Controversies and Update in Fabry's Disease

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Abstract

Fabry disease represents an X-linked systemic lysosomal storage disorder due to mutations in the *GLA* gene encoding alfa galactosidase and was originally described in 1898. Nowadays, the detection of an increasing number of genetic variants and mutations requires individual assessment. Recent newborn screening studies detect a prevalence of 1:1250 regarding *GLA* mutations. Specific enzyme replacement therapy consisting of agalsidase alfa or agalsidase beta has been available since 2001. Still many patients are diagnosed only late in their disease course. This diagnostic delay reflects that non-classical phenotypes are more common than previously thought. Plasma lyso-GL3 levels have emerged as the most accepted diagnostic biomarker in routine clinical use, complementing enzyme activity measurements and genetic analysis. Lysosomal deposits of glycosphingolipids (mostly GL3) in kidney tissue, are characteristic for Fabry disease. Kidney biopsies are important in clinical practice and have a key role in diagnosis, research and understanding of the pathogenesis of Fabry disease. Enzyme replacement therapy, especially given early, can slow down the progression of Fabry disease, such as nephropathy and cardiomyopathy. This is evident despite the lack of a sufficient number of randomized placebo-controlled trials (RCT). In addition, recent studies point towards a dose-effect of enzyme replacement. Major causes for treatment failures are therapy initiation at a too advanced disease state and the formation of neutralizing antidrug antibodies. Recent advances in therapy are represented by migalastat, an oral pharmacological chaperone, already in routine clinical use, and clinical studies to introduce new therapies.

The changing landscape of Fabry disease

Fabry disease is a rare X-linked lysosomal storage disorder due to mutations in the *GLA* gene causing complete or partial deficiency of the enzyme alfa galactosidase A (α-Gal A) and subsequent slow accumulation of mainly globotriaocylceramide (Gb3 or GL3) and its deacylated derivative globotriaosylsphingosine (lyso-GL3, also called Lyso-Gb3) in several cell types and body fluids. Early and often asymptomatic cellular damage typically precedes various degrees of organ affection and late organ failure. Clinical symptoms are highly variable and mostly nonspecific[1]. Kidney cells, cardiomyocytes and vascular endothelium are

target cells of particular interest in a usually slowly progressive disease. Major complications are secondary to renal, cardiac and/or central nervous system affection, usually from the fourth decade onward [2]. The disease has had a long journey from the original description of cutaneous angiokeratoma in 1898 [3] to the current recognition of a treatable highly complex and heterogenous multisystem disease carrying a high rate of morbidity and mortality [4]. The grim natural disease course in the era before enzyme replacement therapy should not be forgotten and was described in 2002 by Branton et al. [5] in 105 hemizygous classical male patients, only 25 of 105 patients survived until the age of 50 and no patients survived past age 60 years. Before the advent of dialysis and kidney transplantation, the most common cause of death was uremia, at a mean age of 41 years [6]. Overall, before enzyme replacement was available a reduced life span of about 25 years in males and 10 years in females was expected compared to the general population [7]. Although the pathophysiology still is only partly understood (Figure 1) the increasing knowledge of the complexity of mutations and disease manifestations has been fueled by a surge of clinical research and numerous publications following the introduction of enzyme replacement therapy nearly 20 years ago. Agalsidase alfa and agalsidase beta was approved in Europe and US (agalsidase beta only) in 2001, licensed doses are 0.2 mg/kg/every other week and 1.0 mg/kg/every other week respectively [8, 9]. Ten years follow-up registry data clearly demonstrate a modifying effect of ERT on serious organ complications and mortality[10, 11], and there has been a change allover in mortality from predominantly kidney to cardiac deaths [12, 13].

Historically, the disease has been hampered by diagnostic delay and subsequent delays of therapeutic intervention until irreversible organ damage prevails. Hence, the median age at diagnosis was 24 years in males and 31 years in females in a survey of more than 2200 patients, the median time between onset of symptoms (usually neurological pain and gastrointestinal dysfunction) and diagnosis was about 11 years in both sexes [14]. The rationale for the increasing focus on early therapy has been clearly demonstrated by several reports highlighting the serious prognostic impact of diagnostic and therapeutic delays[15, 16].

Epidemiology, genetics and characterization of phenotypes

Over the last two decades general knowledge of Fabry disease and therapeutic challenges have changed dramatically and prognosis has improved for several reasons. Enormous progress in genetic sequencing technology has led to a paradigm change in the understanding of the complexity of genotype – phenotype interactions. Recently, a general description of clinically relevant categories of variants in Mendelian disorders using the terminology

"pathogenic", "likely pathogenic", "uncertain significance", "likely benign" or "benign" has been suggested [17, 18]. This is especially relevant for the classification of clinical phenotypes harboring *GLA* missense mutations accounting for about 60 % of more than 900 known mutations (Human Gene Mutation Database, www.hgmd.org). Importantly, the increasing incidence and prevalence of late-onset non-classical mutations and genetic variants of unclear significance with milder disease phenotypes have been acknowledged [17, 19] with symptoms often confined to a single organ (especially cardiac), and some of these presumably have no clinical disease at all [17, 20]. The wide phenotypic spectrum of disease severity, even within the same family, and the fact that not all mutations are disease causing (e.g. polymorphisms) highlight the necessity of careful individual diagnostic and prognostic assessment to allow correct and timely intervention as well as avoidance or postponement of unnecessary high-cost treatment in patients with non-disease causing mutations or very mild disease [19-22]. The increasing birth prevalence of *GLA* mutations from previous estimates of 1:40.000 – 170.000 [23] up to 1:1250 in newborn screening studies [19, 24, 25] reflects the existence of a majority of non-classical mutations and variants of unknown significance where natural history and effectiveness of enzyme replacement are unknown [19]. Currently, research on clinically relevant genotype-phenotype relationships are increasingly prioritized. Clear criteria exist for diagnosis of classical early onset Fabry disease (also called Type 1) with absent or low levels of enzyme activity and typical symptoms [4]. However, a precise diagnosis may be difficult in late-onset, non-classical (also called Type 2) male and female patients harboring any variant in the *GLA* gene with residual enzyme activity and variable X chromosome inactivation patterns (females), often presenting with cardiac, minimal or unclear symptoms[26, 27] in early or late adulthood [17, 28, 29]. A widely used algorithm for diagnosing Fabry disease in these latter categories has been published by van der Tol et al. [19, 30, 31].

New insight in effectiveness of enzyme replacement therapy

The introduction of intravenous enzyme replacement has fueled a tremendous amount of research opening many new avenues for collaborative work involving experts from key medical specialties. The way forward has served as a model for learning and organizing of clinical research, defining challenges and caveats in the field of metabolic rare diseases [15, 32]. Although enzyme replacement therapy undoubtedly has turned Fabry disease into a treatable disease, it has become obvious that intervention should be regarded as a disease modifier rather than a cure, and persistent risk of serious complications and increased mortality raises

major concern over current therapeutic strategies [32, 33]. Furthermore, numerous observational studies and case series published the latter decade have disclosed a conundrum of Fabry disease heterogeneity highlighting the necessity of individual assessment and targeting of therapy, even in patients within the same family [15, 34, 35]. Given a slowly progressive heterogenous disease, new light has been shed on the validity of biases and limitations of few small RCT`s of short duration in comparison with numerous long-term follow-up studies with a high number of patients[36-38]. The value of analysis of unpooled data from systematic comprehensive literature searches of observational studies and case series/reports through January 2017 has recently been reported [38]. These much larger patient cohorts and attempts to separate data among relevant clinical phenotypes (children, females, males, classical and non-classical), some of them treated for more than 15 years, have provided new insight which helps the treating physician better define individual patient risk and adequate therapeutic goals. Importantly, this knowledge has strengthened the need for an individual comprehensive multidisciplinary approach, carefully addressing genotype, phenotype, family history and biomarkers including kidney histology when possible [34, 35, 39, 40].

Individual therapeutic goals and risk profiles

Organ specific therapeutic goal recommendations, covering altogether 249 publications (67 % male patients including 36 clinical trials), suggest a significant slowing of decline of eGFR and reduction/stabilization of cardiac mass (adult males). The kidney and cardiac therapeutic benefits provide new information expanding the knowledge reported in a previous meta-analysis [33]. Although a cardiac benefit was suggested in both sexes, recent data generally were less robust in females, likely because of a wider disease spectrum ranging from asymptomatic to severely (rare) affected individuals [40]. Interestingly, quality of life outcomes was improved in both sexes [34, 40]. The prognostic importance of younger age and absence of organ damage when enzyme replacement therapy is initiated have been shown in several studies [10, 41]. Germain et al. [10] defined “low renal involvement” (LRI) as UPCR < 0.5 g/g and less than 50 % sclerotic glomeruli in a well-defined observational 10 year follow-up study of 52 classical patients (2 females), mean age 30 years and normal eGFR at start of agalsidase beta 1.0 mg/kg/every other week. The LRI group (n=32) was younger (mean 25 years at treatment initiation) than the “high renal involvement” group and showed less deterioration of eGFR (mean slope -1.89 versus -6.82 ml/min/1.73 m^2/year). Of note, 94 % of the patients were alive at the end of the study, and 81 % did not experience any events. In patients on enzyme replacement therapy lower eGFR and higher levels of proteinuria strongly predict faster

disease progression [16]. Supplemental therapy with RAAS-inhibition to lower proteinuria to ≤ 0.5 g/day and potentially stabilize GFR should be considered in classical patients with reduced GFR and severe proteinuria [15, 42]. The effects of enzyme replacement therapy on cerebrovascular events remains unknown, although a recent meta-analysis suggest a potential benefit on stroke prevention[43]. Though no clear consensus exists, recommendations for considering withdrawal of enzyme replacement in patients with advanced disease have also been published [44].

Is higher agalsidase dose beneficial?

Although in vitro mg per mg equipotency of agasidase alfa and beta has been demonstrated [45] the discussion about clinical equipotency of licensed drug regimens remains unsettled. The beneficial effect of higher cumulative agalsidase dose on kidney histology has been reported by Skrunes et al. [41] in serial kidney biopsies in 20 classical patients (median age 21 years, 12 males) with stable microalbuminuria and normal measured GFR followed for ten years. A clear dose-dependent effect on clearance of podocyte GL3 deposits was found in this cohort, and residual lyso-GL3 correlated with the cumulative enzyme dosage in male patients. The clinical benefits of higher enzyme doses have been corroborated and likely underscored in a larger observational multicenter study with systematic follow-up of a high number of patients of both sexes from three European Fabry centers. The compulsory switch from agalsidase beta 1.0 mg/kg/every other week to agalsidase alfa 0.2 mg/kg every other week in many patients (due to the worldwide shortage of agalsidase beta supply from June 2009 to January 2012) and subsequent re-switch to agalsidase beta 1.0 mg/kg every other week in a number of patients showed conspicuous dose-dependent benefits regarding GFR-slopes, lyso-GL3 levels and gastrointestinal symptoms [46]. Moreover, an overview of available evidence indicates that higher doses of agalidase are beneficial given an optimal timing of therapy and selection of patients with classical phenotypes [47, 48]. Importantly, the majority of literature-based observations of dose-dependent clinical effects so far are confined to classical male patients, and further long-term studies in expanded cohorts of high-risk patients are warranted. Long-term data on therapy outcome in general are insufficient in female patients and sex mixed study populations, likely because of variations in X-chromosome inactivation which are usually not reported in clinical studies [34, 40]. This may also in part be the reason why no differences were found in clinical events in a recent European multicenter study including a mixture of classical and non-classical patients (n=387 (192 females), mean age 46 ±15 years at therapy initiation) comparing licensed doses of agalsidase alfa and beta [49]. However, a

more robust decrease of lyso-GL3 and better reduction in left ventricular mass were reported in patients receiving a higher enzyme dose [49]. There is one study reporting kidney benefit of increasing the dose of agalsidase alfa to 0.2 mg/kg every week in a limited number of patients [50], but no such evidence is reported for agalsidase beta. Although current enzyme substitution regimens fail to normalize elevated lyso-GL3, a clear dose- and age-dependent decrease of lyso-GL3 has been observed after therapy [41, 49, 51], and the recent therapeutic goal initiative recommends to strive at the lowest possible level of lyso-GL3 [35]. More importantly, enzyme replacement therapy has limited effect when started late in the course [15, 49, 52, 49] .

Neutralizing anti-agalsidase antibodies

A major reason for treatment failure is formation of neutralizing antidrug antibodies (ADAs) which is reported to affect 40 % of male patients treated with agalsidase beta or alfa and leads to subsequent decline of GFR and increase in lyso-GL3 [56]. Lenders et al. elegantly demonstrated that agalsidase dose escalation may overcome the detrimental inhibitory effects of these antibodies [56]. A potential therapeutic approach has recently been published, highlighting the need of standardizing assays and methods for individual dose escalations to obtain a saturated ADA status [57]. Furthermore, future prospective studies are warranted to elucidate the clinical impact of ADAs [57]. The role of immunosuppressive therapy is unknown.

Initiation of pharmacologic therapy: How early is early enough?

The strategy of "early treatment" of Fabry disease has been a major focus and is based on the experience in classical patients that progressive disease is more frequent when therapy is delayed until irreversible organ damage is manifest [16, 17, 52]. Our experience in a youngish classical symptomatic patient cohort with normal heart and normal measured GFR and normo/microalbuminuria suggests that enzyme replacement should be initiated within the teens (before the age of 18 years) [41, 51, 58] with the goal to prevent or delay the progression to irreversible kidney and heart damage. This "window of opportunity" approach is supported by several authors [15, 39, 44]. Earlier start of therapy in childhood has to be decided on individual basis in cases with severe symptoms and signs. A systematic follow-up to define the individual appropriate window for "early therapy", often at higher age, is mandatory especially in slowly progressive non-classical late onset cases (usually females) [34, 35, 40].

New therapies

The need for more effective therapy of Fabry disease has stimulated research addressing alternative mechanisms to enhance efficacy of endogenous or infused enzyme. Substrate reduction therapy [59] and gene therapy trials as listed by ClinicalTrials.gov [60] are currently recruiting patients for phase I-III studies.

Migalastat, a small-molecule pharmacological chaperone first approved in Europe 2016 and US in 2018, was developed as a stabilizer of specific mutant (*amenable*) forms of α-Gal to facilitate its normal lysosomal trafficking [61, 62]. In an 18-month phase III trial in predominantly female patients, this agent was well tolerated and was associated with a decrease in left ventricular mass index. Migalastat and enzyme replacement therapy had similar effects on kidney function [62]. Another phase III study showed modest reduction of GL 3 in interstitial capillaries and glomerular cells after six and 12 months of therapy [61, 63]. Thus, Migalastat could represent an oral monotherapy alternative therapy to enzyme replacement in respective patients [62]. Notably, the concept of in vitro and in vivo amenability is under scrutiny, especially in patients with lower range (< 10 %) enzymatic activity [64].

Pegunigalsidase alfa, a novel PEGylated enzyme replacement agent, has prolonged halflife and potential benefits regarding immunogeneicity compared to agalsidase. Phase I/II-studies, as well as switch (from agalsidase alfa) and comparative (agalsidase beta) studies have recently been launched [65].

Plasma and tissue specific markers

There is no single ideal biomarker in Fabry disease. Elevated plasma lyso-GL3 has been designated a hallmark of Fabry disease [66]. Currently, measurement of plasma lyso-GL3 has increasingly replaced plasma and urine GL3 as the most significant and technically more easily measured non-invasive diagnostic biomarker [67], supplementing standard measurements of leukocyte *GLA* enzyme activity and genetic analysis. Lyso-GL3 allows a better discrimination between patients with classical and non-classical disease and subjects without Fabry disease. Furthermore, elevated lyso-GL3 has been linked to clinical events and a higher disease burden [21, 29, 68]. Since skewed X-chromosome inactivation may differ between cells and organs in females, a normal plasma lyso-GL3 value does not rule out the existence of Fabry disease [29, 67, 68]. After initiation of enzyme replacement therapy, a rapid reduction in lyso-GL3 levels is seen in classical males, while a slower decline or stabilization typically follows in most of non-classical patients and females [49, 69]. Beyond being a marker of disease lyso-GL3 is likely also directly involved in the disease pathogenesis via stimulation of inflammatory and fibrotic mechanisms which are upregulated in Fabry disease [53, 54]. A novel

experimental finding suggesting persistent dysregulated inflammatory signaling in spite of agalsidase-induced podocyte GL3 elimination was recently published [55], shedding new light on potential contributions of glycolipid stimulated inflammatory markers to vascular remodeling and progressive vasculopathy. Laboratory assay and limited availability of a laboratory assay for lyso-GL3 are still a challenge in many centers. Further elucidation of the specificity of urinary lyso-GL3 analogues is a matter of ongoing research, especially in late-onset variants with cardiac disease [70]. Markers of chronic inflammation in Fabry disease are not yet implemented in clinical practice [53].

In tissue biopsies abundant lysosomal deposits of glycosphingolipids, mainly GL3, are hallmarks of Fabry disease, these are especially conspicuous in podocytes [71, 72] and can easily be diagnosed by bedside stereomicroscopy immediately after a kidney biopsy [73]. Recently, measurement of abnormal podocyturia has been tested as a potential early diagnostic and prognostic non-invasive tool in ascertainment of progressive disease and disease burden in patients with classical disease [74]. Increased podocyturia has even been reported in very young classically affected children [75]. Larger scale validation of the future role of this parameter are needed. General cardiac biomarkers may also be useful in establishing a full assessment and risk profile for the patient **[76]**.

Kidney biopsies

Routine clinical laboratory tests (eGFR and albuminuria) are insensitive markers of early progressive Fabry nephropathy. On the other hand, the assessment of specific and non-specific reversible or irreversible histologic changes provides early information on kidney damage even in patients with normal GFR and normoalbuminuria. These are crucial diagnostic findings for choosing optimal therapeutic strategies and follow-up of high-risk patients [41, 58, 77-80]. In general, a kidney biopsy has been recommended in Fabry patients with atypical symptoms and unclear diagnosis, often with normal kidney function, as well as in cases with unexpected disease course and suspected concomitant diseases [15, 30, 31]. A conspicuous finding in recent case series is the discrepant beneficial effect of enzyme replacement therapy on removal of GL-3 inclusion from podocytes, glomerular capillary endothelial and mesangial cells contrasting with a worrisome lack of vascular protection. In the study of Tøndel et al. [51] in 12 young classical patients (median age 16.5 (range 7-33) years at treatment initiation, one female) treated for five years, total clearance of podocyte GL-3 was obtained in the youngest patient and microalbuminuria normalized in nearly half of the patients. These findings were further expanded by Skrunes et al. [41] reporting paired serial

kidney biopsies after 10 years treatment in an expanded cohort (20 classical patients, 12 males, median age 21 (range 7-61) years) confirming a dose-dependent effect on elimination of podocyte GL3 deposits (Figure 2) contrasting with a persistent failure to protect smooth muscle cells in media layers of kidney arterioles/arteries [41]. This finding suggests that current therapy is insufficient to prevent long-term vascular complications. The underscoring of serious vasculopathy even in young patients was further highlighted by the randomized multicenter study of 31 classical pediatric males with minimal disease symptoms and normal measured GFR (median age 12 (range 5-18) years) receiving enzyme replacement for 5 years comparing two treatment regimens (0.5 mg/kg 2-weekly (*n*=16) or 1.0 mg/kg 4-weekly (*n*=15) [80]. Six patients (mean baseline age 15.5 (range 14-17) years) had repeated paired kidney biopsies, arteriopathy (replacement of arterial/arteriolar muscle cells with hyaline-like material) was evident in all baseline biopsies and surprisingly showed progression in all but one patient despite a mean reduction of lyso-GL3 of 71 %.

Systematic kidney biopsies are underused in Fabry disease and further prospective studies are warranted to help clarify disease mechanisms and potential correlation with clinical phenotypes. Histologic examinations may allow early differentiation between patients with "high", "low" or "no risk" of progressive tissue damage, and sometimes unnecessary treatment can be avoided when normal or only minimally affected tissue or superimposed disease is identified[20, 30, 73]. Kidney biopsies provide the earliest and most sensitive insight into important cellular and vascular involvement, which are surrogate markers of disease activity. New unbiased stereological histologic methods [79] have shown capacity for assessment of therapeutic response after one year`s therapy [61, 79]. To detect and expand potentially relevant pathophysiological mechanisms, kidney biopsies can be used beyond routine diagnostics by the application of omics-related technologies. A preliminary study from our institution exploited next generation mRNA sequencing of mRNA from micro-dissected nephron compartments of serial long-term kidney biopsies with Fabry nephropathy. First analyses pointed towards increased expression of genes e.g. related to extracellular matrix, immune response and inflammation compared to baseline tissues [81]. Thus, RNA sequencing is feasible in archival Fabry disease kidney biopsies and may help to delineate potential novel disease markers and therapeutic targets.

FIGURES

Fig. 2. Histology of Fabry Nephropathy. Dose-dependent clearance of podocyte GL3 (red arrows) in two brothers with classical Fabry disease, aged 13 years and 15 years at initiation of enzyme replacement therapy. Biopsies are baseline (upper and lower left column, respectively), and after 3, 7 and 13 years agalsidase therapy. After 6 years of enzyme replacement therapy the younger brother (upper row) was switched to agalsidase-beta 1.0 mg/kg every other week. After the switch, the podocytes were virtually completely cleared of GL3, whereas his older brother (lower row), who received a lower cumulative agalsidase dose, continued to have a full podocyte score after a total of 13 years (Skrunes R et al.[7])

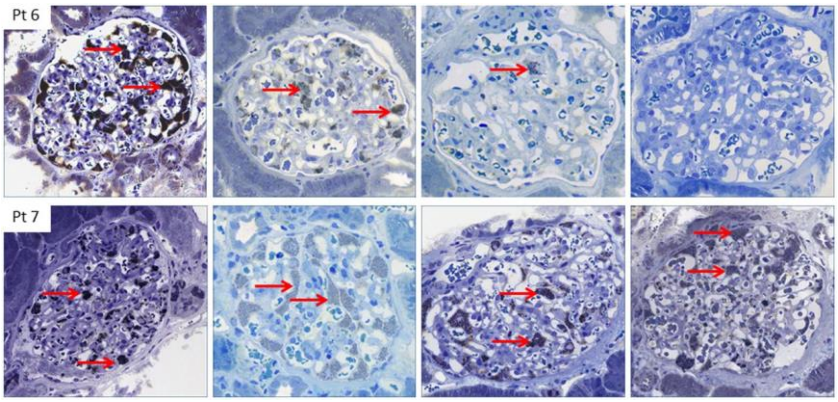
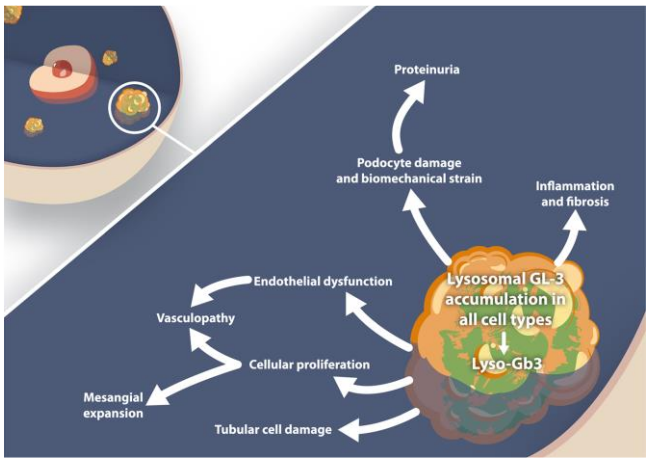


Fig. 1. Pathomechanisms of Fabry nephropathy (Eikrem et al[82])



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