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DOI: https://doi.org/10.1016/j.ymgme.2023.107692

Molecular Genetics and Metabolism 140 (2023) 107692

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Screening for health-related quality of life and its determinants in Fabry disease: A cross-sectional multicenter study

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ARTICLE INFO

Keywords:
Health-related quality of life
Fabry disease
Depression
Enzyme replacement therapy
Chaperone

ABSTRACT

Background: Fabry disease (FD) is a rare X-linked lysosomal storage disorder caused by α-galactosidase A (α-Gal A) deficiency. The progressive accumulation of globotriaosylceramide results in life-threatening complications, including renal, cardiac, and cerebrovascular diseases. In order to improve health care of FD-patients, knowledge of its predictors is important. The aim of our study was to evaluate health-related quality of life (HrQol) in FD and to identify its independent determinants by exploring a wide range of demographic, social and clinical parameters.

Results: In this cross-sectional multicenter study, 135 adult patients with FD were recruited at three specialized European centers in Germany and Switzerland. Demographics, social status and clinical parameters as well as data on HrQol (EQ5D, EQ VAS) and depression were collected by means of self-reporting questionnaires and confirmed by medical records. HrQol and its predictors were evaluated by univariate and multivariate regression analyses.

The study population consisted of 78 female and 57 male FD patients (median age 48 yrs) of whom 80.7% ($N = 109$) were on enzyme replacement therapy (ERT) and 10.4% ($N = 14$) were on chaperone treatment. Univariate analysis revealed various factors reducing HrQol such as age > 40 years, classic phenotype, organ involvement (kidney and heart disease, stroke/*transient ischemic attack (TIA)*, gastrointestinal disturbances), depression, and burning limb pain. However, only the following factors were identified as independent predictors of decreased HrQol: classic phenotype, kidney and heart disease, stroke/TIA, depression, and burning limb pain. ERT and chaperone therapy were independent determinants of increased HrQol.

Conclusions: Modifiable factors, such as burning limb pain and depression, identified as independent predictors of HrQol-deterioration should be addressed in programs aiming to improve HrQol in FD. A multidisciplinary approach is essential in FD-patients since diverse organ involvement prominently compromises HrQol in affected patients. Our findings showed that the classic phenotype is a strong predictor of worsening HrQol.

1. Introduction

Fabry disease (FD) is a rare lysosomal storage disorder due to mutations in the *GLA*-gene which account for the reduced or absent activity of α-galactosidase A (α-Gal A). Deficiency of α-Gal A causes the accumulation of glycoshingolipids, particularly globotriasylceramide

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https://doi.org/10.1016/j.ymgme.2023.107692
Received 7 June 2023; Received in revised form 27 August 2023; Accepted 28 August 2023
Available online 29 August 2023

(Gb3) and globotriasylsphingosine (Lyso-Gb3), in the lysosomes of all cells throughout the body as well as in body fluids [1].The disease is inherited as an X-linked trait, with an estimated incidence of ~1 in 3100 Caucasian males [2]. There are two major phenotypes: classic and later-onset [3]. Males with the classic phenotype have very low enzymatic activity and, consequently, suffer from acroparaesthesia, hypohidrosis, cold and hit intolerance, as well as abdominal cramping, which severely reduces their quality of life (QoL) [4]. They develop skin angiokeratoma and corneal opacities during childhood. With advancing age, progressive Fabry-nephropathy and cardiomyopathy as well as early-onset strokes contribute to the early demise of these patients [1]. In contrast, males with the later-onset phenotype have a significant residual α-Gal A activity and, therefore, lack the early childhood manifestations leading to a normal childhood instead [5]. However, they develop either Fabry-cardiomyopathy [6] or, less frequently, Fabry-nephropathy [7], which can be as severe as in the classic phenotype. For both phenotypes, heterozygous female patients are generally more mildly afflicted because of their random X-chromosomal inactivation, although their phenotypes can vary widely, from asymptomatic to manifestations as severe as those seen in their male family members [8].

Previous studies reported a markedly reduced QoL in FD patients, particularly in conjunction with pains [9], fatigue [10], depression [11], obstructive sleep apnea [12], hearing loss [13], and gastrointestinal symptoms [4]. In this relatively large patient group, we added data such as demographics, social status, clinical parameters, in addition to these manifestations. These evaluations are useful to find independent factors to modulate the health-related quality of life (HrQoL) of Fabry patients. Knowledge of the independent determinants of HrQoL could facilitate early identification of patients who need more intense psychological support and care, increased monitoring, and specifically targeted adjunctive treatment such as pain-medication or antidepressants. This additional knowledge, most importantly, might trigger preventive strategies, best managed by a multidisciplinary team. In a retrospective analysis of medical records, Arends and colleagues found that reduced HrQoL in patients with FD was related to the phenotype, age, pain, and disease severity. The authors encouraged further studies to identify the independent parameters influencing QoL in order to improve patient care [14]. Neto and colleagues emphasized that patient-reported outcomes reflecting physical and mental health should be considered as key aspects of health monitoring and indicators of therapeutic requirements [11]. Since the knowledge of HrQoL-deteriorating or -improving variables may advance the goal-oriented support and treatment of FD patients and, thus, to improve their well-being, we designed a multicenter study analyzing the self-perceived HrQoL dimensions in Fabry patients in order to identify independent HrQol predictors.

2. Methods

2.1. Study design and clinical evaluation

This is a cross-sectional multicenter study including adult Fabry patients from three specialized, German speaking Fabry centers: University Hospital Zurich Switzerland, University Medical Center of the Johannes Gutenberg University Mainz and Interdisciplinary Fabry Center (IFAZ) at the University Hospital Münster, Germany.

Patients ($N = 135$) treated in these centers completed questionnaires, which were distributed during the routine clinical examinations.

The questionnaires consisted mainly of quantitative, closed-ended questions with pre-defined response options. All patients were asked to report their demographic and clinical parameters including their treatment status, symptoms as well as cardiac, renal, and cerebrovascular FD complications, as perceived and known by the patients. The demographics and clinical parameters were confirmed by the medical records. The economic situation of study participants was characterized as low income (<2250CHF monthly in Switzerland and < 1500€ monthly in Germany), moderate income (2250-6500CHF monthly in Switzerland and 1500–3000€ monthly in Germany) or high income (>6500CHF monthly in Switzerland and > 3000€ monthly in Germany). This classification relies on the governmental reports of participating countries.

2.2. Phenotyping

All mutations have been classified as coding for the classic or later-onset phenotype based on genotype and residual α-Gal A activity in males and are published in the International Fabry Disease Genotype/Phenotype Database (www.dbFGP.org) as well as in previous studies [15–19]. Nonsense, frameshift, consensus splice site and some missense mutations encode for 0% to 2% residual α-Gal A activity and lead to the classic phenotype in males. Alternative splicing mutations and certain other missense mutations encode for >2% of mean normal α-Gal A activity and cause the later-onset phenotype in males. All phenotypic assignments of the mutations are supported by the clinical manifestations in males and the age of symptom onset.

2.3. Evaluation of HrQoL and depressive symptoms

We evaluated HrQoL by using the German version of generic EuroQol questionnaire, a validated, non- disease-specific, tool [20] suited to reliably assess Qol in FD [21,22]. This HrQoL questionnaire consists of a five-dimensional self-classifier (EQ5D) and a visual analogue scale (EQ VAS). The EQ5D covers the five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [20]. Each dimension can be described by three levels of severity (1 = no problem, 2 = moderate problem, 3 = severe problem). Based on the results of the EQ5D, we calculated an index score using a regression algorithm developed by Greiner et al. [23]. The second part of the EuroQol is a visual analogue scale (EQ VAS) 'similar to a thermometer' ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).

We used the second version of Beck Depression Inventory (BDI) in our study [24]. The cutoff value for mild or more severe depressive symptoms was ≥14.

2.4. Statistics

The statistical data analysis was performed using IBM SPSS Statistics Version 23.0 (IBM Corp., Armonk, NY, USA). All clinical and Qol data are presented as mean with standard deviation (SD). The Kolmogorov-Smirnov test was used to test data for normal distribution. The *t*-test was used to compare normally distributed data. The Mann-Whitney *U* test was applied to compare not normally distributed data. Statistical significance was assumed for $p < 0.05$. Independent predictors of HrQol were estimated using multivariate regression analysis with forward selection ($p < 0.1$), while the following assumptions were met: linear relationship between outcome and independent variables, residuals were normally distributed, no multi-collinearity was allowed and the variance of error terms were similar across the values of independent variables. The fraction of explained variability was calculated for each prediction model based on the R^2 method, as appropriate [25].

3. Results

3.1. Demographics and clinical parameters

135 patients (78 females and 57 males) (61 from Zurich, Switzerland, 65 from Mainz and 9 Münster, Germany), participated in the study (Table 1). The median age was 49 years for males, 48 years for females. Male patients had a tendency to an earlier median age of symptoms onset (9 years) than female patients (15 years), but this difference was not statistically significant ($p = 0.21$). The economic situation of study participants were as follows: low incomes were reported by 13.3% ($N = 18$), moderate incomes by 70.4% ($N = 95$) and high

Table 1
Clinical parameters and HrQoL of males and females with Fabry disease.

	Males ($n = 57$)	Females ($n = 78$)
Age in years, median (range)	49 (25–75)	48 (18–78)
Year of FD diagnosis, median (range)	2008 (1975–2015)	2007 (1978–2018)
Age (years) of symptom onset, median (range)	9 (5–60)	15 (4–47)
Marital status, n of patients who gave information	55	63
Single n (%)	17 (31.9)	15 (23.8)
Married n (%)	33 (60.0)	39 (61.9)
In partnership n (%)	4 (7.3)	7 (11.1)
Separated or divorced n (%)	1 (1.8)	2 (3.2)
BMI in kg/m^2, median (range)	26 (19–46)	24 (17–53)
On specific therapy, n (%)		
Agalsidase alfa	39 (68.4)	39 (55)
Agalsidase beta	7 (12.3)	15 (29.2)
Migalastat	7 (12.3)	7 (9.0)
Neuropathic pain, n (%)	38 (66.7)	53 (67.9)
Gastrointestinal symptoms, n (%)	33 (57.9)	36 (46.2)
Heat intolerance, n (%)	41 (71.9)	49 (62.8)
Cold intolerance, n (%)	29 (50.9)	30 (38.5)
Sweating problems, n (%)	32 (56.1)	32 (41.0)
Kidney disease, n (%)	33 (57.9)	24 (30.8)
On chronic RRT, n (%)	7* (12.3)	3**(3.8)
Heart disease, n (%)	30 (52.6)	30 (38.5)
Chest pain, n (%)	8 (14.0)	8 (10.3)
Arrhythmias, n (%)	19 (33.3)	16 (20.5)
Stroke or TIA, n (%)	30 (52.6)	32 (41.0)
Hypacusis, n (%)	26 (45.6)	31 (39.7)
Depression		
BDI median (range)	7 (0–57)	10 (0–36)

Abbreviations: BDI, Beck Depression Inventory; HrQol, health-related quality of life; RRT, Renal replacement therapy; TIA, transient ischemic attack; BMI, body mass index.

* 5 FD patients were kidney transplanted, 2 FD patients were on chronic dialysis.

** 2 FD patients were kidney transplanted, 1 FD patient was on chronic dialysis.

incomes by 16.3% ($N = 22$).

80.7% ($N = 109$) of patients received enzyme replacement therapy (ERT) and 10.4% ($N = 14$) were on chaperone therapy with migalastat. Among patients on ERT, 68.8% ($N = 75$) were on agalsidase alfa and 31.2% ($N = 34$) were on agalsidase beta.

66.7% ($N = 90$) of patients reported pain. Burning pain in hands was found in 15.6% ($N = 21$), and painful feet were present in 23.7% ($N = 32$) of patients. Among patients with pain, pregabalin was administered in 42.2% ($N = 38$), gabapentin in 11.1% ($N = 10$), non-steroidal anti-inflammatory drugs in 44.4% ($N = 40$), cannabinoids in 15.6% ($N = 14$) and opiods in 25.6% ($N = 23$).

3.2. Health-related quality of life

There was a slight trend of showing a worse HrQoL in men than in women, which, however, did not reach statistical significance (EQ-5D-index: 0.74 ± 0.21 vs. 0.77 ± 0.22, $p = 0.62$; EQ VAS: 69.4 ± 18.32 vs. 75.9 ± 19.87, $p = 0.09$). Patients at or below the age of 41 years had higher HrQol values than those above the age of 40. HrQoL values were significantly lower in patients with organ involvement, such as kidney disease, heart involvement, and stroke/TIA, than in those without clinically manifested organ involvement (Table 2). Other clinical conditions impairing the HrQoL in FD patients were burning pain in hands and feet and depression. These conditions lowered HrQoL-values by 25%, 30%, and 15% respectively ($p < 0.01$). Gastrointestinal problems showed a minor trend towards decreased HrQoL-values (FD patients with gastrointestinal symptoms vs FD patients: EQ-5D-index: 0.71 ± 0.21 vs. 0.78 ± 0.25, $p = 0.17$; EQ VAS: 70.1 ± 21.6 vs. 77.8 ± 20.1, $p < 0.01$ (Table 2). The body-mass-index (BMI) did not influence HrQoL-values. Marital status also had no influence on HrQoL values. The economic situation did not have influence on the HrQol of study participants ($p = 0.83$). The injections, in terms of ERT, had a negative influence on the HrQol in only 3 patients (2.2%). The presence or absence of antibodies to ERT did not have any influence on the perceived benefits of the treatment.

The distribution of HrQoL values in different dimensions of EQ5D

Table 2
EQ-5D-Index and EQ VAS according to clinical and social parameters.

	EQ-5D-Index Mean ± SD	*P* value	EQ VAS Mean ± SD	P value
Males	0.72 ± 0.20	0.49	68.4 ± 17.83	0.08
Females	0.76 ± 0.21		76.2 ± 18.91	
Age > 40 years	0.64 ± 0.17	0.04	67.57 ± 18.10	<0.01
≤40 years	0.82 ± 0.18		82.34 ± 17.01	
Marital status alone	0.70 ± 0.16	0.07	70.12 ± 19.39	0.53
with partner	0.79 ± 0.21		74.12 ± 20.07	
BMI >25 kg/m^2	0.73 ± 0.22	0.53	71.11 ± 20.15	0.48
≤25 kg/m^2	0.75 ± 0.18		73.99 ± 18.76	
No therapy	0.67 ± 0.17	<0.01	67.11 ± 15.87	<0.01
Agalsidase alfa	0.77 ± 0.20		77.51 ± 19.10	
Agalsidase beta	0.81 ± 0.21		82.31 ± 15.08	
Migalastat	0.78 ± 0.34		77.89 ± 22.76	
Phenotype Classic	0.67 ± 0.21	<0.01	68.65 ± 22.41	<0.01
Later-onset	0.82 ± 0.19		81.74 ± 17.86	
Burning limb pain	0.50 ± 0.16	<0.01	54.12 ± 20.03	<0.01
No burning limb pain	0.79 ± 0.13		77.91 ± 15.31	
Gastrointestinal problems	0.70 ± 0.20	0.15	70.0 ± 22.2	<0.01
No gastrointestinal problems	0.79 ± 0.23		77.9 ± 18.9	
Heat intolerance	0.71 ± 0.17	0.01	72.61 ± 19.81	0.02
No heat intolerance	0.81 ± 0.18		81.97 ± 18.06	
Cold intolerance	0.73 ± 0.22	0.04	68.13 ± 18.77	0.04
No cold intolerance	0.82 ± 0.19		78.25 ± 17.54	
Hypacusis	0.70 ± 0.20	0.04	67.53 ± 19.98	0.03
No hypacusis	0.79 ± 0.18		78.28 ± 17.75	
Kidney disease	0.69 ± 0.22	0.02	65.42 ± 20.58	<0.01
No kidney disease	0.79 ± 0.20		79.73 ± 17.33	
Heart disease	0.69 ± 0.20	0.01	61.99 ± 19.44	<0.01
No heart disease	0.81 ± 0.14		82.72 ± 13.87	
Stroke/TIA in the past	0.69 ± 0.20	<0.01	68.09 ± 18.79	<0.01
No stroke/TIA in the past	0.80 ± 0.18		81.80 ± 15.83	
Depression BDI < 14	0.83 ± 0.15	<0.01	81.60 ± 15.90	<0.01
BDI ≥ 14	0.62 ± 0.20		62.72 ± 18.12	

Abbreviations: BDI, Beck Depression Inventory; BMI, body mass index; SD, standard deviation; TIA, transient ischemic attack.

was analysed. In the EQ5D dimension "mobility", 68.1% of patients ($N = 92$) had no problems, 24.4% ($N = 33$) had moderate problems and 7.4% ($N = 10$) had severe problems. In the dimension "self-care", the corresponding values were 83.7% ($N = 113$), 11.1% ($N = 15$) and 10.4% ($N = 14$). The "usual activities" dimension was associated with no problems in 57.8% of patients ($N = 78$), with moderate problems in 33.3% ($N = 45$) and with severe problems in 8.9% ($N = 12$). The most prominent impairment of HrQol was found in the dimension "pain and discomfort" with only 33.3% of patients reporting no problems ($N = 45$). Moderate problems because of pain and discomfort were found in 48.9% ($N = 66$) and severe problems in 11.1% ($N = 15$). In the dimension "anxiety and depression", no problems were reported by 58.5% of study participants ($N = 79$), moderate problems by 33.3% (N = 45) and severe problems by 8.1% ($N = 11$).

Parameters identified by multivariate regression analysis as independent determinants of decreased HrQol-values in FD patients are shown in Table 3 and include classic phenotype, kidney involvement, heart involvement, stroke/TIA, burning limb pain and depressive symptoms. In contrast, ERT with agalsidase alfa or agalsidase beta was identified as an independent determinant of increased HrQol-values.

These identified predictors of HrQoL could explain 53.1% of the variability of the EQ-5D index scores and 45.8% of the variability of the values on the EQ VAS.

4. Discussion

Our study investigated HrQol in FD patients from two European countries. The sample size of our patient cohort was rather large with respect to the low prevalence of this orphan disease. Previous studies also evaluated associations between HrQol and single symptoms of FD, such as pain [9], fatigue [10], and depressive symptoms [11]. Along these lines, Gold et al. studied 200 untreated male FD patients and found renal involvement, cardiac complications, stroke and pain to be significantly related to HrQol [26]. Wagner et al. 2014 found impaired renal function and pain as the major contributing factors for reduced HrQol [27]. These and other studies on HrQol in FD are summarized by Arends et all in a systematic review concluding that pain, objective renal disease, phenotype, age and gender are some of the major contributors to reduced HrQol in FD [22]. Our study corroborates and extends the previous works by analyzing the potential impact of a wide spectrum of factors associated with FD, as well as including the influence of social life and demographic data on HrQol.

The analyses show that the HrQol of FD patients is mainly influenced by clinical symptoms rather than demographic or social parameters. This is in line with HrQol-evaluations in other diseases and could be explained by the fact that HrQol strongly refers to the health status rather than instruments measuring the general QoL, such as the World Health Organization Quality of Life Brief Version (WHOQOL-BREF) [28–30]. Among all demographic and social parameters, only younger age (<40 years) was associated with higher HrQol-values in the univariate analysis. Similarly, Arends et al. found that higher age was a negative predicting factor for the HrQol in FD patients [14]. However, the multivariate analysis of our data did not identify any of the demographic or social factors as independent predictors of deteriorated or improved HrQol. Surprisingly, there was no significant relation between male or female gender and HrQoL-values, although FD is an X-linked disease and considered to manifest more prominently in male patients [31]. This result supports the conclusions of our previous study that FD manifestations have a greater influence on the health status than the sex of the patient [32]. The result also supports the conclusion that heterozygous females, like male FD patients, need targeted support.

Although disease-specific therapies such as ERT [33] and pharmacological chaperone treatment [34] are available for FD patients, and have been reported to improve neuropathic pain [35], persistent pain is still a therapeutic challenge and compromises HrQol [14] [36]. Morand et al. reported a prominent reduction in the QoL of FD patients who experience pain and gastrointestinal disturbances [4]. In our study, the presence of burning limb pain reduced the patients' HrQol-values by approximately 30%. Indeed, burning limb pain is a modifiable factor and should be more carefully addressed in the treatment programs of Fabry patients in order to improve their HrQol. In FD, pain is a highly relevant clinical aspect that afflicts both sexes and manifests with complex presentations [9]. Similar to the findings of a large German study on pain in FD [9], our patients reported that their hands and feet were the body parts most affected by pain. In patients with the classic phenotype, pain can be burning, stabbing, tingling, or shooting, with the punctum maximum in the distal extremities, radiating towards proximal regions, and it can be permanent, chronic-intermittent, or, sometimes, critically excruciating [9,37]. Since improved pain control quite likely enhances HrQoL, pain needs to be carefully evaluated in every patient and treatment options must be addressed in face-to-face communications between the patient and the treating specialist. Pain intensity and location should be carefully determined using disease-specific tools, such as the FabryScan [38], the Fabry-specific Pediatric Health and Pain Questionnaire [39], or the Wurzburg Fabry Pain Questionnaire [40]. In addition, general pain scales such as the Brief Pain Inventory [11], or the Short-Form McGill Pain Questionnaire [37] may complement the clinical description of pain. Furthermore, the SF-36 health-related quality of life assessment may add to better defining the patient's current condition [11]. Unfortunately, there have so far been no controlled prospective interventional trials that have evaluated adjunctive pain therapies.

Gastrointestinal disturbances had a moderate influence on the HrQol and reduced EQ VAS values by 10%. In fact, the multivariate analysis did not identify gastrointestinal symptoms as one of the independent predictors of HrQol-deterioration, although, it is of course, clinically relevant to alleviate gastrointestinal complaints. Previous studies showed

Table 3
Independent determinants of HrQol in multiple regression analysis.

	EQ5D Index			EQ VAS		
	B	95% CI	*P* value	B	95% CI	P value
Constant	1.19	0.97; 1.25	0.0	111.91	94.58; 122.35	0.0
Classic phenotype	−0.17	−0.25; −0.03	<0.01	−12.72	−21.12; −6.02	<0.01
Kidney disease	−0.06	−0.23; −0.04	0.03	−6.43	−13.61; −2.02	0.04
Heart involvement	−0.18	−0.51; −0.07	<0.01	−21.03	−30.72; −12.38	<0.01
Stroke/TIA	−0.11	−0.22; −0.08	0.03	−5.70	−9.33; −2.93	0.04
Burning limb pain	−0.18	−0.27; −0.09	0.04	−8.60	−18.97; −3.07	0.03
Depression (BDI)	−0.05	−0.21; −0.03	<0.01	−0.95	−3.12; −0.83	<0.01
Agalsidase alfa	0.04	0.01; 0.12	0.04	3.92	1.51; 7.27	0.04
Agalsidase beta	0.11	0.04; 0.29	0.02	15.88	5.69; 28.03	0.01
Migalastat	0.07	0.01; 0.17	0.03	4.79	1.80; 9.65	0.03
Adjusted R^2 *	0.547			0.533		

*Total adjusted R^2 for each model.
Abbreviations: HrQol, health-related quality of life; B, regression coefficient; BDI, Beck Depression Inventory; CI, confidential interval; TIA, transient ischemic attack.

that disease-specific therapy is associated with gastrointestinal improvement but does not abolish gastrointestinal disturbances [34] [41]. So far, there are no interventional clinical studies that identified adjunctive therapies, such as analgesics or smooth muscle relaxants, as effective in the improvement of abdominal pain and cramping. Yet, recently a promising approach to supplement alpha-galactosidase orally has been reported [42]. However, further studies should be encouraged to improve neuropathic limb and gastrointestinal pains in order to increase HrQoL.

Depressive symptoms have been shown to be an important HrQol-reducing factor in patients with FD [4]. Our data support these findings. The presence of depressive symptoms reduced EQ VAS values by 23% and EQ5D Index values by 25% as demonstrated in the univariate analysis. In addition, the multivariate analysis identified depression as one of the modifiable factors that independently affect HrQol-values. It is also a frequent predictor of HrQol in other diseases [28,43–45] with involvement of the central nervous system. Similarly to pain assessment and therapy, screening for and specific treatment of depression should therefore be an integral part of health-care programs for FD patients.

Other important factors independently influencing the HrQol in patients with FD were kidney and heart disease, and the history of stroke/TIA. These findings confirm the fact that the management of FD patients requires a multidisciplinary approach with the exchange of views between nephrologists, cardiologists, and neurologists. Especially, cardiac involvement was among the strongest predictors of HrQol in our analysis. That is why FD patients profit from management by cardiologists with special knowledge in FD.

The classic phenotype was identified as an unmodifiable independent predictor of reduced HrQol in FD. It is known that classic patients are prone to develop more complications during the course of the disease [4]. Our results were in line with the data of Arends et al. who showed a faster decline of HrQol in classic patients than in later-onset patients [14]. No difference between the HrQol values were recorded in patients taking either of the two licensed ERT preparations or chaperone.

Our study has several limitations. We only included patients from two European countries. Consequently, our results might not be representative on a broader scale as the health-care situation differs in other European and non-European countries. However, there are established, internationally known guidelines for the treatment of FD patients. Therefore, treatment patterns should not differ too much between various countries. Second, there were no patients with oral chaperone therapy available at the time of patient recruitment. Therefore, we could not include this treatment option in the current analysis. Third, symptoms and events included in the study were reported by patients instead of retrieving data from medical records. On one hand, associating subjective health, reflected by self-reported kidney and heart disease and history of stroke, may not be the most frequently used way to assess the impact of disease complications on QoL. On the other hand, focusing on subjective health may represent a patients-centered approach helping to search for important clinical manifestations from the patients` views. An interesting approach in a next study would be to compare patient-reported kidney and heart disease with objective parameters such as proteinuria, significantly impaired renal function, diastolic and systolic left ventricular function, arrhythmias etc. in order to analyse their correlation.

Finally, we cannot rule out the presence of further confounders due to variables not assessed in this study, such as the economic situation of patients and their families, in multivariate regression analysis of HrQoL-determinants. Still, this study confirmed the negative impact of pain, depression, gastrointestinal symptoms, kidney and heart disease, and the history of stroke/TIA, and the classic phenotype on the HrQol while sex, surprisingly, had no significant effect but ERT had a beneficial effect on HrQol.

Ethics approval and consent to participate

The study was approved by the local ethic committees of University Hospital Zurich Switzerland, University Medical Center of the Johannes Gutenberg University Mainz and University Hospital Münster, Germany. All participants have signed a written informed consent.

Consent for publication

Not applicable.

Funding

The study was financially supported by Sanofi Genzyme, who had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Authors' contributions

Design of the study: AN, MH, FB, ES, ML, EB, JBH, YW. Statistical analysis and first draft: AN, YW. Wrote the manuscript: AN, YW. In addition, all authors participated in analysis and interpretation of data and provided critical revisions to the manuscript drafts. All authors read and approved the final manuscript.

Declaration of Competing Interest

YW reports honoraria for educational presentations and consultations from Arvelle Therapeutics, Bayer AG, BIAL, Bioprojet Pharma, Eisai, Eythpharm GmbH, LivaNova, Novartis and UCB Pharma, which were not related to the topic of this study. AN received speaker honoraria and research grants from Amicus, Shire/Takeda and Sanofi Genzyme. ML received research grants and speaker honoraria from Amicus Therapeutics, Sanofi Genzyme and Shire/Takeda and consultation honoraria from Avrobio. EB received research grants and speaker honoraria from Amicus Therapeutics, Sanofi Genzyme, Shire/Takeda as well as honoraria for educational presentations and consultations from Chiesi and Greenovation/Eleva.

Data availability

The dataset supporting the conclusions of this article is included within the article and its additional file.

Acknowledgements

Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgme.2023.107692.

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