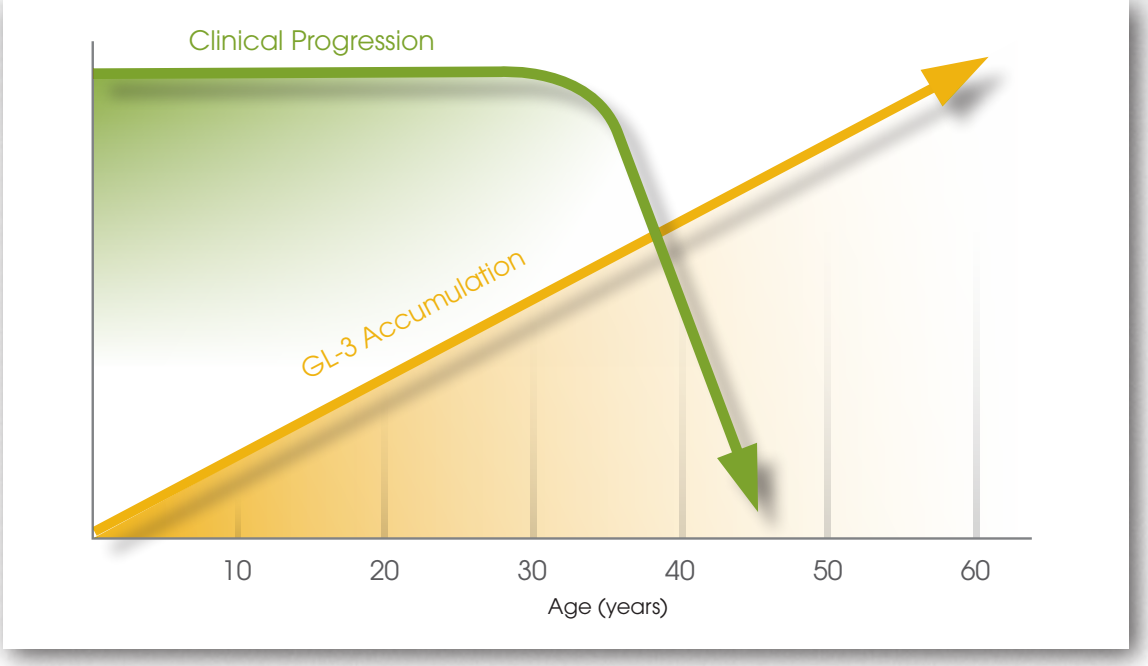
GL-3 accumulates in tissues throughout the body, triggering a cascade of manifestations that begin with pain, gastrointestinal problems and quality of life issues, and lead to life-threatening complications involving the kidney, heart, and brain.

Enzyme deficiency leads to progressive cellular globotriaosylceramide **(GL-3) substrate accumulation**

Pervasive GL-3 accumulation causes **ischemia and fibrosis** of surrounding tissue

Results in life-threatening complications including **kidney failure, heart disease, and early stroke**

Progressive GL-3 Accumulation Leads to Irreversible Damage and an Abrupt Clinical Decline



GL-3 Accumulation Has Devastating Consequences

Over time, GL-3 accumulation evolves to organ failure, leading to a precipitous clinical decline.

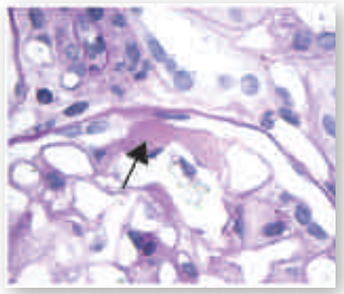
Fabry Disease and GL-3 Substrate Accumulation: Life-Threatening Effects in the Kidney, Heart, and Brain

Without sufficiently lowering GL-3 levels in the kidney, heart, and brain, irreversible tissue damage can result.

Kidney

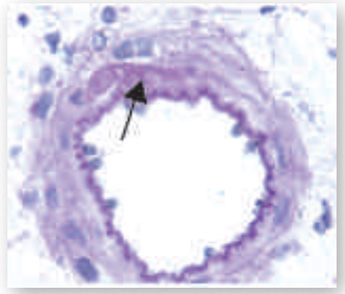
GL-3 Effects in the Kidney

Proteinuria, decreased glomerular filtration rate (GFR), elevated serum creatinine, renal failure.



Glomerular changes in 7-year-old patient with Fabry disease.

Renal biopsy specimen — arrow points to glomerular hyaline.



Arteriopathy in an 11-year-old patient with Fabry disease.

Renal biopsy specimen — arrow points to hyaline-like material in the media of a small artery.

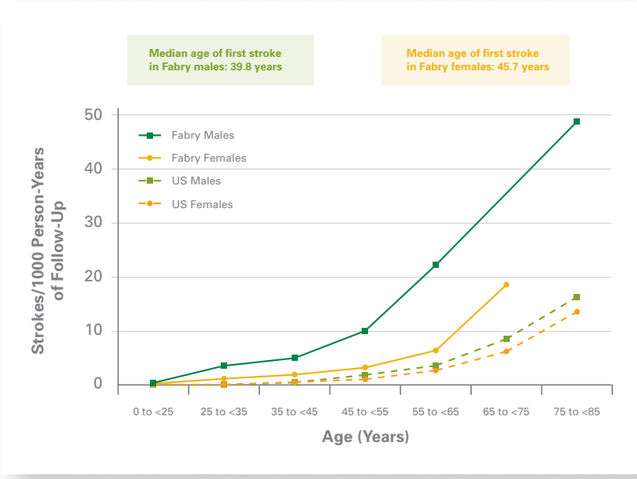
Kidney damage can begin early

Glomerular and vascular changes may be present before progression to overt proteinuria and decreased glomerular filtration rate.[3]

Brain

GL-3 Effects in the Brain

Early ischemic stroke, transient ischemic attacks (TIA).



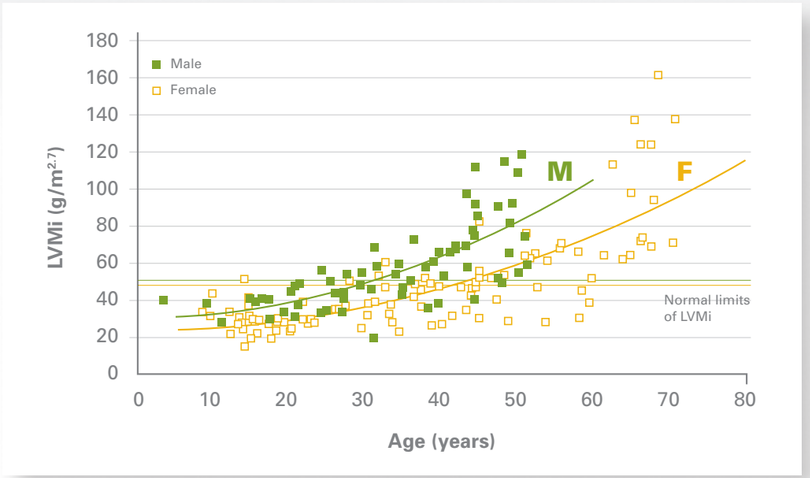
Fabry patients exhibit markedly higher incidence of stroke than general population[5]

Using data from the Fabry Registry, Sims and colleagues reported the mean age of first stroke in Fabry patients was 39.8 for males and 45.7 for females, which is considerably younger than that of the general population (76 for males and 81 for females).[5]

Heart

GL-3 Effects in the Heart

Left ventricular hypertrophy, valvular disease (especially mitral insufficiency), arrhythmias.



LVMi increases with age in both male and female Fabry patients[4]

A natural history study showed that 48.6% of males and 36.4% of females had left ventricular hypertrophy (LVH), the prevalence of which increased with age in both genders.[4]

LVMi = left ventricular mass indexed to height.

Additional Manifestations Resulting from Progressive GL-3 Build-Up

Neuropathic Pain

- Episodic pain crises and neuropathic pain in the hands and feet can be intense and debilitating
- As GL-3 levels increase, pain can diminish as nerve endings die

Gastrointestinal Problems

- Diarrhea, pain and bloating after eating, and nausea/vomiting

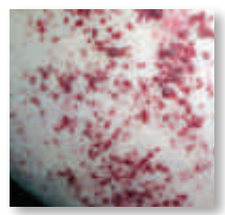
Corneal and Lenticular Opacities

- Visible by slit-lamp exam, and found almost universally among males, and in approximately 70% of females with Fabry disease[6]

Courtesy of RL Abbott, MD

Characteristic Skin Lesions

- Lesions do not blanch with pressure, and are often seen in the midriff and pelvic regions, as well as areas where the skin folds



Additional Signs and Symptoms

- Reduced or complete lack of sweating
- Heat/cold intolerance
- Exercise intolerance and fatigue
- Hearing loss

Overt signs and symptoms do not necessarily correlate with disease progression and underlying organ damage.

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Fabry disease is an inherited disorder marked by the progressive cellular accumulation of globotriaosylceramide (GL-3). GL-3 build-up leads to devastating consequences that can be irreversible.

Although Fabry disease is rare in the general population, diagnosis of one patient may lead to others within that family. In this extended family 41 out of 99 members have been diagnosed with Fabry disease.

X-linked Inheritance Means One Diagnosis Can Lead to Many

- Fathers with Fabry disease will pass it to all daughters but no sons.
- Mothers with Fabry disease have a 50/50 chance with each pregnancy of passing the gene to sons and daughters.
- Easy to determine who is at risk within a Fabry family, enabling earlier diagnosis of family members.

Fabry is Progressive: Early Diagnosis and Intervention are Critical

Diagnosis is straightforward and can be accomplished by enzyme assay in a blood sample. A number of laboratories across the country offer this assay.

1. Fabry Registry Annual Report 2010. Genzyme Corporation, Cambridge, MA.
2. Carandang R, Seshadri S, Beiser A, et al. Trends in incidence, lifetime risk, severity, and 30-day mortality of stroke over the past 50 years. JAMA 2006; 296:2939-46.
3. Tøndel C, Bostad L, Hirth A, Svarstad E. Renal biopsy findings in children and adolescents with fabry disease and minimal Albuminuria. Am J Kidney Dis 2008; 51:767-76.
4. Kampmann C, Linhart A, Baehner F, et al. Onset and progression of the Anderson-Fabry disease related cardiomyopathy. Int J Cardiol 2008;130:367-73.
5. Sims K, Politei J, Banikazemi M, Lee P. 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;40:788-94.
6. Desnick RJ, Brady RO. Fabry disease in childhood. J Pediatr 2004;144:20-26.

Contact Genzyme Medical Information at 800-745-4447 for more information on diagnostic testing or for additional information on Fabry disease.

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