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Fabry disease and the heart

Dr Sajidah Khan
Specialist Cardiologist
Gateway Private Hospital
Umhlanga, Durban
Director: South African Heart Association, South African Society of Interventional Cardiology (SASCI)

Learning objectives

You will learn:

- The pathology and genetics of Fabry disease, an X-linked inherited disorder of glycosphingolipid metabolism
- The range of symptoms affected by specific alpha-galactosidase A mutation and clinical manifestations of type 1 and type 2 disease
- How to diagnose and treat Fabry disease.

Introduction

A rare disease is defined as a condition that affects fewer than five in 10 000 people in the general population. There are between 6 000 and 8 000 distinct rare diseases, of which 72 % have a genetic aetiology. Rare diseases are sometimes referred to as orphan diseases due to neglect by the medical community. The Orphan Drug Act was established to provide incentives to the pharmaceutical industry to encourage new drug development for rare diseases. Given this background, should the average clinician be interested in rare diseases?

Firstly, it is estimated that approximately 400 million people, i.e. 6-8 % of the global population, suffer from these disorders and many healthcare professionals are likely to encounter such patients during their professional career. Secondly, with increasing awareness and research, it has become evident that certain of these conditions are more common than previously suspected. Thirdly, novel treatments that improve survival are available for certain rare diseases and the earlier these therapies are instituted, the greater the impact on prognosis (Table 1).

Fabry disease (FD) is one such rare X-linked inherited disorder of glycosphingolipid metabolism. While its epidemiology is not entirely clear, newborn screenings suggest that its actual prevalence rate is significantly higher than previously suspected. More importantly, advances in therapy have been demonstrated to significantly impact morbidity and mortality.

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Table 1. Reasons for primary care interest in rare diseases

- 6-8 % of the global population are affected
- Increasing awareness has shown higher prevalence than initially thought
- Newborn screening studies contribute to the increased detection of rare disease
- Novel treatments improve survival and quality of life of affected patients
- Earlier diagnosis and treatment improve prognosis.

Pathology of FD

Glycosphingolipid accumulation occurs in vascular cells, as well as cells of the heart, kidney and nervous system

FD belongs to a group of diseases known as lysosomal storage disorders. A lysosome is a component of a cell that functions as a recycling centre, using digestive enzymes to process and recycle worn-out cellular components. The disorder is caused by a deficiency of an enzyme called alpha-galactosidase A (α-Gal A) within lysosomes. The function of α-Gal A is to break down complex sugar-lipid molecules called glycolipids, specifically globotriaosylceramide (Gb3). Deficiency of α-Gal A causes a continuous build-up of Gb3 and related glycolipids, and these accumulations are thought to have cytotoxic, proinflammatory and profibrotic effects.[1,2] Glycosphingolipid accumulation occurs in vascular cells, as well as cells of the heart, kidney and nervous system (Figure 1).[1]

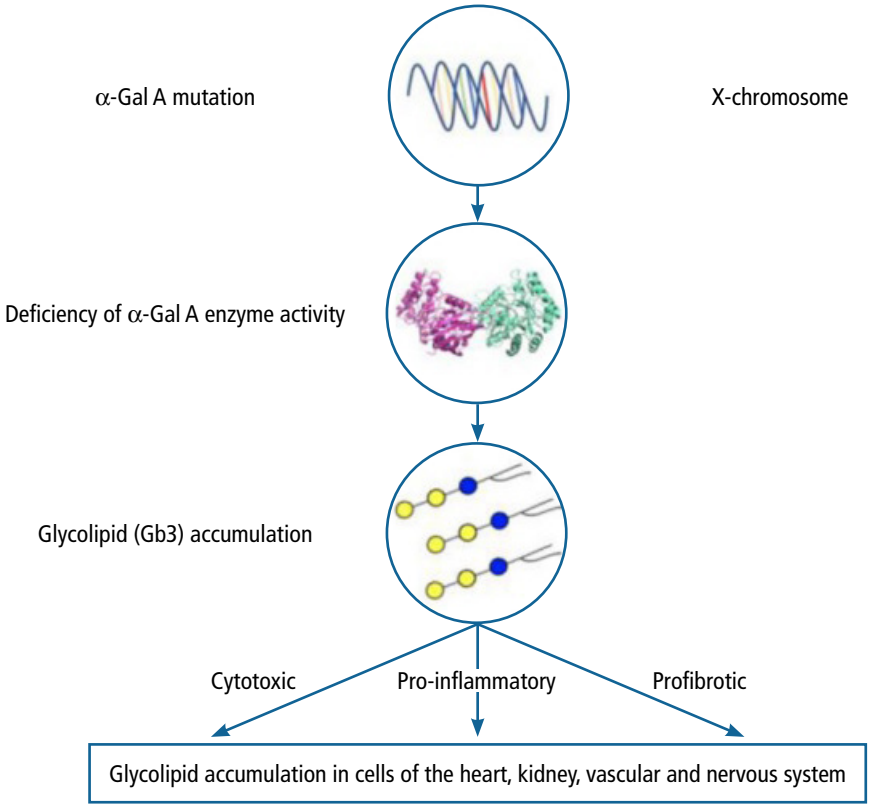

Figure 1. Pathophysiology of FD

Genetics

FD is caused by mutations in the α-Gal A gene located on the X-chromosome. Human chromosomes are organised in pairs, numbered from 1 through 22, with the 23rd pair having an XY-chromosome in males and an XX-chromosome in females. Since males have only one X-chromosome, a gene mutation on the X-chromosome will lead to the affected disorder.

In females, disease traits on the X-chromosome can be masked or reduced by the normal gene on the other X-chromosome; one of the X-chromosomes in each cell of a female is essentially 'turned off', usually in a random pattern. This means that in X-linked disorders, some cells will have the X-chromosome with the mutated gene activated, while others will have the X-chromosome with the

Males with FD are more uniformly affected whereas females range from being asymptomatic to being as severely affected as their male counterparts

functioning, normal gene activated. The severity of organ involvement is thus dependent on the percentage of cells in the organ where the X-chromosome with the gene mutation is active. Males with FD are more uniformly affected whereas females range from being asymptomatic to being as severely affected as their male counterparts.

Males with X-linked FD transmit the gene mutation to all their daughters who are heterozygotes, but never to their sons. Female heterozygotes have a 50 % risk of transmitting the disease to each of their children, both daughters and sons.

Range of symptoms affected by specific α-Gal A mutation

The severity and range of symptoms may vary according to the specific α-Gal A mutation in a family. There are over 965 reported mutations responsible for FD. Some mutations markedly alter the enzyme such that it has little to no activity. These mutations cause the type 1 classic subtype of FD, while other mutations result in some residual enzyme activity and the type 2 later-onset subtype. Patients with the type 1 phenotype generally have <3 % of normal enzyme activity and accumulate Gb3 in most tissues of the body, whereas those with the type 2 phenotype have residual enzyme activity of 3-15 % and accumulate Gb3 to a lesser extent and at a slower rate. Those in the type 2 group have a less severe form of the disease but male subjects develop severe cardiac disease and/or renal failure in later years of life.[3]

FD occurs in all racial and ethnic populations. Type 1 classic FD affects approximately one in 40 000 males (reported range from 1:8 454 to 1:117 000 males). The type 2 phenotype is more frequent by three- to 10-fold and, based on newborn screening studies, may occur as frequently as 1:1 500 to 1:4 000 males in some populations.

Clinical manifestations

Type 1

FD occurs in all racial and ethnic populations

The clinical symptoms of the early-onset form usually begin to appear between childhood and adolescence and include:

Acroparaesthesias

Episodes of severe burning pain in the hands and feet, which may last for hours to days and are frequently triggered by exercise, fever or stress.

Angiokeratomas

Clusters of red to dark blue skin rash often found in the umbilical or genital area.

Hypohidrosis or anhidrosis

Decreased or absent sweat production and heat intolerance.

Gastrointestinal symptoms

Abdominal pain/cramping and frequent bowel movements.

Corneal dystrophy

Star-burst pattern of the cornea seen by slit-lamp ophthalmological examination.

Cardiac disease

Cardiovascular manifestations include left ventricular hypertrophy (LVH), valvular disease, arrhythmias and conduction defects, coronary artery disease, hypertension and aortic root dilation. Unexplained LVH is the hallmark of cardiac disease and is caused by both myocyte hypertrophy and glycolipid deposition. The hypertrophy may be concentric (commonest type), asymmetric (5 % of cases) or eccentric. Dynamic LV outflow tract obstruction is rare, occurring in <1 % of cases. Right ventricular hypertrophy is often present.

Patients frequently have minor thickening of the valves and mild regurgitation of the aortic, mitral or tricuspid valves is common. Angina is a frequent symptom and typically caused by small-vessel disease, although epicardial coronary artery disease can occur.

Endomyocardial biopsy specimens have demonstrated luminal narrowing of the intramural coronary arteries due to hypertrophy and

proliferation of smooth muscle and endothelial cells with glycosphingolipid deposits. Severely narrowed intramural coronary arteries are often surrounded by myocardial fibrosis. Atrial arrhythmias, including atrial fibrillation, are more common in FD and non-sustained ventricular tachycardia may be related to LV wall thickness. Various conduction abnormalities, ranging from changes in PR interval to advanced atrioventricular block, have been reported but progression to requiring a pacemaker is uncommon.

Renal disease

In type 1 males, the decline in renal function progresses from microalbuminuria to frank proteinuria and decreasing glomerular filtration rate, leading to kidney failure and the need for dialysis or transplantation by 35-45 years of age. In type 2 males, kidney involvement occurs in the fourth decade or later, but not all patients develop renal impairment.

The prevalence of FD in dialysis populations has been examined in several screening studies. Random screening has identified < 1% of haemodialysis patients as having FD, most of whom were already known to have the condition.

Cerebrovascular complications

As a result of the progressive Gb3 deposition in the heart (leading to atrial fibrillation) and in the small blood vessels in the brain, about 7 % of males and 4 % of females with FD, particularly those with the type 1 phenotype, experience ischaemic or haemorrhagic strokes, typically in the fourth decade of life or later.

Respiratory abnormalities

Accumulation of glycosphingolipids and consequent fibrosis can cause interstitial lung disease. Pathological changes and tissue remodelling may involve both alveoli and the bronchial tree, leading to restrictive lung disease, obstructive airway disease, or a mixture of both. Respiratory symptoms may occur independently of cardiovascular disease in these patients.

Other pathology

Hearing loss, tinnitus, dizziness and vertigo due to Gb3 deposition in vestibular structures or auditory neuropathy are commonly reported in adult patients and while not life threatening, may adversely affect quality of life.

Type 2 patients have an essentially normal childhood and adolescence, and typically present with cardiac and/or renal disease in the third to seventh decades of life

Type 2

Patients with type 2 FD are seen later in life and their symptoms usually centre around one organ system. Patients have an essentially normal childhood and adolescence, and typically present with cardiac and/or renal disease in the third to seventh decades of life. Most type 2 patients have been identified by enzyme screening of patients in cardiac, haemodialysis, renal transplant and stroke units and, more recently, by newborn screening.

Diagnosis

The diagnosis of both type 1 and 2 males is confirmed by demonstrating the enzyme deficiency and by identifying the specific *GLA* gene mutation. Female heterozygotes can have α-Gal A enzymatic activity from markedly decreased to values in the normal range. Therefore, heterozygous females are only accurately diagnosed by demonstrating the specific α-Gal A gene mutation.

Early prenatal diagnosis at about 15 weeks of gestation can be made with amniocentesis by determining the α-Gal A enzyme activity and demonstrating the family-specific *GLA* mutation. Pre-implantation genetic diagnosis is available when the familial mutation in the *GLA* gene is known.

Prognosis with and without treatment

Prior to renal replacement therapy (i.e. dialysis and transplantation) and enzyme replacement therapy (ERT), the average age of death of affected males with the type 1 classic phenotype was approximately 40 years.

Life expectancy is reduced by approximately 20 years in untreated males and by approximately 15 years in females compared with the general population.

Treatment

ERT is the mainstay of treatment (Figure 2).[4] Synthetic enzymes are produced by recombinant DNA technology. Two forms of the recombinant enzyme are available, agalsidase alpha and agalsidase beta. ERTs are infused intravenously and have been demonstrated to improve symptoms such as neuropathic pain and heat intolerance and, importantly, to prevent or slow the decline of end-organ damage, especially if initiated early.

An oral therapy, migalastat, has been approved in the European Union (2017) and in the USA (2018) to treat adults with FD. The drug is a pharmacological chaperone that can bind to and enhance residual enzymatic activity of certain missense mutations. This agent is not yet available in South Africa.

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Test your skills: Index case study

Mr X was referred in 2017 for a second opinion with regard to a revascularisation strategy for three-vessel coronary artery disease. His cardiologist had advised that he undergo coronary artery bypass grafting but his referring physician had commented that the patient's symptoms were mild and he was reluctant to have open heart surgery.

Clinical history

His symptoms included exertional dyspnoea and fatigue since 2014. He had begun experiencing dizziness sometime in 2016. In October 2017 he made an unscheduled visit to his cardiologist for presyncope. He specifically denied having chest discomfort or palpitations. His cardiologist had performed a computed tomography brain scan, which was normal, a treadmill stress test, which was limited by poor effort tolerance, and subsequently a coronary angiogram that demonstrated multi-vessel disease.

Of note, the patient had been diagnosed with hypertrophic cardiomyopathy (HCM) several years earlier and was monitored by his cardiologist on a regular basis. He had two brothers, both of whom had died prematurely. The one brother was known to have HCM and died suddenly at age 54 years. The other brother had died at age 56 years, reportedly from a brain haemorrhage, and had been in heart failure. A younger sister was on medication for hypertension.

The patient's traditional risk factors included hypertension and hyperlipidaemia since 2002 and he was on treatment with valsartan 160 mg/day and simvastatin 40 mg/day. He was a non-smoker.

On examination, his BMI was 30 kg/m^2 (weight 90 kg). He was in sinus rhythm and had frequent ectopic beats. His blood pressure was adequately controlled at 130/84 mmHg. He had a double apical impulse, a fourth heart sound and a 3/6 ejection systolic murmur with wide radiation over the left precordium. His clinical signs were compatible with HCM. The remainder of his systemic examination was unremarkable.

His electrocardiogram showed LVH with deep symmetrical T-wave inversion. An echocardiogram demonstrated marked concentric LVH with the septal wall thickness reaching a maximum of 26 mm and posterior wall thickness of 20 mm (10 mm is the upper limit of normal LV wall thickness). The LV cavity size was normal at 45 mm at end diastole and the left atrium was dilated at 46 mm. There were no other features of HCM and the valves were normal.

Ancillary tests showed normal renal function (creatinine 98 µmol/l, eGFR 72 ml/min/1.73 m^2) and no proteinuria. His total cholesterol was 5.1 mmol/l with a low-density lipoprotein cholesterol level of 3.5 mmol/l. His full blood count, liver and thyroid function, and glucose tolerance test were normal. Cardiac biomarker levels showed an initial high troponin T level of 902 ng/l. Subsequent testing showed persistent mild elevations of troponin T at 45 ng/l and proBNP at 442 pg/ml.

1. **Which of the index patient's symptoms below could alert the clinician to possible FD?**
   - A. The frequent ectopic beats
   - B. Multi-vessel disease on angiography
   - C. Severe LVH

Expert comment

Since he had unusually severe LVH, the patient was screened for other causes of LVH, including FD.

2. **What other tests would you initiate in this index patient?**
   - A. Cardiac magnetic resonance (CMR) scan
   - B. Repeat echocardiogram
   - C. Genetic screening
   - D. A and C

In the meantime, a CMR scan was undertaken, which showed diffuse wall thickening of the LV myocardium measuring 28-30 mm at its thickest point with enhancement of the mid myocardium of the anterior, lateral and inferior ventricular wall. Reduced T1 mapping times of the septum were also demonstrated. These findings were highly suggestive of FD rather than HCM.

Results of the screening tests showed a reduced α-Gal A level of 8.0 umol/l/h (reference ≥15.3 umol/l/h) and a *GLA* genotype of hemizygous variant c.1153A.G p (Thr385Ala), the findings being compatible with a diagnosis of FD.

3. **Which of this index patient's immediate family would you regard as a priority to screen?**
   - A. His son
   - B. His daughter

His sister (age 54 years) and daughter (32 years) had the same *GLA* gene mutation and were identified as carriers of FD.

Sister
- Lyso-Gb3: 1.1 ng/ml (reference ≤1.8 ng/ml)
- GLA: heterozygous variant c.1153A.G p (Thr385Ala)

Daughter
- Lyso-Gb3: 0.8 ng/ml (reference ≤1.8 ng/ml)
- GLA: heterozygous variant c.1153A.G p (Thr385Ala)

Treatment options

Due to the high costs of ERT, there were protracted negotiations with funders until an agreement was reached almost two years later for a six-month trial of agalsidase alpha. In the meantime, the patient had undergone percutaneous coronary intervention to the culprit vessel only and was maintained on dual antiplatelet therapy, diltiazem (intolerant of β-blockers), valsartan and atorvastatin. Treatment with agalsidase alpha commenced on 16 July 2020. Dosages of 0.2 mg/kg body weight are repeated every alternate week by intravenous infusion over 40 minutes.

4. **What improvements would you expect in the index patient when using ERT?**
   - A. Improvement in LV function
   - B. Reduction in myocardial hypertrophy
   - C. Both of the above

At the end of six months in December 2020, echocardiography and CMR were repeated, both showing significant regression of LVH. Using the latest magnetic resonance imaging heart scan (24/12/2020), comparison was made with both previous studies.

Left ventricular wall thickness:

- Multi-segment thickening persisted but interval improvement was seen in the thickness of the wall of the base
- Basal anterior segment: 17.5 mm, previously 20.5 mm
- Basal inferoseptal segment: 20.7 mm, previously 23.4 mm
- Basal inferior segment: 12.5 mm, previously 13.5 mm
- Basal inferolateral segment: 11.8 mm, previously 14.5 mm
- Basal superolateral segment: 12.4 mm, previously 15.3 mm.

Severe inferoseptal thickening persisted in the mid-chamber *measuring 28-30 mm at its thickest point*, much the same as previously. Severe apical cavity obliteration was previously obvious, and this again was visible and appeared unchanged. Substantial interval improvement in LV function was seen. Ejection fraction was 54 %. Stroke volume had increased from 51 ml to 78 ml and cardiac output from 3.5 l/minute to 5.1 l/minute.

There were areas of reduction in the degree of myocardial hypertrophy as described. There was improvement in LV function. No disease progression was seen, with no new areas of hypertrophy or delayed enhancement.

In the interim, the patient's younger sister died suddenly from a stroke. The sister's clinical profile serves to highlight the often difficult decisions in making a definitive diagnosis of FD. She had longstanding hypertension that was not optimally controlled as she had tolerated the medication poorly. She had LVH of 15 mm on echo and had demonstrated the same familial mutation in the *GLA* gene. It remains speculative whether she too, like her two brothers who experienced sudden premature cardiovascular deaths, also had FD.

5. **Should treatment of the index patient continue for life?**
   - A. Yes
   - B. No

Based on the positive response to therapy, a further six-month course of agalsidase alpha was approved by funders. The patient has remained well thus far.

Key learnings

- The actual prevalence of FD is significantly higher than previously suspected
- Continuous build-up of Gb3 and related glycolipids arising from α-Gal A gene mutations may have cytotoxic, proinflammatory and profibrotic effects
- Males with FD are more uniformly affected whereas females range from being asymptomatic to being severely affected
- Clinical symptoms of early-onset type 1 FD begin to appear between childhood and adolescence
- Type 2 FD is the less severe form of the disease and symptoms usually centre around one organ system
- Diagnosis is confirmed by identifying the specific *GLA* gene mutation and, in males, by demonstrating the enzyme deficiency
- ERT is the mainstay of treatment; migalastat has been approved in the EU and USA to treat adults with FD.

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Dr Sajidah Khan, Specialist Cardiologist

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70 Arlington Street, Everglen, Cape Town, 7550
Tel: (021) 976 0485 | info@denovomedica.com