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Fabry Disease

Ida Kåks and Peter Magnusson

Abstract

Fabry disease (FD) is a lysosomal storage disorder where deficient or completely absent activity of the enzyme α -galactosidase A leads to accumulation of globotriaosylceramide (Gb₃) and other glycosphingolipids in lysosomes. The condition is rare, approximately 1:50,000, although underdiagnosis seems frequent. The condition can affect multiple organ systems, including the skin, nervous system, kidneys, and heart. Early manifestations include skin lesions (angiokeratoma), neuropathic pain, and gastrointestinal symptoms. Later on, FD can result in cardiomyopathy, kidney failure, and stroke. Both lifespan and health-related quality of life are affected negatively by FD. Patients are divided into a classical or a non-classical phenotype based on presentation, where the diagnosis of classical FD requires that a set of specific criteria are met. Patients with non-classical FD often have a less severe disease course, sometimes limited to one organ. The hereditary pattern is X-linked. Thus, men are in general more severely affected than women, although there is an overlap in symptomatic burden. Two types of specific treatment options are available: enzyme replacement therapy and pharmacological chaperone therapy. In addition to this, management of each organ manifestation with usual treatment is indicated.

Keywords: Fabry disease, hypertrophic cardiomyopathy, left ventricular hypertrophy, lysosomal storage disorder

1. Introduction

Anderson-Fabry disease, generally referred to as Fabry disease (FD), is a lysosomal storage disorder where the activity of lysosomal enzyme α -galactosidase A is deficient or completely absent. This leads to accumulation of globotriaosylceramide (Gb₃) and related glycosphingolipids inside the lysosomes [1], organelles which, among other things, are responsible for degradation of cellular waste [2]. FD is a rare condition, and the reported incidence varies greatly between sources, with reported incidences in the ranges of 1 in 40,000 [3], 1 in 117,000 [4], and 1 in 476,000 [5]. However, when screening newborn males a prevalence of around 1 in 3,100 was found in Italy [6] and 1 in 1,250 in Taiwan [7], suggesting the true prevalence is higher than previously thought [1].

2. Historical overview

In 1898, the German physician Johannes Fabry and the British surgeon William Anderson independently of each other reported seeing patients with angiokeratoma, a classical skin lesion associated with the disease [8–10]. Back then, physicians lacked knowledge about the underlying causes for the dermatoses they were

describing, and the meaning of additional symptoms were mostly unknown [11]. Hence, FD was initially considered a purely dermatological disorder. Anderson did, however, describe proteinuria. No one else in the patient's family was affected. Fabry's patient had a paternal grandfather who passed away from "kidney trouble" at an age of 49 years, and the patient himself died of lung disease at 44 years of age. The average life expectancy in the general population in the year 1900 was about 40 years [11]. In 1963 the mainly accumulated substance, Gb₃, was identified [12]. A few years later, deficient α -galactosidas activity was described, followed by the discovery of the gene coding for α -galactosidas A. To date, almost a 1,000 mutations have been identified in this gene, although many of the mutations still have an unknown significance and it is unclear whether they cause FD [8].

3. Disease manifestations

Symptoms generally appear between ages 3 and 10 in males, and a few years later in females [1]. Pain is among the first symptoms to manifest, and it can be either as episodic crises or as chronic pain. Most often, it presents as episodic sensations that radiate proximally from the extremities, which can be burning or shooting in character. The pain crises can consist of excruciating pain spreading all across the body. Physical exercise and thermal stimuli are triggers of the pain [13]. In addition to this, patients with FD can suffer from heat intolerance due to an- or hypohidrosis. In some patients, the pain decreases as they reach adulthood [1]. Other symptoms that may develop early are gastrointestinal problems (abdominal pain, diarrhea, vomiting), angiokeratoma (small spots on the skin, dark-red and raised), tinnitus and corneal changes (cornea verticillata, rarely affecting vision, **Figure 1**) [1].

For a definite diagnosis of FD, presence of an α -galactosidas A gene mutation needs to be present. Furthermore, in males an α -galactosidas A deficiency of $\leq 5\%$ of mean reference value in leukocytes is an additional criterion, whilst in females α -galactosidas A in leukocytes may be normal or deficient. Additionally, one of the

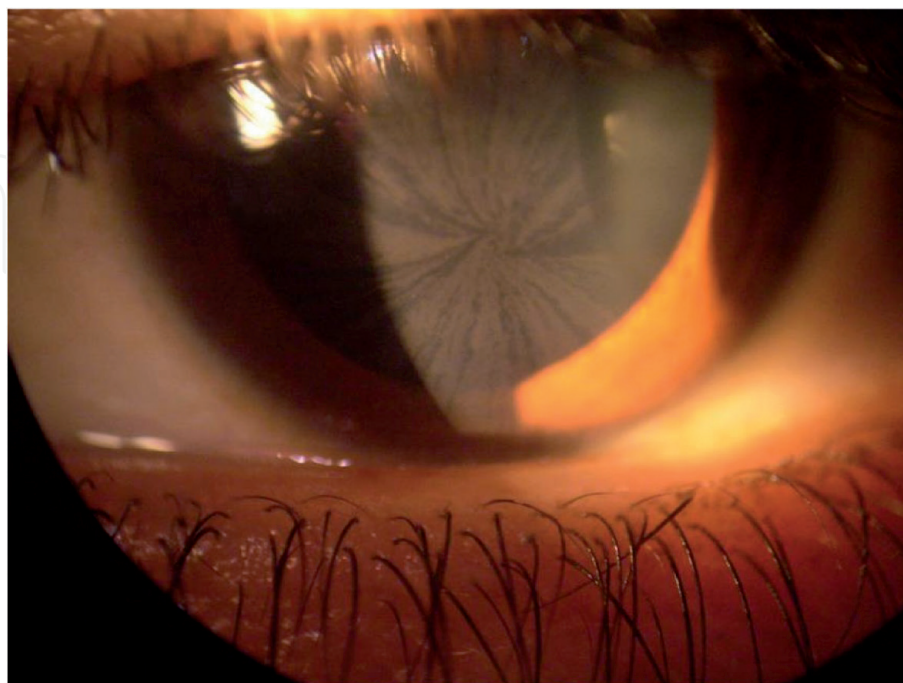


Figure 1. Cornea verticillata, seen as sub-epithelial brown lines. From Germain [1]. Courtesy: Dr. Juan-Manuel POLITEI, Buenos-Aires, Argentina. Licensed under CC BY 2.0.

following must be present: at least one characteristic sign of FD (neuropathic pain, cornea verticillata, or clustered angiokeratoma), increased plasma Gb₃ (in the range of males with definite FD diagnosis), or a family member with definite FD with the same α -galactosidas A gene mutation [14].

FD is divided into a classical or a non-classical phenotype, where the diagnosis of classical phenotype in males is based on presence of an α -galactosidas A gene mutation, very low or completely absent enzyme activity, and one of the following signs: angiokeratoma, cornea verticillata, or very high Gb₃-levels [15]. Hemizygous males are in general the ones most severely affected, although heterozygous females often have serious manifestations, which affect both quality of life and lifespan [16]. The varying severity of FD in females, where some are asymptomatic and others have a disease course comparable to that of males, is believed to be a result of skewed X-chromosome inactivation [17]. Females are considered to have classical FD when they present with angiokeratoma, cornea verticillata, or a very high Gb₃-level [15]. Although the disease course is variable (more so in non-classical than in classical FD), patients with non-classical FD are less severely affected in general, sometimes with disease manifestation limited to one organ [18].

The heart, kidneys and brain may become affected as the disease progresses, and cardiovascular, renal and cerebrovascular disease represent the most common among the known and reported causes for mortality in patients with FD [16].

3.1 Cardiac involvement

Heart involvement is the main reason for impaired quality of life and death in patients with FD [19]. Between 40 and 60% report symptoms including left ventricular hypertrophy (LVH), angina, arrhythmia and dyspnea [1]. In most studies the prevalence of FD in adult patients with left ventricular hypertrophy is estimated at 0.5–1% [20]. For a suggestion on how to further investigate LVH that might be associated with FD, see **Figure 2**. Many patients have a cardiac variant of FD, meaning the disease manifests later in life, primarily as LVH or hypertrophic cardiomyopathy (HCM). This variant generally progresses slower because of

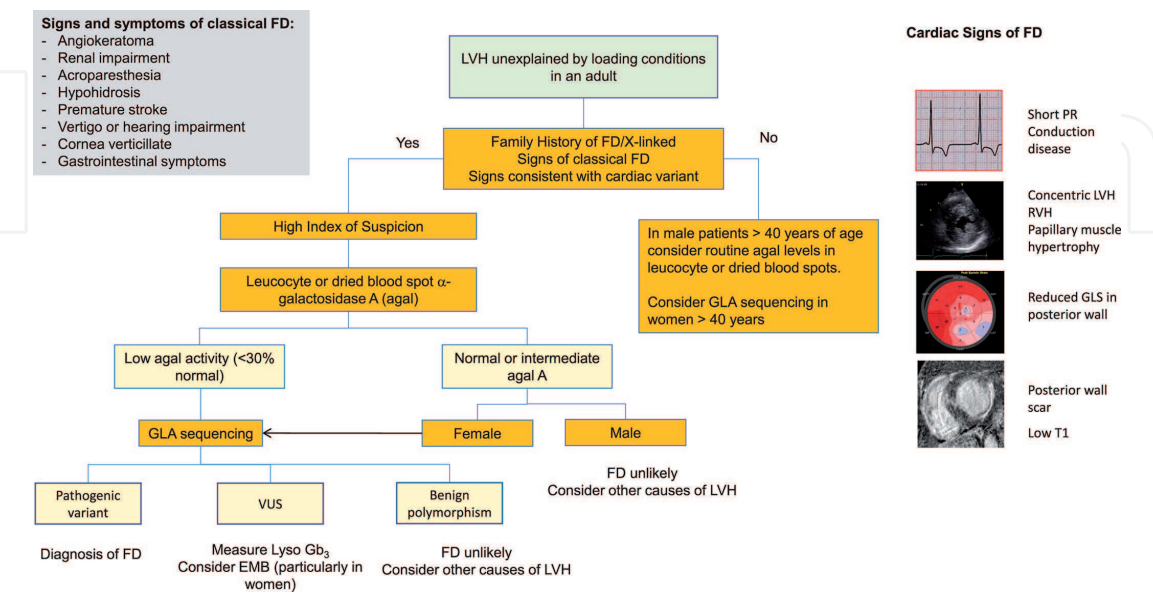


Figure 2.
Suggestion for further investigation of LVH when FD is suspected. Agal, α -galactosidas A; EMB, endomyocardial biopsy; GLA, α -galactosidas A gene; GLS, global longitudinal strain; RVH, right ventricular hypertrophy; VUS, variant of unknown significance. Image by Linhart A et al. [20] licensed under CC BY-NC 4.0.

residual α -galactosidase A-activity [20]. LVH manifests on average at age 32 in males, and at age 40 in women [21]. It is usually not accompanied by significantly impaired systolic function or restrictive diastolic dysfunction [22]. FD is considered a subgroup of HCM by the European Society of Cardiology (ESC), while the American Heart Association uses the term phenocopy to describe FD and other mimics of HCM [23, 24]. The prevalence of FD among patients with HCM above age 35–40 has been estimated to 0.5% [25].

In addition to LVH, cardiac involvement may lead to conduction defects and arrhythmia [8]. Since symptomatic bradycardia, AV block, chronotropic incompetence, supraventricular and ventricular arrhythmias are common, regular 24 h ECG monitoring is recommended [20]. The ESC recommend that patients with HCM who present with AV block or chronotropic incompetence should be suspected of having FD [23]. The arrhythmias in FD are a cause of significant morbidity. Atrial fibrillation is four times more common in patients with FD than in the general population, and twelve times more common in patients above the age of 50 [26]. Death from ventricular arrhythmia has been observed in a number of FD patients [26, 27]. Patients with FD can experience angina despite their coronary arteries being angiographically normal, which can be explained by microvascular dysfunction [28]. Valve disease occurs as a result of infiltrative changes in valvular fibroblasts, most clinically significant changes appear in the left heart valves. Valves become thickened which can lead to mild to moderate regurgitation, but disease requiring surgery is rare [29].

ECG changes associated with FD include shorter PQ interval, P-wave duration and QRS width, and increased QT and QTc duration [30]. As FD cardiomyopathy develops, voltage signs of LVH and inversed T-waves in precordial leads are usually seen [20].

Terminal stage cardiac FD leads to severe left ventricle dysfunction, associated with conduction disturbances and ventricular arrhythmia [27].

3.2 Renal involvement

The kidneys can be affected due to Gb₃ accumulating in renal cells (glomerular endothelial, mesangial, interstitial, podocytes), and the severity increases with age [1]. The first signs are usually microalbuminuria and proteinuria, presenting as early as the second decade of life and worsening with age [1]. In time, the glomerular filtration rate starts to decline, which might lead to end-stage renal failure [8]. Renal involvement is common; signs and symptoms of renal disease have been reported in half of patients in the Fabry Outcome Survey (a European database for all FD patients eligible for, or receiving, enzyme replacement therapy with agalsidase alfa). The most frequent sign was proteinuria, seen in 33% of females and 44% of males. End-stage renal failure affected 17% of males and 1% of females. Among the male patients 10% received a renal transplant and 7% were on dialysis [3].

3.3 Cerebrovascular involvement

Ischemic stroke and transient ischemic attacks are the most common cerebrovascular complications in FD, and occur at a younger age than in the general population [31]. Stroke can affect patients who have no other key signs of FD; data from the Fabry Registry showed that 46% suffered their first stroke prior to being diagnosed with FD [32]. The median age of first stroke was 39 in males and 46 in females. Approximately 87% of strokes were ischemic similar to the numbers in the general population. Among the strokes where vessel size was reported, most occurred in small vessels. The prevalence of stroke was 4.3% in females and 6.9%

in males, which by far exceeds the prevalence in the general population [1]. In men between ages 35 and 45, the risk of stroke is 12.2 times higher in patients with FD than in healthy subjects [31].

The pathological mechanisms for stroke in FD is not clear, but abnormalities in cerebral blood flow as well as in the walls of intracranial vessels have been seen [32]. A possible contributing factor is that formation of thrombi may be enhanced due to increased adhesion of neutrophils and monocytes to the endothelial wall [1, 33].

4. Pathophysiology

That Gb₃ is accumulated in lysosomes is well known, but the specifics regarding what causes cellular dysfunction is not [8]. Accumulation of substrate does lead to enlargement of the affected cells, in turn resulting in enlargement of entire organs. This is, however, not the only explanation [34]. One report presents a case where cardiac hypertrophy resulted in a heart weighing 1100 g, and Gb₃ only accounted for 3.5 g [35, 36]. Mitochondrial metabolism is affected by the substrate accumulation in FD, which is part of the explanation for the organ damage that occurs [37]. There may be dysfunction of the endoplasmic reticulum as well. Fibrosis, inflammation and oxidative stress appear to play important parts in pathogenesis [8].

5. Treatment

In 2001 enzyme replacement therapy (ERT) was introduced; human recombinant α -galactosidase A administered through bi-weekly intravenous infusions. Two recombinant enzyme preparations exist: agalsidase alfa and agalsidase beta. ERT has been shown to reduce pain, improve cardiac function [38], and stabilize kidney function [39]. Treatment is recommended for classically affected males and females and non-classically affected males who show early clinical signs of heart, kidney, or brain involvement. In classically affected males aged 16 or older without signs or symptoms of organ involvement and in non-classically affected females with early clinical signs, treatment should be considered [15]. ERT should be prescribed as early in the disease course as possible, since the benefit in advanced FD seems doubtful [40, 41]. Although the risk of developing a first or second complication is reduced by increased treatment duration, ERT does not seem to prevent disease progression [40].

Since 2016 another treatment option has become available: pharmacological chaperone therapy (PCT). The drug is taken orally, and can restore enzyme activity by promoting correct folding in patients with mutations responsive to the therapy (approximately 35–50% of patients) [8, 42]. Individual eligibility for treatment is tested through an in vitro enzyme activity assay [43]. During long-term therapy it has maintained renal function, and reduced cardiac mass more effectively than ERT [42].

Both ERT and PCT should always be combined with therapies to manage the different organ manifestations clinically [8].

Regarding implantable cardioverter-defibrillator therapy, the ESC state that their risk prediction model HCM Risk-SCD, used for calculating the risk of sudden cardiac death (SCD) in HCM patients, should not be used in patients with FD [23]. There are currently no guidelines for implantation of cardiac devices in FD, and data on risk predictors are scarce. One study showed a higher delivery of device therapy in FD than in HCM. The rates of asymptomatic non sustained ventricular tachycardia were similar, but FD patients experienced a higher rate of ventricular arrhythmia that required anti-tachycardia pacing or defibrillation [44].

6. Health-related quality of life

Patients with FD have a lower quality of life than the population in general; a systematic review found that they score lower in all domains in the SF-36 and EQ-5D questionnaires (the domains include aspects such as a physical and mental component summary score) [45]. However, no studies had examined the difference between classically and non-classically affected individuals. The effect of ERT on quality of life was not conclusive. A qualitative study using in-depth interviews with ten Norwegian women, heterozygous for FD, found that receiving the diagnosis can bring about feelings of relief as well as distress [46]. For symptomatic women the diagnosis can be an explanation of problems they have dealt with for years; many have been burdened by feeling like hypochondriacs because of health issues without an apparent cause. On the other hand, some women saw the diagnosis itself as stigmatizing. Almost every participant had negative feelings about passing the condition on to their children. Another qualitative study of 30 patients from the Netherlands, both male and female, found that many patients had experiences of being misdiagnosed and feeling misunderstood due to delayed correct diagnosis [47]. Others mentioned that presymptomatic diagnosis had drawbacks such as medicalization and labeling.

7. Prognosis

Before ERT, male patients died at a mean age of 50 [48], and a study of females showed a median cumulative survival of 70 years [49]. The long-term prognosis of FD in a modern setting needs to be further elucidated.

8. Future perspectives

There are current studies of gene therapy for FD, as well as substrate reduction therapy, second generation enzyme replacement therapies, and novel PCTs [8, 43]. The second generation enzyme replacement therapies currently in development are plant derived as opposed to agalsidase alfa (produced in human fibroblasts) and agalsidase beta (produced in hamster ovary cells), which could result in a different bio distribution. Substrate reduction therapy is an oral treatment, which aims to limit the formation of metabolites that FD patients cannot degrade. There are currently ongoing Phase I and II clinical trials in which haematopoietic stem cells are recruited from the patient and transduced with the lentivirus vector containing the human α -galactosidase A gene, then re-administered to the patient (NCT02800070 and NCT03454893) [43].

9. Conclusions

FD is a rare disease, generally underdiagnosed, with profound effects on morbidity and mortality. Symptoms, such as debilitating pain, can present themselves early in childhood and in time the disease may lead to severe cardiac, renal, and cerebrovascular complications. The available treatment with ERT has a doubtful effect in advanced FD, making it imperative that the diagnosis is made in time. The Fabry Registry has been used in several studies of FD patients, and registry data is a valuable resource when it comes to evaluating treatment options. In the future, different therapeutic approaches could be compared using the information this

registry can provide regarding clinical and investigative findings. The suffering associated with living with unexplained symptoms for years is yet another reason why increased awareness of FD in the medical community is of great importance.

Conflict of interest

Ida Kåks reports no conflicts of interest. Peter Magnusson has received speaker’s fees or grants from Abbott, Alnylam, Amicus Therapeutics, AstraZeneca, Bayer, BMS, Boehringer-Ingelheim, Coala Life, Internetmedicin, Lilly, MSD, Novo Nordisk, Octopus Medical, Orion Pharma, Pfizer, Sanofi, Vifor Pharma, and Zoll.

Abbreviations

ERT	enzyme replacement therapy
ESC	European Society of Cardiology
FD	Fabry disease
GB ₃	globotriaosylceramide
HCM	hypertrophic cardiomyopathy
LVH	left ventricular hypertrophy
PCT	pharmacological chaperone therapy
SCD	sudden cardiac death

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