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.

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.

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.

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.

Although Fabry disease results in the severe, progressive disease of one patient, it can result in a similar condition in other members of the affected family and lead to untoward health outcomes.

Contact Genzyme Medical Information at 800-745-4447 for more information on diagnostic testing or for additional information on Fabry disease.
Fabry disease is a multisystemic genetic disorder that ultimately results in irreversible, potentially life-threatening disease of the kidney, heart, and brain.

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

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.

- **Silently Progressive.**
- **Increasingly Debatiling.**
- **Often Life-Threatening.**

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

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

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

**Clinical Progression**

**Kidney**

- **GL-3 Effects in the Kidney**
  - Postmenuria, decreased glomerular filtration rate (GFR), elevated serum creatinine, renal failure.

**Heart**

- **GL-3 Effects in the Heart**
  - Sustained ventricular hypertrophy, valvular disease (especially mitral insufficiency), arrhythmias.

**Brain**

- **GL-3 Effects in the Brain**
  - Early ischemic stroke, transient ischemic attacks (TIA).

**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

**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
- - Exercise intolerance and fatigue
- - Heart/cold intolerance
- - Hearing loss

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

**LVMi increases with age in both male and female Fabry patients**

A natural history study showed that 48.6% of males and 34.8% of females had left ventricular hypertrophy (LVMi), the prevalence of which increased with age in both genders.

**Additional Data**

- - **Left Ventricular Mass Index (LVMi)**
  - Male: 24.8 ± 9.3 g/m²
  - Female: 20.9 ± 7.6 g/m²

- - **Median age of first stroke**
  - Fabry females: 45.7 years
  - Fabry males: 39.8 years

- - **Strokes/1000 Person-Years**
  - US Females: 7.32
  - US Males: 9.42
  - Fabry Females: 9.18
  - Fabry Males: 11.07
Fabry Disease and GL-3 Substrate Accumulation: Life-Threatening Effects in the Kidney, Heart, and Brain

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Kidney

GL-3 Effects in the Kidney

Glomerular and vascular changes may be present before progression to overt kidney disease, as indicated by elevated glomerular filtration rate.

Kidney damage can begin early.

Kidney biopsy specimen — arrow points to glomerular hyaline.

Heart

GL-3 Effects in the Heart

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

Heart disease can result.

Heart biopsy specimen — arrow points to hypertrophied media in the media of a small artery.

Brain

GL-3 Effects in the Brain

Early ischemic stroke, transient ischemic attacks (TIA).

Enzyme deficiency leads to progressive cellular glycosphingolipid-enzyme (GL-3) substrate accumulation

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

Pathology at a Glance

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Increasingly Progressive

Silently Progressive

Life-Threatening

Debilitating

GL-3 Accumulation Has Devastating Consequences

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

Clinical Progression

Age (years)

Glycolipid Accumulation

Heart

Kidney

Brain

Additional Manifestations Resulting from Progressive GL-3 Build-Up

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

Fabry patients exhibit markedly higher incidence of stroke than general population

Using data from the Fabry Registry 5 and colleagues reported the mean age of first stroke in Fabry males was 39.8 years and 45.7 years for females which is considerably younger than that of the general population (62 years for male and 61 years for females)

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LVMi increases with age in both male and female Fabry patients

A natural history study showed that 48.6% of males and 36.4% of females had left ventricular hypertrophy (LVMi), the prevalence of which increased with age in both genders. LVMi is a soft ventricular mass indexed to body height.

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