Enzyme replacement therapy in Fabry disease, towards individualized treatment

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Phenotype, disease severity and pain are major determinants of quality of life in Fabry disease: results from a large multicenter cohort study

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Abstract

Quality of life (QoL) is decreased in patients with Fabry disease (FD). To improve QoL, it is important to understand the influence of FD related characteristics, symptoms and complications. In this retrospective cohort study we explored the effect of pain (measured by the Brief Pain Inventory), phenotype, treatment and FD-related complications on QoL. QoL data of Fabry patients as assessed by the EuroQol five dimension questionnaire (EQ-5D) from two international centers of excellence were collected. The aim of this study was to evaluate the effect of sex, phenotype, age, different states of disease severity, pain and ERT on EQ-5D utilities.

For 286 adult FD patients (mean age 42.5 years, 40% men, 60% classical phenotype) 2240 EQ-5Ds were available. QoL is decreased in men as well as women with FD, especially in older men with a classical phenotype. At age 50, utility was lower in men with classical FD compared to those with non-classical disease (β =-0.12, 95% CI: -0.23 – 0.01, p=0.037) with further difference in the years thereafter. Cardiovascular complications, stroke or transient ischemic attacks, multiple FD-related complications and pain were also associated with decreased utilities. Overall, no change in utility was seen in patients on ERT over a mean follow-up of 6.1 years.

FD leads to a decreased QoL compared to the general population. Disease complications and pain both negatively influence QoL. Adequate assessment and treatment of pain as well as improved strategies to prevent disease complications are needed to improve QoL in the FD population.

Introduction

Fabry disease (FD; OMIM 301500) is a rare X-linked lysosomal storage disorder with a heterogeneous disease course. The disease is caused by a deficiency of the enzyme α-galactosidase A (enzyme commission no. 3.2.1.22) due to mutations in the *GLA* gene. This results in accumulation of globotriaosylceramide (Gb3) and related sphingolipids in cells throughout the body and may cause clinical complications, especially in kidney, heart and brain. Despite the X-linked inheritance pattern, women are affected as well, and may develop similar symptoms and complications as men.[1,2] Both men and women with FD experience a decreased QoL.[3-6]

Phenotypically, FD can be divided into classical or non-classical disease. Men with classical FD generally have no residual enzyme activity and often exhibit Fabry-specific symptoms including neuropathic pain, cornea verticillata and angiokeratoma. Men with non-classical FD and women with either classical or non-classical FD have residual enzyme activity, usually resulting in a milder disease course. Older studies showed severely decreased QoL, predominantly in men who nowadays most likely would be considered to have classical FD.[7,8] Also in more recent studies a distinction in phenotypes has not been made. In other words, the effect of phenotype on QoL has yet to be elucidated.

Part of the decreased QoL in patients with FD seems to be associated with the neuropathic pain often seen in men with classical FD.[7] Episodes of severe, debilitating burning pains can be alternated with chronic pain, mostly in hands and feet. Moreover, the presence of gastro-intestinal (GI) symptoms, including GI-pain, is also associated with lower QoL.[9] Several studies reported a positive effect of enzyme replacement therapy (ERT) on pain.[10-12] In contrast, no clear effect of ERT on QoL was established in a recent systematic review from our group.[6] Besides pain, complications linked to FD such as end stage renal disease (ESRD), cardiomyopathy and stroke have been associated with decreased QoL.[7,8,13] For the purpose of a cost-effectiveness analysis, Rombach et al. created mutually exclusive disease states to simulate the disease course of FD.[14] Lower QoL was found in patients in a more severe disease state. However, the sample size necessitated grouping of different complications in one single group, so the effect of individual cerebral, renal or cardiac complications on QoL remained unknown. Better understanding of QoL in different disease states and improved understanding of the influence of specific symptoms and complications on QoL may facilitate targeted treatment, and thereby improve well-being of Fabry patients. With this study we aim to gain insight into the influence of sex, phenotype, age, disease severity and ERT on QoL.

Methods

Study design

Using local databases containing prospectively collected data as well as medical records, demographic, clinical and laboratory data of all FD patients from two centers of excellence (Academic Medical Center (AMC), The Netherlands; and Royal Free London NHS Foundation Trust (RFH), United Kingdom) were merged into one database. This cohort represents the part of a larger study.[15] with available EuroQol five dimension questionnaire (EQ-5D) data. Baseline was defined as the date of the first EQ-5D measurement, except for the evaluation of the influence of ERT on the QoL where the start date of ERT was used as baseline.

Study participants

Adult patients (≥18 years) with a definite FD diagnosis according to previously developed criteria [16] of whom sufficient data for phenotypical classification and one or more EQ-5D measurements were available, were included. They were categorized as classical or non-classical on the basis of enzyme activity and the presence or absence of characteristic FD symptoms (Fabry neuropathic pain, clustered angiokeratoma and/or cornea verticillata).[17] A detailed description of the classification method has been published earlier (supplement material A).[15] According to Dutch law, and after review of the AMC ethics committee, no approval of the study protocol was needed because of the observational nature of the study. All data were obtained from medical records. Patient records were anonymized and de-identified prior to analysis. All patients have provided consent for the use of their medical data and samples in accordance with local ethics requirements.

EQ-5D

The EQ-5D is a QoL questionnaire that covers five different QoL domains: Mobility, Self-care, Anxiety/Depression, Usual activities and Pain/Discomfort.[18] Respondents are asked to choose per domain which one of the following three options describes their situation best: No problems, Some/Moderate problems or Extreme problems.[19] EQ-5D data can be presented as a health profile which shows the frequency of reported problems for each level for each dimension.[19] Also, a utility for the health status can be calculated by combining the responses on all five domains. A utility of 1 means perfect health and a score of 0 represents death. Negative scores can also be obtained representing health states that are considered worse than death. Utilities differ per country. For our study we used the Dutch and UK weighing for Dutch and English patients, respectively.[20,21]

Pain assessment

The AMC and the RHF both used the Brief Pain Inventory (BPI) to assess the presence and severity of pain and its influence on daily life. All BPI scores closest to the utility with a maximum window of ±3 months were used. The BPI assesses pain at its worst, average pain and pain interference with life. The interference score measures the influence of pain on general

activity, walking, work, mood, enjoyment of life, relations and sleep. It is the mean of at least four of these items. Worst pain, average pain and the interference score are graded from 0 (pain is absent) to 10 (worst possible pain).[22]

Disease severity

To evaluate the effect of symptoms, organ involvement and complications in FD, patients were classified in ten mutually exclusive disease states with increasing severity (table 1).[14] According to strict criteria, patients can transition from one state to another in case of disease progression.

Table 1 Description of disease states

Disease state*	Description
Asymptomatic	
No organ involvement	No left ventricular hypertrophy, kidney disease, white matter lesions or complications
Symptoms	
Neuropathic pain	A history of Fabry neuropathic pain in the extremities provoked by heat, fever or exercise (also referred to as acroparesthesia)
Organ involvement	Left ventricular hypertrophy, chronic kidney disease stages 2-4, albuminuria/proteinuria or white matter lesions
Single complication	
End stage renal disease	Chronic kidney disease stage 5 (eGFR <15ml/min/1.73m^2), dialysis or kidney transplant
Cardiac complication(s)	Atrial fibrillation, any other rhythm disturbance needing hospitalization, pacemaker or implantable cardiac defibrillator (ICD) implantation, cardiac congestion for which hospital admittance was needed, myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft
Cerebrovascular accident	Transient ischemic attack (TIA) or stroke, as diagnosed by a neurologist
Multiple complications#	
End stage renal disease and cardiac complication(s)	
End stage renal disease and cerebrovascular accident	
Cardiac complication(s) and cerebrovascular accident	
End stage renal disease and cardiac complication(s) and cerebrovascular accident	

** Typically, patients progress from the asymptomatic state or neuropathic pain state to the symptoms state; from the symptoms state to a single complication state; from a single complication state to a double complication state, and from a double complication state to the triple complication state.*

 # Since the number of patients in the disease states representing more than one complication was low, one combined 'multiple complications' disease state was made.

Clinical and laboratory measurements

Renal function was evaluated by the estimated glomerular filtration rate (eGFR) using the CKD-EPI formula [23] and proteinuria. Cardiac involvement was assessed by echocardiography. Left ventricular mass (LVM) was calculated using the Devereux formula and was corrected for height (m$^{2.7}$).[24] Left ventricular hypertrophy was defined as LVM ≥49 and ≥45 gram/m$^{2.7}$ in men and women, respectively.[24] The presence of white matter lesions (WMLs)/ischemic le-

sions was investigated by cerebral MRI. Plasma lysoGb3 levels were measured with tandem mass spectrometry with glycine labeled (RFH and AMC after August 2015) or isotope labeled lysoGb3 (AMC before August 2015) as an internal standard.[15,25]

Statistical methods

R (version 3.1.5) and SPSS for Windows, version 22.0 (SPSS Inc. Chicago, Illinois, USA) were used. First, utilities per sex and phenotype were calculated, followed by a second order polynomial regression mixed effect model with a random intercept and slope to evaluate the effect of age on utilities, stratified for sex and phenotype. To evaluate the relation between BPI score and utility, the polynomial mixed effect model was extended by including BPI scores as covariate.

Second, the effect of ERT on utilities was investigated with a linear mixed model including time on ERT and age at ERT initiation as time-dependent covariates and a mixed model of the difference between the utility at baseline and follow up measurements. Since QoL is known to fluctuate over time, patients were only included in this analysis if they completed an EQ-5D within three months before the start of ERT. Finally, utilities per disease state for the combined cohort of men and women with classical and non-classical disease were modeled. To account for the fact that one patient may have filled in more than one EQ-5D per disease state, a linear mixed effect model with the disease state as covariate and a random intercept was used to evaluate the utility per disease state. Patient numbers were too small to include sex and phenotype. In order to analyze the effect of eGFR, LVM and WML on QoL within the "organ involvement" disease state, univariate and multivariate analyses were performed within this group. Data are presented as mean ± standard deviation (SD) or median and range dependent on the distribution of data. Where appropriate, 95% confidence intervals (95% CI) are given. P-values <0.05 were considered statistically significant.

Results

The merged database contained data on 439 patients from the AMC and the RFH, of whom 27 patients did not fulfill the criteria for a definite diagnosis, 12 had insufficient baseline data for assessment of disease severity and no follow-up data, and 114 patients did not complete one or more EQ-5D measurements. Two-hundred-eighty-six FD patients (117 patients from the AMC and 169 patients from the RFH) with a mean age: 42.5 ± 12.5 years completed 2240 EQ-5Ds. Each patient completed on average 7.8 ± 4.5 EQ-5Ds during a mean follow-up period of 5.4 ± 3.2 years. Classically affected patients completed more EQ-5Ds compared to non-classically affected patients. Table 2 shows the baseline characteristics at the time of completion of the first EQ-5D.

Table 2 Characteristics of all patients at first EQ-5D measurement

	All	Men		Women	
		Classical	Non-classical	Classical	Non-classical
Patients, n (%)	286	76 (26.6)	38 (13.3)	96 (33.6)	76 (26.6)
Age in years, mean (±SD)	42.5 (±15.5)	37.4 (±12.5)	54.2 (±15.4)	44.0 (±15.5)	40.7 (±15.2)
Age first visit, mean (±SD)	40 (±16.0)	34.2 (±12.5)	52.8 (±15.8)	42.6 (±15.6)	37.8 (±15.5)
History of ERT, n (%)	125 (43.7)	57 (75.0)	13 (34.2)	41 (42.7)	14 (18.4)
Currently on ERT, n (%)	117 (40.9)	52 (68.4)	13 (34.2)	39 (40.6)	13 (17.1)
Time on ERT in years, mean (±SD)	2.97 (±2.38)	3.69 (±2.61)	1.94 (±2.03)	2.73 (±2.05)	1.87 (±1.89)
Events before first EQ-5D					
Any event, n (%)	50 (17.5)	16 (21.1)	14 (36.8)	16 (16.7)	4 (5.3)
Cardiac event, n (%)	33 (11.5)	8 (10.5)	12 (31.6)	9 (9.4)	4 (5.3)
Renal event, n (%)	8 (2.8)	5 (6.6)	2 (5.3)	1 (1.0)	0 (0)
Cerebral event, n (%)	20 (7.0)	8 (10.5)	3 (7.9)	9 (9.4)	0 (0)
WML, n (%)	112 (39.2)	34 (44.7)	11 (28.9)	41 (42.7)	26 (34.2)
eGFR in ml/min/1.73m^2, mean (±SD)	93.8 (±25.9)	99.0 (±30.3)	80.6 (±26.3)	96.7 (±21.6)	91.5 (±23.7)
eGFR <60 ml/min/1.73m^2, n (%)	29 (10.3)	10/76 (13.2)	6/38 (15.8)	5/94 (5.3)	8/73 (11.0)
LVM in gram/m$^{2.7}$, median (range)	42.0 (16.2-139.9)	48.3 (23.6-110.4)	54.2 (16.2-99.9)	40.8 (18.2-139.9)	34.5 (17.1-96.2)
LVM >upper ref limit, n (%)	101 (37.4)	33/74 (44.6)	20/35 (57.1)	32/92 (34.8)	16/69 (23.2)
LysoGb3* in nmol/L, median (range)	7.5 (0.4-150.3)	105.5 (31.8-150.3)	6.0 (1.2-22.4)	7.6 (0.7-27.2)	2.0 (0.4-15.4)
BPI average pain*, median (range)	2 (0-8)	2 (0-8)	0 (0-7)	3 (0-8)	3 (0-8)
BPI worst pain*, median (range)	3 (0-10)	3 (0-10)	0 (0-9)	3 (0-9)	3 (0-10)
BPI average interference*, median (range)	0.6 (0-9.9)	0.5 (0.0-8.4)	0.1 (0.0-9.9)	0.5 (0.0-9.3)	1.1 (0.0-9.7)
EQ-5Ds#, n	2240	668	286	771	515
EQ-5Ds per patient#, mean (±SD)	7.8 (±4.5)	8.8 (±4.8)	7.5 (±4.1)	8.2 (±4.5)	6.8 (±4.4)
Follow-up time#, mean (±SD)	5.38 (±3.15)	5.73 (±3.46)	4.71 (±2.86)	5.56 (±2.98)	5.13 (±3.15)

Events represent the number of patients with one or more events before first EQ-5D. Events were defined as described at end stage renal disease, cardiac complications and cerebrovascular accident similar to the definition of the disease states (table 1). Upper reference limit LVM: ♂ = 51 / ♀ = 48. Normal range lysoGb3 = 0.3-0.6 nmol/L. LysoGb3 represents values before start of ERT.

** Values missing: LysoGb3 32%, BPI Average pain 16%, BPI Worst pain 15%, BPI Average Interference 12%.*

 # Values acquired during follow-up

Health profile at baseline per phenotype and per disease state

The health profile of the first completed EQ-5D (table 3) shows that 35.5% of all men with classical FD reported some/moderate problems of mobility with one patient reporting extreme problems. Lower percentages (21.9% to 28.9%) of women and men with non-classical disease reported some/moderate mobility problems. Self-care was relatively preserved in all subgroups of patients, while 35.3% experienced some/moderate problems with their usual activities with percentages ranging from 25.0% in women with non-classical FD to 42.1% in men with classical disease. Twenty-one patients (7.3%) experienced extreme pain at baseline and almost two-thirds of the men with classical FD experienced at least some/moderate pain. Some/moderate anxiety or depressive symptoms were noted in about one third of men with classical FD and women with classical and non-classical FD.

The health profiles of the first EQ-5D per disease state (supplemental table B) indicated that a large proportion of patients in the 'neuropathic pain' disease state reported problems with their usual activities and anxiety/depression domain, and some/moderate to extreme problems in the pain/discomfort domain. Since the number of patients in the disease states representing more than one complication was low, one combined 'multiple complications' disease state was made, representing patients with complications in at least two organs (kidney, heart and/or brain). Patients in the 'single' and 'multiple complication' disease states reported problems across all domains.

Table 3 Health profile and utility of the first EQ-5D measurement stratified for sex and phenotype

	All	Men		Women	
		Classical	Non-classical	Classical	Non-classical
Mobility					
1*	207 (72.4%)	48 (63.2%)	27 (71.1%)	75 (78.1%)	57 (75.0%)
2	78 (27.3%)	27 (35.5%)	11 (28.9%)	21 (21.9%)	19 (25.0%)
3	1 (0.3%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Self-care					
1	261 (91.3%)	64 (84.2%)	34 (89.5%)	93 (96.9%)	70 (92.1%)
2	22 (7.7%)	10 (13.2%)	4 (10.5%)	3 (3.1%)	5 (6.6%)
3	3 (1.0%)	2 (2.6%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
Usual activities					
1	173 (60.5%)	40 (52.6%)	25 (65.8%)	57 (59.4%)	51 (67.1%)
2	101 (35.3%)	32 (42.1%)	12 (31.6%)	38 (39.4%)	19 (25.0%)
3	12 (4.2%)	4 (5.3%)	1 (2.6%)	1 (1.0%)	6 (7.9%)
Pain/discomfort					
1	138 (48.3%)	29 (38.2%)	22 (57.9%)	47 (49.0%)	40 (52.6%)
2	127 (44.4%)	43 (56.6%)	15 (39.5%)	40 (41.7%)	29 (38.2%)
3	21 (7.3%)	4 (5.3%)	1 (2.6%)	9 (9.4%)	7 (9.2%)
Anxiety/depression					
1	191 (66.8%)	51 (67.1%)	27 (71.1%)	65 (67.7%)	48 (63.2%)
2	90 (31.5%)	25 (32.9%)	9 (23.7%)	31 (32.3%)	25 (32.9%)
3	5 (1.7%)	0 (0.0%)	2 (5.3%)	0 (0.0%)	3 (3.9%)
Utility#, mean (±SD)	0.77 (±0.26)	0.75 (±0.25)	0.81 (±0.27)	0.79 (±0.23)	0.76 (±0.30)

** 1 = No problems, 2 = Some/Moderate problems, 3 = Extreme problems*

 # Please note that a baseline utility is presented in contrast to Figure 1 which presents longitudinal utilities

Relation between phenotype, age and utilities

A decrease in utilities with age was seen in all subgroups (figure 1), although the extent of this relation differed between the subgroups. The mixed model revealed that the utility of a 50-year-old man with classical FD is on average 0.12 points lower (95% CI: -0.23 – 0.01, p=0.037) compared to a man with non-classical FD of the same age. At age 60 this mean difference has increased to 0.21 points (95% CI: -0.36 – -0.07, p=0.004). This illustrates the progressive worsening of utilities in men with classical FD with increasing age. In women and men with non-classical FD the decline in utilities with age was less strong (figure 1).

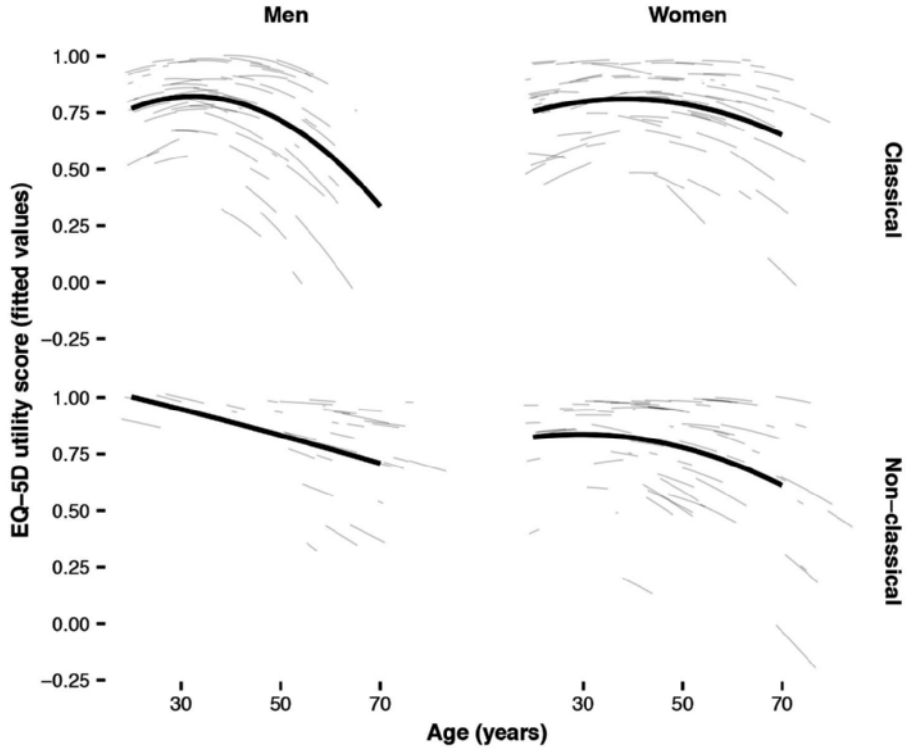

Figure 1 Polynomial mixed effect model of EQ-5D in relation to age, stratified for sex and phenotype. Large lines represent fitted values at group level, the smaller lines represent the fitted values at individual patient level.

Relation between BPI scores and utilities

In total 1559 BPIs of 276 patients were matched to an EQ-5D. Of the patients that completed BPIs 45.3% were men, 61.2% had the classical phenotype and the mean age was 44.8 ± 14.9 years. Utilities decreased with higher BPI scores: with every one point higher BPI average pain score, the utility decreased on average with 0.045 points (β = -0.045, 95% CI: -0.049 – -0.040, p<0.001). Similarly, an increase in BPI worst pain score (β = -0.035, 95% CI: -0.039 – -0.031, p<0.001) or BPI interference score (β = -0.058, 95% CI: -0.063 – -0.053, p<0.001) resulted in lower utilities. A sensitivity analysis without the pain/discomfort domain in the calculation of the utilities did not change the results.

The effect of ERT on utilities

For the evaluation of the effect of ERT on utilities, 61 patients were analyzed who completed at least one EQ-5D before the initiation of ERT. The mean age of patients at ERT initiation was 44.2 ± 15.5 years, and the mean follow-up time after initiation of ERT was 6.1 ± 2.5 years. The median utility score before ERT was 0.796 (-0.166 – 1.000). Utility remained unchanged after start of treatment (β = -0.004, 95% CI: -0.066 – -0.058, p=0.89). Furthermore, there was no relation between change in utility, time on ERT (β = -0.005, 95% CI: -0.016 – -0.006, p=0.40) and age at ERT initiation (β = -0.002, 95% CI: -0.006 – 0.001). In a subgroup analysis, we found that utilities increased after initiation of ERT in the 13 men with classical FD (β = 0.17, 95% CI: 0.06 – 0.28, p=0.003). This was primarily attributable to 3 patients with a very low utility before the start of ERT due to extreme pain/discomfort which improved substantially after the start of treatment. One of them started taking carbamazepine for his neuropathic pains during the same period, leading to a substantial decrease in neuropathic pain in the months thereafter. Without these three patients no change in utility was observed (β = 0.04, 95% CI: -0.07 – 0.14, p=0.50). Additional subgroup analyses revealed that no annualized change in utility was observed in women with classical or non-classical disease, while in men with non-classical FD a 0.027 point decline per year on ERT (95% CI: -0.053 – 0.001, p=0.04) was found.

Relation between disease severity and utilities

Table 4 shows the mean utility per disease state for men and women with classical and non-classical FD combined. Within the "organ involvement" disease state we found no relation between eGFR, LVMI and WML on the one hand and utilities on the other hand. Patients included in the advanced disease states, and thus with more severe disease, were older and more often men with classical FD. Compared to the 'no organ involvement' disease state, the utilities were significantly lower in the 'cardiac complication(s)', 'cerebrovascular accident' and the 'multiple complications' disease states but not the 'end stage renal disease' disease state. The utility of the latter was based on a low number of patients (n=7) who showed divergent utility scores. The lowest utility was found in the 'multiple complications' disease state (β = 0.530, 95% CI: 0.42-0.63). The 'neuropathic pain' disease state also showed a trend towards lower utility compared to the 'no organ involvement' disease state (p=0.054).

Table 4 Utility per disease state

Disease state	No organ involvement	Neuropathic pain	Organ involvement	End stage renal disease	Cerebrovascular accident	Cardiac complication(s)	Multiple complications
Patients*, n	31	21	221	7	16	45	18
EQ-5Ds, n	103	71	1521	56	100	290	99
Health utility, mean (95% CI)	0.851 (0.77 - 0.93)	0.725 (0.63-0.82)	0.783 (0.75-0.81)	0.828 (0.67-0.99)	0.705 (0.60-0.81)	0.732 (0.67-0.80)	0.530 (0.42-0.64)
P-value#	-	0.053	0.123	0.796	0.037	0.026	<0.001
Woman, n (%)	26 (83.9)	15 (71.4)	138 (62.4)	1 (14.3)	8 (50.0)	20 (44.4)	6 (33.3)
Classical phenotype, n (%)	5 (16.1)	19 (90.5)	136 (61.5)	6 (85.7)	15 (93.8)	21 (46.7)	14 (77.8)
Age in years, mean (±SD)	32.0 (±10.1)	26.5 (±8.6)	41.0 (±14.1)	45.8 (±12.9)	49.3 (±10.1)	59.2 (±11.0)	60.5 (±8.4)
History of ERT, n (%)	3 (9.7)	2 (9.5)	107 (48.4)	5 (71.4)	13 (81.2)	32 (71.1)	14 (77.8)
Now ERT, n (%)	3 (9.7)	2 (9.5)	97 (43.9)	5 (71.4)	13 (81.2)	31 (68.9)	13 (72.2)
Time on ERT in years, mean (±SD)	1.40 (±0.49)	0.98 (±1.31)	2.72 (±2.14)	3.06 (±1.72)	4.67 (±4.08)	4.91 (±4.04)	6.14 (±2.81)

** Patients may have more than one EQ-5D per disease state and may contribute to more than one disease state. # P-values were calculated with 'No organ involvement' as reference group.*

Discussion

This study shows that QoL in patients with FD is related to phenotype, age, pain and disease severity. Obviously, these features are related to each other; classically affected patients of older age will have more severe disease with a higher chance of developing FD-related complications and thus a decreased QoL. Additional analyses to study the independent effects of these features on QoL were not feasible due to limited patient numbers and the expectation of high multicollinearity.

The mean utility of FD patients in the present study ranged from 0.75 in men with classical FD to 0.81 in men with non-classical disease, and QoL decreased with advancing age. Comparison of the health profile of these patients to the health profile of the general population in the UK and the Netherlands supports a higher prevalence of impaired QoL in FD (supplemental table C).[26,27] In line with the current results, a recent study in a mixed cohort of treated and untreated men and women with FD showed a mean utility of 0.79.[28]

In contrast, a cohort study from the pre-ERT era in which 38 men of similar age and with presumed classical disease were included, showed a substantially lower utility of 0.56.[8] These patients had more often suffered from one or more complications.[8] Therefore, a possible explanation for the difference in utilities is that in our cohort ERT delayed the occurrence of complications and therefore delayed the decrease in QoL caused by complications.[29] Indeed, in a recent study from our group on the natural course of FD stratified by sex and phenotype, men with classical disease were shown to have the highest risk of developing complications.[15] The median age at first complication was approximately 50 years, which corresponds with the age after which the decrease in QoL accelerates in these men in the present study. The fact that the utility in the pre-ERT cohort resembles the utility in our 'multiple complications' disease state further supports this. It is unlikely that QoL scores in the investigated FD populations are influenced by regional differences, since the QoL scores in the general population in the UK and the Netherlands are comparable (supplemental table C). However, other factors may have contributed to the higher QoL in the present study compared to the pre-ERT cohort, such as pain management. Indeed, a detailed look at the health profiles of the different subgroups of patients indicates that the prevalence of extreme pain seems to have decreased when compared to older studies (supplemental table C).[8,11] However, pain is still present in around half of the patients and associated with lower QoL in FD, as also established in a Fabry Outcome Survey study.[11] Moreover, chronic pain is related to decreased QoL in all domains in the general population.[30] Therefore, QoL is expected to increase if pain control is improved. An often mentioned cause of pain in patients with FD is neuropathic pain in the extremities (also called acroparesthesia), which is associated with decreased QoL.[7] However, in this study, men with non-classical FD and women, who are known to have a low prevalence of Fabry-related neuropathic pain, also frequently reported pain. Indeed, a previous study has shown that other types of pain (*e.g.* musculoskeletal pain

or GI-pain) may play an important role in the life of FD patients.[31] As a consequence, it is recommended to assess individual causes of pain and manage it accordingly.[31-33]

The reported percentage of extreme anxiety/depression in the health profile has also decreased compared to older studies.[8,11] The availability of treatment in itself can provide hope or relief of complaints and might reduce anxiety/depressive complaints.[34] On the other hand, in other metabolic diseases it has been speculated that biweekly infusions are burdensome, especially in the hospital setting, thereby potentially affecting QoL.[35,36] In our study, no effect of ERT was seen on the percentage of patients with anxiety/depression.

Previous studies have not been able to unequivocally determine the effect of ERT on QoL.[6] The current study showed that QoL did not change over six years of follow-up in patients receiving ERT. Since age is associated with an increased complication risk as well as lower QoL[6,15,29] a lack of change in QoL scores could be interpreted as a positive effect of treatment, wither ERT or supportive care. However, there are individual differences in the course of QoL with some patients deteriorating while others improve. Of interest to this end is the observation that three out of thirteen men with classical FD had higher utilities after start of ERT, especially in the Pain and Activity domain. However, it is difficult to attribute the improvement in QoL to the start of ERT, because pain may subside spontaneously.[37,38] Moreover, we could not correct for concomitant analgesic or antidepressant treatment that might improve or stabilize QoL.

In patients with deteriorating QoL, ERT may have been started too late. Indeed, it has been previously shown that ERT is of limited benefit in patients with advanced organ involvement and complications.[29] In the present study complications are clearly associated with a decreased QoL: cerebrovascular accidents, cardiovascular complications and multiple complications resulted in a decrease in utilities of 0.15, 0.12 and 0.32 respectively, all exceeding the minimally clinically important difference of 0.074.[39]

Our study has several limitations. Firstly, the EQ-5D offers three answer options per domain, limiting the detection of small changes in health.[40] Secondly, questionnaire data were gathered during clinical visits, in some patients for up to 15 years in a row. Habituation to repeatedly filling out a questionnaire as well as coping might have influenced the questionnaire accuracy. Thirdly, the lack of a control group hampered the interpretation of the effect of ERT on QoL. Finally, since the QoL data were gathered in an uncontrolled, real-life environment, they were more prone to be influenced by known and unknown confounders, such as presence of concomitant diseases and the use of pain medication. On the other hand, real-life data provides an opportunity to assess QoL in actual practice conditions. Despite these shortcomings an insight has been gained into QoL in FD and its determinants, which can be used to improve the care for these patients.

In conclusion, QoL is decreased in men as well as women with FD compared to the general population, especially in older men with a classical phenotype. QoL is lower in patients with FD-related complications and ERT does not seem to have a major impact on QoL. This necessitates the improvement of treatment and preventive strategies. Pain also has a severe impact on QoL. It is prevalent in both sexes and phenotypes and comprises more than neuropathic pain alone. Pain assessment should be an important part of routine follow-up and treatment should be standardized and evaluated accordingly.

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Supplemental material A

Phenotypic classification adapted from Arends et al (2017) with permission

Patients were classified as classical or non-classical FD on the basis of their enzyme activity (men only) and the presence or absence of characteristic symptoms.[16] Men were considered to have a classical phenotype when they met the following criteria: 1) a *GLA* mutation, 2) enzyme activity ≤5% of the mean reference range, 3) ≥1 characteristic FD symptoms (*i.e.* Fabry neuropathic pain, angiokeratoma and/or cornea verticillata, for definitions see.[17] Men not fulfilling these criteria were categorized as non-classical FD. Women with a *GLA* mutation and ≥1 characteristic FD symptoms (*i.e.* Fabry neuropathic pain, angiokeratoma and/or cornea verticillata[17]) were classified as having a classical phenotype. Women without these characteristic FD symptoms were classified as non-classical FD.

Classification on the basis of phenotypic features and residual enzyme activity was challenging in two groups of patients. It was decided that in these cases a final judgement was made by the treating physician. These groups were:

1) Patients with the N215S mutation: this group is especially prevalent in the UK. According to literature and physician experience, patients exhibit a non-classical (mostly cardiac) phenotype, but exceptions may occur. In this group of 90 patients, 12 had a characteristic symptom, but without confirmatory deficiency of *GLA* activity in leucocytes in men (*n = 5*). Notably, one of the N215S patients presented with severe renal disease at young age and had a renal transplantation at age 29. According to the judgement of the treating physician this patient was classified as classical FD while the other N215S patients were all classified as non-classical FD. Similarly, three patients with characteristic symptoms and the P389A mutation (1 man, 1 woman) or R112H (1 woman) mutation were discussed with the treating physician. These patients all had a late onset presentation, only minimal cornea verticillata (no other characteristic FD symptoms) and a family history of non-classical FD. Consequently they were classified as non-classical FD.

2) Men with slightly higher than 5% enzyme activity in the presence of 1 or more characteristic symptoms (*n = 13*). Residual enzyme activity ranged from 6% to 10% in leucocytes (*n = 10)*, and from 6% to 20% in plasma (*n = 3*). All had at least one characteristic FD symptom and the majority had a relative with classical FD and consequently were considered having classical FD. In four men the enzyme activity and/or the data on characteristic FD symptoms were missing. These patients were classified as classical FD according to the opinion of the treating physician, which was mainly based on their family history.

Furthermore, we included three patients (one man, two women, all from the same family) with the A143T mutation. They were classified as having classical FD based on the combina-

tion of characteristic deposits on renal biopsy or post mortem biopsy, the presence of one or more characteristic FD symptoms, low enzyme activity (3,9%, 21% and 38% respectively) and high plasma lysoGb3 concentrations (men: 35-50 nmol/l while receiving ERT; woman 1: 16 nmol/l while receiving ERT; woman 2: 8 nmol/l while not receiving ERT). In these cases, a combination of the A143T mutation and an unknown mutation and/or other (genetic) disease modifiers may have caused the classical FD presentation.

Supplemental table A Criteria for phenotypic classification

Classical FD	
Men	**Women**
A mutation in the *GLA* gene* ≥ 1 of the following characteristic Fabry disease symptoms: Fabry neuropathic pain, angiokeratoma and/or cornea verticillata Severely decreased or absent leukocyte AGAL activity (<5% of the normal mean)	A mutation in the *GLA* gene ≥ 1 of the following characteristic Fabry disease symptoms: Fabry neuropathic pain, angiokeratoma and/or cornea verticillata
Non-classical FD	
A mutation in the *GLA* gene, and not fulfilling the criteria for classical FD	

**The following genetic variants were considered not FD (neutral variants): A143T, P60L, D313Y, R118C, T385A, IVS0-10 C>T, the complex haplotype: IVS0-10 C>T/IVS4-16A>G/IVS6-22C>T. In patients in whom classification on the basis of these criteria was not feasible, the final judgement was made by the treating physician.*

Supplemental material B

Supplemental table B Health profile of first EQ-5D measurement per disease state

Disease state	No organ involvement	Neuropathic pain	Organ involvement	End stage renal disease	Cerebrovascular accident	Cardiac complication(s)	Multiple complications
Patients#, n	31	21	221	7	16	45	18
Mobility							
1*	28 (90.3%)	17 (81%)	169 (76.5%)	4 (57.1%)	9 (56.2%)	24 (53.3%)	5 (27.8%)
2	3 (9.7%)	4 (19%)	52 (23.5%)	3 (42.9%)	7 (43.8%)	21 (46.7%)	12 (66.7%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
Self-care							
1	30 (96.8%)	20 (95.2%)	209 (94.6%)	5 (71.4%)	13 (81.2%)	40 (88.9%)	12 (66.7%)
2	1 (3.2%)	1 (4.8%)	10 (4.5%)	2 (28.6%)	3 (18.8%)	5 (11.1%)	5 (27.8%)
3	0 (0.0%)	0 (0.0%)	2 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
Usual activities							
1	25 (80.6%)	11 (52.4%)	143 (64.7%)	4 (57.1%)	7 (43.8%)	20 (44.4%)	5 (27.8%)
2	5 (16.1%)	10 (47.6%)	69 (31.2%)	3 (42.9%)	9 (56.2%)	24 (53.3%)	11 (61.1%)
3	1 (3.2%)	0 (0.0%)	9 (4.1%)	0 (0.0%)	0 (0.0%)	1 (2.2%)	2 (11.1%)
Pain/discomfort							
1	20 (64.5%)	8 (38.1%)	108 (48.9%)	5 (71.4%)	5 (31.2%)	19 (42.2%)	2 (11.1%)
2	9 (29.0%)	8 (38.1%)	96 (43.3%)	2 (28.6%)	10 (62.5%)	22 (48.9%)	15 (83.3%)
3	2 (6.5%)	5 (23.8%)	17 (7.7%)	0 (0.0%)	1 (6.2%)	4 (8.9%)	1 (5.6%)
Anxiety/Depression							
1	20 (64.5%)	13 (61.9%)	149 (67.4%)	5 (71.4%)	12 (75.0%)	27 (60.0%)	11 (61.1%)
2	10 (32.2%)	8 (38.1%)	69 (31.2%)	2 (28.6%)	4 (25.0%)	15 (33.3%)	6 (33.3%)
3	1 (3.2%)	0 (0.0%)	3 (1.4%)	0 (0.0%)	0 (0.0%)	3 (6.7%)	1 (5.60%)

 # Patients may have more than one EQ-5D per disease state and may contribute to more than one disease state

** 1 = No problems, 2 = Some/Moderate problems, 3 = Extreme problems*

Supplemental material C

Supplemental table C Comparison of health profile first EQ-5D of present study with literature

	Present study	Present study	Miners et al (2002)	Kind et al (1998)	Lamers et al (2006)
	FD (all patients)	FD (men with classical disease)	FD (pre-ERT cohort)	Sample general population	Sample general population
N	286	76	38	3395	298
Age, years (±SD)	42.5 (±15.5)	37.4 (±12.5)	37.2 (±9.2)	Unknown	43.4 (±15.0)
Men, n (%)	114 (39.8)	76 (100)	38 (100)	1562 (46)	152 (51.0)
Classical phenotype, n (%)	172 (60.1)	76 (100)	Unknown	-	-
Country	UK/NL	UK/NL	UK	UK	NL
Mobility					
1*	207 (72.4%)	48 (63.2%)	19 (50.0%)	2424 (71.6%)	258 (86.5%)
2	78 (27.3%)	27 (35.5%)	18 (47.4%)	620 (18.3%)	40 (13.5%)#
3	1 (0.3%)	1 (1.3%)	1 (2.6%)	3 (0.1%)	
Self-care					
1	261 (91.3%)	64 (84.2%)	28 (73.7%)	3285 (95.8%)	292 (98.0%)
2	22 (7.7%)	10 (13.2%)	9 (23.7%)	139 (4.1%)	6 (2.0%)#
3	3 (1.0%)	2 (2.6%)	1 (2.6%)	5 (0.1%)	
Usual activities					
1	173 (60.5%)	40 (52.6%)	17 (44.7%)	2829 (83.7%)	257 (86.2%)
2	101 (35.3%)	32 (42.1%)	20 (52.7%)	481 (14.2%)	41 (13.8%)#
3	12 (4.2%)	4 (5.3%)	1 (2.6%)	70 (2.1%)	
Pain/discomfort					
1	138 (48.3%)	29 (38.2%)	10 (26.3%)	2268 (67.0%)	193 (64.8%)
2	127 (44.4%)	43 (56.6%)	21 (55.3%)	988 (29.2%)	105 (35.2%)#
3	21 (7.3%)	4 (5.3%)	7 (18.4%)	129 (3.8%)	
Anxiety/depression					
1	191 (66.8%)	51 (67.1%)	19 (50.0%)	2687 (79.1%)	255 (85.6%)
2	90 (31.5%)	25 (32.9%)	14 (36.8%)	648 (19.1%)	43 (14.4%)#
3	5 (1.7%)	0 (0.0%)	5 (13.2%)	62 (1.8%)	

** 1 = No problems, 2 = Some/Moderate problems, 3 = Extreme problems*

N = Number of respondents, UK = United Kingdom, NL = Netherlands.

 # Dutch sample of general population only provided combination of some/moderate and extreme problems as "any problems".