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Fabry Disease: A Metabolic Proteinuric Nephropathy

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1. Introduction

Fabry disease is a rare disease. However, Fabry disease is more common than other inherited lysosomal storage disorders, affecting 1 in 40,000 to 1 in 117,000 worldwide (Mehta et al., 2004, Germain, 2010). Fabry disease is caused by an inherited deficiency of galactosylgalactosylglucosylceramidase" (EC 3.2.1.14), commonly referred to as α -galactosidase A (α -Gal A). As a result, there is progressive cellular accumulation of glycosphingolipids, leading to organ failure and premature death. For decades, only symptomatic therapy was available, that did not prevent the fatal evolution of the disease. In the last decade, two forms of Enzyme Replacement Therapy (ERT), that prevent disease progression as well as potentially reverse symptoms, have been developed. However, these drugs are expensive and do not cure the disease.

2. Fabry disease: concept

Fabry disease is an X-linked lysosomal storage disorder caused by mutations in the gene encoding the lysosomal enzyme α -galactosidase A (α -Gal A). α -galactosidase A catalyzes the hydrolytic cleavage of the terminal alpha-galactosyl moieties from globotriaosylceramide (Gb3) and glycoproteins. The deficiency of α -galactosidase leads to accumulation of Gb3 and other glycosphingolipids in plasma and different cell types throughout the body (Nance et al., 2006) (Figure 1). Glycosphingolipid storage may interfere with cellular membrane proteins, such as ion channels, become cytotoxic, or lead to accumulation of soluble cytotoxic metabolites (Schiffmann et al., 2002, Aerts et al., 2008, Sanchez-Niño et al., 2010), although the precise molecular link between lipid storage and disease manifestations is unclear. Progressive accumulation of Glycosphingolipid is associated with systemic disease, with a wide spectrum of clinical manifestations that reduce the life expectancy of patients.

3. Genetics

The α -galactosidase A gene (*GLA*) is located on the minus strand of the chromosome X on the locus Xq22.1. The *GLA* gene is 10,223 base pairs long and contains 7 exons. *GLA* gene

may give rise to 7 different processed transcripts by alternative splicing. However, just one of these encodes the 429-aminoacid lysosomal α -Gal A with a molecular mass of 48.7 kD.

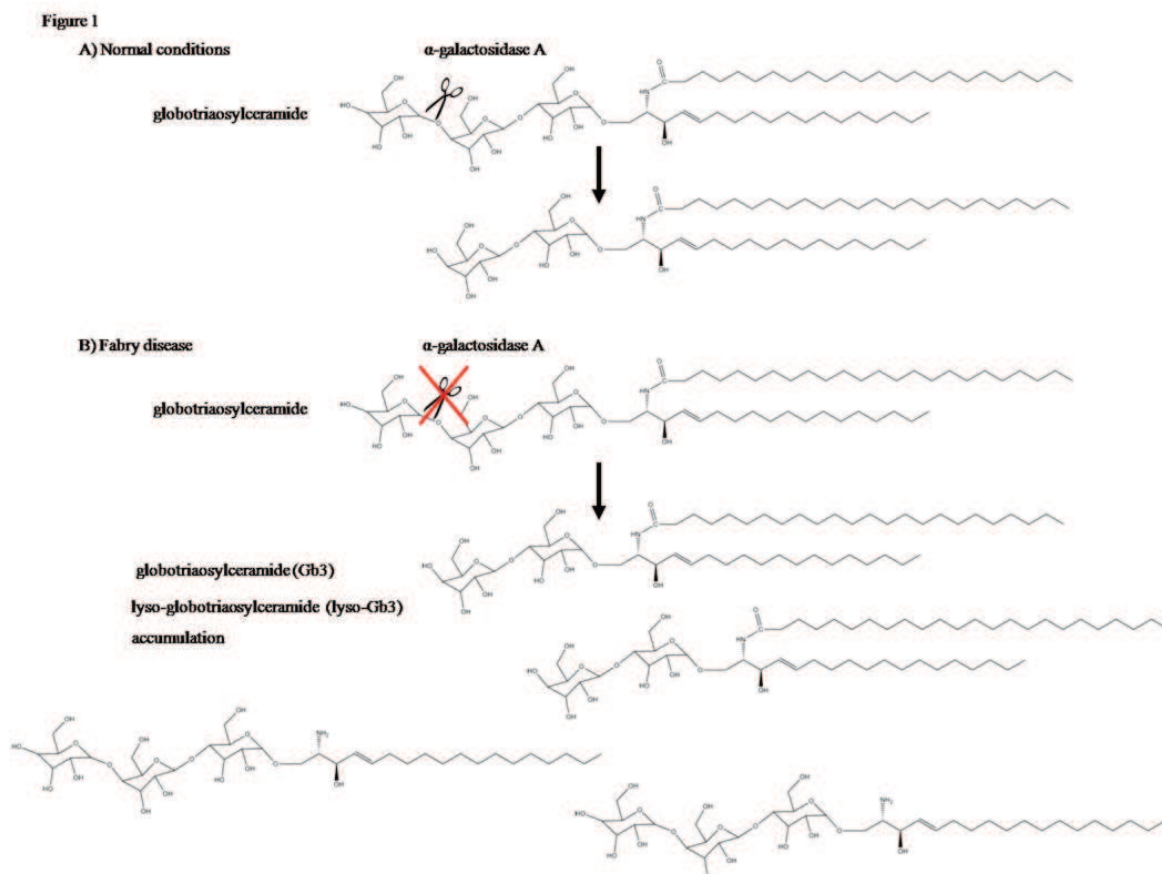


Fig. 1. A) α -galactosidase A catalyzes the hydrolytic cleavage of the terminal galactose from globotriaosylceramide (Gb3). B) The deficiency of α -galactosidase leads to accumulation of Gb3 and other glycosphingolipids, such as lyso-globotriaosylceramide (lyso-Gb3)

Within the coding region, 239 single nucleotide polymorphisms present in the general population and more than 400 *GLA* mutations that lead to Fabry disease have been found. Exons 5, 6 and 3 comprise the majority of point mutations respectively. Missense mutations may be classified in 3 groups in accordance with the effect they have on the protein function (Garman & Garboczi, 2004). First, mutations that alter the active site of the enzyme; second, mutation that interfere with the correct folding and stability of the protein; and finally, the remaining mutations that negatively affect the function of the enzyme. The nature of the mutation may influence therapeutic approaches. Most mutations are family-specific, which explains the marked variability in the residual enzyme activity and precludes the use of a single, fast genetic testing technique. Rather, the whole gene should be sequenced.

4. Clinical manifestations of Fabry disease

4.1 Early clinical features

Although glycolipid accumulation begins in the prenatal period, symptoms of the classic form of Fabry disease do not arise until childhood (Vedder et al., 2006). Symptoms include

episodes of extremity pain or acroparesthesia, gastrointestinal symptoms, hypohidrosis and associated heat sensitivity (Cable et al., 1982; Ries et al., 2005; Rowe et al., 1974) (Table 1). Pain has been linked with small fiber neuropathy (Attal & Bouhassira, 1999) and is thought to be caused by either reduced perfusion of peripheral nerves or glycosphingolipid accumulation in neural or perineural cells (Gadoth & Sandbank, 1983; Gemignani et al., 1984). Pain has been described as burning and starts in the hands and feet but can radiate proximally. It may be present throughout the life of the patient, but frequently peaks in childhood or adolescence and then decreases. This has been attributed to end-stage nerve injury. Pain may be continuous or episodic, but is triggered by extreme temperature changes, fever, stress or physical exercise (MacDermot et al., 2001). Both, acute and chronic pains are difficult to deal with medically, requiring the use of narcotic or neuroleptic drugs respectively (Schiffmann & Scott, 2002).

Organ system	Sign/Symptom
Nervous system	Acroparesthesias Nerve deafness Heat intolerance, hypohidrosis Hearing loss, tinnitus
Gastrointestinal tract	Nausea, vomiting, diarrhea Postprandial bloating and pain, early satiety
Skin	Angiokeratomas
Eyes	Corneal and lenticular opacities Vasculopathy (retina conjunctiva)
Kidneys	Microalbuminuria, proteinuria Impaired concentration ability
Heart	Impaired heart rate variability ECG abnormalities (shortened PR interval) Mild valvular insufficiency Left ventricular hypertrophy

Table 1. Early signs and symptoms of Fabry disease

Gastrointestinal manifestations include nausea, vomiting, abdominal pain, early satiety, diarrhea and constipation (Hoffmann & Keshav, 2007). It has been proposed that delayed gastric emptying, in conjunction with lipid accumulation within ganglion cells of the autonomic nervous system, are responsible for the early satiety, whereas diarrhea has been linked to bacterial overgrowth (O’Brien et al., 1982).

Decreased sweating or hypohidrosis is another common feature of Fabry disease. It causes heat intolerance and inability to physical exercise. Hypohidrosis has also been attributed to autonomic neuropathy (Zarate & Hopkin, 2008). Less frequent than hypohidrosis is hyperhidrosis (excessive sweating), which is especially noticeable in the palms of the hands and soles of the feet (Zarate & Hopkin, 2008).

These symptoms highly reduce the quality of life of patients. However, the lack of physical findings frequently preclude the correct diagnosis in the absence of family history (Ries et al., 2005).

More characteristic disease manifestations arise in adolescence, such as angiokeratomas and corneal opacities. Angiokeratomas are reddish-purple vascular skin lesions, usually clustered around the swimming trunk region, which tend to increase in size and number with age (Zarate & Hopkin, 2008).

Corneal opacity (cornea verticillata) is the most characteristic ophthalmological abnormality observed in Fabry patients. They are the result of glycosphingolipids deposition between the basal membrane of the corneal epithelium and Bowman’s membrane (Rodríguez-González-Herrero et al., 2008). Corneal opacities usually do not interfere with visual acuity. Other ophthalmological manifestations include conjunctival and retinal vascular tortuosity (Nguyen et al., 2005) and occlusion of retinal vessels (Utsumi et al., 1997).

Later in life many patients develop life-threatening complications including end-stage renal disease, heart and cerebrovascular diseases that may cause death (Table 2).

Organ system	Sign/Symptom
Central nervous system	Stroke
Kidneys	End-stage renal disease
Heart	Arrhythmia, sudden death Ischemis Heart failure Heart fibrosis

Table 2. Life threatening signs and symptoms of Fabry disease

4.2 Life-threatening complications

Classical Fabry disease progresses to irreversible tissue damage and organ dysfunction, limiting life-expectancy in middle-age patients (Zarate & Hopkin, 2008). The main cause leading to death in men suffering from classic Fabry disease was renal failure before the widespread availability of renal replacement therapies, while now cardiac causes predominate (Mehta et al., 2006.).

Renal abnormalities include proteinuria, nephrotic range proteinuria, rarely nephrotic syndrome and chronic renal failure, requiring dialysis or kidney transplantation (Branton et al., 2002; Tsakiris et al., 1996, Ortiz et al., 2008, Ortiz et al., 2010)

Some patients develop end-stage renal disease at the same age as those with the classic form but lack other characteristic signs of the classical phenotype such as angiokeratomas, acroparesthesias or hypohidrosis, thus hindering the diagnosis of the condition (Nakao et al., 2003).

Cardiac disease may have several clinical manifestations. (Patel et al, 2011) The most frequent cardiac abnormality is progressive hypertrophic cardiomyopathy, although diastolic dysfunction, arrhythmia, myocardial fibrosis and short P-R are also seen (Linhart & Elliott, 2007). Fabry patients are frequently hypotensive. However, Fabry patients may have blood pressure that may be above recommended targets for chronic kidney disease patients (which are below 130 mmHg systolic and below 80 mmHg diastolic) (Ortiz et al., 2008). Cardiac symptoms may include palpitations, angina, shortness of breath and sudden death (Shah & Elliott, 2005).

The mechanisms leading to myocardial hypertrophy are not completely understood. The fact that only 1-2% of heart hypertrophy is attributable to actual storage of glycosphingolipids within the cardiac cells suggests that activation of signaling pathways leading to fibrosis play an important role (Linhart & Elliott, 2007). In this regard, much of the heart volume consists of fibrosis. Actual promoters of fibrosis are unknown. However, if we take a clue from the kidney, both death of myocardial cells and the presence of fibrogenic soluble mediators, such as lyso-gb3, that promote release of transforming growth factor beta 1 (TGF β 1), a fibrogenic cytokine, may be contributors (Sanchez-Niño et al, 2010).

A cardiac variant of Fabry disease has been described. In these patients, clinical manifestations and Gb3 storage are almost restricted to the heart (Ogawa et al., 1990). This is associated with residual α -galactosidase A activity or certain mutations. There is no clinical evidence of classical Fabry disease in other organs, although mild proteinuria has been observed (Ishii et al., 2002). Clinical manifestations appear later in life than in classical Fabry disease.

Cerebrovascular complications, mainly ischemic episodes, occur in Fabry disease (Sims et al. 2009). This is thought to be due to the accumulation of Gb3 in the cerebral blood vessels (Altarescu et al., 2001). However, the effect of sphingolipid storage is different depending on vessels' diameter. Thus, Gb3 deposition leads to progressive stenosis in small blood vessels, whereas in larger vessels weakened walls dilate, causing hyper-perfusion and tortuosity (Mitsias P, 1996). Clinical consequences of cerebrovascular injury include stroke, transient ischemic attacks, epilepsy, vertigo and headache (Mehta & Ginsberg, 2005).

Arterial remodeling and intima-media thickening have been described and may explain ischemic events. By contrast, classical atherosclerotic lesions are uncommon. It is unclear whether this is due to the relative young age of most patients or to a specific change in the vascular response to injury brought about the glycolipid accumulation or the metabolic consequences of the disease. In this regard, high HDL cholesterol levels have been described in Fabry patients (Cartwright et al., 2004). In at least in some Fabry patients HDL particles contribute disproportionately to carry glycosphingolipids (Clarke et al., 1976).

4.3 Other clinical manifestations

Additional clinical manifestations may include anemia, azoospermia, depression, facial dysmorphism, hypothyroidism, lymphoedema, parapelvic kidney cysts and priapism (Ries et al., 2004, Sunder-Plassmann, 2006), although there is discussion whether some of these, such as hypothyroidism, are real Fabry disease manifestations.

Tinnitus and substantial hearing loss have been described, especially in men (Hegemann et al., 2006). Hearing loss seems to be directly related to neuropathy (Ries et al., 2007).

Significant airflow reduction is common in Fabry patients. Respiratory involvement manifests as shortness of breath and dyspnea with exercise, chronic cough, and less frequently asthma (Rosenberg et al., 1980).

4.4 Fabry disease in women

Traditionally females were considered to be at low risk of clinical manifestations of Fabry disease. However, there is accumulating evidence that some females may suffer symptoms as severe as males (Wilcox et al., 2008). In this regard, Fabry disease may be considered as an X-linked disease with a high penetrance in females. Terms such as "recessive X-linked

disease" are no longer used. It has been estimated that only 70% of women with *GLA* mutations develop clinical manifestations of the disease, which tend to be less severe and more variable than in men (Dobyns, 2006, Schiffmann R, 2009). As a result, it is likely that a large number of affected women remain undiagnosed. Women are affected because of the lack of cross-correction between cells with normal α -Gal A activity and cells with deficient α -Gal A (Romeo et al., 1975). Female cells have two X chromosomes, but one of them is randomly inactivated (lyonization). It is thought that the percentage of disease-carrying X chromosomes that are inactivated is a key factor contributing to disease expression variability in females (Dobrovolsky et al., 2005).

5. Fabry nephropathy

5.1 Natural course

Fabry nephropathy is one of the most severe manifestations of Fabry disease and was the cause of death before the widespread availability of dialysis and kidney transplantation. Like most aspects of Fabry disease, kidney disease is thought to result from Gb3 accumulation in glomerular endothelial, mesangial and interstitial cells, podocytes and renal vasculature. Progressive intracellular accumulation of Gb3 is thought to cause glomerulosclerosis and interstitial fibrosis (Alroy J, 2002) as well as its urinary excretion together with other lipids (Branton MH, 2002). More recently a role of soluble glycolipid metabolites in the pathogenesis of podocyte injury has been suggested (Sanchez-Niño et al, 2010). As a result of lipid storage, kidneys may increase in size, although, as is the case with other renal disease characterized by enlarged kidney, such as diabetic nephropathy, in advanced renal failure the kidneys eventually shrink (Torra R, 2008).

Manifestations of kidney injury in Fabry disease include urinary concentrating defect, proteinuria, renal insufficiency and eventually renal failure requiring renal replacement therapy. The severity of kidney manifestations increases with age.

5.1.1 Renal function

Progressive loss of kidney function is characterized by elevated serum creatinine levels and decreasing glomerular filtration rates (GFR) (Ortiz et al, 2008). There is some debate as to the existence of an early hyperfiltration period, analogous to that observed in diabetic nephropathy, since assessment with of GFR by precise, research-grade technique is lacking. Early reports indicated that the loss of GFR was similar to that observed in diabetic nephropathy, around 10 ml/min/year (Branton et al., 2002). Lower rates have been described in recent times, that may be partially attributed to an overall better symptomatic control of chronic kidney disease aimed at proteinuria and blood pressure targets. Urinary protein excretion is the main predictor of GFR loss. Males with urinary protein/creatinine > 1.5 had a mean eGFR slope -5.6 ml/min per 1.73 m² per year, while this value was -1.3 ml/min per 1.73 m² per year for women with the highest urinary protein/creatinine (> 1.2) (Wanner et al., 2010).

Men with classical Fabry disease reach end-stage renal disease requiring dialysis or transplantation at a mean age of 40 years (Ortiz et al, 2010). Females reaching end-stage renal disease do so at the same mean age as males. However, there are ten-fold less females than males in both United States and European end-stage renal disease registries (Tsakiris et al., 1996, Thadhani et al, 2002). This suggests that in most females, Fabry nephropathy does

not progress to reach end-stage renal disease, but in those in whom progression occurs, the time-course is similar to males.

5.1.2 Proteinuria

Early kidney injury is manifested as microalbuminuria which progresses to overt proteinuria (Schiffmann, 2009, Ortiz et al, 2008). Microalbuminuria is a misnomer that only indicates that pathological abnormalities may be detected by methods not available when the first tests to study albuminuria were commercialized. The term microalbuminuria indicates a urinary albumin excretion of $> 30 \text{ mg}/24\text{h}$ or $>30 \text{ mg}/\text{g}$ creatinine. In this regard, Fabry nephropathy usually recapitulates the sequence of events observed in diabetic nephropathy, another proteinuric nephropathy also consequence of a metabolic derangement. Overt proteinuria ($>300 \text{ mg}/24 \text{ h}$) was present in 43 and 26% of males and with early Fabry disease, respectively, and the proportions were higher with more severe kidney involvement (Ortiz et al, 2008). Established proteinuria (Albuminuria $> 300 \text{ mg}/\text{day}$) is a sign of irreversible damage to the kidney (Zarate & Hopkin, 2008). Numerous experimental studies have shown a direct relationship between the degree of proteinuria and the rate of decline of renal functions (Tryggvason & Pettersson, 2003). Proteinuria is a consequence of glomerular damage but itself causes tubulointerstitial injury. Reabsorption of excess specific proteins filtered at the glomerulus by the proximal tubule activates these cells to release inflammatory factors and undergo apoptosis (Thomas ME, 1999). Thus, the magnitude of proteinuria could be used as a marker of glomerular damage. Interestingly, morphological studies, not specifically performed in Fabry disease, have confirmed a stronger correlation between tubulo-interstitial damage and renal function than between glomerular injury and renal function (Nath, 1992). Little is known about the factors that may speed up the process of Fabry nephropathy. Proteinuria is clearly a risk factor (Wanner et al., 2010). Thus, controlling proteinuria is thought to be important to for the progression of Fabry disease and evidence for this approach is discussed below.

5.1.3 Blood pressure

Hypertension is rarely found as an early symptom in Fabry disease but becomes more prevalent with the progression of the condition, indicating kidney declining function (Branton et al., 2002). Higher blood pressure values favor glomerular hyperperfusion as a compensatory response to nephron loss (Schieppati & Remuzzi, 2003). However, glomerular hypertension promotes kidney disease progression. Although not specifically tested in Fabry disease, lowering blood pressure to below 130 mmHg systolic AND 80 mmHg diastolic is recommended in patients with chronic kidney disease in order to slow the progression of nephropathy (K/DOQI clinical practice guidelines, 2004).

5.2 Heterogeneity

There is a great variability both in disease manifestations and the timing of kidney disease progression within and between families. Thus, the age at initiation of renal replacement therapy in the Fabry Registry data had a range of 15 to 79 years in males and 17 to 78 years in females (Ortiz A et al., 2010). The genetic or environmental factors that influence disease heterogeneity are unknown. However, unraveling them is a key priority since it will lead to a better understanding of the disease and potentially to novel therapeutic approaches.

5.3 Women

Most heterozygous women with Fabry disease used to be considered asymptomatic carriers. However, they may be as severely affected as men with the classic phenotype (Desnick et al., 2001, Wang et al., 2007, Wilcox et al., 2008). The clinical manifestation of Fabry disease in females tend to be less severe and to arise later than in males (Schiffmann. 2009). In this regard they may develop albuminuria and progressive renal dysfunction leading to the need of renal replacement therapy (Ortiz et al., 2008; Ortiz et al; 2010). If this occurs the mean age at initiation of renal replacement therapy is similar to men (Ortiz et al, 2010).

5.4 Diagnosis

In spite of the early onset of Fabry disease in some cases, the absence of family history, the variety of clinical manifestations and their similarity with those of other conditions may delay the diagnosis of Fabry disease, in some cases for years. Due to the availability of specific therapy, an early diagnosis would be desirable.

5.4.1 Diagnosis of Fabry disease

Diagnosis involves measuring residual enzyme activity in plasma, leukocytes or whole blood as well as sequencing of the gene to characterize the genetic defect (Ortiz et al., 2010b). Confirming the genetic defect may be important for the eligibility for treatment with novel approaches, such as chaperones. In the absence of family history, confirmation of the genetic defect by gene sequencing is mandatory in females when Fabry disease is suspected, since enzymatic assays may be normal even in the presence of Fabry disease due to random chromosome X inactivation. Genetic confirmation is also highly recommended in males.

A key, often forgotten aspect of Fabry disease, is the need to take a careful family history which allows the diagnosis of individuals in early stages of the disease.

5.4.2 Screening for Fabry disease

Screening by means of rapid and low-cost strategies to detect Fabry disease is indicated in high-risk populations (Oqvist et al., 2009). These include patients with unexplained left ventricular hypertrophy, younger patients with unexplained stroke and patients with chronic kidney disease of unknown etiology. However, neonatal screening has not yet been incorporated into routine clinical practice. Current screening methods are based on quantification of enzyme activity in dry blood spots. Performance for males is adequate. However, given the mosaicisms of females regarding X chromosome inactivation, Fabry women may have near normal whole blood enzyme activity and still have the disease. Thus, dried blood spot analysis is unable to detect about a 33% of heterozygous females leads to the need for more efficient strategies (Linthorst GE, 2005). Novel screening methods, such as proteomic analysis of urine, and quantification of urinary Gb3 or lyso-Gb3 are under study.

5.4.3 Renal biopsy for diagnosis of Fabry nephropathy

Kidney biopsy is recommended in Fabry patients exhibiting reduced GFR or proteinuria to confirm the diagnosis of Fabry kidney involvement (Ortiz et al., 2008b). In addition, renal biopsy for kidney disease of unknown origin may reveal unsuspected Fabry disease. Biopsies reveal typical Gb3 accumulation in tubular epithelial cells, glomerular and endothelial cells, and provide information on the extent of renal damage. In patients with Fabry disease, glomeruli present a striking white color under illumination in a

stereomicroscope as a result of lipid-laden podocytes in contrast to the usual red color of normal glomeruli (Svarstad et al., 2004).

5.5 Pathogenesis and pathology

Fabry disease manifestations had traditionally been ascribed to intracellular accumulation of Gb3 and related glycosphingolipids (Figure 1). However, the precise pathways leading to tissue injury were unknown. Recent evidence suggests a role for more soluble molecules, such as lyso-Gb3, that may activate target tissue cells, such as podocytes, to release secondary mediators of injury that would be responsible for tissue injury and disease manifestations (Figure 2). This model (accumulation of a soluble metabolite with cytotoxic properties) would be analogous to the diabetes situation, where high glucose concentrations as a result of the metabolic derangement promote activation of target tissue cells to release mediators that cause tissue injury. If correct, this paradigm would greatly enhance research into novel therapeutic approaches to Fabry nephropathy by allowing the extrapolation of concepts from diabetic nephropathy, a better understood and more common disease (Sanchez- Niño et al., 2010b).

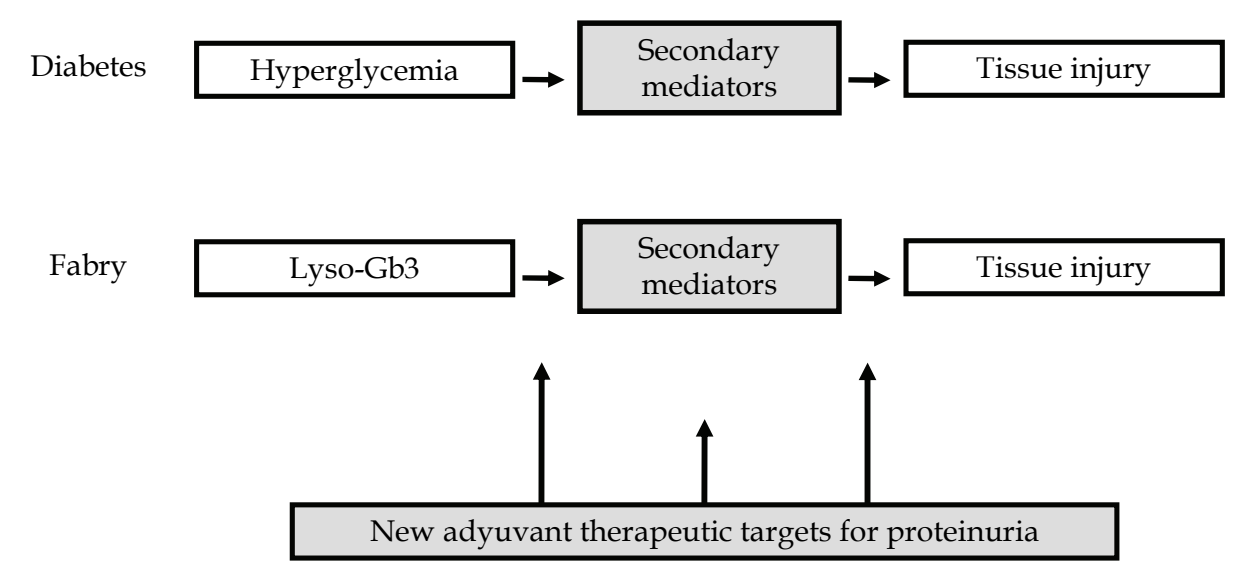


Fig. 2. Hypothetical similarities between the pathogenesis of diabetic nephropathy and Fabry disease nephropathy and potential therapeutic implications

Detailed descriptions of kidney pathology in children and adults with Fabry disease have recently been published (Tondel et al., 2008, Fogo et al., 2010, Najafian et al., 2010). There is widespread glycolipid accumulation in glomerular podocytes, mesangial and endothelial cells, as well as proximal and distal tubular cells, interstitial endothelial cells and other endothelial cells. While early pathogenic theories were centered in endothelial cell glycolipid accumulation, that was thought to lead to ischemic injury, the total early clearance of endothelial deposits by ERT, but persistence of proteinuria and chronic kidney disease progression despite this endothelial clearance have focused the attention to podocytes. In this regard, podocytes are the cells with a worse response to ERT in terms of

glycolipid clearance (Germain et al, 2007). Only after 5 years of ERT a mild decrease in podocytes glycolipid deposition was noted. Furthermore, podocyte injury is a key feature of other proteinuric kidney diseases (Moreno et al., 2008). In addition, in children with early Fabry nephropathy the best pathological correlate of albuminuria was the presence and amount of podocytes glycolipid accumulation (Najafian et al., 2010). Thus, recent research into the pathogenesis of Fabry nephropathy has focused on the cell biology of the podocyte (Sanchez-Niño et al., 2010). The other key pathology feature of Fabry nephropathy is glomerular (glomerulosclerosis) and interstitial fibrosis, which is associated with loss of parenchymal renal cells (podocytes and tubular cells)(Fogo et al., 2010). Thus, there is renewed interest in the link between metabolites accumulated in Fabry disease and the synthesis and deposition of extracellular matrix components.

5.5.1 Metabolic initiators: Gb3 and lyso-Gb3

In Fabry disease, Gb3 is widely distributed in lysosomes and other cellular compartments such as the cell membrane, the ER or the nucleus (Askari et al., 2007). It was hypothesized that Gb3 may disrupt intracellular trafficking (Pagano RE, 2003) or alter the composition of membrane lipid rafts. Lipid rafts interact with other lipids and proteins that signal from cell surface receptors (Galbiati et al., 2001), such as endothelial nitric oxide synthase (eNOS) (Mogami et al., 2005). It was further hypothesized that cell stress due to Gb3 accumulation could promote the production of reactive oxygen species (ROS) that induce cell death (Shen et al., 2008).

Although Gb3 accumulation is widespread, serum Gb3 or Gb3 deposits do not necessarily correlate with clinical manifestations (Aerts et al., 2008). Instead, a new biologically active soluble glycolipid metabolite, globotriaosylsphingosine (lyso-Gb3), has been found in high serum, kidney and urinary concentrations in Fabry patients (Aerts et al., 2008, Auray-Blais et al., 2010, Togawa et al.2010b). Lyso-Gb3 is involved in vascular smooth muscle cell proliferation and induces in podocytes the production of mediators of glomerular injury such as TGF- β 1, a critical mediator of extracellular matrix (ECM) production, fibrosis and podocyte injury (Alsaad & Herzenberg, 2007; Mason & Wahab, 2003; Pantsulaia. 2006; Park et al., 1997) (Sharma et al, 1997) and CD74, a MIF receptor that regulates the expression of lethal cytokines (Sanchez-Niño et al., 2009), suggesting a role in the pathogenesis of Fabry disease (Sanchez-Niño et al., 2010).

Lyso-Gb₃ seems to be involved in glomerular injury in Fabry disease by triggering the release of TGF-beta1 and CD74, both secondary mediators of glomerular injury common to diabetic nephropathy (Sanchez-Niño et al., 2010). TGF-beta1, in turn, leads to release of excess ECM components, including type IV collagen and fibronectin, by podocytes, contributing to the characteristic glomerulosclerosis of Fabry nephropathy. Further unpublished data suggest a more widespread release of inflammatory mediators by podocytes exposed to lyso-Gb3.

5.6 Therapy of Fabry nephropathy

The first therapies for Fabry disease were oriented to deal with the symptomatic effects of the disorder, such as pain, cardiac and cerebrovascular complications. However, most patients would die for ESRD unless kidney transplantation or renal dialysis was applied. Guidelines for the management of Fabry nephropathy have recently been published (Ortiz et al., 2008b).

5.6.1 Enzyme replacement therapy (ERT)

Until 2000, recognition of Fabry disease did not change the patient management or prognosis, since no specific treatment was available. However, in the last decade enzyme replacement therapy (ERT) is available and addresses the metabolic defect, although it does not cure the disease. ERT provides the chance to modify the natural history of Fabry disease. Two companies commercialize human recombinant α -galactosidase synthesized by genetically engineered cell lines.

Indications: ERT is indicated in every male with classical Fabry disease. In this population ERT should be initiated as early as possible. In addition, ERT should be prescribed to females with any evidence of injury to the heart, central nervous system or kidney and considered in females with symptoms in other organs and systems (Germain DP, 2010, Ortiz et al., 2010b). In case of a transitory limitation in ERT supplies, prioritization guidelines have been published (Linthorst et al., 2011). These guidelines should not be considered compelling indications in the absence of limited availability of treatment. Furthermore, these guidelines do not apply to a chronic limitation of resources since they take into account both the indication of ERT as well as the urgency of the need of ERT. Thus, they do not answer the question who should and should not be treated. They answer the question, if therapy is indicated but ERT availability is limited, who should be treated first, implying that not prioritized patients will also be treated but later, as soon as supplies are available.

There are currently two commercially available enzyme preparations for the treatment of Fabry disease: (1) Replagal® (agalsidase alfa; Shire Human Genetic Therapies, Inc., Cambridge, MA) and (2) Fabrazyme® (agalsidase beta; Genzyme Corporation, Inc., Cambridge, MA). Agalsidase alfa is produced by cultured human fibroblasts, whereas agalsidase beta produced by the expression of human α -galactosidase cDNA in Chinese Hamster Ovary (CHO) cells. In the USA, only agalsidase β has been approved by the US Food and Drug Administration, while in Europe both enzymes are available for clinical use.

The approved doses of agalsidase-alfa and agalsidase-beta are 0.2 mg/kg and 1.0 mg/kg, given intravenously every 2 weeks, respectively. There is evidence that agalsidase-beta may be used at 0.3 mg/kg every two weeks for certain patients. This difference in dose remains unexplained by the molecular nature of the preparations and there is an ongoing debate whether they are similarly effective. The only published head-to-head clinical trial concluded that disease progression occurred when both enzymes were used at a dose of 0.2 mg/kg every two weeks (Vedder et al, 2007). We must emphasize that this dose is the approved one for agalsidase-alfa, but was 5-fold lower than the approved dose for agalsidase-beta. There is some indication, although the evidence is not strong, for a superiority of the higher dose in patients who develop anti-agalsidase antibodies. Furthermore a doubling of the approved agalsidase alfa dose provided further benefit in terms of nephroprotection for patients whose disease was progressing despite treatment with the approved dose. In addition, only agalsidase beta has shown a benefit on hard endpoints in a phase IV randomized clinical trial (Banikazemi et al., 2007). Despite these considerations, a number of publications have documented that both enzymes at approved doses have proved effective in reducing glycolipid deposits and disease manifestations at least if used early (Eng et al, 2001, Schiffmann et al., 2001; Schiffmann et al., 2006; Germain et al., 2007; Mehta et al., 2009; Schaefer et al., 2009).

5.6.2 Benefits and unmet needs of ERT

ERT addresses the underlying metabolic cause of Fabry disease. ERT slows the loss of kidney function in patients with relatively preserved renal function and low proteinuria (Schiffmann et al., 2006) (Germain et al., 2007). However, progression occurs despite ERT in patients with more advanced renal disease, including those with proteinuria > 1g/d or glomerulosclerotic lesions in renal biopsy, as ERT does not reduce proteinuria and may be unable to avoid its development in treated pediatric patients (Tøndel et al., 2008). Thus, since proteinuria is a major risk factor for progression of Fabry disease, it is advisable to combine antiproteinuric therapy with early institution of ERT.

5.6.3 Antiproteinuric approaches

ACEI/ARBs: the lesser efficacy of ERT once Fabry nephropathy has caused proteinuria or glomerulosclerosis (Germain et al., 2007) raises the need for adjuvant therapies that cooperate with ERT in improving outcomes. Co-treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARB) decreases proteinuria (Tahir et al., 2007). These agents help to control hypertension when present, although in some case a low blood pressure may limit their use. To prevent unwanted blood pressure lowering effects initiation of therapy with low, fractionated doses is recommended.

Active vitamin D has pleiotropic effects that go well beyond the regulation of bone metabolism (Rojas-Rivera et al., 2010). Vitamin D receptor (VDR) activators such as calcitriol and paricalcitol prevent podocyte activation by lyso-Gb3 in podocytes (Sanchez-Niño et al., 2010). In this regard, there is some evidence that paricalcitol, a selective VDR activator, reduces proteinuria in diabetic nephropathy, even in patients treated with ACEIs or ARBs (Agarwal et al., 2005; Lambers Heerspink et al., 2009; de Zeeuw et al., 2010). Interestingly, patients suffering from chronic kidney disease frequently have deficiencies of both 25(OH) vitamin D and calcitriol. Vitamin D deficiencies should be corrected in these patients and VDR agonists are indicated for the prevention and treatment of secondary hyperparathyroidism in chronic kidney disease (Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. 2009) (National Kidney Foundation. 2003). Thus, VDR agonist therapy used to treat vitamin D deficiency or secondary hyperparathyroidism might be beneficial for proteinuria in Fabry disease.

5.6.4 Novel therapies in the horizon

The search for an ideal treatment of the underlying enzymatic defect is still ongoing. Current ERT is expensive, inconvenient and may not reach certain key cells such as the podocytes. Additional therapeutic approaches are being explored.

Substrate reduction therapy by small molecules may be associated with ERT to improve efficacy or reduce ERT dose. Gene therapy is also being explored. In addition certain mutations may benefit from novel therapeutic strategies. Thus, individuals carrying mutation that interfere with the correct folding and stability of the protein may benefit from small molecule chaperone therapy. In addition, an orally active small molecule, ataluren, might be useful in individuals carrying premature stop codons (Torra et al. 2010). Although never tested in Fabry disease, clinical trials in other genetic diseases are underway or have been completed (Kerem et al., 2008).

5.6.5 Monitoring therapy and disease progression

We lack reliable biomarkers that enable assessing disease progression, monitoring treatment response and individualizing ERT dose in Fabry disease. Biomarkers may represent lipid storage burden or target organ injury or response to therapy. Potential biomarkers of glycolipid storage include plasma or urine Gb3 and lyso-Gb3. Lyso-Gb₃ plasma and urinary levels are elevated in Fabry disease. Plasma lyso-Gb3 was found to be useful to diagnose Fabry disease (Rombach et al., 2010). Furthermore, while multiple regression analysis did not demonstrate correlation between plasma lyso-Gb3 concentration and total disease severity score in Fabry males, plasma lysoGb3 concentration did correlate with white matter lesions. In addition, in females, plasma lyso-Gb3 concentration correlated with overall disease severity (Rombach et al., 2010). In Fabry patients plasma lyso-Gb3 falls on ERT, and even more dramatically than Gb3 levels (Togawa et al., 2010, Van Breemen et al., 2011). Urinary lysoGb3 was also correlated with type of mutations, enzyme replacement therapy status and with a number of indicators of disease severity (Auray-Blais et al, 2010). Decreased urinary lyso-Gb3 may reflect decreased kidney lyso-Gb3 burden, since renal tissue lyso-Gb3 was decreased in Fabry mice upon ERT (Togawa et al., 2010b). Despite these promising observations, studies approaching the potential value of lyso-Gb3 concentrations to make clinical decisions regarding ERT dose have not been performed and, thus, it cannot be considered a biomarker for such purpose.

Albuminuria is a biomarker of kidney injury. Both in Fabry and non-Fabry kidney injury the magnitude of albuminuria predicts renal disease progression. In this regard there is solid evidence supporting targeting albuminuria as a therapeutic objective in non-Fabry disease. Anecdotal evidence suggests that this is the case too in Fabry disease, where lowering albuminuria is considered a target to be pursued through adjunctive antiproteinuric therapy (Tahir et al., 2007). A clinical trial (FAACET) is underway to test this hypothesis. Unfortunately, since albuminuria does not improve on ERT in adults, it cannot guide ERT dosing.

Finally promising preliminary data are available of the use of urinary proteomics for the diagnosis and eventual monitoring of Fabry disease. The most promising technique is capillary electrophoresis coupled to mass spectrometry (CE-MS) (Mischak H et al., 2010).

6. Conclusions

Research in Fabry disease is very active in recent times and has led to a paradigm shift in our understanding of the disease and its management (Table 3). The advent of ERT has changed the prospects for Fabry disease patients. However, there are, still unsolved problems:

1. ERT does not modify proteinuria, a key risk factor for renal disease progression (Wanner et al., 2010), in adults and does not stop renal disease progression once a certain degree of renal injury, manifested as histological injury, decreased eGFR or proteinuria (>1g/d), has been reached (Germain DG et al., 2007).
2. Despite adequate endothelial cell clearance, ERT does not clear deposits in podocytes, key cells responsible for avoiding proteinuria (Germain DG et al., 2007). This and the correlation of early podocyte injury with proteinuria (Najafian et al., 2010) support a more central role of podocytes in the pathogenesis of renal disease than previously thought.

- 3. The lack of biomarkers of tissue injury activity and response to therapy hinders dose individualization, the follow-up of the therapeutic response and early identification of females most at risk for progressive disease.
- 4. The molecular link between the metabolic defect and tissue injury is still poorly characterized. This hinders the development of adjuvant therapies.

The full scope of these gaps in knowledge became evident during the global shortage on ERT availability, which took place in 2009-2010 (Linthorst et al, 2011). Hopefully this realization, as well as recent advances in the pathogenesis and treatment approaches for the disease will further improve the outcome of Fabry patients.

Classical concepts	New paradigms
Endothelium as key target cell	Podocyte as key target cell
Intracellular deposits cause injury	Soluble metabolites cause injury
Deposits injure cells containing them	Injury of distant or adjacent cells
Unknown tissue injury mechanisms	Recruitment of secondary mediators
ERT as only therapy	Need for adjuvant therapies
Same dose fits all	Individualize dose: biomarkers need
Therapeutic nihilism for advanced tissue injury	Target secondary mediators of injury in advanced tissue injury

Table 3. Classical concepts and new paradigms in Fabry nephropathy

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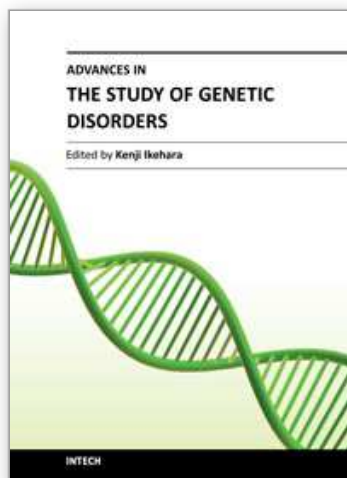
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The studies on genetic disorders have been rapidly advancing in recent years as to be able to understand the reasons why genetic disorders are caused. The first Section of this volume provides readers with background and several methodologies for understanding genetic disorders. Genetic defects, diagnoses and treatments of the respective unifactorial and multifactorial genetic disorders are reviewed in the second and third Sections. Certainly, it is quite difficult or almost impossible to cure a genetic disorder fundamentally at the present time. However, our knowledge of genetic functions has rapidly accumulated since the double-stranded structure of DNA was discovered by Watson and Crick in 1956. Therefore, nowadays it is possible to understand the reasons why genetic disorders are caused. It is probable that the knowledge of genetic disorders described in this book will lead to the discovery of an epoch of new medical treatment and relieve human beings from the genetic disorders of the future.

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