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A survey on the patient journey in Fabry disease in Japan

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ABSTRACT

Background: Fabry disease (FD) is a rare X-linked lysosomal storage disease caused by a deficiency in α-galactosidase that is frequently diagnosed late after disease onset. While previous studies have focused on the multisystem manifestations that can lead to delayed or incorrect diagnosis and management, none have investigated the entire patient journey, and few have examined the patient's disease experience.
Objective: To investigate the path to diagnosis from disease onset, and the impact of the disease on daily life, among individuals with FD in Japan.
Methods: A nationwide survey of patients with FD receiving enzyme replacement therapy (ERT) was conducted between March 27 and June 11, 2018. Participants were recruited via patient support groups or physicians. Respondents completed a questionnaire eliciting information on sociodemographic status, self-perceived health status, initial and current clinical manifestations, the process of diagnosis, and impact on their life. Responses were analyzed descriptively.
Results: Data from 40 respondents were analyzed (17 males and 23 females; 77.5% aged ≥30 years). Mean ERT duration was 7.7 years. Mean time from disease onset to diagnosis was 18.7 years (16.7 years [males] vs 20.3 years [females]). The final diagnosis was made most commonly by pediatricians (38%). Forty percent of respondents felt relieved and 30% felt anxious when diagnosed, and when initiating ERT, 48% felt more positive about their daily life. Nevertheless, 85% reported that treatment affected their lives/work, and most (73%) experienced difficulties in their relationships with others.
Conclusion: Efforts are needed to achieve early diagnosis of patients with FD in Japan, to improve clinician awareness, and improve the psychosocial issues associated with FD.

1. Introduction

Fabry disease (FD) is caused by a decrease in, or absence of, activity of α-galactosidase, one of the hydrolytic enzymes present in lysosomes [1]. This leads to the ubiquitous accumulation of its substrate, globotriaosylceramide, resulting in neurological (limb pain), cutaneous (angiokeratoma), renal (proteinuria, kidney failure), cardiovascular (cardiomyopathy, arrhythmia), cochleo-vestibular and cerebrovascular (transient ischemic attacks, strokes) complications. It is inherited in an X chromosome-linked manner, but heterozygous females can characteristically also develop the disease [1]. Patients with classic FD develop manifestations in childhood and those with other forms of FD, such as the cardiac or renal variants, in later adulthood (4th to 6th decade of life). Diagnosis is often delayed by a mean of ~4 years in children and ~15 years in adults [2]. This delay is due to the large variability in organ system involvement, wide variety of age at onset, and varying severity of its clinical manifestations [2]. Prior to definitive diagnosis with FD, individual manifestations are often attributed to other more common diseases (e.g., FD pain in childhood is frequently misdiagnosed as 'growing pains') [1], and misdiagnosis is common [3]. Common misdiagnoses include rheumatologic disease/rheumatic fever, arthritis, and neuropsychological disease [3].

Enzyme replacement therapy (ERT) has become the standard treatment for FD in Japan subsequent to approval of agalsidase β (Fabrazyme®, Sanofi Genzyme) in 2001.

FD has long been considered a rare disorder. However, the incidence of Fabry disease detected through newborn screening programs, for example in Japan (~1 in 6212 newborn males [4]), Taiwan (~1 in 1250 [5]) and Italy (1 in ~4600 [6]), is much higher than previously reported, which suggests that the disease prevalence was previously

Abbreviations: ERT, enzyme replacement therapy; FD, Fabry disease; FOS, Fabry Outcome Survey; GLA, galactosidase α; QOL, quality of life.

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underestimated. With the availability of diagnostic testing and effective therapies, early diagnosis and prompt treatment of FD have become even more important to limit the chronic disease burden and improve patient quality of life (QoL).

In order to address the issue of how to diagnose FD early and initiate effective treatment while also optimizing QoL, it is necessary to understand the real-life experiences of patients with FD, of which there is only limited insight in Japan. The objectives of this research survey were to extract the disease history of, and challenges experienced by, Japanese patients with FD from the time of their first manifestations (i.e., signs and symptoms) to their diagnosis, as well as to characterize the psychosocial challenges they experience when receiving ERT.

2. Materials and methods

This was a questionnaire-based survey conducted between March 27, 2018, and June 11, 2018. The questionnaire formed the quantitative component of a broader survey that included qualitative research; the current report includes only the quantitative component. Some quantitative questions had a qualitative component, for example, where an open-ended explanatory response could be provided. The recruitment target was ~20 patients.

2.1. Patient inclusion criteria and recruitment

Patients currently treated with ERT after a definitive diagnosis of FD were recruited through patient support groups or via their treating physician. There were no exclusion criteria.

Potential participants received a letter clearly stating the purpose of the research and that it was conducted at the request of a pharmaceutical company (a copy of the translated letter is provided in the online Supplementary Appendix). Completion of the questionnaire was taken as consent (i.e., respondents did not give explicit written consent to participate in the study). The questionnaire was anonymous and no personal information that could lead to personal identification was collected. This study was conducted appropriately in accordance with the domestic Ethical Guidelines for Medical Research Involving Human Subjects and Ethical Guidelines for Human Genome and Genetic Analysis Research.

2.2. Survey questionnaire

The questionnaire was developed by Macromill CareNet, Inc., Japan, to be appropriate for the Japanese situation and suitable for this research. This questionnaire was not validated against medical records, instruments used in other studies, or other documents.

The questionnaire items included sociodemographic questions, self-perceived health status, clinical manifestations, challenges in daily life, manifestations that first raised suspicion about the presence of a rare disease and the process of diagnosis (see the online Supplementary Appendix for a copy of the translated questionnaire). Most questions were closed questions with specific response options. Patients returned the questionnaire by post.

2.3. Data extraction and analysis

Macromill CareNet, Inc., Japan, acted on behalf of Sanofi K.K. to design and distribute the questionnaires to FD patient groups and physicians, and to collect completed questionnaires and analyze the data. Individual participant responses were later shared with the authors, and the analysis was double-checked by the authors against both the raw data and the research report provided by Macromill CareNet, Inc.

2.4. Statistical analysis

Analysis of the answers for each question excluded any respondents who had not provided an answer, and as such, the total number of included respondents could vary between questions. Data were analyzed using descriptive statistics. Proportional values, measures of central tendency, and corresponding measures of variance were calculated using Excel and IBM® SPSS® Statistics version 26.

3. Results

3.1. Respondent characteristics

Forty respondents with FD treated with ERT were recruited and submitted completed/semi-completed questionnaires. Respondent demographic characteristics at the time of the survey are shown in Table 1. Seventeen respondents were male and 23 were female. The majority of respondents (77.5%) were aged ≥30 years; none were very elderly (aged ≥70 years) and only one (2.5%) was of pediatric/adolescent age.

3.2. Disease onset to diagnosis

The mean age at which manifestations first appeared was 13.7 years (median 10 years). By 12 years of age, 70% of respondents had experienced their first manifestations (32% aged 0–6 years and 38% aged 7–12 years; Fig. 1A). The mean and median ages of first manifestations were 10.8 and 8.0 years, respectively, for males and longer for females at 15.9 and 11.0 years, respectively (Fig. 1B and C). Based on the age at disease onset, 81% of patients had the classic form of FD and 19% had late-onset FD.

The mean age at which respondents received a definitive diagnosis of FD was 32.0 years, with most aged either 30–39 years, 40–49 or 50–59 years (Fig. 1A). The age of a confirmed diagnosis was numerically earlier for males than females, with a mean and median age of 26.1 and 21.0 years, respectively, for males and 36.4 and 38.0 years, respectively, for females (Fig. 1B and C).

The mean time from the disease onset to definitive diagnosis was 18.7 years. The mean and median time from disease onset to diagnosis were numerically shorter for males than females (16.7 and 11.0 years for males and 20.3 and 15.0 years for females, respectively). At the time of their diagnosis, 40% of patients (47% of males and 35% of females) said they had felt relieved receiving a definitive diagnosis, whereas 30% (24% of males and 35% of females) said they had felt anxious when their diagnosis was confirmed.

The time from disease onset to diagnosis of FD, presented in 5-year-duration intervals is presented for all respondents in Fig. 2A, and by sex in Fig. 2B and C.

Table 1
Respondent demographic and clinical characteristics.

Characteristic, *n* (%)		Patients (*n* = 40)
Age category, years	10–19	1 (2.5)
	20–29	8 (20)
	30–39	9 (22.5)
	40–49	8 (20)
	50–59	10 (25)
	60–69	4 (10)
	≥70	0
Sex	Female	23 (57.5)
	Male	17 (42.5)
Current occupation	Student	1 (2.5)
	Company employees, public servants, and organization employees	15 (37.5)
	Self-employed or free enterprise	2 (5)
	Stay-at-home mom and stay-at-home dad	6 (15)
	Part-time	12 (30)
	Unemployed	4 (10)
	Other	0
Duration of ERT, years	Mean (SD)	7.7 (4.8)
	Median (range)	7.5 (0–19)

ERT = enzyme replacement therapy, SD = standard deviation.

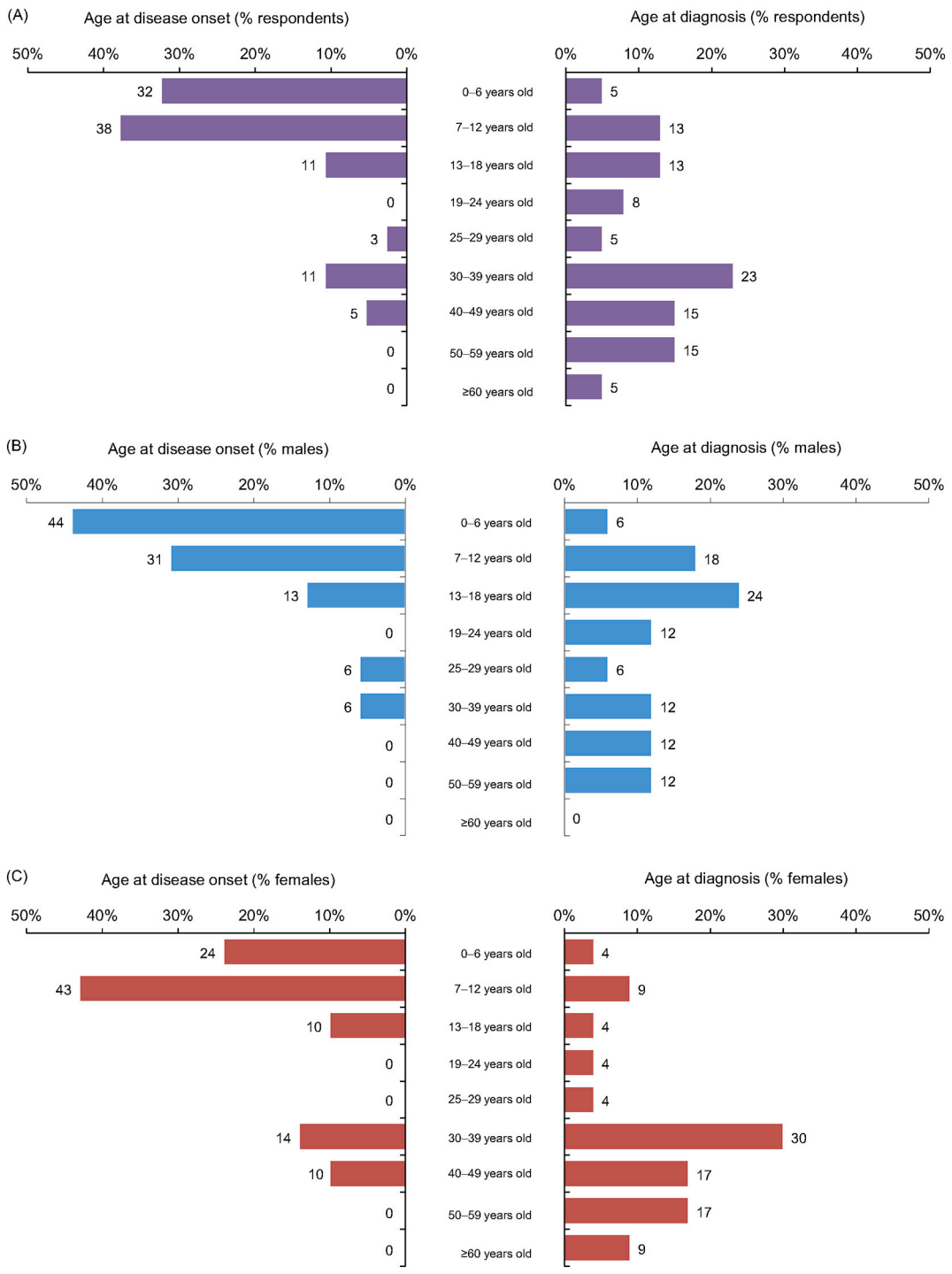

Fig. 1. Age at disease onset and age at diagnosis of Fabry disease, (A) in the overall population ($n = 37$ and $n = 40$, respectively), (B) in males ($n = 16$ and $n = 17$, respectively), and (C) in females ($n = 21$ and $n = 23$, respectively).

3.3. Manifestations of Fabry disease

The most common initial manifestations were limb pain (76% of respondents), an inability to sweat or difficulty in sweating (49%), and fatigue (41%), and the most common current manifestations included cardiac function-related manifestations (63%), fatigue (58%), limb pain (55%), and neurologic manifestations (53%). Initial and current manifestations shown separately for each sex are presented in Fig. 3.

When respondents first developed manifestations, 51% went to a hospital (47% of males and 55% of females) and 43% went to a doctor's office/clinic (47% of males and 40% of females). They were most commonly seen at a pediatric department (34% of respondents; 47% of males and 25% of females), followed by departments of general internal medicine (23% overall; 20% of males and 25% of females) and cardiology (14% overall; 20% of males and 10% of females) (Supplementary Fig. S1).

On average, respondents visited 2.3 facilities (medical institutions) and 2.4 specialties before receiving their diagnosis of FD; 5% (all female) visited more than five medical facilities and 11% (19% of males and 5% of females) required the involvement of more than five medical specialties before a diagnosis was made (Fig. 4). The majority of respondents (98%) received their diagnosis at a large medical institution

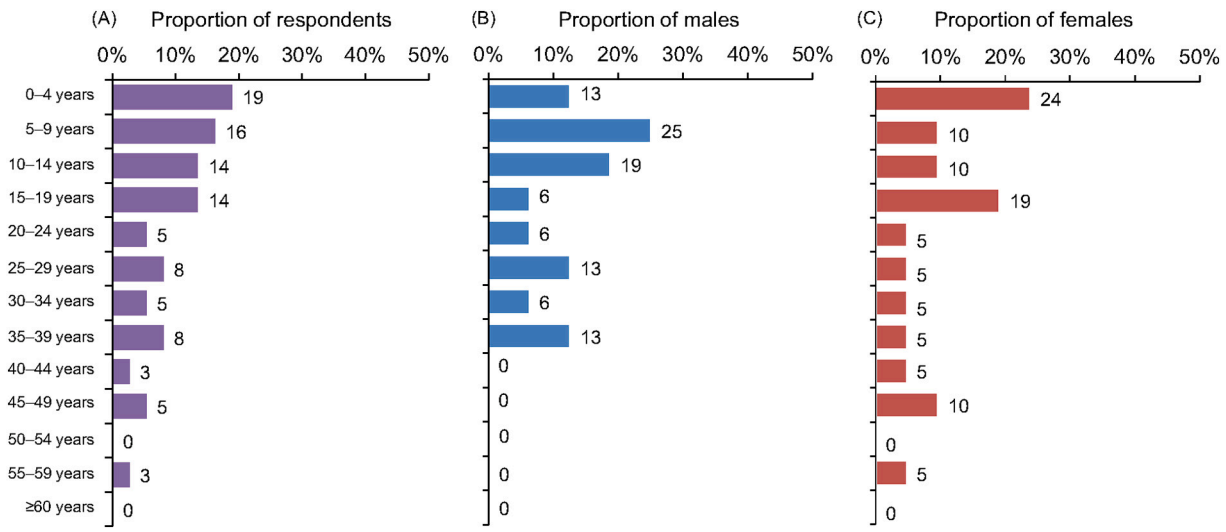

Fig. 2. Time from disease onset to diagnosis of Fabry disease, (A) in the overall population ($n = 37$), (B) in males ($n = 16$), and (C) in females ($n = 21$).

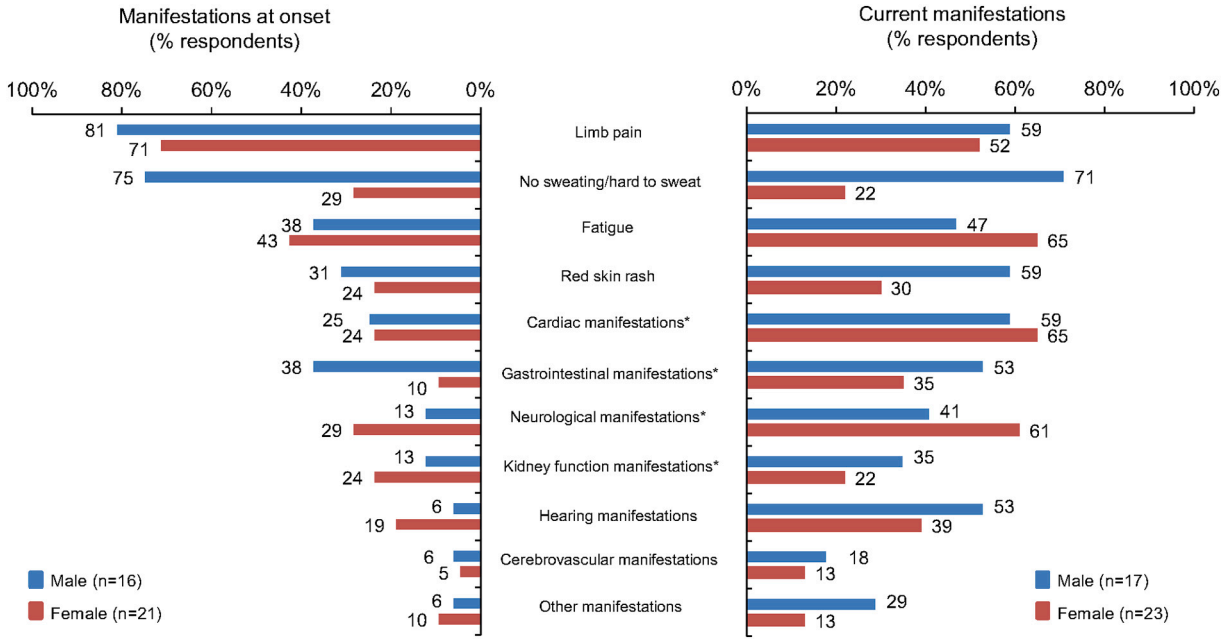

Fig. 3. Initial and current manifestations of Fabry disease ($n = 37$ and $n = 40$, respectively), shown by sex (males, $n = 16$ and $n = 17$, respectively; females, $n = 21$ and $n = 23$, respectively). Terminology used is the same as that used in the questionnaire. *Cardiac manifestations included: left ventricular hypertrophy; gastrointestinal manifestations included: postprandial stomach pain, diarrhea, vomiting and nausea; neurologic manifestations included: dizziness, headache and numbness; kidney function manifestations included proteinuria.

(100% of males and 96% of females). Diagnosis was made most commonly at a pediatrics department (38% of respondents; 41% of males and 35% of females), followed by cardiology (18% overall; 12% of males and 22% of females) or nephrology (15% overall; 24% of males and 9% of females; Fig. 5).

3.4. Living with Fabry disease

All respondents were undergoing ERT at the time of study recruitment. The mean duration of treatment was 7.7 years (9.1 years in males and 6.6 years in females) and the median duration 7.5 years (8 years in males and 6 years in females).

Prior to first attending a hospital for FD, the majority of respondents described their FD-related manifestations as having an impact or a great impact on their life (63% overall; 76% of males and 52% of females; Supplementary Fig. S2). Forty-eight percent of the respondents (53% of males and 43% of females) felt positive or very positive about their daily life and future after the initiation of treatment, while 23% felt more anxious (18% of males and 26% of females; Fig. 6).

The majority of respondents (85%; 88% of males and 83% of females) said that their lives and work were affected by undergoing treatment for FD (Supplementary Fig. S3). However, 28% of respondents (47% of males and 13% of females) became capable of engaging in normal activities after starting ERT for FD; when asked to name these activities, respondents listed schoolwork, work, exercise and travel (data not shown).

Overall, 65% of respondents (82% of males and 52% of females) agreed that FD restricted them in their daily life (35% [18% of males and 48% of females] reported no limitations to their daily life). They described limitations due to FD impacting their studies, work, physical

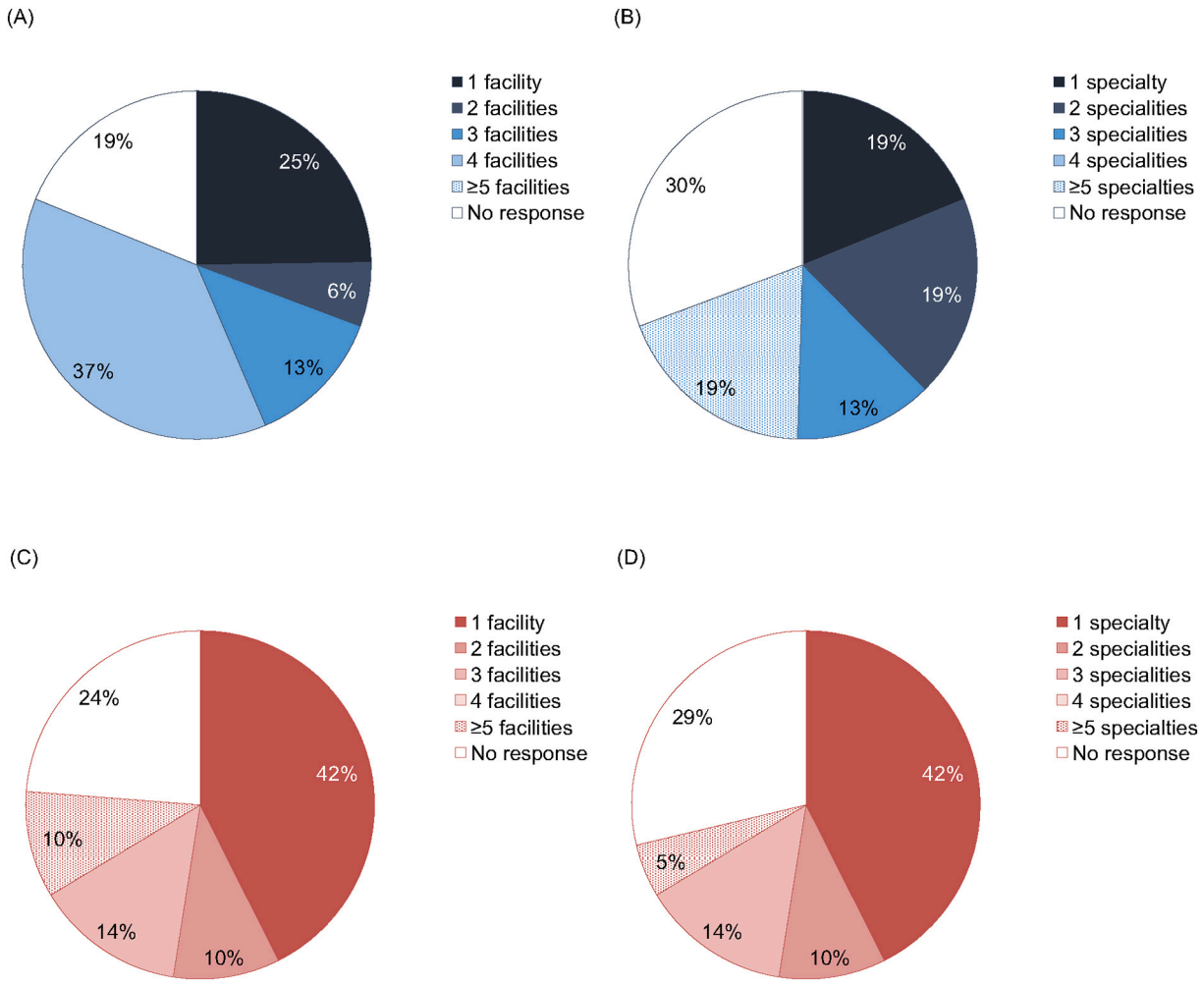

Fig. 4. Number of (A) medical facilities and (B) specialties visited by males ($n = 16$), and (C) medical facilities and (D) specialties visited by females ($n = 21$), before receiving a diagnosis of Fabry disease.

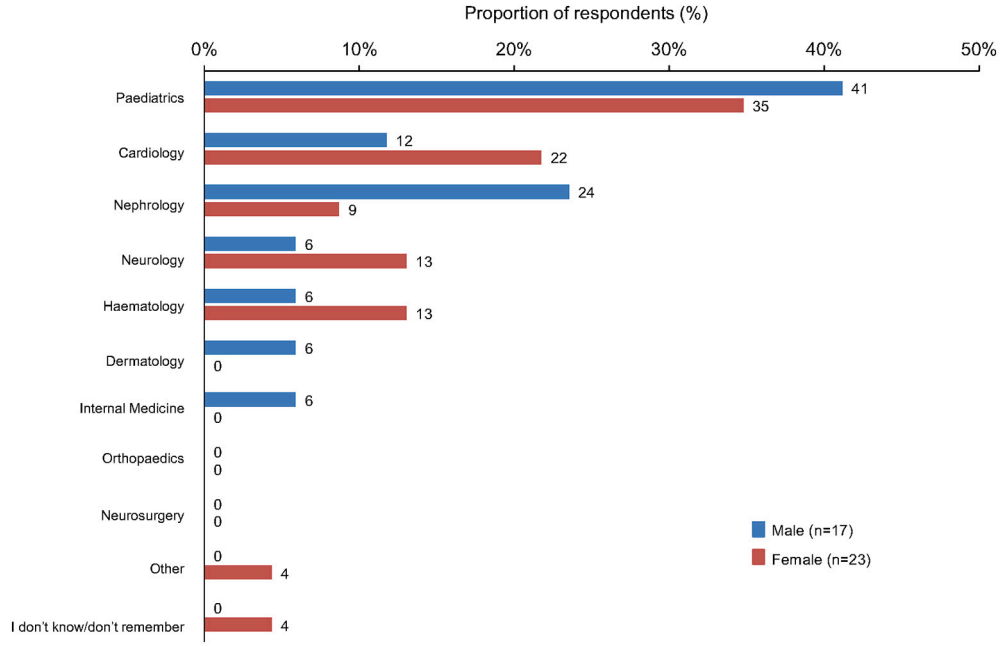

Fig. 5. Medical department at which respondents received their definitive diagnosis of Fabry disease ($n = 40$).

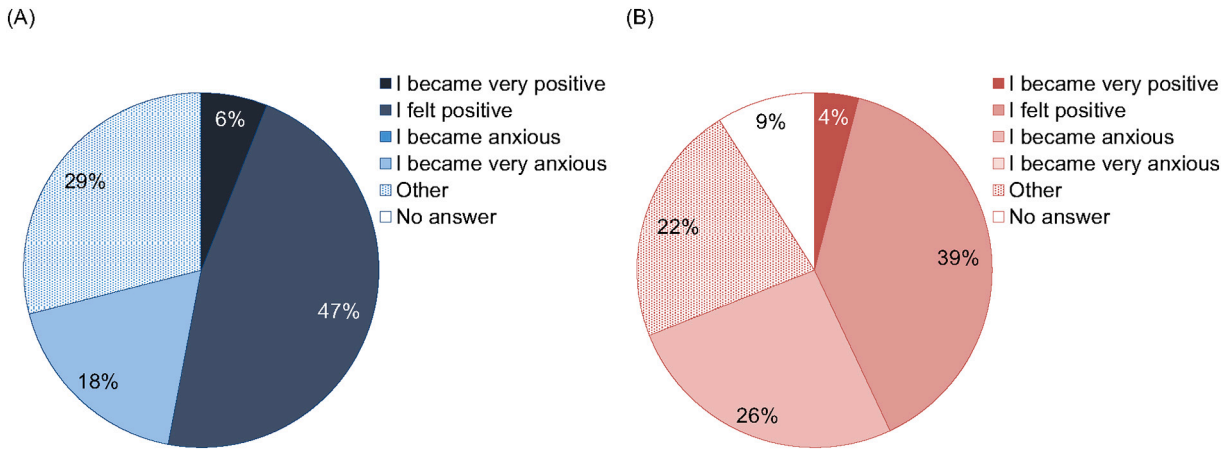

Fig. 6. Change (if any) in (A) male (n = 17) and (B) female (n = 23) respondents' feelings/mood after starting treatment for Fabry disease.

education/exercise, and travel and other excursions (data not shown).

Sixty-five percent of respondents had told people outside their immediate family (distant relatives/friends/work colleagues/school) about their disease, with a similar proportion of males and females disclosing their diagnosis (Supplementary Fig. S4). Most patients (73%; 65% of males and 78% of females) had experienced difficulties in their relationships with those around them, and 48% (65% of males and 35% of females) stated that FD had affected their life events, such as marriage or childbirth.

3.5. Methods of information gathering

The majority of the respondents (85%; 82% of males and 87% of females) claimed they had done research on FD. The most common research medium was the internet (88% of respondents). Most (95% overall; 94% of males and 96% of females) answered that they had received an explanation of FD from their physician (Supplementary Fig. S5A), and the majority (88%; 82% of males and 91% of females) claimed to understand the explanation from their doctor, but only 13% (6% of males and 17% of females) answered that they understood their disease very well (Supplementary Fig. S5B).

4. Discussion

This survey of 40 Japanese patients undergoing ERT for FD is the first study of its kind in Japanese individuals. The survey population represents 9% of the 462 patients with FD in Japan (2019 data from the Fabry Outcome Survey [FOS], a worldwide registry of FD patients) [7], and highlights a significant opportunity for improvement in the diagnosis and care of individuals with FD in Japan.

The mean delay in diagnosis of FD in our respondents was 16.7 years in males and 20.3 years in females, which is numerically longer (especially in females) than the delay reported from the FOS (14.7 and 15.1 years, respectively) [2]. The longer delay in females is not unexpected given the later disease onset in this population, and the different presentation in females who frequently lack the classical manifestations of neuropathic pain (limb pain), angiokeratomas and/or cornea verticillata, and who express some residual normal enzyme activity [8].

Diagnostic delay is a significant clinical concern because the cardiovascular, cerebrovascular and renal complications of FD continue to progress as long as the condition remains untreated [9], leading ultimately to premature death [10]. Early initiation of appropriate treatment may help to prevent or delay organ damage [8].

About one-half of respondents (51%) in our survey visited a hospital at the first disease manifestations (pain in hands and feet and/or no sweat), yet the diagnosis of FD was ultimately made much later, usually at a large hospital (98% of respondents), and only after many years of visiting multiple medical facilities/institutions. In this respect, our data are consistent with a previous report from Germany showing that hospital-based physicians are most likely to make the FD diagnosis [11]. Since pediatricians were the most common medical specialists to diagnose respondents in our survey, followed by cardiologists and nephrologists, our results suggest that an increased awareness of FD is needed across multiple medical specialties, particularly for adults with manifestations.

There is some evidence from the global FOS study (n = 598) that FD awareness has improved over time: the proportion of patients diagnosed by geneticists, general practitioners, pediatricians and internists collectively significantly increased between pre-2006 and 2007–2013 (from 18.9% to 39.6%, $p < 0.001$), approaching the levels of diagnosis made by cardiologists, nephrologists and neurologists (~41.6% in 2007–2013) [2]. However, our results suggest that the education and training of Japanese physicians – hospital- or clinic-based specialists and general practitioners – needs to be improved. Specifically, clinicians need to have a high degree of clinical suspicion when patients present with any of the common/clinically characteristic FD manifestations. Further, physicians should be able to test for FD or easily refer the patient to a specialty center for testing. Recent data from Japan demonstrate the feasibility of screening high-risk individuals (i.e., those with neurologic, cardiac, or renal disease during adolescence or adulthood), first by measuring α-galactosidase levels and then, depending on the results, by *GLA* gene testing, in order to reduce diagnostic delays [12].

The risk of misdiagnosis is a serious problem for patients with FD, reportedly occurring in up to 25% of patients [3], leading to incorrect, ineffective or unnecessary treatment [11], when there are now effective treatments available (ERT or the newer pharmacologic chaperone therapies). Systematic reviews confirm that ERT reduces the decline in glomerular filtration rate, improves cardiac outcomes, and may improve nervous system, gastrointestinal, and pain manifestations, as well as QoL, in male patients [13], cardiac outcomes and QoL in female patients [14], and neuropathic pain and gastrointestinal manifestations and QoL in pediatric patients [15].

Further important aspects of the diagnosis and initial management of a patient with FD include access to genetic testing, counselling and support, and provision of appropriate information to the patient and their family [16,17]. If patients are to receive ERT, it is important that they have a full understanding of the rationale and the process involved, because it requires biweekly injections. Unfortunately, in Japan, patient consultation time is frequently short, and genetic counselling is not readily available.

The survey investigated the emotional status of patients. Upon diagnosis, 40% of respondents felt relief, but at the same time, a considerable proportion (30%) felt anxiety. Approximately half of patients (48%) felt positive or very positive after starting ERT, but 23%

became anxious. Interestingly, our study found that, while men reported a higher impact of FD on their lives, more women than men felt anxiety about their diagnosis and about ERT. Our findings are consistent with previous studies. An in-depth qualitative study of female patients with FD by von der Lippe and colleagues reported that, upon diagnosis, patients commonly experienced relief in getting an explanation for their previously unexplained manifestations, and a component of that relief was having doctors finally recognize their manifestations as being related to their diagnosis [18]. Mengel and colleagues reported that more patients rated their health as satisfactory or better after their final diagnosis compared with before, attributed by the authors to patients feeling that they had been taken seriously and that diagnosis provides the opportunity for effective treatment [11]. However, the von der Lippe et al. study also reported that some female patients felt distress on diagnosis, or even both relief and distress [18]. This signals the importance of providing psychosocial support for patients with rare diseases [19].

Many respondents (65%) reported that living with FD had an impact or great impact on their daily life, affecting important life-events, such as marriage or childbirth (48%), and complicating their relationships with others (73%). Rare diseases are often stigmatizing, limiting patients' ability to participate in social roles and activities and hampering their relationships with others because of a lack of understanding [19]. Patients may therefore find it difficult to disclose their disease and manifestations to others. Encouragingly, 98% of respondents in our survey shared their condition with their immediate family, although fewer (63–68%) told people outside their immediate family about their disease. The X-linked inheritance of FD imposes an additional burden on mothers with FD, who often feel guilt or fear about the possibility of passing the disease onto their children [18]. Our results underscore the importance of FD patients being able to openly share their concerns and discuss their manifestations, and to access genetic counselling and mental health support.

A number of limitations in the design and conduct of this research should be acknowledged. We did not use validated disease-specific questionnaires in the assessment of manifestations or QoL. As with any other survey, the results may be affected by recruitment bias, recall bias, and by the respondents' understanding/interpretation of the questions. Despite these limitations, this is the first survey of its kind in Japanese patients with FD and offers valuable insights into the patient experience in their diagnostic and therapeutic journey.

5. Conclusion

This is the first published report of the patient journey in individuals with FD in Japan. Respondents reported considerable diagnostic delays, and despite an improved mental outlook after starting treatment, many continue to experience psychosocial challenges and daily life limitations despite receiving ERT. Our results highlight the need in Japan for earlier diagnosis and specific treatment of FD and increased awareness and understanding of this disease among medical professionals and society, as well as studies using validated instruments to investigate the relationship between disease severity and health-related QoL.

Role of the funding source

This work was supported by Sanofi K.K. and conducted by Macromill CareNet Inc., Japan. Sanofi K.K. was involved throughout the study and in the preparation of this manuscript as two study authors who are employees of Sanofi K.K. (MT and AO, see below) contributed to the conceptualization, methodology, validation, data acquisition and interpretation, and the reviewing and editing of the manuscript.

Data statement

All data generated from this study are available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Mina Tsurumi: Methodology, Validation, Writing – review & editing. **Asuka Ozaki:** Conceptualization, Methodology, Validation, Writing – review & editing. **Yoshikatsu Eto:** Methodology, Writing – review & editing.

Declaration of Competing Interest

Mina Tsurumi and Asuka Ozaki are employees of Sanofi. Yoshikatsu Eto has received research grants and honoraria from BioMarin Pharmaceutical Inc., Alexion Pharmaceutical Inc., Sanofi Genzyme and Actelion Pharmaceuticals Ltd., and honoraria from Dainippon Sumitomo Inc., Japan Chemical Research and Shire Japan.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgmr.2022.100909.

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