Fabry meets Markov: evaluating biochemistry, disease course and costs in support of health care policy
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General introduction
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Background

Fabry disease was first described in 1898 by two dermatologists. Johannes Fabry in Germany and William Anderson in England independently reported a new disease entity with characteristic skin lesions. The skin lesions, called angiokeratoma corporis diffusum are features of a disorder now known as Anderson-Fabry disease, or just Fabry disease. In the following decades, other symptoms were recognized as part of this disorder. Besides angiokeratoma, the co-existence of neurological symptoms, cardiomyopathy and ophthalmological characteristics were noted and a common cause for the complex of symptoms was suspected. A breakthrough that led to the biochemical elucidation of the disorder was the discovery of the lysosome by de Duve in 1955. De Duve and co-workers demonstrated that this cellular organelle is responsible for intracellular digestion and recycling of macromolecules. Ultimately, the lysosome turned out to play a key role in the pathogenesis of Fabry disease: electron microscopy revealed inclusion bodies in lysosomes of endothelial cells, smooth muscle cells, fibrocytes, and perivascular cells of patients with Fabry disease, described as overcrowded lysosomes. The storage material appeared to be globotriaosylceramide (Gb3, Gl-3 or CTH) and to a lesser extent galabiosylceramide. In 1967, Brady demonstrated an enzymatic defect in Fabry disease, which was studied in more detail by Kint in 1970. This enzyme, alfa galactosidase A (aGal A; E.C. 3.2.1.22) catalyzes the removal of a terminal alfa-galactose residue from several substrates, the most important being Gb3. Analysis of Dutch families with Fabry disease hinted towards an X-linked inheritance, and directed towards the discovery of the corresponding gene for alfa-Galactosidase A on the X-chromosome at position Xq22.1. Fabry disease appears to be panethnic with an estimated birth prevalence of 1:40,000 although recent screening studies indicate a much higher prevalence, including subjects with unclear phenotypes. Most families have private mutations. In classically affected males the diagnosis can be confirmed by measurement of enzyme activity in leukocytes.

Figure 1. Biochemical structure of globotriaosylceramide.
addition, gene analysis can demonstrate the presence of mutations in the aGal A gene. A complication in laboratory confirmation of the diagnosis of Fabry disease forms the frequent occurrence of pseudo-deficiencies, i.e. abnormalities in the aGalA gene and protein that are not obligatory disease causing. Accurate diagnosis of females with Fabry disease based on residual enzyme activity is not feasible and their diagnosis is usually confirmed by mutation-analysis. With the recent increase in the number of screening studies, abnormalities in the alpha Galactosidase A gene with unclear pathological consequences have been identified. This phenomenon of so-called fringe alleles further complicates molecular confirmation of the diagnosis of Fabry disease.

**Clinical manifestations of classical Fabry disease**

At birth, patients with Fabry disease do not present disease manifestations yet. During childhood, the first disease manifestations may become evident. These first symptoms are acroparesthesia (neuropathic pain in hands and feet), angiokeratoma (skin lesions) and anhidrosis (absent sweat function). During childhood and adolescence microalbuminuria may develop, which is an early sign of kidney involvement. Furthermore (asymptomatic) cerebral white matter lesions may be detected in some cases already at young age on cerebral MRI. During adulthood, most males develop cardiac hypertrophy and/or diastolic dysfunction. Microalbuminuria may progress to proteinuria and is frequently present. Although renal function may be preserved, renal function usually gradually declines, both in males with and without microalbuminuria/proteinuria. Eventually end-organ complications develop of which arrhythmia, congestive heart failure, renal insufficiency necessitating dialysis or kidney transplantation and stroke are the most prominent. Females can present with the same symptoms, though are usually less severely affected and develop symptoms several years later. However some females can exhibit organ involvement as severe as in males. In conclusion, there is a wide spectrum of disease, even in family members (siblings). Some individuals present with single organ involvement: these patients are mostly referred to as atypical patients and present with kidney involvement or cardiac manifestations only. These patients have residual enzyme activity.

**Pathophysiology**

The pathophysiology in Fabry disease is still not completely understood. Lysosomal accumulation of globotriaosylceramide is thought to be the primary event that ultimately results in symptoms such as renal insufficiency, cardiac involvement and central nervous system involvement, but the precise cascade of events is not entirely clear. In Fabry disease, storage of glycolipids is detected in many cells, however, it is most extensively found in vascular cells, kidney epithelial cells, podocytes, cardiomyocytes, dorsal root ganglia and central nervous system neurons (figure 2). Previous observations indicate that the vascular complications may occur as a result of vascular dysfunction, including...
endothelial dysfunction, alterations in cerebral perfusion and pro-thrombotic factors. The cause of the recurrent neuropathic pains in Fabry disease are incompletely understood but accumulation of Gb3 in the dorsal root ganglia has been suggested as a possible pathological substrate.

Although Gb3 is still believed to be the main driver of the pathophysiological process in Fabry disease, there are some missing links. For instance, no clear correlation between Gb3 storage and disease manifestations has been discovered so far. Already before birth, prominent Gb3 accumulation in Fabry hemizygotes has been detected while actual clinical symptoms develop much later in life. Furthermore, plasma and urinary Gb3 levels can be normal in females despite clinical symptoms and signs of the disease. This has led some to conclude that plasma and urinary Gb3 is not an appropriate surrogate marker for disease severity. Furthermore progression of disease in patients following therapeutic intervention is observed, despite sustained clearance of Gb3 from the endothelium.

A search has been conducted for other factors besides Gb3 that might reflect disease manifestation and even play a direct role in the pathophysiology. Plasma of symptomatic Fabry patients has been shown to promote vascular smooth muscle cell and cardiomyocyte proliferation. In other lysosomal storage disorders, such as Krabbe disease, deacylated glycosphingolipids can cause disease manifestations. In analogy to this, the discriminatory presence of the deacylated form of Gb3, globotriaosylsphingosine (abbreviated as lysoGb3) in Fabry patients and its potential role in the pathophysiology was investigated. The results are included in this thesis.

**Treatment**

The concept of enzyme replacement therapy for lysosomal storage disorders was already proposed by the Duve and Hers following the discovery of lysosomes and storage disorders, but it took decades for this concept to become reality. Uptake of lysosomal enzymes is receptor mediated. Like most lysosomal enzymes, alfa-Galactosidase A is routed to lysosomes by recognition of mannose-6-phosphate (M-6-P) moieties in its N-linked glycans, allowing binding to M6P receptors. The same receptors also allow
uptake of enzyme from the extracellular space, followed by delivery to lysosomes. Targeting of enzymes towards the lysosome using this M6P receptor pathway, is used for treatment by enzyme supplementation. The presence of M6P in glycans of a recombinantly produced lysosomal enzyme indeed enables uptake by many cells of the body following an intravenous infusion, when given at appropriate dosages. Unfortunately, the blood-brain barrier precludes uptake of intravenously infused lysosomal enzymes in the brain, making it a less attractive approach for lysosomal storage disorders with extensive cerebral manifestations.

In 2001 the European Medicines Authority authorized two enzymes: agalsidase alfa and agalsidase beta. Agalsidase alfa (Replagal®) is produced by overexpression of alfa Galactosidase A in human skin fibroblasts and administered at a dose of 0.2 mg/kg/2 weeks. Agalsidase beta (Fabrazyme®) is produced by recombinant engineering in CHO cells administered at a dose of 1.0 mg/kg/2 weeks. Both are administered by intravenous infusion every two weeks. The first randomized controlled trials showed clearance of Gb3 from vascular endothelium and decrease of pain in hands and feet, after 20 weeks and 6 months respectively. Since then several studies on short and long term clinical outcome have been published. Initial short-term studies suggested that renal function remained stable. Other studies showed decrease or stabilization of cardiac mass. Furthermore, improvement of diastolic dysfunction has been reported. Studies with longer follow-up, however demonstrated progression of disease despite treatment, in patients with pre-existing advanced disease such as cardiac fibrosis and advanced kidney involvement at the time of initiation of treatment. Other studies also reported progression of cerebral white matter lesions and stroke during treatment. Only one placebo controlled phase IV study concerning agalsidase beta has been published on the development of end-organ complications, showing a modest reduction of complications after 18 months of follow-up. In this study, patients generally had already advanced Fabry disease manifestations and the presence of proteinuria appeared to be a major driving force in the development of complications. This observation, as well that of others emphasized the importance of additional supportive measurements such as ACE-ARB medication for treatment of microalbuminuria/proteinuria and anti-platelet therapy for prevention of cerebrovascular events.

Only one study has been performed comparing both products at the same dose. In this study, patients were randomized to start treatment with either agalsidase alfa 0.2 mg/kg/2 weeks or agalsidase beta 0.2 mg/kg/2 weeks. After 12 and 24 months there was no difference in reduction of left ventricular mass, and change of renal function, but patient numbers were small. Disease progression defined as progression of renal function (> 33% increase in serum creatinine, need for dialysis or transplantation), progression of cardiac disease (development of cardiac complications) and development of new cerebral white lesions occurred in both treatment groups.
As progression of disease mainly involves patients with more advanced disease, it has been suggested that enzyme replacement therapy should be initiated early at least before end organ damage has developed. However, data on this topic are limited. Studies in children concern mainly open-label, uncontrolled studies and follow-up has been too limited to make definite conclusions 62-64.

The introduction of enzyme replacement therapy also revealed a potential adverse effect: the development of high affinity antibodies against the infused recombinant enzyme 65. In males, antibodies towards the enzyme frequently develop as males usually do not express residual enzyme activity. Previous studies have reported emergence of IgG antibodies in 56% up to 88% of male treated patients47, 66. In the Dutch cohort, decreased reduction of urinary Gb3 was noted after 1 year of treatment, in patients with anti-alfa-Galactosidase A antibodies67. In contrast, no impact of antibodies on clinical response to enzyme treatment after 24 months was observed 67. In this thesis additional analyses are performed with regard to impact of these antibodies.

**Cost-effectiveness of enzyme replacement therapy**

The last decade the European Union has promoted the development of treatments for rare diseases, so called orphan drugs. This led to legislation promoting pharmaceuticals industries to develop medicines, which have often been marketed at exorbitant prices 68. Both agalsidase alfa and agalsidase beta are authorized orphan drugs being approved under ‘exceptional circumstances’. Due to the rarity of Fabry disease it was deemed unlikely that sufficient evidence from clinical trials would be available in a short period of time to gain sufficient knowledge on effectiveness. Interestingly, marketing authorization for both agalsidase preparations was granted in the EU. In the USA, only agalsidase beta was authorized. Only one phase IV placebo controlled trial was performed following authorization 61. In Europe, EMA requested the installation of drug-registries to evaluate effectiveness. However, these registries have several limitations, most importantly the lack of complete datasets and absence of previously defined clinically important outcomes 69.

The annual costs of agalsidase alfa as well as agalsidase beta are high, around €200,000 for an average 70 kg adult. These new and expensive enzyme replacement therapies are suitable targets for economic evaluation in order to assess the benefit versus the costs (‘bang for the buck’). Given the scarcity of health care resources and need for health care cost containment the Dutch government provisionally regulated the access of these drugs to the market. This was done by allowing these drugs to be reimbursed for a period of four years, while insisting that the drugs would simultaneously be economically evaluated. In economic evaluations the health effects and costs of an intervention like enzyme replacement therapy are measured and compared with the health impact and costs of its best alternative, in this case ‘treatment as usual’ in absence of enzyme replacement therapy. Two modes of economic evaluation are frequently applied for this purpose: cost-effectiveness and cost-utility analyses. When opportune, both types of analyses are supported with
health economic modelling techniques. Both analyses are also performed in this thesis. The primary outcome for the cost-effectiveness analysis of enzyme replacement therapy is the costs per year free of end-organ damage, which closely relates to the expected clinical benefit from enzyme replacement therapy, ideally: preventing disease complications. The primary outcome for the cost-utility analysis is the costs per quality adjusted life-year or QALY. The QALY is derived from putting a population-based utility weight to a person's health status, while accounting for the duration of being in that state. A whole year in full health is equal to 1 QALY. Because the QALY is a general, disease non-specific concept, the outcome measure ‘costs per QALY’ allows for priority setting in resource allocation across patient groups, interventions, and health care settings.

In Fabry disease, two cost-effectiveness studies have been conducted so far, although these were hampered by lack of sufficient data. In the UK, the cost-effectiveness of enzyme replacement therapy in Fabry disease and mucopolysaccharidosis type 1 was addressed and it was concluded that insufficient information was available to allow an adequate assessment. The authors assumed in their analysis that patients would completely recover from their disease with treatment and estimated the incremental cost-effectiveness £252,000 per QALY. In the case of ERT for Fabry disease, a complete recovery is not a realistic assumption and therefore this estimation is rather optimistic. In the second study conducted in the USA, the costs per QALY were estimated to be around $300,000. Again, this was based on literature data only. Given current drug prices and the current range for acceptable costs per QALY in the Netherlands (€20,000 to €80,000), one may expect that the cost-effectiveness of the present enzyme replacement therapy for Fabry disease remains at stake, if results similar to the UK and USA data were to be reported. The cost-effectiveness and cost-utility are analyzed for the Netherlands (this thesis). It should be kept in mind though, that development of orphan drugs raises costs due to the rarity of disease and it may be argued that for equity reasons one could forego the ‘efficiency’-paradigm and grant each individual access to expensive enzyme replacement therapy, where no other treatment exists.

Outline of this thesis

The aim of this thesis was to gain more insight into Fabry disease and its treatment by enzyme supplementation. Chapter 2 describes the discovery of elevated levels of deacylated Gb3, globotriaosylsphingosine or lysoGb3 in Fabry disease patients. Chapter 3 provides a review of the literature on the vasculopathy of Fabry disease and proposes a unifying pathophysiological mechanism. In chapter 4, the diagnostic value of lysoGb3 is evaluated as well as the clinical implications of this new marker. Chapter 5 shows the results of vascular measurements that have been performed in male and female Fabry patients to study the vascular function in Fabry disease and its association with plasma
lysoGb3. The effect of enzyme replacement therapy on plasma lysoGb3 is described in **Chapter 6**. The impact of development of antibodies against the infused alfa-Galactosidase A on Gb3 and lysoGb3 correction as well as the effect of antibodies on clinical outcome is described in **Chapter 7**. The following chapters all address the course of disease and the outcome of enzyme treatment. The course of renal function and optimal method for its monitoring is discussed in **Chapter 8**. The effectiveness and cost-effectiveness for enzyme replacement therapy is studied in **Chapter 9** and **10**, respectively. **Chapter 11** includes a meta-analysis and systemic review on the effectiveness of enzyme replacement therapy by comparison of the course of disease during ERT treatment to the natural course of disease. **Chapter 12** includes the summary and general discussion of this thesis.
Reference List


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