NDT Perspectives

Fabry nephropathy: indications for screening and guidance for diagnosis and treatment by the European Renal Best Practice

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ABSTRACT

Fabry disease (FD) is an X-linked disorder of glycosphingolipid catabolism resulting in the accumulation of glycolipids including globotriaosylceramide in cells of various tissues resulting in end-organ manifestations. Initially, FD is typically characterized by angiokeratoma and recurrent episodes of neuropathic pain in the extremities occurring during childhood or adolescence. Most affected patients also exhibit a decreased ability to sweat. Later in life, FD results in left ventricular hypertrophy, proteinuria, renal failure and stroke. These later disease manifestations are non-specific and also common in diabetes, hypertension and atheromatosis and thus for most practitioners do not point into the direction of FD. As a consequence, FD is under-diagnosed and screening of high-risk groups is important for case finding, as is a thorough pedigree analysis of affected patients. In the nephrology clinic, we suggest to screen patients for FD when there is unexplained chronic kidney disease in males younger than 50 years and females of any age. In men, this can be performed by measuring α-galactosidase A activity in plasma, white blood cells or dried blood spots. In women, mutation analysis is necessary, as enzyme measurement alone could miss over one-third of female Fabry patients. A multidisciplinary team should closely monitor all known Fabry patients, with the nephrologist screening kidney impairment (glomerular filtration rate and proteinuria) on a regular basis. Transplanted Fabry patients have a higher mortality than the regular transplant population, but have acceptable outcomes, compared with Fabry patients remaining on dialysis. It is unclear whether enzyme replacement therapy (ERT) prevents deterioration of kidney function. In view of the lack of compelling evidence for ERT, and the low likelihood that a sufficiently powered randomized controlled trial on this topic will be performed, data of all patients with FD should be collected in a central registry.

INTRODUCTION

European Renal Best Practice (ERBP) is the official guideline body of the European Renal Association/European Dialysis and Transplant Association (ERA/EDTA). The mission of ERBP is to improve the outcome of patients with kidney disease in a sustainable way, through enhancing the accessibility of knowledge on patient care, in a format that stimulates its use in clinical practice. In line with this mission, and in view of its philosophy [1], the ERBP advisory board considered it useful to develop guidance in the field of orphan diseases with nephrological relevance. Typical for these diseases are the rather low patient number, and consequently, the lack of large trials. As a consequence, formal evidence-based medicine is nearly impossible in this field. Nevertheless, nephrologists need guidance on how to approach patients with these diseases. Therefore, ERBP decided to use the combination of formal systematic literature reviews, a consensus meeting with an international panel of experts and peer review as a suitable model to develop guidance in the field of orphan diseases. A first paper on oxalosis has already been published in this series [2]. This paper presents the results of a guidance process on the topic of Fabry disease (FD).

FD (OMIM ID #301500) is an X-linked inborn error of glycosphingolipid catabolism caused by quantitative or qualitative defects in the lysosomal enzyme α-galactosidase A (α-Gal A). As a result, glycosphingolipids, mainly globotriaosyl-ceramide (Gb-3), accumulate in the lysosomes of different cells throughout the body, ultimately resulting in organ failure [3, 4]. Patients with FD have a markedly limited life expectancy due to cardiovascular, neurological and renal involvement. Enzyme replacement therapy (ERT) has been made available since 2001. Intravenous infusion every other week results in the removal of a part of the Gb-3 deposits, diminishes Fabry-related symptoms and possibly protects organs to a certain extent [5, 6]. The effects of ERT on progression of renal disease (proteinuria and renal function) are unclear.

AIMS OF THIS PUBLICATION

The first aim of this paper is to review the current literature on renal disease in Fabry patients, in order to provide guidance to the nephrologist on when to screen for this disease and why, and to understand the preferred methods that should be used for screening.

The second aim is to provide guidance on the follow-up, prevention and treatment of renal disease, and its complications (proteinuria, renal failure). The role of ERT, angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB) and renal replacement therapy (RRT) is reviewed.

METHODS

A literature search was conducted using the PubMed database (most recent search July 2012). The search term used was 'Fabry Disease' with limits: 'Humans', 'Clinical Trial', 'Meta-Analysis', 'Practice Guideline', 'Randomized Controlled Trial', 'Review', 'English', 'French'. A total of 357 articles were retrieved; the articles were classified to the following topics (one paper can be attributed to more than one classification):

(i)   epidemiology, screening studies;

(ii) diagnostic methods;

(iii) Fabry nephropathy: natural history, complications (hypertension), mechanisms, renal pathology;

(iv) treatment of Fabry nephropathy; with ERT, ACEi and ARB, RRT; efficacy and safety issues.

Articles out of scope and review articles that presented no new data were excluded. Articles on experimental, non-registered treatments were also excluded.

The reference lists of the identified relevant studies were manually searched for additional citations.

After all relevant publications were retrieved, a consensus meeting was held with all co-authors. The resulting paper was sent for internal review before submission, as explained in the 'instructions to authors' section of the ERBP website [7].

EPIDEMIOLOGY AND THE NEED FOR SCREENING

1.1 We do not recommend screening in the general population. (Ungraded statement)

1.2 We recommend obtaining informed consent from the patient before screening, using an information form drafted in collaboration with a clinical geneticist. (Ungraded statement)

1.3 We recommend screening for FD in male chronic kidney disease (CKD) patients below 50 years of age in whom a reliable renal diagnosis is absent. (Ungraded statement)

1.4 We suggest screening for FD in females with unexplained CKD, irrespective of age, with other unexplained symptoms potentially associated with FD. (Ungraded statement)

1.5 We recommend discussing with the patient the implications of diagnosing a genetic disease and the possible implications for the at-risk relatives. (Level 1C)

Rationale

Classical FD is a progressive multisystem disease predominantly presenting in males, characterized by angiokeratoma, hypohidrosis and acroparesthesia (neuropathic pain) in childhood, followed by renal failure, left ventricular hypertrophy (LVH), stroke and premature death in the fourth or fifth decade of life [8]. In male patients, levels of α-Gal A activity

are classically very low or undetectable. However, as a result of screening studies during the past decade, clinical variants of FD in male patients with varying degrees of residual activity of α-Gal A have been described. The first described was the 'cardiac variant' with isolated LVH and/or cardiomyopathy presenting in the sixth or seventh decade, lacking the classical disease symptoms and time course [9, 10]. Patients suffering from this variant may have proteinuria, but their renal function is typically normal for their age. Later a 'renal variant' phenotype was described in a screening study in a dialysis population, where patients again were lacking the classical manifestations. This phenotype was described as 'intermediate' between the cardiac variant and the classic phenotype [11]. These patients with cardiac and renal variants are called 'atypical' or 'attenuated' FD patients. The genetic basis of this variable penetrance and expression is unclear. It is believed that the atypical cases are the result of missense mutations that encode mutant enzyme protein or intronic lesions that reduce transcript levels, both resulting in a reduced but significant residual enzyme function (1–12% of normal) [12], although this has been debated, and others found no genotype–phenotype correlation [13]. Heterozygous women, in spite of having a mutation compatible with typical disease, can also present this attenuated phenotype as it was hypothesized that skewed X-inactivation can result in significant residual enzyme function. However, it must be stressed that most females have the classical phenotype, but with a delayed and/or milder presentation of symptoms [14].

As a consequence, reported prevalence varies with the population studied and the test used for screening, and genetic screening might find female index cases that are not found by enzyme-based methods [15]. The prevalence of classical FD has been estimated at 1 in 117 000 births [14] and 1 in 40 000 males [8]. In several screening studies in high-risk populations, the frequency was up to 1% or even higher, especially in populations with unexplained LVH [16]. In newborns [17–19], the incidence of α-Gal A deficiency was 1 in 3100 with an 11 to 1 ratio of patients with the later-onset versus the classic phenotype. In the haemodialysis population, a prevalence of 0.33% in male and 0.10% in female patients has been found in a cross-sectional screening study [16]. Only two studies screened kidney transplant patients. In cryptogenic stroke, a prevalence of 0.8% [20] up to 2.4% [21] and 3.9% [22] was found; however, in the second study [21], half of the patients had the p.D313Y mutation, which is now generally regarded as a pseudo-deficiency, and in the last study [22], the specific mutations were not mentioned and could also have been polymorphisms. Many screening studies are not conclusive for the female population, as they most frequently used α-Gal A activity screening, which is in women, as described above, not a sensitive screening tool.

Although there are no studies in the CKD population not on dialysis, we recommend screening for FD in patients with CKD without a clear diagnosis. In classical FD, most males reach CKD Stage 5 or die before the age of 50 [12, 23]. As a consequence, we recommend screening in males only below the age of 50 years. We recommend screening even in the case of a negative family history as *de novo* mutations can occur, and the family history is not always suggestive for FD,

given the broad phenotypic spectrum of the disease. Arterial hypertension should not be an exclusion criterion as more than 50% of FD patients have mild to moderate hypertension, especially when estimated glomerular filtration rate (eGFR) is <60 mL/min/1.73 m^2 [23–25]. In women, disease onset can be later, so when there is unexplained kidney disease associated with manifestations suggestive of FD, we suggest screening for FD regardless of age.

The real prevalence should be derived from screening in the healthy population at a young age; this has been done in four studies in newborns [17–19, 26]. However, this approach remains problematic for several reasons. The American College of Medical Genetics (ACMG) has proposed newborn screening for 29 disorders, but screening for FD was not included in this list (available online at: http://mchb.hrsa.gov/screening/). Although measurement of α-Gal A has a good sensitivity and specificity in males, it has a low positive predictive value in the healthy population. This will result in unnecessary expensive tests. In addition, the majority of the detected cases in the newborn studies are 'atypical' mutations, giving an attenuated phenotype or a cardiac variant. The finding of a genetic predisposition for a possible late-onset disease where the treatment effectiveness is unclear has ethical and legal implications that constrain a systematic screening of newborns. In these cases, it would be difficult to decide on ERT, as the natural history of patients carrying atypical mutations is poorly characterized, effects of ERT in mild cases have not been studied, and a lifelong treatment is a psychological burden for the patient and a financial one for both the individual and society with, on top of that, uncertain results. As a consequence, we do not recommend screening for FD in the general population.

As FD is an X-linked disease with variable but significant morbidity both in males and females, its diagnosis might have profound consequences for the proband and his relatives. As a consequence, we recommend obtaining informed consent from the proband before screening, when possible in cooperation with an expert in genetic counselling. (Example in Supplementary appendix.)

Once the diagnosis is made, it is important to make up a pedigree in order to identify all relatives at risk. FD is an X-linked disease where all carriers can be symptomatic. It should be kept in mind that 'skipping' of a generation is possible because of variable expression.

The patient should receive further guidance in communication with his family. He must be able to provide sufficient information (e.g. by using flyers written by the treating team), and one must anticipate a number of possible problems in the communication with his family. Some people do not want a work-up to the diagnosis of FD, and it should be explained to the patient that they do have the right not to know their genetic status.

SCREENING METHODS

2.1 We recommend using enzyme activity measurement for α-Gal A as a primary tool in males, followed by

confirmation with mutation analysis when positive. (Ungraded statement)

2.2 We suggest using mutation analysis as a primary tool for screening in females. (Ungraded statement)

Measurement of α-Gal A activity in leucocytes using the fluorogenic substrate 4-methylumbelliferyl-α-D-galactopyranoside is the gold standard for FD in men, with a sensitivity and specificity of nearly 100%. Recently, a dried blood spot test (DBS) using filter paper has been proposed as an alternative to the leucocyte tests [27]. These samples are easy to transport and are stable at room temperature for many days, making it a most convenient screening tool in men, as it is a very sensitive tool with a negative predictive value reaching 100%.

In women, due to skewed X inactivation, enzyme activity measurement has a low sensitivity, as one in three women with FD have normal or nearly normal α-Gal A activity [15]. For this reason, enzymatic tests are less suitable and systematic genetic testing should be encouraged in females with unexplained CKD and manifestations suggestive for FD. As genetic testing is expensive (150–1000 Euro and more per test), a thorough anamnesis, family history and clinical investigation could help to select female CKD patients in whom testing is cost-effective (Figure 1).

In FD, gene mutation analysis is a way of confirming diagnosis in male patients, subsequent to enzyme activity measurement. A fresh blood sample can be collected for this purpose, or polymerase chain reaction amplification can be performed on DNA eluted directly from the filter paper used for the DBS α-Gal A measurement [28].

GLA gene mutations causing FD include single base changes leading to missense or nonsense mutations, or affecting consensus splice sites, small deletions or insertions, but also large gene rearrangements in <5% of the patients. Correlations between a specific mutation, i.e. the genotype, and the severity of the disease, the phenotype, are poor in FD. In a few cases, however, knowledge on the underlying mutation can provide information concerning prognosis and therapy and help the clinician in counselling. Some mutations are frequently associated with an attenuated phenotype, such as the mutation p.N215S, which gives a cardiac phenotype with only LVH [29]. These mutations are associated with a residual enzyme function [30]. A significant proportion of the mutations in men are, however, associated with a very low or absent enzyme function and the classic phenotype.

The GLA gene should be sequenced. As most of the mutations are 'private', i.e. unique to a family, it is always possible to completely identify a previously undetected mutation, and regular updates of such new mutations are available (http://www.hgmd.cf.ac.uk/ac/index.php). The pathogenicity of novel gene alterations such as missense or intronic mutations must always be evaluated. However, in females with normal biochemical tests, it may be difficult to confirm or exclude the diagnosis of FD when a variant of unknown significance is present.

In a suggestive clinical situation, most sequence alterations in exonic regions are pathogenic with very few exceptions.

One example of such inert exonic polymorphism is the p. 'D313Y' substitution (G to T at cDNA nucleotide 937); while the plasma enzyme activity towards the artificial substrate is significantly reduced, additional studies demonstrated high residual lysosomal enzyme activity and no pathologic excretion of urinary Gb-3. As a result, the p.D313Y substitution is now generally considered to be a so-called pseudo-deficiency.

If one finds a novel sequence variation in an intronic region or a novel missense mutation that is not known to be a polymorphism present in the general population, several methods allow non-invasive diagnostic analysis to establish whether it is disease causing. First, it should be checked whether these sequence variations exist in the normal population (using electronic databases or an own control population). The second step is to check male relatives of the index case who are carriers of the sequence variation for α- A activity. If the sequence variation is present in some of them, despite a normal α-Gal A activity and absence of clinical manifestations of FD, the sequence variation can be considered to be a polymorphism. If it coincides with a deficient α-Gal A in one or more of the male relatives, the possibility of a disease causing mutation is realistic, and in this case, a work-up of all carriers for the presence of (subclinical) FD disease manifestations should be considered.

Besides enzyme activity measurement and mutation analysis, detection of the accumulating substances (glycosphingolipids) has been studied as a tool for diagnosis. Globotriaosylceramide (Gb-3) is the most important glycosphingolipid, and it should be measured in urine rather than in plasma. Urinary Gb-3 can be a useful diagnostic tool in female heterozygotes with classical FD as it is increased in 95% of them. However, the proportion is much lower in heterozygotes with variant forms. It can also be used in males as a surrogate marker to evaluate the response to ERT [31]. Mass spectrometric profiling of Gb-3 isoforms may also help to identify heterozygotes [32].

In plasma, deacylated Gb-3 (globotriaosylsphingosine, 'lysoGb-3') has been shown to have a better correlation with FD. It is elevated 200–400 times in males with classical disease, from an early phase in the disease, but its levels can remain low in asymptomatic females or in the 'cardiac variant' p.N215S in males [33–37]. The examination of the urinary sediment with phase-contrast microscopy under polarized light shows tubular cells containing particles with birefringent Maltese Crosses, having a lamellated appearance with protrusions, and consisting of accumulated Gb-3. In the hands of Selvarajah et al. [38], this was a highly sensitive and specific tool for screening of FD, but its accuracy is strongly operator-dependent and therefore, it is probably an unrealistic option for large-scale screening studies.

WORK-UP OF A PATIENT WITH FD

3.1 We recommend that the detailed baseline and follow-up data of all patients with established FD should be transferred to a central registry. (Ungraded statement)
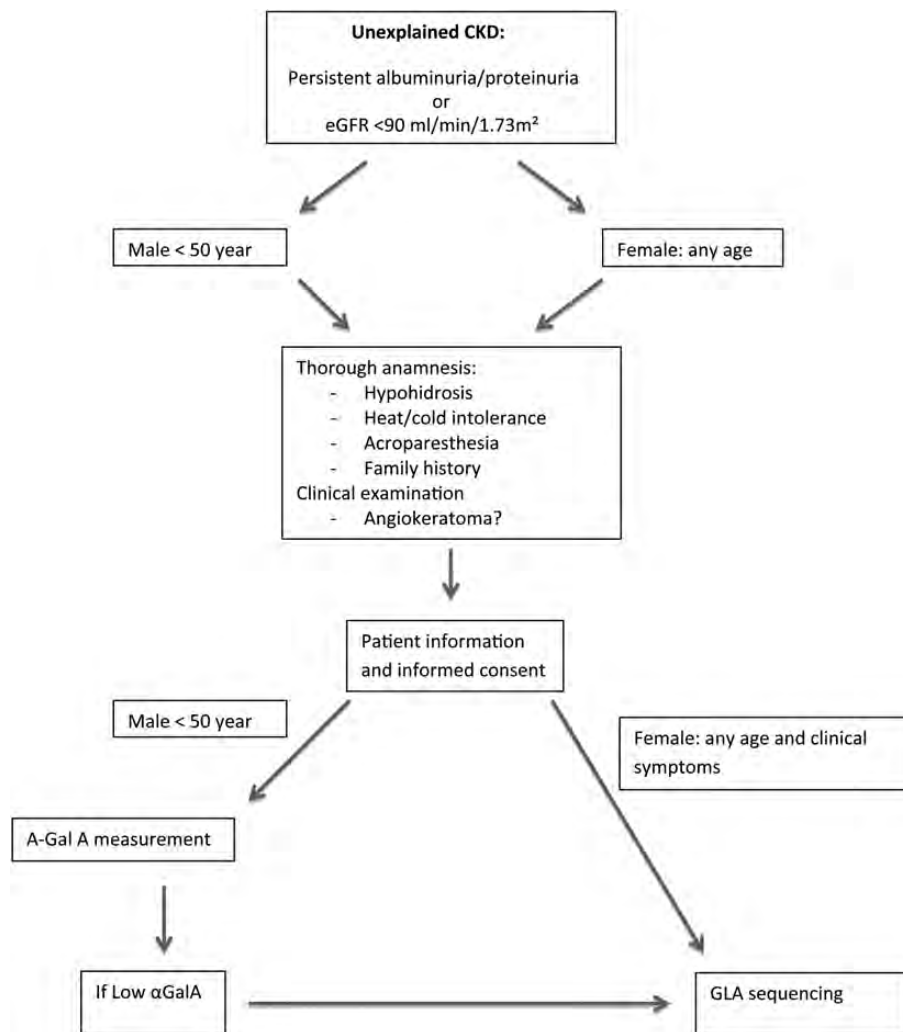
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FIGURE 1: Flowchart for screening for FD in CKD patients.

3.2 We recommend baseline and subsequent yearly evaluation by a multidisciplinary team, including kidney function and albuminuria, in all patients with established FD (cardiology, neurology and nephrology). (Ungraded statement)

3.3 We recommend not considering female carriers for living donation, unless in exceptional cases. In these cases, we recommend a kidney biopsy to evaluate the risk for the donor and acceptor. (Ungraded statement)

Once an index patient is diagnosed, a baseline evaluation is indicated. As FD is a progressive multisystem disease, baseline evaluation is optimally performed by a multidisciplinary team (Table 1, adapted from Eng *et al.* [39]). The baseline evaluation should be performed in male and all female carriers, as the phenotype can be equally severe.

As this document is written from the nephrology perspective, we will focus on renal involvement in what follows. For evaluation and pathophysiology of other organs, we refer to the guidelines of the respective subspecialities.

Renal involvement is a cardinal feature of FD. Gb-3 deposition in renal cells is progressive and begins early in life. Besides these deposits, pathogenic mechanisms result in glomerular ischaemia with subsequent glomerulosclerosis and tubular atrophy, even very early in the disease course. Vacuolization of podocytes and epithelial cells is a characteristic optical microscopy histological finding. These vacuoles are filled with deposits on electron microscopy, or following toluidine blue staining of samples prepared for electron microscopy. At an early stage, hyperfiltration may, as in diabetes, be the first sign of kidney damage.

As FD can progress subclinically, adolescent and adult patients should have urinary albumin measurement, as this is one of the first signs of Fabry nephropathy. We suggest assessing the amount of albumin normalized for creatinine on a fresh morning sample as diagnostic test. We suggest measuring urinary albumin rather than total protein, as it is more sensitive. Renal function can be assessed using serum creatinine and eventually formulas to translate serum creatinine to estimated clearances. Even in the absence of albuminuria or renal failure, all these parameters should be re-evaluated at least yearly in order to detect progressive disease.

Renal intracellular Gb-3 deposits may be present even in young children with normal GFR and minimal or absent micro-albuminuria. In a recent study of 14 young Fabry patients aged 4–19 years with normal GFR, there was an

Table 1. Proposed assessments in FD patients (reproduced with permission from Eng *et al.* [39])

Organ system	Assessment	Recommendation
General	General status, school or work performance, sports, depression, anxiety, drug use, pedigree update, somatic growth	Baseline (at first visit), every 6 months
	Complete physical examination SF-36°Health Survey, or PedsQL™ Measurement Mode	Baseline, every 6 months
	Genetic counselling	Baseline, every 6 months for new issues
	Genotype	If not previously determined
Kidney	Serum electrolytes, creatinine, BUN; 24-h urine or spot urine for total protein/creatinine, albumin/creatine, sodium, creatinine	Baseline, every 3 months if CKD Stage 1 or 2 and >1
		g/day of proteinuria or CKD Stage 4
		Every 6 months if CKD Stage 3
		Every 12 months if CKD Stage 1 or 2 and <1 g/day of proteinuria
Cardiac	Palpitations, angina	Baseline, every 6 months
	Blood pressure, rhythm	Every evaluation visit
	ECG, echocardiography 2D with Doppler	Baseline, every other year for patients ≤35 years of age, every year thereafter
	Holter monitoring, 30-day event monitoring	If an arrhythmia is suspected or palpitations are present
	MRI, strain rate imaging	Optional
	Coronary angiography	If clinical signs of angina
Neurologic	Acroparesthesias, fatigue, fever, sweating, heat and cold intolerance, joint pains, stroke-related symptoms, TIA	Baseline, every 6 months
	Neurologic exam, Brief Pain or McGill Pain Inventory	Baseline, every 6 months
	Brain MRI without contrast	Baseline, at the time of a TIA or stroke event or in females to document CNS involvement
	Magnetic resonance angiography	If cerebral vasculopathy should be excluded
	Cold and heat intolerance, pain, vibratory thresholds, sweat output, post-ganglionic sudomotor function, superficial skin blood flow	When available
	Co-morbid stroke risk factors: cholesterol (Total, LDL, HDL), triglycerides	Annually
	Lipoprotein A, total plasma homocysteine, factor V Leiden (G1691A), Protein C, Protein S, prothrombin G20210A, antithrombin III, abticardiolipin antibody, lupus anticoagulant	At baseline, single assessment

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Table 1. Continued

Organ system	Assessment	Recommendation
ENT	Tinnitus, hearing loss, vertigo, dizziness	Baseline, every 6 months
	Audiometry, tympanometry, otoacoustic emissions	Baseline, and yearly thereafter
Ophthalmologic	Visual disturbances, light sensitivity	Baseline, every 6 months
	General pohtalmologic exam (slit-lamp, direct ophtalmoscopy, best corrected visual acuity, visual fields)	Baseline, every 12 months
	Retinal disfunction testing (ERG, colour vision testing, visual-evoked potentials, retinal angiography), tear secretion testing	If clinically indicated
Pulmonology	Cough, exertional dyspnoea, wheezing, exercise intolerance	Baseline, every 6 months
	Spirometry, including response to bronchodilators, treadmill exercise testing, oximetry, chest X-ray	Baseline, every 2 years or more frequently for clinical indications
Gastrointestinal	Postprandial abdominal pain, bloating, diarrhoea, nausea, vomiting, early satiety, difficulty gaining weight	Baseline, every 6 months
	Endoscopic or radiographic evaluations	If symptoms persist or worsen despite treatment
Skeletal	Bone mineral density	Baseline

association between the volume of Gb-3 deposition in the podocytes, and age. The volume of Gb-3 deposition was also correlated with urinary protein excretion rates [40]. Tøndel et al. [41] found segmental foot process effacement in all young Fabry patients, despite the fact they were normo-albuminuric (below 30 mg/day). Thus, in the case of patients at risk of FD, any albuminuria, even if in the 'normal' range, should be considered as suspect.

Proteinuria progresses and correlates with and probably also contributes to the decline in renal function, e.g. male Fabry patients with a proteinuria >1 g/24 h had a greater yearly decline in renal function (-6.9 mL/min/1.73 m^2) than patients with proteinuria between 0.1 and 1 g/24 h (-2.2 mL/min/1.73 m^2) and patients with proteinuria <0.1 mg/24 h (-0.6 mL/min/1.73 m^2) [42]. Other studies confirm that the urinary protein to urinary creatinine ratio (UP/Cr) is the most important indicator of renal disease progression [43]. The yearly decline in renal function also correlates with GFR at presentation (in males, -3 mL/min/1.73 m^2 with GFR >60 mL/min/1.73 m^2 versus -6.8 mL/min/1.73 m^2 with GFR $\leq$ 60 mL/min/1.73 m^2; in females -0.9 mL/min/1.73 m^2 versus -2.1 mL/min/1.73 m^2) [42].

Most patients with CKD Stages 3–5 have some degree of proteinuria [23]. Proteinuria in the nephrotic range (>3.5 g/24 h) is, however, rarely seen (maximal 18% in [12]).

CKD Stage 5 usually develops between the third and the fifth decade, with a mean age at diagnosis of 38, but can appear as early as at the age of 16 [44, 45]. Interestingly, the mean age at initiation of RRT is similar for males and females, although the proportion of male versus female FD patients on RRT was 9 to 1 [42].

Living related donation in FD can pose a problem if apparently asymptomatic female carriers consider donating a kidney. Even in the case of a normal renal function and in the absence of albuminuria, significant Gb-3 deposits can be abundant in a renal biopsy [46] and thus female carriers are, in our opinion, not eligible for living kidney donation.

The Fabry population is small and heterogeneous which makes it difficult to study its natural course and to conduct larger-scale, placebo-controlled or open-label clinical trials. For these reasons, a high quality registry with all treated and untreated patients on a European scale, developed independently of industry, is highly desirable.

TREATMENT OF FABRY NEPHROPATHY

4.1 We do not recommend starting ERT in patients with proteinuria [protein-to-creatinine ratio >1 g/g (>0.1 = gram/mol) creatinine] or eGFR <60 mL/min/1.73 m^2, except for non-renal indications. (1D)

4.2 We recommend that when ERT is deemed indicated, it should be started as part of a well-designed clinical trial, either observational or interventional. (Ungraded statement)

4.3 In a patient on haemodialysis, and when ERT is deemed indicated, we recommend administering the ERT during a haemodialysis session. (1A)

4.4 We recommend kidney transplantation as a valuable option in patients who are eligible for this intervention. (Ungraded statement)

4.5 After renal transplantation, we do not suggest ERT for renal indications, but it can be continued for non-renal indications. (Ungraded statement)

As discussed above, proteinuria is an important risk factor for the progression of renal FD. The use of ACE-i and ARB has been shown to be nephro-protective in other proteinuric renal diseases, and could thus be important in FD as well. As such, the use of ACE-i or sartane would be acceptable in FD. In a recent paper [47], it has been demonstrated that ERT interacts with ACE and inhibits its activity, possibly by removing the galactose residues from the enzyme. The clinical relevance of this observation is unclear, and should not be seen as a reason to prohibit the use of ACE-i.

Kidney Disease Improving Global Outcomes (KDIGO) guidelines suggest that in patients with CKD Stages 3–5, vitamin D deficiency be corrected [48]. Emerging evidence in patients with CKD show that vitamin D can reduce proteinuria or albuminuria even in the presence of angiotensin-converting enzyme inhibition [49]. Selective activation of the vitamin D receptor with paricalcitol lowered urinary albumin excretion, as was demonstrated in patients with Type 2 diabetes in a recent randomized controlled trial [50]. In cultured human podocytes, vitamin D receptor activation prevented lyso-Gb-3-induced, TGFβ1-mediated, up-regulation of extracellular matrix proteins [51]. Even lacking more definitive evidence of a beneficial effect of vitamin D on Fabry nephropathy, it seems advisable to place particular emphasis in following guidelines on vitamin D management in CKD patients in patients with FD.

Two forms of recombinant α-Gal A have been approved in Europe: agalsidase alpha (Replagal˚; Shire Human Genetic Therapies, Boston, MA) and agalsidase beta (Fabrazyme˚; Genzyme, Cambridge, MA). Agalsidase alpha is produced in a continuous human cell line and is administered as an intravenous infusion over 40 min at a dose of 0.2 mg/kg body weight every 2 weeks. Agalsidase beta is produced in Chinese hamster ovary (CHO) cells and is given as an intravenous infusion over a 4-h period at a dose of 1.0 mg/kg body weight every 2 weeks.

According to a recent Cochrane review, the evidence base in favour of ERT is weak. Only five (total $n = 187$) poor quality randomized controlled trials are available. They all concern surrogate end points, such as decrease in plasma Gb-3 levels in plasma and tissues and evolution of renal function. According to the Cochrane review, these studies show no evidence for a clinical benefit of the use of agalsidase alpha or beta to treat Fabry nephropathy [52]. As there are at present no hard data that ERT alters the natural course of Fabry nephropathy (Table 2), we recommend starting ERT only in the context of a clinical trial, interventional or observational. All data from observational trials should be entered in a central registry.

Besides randomized controlled trials open-label studies and retrospective analyses have been performed. It is of interest to compare the evolution of renal disease in the historical untreated and treated cohorts of an international industry sponsored registry on FD [43, 53]. It is difficult to compare the data presented in both publications, as the design of the analyses and the presentation of data were different, and there was a substantial risk for selection bias, as only a minor proportion of all those enrolled could be evaluated because of missing data. Nevertheless, in both studies, patients were stratified into quartiles according to severity indices of renal involvement. The slope of change in GFR was similar in comparable quartiles of the treated and untreated cohorts, especially in men. Hence, one cannot deny the reflection that ERT might have no marked impact on the decline of kidney function. From this comparison, it is also clear that, irrespective of ERT, proteinuria was the strongest predictor of outcome. In patients without proteinuria, renal function remained stable, equally in males as in females. In those with proteinuria, the slope of deterioration of eGFR appeared to be similar with or without ERT. It is unclear what the implications of these observations are with regard to ERT: either it implies that ERT should be given before proteinuria develops (but these subjects have no deterioration of kidney function anyway) or that it should not be given for renal protection in those with already existing heavy proteinuria. It would be interesting to include complete data sets in a registry of patients developing proteinuria at early stages to see how the evolution of renal function is in this cohort. Remarkably, in the Fabry Registry, data on proteinuria were available in only 462 of 2850 (historical cohort) and 213 of 2887 (ERT cohort) patients [43].

Other observational studies in male FD patients showed that renal function remained stable under ERT during a follow-up period up to 54 months in the case of normal or near normal baseline function (CKD 1–2) and low proteinuria (<1 g/g creatinine) in the majority of patients [54]. However, as only treated patients were observed, it cannot be excluded that these patients would have had no progression even without therapy, as it is clear from registry data that proteinuria <0.3 g/g creatinine is a favourable prognostic marker. Other publications demonstrate that in FD patients with CKD Stage 4, or with glomerulosclerosis >50% or proteinuria >1 g/g creatinine, renal function continues to deteriorate despite ERT (decline in renal function varying from 6.4 to 8.9 mL/min/1.73 m^2/year [54, 55]. In the case of CKD Stage 3, the decline in eGFR seems to be attenuated by ERT in comparison with historical data [−3.0 (male) and −1.0 versus −6.8 mL/min/1.73 m^2/year) [56]. Again, these data are small-scaled and use historic data as controls.

Few studies report on the effect of ERT on renal function in females. In a recent retrospective study of the Fabry Outcome Survey (FOS), the rate of decline in eGFR in females under ERT was similar to the normal expected age-related rate over a 4-year follow-up period, whereas the rate

Comparison I: Agalsidase alpha versus placebo	Agalsidase alpha (*n*)	Mean (SD)	Placebo (*n*)	Mean (SD)	Mean difference, 95% CI
Urinary sediment Gb3					
Schiffmann 2001 up to 6 months	14	1683 (1657)	11	2495 (1104)	−812,00 (−1897.83, 273.83)
Kidney Gb3					
Schiffmann 2001 up to 6 months	14	15.6 (5.98)	11	18.1 (10.54)	−2.5 (−9.47, 4.47)
Creatinine clearance					
Schiffmann 2001 up to 6 months	13	94.8 (27.76)	11	84.5 (35.15)	10.30 (−15.37, 35.97)
Insulin clearance					
Schiffmann 2001 up to 6 months	13	71 (16.11)	11	71.5 (32.03)	−0.50 (−21.36, 20.36)
Mesangial widening					
Schiffmann 2001 up to 6 months	12	25.7 (20.78)	9	40.4 (28.5)	−14.70 (−36.72, 7.32)
Glomeruli with segmental sclerosis					
Schiffmann 2001 up to 6 months	12	6.8 (8.66)	9	3 (5.7)	3.80 (−2.35, 9.95)
Obsolescent glomeruli					
Schiffmann 2001 up to 6 months	12	19.5 (20.78)	9	13 (15.3)	6.50 (−8.93, 21.93)
Comparison II: Agalsidase beta versus placebo	Agalsidase beta (*n*)	Mean (SD)	Placebo (*n*)	Mean (SD)	Mean difference, 95% CI
Renal microvascular endothelial deposits					
Eng 2001 up to 6 months	29	0.4 (0.7)	29	2.1 (0.8)	−1.7 (2.09, −1.31)
Renal events					
Banikazemi 2007 intention-to-treat	10/51		7/31	13 (15.3)	0.87 (0.37, 2.04)

Table 2. Randomized controlled trials in ERT; data concerning the kidney, reproduced from Dib *et al.* [52]

in men was approximately double the expected age-related rate of decline [57]. Another study reported on a stable renal function in female patients treated with ERT [58].

In summary, these studies suggest that, for the renal aspect of FD, treatment is at best only effective in CKD Stage 1 or 2, before the deterioration of renal function or onset of overt proteinuria, as it does not reduce proteinuria *per se*. Once proteinuria (>1 g/day) or CKD Stage 3 (eGFR <60 mL/min/1.73 m^2) develops, there are no data supporting a potential protective effect of ERT. Taking this and the very high cost (>200 000 Euro/year) into account, we do not recommend treatment in these cases.

ERT has few side effects, except for mild infusion-related reactions consisting primarily of chills that can be treated with paracetamol, antihistamines or steroids. It has been shown that the infusions can be safely performed in a home setting [59, 60].

The administration of ERT leads to the formation of antibodies in the majority of patients, and this is for both brands. These antibodies, especially the IgG, have inhibitory effects

on the enzyme activity *in vitro* [5, 6, 61, 62]. Although both agalsidase alpha and agalsidase beta have been associated with IgG formation, the reported incidence of antibodies has generally been higher for agalsidase beta [62]. In a study in 134 males and females, there was no correlation between anti α-Gal A IgG titres and the onset of clinical events or the rate in change in estimated GFR during treatment. However, a statistically significant association was found between anti-α-Gal A IgG titers and Gb-3 deposition in the dermal capillary endothelial cells during treatment, suggesting that Gb-3 clearance could be impaired [63]. In another study, there was less normalization of urinary Gb-3 in the seropositive patients compared with the seronegative ones [64, 65].

Analysing the consequences of antibodies is challenging because the assays are not uniform and there are no international antibody standards. Currently, numerous laboratories are performing α-Gal A-antibody testing. Potential differences between antibody assays and their respective sensitivities make comparison of titre values across the Fabry community difficult. The objective of the Fabry Antibody Standardization Initiative is to identify differences in analytical methods and to standardize α-Gal A antibody assays across the industry to allow the medical community involved in treatment to interpret antibody data equally [66].

We have very few data on the efficiency of higher doses than the ones registered for agalsidase alpha (0.2 mg/kg EOW) and agalsidase beta (1 mg/kg EOW). One open-label trial studied 11 adult male patients with FD who demonstrated a continuing decline in renal function despite 2–4 years of conventionally dosed agalsidase alpha therapy (0.2 mg/kg EOW) [67]. After switching to weekly dosing, three patients demonstrated an improvement in eGFR and six patients demonstrated a slow down in the rate of eGFR decline. Two patients failed to improve their eGFR slope. A multiple regression model confirmed that the weekly infusion regimen was the strongest explanatory variable for the change in eGFR, with a weaker contribution from the concomitant use of angiotensin-converting enzyme inhibitors/ARB, but the patient number was too low to allow meaningful conclusions.

We also have very few data comparing the two formulas. In a study by Vedder *et al.* [65], the low number of patients and the dose of agalsidase beta that was used (0.2 mg/kg instead of the licensed 1.0 mg/kg) precluded firm conclusions. In a larger group of patients ($n = 146$), there was no difference in a composite outcome of renal, cardiac and neurological events after 30 months of treatment (West, Molecular Genetics and Metabolism, 2011, abstract).

Tahir *et al.* found stabilization of renal function in a small open-label observational study in patients with CKD Stage 1–2 ($n = 4$) and CKD Stage 3–4 ($n = 6$) treated with a combination of agalsidase beta 1 mg/kg EOW and ACEi or ARB. The surprisingly favourable response in patients with GFR <60 mL/1.73 m^2/min and proteinuria >1 g/day was unexpected and should be confirmed in a larger study [68]. It is unclear in how far the positive effect, when confirmed, should be attributed to the ACE-i or the ERT. There is an on-going open-label, prospective, multi-centre study [The

Fabrazyme® and ARB's and ACE Inhibitor Treatment (FAACET) Study, registered at ClinicalTrials.gov NCT00446862], with as primary hypothesis that titration of ACEi and ARBs to reduce urine protein excretion to <500 mg/day in Fabry patients receiving agalsidase beta therapy at 1 mg/kg every 2 weeks will slow the progression rate of decline of GFR compared with case–controls drawn from a Genzyme-sponsored Phase III extension study (GFR 60–125 mL/min/1.73 m^2, urine protein >1 g/day) or the Phase IV study (GFR 20 to 60 mL/min/1.73 m^2, urine protein >0.5 g/day).

Survival of Fabry patients on RRT is poor, with a reported 3-year survival of 60–63%, which is lower than that of non-diabetic-matched controls [69]. There is no proof of an improved survival in RRT patients on ERT.

In patients with CKD Stage 5, where ERT is deemed to be an appropriate option, ERT can be performed during the haemodialysis sessions, which do not alter pharmacokinetics [70].

ERT diminished extra renal symptoms, and improved quality of life and in CKD Stage 5 patients on dialysis in a small ($n = 9$), non-placebo controlled cross-sectional study [71]. In another observational cross-sectional study ($n = 16$) on dialysis patients, with a mean follow-up of 45 months of ERT, mortality was very high (7/11), when patients were not transplanted [72]. These limited data suggest that, although typical Fabry symptoms such as pain crises can be controlled with ERT, we have no proof of improvement of cerebrovascular or cardiac morbidity or mortality in CKD Stage 5. Instead, mortality remains high if these patients are not transplanted. Transplantation without ERT has shown acceptable results. In a retrospective study, patient and graft survival was good for the first 10 years, although this study was probably undertaken in a selected patient group with little co-morbidity. After 10 years, mortality increases very quickly, probably due to progression of FD [73]. Data from the organ procurement Transplant Network/United Network for Organ Sharing ($n = 197$) were compared with a matched cohort of non-Fabry and non-diabetic CKD Stage 5 patients; although 5-year graft survival was similar, Fabry patients had a higher risk of death [RR 2.15 (1.52–3.02)] [74]. All these data seem to indicate that transplantation can be successful in patients with Fabry nephropathy, and that transplanted patients have a stable kidney function without ERT.

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CONFLICT OF INTEREST STATEMENT

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