

Quality of Life Among Polish Fabry Patients – A Cross-sectional Study

Quality of Life Among Polish Fabry Patients

Research Article

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Abstract: This study sought to explore the following issues 1) health-related quality of life (HRQoL) in Fabry patients relative to the general population 2) the quality of life (QoL) level in heterozygous females as compared to hemizygous males and the general population. A prospective, cross-sectional study was performed in patients diagnosed with Fabry disease in Poland (n=33). HRQoL was assessed with two generic questionnaires: the Medical Outcomes Study Short Form-36 (SF-36) and EuroQol questionnaire (EQ-5D), which includes the EQ-5D descriptive system and the EQ-visual analogue scale (EQ VAS), as well as a disease-specific author's questionnaire. When measured with EQ-VAS, the subjective perception of health status was significantly lower in Fabry patients than that of the general population. SF-36 norm-based scores showed that patients are disadvantaged mainly in social functioning, bodily pain, and mental health. Objective assessments of HRQoL according to the EQ-5D Index tend to be lower for males than for females. Only male patients experienced extreme problems identified by the EQ-5D descriptive system. HRQoL of Fabry patients, measured by EQ-5D and SF-36, is lower as compared with that of the general population. Fabry disease affects QoL in its physical, mental and social dimensions.

Keywords: Fabry disease • Quality of life • SF-36 • EQ-5D

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1. Introduction

Fabry disease is an inborn error of metabolism caused by a genetic defect of the *GLA* gene in the X chromosome; this results in a deficiency of the lysosomal enzyme α -galactosidase A. Deficient α -galactosidase A activity leads to the progressive accumulation of globotriaosylceramide (Gb3) in many different cells and tissues, including renal glomerular and tubular epithelial cells, myocardial cells, valvular fibrocytes, neurons of the ganglia, and autonomic nervous system, and vascular endothelial cells [1]. This leads to a wide range of symptoms in various organs, most notably in

the kidney, heart, and brain. The clinical manifestations of Fabry disease, which usually appear in childhood or adolescence, include pain, skin angiokeratoma, hypohidrosis, and gastrointestinal disturbances. Pain is an early, and the most debilitating, symptom. Other symptoms such as tinnitus, recurrent vertigo, headache, fatigue, depression, and a diminished level of physical activity appear most commonly in the second decade of life. As the disease progresses, there is increasing renal, cardiac and vascular involvement, including renal insufficiency, heart disease, and stroke. The lifespan is reduced compared with that of the general population. Fabry disease is transmitted in an X-linked manner, but

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heterozygotes are very often symptomatic. However, the symptoms are never as severe as those found in men (hemizygotes) [1].

The symptoms of Fabry disease have a significant impact upon the quality of life. The health-related quality of life (HRQoL) in Fabry patients is significantly lower than that in the normal population [2,3]. Quality of life (QoL), a multidimensional term relating to varied levels of human existence, includes social, cultural, and economic components, health-related factors, and ability to perform professional work. QoL may be regarded as an individual sense of fulfilment and the achievement of long-term goals; in turn, this is determined to a significant extent by the personal traits, value system, and individual urges experienced by each human being [4,5]. With reference to medical sciences, HRQoL as introduced in 1990 by Schipper, is of particular importance; it is defined as the “functional effects of a disease and its treatment, as experienced by patients” [5].

The selection of appropriate and reliable research methods, aimed at the quantification of HRQoL, relates to the purpose of the studies, the structure of the studied group, and the adopted QoL concept [6]. The questionnaires used for HRQoL evaluation were classified into two groups. Generic instruments were used to compare the QoL level in different groups of patients and large populations. Specific instruments were used to measure the HRQoL level in specific groups of patients (e.g., suffering from a specific disease, patients of a specific age and gender or to measure specific aspects of functioning, such as activities of daily living). To date, no validated specific questionnaire has been developed for use in patients with Fabry disease.

The main objective of this study was to measure the HRQoL level in Polish Fabry patients in relation to that of the general population. A secondary objective was to compare the QoL level in Polish Fabry heterozygous females and hemizygous males.

2. Subjects and Methods

2.1. Study Population

The study was performed at The Children's Memorial Health Institute, Warsaw, Poland. To date, Fabry disease has been diagnosed in 38 Polish patients. The diagnoses were based on the activity level of α -galactosidase ($A < 4$ nmol/h/ml) in peripheral blood leukocytes [1]. In the case of heterozygotes, the diagnosis was based on the results of gene mutation identification. All homozygous Fabry patients (all males) received enzymatic replacement therapy (ERT). None of the Fabry heterozygotes (all females) received ERT.

2.2. Assessments and data collection

HRQoL was measured with two generic instruments: the Medical Outcomes Study Short Form-36 (SF-36) and EuroQol questionnaire (EQ-5D), as well as an author's questionnaire that was used because of the lack of a validated disease-specific instrument.

EQ-5D - The EQ-5D questionnaire is the instrument most frequently used to measure patient health preferences. It consists of two parts: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS) [17]. The EQ-5D descriptive system comprises the following five dimensions: Mobility (MO), Self-Care (SC), Usual Activities (UA), Pain/Discomfort (PD), and Anxiety/Depression (AD). Each dimension has three levels: no problems, some problems, and severe problems. A health state is defined by combining one level from each of the five dimensions. In total, 243 possible health states are defined. EQ-5D health states, defined by the EQ-5D descriptive system, may be converted into a single summary index by applying a formula that attaches values (also called weights) to each of the levels in each dimension. Information in this format is useful, for example, in pharmacoeconomic analyses.

The visual analogue scale (EQ-VAS) forms the second part of the EQ-5D questionnaire. The endpoints of the scale are labelled “worst imaginable health” and “best imaginable health”, anchored at 0 and 100, respectively. The Polish adult population normative data for both descriptive system and EQ-VAS, as well as the Polish value set for the EQ-5D Index, had been determined recently and were used in our analysis [8,9].

SF-36 – the Medical Outcomes Study Short Form-36 (SF-36) is the generic instrument most frequently used to measure overall HRQoL [10]. Thirty-six items cover 8 domains of physical, psychological, and social functioning. “Physical Functioning” (PF) scores patients' performance related to daily activities; “Role-Physical” (RP) regards the impact of physical health on life; “Bodily Pain” (BP) evaluates the pain level and its impact on normal daily activities; “General Health” (GH) evaluates subjective perception about present and future health status and resistance to illness; “Vitality” (VT) scores patients' feelings about their energy, vitality and moments of fatigue; “Social Functioning” (SF) scores the impact of health on routine social activities; “Role Emotional” (RE) measures the influences of emotional status on daily activities; and “Mental Health” (MH) scores mood and well-being, including depression and anxiety. Each domain is scored from 0 (worst) to 100 (best).

Table 1. Demographic characteristics of Polish patients with Fabry's disease included in the study.

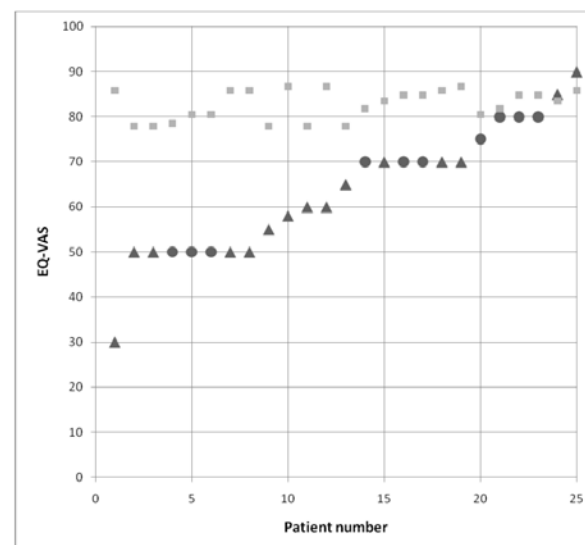
	Polish patients with Fabry's disease (n=33)
Age, years, mean (SD)	31 (15)
Masculine, n (%)	20 (61)
Age at diagnosis, years, mean (SD)	26 (15)
Time from diagnosis, years, mean (SD)	6 (5)
ERT* at the moment, n (%)	14 (42)
ERT duration, years, mean (SD)	3.4 (1.5)

* ERT with agalsidase beta (Fabrazyme; Genzyme Corp.)

ERT: enzyme replacement therapy; SD: standard deviation

SF-36 general population norms have been developed for several countries, for example, Sweden, Norway, the United Kingdom, Canada, and the United States, but not for Poland. To compare Fabry patients with the mean in the general population, we derived SF-36 Norm Based Scores (NBS) using normative data for the Swedish general population (n=8,930), [11]. In NBS, each scale is scored to have the same average (50) and the same standard deviation (10), meaning each point equals one-tenth of a standard deviation as observed in the general population. SF-36 physical (PCS) and mental (MCS) component summary scores were calculated on the same basis [12].

Author's questionnaire survey - Because there is no validated disease-specific questionnaire for use on Fabry's disease patients, an author's questionnaire has been developed based on the literature, personal experiences, patient-related observations, and patient-collected information. The questionnaire consists of 25 questions and 4 parts. The first 5 questions concern personal details. The second part of the questionnaire includes 6 closed questions with conjunctive choices, aimed at identifying the health problems that generate a significant impact on the HRQoL (an example of the possible problems evaluated is presented in Figures 2 and 3). Here the respondents were also asked to evaluate their health status in both the physical and mental sense. The subsequent 9 questions were directed at patients undergoing enzymatic replacement therapy (ERT). The respondents were asked to state their opinion whether the ERT produced any effects on their current health condition, and if so, in relation to which symptoms. The questionnaire contained 8 closed questions and one open question where the respondents were asked to indicate in relation to which symptoms they expected more significant health improvement. The fourth part of the questionnaire sought to determine whether patients receive support from their families and community and to investigate the

Figure 1. Comparison of EQ-VAS scores in Polish adult Fabry male (▲) and female (●) patients with age and gender matched Polish normative data (■) (n=25).

importance of the patients' organizations, in this case the "Association of Fabry Families". The respondents were asked 5 questions, 4 closed and one question with half-open choices, including a set of responses with an additional item "others" in case that the response that is incompatible with any of the provided options. Before being used in the study, the questionnaire was tested for face and content validity in patients with Fabry disease and in health professionals taking care of that group of patients. One person was trained in the use of all instruments chosen and performed all surveys.

2.3. Statistical analysis

In all calculations, two-sided confidence intervals were used. The significance level was defined as $p \leq 0.05$, and statistical trends were identified within the range $0.1 > p > 0.05$. The Shapiro-Wilk test was used to gather the evidence about the "non-normality" of a sample. The statistical analysis of categorical data was based on Fisher's exact test, and interval scale data on a Mann-Whitney test. Statistical analysis was performed with StatsDirect software (ver. 2.6.1) [13].

3. Results

3.1. Characteristics of the study population

Demographic data of the participants is shown in Table 1. Of 38 Polish patients with Fabry disease, 33 patients were included in the study (87%). Adult patients (n=25; 76%) self-completed the questionnaires, whereas the other 8 respondents were assisted by their

Table 2. Mean SF-36 scores (standard deviations) in Polish Fabry patients (n=31). Score range: 0 – 100.

	n	PF	RP	BP	GH	VT	SF	RE	MH
All	31	75.5 (22.1)	54.0 (41.9)	37.1 (24.5)	60.0 (12.5)	52.3 (8.0)	46.0 (10.4)	65.6 (42.6)	59.0 (9.4)
Females	13	84.2 (16.4)	61.5 (40.3)	29.2 (22.5)	53.1 (9.5)	52.3 (6.0)	47.1 (7.5)	61.5 (42.7)	58.8 (7.4)
Males	18	69.2 (23.9)	48.6 (43.3)	42.8 (24.9)	65.0 (12.2)	52.2 (9.4)	45.1 (12.2)	68.5 (43.5)	59.1 (10.9)
ERT	12	67.9 (20.4)	50.0 (41.3)	41.7 (22.1)	66.7 (11.3)	53.3 (8.9)	46.9 (12.1)	61.1 (44.6)	62.0 (8.9)
No ERT	6	71.7 (31.9)	45.8 (51.0)	45.0 (32.1)	61.7 (14.4)	50.0 (11.0)	41.7 (12.9)	83.3 (40.8)	53.3 (12.8)

ERT: enzyme replacement therapy; PF: Physical Functioning; RP: Role-Physical; BP: Bodily Pain; GH: General Health; VT: Vitality; SF: Social Functioning; RE: Role-Emotional; MH: Mental Health.

Table 3. SF-36 scoring in Polish Fabry patients using normative data (Norm Based Scoring, NBS) for Swedish general population (n=8930). Score range: 0 – 100.

	PF	RP	BP	GH	VT	SF	RE	MH	PCS	MCS
All	43.7	40.8	35.6	42.9	42.8	29.0	43.1	38.4	41.6	38.1
Females	48.1	43.2	32.5	39.8	42.8	29.6	41.7	38.3	42.8	36.7
Males	40.5	39.1	37.7	45.1	42.7	28.6	44.1	38.5	40.7	39.2
ERT	39.8	39.6	37.3	45.9	43.2	29.5	41.6	40.0	40.7	39.3
No ERT	41.7	38.2	38.6	43.6	41.8	26.9	49.2	35.4	40.5	39.0

ERT: enzyme replacement therapy; PF: Physical Functioning; RP: Role-Physical; BP: Bodily Pain; GH: General Health; VT: Vitality; SF: Social Functioning; RE: Role-Emotional; MH: Mental Health; PCS: Physical Component Summary measure; MCS: Mental Component Summary measure.

parents or proxies. The respondents' age ranged from 6 to 56 years, with the median age of 33 years. The group studied included 20 (61%) males, 14 of them on ERT.

3.2. Quality of life of Fabry patients in comparison with that of the general population

According to the EQ-Visual Analogue Scale, subjective perception of health status is significantly lower in Polish adult Fabry patients than in an age- and sex-matched Polish cohort, with a mean difference of 19.2 (SD 13.8) points ($p < 0.0001$; Figure 1).

A comparison with the general population using the SF-36 questionnaire (Table 2) was limited by a lack of Polish normative data. The SF-36 norm-based scores, elicited using normative data from the Swedish Fabry population (n=8930) [11], showed that Polish Fabry patients are disabled in all 8 domains and in both summary scores; particularly in SF (scores ≥ 2 SD lower than population mean), BP, MH and Mental Component Summary scores (scores ≥ 1 SD lower than population mean; Table 3).

3.3. Quality of life of Fabry male patients vs. symptomatic Fabry females

EQ-5D index scores showed that objective assessments of HRQoL tend to be lower for male Fabry patients than symptomatic Fabry females (0.74 vs. 0.88 points; $p = 0.064$; Table 4). Differences in subjective perception of health status were observed (65 vs. 72 EQ-VAS

points), but were not statistically significant. According to the EQ-5D descriptive system, only male Fabry patients experienced extreme problems: Pain/Discomfort (20% of respondents), Self-Care (5%) and Usual Activities (5%). The frequency of any problems in individual domains was noted, but only in Mobility was this statistically significant: 45% males vs. 15% females ($p = 0.09$).

Analysis of SF-36 scores showed that perception of General Health was lower in female heterozygotes than in male patients: 53.1 vs. 65.0 points ($p = 0.0066$). SF-36 Norm Based Scores differed between men and women more than 1 SD in no domain and more than 0.5 SD in Physical Functioning (with women functioning better) and Bodily Pain and General Health (with better scores for men).

3.4. Fabry disease specific questionnaire

According to the study population, burning extremity pain, skin lesions and gastrointestinal disorders are the most significant HRQoL-symptoms that have decreased with ERT (Figure 2).

In the group studied, 14 patients (42%) received ERT; 36% of those patients considered it very important, 50% extremely important. However, 43% of respondents stated that ERT has only partially satisfied their expectations. The ERT patients started this therapy at various stages of disease advancement; also, the severity of clinical symptoms was different between patients. According to the author's questionnaire, the results of the treatment were considered to be good in 50% of patients (Figure 3).

Table 4. Frequency of reported problems according to dimensions of EQ-5D descriptive system and overall estimate of quality of life according to EQ-5D index and EQ-VAS in Polish Fabry patients.

Problems	n	Mobility			Self-Care			Usual Activities			Pain/Discomfort			Anxiety/Depression			EQ-5D Index	EQ-VAS
		Moderate	Extreme	Any problems	Moderate	Extreme	Any problems	Moderate	Extreme	Any problems	Moderate	Extreme	Any problems	Moderate	Extreme	Any problems		
All	33	33%	0%	33%	6%	3%	9%	30%	3%	33%	73%	12%	85%	61%	0%	61%	0.79	68
Females	13	15%	0%	15%	0%	0%	0%	23%	0%	23%	77%	0%	77%	62%	0%	62%	0.88	72
Males	20	45%	0%	45%	10%	5%	15%	35%	5%	40%	70%	20%	90%	60%	0%	60%	0.74	65
ERT	14	50%	0%	50%	14%	0%	14%	43%	0%	43%	86%	7%	93%	64%	0%	64%	0.80	65
No ERT	6	33%	0%	33%	0%	17%	17%	17%	17%	34%	33%	50%	83%	50%	0%	50%	0.58	65

ERT, enzyme replacement therapy.

Figure 2. Self-perception of health status in Polish Fabry patients (n=32), based on author's questionnaire.

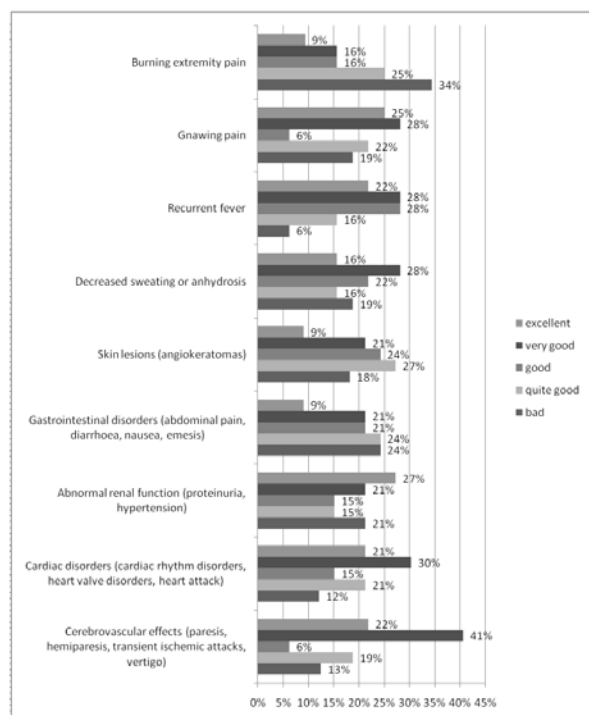
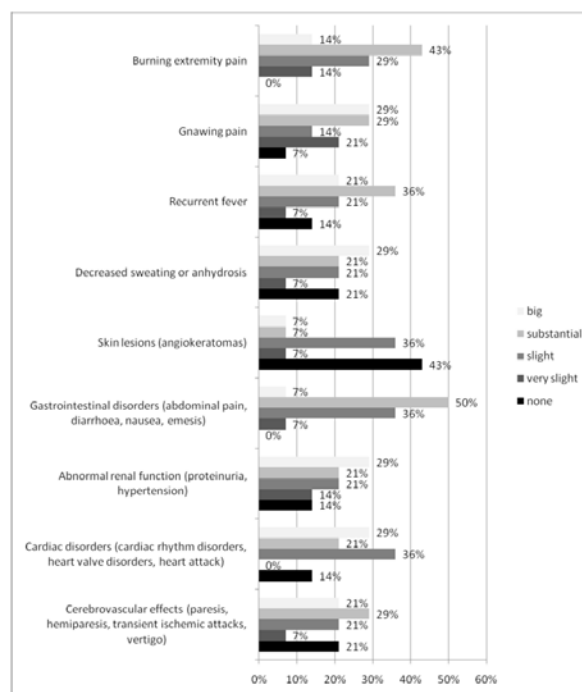


Figure 3. Assessment of ERT effect on symptoms of Fabry disease (n=14), based on author's questionnaire.



One of the elements having an effect on the QoL is a feeling of acceptance, safety, care, and support from the family and environment. Among the respondents, 17 patients (52%) receive active assistance from their family members regarding the handling of disease symptoms. Understanding for their health-related situation was found by 23 respondents (70%). Family support was received by all the patients in the studied group. Active assistance and understanding was received by 7 patients (21%).

The “Association of Fabry Families” was considered the source of information for 12 patients (60%), a support organization for 13 patients (65%), and is also regarded as an influential group that supports provision of treatment for diagnosed patients and heterozygotes. Two patients were not aware that such an organization exists (11%).

4. Discussion

Our study confirmed that perception of QoL according to EQ-5D in Polish Fabry patients is significantly lower than that in an age and sex matched Polish cohort. Studied patients were disabled in all 8 SF-36 domains, particularly in Social Functioning, Bodily Pain, Mental Health, as well as in Mental Component Summary scores. The HRQoL

tended to be lower in males than in symptomatic Fabry females. Only males experienced extreme problems, particularly with pain and discomfort.

Our study has several limitations. Firstly, the size of the studied population is relatively small, although we did approach all patients with Fabry disease diagnosed in Poland, and of those patients 87% gave consent to take part in the study. Secondly, our study had a cross-sectional, not longitudinal, construction and we were not able to follow QoL changes over time, or the effect of introducing ERT. We used well-known, validated generic questionnaires, but given the lack of a validated Fabry disease-specific questionnaire, we had to prepare our own instrument. Although it was based on the literature review, patient-related observations, patient opinions and personal experiences, there is no assurance of content validity, as it didn't undergo a complete formal validation process. Additionally, there is no Polish normative data for the SF-36 and we were forced to use normative data from the nearest country—Sweden. As there are some cultural differences, the SF-36 Swedish population norm based scores, especially in relation to domains such as Social Functioning, should be treated with caution.

Another important limitation is that we analyzed children and adults together. According to ProQolid database (<http://www.proqolid.org/>), EQ-5D and SF-36 questionnaires are suitable for respondents with a minimum age of 12 and 14 years old, respectively.

In our sample, there were 4 patients with Fabry disease, younger than 12 years old. QoL data was gathered using a proxy method, i.e., asking a parent or caregiver. Although it is not an optimal solution, in some situations it can be accepted. There are official special versions of EQ-5D for proxy assessment. The comparison of EQ-VAS scores in Polish Fabry patients whose age- and gender-matched Polish normative data was conducted in only 25 patients 18 years of age or older (Figure 1), as available normative data were obtained only in the adult population.

In Poland, the situation is different from that in other European countries, as ERT for Fabry disease is not reimbursed by the government. The patients receive ERT either during clinical trials or as a compassionate continuation of clinical trials. The lack of full access to the therapy changes the perception of the disease. Fabry male patients were tested when already on ERT and their results were compared with female heterozygotes who had no access to the therapy. Although it is well known that ERT affects QoL for both genders [16,18], in our sample males on ERT tended to have lower QoL in terms of EQ-VAS, EQ-index and EQ dimensions, than females without ERT.

There have been several studies of QoL in patients with Fabry disease that have used different validated questionnaires. Global reduction of QoL in patients with Fabry disease has been confirmed in studies using SF-36 questionnaire [2,3,14–16]. Gold et al. found that patients with Fabry disease have a score profile most similar to patients with AIDS and that in comparison with patients with Gaucher disease, Fabry patients score substantially lower across all QoL domains [2]. Wilcox et al. indicated that QoL in symptomatic Fabry females became impaired at a later age than in males, but both genders experience significantly impaired QoL from the third decade of life onward [3]. Three studies using the EQ-5D questionnaire found an improvement in the QoL of Fabry patients receiving ERT after one year of treatment, with improvement maintained during the second year [17,18] and after 5 years of supplementation [19].

In another study, improvement in EQ-5D scores was entirely attributable to male patients, because female patients maintained an EQ-5D score and the change in the studied population as a whole was not statistically significant [20]. Our study was the only one, except that of Miners et al., in which both SF-36 and EQ-5D, were used simultaneously [21]. Similarly, deterioration of QoL in Fabry patients was showed equally well by both instruments. Contrary to Miners et al., we noticed a higher percentage of patients experiencing at least some pain according to the EQ-5D descriptive system

(85% vs. 74%). Although, some studies using SF-36 showed similar levels of QoL deterioration in females as in males [3], in our sample, when EQ-5D was used, only males experienced extreme problems. These issues can be a consequence of known limitations of the EQ-5D descriptive system, i.e., a choice among only 3 response options. Neither of these 2 disease specific questionnaires prepared and used in previous studies underwent a formal validation process [2,21].

The results of our study indicate that Fabry males and symptomatic Fabry females have a different spectrum of health problems, and that medical care aimed at improving QoL should be individualized. Disease-specific questionnaire outcomes showed that the major burdens of this disease result from burning extremity pain, skin lesions and gastrointestinal disorders. Future studies of QoL in Fabry disease patients should address the problem of the formal validation of disease specific questionnaire, i.e., defining its validity, reliability, and responsiveness. Studies of children with Fabry disease should use a recently published child-friendly version of EQ-5D (EQ-5D-Y) [22,23]. Our SF-36 questionnaire outcomes should be re-analyzed when Polish normative data becomes available.

5. Conclusions

Based on the analysis of the results of the conducted studies, the following conclusions can be drawn:

1. Global QoL and self-assessment of health conditions in Fabry patients, regardless of the applied research instruments, is lower as compared with that of the general population.
2. Fabry disease affects QoL in relation to physical, mental and social dimensions.
3. Particularly burdensome symptoms that reduce the QoL for Fabry patients, include tingling and burning pain, skin lesions, and digestive ailments. Despite that these symptoms do not underlie the most serious clinical complications, they play a decisive role in that the disease is perceived as troublesome, therefore have a negative impact on QoL.
4. HRQoL in symptomatic Fabry females is higher compared with male Fabry patients, but lower as compared to the general population.

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