Molecular Genetics and Metabolism Reports 32 (2022) 100899

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

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

Shared decision making between patients with Fabry disease and physicians in Japan: An online survey

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ARTICLE INFO

Keywords:
Perception gaps
Fabry disease
Patients
Physicians
Shared decision making

ABSTRACT

Background: Fabry disease is a rare, progressive genetic lysosomal disorder that can cause multisystem organ dysfunction. With increasing treatment options for Fabry disease, it is imperative that patients discuss and select treatment plans in conjunction with their physicians. Although shared decision making (SDM) should be recommended for clinical decision making in disease management, evidence is limited as to how patients in Japan are involved in the choice of their Fabry disease treatment and if other gaps exist with physicians in the perception of Fabry disease management.

Objective: The main objective of the study was to assess the degree of agreement between patients and treating physicians in the SDM process as assessed by the SDM-Q-9 and SDM-Q-Doc questionnaires. In parallel, this study also investigated other factors that might impact the SDM process.

Methods: This was a cross-sectional web-based questionnaire survey of Japanese patients with Fabry disease and their treating physicians conducted from February 2021 to June 2021. Online surveys were developed for patients and physicians, consisting of seven items, including the Japanese version of the 9-item SDM Questionnaire for patients (SDM-Q-9) and physicians (SDM-Q-Doc). Physicians were divided into two cohorts: non-paired and paired with patients. Only the paired cohort physicians answered the SDM questionnaire.

Results: A total of 99 physicians and 30 patients answered the respective questionnaires. Among these, 13 physicians were included in a paired SDM analysis with patients. Mean (standard deviation [SD]) patient age at diagnosis of Fabry disease was 47.5 (15.8) years, and 14 (46.7%) were male. Both physicians in the paired cohort and patients considered patient-reported outcomes (both 76.7%) and the findings from laboratory testing as important (90.0% and 60.0% respectively). However, regarding symptoms that affect quality of life of patients, perception gaps were identified in that physicians in the paired cohort placed less importance on patient-reported outcome-related symptoms such as sweating abnormalities and gastrointestinal symptoms than their patients (0% [0/17] and 44.4% [8/18], 11.8% [2/17] and 38.9% [7/18], respectively). In the paired analysis, there was no significant difference in total SDM score between patients and physicians ($p = 0.82$). However, the largest discordance in perception between patients and physicians was identified for the explanation of the advantages and disadvantages of the treatment options (weighted Kappa coefficient = 0.14).

Conclusion: This survey revealed a gap in the perception of disease burden affecting patients' quality of life, and a recognition gap between physicians and patients when they discussed the advantages and disadvantages of treatment options. To improve the SDM process in Fabry disease management and treatment, practical solutions for bridging these gaps should be considered.

Abbreviations: α-Gal A, α-galactosidase A; CI, confidence interval; ERT, enzyme replacement therapy; GL-3, globotriaosylceramide; QoL, quality of life; SD, standard deviation; SDM, shared decision making; SDM-Q-Doc, physician version of the Shared Decision-Making Questionnaire; SDM-Q-9, 9-item Shared Decision-Making Questionnaire.

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https://doi.org/10.1016/j.ymgmr.2022.100899
Received 25 May 2022; Received in revised form 8 July 2022; Accepted 9 July 2022
Available online 10 August 2022

1. Introduction

Fabry disease is a rare lysosomal, X-linked disease caused by a genetic mutation in *GLA*, the gene encoding the enzyme α-galactosidase A (α-Gal A). The decreased activity of α-Gal A leads to progressive accumulation of glycolipids such as globotriaosylceramide (GL-3) in lysosomes and lysosomal dysfunction [1,2] in multiple organs, resulting in inflammation and fibrosis with subsequent multisystemic involvement. Clinical manifestations of Fabry disease include gastrointestinal symptoms, such as abdominal pain and vomiting, pain in the hands and feet, cerebrovascular disorders, hearing impairment, progressive renal damage, cardiomyopathy, and clinical signs and symptoms such as arrhythmias [3–5]. Other Fabry disease manifestations include sweating abnormalities, angiokeratomas, and otorhinolaryngological manifestations such as vertigo and tinnitus [3]. Fabry disease is debilitating and progressive, with cardiovascular complications, end-stage kidney disease, and cerebrovascular disease as the leading causes of death [4,6].

Management of Fabry disease includes Fabry-specific therapy as well as adjunctive treatment for pain, gastrointestinal symptoms, and cardiorenal function. Currently available Fabry-specific therapies include pharmacological chaperone therapy with migalastat and enzyme replacement therapies with recombinant α-Gal A [7,8]. Substrate reduction therapy and gene therapy are currently under development [8,9]. Therefore, it is expected that treatment options for Fabry disease will increase in the future.

Typical methods of treatment decision making include paternalistic, informed, and collaborative approaches [10]. Paternalism is a physician decision-making approach based on clinical experience and evidence-based medicine; the patient is only passively involved. In the informed approach, the practicing physician presents information and treatment options to the patient, and the patient then decides. In the collaborative approach, decisions are based on information provided by both the treating physician and the patient after discussion between both parties. This approach is also known as shared decision making (SDM) [10]. No decision-making approach is inherently superior or inferior. Instead, successful treatment depends on the specific treatment goals that the patient wants to achieve. The paternalistic and informed approaches are characterized by one-way communication and limited information exchange. However, SDM is a joint process in which information is provided and received by both the patient and the physician to align with health-related decisions that are right for the patient. Therefore, when selecting a treatment plan for a chronic disease for which many treatment options with varying effects on quality of life (QoL) are possible, SDM may be the most appropriate approach [11].

Fabry disease requires life-long treatment, and treatment options have increased in recent years. Thus, patients need to consider and discuss treatment options with treating physicians and decide which plan to apply. Although previous surveys on QoL and clinical manifestations in patients with Fabry disease have been reported, information on treatment decision making in Fabry disease management in Japan has not been fully reported [12–14]. The main objective of the study was to assess the degree of agreement between patients and treating physicians in the SDM process as assessed by the SDM-Q-9 and SDM-Q-Doc questionnaires. In parallel, we also assessed other factors that might impact the SDM process (e.g., perception of disease severity).

2. Materials and methods

2.1. Study design and survey questionnaire

To investigate whether there are any potential perception gaps between patients with Fabry disease and physicians in Japan, a cross-sectional web-based questionnaire survey of Japanese patients with Fabry disease and their treating physicians was conducted. The survey was conducted online in paired and non-paired cohorts. The paired cohort consisted of paired physicians and patients who were eligible for the primary analysis on SDM agreement. The non-paired cohort consisted of physicians only, who were not eligible for the primary analysis (e.g., patient consent was not obtained). In the paired cohort we used the validated Japanese version of the 9-item Shared Decision-Making Questionnaire (SDM-Q-9) to assess patients and the Japanese physician version of the SDM-Q (SDM-Q-Doc) [15,16] to assess physicians. We also developed, for both cohorts, an additional questionnaire to assess potential factors that may impact the SDM process and/or gaps in communication. In addition to the SDM questionnaire, a total of 18 and 19 questions (for patients and physicians, respectively) were asked in six categories as follows: 1. Demographic characteristics; 2. Perceptions about disease severity and progression; 3. Perceptions about symptoms affecting patient's daily life; 4. Communication between patients and healthcare providers at the time of diagnosis; 5. Perception of disease awareness and control; and 6. Perception of treatment awareness and treatment satisfaction. An English-translated version of each questionnaire is shown in Appendix Table A1 and A2. The study duration was from February 2021 to June 2021.

Documents outlining ethical considerations were uploaded to the website developed for this study by M3, Inc. (m3.com; https://www.m3.com/). Patients and physicians read the explanations about this study provided via the website and provided written informed consent for study participation before completing the survey. All data were anonymized. This study was approved by a central ethical review board (MINS Research Ethics Review Board: Approval No. MINS-REC-210208) and was conducted according to the principles of the Declaration of Helsinki and in compliance with the Ethical Guidelines for Medical Research for Humans.

2.2. Inclusion and exclusion criteria of participants

Patients aged ≥16 years at the time of Fabry disease diagnosis, who had a confirmed diagnosis within 10 years, had access to the website, provided consent for study participation, and could answer the questionnaire were enrolled in this study. Patients participating in clinical trials of any Fabry disease treatment that had yet to be approved in Japan were excluded from this study.

Practicing physicians with clinical experience in treating at least one patient with Fabry disease at the time of providing informed consent and who had access to the website, provided consent for study participation, and could answer the questionnaire were enrolled in this study via a physician panel of M3, Inc. There are more than 300,000 medical doctors registered with m3.com, which accounts for more than 90% of Japan's total number of physicians. No exclusion criteria were applied to physicians.

Physicians were divided into those who were not paired with patients (non-paired cohort) and those who were paired with patients (paired cohort). The paired cohort comprised only physicians who agreed to introduce eligible patients to this survey and confirmed their patients' consent to participate in this survey. Only physicians in the paired cohort answered the SDM questionnaire (SDM-Q-Doc).

2.3. Statistical analysis

The target sample size was 30 patients and 100 physicians to ensure feasibility.

All variables in this study were analyzed using descriptive statistics. Mean, standard deviation (SD), minimum, median, and maximum were calculated for continuous variables, and frequency distribution was calculated for quantitative variables. Participants with any missing values were excluded from the analysis.

In the paired cohort, the agreement between physicians and patients in their assessment of the questionnaires was analyzed by calculating the weighted Kappa coefficient. In the SDM-Q-9 and SDM-Q-Doc questionnaires, each of the nine question items consisted of a six-point Likert scale scored from 0 (no SDM) to 5 (ideal SDM), resulting in a possible

score of 0–45 points. Furthermore, the total score in the SDM questionnaire was converted to a score of 0–100 points and evaluated using the Mann–Whitney *U* test. The correlation between patient and physician scores (total scores and scores for each domain) was assessed by calculating Spearman's rank correlation coefficient. Statistical analyses were performed using SAS software, version 9.4 for Windows (SAS Institute, Cary, NC, USA).

3. Results

3.1. Characteristics of respondents

A total of 99 physicians and 30 patients answered the questionnaire (Fig. 1). Of these, 13 physicians and 30 patients were included in the paired cohort. The physicians in the paired cohort completed a questionnaire about the enrolled patients with whom they were paired. Therefore, the total number of questionnaires completed by physicians was 116 (86 non-paired and 30 paired with patients).

Patients had a mean (SD) age of 52.2 (16.1) years, and 14 (46.7%) were male. Overall, the mean age at diagnosis of Fabry disease was 47.5 (15.8) years. Twenty patients (66.7%) were aged ≥40 years at the time of diagnosis, and nine (30%) were aged ≥60 years (Table 1A). The majority of the physicians in the paired cohort (9; 69.2%) were aged 40–49 years, and 11 (84.6%) were male. Their specialties were mainly distributed among three departments: nephrology, cardiology, and neurology. Five physicians in the paired cohort (38.5%) and 58 physicians in the non-paired cohort (67.4%) were treating one patient with Fabry disease when the survey was conducted (Table 1B).

3.2. Perceptions about disease severity and progression

Of the 30 patients enrolled in this study, nine (30.0%) reported severe symptoms, while six (20%) paired physicians considered their patients' symptoms to be severe (Table 2). Regarding the degree of agreement between patient and physicians in the paired cohort, the cross-tabulated analyses revealed that patients perceived their symptoms as more severe (weighted Kappa coefficient [95% confidence interval; CI], 0.20 [−0.07, 0.48]).

Regarding the perception of disease progression over the previous 6 months, the most frequent response was "unchanged" by both physicians in the paired cohort and their patients (73.3% [22/30] and 83.3% [25/30], respectively) (Table 2).

In terms of the evaluation of disease progression, both physicians and patients in the paired cohort (76.7% [23/30]) considered patient-reported outcomes and the findings from laboratory testing including cardiac echocardiography, electrocardiography, urinary testing, and brain magnetic resonance imaging (90.0% [27/30] and 60.0% [18/30], respectively) to be important (Table 2).

3.3. Perceptions about symptoms affecting patient's daily life

Overall, 56.7% (17/30) of physicians in the paired cohort, 39.5% (34/86) of physicians in the non-paired cohort, and 60.0% (18/30) of patients indicated that some symptoms affect patient QoL (Fig. 2A). According to the physicians in the paired cohort, the three symptoms that were most frequently reported to affect QoL were cardiac symptoms (58.8% [10/17]), acroparesthesia (29.4% [5/17]), and cerebrovascular disorders (17.6% [3/17]). According to their paired patients, sweating abnormalities (44.4% [8/18]), gastrointestinal symptoms (38.9% [7/18]), and cardiac symptoms/acroparesthesia (33.3% [6/18]) were the most frequently reported symptoms affecting QoL (Fig. 2B). Regarding sweating abnormalities and gastrointestinal symptoms, the response frequency of the physicians in the paired cohort was low compared with the patients (0% [0/17] and 11.8% [2/17], for sweating abnormalities and gastrointestinal symptoms respectively). A similar trend was observed in the physicians in the non-paired cohort. Further analysis stratified by the medical specialty of physicians indicated that physicians mainly selected symptoms related to their specialties.

3.4. Communication between patients and healthcare providers at diagnosis

Of the116 physicians surveyed, 86 (74.1%) answered that they collaborated with specialists and/or other healthcare providers when developing a disease management plan at the time of diagnosis. The most frequently reported type of healthcare provider involved at the time of diagnosis was a Fabry disease specialist (57.0% [49/86]). Other healthcare providers, including genetic specialists, nurses, medical social workers, and certified genetic counselors, were also mentioned with a similar frequency (Table 3).

Twelve out of 30 (40.0%) patients answered that they discussed their treatment with other than the physician in charge of developing the disease management plan at diagnosis. At least 50% of patients participated in discussions with nurses (58.3% [7/12]) and Fabry disease specialists (50.0% [6/12]) (Table 3).

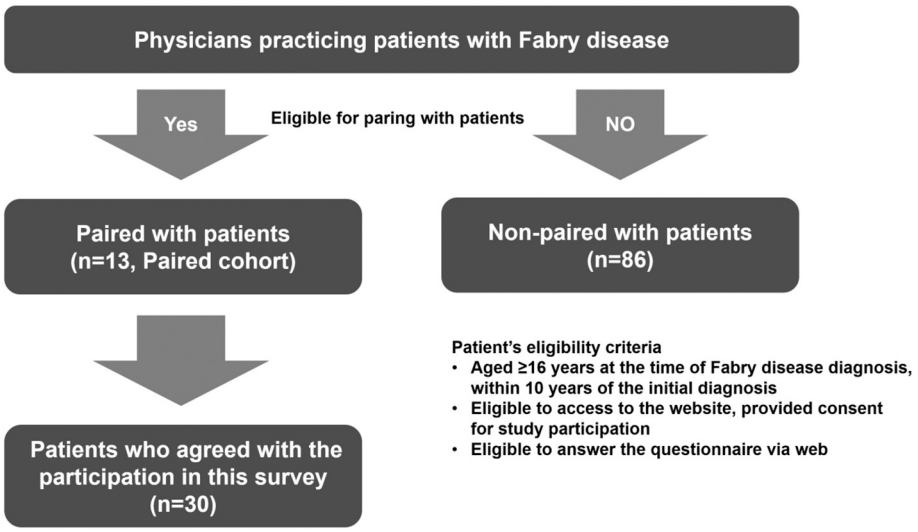

Fig. 1. Survey flow and subject disposition.

Table 1
Background characteristics of physicians and patients. (A) Patients' characteristics. (B) Physicians' characteristics.

(A)

	Patient (Total)	Male	Female
N, (%)	30 (100.0)	14 (46.7)	16 (53.3)
Age, years, mean (SD)	52.2 (16.1)	43.0 (13.5)	60.3 (13.1)
20–29, n (%)	2 (6.7)	2 (14.3)	0 (0.0)
30–39, n (%)	5 (16.7)	4 (28.6)	1 (6.3)
40–49, n (%)	10 (33.3)	5 (35.7)	5 (31.3)
50–59, n (%)	1 (3.3)	1 (7.1)	0 (0.0)
≥60, n (%)	12 (40.0)	2 (14.3)	10 (62.5)
Age at diagnosis of Fabry disease, years, mean (SD)	47.5 (15.8)	38.8 (13.4)	55.1 (13.1)
10–19, n (%)	1 (3.3)	1 (7.1)	0 (0.0)
20–29, n (%)	4 (13.3)	3 (21.4)	1 (6.3)
30–39, n (%)	5 (16.7)	4 (28.6)	1 (6.3)
40–49, n (%)	7 (23.3)	3 (21.4)	4 (25.0)
50–59, n (%)	4 (13.3)	2 (14.3)	2 (12.5)
≥60, n (%)	9 (30.0)	1 (7.1)	8 (50.0)

(B)

	Physician	
	Paired to patients	Not paired to patients
N, (%)	13 (100.0)	86 (100.0)
Sex, Male, n (%)	11 (84.6)	78 (90.7)
Age, years		
20–29, n (%)	1 (7.7)	4 (4.7)
30–39, n (%)	0 (0.0)	26 (30.2)
40–49, n (%)	9 (69.2)	29 (33.7)
50–59, n (%)	0 (0.0)	18 (20.9)
≥60, n (%)	3 (23.1)	9 (10.5)
Medical specialty, n (%)		
Pediatrics	2 (15.4)	20 (23.3)
Cardiology	3 (23.1)	26 (30.2)
Nephrology	5 (38.5)	16 (18.6)
Neurology	3 (23.1)	22 (25.6)
General internal medicine	0 (0.0)	2 (2.3)
Other	0 (0.0)	0 (0.0)
Fabry disease patients currently being treated, n (%)		
0	0 (0.0)	0 (0.0)
1	5 (38.5)	58 (67.4)
2	1 (7.7)	14 (16.3)
3	3 (23.1)	5 (5.8)
4	1 (7.7)	2 (2.3)
5	0 (0.0)	3 (3.5)
6–10	2 (15.4)	2 (2.3)
≥11	1 (7.7)	2 (2.3)

SD, standard deviation.

3.5. Perceptions of Fabry disease management and treatment

Regarding the perception of patients' understanding of the disease, most physicians in the paired cohort and their patients (93.3% [28/30] and 83.4% [25/30], respectively) considered that they had an understanding or good understanding of the disease (Table 3).

For the perception of control of patients' symptoms, 66.7% (20/30) of physicians in the paired cohort thought they could control their patients' symptoms, whereas 53.3% (16/30) of patients felt they could manage their symptoms through hospital visits and treatment (Table 3). A trend for patients to have a less favorable opinion of the disease management plan was identified in cross-tabulation between the physicians and patients in the paired cohort (weighted Kappa coefficient [95% CI], 0.23 [−0.03, 0.49]).

The total numbers of physicians and patients whose treatment plan included disease-specific therapy (chaperone therapy or enzyme replacement therapy) and adjunctive therapy were 111 and 30, respectively. Twenty-seven (90%) patients received disease-specific therapy. Among those respondents, 62.0% (18/29) of physicians in the paired cohort and 70.0% (21/30) of patients reported that patients were satisfied or somewhat satisfied with the current treatment (Table 3).

Table 2
Results of a questionnaire on perceptions about disease severity and progression.

	Physician		Patient
	Paired to patients	Not paired to patients	Total
N (%)	30 (100.0)	86 (100.0)	30 (100.0)
Severity of Fabry disease in patients			
Severe	6 (20.0)	9 (10.5)	9 (30.0)
Moderate	14 (46.7)	38 (44.2)	10 (33.3)
Mild	10 (33.3)	39 (45.3)	11 (36.7)
Changes in symptoms of Fabry disease within the previous 6 months			
Improved	2 (6.7)	11 (12.8)	1 (3.3)
Unchanged	22 (73.3)	69 (80.2)	25 (83.3)
Worsened	4 (13.3)	3 (3.5)	3 (10.0)
No treatment in the past 6 months	2 (6.7)	3 (3.5)	1 (3.3)
Items considered important in determining changes in symptoms			
PRO (subjective symptoms)	23 (76.7)	64 (74.4)	23 (76.7)
Laboratory findings (e.g., echocardiography, electrocardiography, urinalysis, brain MRI)	27 (90.0)	70 (81.4)	18 (60.0)
Measures of Fabry disease-related biomarkers (e.g., Lyso-Gb3)	12 (40.0)	31 (36.0)	8 (26.7)
Other	0 (0.0)	0 (0.0)	1 (3.3)

MRI, magnetic resonance imaging; PRO, patient-reported outcome.

3.6. Communication between patients and physicians in treatment decision making measured by SDM-Q-Doc and SDM-Q-9

Only the paired cohort of physicians completed the SDM-Q items of the questionnaire ($n = 30$). The mean total score (range: 0–45) of the SDM-Q items was higher for physicians (35.6 ± 7.4) than for their patients (33.9 ± 10.7), and Spearman's rank correlation coefficient was 0.58. After converting these scores to a scale of 0–100, the mean (SD) SDM-Q-Doc and SDM-Q-9 scores were 79.0 ± 16.5 and 75.4 ± 23.8, respectively ($p = 0.82$). Table 4 shows the reproducibility and correlation between SDM-Q-9 and SDM-Q-Doc in paired populations by each of the nine questions. In the paired analysis, physician and patient perceptions differed the most regarding the advantages and disadvantages of the treatment options (Q4; Table 4). For these analyses, the weighted Kappa coefficient was 0.14 (95% CI: −0.05, 0.33), and Spearman's rank correlation coefficient was 0.35.

4. Discussion

This cross-sectional web-based survey evaluated the perceptions and attitudes of patients and physicians during Fabry disease management and treatment. Key findings from the survey were that perception gaps were identified for symptoms that affect patients' QoL. The paired analysis of the SDM questionnaire revealed a considerable gap between patients and physicians in their perceptions of the treatment options. The findings from this survey provide insights into the factors facilitating SDM in clinical practice for Fabry disease in Japan.

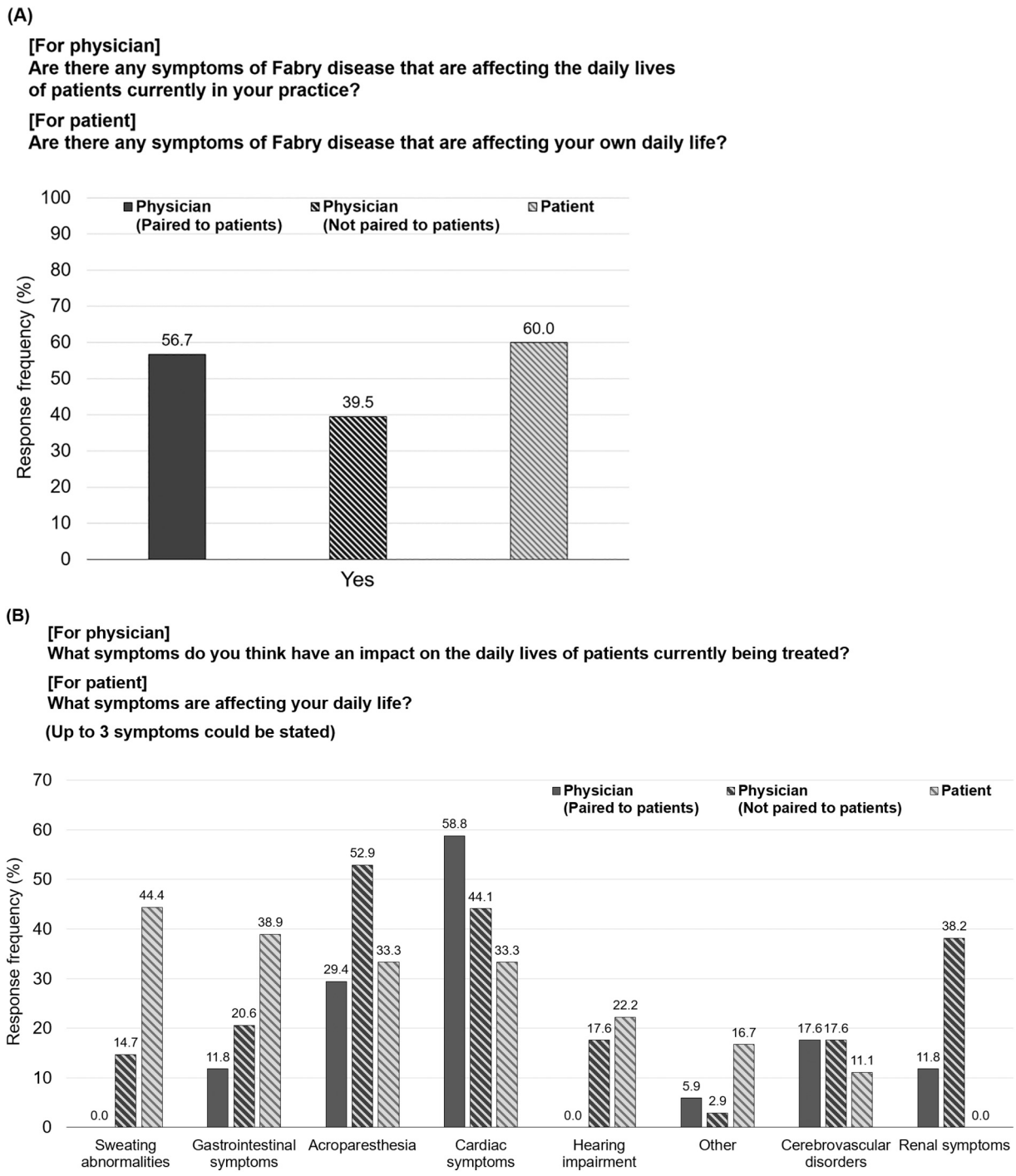

Fig. 2. Perceptions of disease burden based on daily symptoms affecting the quality of life of patients. (A) Presence or absence of symptoms of Fabry disease that affect daily life. (B) Symptoms of Fabry disease that affect daily life.

4.1. Perceptions of disease burden

In terms of the perception of Fabry disease management, physicians placed less importance on patient-reported outcome symptoms, such as sweating abnormalities and gastrointestinal symptoms. This perception gap could make it difficult for physicians and patients to align with treatment goals. By contrast, a previous international survey revealed that frequent diarrhea affects patients' QoL [12]. According to registry data, approximately half of patients with Fabry disease report gastrointestinal symptoms [17]. Furthermore, a Fabry disease-specific measurement scale for gastrointestinal symptoms was recently developed [18], highlighting the importance of gastrointestinal symptoms in clinical settings. Thus, in addition to acroparesthesia, attention should be paid to gastrointestinal symptoms.

Recently, digital tools were developed for recording daily symptoms in patients with chronic disease [19]; such practical solutions should also be applied to Fabry disease management to enhance communication between physicians and patients about the QoL-related symptoms that cannot be evaluated or monitored using laboratory findings. For instance, in the present study, we observed that sweating abnormalities, which have not been well investigated previously [20], were an important symptom in terms of impact on the patients' QoL. These

Table 3
Results of a questionnaire on management, treatment, and understanding of Fabry disease.

	Physician		Patient
	Paired to patients	Not paired to patients	Total
N (%)	30 (100.0)	86 (100.0)	30 (100.0)
Collaboration with specialists and other professionals in planning management of Fabry disease			
Absent	10 (33.3)	20 (23.3)	–
Present	20 (66.7)	66 (76.7)	–
Fabry disease specialist	10 (50.0)	39 (59.1)	–
Clinical geneticist	9 (45.0)	24 (36.4)	–
Certified genetic counselor	4 (20.0)	15 (22.7)	–
Nurse	8 (40.0)	24 (36.4)	–
Medical social worker	4 (20.0)	22 (33.3)	–
Other	2 (10.0)	2 (3.0)	–
Discussions with healthcare professionals other than treating physician[1]			
Absent	–	–	13 (43.3)
Present	–	–	12 (40.0)
Fabry disease specialist	–	–	6 (50.0)
Clinical geneticist	–	–	3 (25.0)
Certified Genetic Counselor	–	–	2 (16.7)
Nurse	–	–	7 (58.3)
Medical social worker	–	–	1 (8.3)
Other	–	–	1 (8.3)
Understanding of Fabry disease by patients			
Good understanding	12 (40.0)	20 (23.3)	8 (26.7)
Understanding	16 (53.3)	46 (53.5)	17 (56.7)
Neither[2]	1 (3.3)	15 (17.4)	3 (10.0)
Limited understanding	1 (3.3)	5 (5.8)	2 (6.7)
No understanding	0 (0.0)	0 (0.0)	0 (0.0)
Status of control of Fabry disease symptoms according to patients			
Very well	11 (36.7)	13 (15.1)	9 (30.0)
Favorable	9 (30.0)	50 (58.1)	7 (23.3)
Neither[2]	6 (20.0)	19 (22.1)	13 (43.3)
Slightly faulty	3 (10.0)	3 (3.5)	1 (3.3)
Failure	1 (3.3)	1 (1.2)	0 (0.0)
Current treatment for Fabry disease			
Only chaperone therapy or ERT	16 (53.3)	37 (43.0)	17 (56.7)
Only symptomatic treatment	2 (6.7)	17 (19.8)	3 (10.0)
Both disease-specific treatment (chaperone or ERT) and symptomatic treatment	11 (36.7)	28 (32.6)	10 (33.3)
No treatment	1 (3.3)	4 (4.7)	0 (0.0)
Patient satisfaction with current treatment[3]			
Very satisfied	7 (24.1)	8 (9.8)	11 (36.7)
Satisfied	11 (37.9)	53 (64.6)	10 (33.3)
Neither[2]	8 (27.6)	19 (23.2)	7 (23.3)
Somewhat unsatisfied	3 (10.3)	2 (2.4)	2 (6.7)
Unsatisfied	0 (0.0)	0 (0.0)	0 (0.0)

ERT, enzyme replacement therapy.
[1] 25 patients who underwent a test, such as enzyme activity assay or genetic testing, were included.
[2] Neither indicates neutral or moderate.
[3] Only patients and physicians who were receiving or providing treatment responded.

Table 4
Correlations and agreements of shared decision making at the time of selecting treatment for Fabry disease between patients and physicians in results of SDM-Q-9 and SDM-Q-Doc.

	Question SDM-Q-Doc [SDM-Q-9]	Spearman's rank correlation coefficient	Weighted Kappa coefficient (95% CI)
Q1	I made clear to my patient that a decision needs to be made. [My doctor made clear that a decision needs to be made.]	0.44	0.33 (0.05, 0.62)
Q2	I wanted to know exactly from my patient how he/she wants to be involved in making the decision. [My doctor wanted to know exactly how I want to be involved in making the decision.]	0.53	0.41 (0.17, 0.66)
Q3	I told my patient that there are different options for treating his/her medical condition. [My doctor told me that there are different options for treating my medical condition.]	0.51	0.30 (0.07, 0.53)
Q4	I precisely explained the advantages and disadvantages of the treatment options to my patient. [My doctor precisely explained the advantages and disadvantages of the treatment options.]	0.35	0.14 (−0.05, 0.33)
Q5	I helped my patient understand all the information. [My doctor helped me understand all the information.]	0.51	0.27 (0.06, 0.48)
Q6	I asked my patient which treatment option he/she prefers. [My doctor asked me which treatment option I prefer.]	0.52	0.38 (0.16, 0.60)
Q7	My patient and I thoroughly weighed the different treatment options. [My doctor and I thoroughly weighed the different treatment options.]	0.62	0.49 (0.28, 0.71)
Q8	My patient and I selected a treatment option together [My doctor and I selected a treatment option together.]	0.58	0.46 (0.23, 0.68)
Q9	My patient and I reached an agreement on how to proceed. [My doctor and I reached an agreement on how to proceed.]	0.50	0.37 (0.14, 0.61)

Q, question; CI, confidence interval.

findings underscore the need for further studies to clarify the symptoms that affect patient QoL, especially as the number of patients in the present survey was limited.

In contrast to physicians' perceptions, patients did not prioritize major organ events such as renal, cerebrovascular, and cardiac symptoms as disease burdens affecting their QoL, even though such events could affect their prognosis. These symptoms are not subjective, which may have led to the low response frequency among patients. However, such differences between patient and physician perceptions indicate a communication gap that may limit the awareness of relevant symptoms for both physicians and patients, ultimately affecting long-term patient outcomes and QoL. Because SDM is a joint process between the patient and the physician, it is necessary to consider the development of a communication tool to facilitate discussion with patients about symptoms that are considered important from their perspective and the physician's perspective.

In this survey, patients perceived that they had worse disease

severity and less control of their symptoms than physicians. However, only 60% of patients discussed the disease management plan with other than their treating physician. Some Fabry disease management guidelines recommend multidisciplinary team support for patients, including a neurologist, nephrologist, cardiologist, medical geneticist, genetic counselor, psychologist, and nurse [21]. A multidisciplinary approach could help patients become more informed regarding Fabry disease management.

4.2. Communication between patients and physicians in treatment decision making

To our knowledge, this is the first study to evaluate the communication between patients with Fabry disease and physicians using the SDM questionnaire. In contrast with a previous SDM study on an unrelated disease indicated that physicians experienced a significantly higher degree of SDM compared with patients [22], the results from this study showed no significant difference in total SDM scores between patients and physicians. Additionally, we did not observe differences in physician and patient perceptions regarding the understanding of Fabry disease and patient satisfaction with treatment. However, interestingly, the paired SDM questionnaire analysis revealed a considerable perception gap between patients and physicians when they discussed the advantages and disadvantages of the treatment options. Despite the rarity of the disease, there are currently four drugs available in Japan for the treatment of Fabry disease, and this complexity may have influenced our findings. As new treatments for Fabry disease are under development, treatment strategies for Fabry disease are expected to become even more complex. The effectiveness of decision aids regarding knowledge of treatment options and awareness of risk has been revealed in primary care [23]; therefore, in Fabry disease, it is essential to consider concrete measures to improve the SDM process, such as developing decision aids specific to Fabry disease treatment and adjunctive therapy in collaboration with physicians, industry, and patients.

4.3. Strengths and limitations

Regarding the representability, the physician panel of M3, Inc. was used for the survey enrollment. Approximately 90% of medical doctors in Japan are included in this panel, and the questionnaire was sent to around 80,000 physicians in the panel. A total of 99 physicians answered the questionnaire and based on their responses, they are currently treating over 200 patients. According to the nationwide survey [24], the estimated number of Fabry disease patients in Japan was 1658 (±264.8). Therefore, the physicians enrolled in this survey treat approximately 12% of Japanese patients. As for the patients, physicians in the paired cohort treated at least 43 patients. Among these, 30 patients were eligible and enrolled via physicians. Data on patient phenotype was not collected in this survey, but data regarding mean age and sex ratio from nationwide and post-marketing surveys [24,25] were comparable to the data from this survey. The total number of patients and physicians in our study compares favorably with a recent study of SDM conducted in in patients with type 2 diabetes mellitus [26].

This study has some limitations, including those inherent to web-based surveys, such as physician and patient selection bias. Patients were enrolled via their physician, and their respective data were used for conducting paired analyses. All responses were analyzed anonymously; however, reporting bias of patients should be considered. Even if reporting bias occurred, perception gaps between patients and physicians were identified. Furthermore, the generalizability of the findings may be limited to Japanese populations because this study only included Japanese participants.

5. Conclusion

The results of this survey indicated that there was a gap in the perception of disease burden affecting patient's QoL. The survey also identified a recognition gap between physicians and patients when they discussed the advantages and disadvantages of the treatment options. To improve the SDM process in Fabry disease management and treatment, practical solutions for bridging these gaps should be considered in collaboration with physicians, patients and the wider healthcare system.

Role of the funding source

This research was supported by Amicus Therapeutics K.K., Japan. The sponsor was involved in the study design and the interpretation and publication of the results, but not in the data collection and statistical analysis.

Author contributions

Kazuki Otani and Mio Tsuchiya contributed to the development of the study design and the protocol. All authors made interpretations of the results, drafting and critically reviewing the manuscript of the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Data sharing

Data used in this study will not be shared.

Declaration of Competing Interest

Natsuko Inagaki has no conflict of interest to disclose. Takeo Nakayama received grants or contracts from I&H Co., Ltd. and Nakagawa Pharmacy Co., consulting fees from Otsuka Pharmaceutical Co., Ltd., and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Pfizer Japan Inc., MSD K.K., Chugai Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Janssen Pharmaceutical K.K., Boehringer Ingelheim International GmbH, Eli Lilly Japan K.K., Baxter Ltd., Mitsubishi Tanabe Pharma Corporation, Novartis Pharma K.K., and Allergan Japan K.K. Kazuki Otani and Mio Tsuchiya are full-time employees of Amicus Therapeutics K.K., Japan.

Acknowledgments

The authors wish to thank the patients and physicians who participated in this survey, and Mebix for providing support for protocol development and statistical analysis as the CRO which was funded by Amicus Therapeutics K.K., Japan, the authors also thank Keyra Martinez Dunn, MD, of Edanz (www.edanz.com) for providing medical writing support, which was funded by Amicus Therapeutics K.K., Japan, in accordance with Good Publication Practice guidelines (http://www.ismpp.org/gpp3).

Appendix A. Appendix

Appendix Table A1
Questionnaire for physicians (English-translated version).

Questions for physicians who treat patients with Fabry disease		
#	Questions	Answers
1–1	What is your sex?	1. Male 2. Female
1–2	What is your current age?	1. 20s 2. 30s 3. 40s 4. 50s 5. 60s and older
1–3	Please select your main clinical department. *Please select only one.	1. Pediatrics 2. Cardiology 3. Nephrology 4. Neurology 5. General internal medicine 6. Other (_____)
1–4	Have you treated patients with Fabry disease?	1. Yes 2. No
1–5	How many patients with Fabry disease do you currently see?	1. 0 2. 1 3. 2 4. 3 5. 4 6. 5 7. 6–10 8. ≥11
Patients' awareness of symptoms of Fabry disease		
#	Questions	Answers
2–1	Please tell us about the severity of Fabry disease in the patients you currently see. *If you see ≥2 patients, please recall the specific patient you treated most recently and answer the following questions.	1. Severe 2. Moderate 3. Mild
2–2	Please tell us about changes in the patient's symptoms six months ago and now. *If you see ≥2 patients, please recall the specific patient you treated most recently and answer the following questions.	1. Improved 2. No change 3. Deteriorated 4. Did not see the patient 6 months ago
2–3	Do you explain to the patient about your assessment of the changes in symptoms?	1. Yes 2. No
2–4	What do you consider important in assessing the patient's symptom changes? (Multiple answers)	1. Patient's subjective symptoms 2. Laboratory findings (e.g., echocardiography, electrocardiography, urinalysis, brain MRI) 3. Measurements of Fabry disease-related biomarkers (Lyso-Gb3, etc.) 4. Other (_____)
Disease burden of Fabry disease		
#	Questions	Answers
3–1	Are there any symptoms of Fabry disease affecting the daily life of patient(s) you currently see?	1. No 2. Yes
3–1-a	Answer only if you answered "Yes" in question 3–1 above. What symptoms do you think are affecting the daily life of the patient(s) you currently see? (You may select up to 3 responses)	1. Acroparesthesia 2. Sweating abnormalities 3. Hearing impairment 4. Gastrointestinal symptoms 5. Cardiac symptoms 6. Renal symptoms 7. Cerebrovascular disorders 8. Other (_____)
Communication between the patient and the physician (at the time of diagnosis)		
#	Questions	Answers
4–1	What tests were performed at the time of the definitive diagnosis of Fabry disease for your current patient(s)? (Multiple answers)	1. Enzyme activity assay 2. Genetic testing 3. Not involved in diagnosis
4–1-a	Answer only if you answered "1" and "2" in question 4–1 above. After the definitive diagnosis, did you discuss plans for disease management of Fabry disease with the patient(s) (e.g., follow-up schedule, etc.)?	1. Yes 2. No
4–2	Did you collaborate with specialists and other professionals in planning disease management for Fabry disease?	1. Yes 2. No
4–2-a	Answer only if you answered "Yes" in question 4–2 above. What type of professionals did you collaborate with? (Multiple answers)	1. Fabry disease specialist 2. Clinical geneticist 3. Certified genetic counselor 4. Nurse 5. Medical social worker 6. Other (_____)
Awareness of disease management of Fabry disease		
*If you see ≥2 patients, please recall the specific patient you treated most recently and answer the following questions.		

(*continued on next page*)

Appendix Table A1 (*continued*)

Questions for physicians who treat patients with Fabry disease		
#	Questions	Answers
#	Questions	Answers
5–1	Please tell us about insight into disease (level of understanding of Fabry disease) of the patient you currently see.	1. Understands very well 2. Understands relatively well 3. Neither 4. Does not understand very well 5. Does not understand
5–2	Do you feel that you manage to control the symptoms of Fabry disease for the patient you currently see?	1. Strongly agree 2. Somewhat agree 3. Neither 4. Somewheat disagree 5. Disagree
Awareness of treatment for Fabry disease		
#	Questions	Answers
6–1	Please select treatment of Fabry disease that you currently provide to patient(s).	1. Enzyme replacement therapy or chaperone therapy only 2. Symptomatic treatment only 3. Both 1 and 2 4. No treatment, only examination
6–1-a	Answer only if you answered "1" to "3" in question 6–1 above. Do you think the patient is satisfied with the treatment currently provided? Please select the level of patient satisfaction with treatment. *If you see ≥2 patients, please recall the specific patient you treated most recently and answer the question.	1. Very satisfied 2. Somewhat satisfied 3. Neither 4. Somewhat dissatisfied 5. Dissatisfied
Patient-physician communication (when deciding on a treatment plan)* Using SDM-Q-Doc		
*Nine statements related to the decision-making in the above-mentioned consultation are listed below. For each statement, please indicate how much you agree or disagree.		
#	Questions	Answers
7–1	I made clear to my patient that a decision needs to be made.	1. Completely disagree 2. Strongly disagree 3. Somewhat disagree 4. Somewhat agree 5. Strongly agree 6. Completely agree
7–2	I wanted to know exactly from my patient how he/she wants to be involved in making the decision.	1. Completely disagree 2. Strongly disagree 3. Somewhat disagree 4. Somewhat agree 5. Strongly agree 6. Completely agree
7–3	I told my patient that there are different options for treating his/her medical condition.	1. Completely disagree 2. Strongly disagree 3. Somewhat disagree 4. Somewhat agree 5. Strongly agree 6. Completely agree
7–4	I precisely explained the advantages and disadvantages of the treatment options to my patient.	1. Completely disagree 2. Strongly disagree 3. Somewhat disagree 4. Somewhat agree 5. Strongly agree 6. Completely agree
7–5	I helped my patient understand all the information.	1. Completely disagree 2. Strongly disagree 3. Somewhat disagree 4. Somewhat agree 5. Strongly agree 6. Completely agree
7–6	I asked my patient which treatment option he/she prefers.	1. Completely disagree 2. Strongly disagree 3. Somewhat disagree 4. Somewhat agree 5. Strongly agree 6. Completely agree
7–7	My patient and I thoroughly weighed the different treatment options.	1. Completely disagree 2. Strongly disagree 3. Somewhat disagree 4. Somewhat agree 5. Strongly agree 6. Completely agree
7–8	My patient and I selected a treatment option together.	1. Completely disagree 2. Strongly disagree 3. Somewhat disagree 4. Somewhat agree 5. Strongly agree 6. Completely agree

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Appendix Table A1 (*continued*)

Questions for physicians who treat patients with Fabry disease		
#	Questions	Answers
7–9	My patient and I reached an agreement on how to proceed.	1. Completely disagree 2. Strongly disagree 3. Somewhat disagree 4. Somewhat agree 5. Strongly agree 6. Completely agree

Appendix Table A2
Questionnaire for patients (English-translated version).

Questions for the patient diagnosed with Fabry disease		
#	Questions	Answers
1–1	What is your sex?	1. Male 2. Female
1–2	How old are you now?	(years old)
1–3	How old were you when you were diagnosed with Fabry disease?	(years old)
Symptoms of Fabry disease		
* Please recall your current treatment situation and answer the following questions.		
#	Questions	Answers
2–1	How do you feel about your current health condition?	1. Very good 2. Somewhat good 3. Neither 4. Somewhat bad 5. Very bad
2–2	Are there any changes in your symptoms between six months ago and now?	1. Improved 2. No change 3. Deteriorated 4. No treatment 6 months ago
2–3	Did your doctor explain about any change in your symptoms?	1. Yes 2. No
2–4	What do you consider important in determining whether there has been any change in your symptoms? (Multiple answers)	1. Changes in symptoms (subjective symptoms) that you perceive yourself 2. Results of tests explained by the physician (e.g., echocardiography, electrocardiogram, urinalysis, brain MRI, etc.) 3. Measurement results of substances related to Fabry disease as explained by the physician *Lyso-Gb3 and other biomarkers 4. Other (_____)
How Fabry disease affects your daily life		
* Please recall your current treatment situation and answer the following questions.		
#	Questions	Answers
3–1	Are there any symptoms of Fabry disease affecting your daily life?	1. No symptom affecting me. 2. There are symptoms affecting me.
3–1-a	Answer only if you answered "There are symptoms affecting me" to question 3–1 above. What symptoms affect your daily life? (You may select up to 3 responses)	1. Pain in limbs 2. Inability or difficulty sweating 3. Poor hearing 4. Gastrointestinal symptoms (abdominal pain, diarrhea, etc.) 5. Heart symptoms (cardiac hypertrophy, abnormal heart valves, arrhythmia, myocardial infarction, etc.) 6. Renal symptoms (proteinuria, renal failure, dialysis, etc.) 7. Cerebrovascular disorder (stroke, etc.) 8. Other (_____)
Communication between the patient and the physician at the time of diagnosis		
*** Please recall your current treatment situation and answer the following questions.**		
#	Questions	Answers
4–1	What tests were performed at diagnosis of Fabry disease? (Multiple answers)	1. Tests to examine the function of enzymes (enzyme activity assay) were performed 2. Tests for genetic changes (genetic testing) were performed 3. Do not remember/do not know
4–1-a	Answer only if you answered "1" and "2" in question 4–1 above. After the diagnosis of Fabry disease, did you discuss your future treatment plan with your primary care physician (e.g., how often you will visit the hospital, etc.)?	1. Discussed with my doctor 2. Did not discuss with my doctor
4–2	Did you discuss your future treatment plans for Fabry disease with anyone other than your primary care physician?	1. Yes 2. No
4–2-a	Answer only if you answered "Yes" in question 4–2 above. With whom did you have discussions? (Multiple answers)	1. Fabry disease specialist 2. Clinical geneticist 3. Certified genetic counselor 4. Nurse 5. Medical social worker

(*continued on next page*)

Appendix Table A2 (*continued*)

Questions for the patient diagnosed with Fabry disease		
#	Questions	Answers
		6. Other (_____)
4–3	Answer only if you answered "1" and "2" in question 4–1 above. Did you discuss your future treatment plans with your spouse, children, or other family members?	1. Yes 2. No
Awareness of disease management of Fabry disease		
* Please recall your current treatment situation and answer the following questions.		
#	Questions	Answers
5–1	Please select your level of understanding of Fabry disease.	1. Understand very well 2. Understand relatively well 3. Neither 4. Do not understand very well 5. Do not understand
5–2	Do you feel that your Fabry disease symptoms are under control because of hospital visits and treatment?	1. Strongly agree 2. Somewhat agree 3. Neither 4. Somewhat disagree 5. Disagree
Awareness of the treatment for Fabry's disease		
*** Please recall your current treatment situation and answer the following questions.**		
#	Questions	Answers
6–1	Please select the treatment you are currently receiving for Fabry disease.	1. Receiving only enzyme replacement therapy or chaperone therapy 2. Receiving treatment only for emergent symptoms (e.g., taking painkillers for pain, etc.) 3. Receiving both 1 and 2 4. Not receiving treatment, but seeing my primary care physician
6–1-a	Answer only if you answered "1" to "3" in question 6–1 above. Please indicate your level of satisfaction with your current treatment for Fabry disease.	1. Very satisfied 2. Somewhat satisfied 3. Neither 4. Somewhat dissatisfied 5. Dissatisfied
Patient–physician communication (when deciding on a treatment plan)* Using SDM-Q-9*Nine statements related to the decision-making in your consultation are listed below. For each statement, please indicate how much you agree or disagree.		
#	Questions	Answers
7–1	My doctor made clear that a decision needs to be made.	1. Completely disagree 2. Strongly disagree 3. Somewhat disagree 4. Somewhat agree 5. Strongly agree 6. Completely agree
7–2	My doctor wanted to know exactly how I want to be involved in making the decision.	1. Completely disagree 2. Strongly disagree 3. Somewhat disagree 4. Somewhat agree 5. Strongly agree 6. Completely agree
7–3	My doctor told me that there are different options for treating my medical condition.	1. Completely disagree 2. Strongly disagree 3. Somewhat disagree 4. Somewhat agree 5. Strongly agree 6. Completely agree
7–4	My doctor precisely explained the advantages and disadvantages of the treatment options.	1. Completely disagree 2. Strongly disagree 3. Somewhat disagree 4. Somewhat agree 5. Strongly agree 6. Completely agree
7–5	My doctor helped me understand all the information.	1. Completely disagree 2. Strongly disagree 3. Somewhat disagree 4. Somewhat agree 5. Strongly agree 6. Completely agree
7–6	My doctor asked me which treatment option I prefer.	1. Completely disagree 2. Strongly disagree 3. Somewhat disagree 4. Somewhat agree 5. Strongly agree 6. Completely agree
7–7	My doctor and I thoroughly weighed the different treatment options.	1. Completely disagree 2. Strongly disagree 3. Somewhat disagree 4. Somewhat agree

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Appendix Table A2 (*continued*)

Questions for the patient diagnosed with Fabry disease		
#	Questions	Answers
7–8	My doctor and I selected a treatment option together.	5. Strongly agree 6. Completely agree 1. Completely disagree 2. Strongly disagree 3. Somewhat disagree 4. Somewhat agree 5. Strongly agree 6. Completely agree
7–9	My doctor and I reached an agreement on how to proceed.	1. Completely disagree 2. Strongly disagree 3. Somewhat disagree 4. Somewhat agree 5. Strongly agree 6. Completely agree

References

[1] R.O. Brady, A.E. Gal, R.M. Bradley, E. Martensson, A.L. Warshaw, L. Laster, Enzymatic defect in Fabry's disease. Ceramidetrihexosidase deficiency, N. Engl. J. Med. 276 (1967) 1163–1167, https://doi.org/10.1056/NEJM196705252762101.

[2] S.R.A. Bokhari, H. Zulfiqar, A. Hariz, Fabry Disease. [Updated 2021 Jul 10], StatPearls Publishing, StatPearls. Treasure Island (FL), 2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK435996/ (accessed 17 February 2022).

[3] D.P. Germain, Fabry disease, Orphanet. J. Rare Dis. 5 (2010) 30, https://doi.org/10.1186/1750-1172-5-30.

[4] J.A. Kint, Fabry's disease: alpha-galactosidase deficiency, Science. 167 (1970) 1268–1269, https://doi.org/10.1126/science.167.3922.1268.

[5] T.W. Crosbie, W. Packman, S. Packman, Psychological aspects of patients with Fabry disease, J. Inherit. Metab. Dis. 32 (2009) 745–753, https://doi.org/10.1007/s10545-009-1254-1.

[6] Y.A. Zarate, R.J. Hopkin, Fabry's disease, Lancet. 372 (2008) 1427–1435, https://doi.org/10.1016/S0140-6736(08)61589-5.

[7] C.M. Eng, D.P. Germain, M. Banikazemi, D.G. Warnock, C. Wanner, R.J. Hopkin, J. Bultas, P. Lee, K. Sims, S.E. Brodie, G.M. Pastores, J.M. Strotmann, W.R. Wilcox, Fabry disease: guidelines for the evaluation and management of multi-organ system involvement, Genet. Med. 8 (2006) 539–548, https://doi.org/10.1097/01.gim.0000237866.70357.c6.

[8] S.J. van der Veen, C.E.M. Hollak, A.B.P. van Kuilenburg, M. Langeveld, Developments in the treatment of Fabry disease, J. Inherit. Metab. Dis. 43 (2020) 908–921, https://doi.org/10.1002/jimd.12228.

[9] I. Simonetta, A. Tuttolomondo, T. Di Chiara, T.S. Miceli, D. Vogiatzis, F. Corpora, A. Pinto, Genetics and gene therapy of Anderson-Fabry disease, Curr. Gene. Ther. 18 (2018) 96–106, https://doi.org/10.2174/1566523218666180404161315.

[10] C. Charles, A. Gafni, T. Whelan, Decision-making in the physician-patient encounter: revisiting the shared treatment decision-making model, Soc. Sci. Med. 49 (1999) 651–661, https://doi.org/10.1016/s0277-9536(99)00145-8.

[11] L.A. Shay, J.E. Lafata, Where is the evidence? A systematic review of shared decision making and patient outcomes, Med. Decis. Mak. 35 (2015) 114–131, https://doi.org/10.1177/0272989X14551638.

[12] O. Morand, J. Johnson, J. Walter, L. Atkinson, G. Kline, A. Frey, J. Politei, R. Schiffmann, Symptoms and quality of life in patients with Fabry disease: results from an international patient survey, Adv. Ther. 2019 (36) (2019) 2866–2880, https://doi.org/10.1007/s12325-019-01061-x.

[13] B. Hoffmann, A. Garcia de Lorenzo, A. Mehta, M. Beck, U. Widmer, R. Ricci, FOS European Investigators, Effects of enzyme replacement therapy on pain and health related quality of life in patients with Fabry disease: data from FOS (Fabry outcome survey), J. Med. Genet. 42 (2005) 247–252, https://doi.org/10.1136/jmg.2004.025791.

[14] A. Ivleva, E. Weith, A. Mehta, D.A. Hughes, The influence of patient-reported joint manifestations on quality of life in Fabry patients, JIMD Rep. 41 (2018) 37–45, https://doi.org/10.1007/8904_2017_84.

[15] Y. Goto, H. Miura, D. Son, H. Arai, L. Kriston, I. Scholl, M. Härter, K. Sato, T. Kusaba, Psychometric evaluation of the Japanese 9-item shared decision-making questionnaire and its association with decision conflict and patient factors in Japanese primary care, JMA. J. 3 (2020) 208–215, https://doi.org/10.31662/jmaj.2019-0069.

[16] Y. Goto, H. Miura, D. Son, I. Scholl, L. Kriston, M. Härter, K. Sato, T. Kusaba, H. Arai, Association between physicians' and patients' perspectives of shared decision making in primary care settings in Japan: the impact of environmental factors, PLoS One 16 (2021), e0246518, https://doi.org/10.1371/journal.pone.0246518.

[17] A. Mehta, J.T. Clarke, R. Giugliani, P. Elliott, A. Linhart, M. Beck, G. Sunder-Plassmann, F.O.S. Investigators, Natural course of Fabry disease: changing pattern of causes of death in FOS - Fabry outcome survey, J. Med. Genet. 46 (2009) 548–552, https://doi.org/10.1136/jmg.2008.065904.

[18] A.L. Shields, R.E. Lamoureux, F. Taylor, J.A. Barth, A.E. Mulberg, V. Kessler, N. Skuban, FABry disease patient-reported outcome-GASTROINTESTINAL (FABPRO-GI): a new Fabry disease-specific gastrointestinal outcomes instrument, Qual. Life Res. 30 (2021) 2983–2994, https://doi.org/10.1007/s11136-021-02847-9.

[19] S. Gilbert, A. Mehl, A. Baluch, C. Cawley, J. Challiner, H. Fraser, E. Millen, M. Montazeri, J. Multmeier, F. Pick, C. Richter, E. Türk, S. Upadhyay, V. Virani, N. Vona, P. Wicks, C. Novorol, How accurate are digital symptom assessment apps for suggesting conditions and urgency advice? A clinical vignettes comparison to GPs, BMJ Open 10 (2020), e040269, https://doi.org/10.1136/bmjopen-2020-040269.

[20] O. Lidove, U. Ramaswami, R. Jaussaud, F. Barbey, T. Maisonobe, C. Caillaud, M. Beck, G. Sunder-Plassmann, A. Linhart, A. Mehta, FOS European investigators, Hyperhidrosis: a new and often early symptom in Fabry disease. International experience and data from the Fabry Outcome Survey, Int. J. Clin. Pract. 60 (2006) 1053–1059, https://doi.org/10.1111/j.1742-1241.2006.01061.x.

[21] A. Ortiz, D.P. Germain, R.J. Desnick, J. Politei, M. Mauer, A. Burlina, C. Eng, R. J. Hopkin, D. Laney, A. Linhart, S. Waldek, E. Wallace, F. Weidemann, W. R. Wilcox, Fabry disease revisited: management and treatment recommendations for adult patients, Mol. Genet. Metab. 123 (2018) 416–427, https://doi.org/10.1016/j.ymgme.2018.02.014.

[22] G.E. van der Kraaij, F.M. Vermeulen, P. Smeets, E. Smets, P.I. Spuls, The current extent of and need for shared decision making in atopic dermatitis and psoriasis in the Netherlands: an online survey study amongst patients and physicians, J. Eur. Acad. Dermatol. Venereol. 34 (2020) 2574–2583, https://doi.org/10.1111/jdv.16340.

[23] V. Coronado-Vázquez, C. Canet-Fajas, M.T. Delgado-Marroquín, R. Magallón-Botaya, M. Romero-Martín, J. Gómez-Salgado, Interventions to facilitate shared decision-making using decision aids with patients in primary health care: a systematic review, Medicine (Baltimore) 99 (2020), e21389, https://doi.org/10.1097/MD.0000000000021389.

[24] Y. Koto, N. Sakai, Y. Lee, N. Kakee, J. Matsuda, K. Tsuboi, N. Shimozawa, T. Okuyama, K. Nakamura, A. Narita, H. Kobayashi, R. Uehara, Y. Nakamura, K. Kato, Y. Eto, Prevalence of patients with lysosomal storage disorders and peroxisomal disorders: a nationwide survey in Japan, Mol. Genet. Metab. 133 (2021) 277–288, https://doi.org/10.1016/j.ymgme.2021.05.004.

[25] H. Sasa, M. Nagao, K. Kino, Safety and effectiveness of enzyme replacement therapy with agalsidase alfa in patients with Fabry disease: post-marketing surveillance in Japan, Mol. Genet. Metab. 126 (2019) 448–459, https://doi.org/10.1016/j.ymgme.2019.02.005.

[26] H. Den Ouden, R.C. Vos, A.H. Pieterse, G. Rutten, Shared decision making in primary care: process evaluation of the intervention in the OPTIMAL study, a cluster randomised trial, Prim. Care. Diabetes 16 (2022) 375–380, https://doi.org/10.1016/j.pcd.2022.02.006.