Original Article

Quality of life in patients with Fabry's disease: a cross-sectional study of 86 adults

Caroline Andonian[1,2,3], Jürgen Beckmann[2,4,5], Oliver Mayer[1], Peter Ewert[1], Annika Freiberger[1], Maximilian Huber[1], Harald Kaemmerer[1], Christine Kurschat[6], Florian Lagler[7], Nicole Nagdyman[1], Lars Pieper[1], Claudia Regenbogen[8], Sebastian Freilinger[1,9]

[1]Department of Congenital Heart Disease and Pediatric Cardiology, German Heart Center Munich, Technical University Munich, Munich, Germany; [2]Department of Sport and Health Sciences, Chair of Sport Psychology, Technical University Munich, Munich, Germany; [3]Department of Psychosomatic Medicine and Psychotherapy, University Hospital Rechts der Isar, Technical University Munich, Munich, Germany; [4]School of Human Movement and Nutrition Sciences, University of Queensland, Queensland, Australia; [5]Health Research Institute, University of Limerick, Limerick, Ireland; [6]Department II of Internal Medicine and Center for Molecular Medicine Cologne, University of Cologne, Faculty of Medicine and University Hospital Cologne, Cologne, Germany; [7]Institute for Hereditary Metabolic Diseases, Paracelsus Medical University Salzburg, Salzburg, Austria; [8]Department of Nephrology, Technical University of Munich, School of Medicine, Klinikum Rechts der Isar, Munich, Germany; [9]Department of Sport and Health Sciences, Chair of Preventive Pediatrics, Technical University of Munich, Munich, Germany

Contributions: (I) Conception and design: C Andonian, H Kaemmerer, C Kurschat, C Regenbogen, S Freilinger; (II) Administrative support: O Mayer, P Ewert, A Freiberger, F Lagler, N Nagdyman; (III) Provision of study materials or patients: P Ewert, H Kaemmerer, C Kurschat, F Lagler, C Regenbogen; (IV) Collection and assembly of data: P Ewert, H Kaemmerer, C Kurschat, F Lagler, C Regenbogen, S Freilinger; (V) Data analysis and interpretation: C Andonian, O Mayer, S Freilinger; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Caroline Andonian, MSc. Department of Congenital Heart Disease and Pediatric Cardiology, German Heart Center Munich, Technical University Munich, Munich, Germany. Email: andonian@dhm.mhn.de.

Background: Fabry disease (FD) is a multi-organ disorder associated with severe physical and psychological impairments, particularly in adulthood. To date, comprehensive data on the psychological burden of FD are lacking. The present study assessed quality of life (QOL) in a representative cohort of adults with FD.

Methods: Patient-reported outcome measures were retrospectively analyzed in 86 adults with FD (49.6± 16.6 years; 62.8% female) and compared to adults with congenital heart defects (ACHD) which is another lifelong disease and affliction. QOL was assessed using the European Quality of Life 5 Dimensions 5 Levels questionnaire (EQ-5D-5L).

Results: Subjects affected by FD reported an overall reduced QOL (EQ-VAS: 71.8±20.0). Most frequently reported complaints occurred within the dimensions pain/discomfort (69.7%), daily activities (48.9%) and anxiety/depression (45.4%). Compared to ACHD, individuals with FD scored significantly lower in the areas of pain/discomfort, usual activities and mobility (all $P<0.05$). Older age and female sex were particularly associated with diminished QOL ($P=0.05$).

Conclusions: Patients with FD are at high risk for impaired QOL. They require additional support to cope with disease-related challenges. Increased attention should be directed towards improving their subjective well-being to potentially increase their QOL and long-term health outcomes.

Keywords: Fabry disease (FD); morbus Fabry; quality of life (QOL); European Quality of Life 5 Dimensions (EQ-5D)

Submitted Apr 29, 2022. Accepted for publication Jul 18, 2022.
doi: 10.21037/cdt-22-215
View this article at: https://dx.doi.org/10.21037/cdt-22-215

Introduction

Fabry disease (FD) is a rare X-linked lysosomal storage disorder, affecting men and women of all age classes (1). In FD, mutations in the *GLA* gene cause defects in the synthesis and/or function of alpha-galactosidase A (α-Gal A) (2,3). α-Gal A is a lysosomal enzyme that normally metabolizes globotriaosylceramide (GL-3 or Gb3) and prevents its accumulation (4). A total or partial lack of α-Gal A activity results in a progressive accumulation of glycosphingolipids, especially GL-3, in the lysosomes of many cell types (5).

FD is divided into classic early onset disease and non-classic later-onset disease (6). Reported incidence rates of FD vary depending on the investigated phenotypes. The incidence of FD was estimated to be 1 in 40,000 live births (7). Compared to males, females are usually affected with manifestations at a later age of onset (8). According to data from a global FD registry, the non-specific and heterogeneous appearance of FD often leads to misdiagnoses or significant delays in diagnosis (9).

If left untreated, this multisystemic disease is progressive, resulting in life-threatening functional impairment of the heart, kidney, and brain (1,10,11). The signs and symptoms of FD are heterogenous and often have its onset in childhood or adolescence with episodic pain crises, gastrointestinal disturbances, angiokeratomas, hypohidrosis, proteinuria, arrhythmias, corneal and lenticular opacities, heat and cold/exercise intolerance, peripheral neuropathy of extremities, hearing loss and tinnitus (5). As FD progresses, a deterioration of kidney function and hypertrophic cardiomyopathy may develop and consequently, the risk for fatal complications such as end-stage renal disease, early ischemic stroke, cardiac fibrosis, cardiac arrhythmias, and premature death increases (5,12,13).

The multifaceted impact of medical complications associated with FD can have long-lasting consequences on an individual's sense of well-being, in terms of quality of life (QOL). It has previously been reported that ongoing psychosocial difficulties, such as depression, anxiety, fatigue, and unemployment may negatively impact on QOL in both, males and females with FD, as compared to healthy individuals (14). However, systematic assessments of QOL using standardized instruments and disease-specific questionnaires are still scarce.

In light of this, the present study aimed to (I) systematically assess QOL within a large sample of patients affected by FD, to (II) compare the results with findings of patients with congenital heart defects (CHD), and to (III) determine potential predictors of QOL for patients with FD. Detailed knowledge on this topic can be highly relevant for raising awareness for the psychosocial implications of FD and enhancing multidisciplinary treatment options for affected patients. We present the following article in accordance with the STROBE reporting checklist (available at https://cdt.amegroups.com/article/view/10.21037/cdt-22-215/rc).

Methods

Study population

The present study represents the first large-scale initiative to comprehensively assess the psychological situation of FD patients across German-speaking countries. The questionnaire-based survey was initiated by the Department of Congenital Heart Disease of the German Heart Centre Munich, Technical University Munich, and the Department of Nephrology, University Clinic Rechts der Isar, Technical University Munich, and carried out in collaboration with the Institute for Hereditary Metabolic Diseases, and the Paracelsus Medical University Salzburg. The study was supported by the national patient organization "Morbus Fabry Selbsthilfegruppe e.V.", reaching members from all over Germany, as well as the health insurance company "AOK Bayern" by sending out the questionnaires to patients across Bavaria. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and under the approval of the Ethics Committee of the participating institutions. Data collection took place between 08/2020 and 02/2022. Written informed consent was obtained from all participating patients before the start of documentation. Guidelines on good epidemiological practice and data protection guidelines were followed.

Patients were selected according to the following inclusion criteria: (I) confirmed diagnosis of FD; (II) participant aged 18 years and older; (III) necessary physical, cognitive and language capabilities to complete self-report questionnaires; (IV) German speaking.

Measures

An observational study was performed using the European Quality of Life 5 Dimensions 5 Levels questionnaire (EQ-5D-5L). The questionnaire was completed in person, online or by mail. The EQ-5D-5L provides a short and simple

Table 1 Demographics of the FD and ACHD collective

Demographics	Fabry (n=86)	ACHD collective (n=4,014)	P value
Age (in years), mean ± SD [range]	49.6±16.6 [18–94]	41.8±17.3 [18–97]	<0.001*
Sex (female in %)	62.8	46.5	0.003*
Age group (in years), n (%)			<0.001*
18–34	15 (17.4)	1,663 (41.4)	
35–64	53 (61.6)	1,733 (43.2)	
65+	17 (19.8)	507 (12.6)	
Missing	1 (1.2)	111 (2.8)	

*, statistically significant (P≤0.05). n, absolute number; FD, Fabry disease; ACHD, adults with congenital heart defects.

measure of a patient's perceived health status. It has been validated for self-administration with high psychometric properties (15). The EQ-5D-5L consists of two sections: a descriptive system questionnaire (EQ-Index) and a Visual Analogue Scale (EQ-VAS). The descriptive system covers five dimensions: three referred to functional aspects (mobility, self-care, routine activities), and the other two to the perception of physical and mental well-being (pain/discomfort and anxiety/depression). For each item, the patient is asked to indicate his perceived impairments on a 5-point Likert scale ranging from moderate to severe problems. Responses are coded as single-digit numbers expressing the severity of impairment on each dimension. Responses can be converted into a single weighted index score (EQ-5D index) using population preference scores. A value set for the EQ-5D-5L based on a representative sample of the German population has recently been developed (16). The EQ-VAS indicates a patient's overall health state on a graduated scale which ranges from 0 ("the worst health you can imagine") to 100 ("the best health you can imagine"). It therefore provides a quantitative measure of a patient's perceived health.

To better frame the results, QOL in FD was compared to ACHD, which represents another chronic medical condition. The comparison population was recruited in the same institution and under the same modalities (17). For demographics patient-reported age and sex were assessed.

Statistical analysis

Statistical analysis was performed using SPSS 28.0 (IBM Inc., Armonk, NY, USA). Statistical evaluations were pseudonymized and not person-related. Descriptive measures were calculated for sociodemographic sample characteristics. Differences between the respective patient populations were evaluated applying Chi-Squared tests. *T*-tests were used for comparisons between mean values. Continuous data was expressed as mean ± standard deviation, categorical or interval scaled variables as absolute numbers or percentages. Missing data was accounted for using list wise case exclusion. The Crosswalk-Index-value of the EQ-5D-5L was calculated using the German value set (16). All occurring P values and tests for significance were performed two-sided. Statistical significance was indicated by a P value <0.05.

Results

Demographics and QOL

A total of 86 adults with FD was retained for final analysis (62.8% female). The mean age of patients with FD was 49.6±16.6 years (range, 18–94 years) (*Table 1*). A population of 4,014 ACHD [42.0±17.3 years (range, 18–97 years); 46.5% female] was consulted to offer a point of reference. Both populations differed significantly in their age distribution with the proportion of FD patients in older age groups being significantly larger [95% CI: ACHD (40.82, 41.95) *vs.* FD (45.33, 52.52); P<0.001]. Further, QOL significantly declined with increasing age in patients with FD on the EQ-VAS (P<0.001), as well as the Index value (P=0.010). Sex comparison shows that females exhibit lower scores than males on all EQ-dimensions, with most significant differences on the anxiety/depression dimension (P=0.050). This trend also becomes evident when comparing combined metric values of QOL between both sexes, although differences were not statistically significant (EQ-Index $_{female}$: 84.7; EQ-Index $_{male}$: 87.3; P=0.459). Regarding

the respective EQ-5D dimensions, pain (69.7%), mobility (36.0%), usual activities (i.e., work, study, housework, family or leisure activities) (48.9%), and anxiety/depression (45.4%) were the most commonly affected domains in patients with FD.

Comparison of QOL between FD and CHD patients

Table 2 compares the subscales of the EQ-5D-5L for the FD sample and for the CHD comparison group. Compared to ACHD, patients with FD reported significantly worse QOL in mobility [95% CI: ACHD (1.35, 1.40) *vs.* FD (1.38, 1.79); P=0.005], usual activities [95% CI: ACHD (1.45, 1.50) *vs.* FD (1.56, 2.00); P=0.004], and pain/discomfort [95% CI: ACHD (1.58, 1.64) *vs.* FD (1.93, 2.37); P<0.001]. No significant differences could be observed on the dimension self-care [95% CI: ACHD (1.10, 1.14) *vs.* FD (1.04, 1.30); P=0.634].

When comparing the combined metric measures of QOL between patients with FD and CHD (*Table 3*), patients with FD scored markedly lower on the EQ-VAS [95% CI: ACHD (76.18, 77.44) *vs.* FD (68.28, 76.87); P=0.038] as well as the EQ-Index [95% CI: ACHD (90.18, 91.21) *vs.* FD (81.03, 88.30); P=0.001]. The observed differences between both populations were less extreme in regard to the VAS scores. Additionally, variations in QOL within the same patient group were observed depending on the type of measurement which was applied. Accordingly, the mean VAS score displayed a markedly lower QOL than the descriptive index value.

Discussion

To date, this is the largest cross-sectional study within German speaking countries to investigate psychosocial implications of FD.

Although medical advances in the therapy of FD, such as the introduction of chaperone therapy have had a considerable impact on the clinical management of patients, it is essential to devote attention to general patient care (18,19). Patient-reported outcomes on subjective well-being are meanwhile considered central indicators of health surveillance and treatment efficiency (20). This study contributes to this topic by employing the EQ-5D-5L which is considered a highly reliable and valid measure to quantify mental and physical concerns in affected patients.

The present study provides compelling evidence that almost all components of QOL are impaired in FD patients. Pain, mobility, day-to-day related problems, and anxiety/depression were the most commonly affected domains in patients with FD, comparable to a recently published findings by Polistena *et al.* (21). Sociodemographic correlates of decremented QOL included female sex and older age. Given the varied clinical and psychosocial problems faced by patients with FD, a coordinated multidisciplinary approach is necessitated to ensure high quality patient care and achieve a long-lasting impact on both, physical and mental health.

Correlates of QOL in patients with FD

In accordance with earlier findings, patients with FD present a significantly compromised QOL compared to counterparts with CHD. Even in comparison to other types of chronic inflammatory disorders, FD has been associated with substantially inferior QOL across several health domains (21,22). This observation further reflects the divergent sources of physical, functional and mental morbidity and the overall difference in the natural history of disease encountered by patients with FD (23). FD subverts various aspects of patients' lives, including their perception of themselves, state of mind, work and social functioning (21). The multi-facet nature of FD highlights the need for comprehensive monitoring of a wide variety of signs and symptoms in order to achieve optimal health response.

Apparently, the overall VAS score indicated a significantly lower QOL than the descriptive EQ-5D Index value. This discrepancy might be explained by respective differences in the content coverage of QOL. Accordingly, the descriptive system might encourage patients to explore their well-being from different angles, while the VAS represents a one-dimensional view of perceived health restrictions imposed by FD. Given the current evidence that emotional outcomes are mainly determined by a patient's subjective health perception as opposed to factual clinical complications in FD, additional attention needs to be devoted towards assessing and, if required, correcting a patient's subjective health appraisals by additional psychoeducational interventions (24,25). Alongside biomedical treatment of FD, addressing surrounding subjective factors, such as delayed diagnosis, uncertainties about heritability, stigmatization or future planning, would enhance individual outcomes by changing a patient's perception of disease and enabling efficient coping styles (24).

Present findings have shown that females reported significantly lower life satisfaction than their male

Table 2 QOL from the patient's perspective (by collective, in absolute numbers and %)

EQ-5D-5L dimension	Fabry, n (%)	CHD, n (%)	P value
Mobility			0.005*
No problems	55 (64.0)	2,899 (75.9)	
Slight problems	16 (18.6)	467 (12.2)	
Moderate problems	7 (8.1)	319 (8.3)	
Severe problems	8 (9.3)	119 (3.1)	
Extreme problems	0 (0.0)	18 (0.5)	
Missing	0	192	
Self-care			0.634
No problems	77 (90.6)	3,547 (92.8)	
Slight problems	4 (4.7)	144 (3.8)	
Moderate problems	3 (3.5)	71 (1.9)	
Severe problems	0 (0.0)	34 (0.9)	
Extreme problems	1 (1.2)	25 (0.7)	
Missing	1	193	
Usual activities			0.004*
No problems	44 (51.2)	2,666 (70.0)	
Slight problems	22 (25.6)	643 (16.9)	
Moderate problems	13 (15.1)	333 (8.7)	
Severe problems	6 (7.0)	125 (3.3)	
Extreme problems	1 (1.2)	44 (1.2)	
Missing	0	203	
Pain/discomfort			<0.001*
No problems	26 (30.2)	2,199 (58.2)	
Slight problems	32 (37.2)	963 (25.5)	
Moderate problems	18 (20.9)	466 (12.3)	
Severe problems	10 (11.6)	137 (3.6)	
Extreme problems	0 (0.0)	15 (0.4)	
Missing	0	234	
Anxiety/depression			0.716
No problems	47 (54.7)	2,239 (59.0)	
Slight problems	28 (32.6)	1,015 (26.7)	
Moderate problems	8 (9.3)	360 (9.5)	
Severe problems	3 (3.5)	151 (4.0)	
Extreme problems	0 (0.0)	32 (0.8)	
Missing	0	217	

*, statistically significant (P≤0.05). EQ-5D-5L, European Quality of Life 5 Dimensions 5 Levels questionnaire; QOL, quality of life; n, number of cases in subgroup; CHD, congenital heart defects.

Table 3 Comparison of the EQ-5D crosswalk index value and VAS, overall

QOL measures	Fabry			CHD			P value
	Mean ± SD	Range	Missing	Mean ± SD	Range	Missing	
Crosswalk	84.72±16.48	29.7, 100	1	90.58±15.51	−13.9, 100	324	<0.001*
VAS	71.80±20.01	10, 100	2	76.15±18.98	0, 100	253	0.038*

*, statistically significant (P≤0.05). EQ-5D, European Quality of Life 5 Dimensions; VAS, Visual Analogue Scale; QOL, quality of life; SD, standard deviation; CHD, congenital heart defects.

counterparts. While women were previously assumed to be asymptomatic or minorly affected throughout a normal life span, an extensive survey of 1,077 females with FD confirmed that females are at significant risk for major organ involvement and frequently suffer from pain, gastrointestinal and neurological complications as well as fatigue (9,23,26). Consequently, the investigation of female patients with FD deserves particular clinical and scientific attention (26). Another reason for sex-/gender-related differences in QOL might be attributed to psychosocial factors research has demonstrated that chronically ill women were less likely to remain economically and socially active and independent compared to males (27). Other findings demonstrate that women were generally more willing to disclose problems concerning their QOL and have higher expectations and stronger demands regarding their healthcare encounters (28). Improved recognition and understanding of gender-related disparities and challenges among FD patients is vital to improve treatment satisfaction and increase adherence (29).

Apparently, FD patients were on average 8 years older than ACHD. One reason for the observed age difference could be the delay in the correct diagnosis of FD despite the long-lasting presence of characteristic clinical symptoms. Approximately 2 out of 11 Fabry patients are erroneously misdiagnosed with a "psychosomatic disorder" which potentially causes a considerable diagnostic and therapeutic delay of up to 15 years after the onset of first typical symptoms (26,30). Regarding the effects of age on QOL, QOL appeared to gradually deteriorate with increasing age (22). This finding is remarkably similar to other studies which have shown a continuing decline in QOL with disease progression over time (9,14,31). Negative changes occurred especially in the domains of physical and social functioning indicating difficulties in physical health and personal relationships (31). It is therefore conceivable, that QOL scores in older patients reflect disease burden, rather than an association of age alone (14,31). Clinicians should be encouraged to detect and target their patients' physical and mental health, as well as social participation in order to maintain and preserve an acceptable QOL as long as possible.

Mobility

FD was significantly associated with the occurrence of mobility impairments which is hardly surprising given the findings related to pain in affected patients. Physical symptoms commonly associated with FD, such as neuropathic pain and chronic fatigue, were found to directly and indirectly impact social and adaptive functioning via physical (mobility-related) and behavioral (emotion-related) pathways (32). Indeed, exercise impairment has been found to adversely impact the achievement of certain psychosocial milestones, such as engagement in sports activities or active recreational activities during youth and adolescence (33). Physical impairment appears to worsen with increasing age and most FD patients (68.9%), especially those aged 60 and older, are largely concerned about the risk of physical disability and its secondary consequences on their private and professional lives (21). These concerns are well justified since a large proportion of affected patients has been found to become disabled and dependent at an early age, when residential care is either not available or unsuitable (34). Based on present findings, substantially inferior perceptions of physical and functional well-being among FD patients are currently not properly addressed. Greater appreciation of their daily burden and regular pain-assessments should become an integral part of routine care in order to foster a more positive experience through therapy (22,35).

Usual activities (i.e., work, study, housework, family or leisure activities)

According to present findings, having FD was associated with reporting significant problems in the domain of usual

activities). Present rates of moderate-to-severe problems on this dimension were strikingly higher than those recently published by Polistena *et al.* in an Italian cohort of FD patients (21). Until now, the impact of FD on day-to-day activities is not well understood. Anecdotal evidence points towards a high prevalence of difficulties in performing daily activities, keeping a full-time job and adhering to medical regimens despite adverse health effects (36). Impairment on this dimension might be attributed to verified neuropsychological symptoms, such as reduced executive functioning (i.e., verbal generation, reasoning, problem solving), slower information processing, and attention deficit disorders (31,32). Laney *et al.* showed that FD patients were further affected by decreased social-adaptive functioning referred to as the effectiveness with which an individual copes with daily demands and responsibilities as parents, caregivers, or employees (36). It has been documented that over half of adult FD patients have never married and continued to live with their parents in a protective environment (34). Since adaptive functioning has been linked to higher rates of mental illness and non-adherence with treatment, concentrated psychosocial strategies of how to cope with day-to-day challenges could result in increased QOL and better treatment adherence among FD patients.

Pain

Current findings indicate that patients with FD experience significant difficulties with pain compared to CHD counterparts. Indeed, pain is recognized as the most persistent and debilitating symptom of FD with half of the patients experiencing moderate to severe pain, especially in their hands and feet. Pain frequency, intensity and location were similar between males and females, with joint problems and swelling being frequent symptoms (37,38). This is especially worrying against the background that chronic pain has been linked to significant psychological burden and diminished QOL over the long term (14, 24,38). Interestingly, a recent survey of 367 FD patients found that the occurrence of pain was irrespective of the use of ERT, ranging up to 80% in patients who received ERT (38). This suggests that healthcare needs of FD patients are not being fully met and adjunctive pain-management strategies are required alongside ERT. Patients might particularly benefit from a multimodal treatment approach combining pharmacological, orthopedic, rheumatologic and psychosocial techniques for long-term pain relief and better QOL. Even though it might not always be possible to fully eliminate pain, the treatment goal should be to make pain manageable in order to be able to successfully cope with everyday life.

Depression/anxiety

The present study indicates a high prevalence of depressive and anxiety symptoms among patients with FD, comparable to earlier work published within this context (20,24,26). Depression has become increasingly recognized as a major complication of FD, with prevalence rates ranging from 15% to 62% (39). Despite the high prevalence of depression, roughly half of FD subjects reporting severe symptoms are not recognized and even fewer receive psychotherapeutic treatment (20,40). While it is not understood whether depression is a result of Fabry-related cerebrovascular impairment or a complication of struggling to cope with a chronic condition, it needs to be taken seriously (39). Despite a paucity of reliable data on patients with FD, co-morbid and untreated depression is known to affect the prognosis of chronic illness and a patient's QOL over the long term (26). Remarkably, while most studies failed to establish a connection between organ involvement and mental health outcomes, a recent study by Körver *et al.* (2020) identified pain, negative health perception, and dysfunctional coping styles as potentially important variables for QOL of FD patients (24). This is in line with our previous research on ACHD, which indicated that a patient's subjective perception of symptoms affects their mental health far more than their objective physical condition (41). While the relation between pain experience, coping and depression is not well understood, there is preliminary evidence that coping may influence pain experience and the effect of treatment on pain in FD (24,32). The identification of predictive variables and mechanisms that affect physical and emotional outcomes in FD is an important task for future research in order to improve early detection and better management of FD. Considering the high prevalence of depressive and anxiety symptoms, regular mental health assessments should become part of a routine follow-up.

Limitations

Since FD is a rare disease, it is a general challenge to obtain a representative sample of patients. Major strengths of this study include a comparatively large sample size of patients

with FD, the use of a normative reference group ascertained with the same methods to ensure maximum comparability, as well as the combination of disease-specific and validated generic instruments to detect and quantify particular health problems among FD patients.

However, the present study may be subject to certain limitations. First, the study was cross-sectional in nature and therefore conveys a snapshot of a patient's health status. It does not allow to draw conclusions about the etiology of psychological and physiological effects or the development of QOL in FD patients. Longitudinal studies are required to gather an adequate picture of their general disease-related burden over time. Second, since several recruitment strategies were applied, the response rate among patients was currently not detectable. Some selection bias in respondents willing to participate appears unavoidable, such that more serious disease manifestations, psychological issues or fatigue might be more (or less) frequent among non-responders (42). Also due to the study design and the different survey modalities, it was not possible to determine a response rate. Third, the study relied on self-report outcomes and might be subject to recall and self-presentation bias. Therefore, a lack of information on medication use, pain modulation, psychotherapeutic drugs, may interfere with the results. Other approaches, such as direct interview, might yield a more detailed picture of present difficulties and psychosocial impairments, as well as lifetime history (35). Finally, the influence of genotype, phenotype, disease severity and treatment status of FD patients was currently not investigated, although this would have been interesting considering their different disease courses. Indeed, recent studies have reported differences depending on the inclusion of clinically distinct patient groups (14). More studies in subgroups of patients are necessitated to gain a better insight into the influence of clinical manifestations and treatment on QOL.

Despite these potential limitations, the present study sheds light on the psychosocial status disease-related complications in patients with FD. This information underscores the need for regular psychological evaluation and treatment to be added for all FD patients in order to increase their medical adherence and QOL (24).

Conclusions

Due to both, somatic and psychological impairment, QOL is considerably impaired in FD patients. Currently, their respective healthcare needs are not being addressed sufficiently. Pronounced pain, physical impairment, struggle to cope with everyday life and debilitating psychiatric symptoms substantially impact on their general health and functioning. Especially, delayed diagnosis after decades of characteristic clinical symptoms may severely hamper adjustment to illness and the development of active coping strategies. Given the complex nature of FD, effective management requires a multidisciplinary approach, including physicians, specialist nurses and psychological staff with experience in a wide range of clinical specialties. Early psychosocial assessments and counselling should be provided throughout the process of diagnosis and treatment in order to prevent a decrement in QOL and make treatment as convenient as possible for all affected FD patients.

Acknowledgments

We would like to thank AMICUS Therapeutics for their ongoing support in M. Fabry research.
Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Cardiovascular Diagnosis and Therapy* for the series "Current Management Aspects in Adult Congenital Heart Disease (ACHD): Part V". The article has undergone external peer review.

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://cdt.amegroups.com/article/view/10.21037/cdt-22-215/rc

Data Sharing Statement: Available at https://cdt.amegroups.com/article/view/10.21037/cdt-22-215/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cdt.amegroups.com/article/view/10.21037/cdt-22-215/coif). The series "Current Management Aspects in Adult Congenital Heart Disease (ACHD): Part V" was commissioned by the editorial office without any funding or sponsorship. HK served as the unpaid guest editor of the series. CA and SF report grants/contracts received from AMICUS. CK reports payment or honoraria, support for attending meetings/travel received from AMICUS, Chiesi, Sanofi and Takeda. CK served on the Advisory Board for AMICUS, Chiesi,

Sanofi and Takeda. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics boards of the participating clinics (Master-Votum: 484/20 S). Written informed consent was obtained from all participating patients before the start of documentation. Guidelines on good epidemiological practice and data protection guidelines were followed.

References

1. Desnick RJ, Brady R, Barranger J, et al. Fabry disease, an under-recognized multisystemic disorder: expert recommendations for diagnosis, management, and enzyme replacement therapy. Ann Intern Med 2003;138:338-46.
2. Zarate YA, Hopkin RJ. Fabry's disease. Lancet 2008;372:1427-35.
3. Nagueh SF. Anderson-Fabry disease and other lysosomal storage disorders. Circulation 2014;130:1081-90.
4. Ortiz A, Oliveira JP, Waldek S, et al. Nephropathy in males and females with Fabry disease: cross-sectional description of patients before treatment with enzyme replacement therapy. Nephrol Dial Transplant 2008;23:1600-7.
5. Germain DP. Fabry disease. Orphanet J Rare Dis 2010;5:30.
6. Arends M, Wanner C, Hughes D, et al. Characterization of Classical and Nonclassical Fabry Disease: A Multicenter Study. J Am Soc Nephrol 2017;28:1631-41.
7. Poorthuis BJ, Wevers RA, Kleijer WJ, et al. The frequency of lysosomal storage diseases in The Netherlands. Hum Genet 1999;105:151-6.
8. Deegan PB, Bähner F, Barba M, et al. Fabry disease in females: clinical characteristics and effects of enzyme replacement therapy. In: Mehta A, Beck M, Sunder-Plassmann G, eds. Fabry Disease: Perspectives from 5 Years of FOS. Oxford: Oxford PharmaGenesis, 2006.
9. Wilcox WR, Oliveira JP, Hopkin RJ, et al. Females with Fabry disease frequently have major organ involvement: lessons from the Fabry Registry. Mol Genet Metab 2008;93:112-28.
10. Eng CM, Fletcher J, Wilcox WR, et al. Fabry disease: baseline medical characteristics of a cohort of 1765 males and females in the Fabry Registry. J Inherit Metab Dis 2007;30:184-92.
11. Regenbogen C, Braunisch MC, Schmaderer C, et al. Fabry disease: what the cardiologist should consider in non-cardiac screening, diagnosis, and management—narrative review. Cardiovasc Diagn Ther 2021;11:661-71.
12. Kurschat CE. Fabry disease-what cardiologists can learn from the nephrologist: a narrative review. Cardiovasc Diagn Ther 2021;11:672-82.
13. Linhart A, Paleček T. Narrative review on Morbus Fabry: diagnosis and management of cardiac manifestations. Cardiovasc Diagn Ther 2021;11:650-60.
14. Arends M, Hollak CE, Biegstraaten M. Quality of life in patients with Fabry disease: a systematic review of the literature. Orphanet J Rare Dis 2015;10:77.
15. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20:1727-36.
16. Grochtdreis T, Dams J, König HH, et al. Health-related quality of life measured with the EQ-5D-5L: estimation of normative index values based on a representative German population sample and value set. Eur J Health Econ 2019;20:933-44.
17. Andonian CS, Freilinger S, Achenbach S, et al. 'Well-being paradox' revisited: a cross-sectional study of quality of life in over 4000 adults with congenital heart disease. BMJ Open 2021;11:e049531.
18. Hughes DA, Evans S, Milligan A, et al. A multidisciplinary approach to the care of patients with Fabry disease. Fabry disease: perspectives from 5 years of FOS. In: Mehta A, Beck M, Sunder-Plassmann G, eds. Fabry Disease: Perspectives from 5 Years of FOS. Oxford: Oxford PharmaGenesis, 2006.
19. Oder D, Müntze J, Nordbeck P. Contemporary therapeutics and new drug developments for treatment of Fabry disease: a narrative review. Cardiovasc Diagn Ther 2021;11:683-95.
20. Rosa Neto NS, Bento JCB, Pereira RMR. Depression,

sleep disturbances, pain, disability and quality of LIFE in Brazilian Fabry disease patients. Mol Genet Metab Rep 2019;22:100547.
21. Polistena B, Rigante D, Sicignano LL, et al. Survey about the Quality of Life of Italian Patients with Fabry Disease. Diseases 2021;9:72.
22. Gold KF, Pastores GM, Botteman MF, et al. Quality of life of patients with Fabry disease. Qual Life Res 2002;11:317-27.
23. Street NJ, Yi MS, Bailey LA, et al. Comparison of health-related quality of life between heterozygous women with Fabry disease, a healthy control population, and patients with other chronic disease. Genet Med 2006;8:346-53.
24. Körver S, Geurtsen GJ, Hollak CEM, et al. Depressive symptoms in Fabry disease: the importance of coping, subjective health perception and pain. Orphanet J Rare Dis 2020;15:28.
25. Andonian C, Freilinger S, Kaemmerer H, et al. Psychological well-being in adults with congenital heart disease: Testing the predictive value of illness identity. Heart Mind 2021;5:45-51.
26. Müller MJ, Mehta ABeck M, et al. Neuropsychiatric and psychosocial aspects of Fabry disease. In: Mehta A, Beck M, Sunder-Plassmann G, eds. Fabry Disease: Perspectives from 5 Years of FOS. Oxford: Oxford PharmaGenesis, 2006.
27. Ford ES, Mokdad AH, Li C, et al. Gender differences in coronary heart disease and health-related quality of life: findings from 10 states from the 2004 behavioral risk factor surveillance system. J Womens Health (Larchmt) 2008;17:757-68.
28. Barsky AJ, Peekna HM, Borus JF. Somatic symptom reporting in women and men. J Gen Intern Med 2001;16:266-75.
29. Chiolero A, Burnier M, Santschi V. Improving treatment satisfaction to increase adherence. J Hum Hypertens 2016;30:295-6.
30. Politei JM, Bouhassira D, Germain DP, et al. Pain in Fabry Disease: Practical Recommendations for Diagnosis and Treatment. CNS Neurosci Ther 2016;22:568-76.
31. Sigurdardottir S, Bjerkely B, Jenssen TG, et al. The impact of demographic and clinical characteristics on the trajectories of health-related quality of life among patients with Fabry disease. Orphanet J Rare Dis 2021;16:427.
32. Bolsover FE, Murphy E, Cipolotti L, et al. Cognitive dysfunction and depression in Fabry disease: a systematic review. J Inherit Metab Dis 2014;37:177-87.
33. Bouwman MG, Maurice-Stam H, Linthorst GE, et al. Impact of growing up with Fabry disease on achievement of psychosocial milestones and quality of life. Mol Genet Metab 2011;104:308-13.
34. MacDermot KD, Holmes A, Miners AH. Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 98 hemizygous males. J Med Genet 2001;38:750-60.
35. Körver S, Geurtsen GJ, Hollak CE, et al. Cognitive functioning and depressive symptoms in Fabry disease: a follow-up study. J Inherit Metab Dis 2020;43:1070-81.
36. Laney DA, Gruskin DJ, Fernhoff PM, et al. Social-adaptive and psychological functioning of patients affected by Fabry disease. J Inherit Metab Dis 2010;33 Suppl 3:S73-81.
37. Ivleva A, Weith E, Mehta A, et al. The Influence of Patient-Reported Joint Manifestations on Quality of Life in Fabry Patients. JIMD Rep 2018;41:37-45.
38. Morand O, Johnson J, Walter J, et al. Symptoms and Quality of Life in Patients with Fabry Disease: Results from an International Patient Survey. Adv Ther 2019;36:2866-80.
39. Ali N, Gillespie S, Laney D. Treatment of Depression in Adults with Fabry Disease. JIMD Rep 2018;38:13-21.
40. Cole AL, Lee PJ, Hughes DA, et al. Depression in adults with Fabry disease: a common and under-diagnosed problem. J Inherit Metab Dis 2007;30:943-51.
41. Andonian C, Beckmann J, Ewert P, et al. Assessment of the Psychological Situation in Adults with Congenital Heart Disease. J Clin Med 2020;9:779.
42. Pihlstrøm HK, Weedon-Fekjær MS, Bjerkely BL, et al. Health-related quality of life in Norwegian adults with Fabry disease: Disease severity, pain, fatigue and psychological distress. JIMD Rep 2021;62:56-69.

Cite this article as: Andonian C, Beckmann J, Mayer O, Ewert P, Freiberger A, Huber M, Kaemmerer H, Kurschat C, Lagler F, Nagdyman N, Pieper L, Regenbogen C, Freilinger S. Quality of life in patients with Fabry's disease: a cross-sectional study of 86 adults. Cardiovasc Diagn Ther 2022;12(4):426-435. doi: 10.21037/cdt-22-215

