Fabry disease

Genetics

-Gene: GLA (alpha-galactosidase A, Xq22.1)

-XLR

Clinical findings/Dysmorphic features

1) Classic form (males with < 1% α-Gal A activity): onset in childhood to adolescence; periodic crises of severe pain in extremities (acroparesthesia); vascular cutaneous lesions (angiokeratomas); sweating abnormalities (anhidrosis, hypohidrosis, hyperhidrosis); corneal and lenticular opacities (cornea verticillate and fabry cataract) ; proteinuria; ESRD (in men in the 3rd -5th decade); most males treated for ESRD develop cardiac and/or cerebrovascular disease (major cause of morbidity and mortality)

2) Non-classical form (males with > 1% α-Gal A activity):

-cardiac variant: 6th-8th decade with left ventricular hypertrophy, cardiomyopathy and arrhythmia, proteinuria, but without ESRD

-renal variant: associated with ESRD but without the skin lesions or pain

-cerebrovascular variant: presenting as stroke or transient ischemic attack

Etiology

-Incidence at 1:50,000 to 1:117,000 males

Pathogenesis

-Deficiency of alpha-galactosidase A (α-Gal A) --> progressive lysosomal deposition of globotriaosylceramide (GL-3) in cells throughout the body

Genetic testing/diagnosis

-Deficient α-Gal A enzyme activity in plasma, isolated leukocytes, and/or cultured cells is the most efficient and reliable method in males

-Identification of hemizygous GLA pathogenic variant (>800 mutations identified; most private)

Others

-Heterozygous females typically have milder symptoms at a later age of onset than males

-ERT is disputable