Anderson-Fabry Disease

Synonyms: Fabry's disease, alpha-galactosidase A deficiency, hereditary dystopic lipidosis, GLA deficiency

Anderson-Fabry disease is an X-linked recessive inborn error of glycosphingolipid metabolism caused by deficiency of alpha-galactosidase A.\[^1\] It was first described independently in 1898 by Anderson and Fabry but the enzyme deficiency was not defined until the 1960s.

The enzyme deficiency leads to defective storage of sphingolipid and progressive endothelial accumulation causing abnormalities in the skin, eye, kidney, heart, brain and peripheral nervous system.

The gene responsible for alpha-galactosidase is located on the long arm of the X chromosome. There have been almost 200 mutations identified.

Along with Gaucher's disease it is one of the most prevalent metabolic storage diseases (or lysosomal storage diseases). The gene mutation and enzyme deficiency result in insufficient activity of enzymes required for the breakdown of substances that arise from cell turnover in the body, also as in Gaucher's disease.\[^2\]

Epidemiology

- It is estimated to occur in 1 in 55,000 males in the classical form but the atypical variant may be more common.\[^3\]
- It has been described in many racial groups.
- As an X-linked recessively inherited condition, female carriers exist and can exhibit mild-to-moderate symptoms (variable expression according to random X inactivation of the affected gene in embryogenesis).

Presentation\[^1, 4\]

There are three distinct clinical entities:

**Male homozygotes with classical manifestation**

*No alpha-galactosidase activity in plasma:*

- Onset is usually in childhood. Often patients have slight builds with characteristic coarse facial features and delayed puberty.
- Early symptoms of burning pain and paraesthesia in the extremities (acroparaesthesia) are a major cause of morbidity. Painful crises may be triggered by temperature change, fever, sun, physical exertion, etc. General fatigue and weakness are common.
- There is progressive development of symptoms consistent with disease affecting many different systems. For example:
  - Skin: angiokeratomas occur early and are small punctate red to blue-black telangiectasias, typically in a 'bathing suit' distribution. Hypohydrosis. Lymphoedema in the lower extremities.
  - Eye: lens, cornea, conjunctiva and retina may all be involved. Particular types of pathognomonic lens opacity have been described (the propeller- or wedge-shaped opacity and the Fabry cataract).
  - Cardiovascular system: problems typically develop in the fourth decade. This can produce anginal pain in adulthood with varied complications ranging from arrhythmias to myocardial infarction and heart failure.\[^5\]
  - Cerebrovascular disease: this can produce problems ranging from personality change and psychosis to varied manifestations of multifocal cerebrovascular disease. It typically develops in the fourth decade.
  - Gastrointestinal disease: this can include symptoms of diarrhoea, weight loss abdominal pain, nausea and vomiting.
  - Renal disease: this produces hypertension, proteinuria and progressive kidney disease. Such symptoms typically develop in the second and third decade.
  - Other organs and systems: widespread involvement produces many other manifestations of the disease, including cough, breathlessness, wheeze, etc.

**Male homozygotes with atypical manifestation**

*Some alpha-galactosidase activity in plasma (5-35%).* Probably the most common variant:

- Often asymptomatic.
- Adult onset.
- Presenting late - often in the sixth to eighth decade.
- Usually present with cardiac involvement including cardiomegaly, mitral insufficiency, and cardiomyopathy.
- Can present with proteinuria.
- Occasionally developing acroparaesthesia.

**Female heterozygotes**
Variable (0-100%) plasma alpha galactosidase activity depending on random X-chromosomal activation:

- Variable presentation.
- Tend to present later than males.
- Dystrophy of cornea in the subepithelial layer with whorled streaks in 70%.
- Angiokeratomas in 30%.
- Occasionally acroparæsthesia.
- Rarely, hypohidrosis and other organ involvement (renal failure less than 1%).

Differential diagnosis

There is a large list of possible differential diagnoses according to the varied clinical presentations.

Investigations

- Confirmation of diagnosis is by demonstration of absent or deficient levels of alpha-galactosidase A in leukocytes, plasma or cultured fibroblasts.
- Glycosphingolipid is deposited in urine in complexes. Urine microscopy with polarised light may show a 'Maltese cross' appearance (birefringent lipid molecules).
- Prenatal diagnosis by enzyme activity or DNA testing in chorionic villi or cultured amniotic cells is considered in male fetuses. Pre-implantation diagnosis is possible.⁴
- Other helpful investigations include ECG, MRI, echocardiography, etc.⁵ Eye examination may show diagnostic corneal or lenticular deposits.
Management
Correct diagnosis is important because of the progressive morbidity associated with advancing disease.
Early diagnosis is now important because some disease manifestations (Fabry cardiomyopathy) can be modified with enzyme replacement therapy.[7, 8]

- General support and advice:
  - Psychological support (patient and families).
  - Avoidance of precipitating factors for pain (acroparaesthesia) and tiredness (limiting physical exertion).
  - Maintaining increased fluid intake during exercise and in warm weather.
  - Avoiding smoking (cardiovascular and cerebrovascular risk).
  - Low-fat diet (may help gastrointestinal symptoms).
  - Genetic counselling is very important where there is a family history.

- Enzyme replacement therapy (ERT) is available and well-tolerated:[9]
  - ERT provides the patient with the biologically functional protein.
  - However, there is currently no robust evidence for the use of either agalsidase alfa or beta to treat Anderson-Fabry disease.[10]
  - Reversal of the metabolic and pathological abnormalities in the cells and tissues are the key therapeutic goals.
  - These changes should, in turn, result in improvement of symptoms and prevention of disease complications.
  - There is evidence that this may reduce pain and rate of progression of renal, cardiac, and cerebrovascular complications.

- ERTs have been limited by the blood-brain barrier, but new therapies such as gene therapy have been initiated.[2]
- Drug treatments:
  - Prophylactic antibiotics should be considered (see the separate article on Prevention of Infective Endocarditis).
  - Carbamazepine and phenytoin may help with prevention of pain attacks.
  - Antiplatelet agents or anticoagulants (preventative for cerebrovascular disease).

- Management of advanced disease.
  - End-stage renal disease: renal dialysis, renal transplantation (but disease develops in transplanted kidneys eventually).[11]
  - Cardiac intervention - eg, pacemakers, valve and coronary artery surgery.

Prognosis
Before dialysis and renal transplantation, death often occurred in the fourth or fifth decade in male homozygotes particularly. Treatments now available can improve both morbidity and mortality.[6, 12] It is likely that for maximum benefit these treatments will have to be started early and given long-term.[13]

Further reading & references
3. Fabry Disease; Online Mendelian Inheritance in Man (OMIM)

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