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Translation of quality of life scale for pediatric patients with Fabry disease in Japan

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ABSTRACT

Introduction: Fabry disease is a rare, X-linked lysosomal storage disorder that begins in childhood with a wide variety of symptoms, including neuropathic pain, gastrointestinal abnormalities, and skin abnormalities. Despite the substantial impact of these symptoms on children's quality of life (QOL), systematic QOL analysis of Japanese pediatric Fabry disease patients has been limited. Therefore, to evaluate the QOL of Japanese pediatric Fabry disease patients using standardized and disease-specific scales, we used the Fabry-specific Pediatric Health and Pain Questionnaire (FPHPQ), which was developed by the Fabry Outcome Survey.

Methods: The FPHPQ was translated in accordance with the Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes. A back-translated version was reviewed twice by the original lead author of FPHPQ to confirm the conceptual equivalence. The questionnaire was then validated by cognitive debriefing, and distributed to pediatric Fabry disease patients in Japan.

Results: Questionnaire responses were obtained from eight patients. The mean scores on the FPHPQ were 11.0 (± 11.43) for heat-associated pain, 5.5 (± 4.60) for cold-associated pain, and 14.8 (± 5.97) for abdominal pain and fatigue. In addition, heat-associated pain negatively correlated with physical well-being, whereas cold-associated pain positively correlated with good friendships.

Conclusion: We established the Japanese version of the FPHPQ to assess the QOL of pediatric Fabry disease patients. The internal consistency and partial criterion-related validity of the Japanese version were confirmed. Analysis of a larger number of patients should be performed in the future to further validate the outcomes of this study.

1. Introduction

Fabry disease is a rare, X-linked lysosomal storage disorder. The prevalence of Fabry disease per 10,000 live births has been estimated to be between 0.85 and 1.29 in the cohort studies [1,2], and the results of newborn screening for Fabry disease in Japan demonstrated that the prevalence is 1/7057 [3]. Fabry disease is characterized by a deficiency in the activity of the lysosomal enzyme alpha-galactosidase A. This leads to the deposition of globotriaosylceramide and causes various complications, such as neuropathic pain, gastrointestinal symptoms, cornea verticillata, angiokeratoma, hypohidrosis, hypertrophic cardiomyopathy, cardiac rhythm disturbances, progressive renal failure, and stroke [4]. Patients may also have hearing loss, tinnitus, and vertigo [5]. Symptoms of Fabry disease occur in multiple organs, such as the kidneys, heart, and brain, leading to kidney failure, transient ischemic attacks, and stroke, respectively, which substantially affect the quality of life (QOL) of patients [6,7].

For the multiorgan disease of Fabry disease, it is important to periodically analyze not only the clinical phenotype, but also lysoglobotriaosylceramide as a biomarker [8].

The most frequent symptom in pediatric patients (age < 18 years) is Fabry disease-specific neuropathic pain, which is experienced by 58.8% of male patients and 40.5% of female patients [9]. In addition, gastrointestinal symptoms have been reported to occur in 17.9% of pediatric patients, and skin abnormalities in 14.2% patients [9]. A systematic review of Fabry disease patients younger than 5 years of age reported

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that the earliest age of onset of gastrointestinal problems was 1.0 years, that of neuropathic pain was 2.0 years, and that of hypohidrosis or the anhidrosis was 2.5 years [10].

In considering the support required by Fabry disease patients, evaluation of only the symptoms is insufficient. It is important to consider the impact that the symptoms and treatments have on the daily life and the QOL of pediatric patients. In particular, evaluation of QOL is important for pediatric patients, who have symptoms such as neuropathic pain, which are difficult for others to empathize with. However, the QOL of pediatric Fabry patients has not yet been reported in Japan. A systematic review of the health-related QOL of Fabry disease patients showed that the QOL of Fabry disease patients is lower than that of the general population [11]. In most studies included in the systematic review, the generic QOL questionnaire was used to measure the QOL of Fabry disease patients. For example, the 36-Item Short Form Health Survey [12], Euro Qol 5 Dimension [13], KINDL-R questionnaire [14], etc., were used.

On the other hand, only two studies in the systematic review used the disease-specific health- related QOL questionnaire [11]. One previous study investigated the extent of symptoms and the effect of symptoms on the social life of adult Fabry disease patients [15]. The results showed that male patients with Fabry disease had a significantly lower health-related QOL than healthy controls. Another study focused on the QOL of pediatric Fabry disease patients by the pediatric working group for the Fabry Outcome Survey (FOS), with Uma Ramaswami being as the group chair and leading the development of the questionnaire [16]. The FOS is an international long-term observational registry for patients with Fabry disease who are treated with agalsidase alfa [17]. The results were used to establish the Fabry-specific Pediatric Health and Pain Questionnaire (FPHPQ), and its reliability and validity as a measure of disease-specific health-related QOL was verified. Although the FPHPQ is useful for measuring QOL in pediatric Fabry disease patients, because it had not been translated into Japanese, the disease-specific QOL of pediatric patients with Fabry disease in Japan had remained unclear. Therefore, in this study, we translated the FPHPQ into Japanese and clarified the QOL of Japanese pediatric Fabry disease patients.

2. Materials and methods

2.1. Fabry-specific Pediatric Health and Pain Questionnaire (FPHPQ)

The FPHPQ was developed by the FOS Pediatric Working Group [16]. There are three versions of the FPHPQ for children, namely, versions for children aged 4 to 7, 8 to 12, and 13 to 18 years. All three versions consist of 40 items that ask the same questions, although they are worded according to the target age group. Of these, 35 items measure the frequency of specific symptoms, such as pain, dizziness, tiredness, abdominal symptoms, and participation in sports, using a five-point Likert scale (4 = always, 3 = often, 2 = sometimes, 1 = seldom, and 0 = never). In addition, one item measures the pain intensity using a 0 to 10 numeric rating scale (0 means “no pain” and 10 means “pain as bad as you can imagine”), two items ask “how many times the patient has experienced pain” and “how many days he or she missed school”, and the remaining two items are “yes” or “no” questions asking about the difficulties in hearing and other problems that are not mentioned in the above questions. A higher score indicates a lower QOL. Exploratory factor analysis has shown that the 23 items of the FPHPQ comprise the following three factors: pain associated with heat or exertion (9 items), pain associated with cold (5 items), and abdominal pain and fatigue (9 items). The question numbers constituting each factor are shown in Table 1. The FPHPQ has been translated into Spanish, Swedish, English, Norwegian, French, Dutch, Italian, and German.

2.2. KINDL-R

The KINDL-R was used to perform criterion-associated validation of the FPHPQ. The KINDL-R questionnaire is a generic health-related QOL questionnaire for children and adolescents [14]. There are five versions of the KINDL-R. Three of the versions target children of ages 4 to 6, 7 to 13, and 14 to 17 years, and two of the versions are for the parents of children who are 3 to 6, and 7 to 17 years. KINDL-R consists of 24 items scored on a five-point Likert scale (never, seldom, sometimes, often, and all the time), except for the two infant versions, for children of ages 4 to 6 years and for the parents of children who are 3 to 6 years, which consist of 12 items. The KINDL-R has six subscales; i.e., physical well-being, emotional well-being, self-esteem, family, friends, and everyday functioning at school, nursery school, or kindergarten. The total score and subscale scores are converted to values between 0 and 100. A higher value means a higher QOL. For the two infant versions, as the number of items is small, the value of the subscales cannot be calculated, except for the total value. In the present study, the three self-report questionnaires were used.

Table 1
Composition of the factors of FPHPQ.

Factor	Name	Number of items	Question no.
1	Pain associated with heat or exertion	9	2a, 20, 22a, 22b, 22d, 23a, 23b, 23d, 26
2	Pain associated with cold	5	3a, 22c, 23c, 24 25
3	Abdominal pain and fatigue	9	2c, 3c, 5, 6, 7, 9, 10, 12, 13

See Ramaswami U (2012) [16] for the question text and factor structure of the FPHPQ.

2.3. Translation of the questionnaire

The FPHPQ was translated in accordance with the Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes [18]. The translation process consists of the following 10 steps: 1) preparation, 2) forward translation, 3) reconciliation, 4) back translation, 5) back translation review, 6) harmonization, 7) cognitive debriefing, 8) review of cognitive debriefing results and finalization, 9) proofreading, and 10) final report.

First, approval to translate the FPHPQ was obtained from Shire Human Genetic Therapies, Inc. Second, two researchers independently carried out the forward translation into Japanese. Then, the forward translation was discussed by the research team consisting of medical doctors and nurses, and reconciled into a single version. In the translation process, the opinions of patients with Fabry disease were incorporated as appropriate. Then, a translator (a native speaker of English) back-translated the reconciled translation into English. The back-translated version was reviewed twice by the original lead author of the FPHPQ to confirm the conceptual equivalence. Then, a pretest and a cognitive debriefing was performed to confirm the feasibility of the questionnaire. For the pretest, the translated FPHPQ was given to the patients or their parents when they visited the outpatient clinic, and was collected by mail. For cognitive debriefing, the patients or their parents wrote comments in the free text box after answering the pretest. Finally, the final version of the Japanese FPHPQ was established.

2.4. Subjects

For the pretest and cognitive debriefing of the Japanese version of the FPHPQ, subjects were recruited from the coauthor’s outpatients. For the actual survey using the final version of the questionnaire, patients were recruited through the Japan Registration System for Metabolic & Inherited Diseases, and the Family Association of Fabry disease patients.

2.5. Survey methods

The questionnaire package was distributed to the subjects by mail

and completed questionnaires were collected by mail. The questionnaire package contained the cover letter, the FPHPQ, the KINDL-R questionnaire, and the Brief Pain Inventory.

This study was conducted between May and September 2019.

2.6. Statistics

Descriptive statistics (mean and standard deviation) were performed. Owing to the limited number of subjects in this study, confirmatory factor analysis was not conducted to check the factor structure of the Japanese version of the FPHPQ. Therefore, the three factors of the original version of the FPHPQ were used for the present analysis [16]. Internal consistency was calculated for each factor and subscale separately using Cronbach's alpha coefficients. Correlations between FPHPQ score and KINDL-R values were analyzed for criterion-related validity.

P-values of less than 0.05 were considered to indicate a statistically significant difference between groups. Statistical analysis was performed using SPSS version 24.

2.7. Ethical considerations

This study was approved by Osaka University Clinical Research Review Committee. The document explaining the purpose of the study, the freedom of participation, and the protection of patient privacy was distributed to the patients in the questionnaire package. As the subjects were children, an informed assent document was also included. The subjects and parents were requested to check and fill out the consent forms for research cooperation, and to mail them back together with the questionnaire package.

3. Results

3.1. Pretest and cognitive debriefing

In this process, we asked four pediatric patients (three females and one male) to answer the Japanese version of the FPHPQ, to confirm whether there were any items that were difficult to understand. Of the collected questionnaires, there were only two unanswered questions (Question no.2d: "If you are in hot surroundings, do you experience other problems?" and no.3d: "If you are in cold surroundings, do you experience other problems?"), and all other items were answered. As these questions are additional questions, we determined that the lack of the answers were not a problem.

In addition, we received two comments. One was about item (Question no. 7: After eating, do you feel bloated or full?). The subject was unable to answer this question because the subject had only ever experienced being bloated. This was a problem associated with the Japanese expression of "or", which can also be interpreted as "and". However, the other subjects answered this question without any apparent difficulty. Therefore, after discussion, we modified the wording so that the meaning of "or" became clear.

Another opinion was about item (Question no. 15: Do you notice any ringing or buzzing noise in your ears?). The expression of "buzzing noise" was difficult to understand for one of the subjects. Our team tried to change the expression of the question by using the onomatopoeia. However, there are individual differences in how people hear the sound. Therefore, it was difficult to make major changes to the text from the original version of the FPHPQ while maintaining the equivalence of the scale translation, and hence we decided not to change the question text.

3.2. Survey results

We collected eight questionnaires, one for the 4 to 7 years version, two for the 8 to 12 years version, and five for the 13 to 18 years version of the FPHPQ.

The mean age of the subjects was 12.0 (± 3.59) years, and seven subjects were female (87.5%). The subjects included one male patient with the classical type and seven heterozygous female patients. Four of the subjects had received enzyme replacement therapy, and the other four subjects had not received any disease-specific treatment.

3.3. FPHPQ scores

The mean scores for each factor of the FPHPQ were 11.0 (± 11.43) for factor 1 (regarding pain associated with heat), 5.5 (± 4.60) for factor 2 (regarding pain associated with cold), and 14.8 (± 5.97) for factor 3 (regarding abdominal pain and fatigue). The Cronbach's alpha-coefficients were 0.956, 0.828, and 0.788 for factors 1, 2, and 3, respectively. (Table 2) The mean score of the severity of pain at the time of answering the questionnaire, using a 0 to 10 numeric rating scale was 1.3 (± 2.38). In terms of the number of episodes of the sudden onset of pain in the previous three months, four subjects had no experience and four had experienced pain between one to three times. Only one subject was absent from school for three days in the previous three months owing to being tired or unwell.

3.4. KINDL-R values

Six subjects answered the KINDL-R questionnaire together with the FPHPQ. One of them answered the infant version of the KINDL-R for children aged 4 to 6 years, and the other five answered the version targeting children older than 7 years. The total value of the infant version was 91.7, but the subscales of the infant version could not be calculated.

In the version of KINDL-R that targets children older than 7 years, the mean total value was 57.9 (± 8.51). The mean of the subscale values were 58.8 (± 39.18) for physical well-being, 68.8 (± 11.69) for emotional well-being, 42.5 (± 13.55) for self-esteem, 68.8 (±18.22) for family, 67.5 (± 10.27) for friends, and 41.3 (± 14.39) for everyday functioning at school, nursery school, or kindergarten. (Table 3).

3.5. Criterion-related validation of the FPHPQ

We calculated the correlation between the scores of the FPHPQ factors and the subscale values of the KINDL-R to analyze criterion-related validity. (Table 4).

A negative correlation between each FPHPQ factor score and total value of the KINDL-R was observed. There was also a significant negative correlation between factor 1 of the FPHPQ and physical well-being in the KINDL-R. In addition, the correlation between factor 2 of the FPHPQ and friends in KINDL-R was significantly positive.

4. Discussion

4.1. Number of subjects in this study

We were able to collect the data of eight pediatric patients with Fabry disease in this study. The number of patients with Fabry disease in Japan is estimated to be almost 1700 [19]. It has been reported that the mean age at diagnosis of Fabry disease is 22.3 years old for classic-type patients, and in the forties for late-onset and heterozygous female types [9]. Therefore, we expect that few patients are diagnosed during childhood. According to a report on the age distribution of Fabry disease

Table 2
FPHPQ scores of the patients in this study ($n = 8$).

Factor	Mean	Standard deviation	Cronbach's α coefficient	95% confidence interval
1	11.0	11.43	0.956	0.889–0.990
2	5.5	4.60	0.828	0.521–0.961
3	14.8	5.97	0.788	0.465–0.950

Table 3
Results of the kid version of the KINDL-R ($n = 5$).

Subscale	Mean	Standard deviation
Physical well-being	58.8	39.18
Emotional well-being	68.8	11.69
Self esteem	42.5	13.55
Family	68.8	18.22
Friends	67.5	10.27
Everyday functioning	41.3	14.39
Total score	57.9	8.51

Table 4
Spearman's correlation between FPHPQ and KINDL-R ($n = 5$).

Subscale of KINDL-R	FPHPQ		
	Factor 1	Factor 2	Factor 3
Physical well-being	−0.975*	−0.667	−0.718
Emotional well-being	−0.105	0.526	0.026
Self esteem	0.132	−0.263	−0.132
Family	−0.051	−0.359	0.462
Friends	0.730	0.973*	0.460
Everyday functioning	−0.026	−0.263	−0.684
Total score	−0.763	−0.526	−0.763

* $p < 0.05$.

patients in Japan, the number of patients under the age of 20 was 24, of which 18 were boys [20]. In the international collaboration study for the development of the FPHPQ, the number of pediatric patients in each country ranged from two to 24 [16]. Although the number of subjects in our present study was small for a quantitative study, it is acceptable because of the nature of the study being on pediatric patients with a rare disease.

4.2. Japanese FPHPQ

We translated the FPHPQ from English to Japanese according to the guidelines of the patient reported outcome scale [18]. We conducted the translation not only linguistically, but also in terms of culture background, to make the questionnaire easier to understand for patients. As a result, no major problems occurred in the cognitive debriefing, and we were able to create a Japanese version of the FPHPQ with high validity.

The Cronbach's alpha coefficients for each factor of the FPHPQ in this study were more than 0.75, using the same factor structure as in the original version [16]. However, for factors 2 and 3, the 95% confidence intervals of the alpha-coefficient were large. Therefore, the Japanese version of the FPHPQ appears to have partial internal consistency; however, this needs to be further confirmed by increasing the sample size.

The scores of factor 1 and factor 2 obtained in this study were similar to those of the original report [16]. Therefore, we think that the Japanese version of the FPHPQ is able to measure the same factors as the original version. However, a consensus interpretation of the scores and the cutoff points have not yet been obtained. This is because the number of pediatric patients with Fabry disease is small and sufficient information is still lacking. Therefore, we expect that the FPHPQ will be used in Japan in the future to collect data and to analyze the association between symptoms and treatment effects, which will enable more accurate interpretation of the factor scores.

In this study, the average score of factor 3 was 14.8. However, in the original article regarding the establishment of the FPHPQ, the average score of factor 3 was 3.5 [16]. Factor 3 is associated with abdominal symptoms and fatigue. A study on chronic fatigue syndrome demonstrated that the prevalence of chronic fatigue syndrome in the Japanese population was similar to that in Western countries [21]. Therefore, the high score of factor 3 in the present study may be owing to differences in the abdominal symptoms and fatigue experienced by Japanese patients with Fabry disease compared with patients from other countries. However, as this point remains unclear, it is necessary to analyze a larger number of patients in the future.

4.3. QOL of Japanese pediatric patients

The results of KINDL-R showed that the QOL of Japanese pediatric patients with Fabry disease was favorable in terms of their emotional well-being, family relationships, and friendships. On the other hand, the scores on the subscales of self-esteem and school were low. However, this is similar to the results of healthy Japanese children [22,23]. In previous studies, the QOL of pediatric patients with Fabry disease has been shown to be lower than our present study regarding family relationships, friendships, and physical function [11]. In these previous studies, the mean physical well-being value was more than 50, indicating that physical well-being may be favorable on the KINDL-R. However, another study assessing the QOL of pediatric Fabry patients has shown that they have a lower QOL than the general population owing to body pain and decreased mental health [24]. In this study, the standard deviation of the physical well-being value was much larger than the standard deviations of the other subscales, suggesting that there was substantial individual variation in patients' physical well-being. In other words, we were able to confirm that the physical well-being of patients is an important factor in estimating the QOL of pediatric patients with Fabry disease.

4.4. Criterion- related validity of the Japanese FPHPQ

We calculated the correlation between factors of the FPHPQ and the subscales of the KINDL-R, to confirm the criterion-related validity of the Japanese FPHPQ. The results demonstrated a significant negative correlation between factor 1 of the FPHPQ and physical well-being. This indicates that pain-associated heat causes lower physical well-being in pediatric patients, and suggests that the Japanese FPHPQ has partial criterion- related validity. On the other hand, there was a significantly positive correlation between factor 2 of the FPHPQ and the friend subscale of the KINDL-R. It is presumed that patients with many symptoms receive a large amount of help from their friends. However, we have not been able to obtain information to prove this hypothesis, and it is necessary to increase the sample size in future surveys and to analyze the correlations between factors of the FPHPQ and the friend subscale of the KINDL-R, including information about friendships. The article on the development of the FPHPQ also stated that the FPHPQ was significantly associated with physical well-being and social domains [16]. However, as the sample size was small in the present study, it is difficult to make any definite conclusions, and hence further analysis with a larger number of patients should be performed in the future.

4.5. Limitations

This Japanese version of the FPHPQ is the first health-related QOL scale established for pediatric Fabry disease patients in Japan. However, in this study, most of the subjects were female and the data for patients with the classic type of Fabry disease was limited. As this study was based on a questionnaire survey answered by pediatric patients or their family members, it was not possible to obtain information on the causative genetic mutations and disease subtypes of the patients. In the future, to utilize the Japanese version of the FPHPQ, it will be necessary to link it with medical information, as well as investigate the association between specific mutations and disease subtypes.

In addition, owing to the small number of patients, confirmation of the validity of the Japanese translation of the FPHPQ is required in the future. In particular, whether the Japanese version of the FPHPQ has the same factor structure as the other language versions should be confirmed. Japanese version of the FPHPQ is expected to be used in case studies and clinical trials of Japanese pediatric patients with Fabry

disease.

The original report on FPHPQ analyzed the associations among FPHPQ, Euro Qol 5 Dimension, and Brief Pain Inventory, but we did not obtain such data in the present study. This is owing to the fact that these scales have not been made applicable to younger children in Japan. Therefore, in future surveys, it will be necessary to confirm the validity of FPHPQ using alternative methods, such as by asking the patients' parents to answer these scales.

5. Conclusion

The Japanese version of the FPHPQ was adequately translated accordance with the Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes. This is the first disease-specific QOL scale for pediatric patients with Fabry disease in Japan. In the future, it will be necessary to analyze a larger number of samples and further analyze the validity of the Japanese version of the FPHPQ, for its use in clinical research.

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Declaration of Competing Interest

Yuta Koto, Yoko Lee, Nozomi Hadano, Wakana Yamashita, Chikara Kokubu and Norio Sakai declare that have no conflicts of interest in association with this study.

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