Comparison of health-related quality of life between heterozygous women with Fabry disease, a healthy control population, and patients with other chronic disease

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Purpose: Fabry disease is an X-linked lysosomal disorder due to mutations in the GLA gene. Manifestations of the disease are documented in hemizygous males. Recent studies have indicated that women with GLA mutations may report symptoms. The impact on their health-related quality of life is unclear. This study compares the quality of life of obligate heterozygotes to a historical healthy control population and to populations with multiple sclerosis and rheumatoid arthritis. **Methods:** The RAND-36 and Fabry-disease specific questions were administered to study participants. Study subjects were obligate heterozygotes for mutations in GLA. Mean scores in each of the subscales from the RAND-36 were compared between study subjects and previously published data from the Women's Health Initiative and studies on multiple sclerosis and rheumatoid arthritis. **Results:** Comparisons between 202 study participants and the Women's Health Initiative indicated that all eight subscale scores of the RAND-36 were significantly lower for women with Fabry disease ($P < 0.0001$). The mean scores of the study participants more closely resembled the mean scores of the participants in the multiple sclerosis and rheumatoid arthritis studies. **Conclusion:** Study participants reported clinically important effects on health-related quality of life. It is critical to develop management protocols for this population. ***Genet Med* 2006:8(6):346–353.**

Key Words: *Fabry disease, women, heterozygote, health-related quality of life, RAND-36*

Fabry disease is an X-linked lysosomal storage disorder caused by mutations in the GLA gene. This leads to deficiency of the enzyme α-galactosidase A (α-gal A) which causes buildup of glycosphingolipids in the lysosomes of cells.[1] Manifestations of the disease have been well-documented in hemizygous males and include acroparesthesias, pain crises, angiokeratomas, hypohidrosis, and exercise intolerance.[1] The main causes of mortality in affected men (renal, cardiac, and cerebrovascular disease) develop with increasing age.[1]

Studies have found that men with Fabry disease have a significantly poorer quality of life than men of the general population and that health-related quality of life (HRQoL) scores of men with Fabry disease were similar to men affected with AIDS.[2,3]

Heterozygous females have also been reported to have signs and symptoms of Fabry disease. However, until recently the medical community has considered the majority of women heterozygous for Fabry disease to be asymptomatic.[1] Many of the signs and symptoms of Fabry disease are nonspecific (e.g., fatigue, pain, heart disease) and may overlap with other common diseases. Recent studies indicate that these women have many symptoms similar to those of men with Fabry disease and that a higher proportion of women may be symptomatic than previously recognized.[4–9]

The great variability in expression of Fabry disease among heterozygous women is not well understood. Random X inactivation is one explanation for such variability; however, undiscovered genetic and environmental factors are also likely to influence the expression of Fabry disease in heterozygotes.

The purpose of this study was to assess the health-related quality of life (HRQoL) of obligate heterozygotes and to compare them to previously published findings in a healthy historical control population and cohorts with other chronic diseases. We hypothesized that HRQoL would be generally poorer in obligate heterozygotes when compared to healthy controls.

MATERIALS AND METHODS

Participating centers

The Fabry Support and Information Group (FSIG), an online support group for families and those affected with Fabry disease, was contacted for participation of its members in the

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study. Several Lysosomal Disease Centers in the United States also sent the questionnaire to their patients. Approval for the study was obtained from the Cincinnati Children's Hospital Medical Center institutional review board and at the individual centers that participated.

Study subjects

Women heterozygous for Fabry disease were eligible for study inclusion. A woman was considered an obligate heterozygote if she was the mother of two or more affected males, the mother of one affected male with another affected blood relative, or the daughter of an affected male. Women with a clinical diagnosis of Fabry disease and/or those who had been identified through mutation analysis of the α-galactosidase-A gene or demonstration of deficient enzyme activity were also eligible.

The questionnaire

The study questionnaire consisted of the RAND 36-Item Health Survey questionnaire and a Fabry disease-specific questionnaire of our own design.[10] The RAND-36 is a validated tool used in a number of studies to assess quality of life in the general population and populations with a variety of chronic diseases.[11–13] It consists of 8 HRQoL domains: physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain, and general health.[10] Each domain represents a different aspect of health status and a separate question also measures perceived health changes.[10] The RAND-36 was developed to assess the physical, mental, and social aspects of HRQoL. Items in each domain are scored so that higher scores represent better health (100 being the best) and lower scores poorer health (0 being the worst). Calculating the mean scores of the items in each domain gives a subscale score between 0 and 100.[10] The Fabry-specific questionnaire was designed to assess the type, frequency, and severity of several disease manifestations common to those affected by Fabry disease. Health care professionals familiar with lysosomal storage diseases reviewed the study tool. As an incentive to complete the questionnaire, each subject had the option to fill out an additional form with her name and address that would enter her into a raffle. All personal identifiers remained confidential and were shredded after the raffle drawing.

Distribution of the questionnaire

Participating centers forwarded the survey to their female patients and to females who were obligate heterozygotes because of their relation to affected male patients. A fact sheet explaining the details of the study was attached to each survey. Consent to participate was implied if the subject returned the completed survey.

The FSIG posted a message containing information about filling out the questionnaire on their website and a link to an electronic version of the questionnaire that could be completed online was provided on the group's home page. In addition, 650 paper copies of the survey were sent to the FSIG for distribution to their members. Questionnaires were sent to all families on the FSIG member list whether or not there were female family members listed as having Fabry disease.

Questionnaires were distributed in the spring and summer of 2004. The electronic version of the questionnaire was online from May–August, 2004.

Data analysis

Data were entered into a database in Microsoft Excel and analyses were performed using SAS, version 8.02 (SAS Institute, Cary, NC). The RAND-36 data obtained from subjects was compared to HRQoL data available through studies of the Women's Health Initiative.[11] In addition, we compared our results to studies published on multiple sclerosis and rheumatoid arthritis.[12,13] Group-level statistical analyses were performed since individual observations for those studies were not available. We used Student's *t*-test to evaluate for statistical differences between the mean scores of the 8 HRQoL domains of the RAND-36 between study subjects with Fabry disease and each comparison group. $P < 0.05$ was considered statistically significant. There is currently no gold standard by which clinical relevance of HRQoL scores can be determined, but methods have been developed to estimate a minimal clinically important difference in HRQoL scores. Clinically important differences (CID) were inferred by estimating effect sizes.[14] As previously described by others, an effect size of $\geq$0.80 indicates a large difference, an effect size of 0.50–0.79 indicates a moderate difference, and an effect size of 0.20–0.49 indicates a small HRQoL difference between groups $[(\text{mean}_{\text{WHI}} - \text{mean}_{\text{Fab}})/ \text{SD}_{\text{WHI}}]$ where WHI indicates the scores from the Women's Health Initiative and Fab indicates the scores of the study participants.[14] A negative sign by a CID indicates that the HRQoL subscale for the comparison group is lower than for the study subjects with Fabry disease.

In the Fabry-specific portion of the questionnaire, women were asked to document the presence, frequency, and severity of several general health problems that are often part of Fabry disease. To estimate the proportion of subjects who have symptoms of Fabry disease that impact HRQoL, we established criteria to separate women who experience symptoms that may lower HRQoL from women who do not have symptoms that impact HRQoL. Subjects who did not have pain, vertigo, GI problems, hypohidrosis, or heat/cold intolerance more than a few times per month and who had no cerebrovascular, cardiac, or renal health problems were considered to be asymptomatic. Furthermore, we used *t*-tests to compare the HRQoL of participants reporting specific symptoms with participants who did not report the symptoms for each of the following symptoms: acroparesthesia, nausea/vomiting, diarrhea/frequent bowel movements, transient ischemia attacks (TIA), stroke, left ventricular hypertrophy (LVH), arrhythmia, valve abnormalities, heart failure, proteinuria, renal insufficiency, and renal failure. We evaluated the statistical difference in means for each HRQoL subscale. $P < 0.05$ indicated statistical significance.

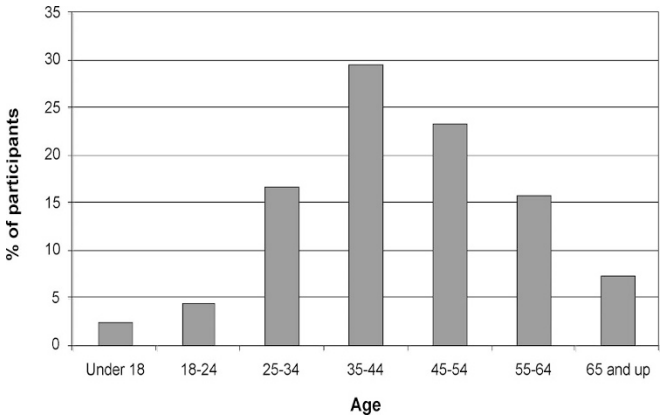

Fig. 1. Age range of Fabry study participants.

Comparison populations

Population One: Data for healthy women controls were obtained from the Women's Health Initiative (WHI), a large prospective study of postmenopausal women with the goal of identifying approaches to disease prevention, health behaviors, and disease predictors. In the estrogen/progestin study, 16,608 postmenopausal women between the ages of 50 and 79 years of age participated in a randomized, double-blind, placebo-controlled trial assessing the use of estrogen plus progestin and its impact on quality of life.[11] We used RAND-36 HRQoL scores from the placebo group of 8,102 women. Using a large historical control population greatly increased the power to detect differences in HRQoL between healthy women and study subjects.

Population Two: Both men and women with multiple sclerosis (MS) were participants in the study evaluating quality of life of patients with MS using the RAND-36. Subjects included 179 adult patients who represented a spectrum of disease severity.[12] The mean duration of disease was 9 years with a range of 1–40 years. Seventy-two percent of subjects were women. Mean age of the group was 45 years with a range of 20–67 years.

Population Three: A study of 679 patients with rheumatoid arthritis (RA) that used the RAND-36 was also used as a comparison group.[13] Seventy-one percent of subjects were women. Mean (SD) age of the subjects was 59.6 (13.8) years.

RESULTS

Demographics

A total of 226 surveys were received. Fourteen of the questionnaires filled out by women did not meet criteria for inclusion due to uncertainty in their Fabry heterozygote status. Ten questionnaires completed by men were excluded. The number of surveys analyzed was 202. Greater than 90% of participants provided their name and address for entry into the raffle.

Individuals identified through lysosomal disease centers returned fifty surveys. FSIG members completed 52 electronic and 100 written surveys. The majority of participants were from the United States while less than five questionnaires came from Canada and the United Kingdom. Figure 1 represents the age range of participants with both the mean and median age in the range of 35–44 years.

Health-related quality of life scores

The differences in the mean scores between the study subjects and each comparison group are shown for each HRQoL domain in Figure 2.

Comparisons between our study population and WHI cohort indicated that all eight domains of HRQoL were significantly

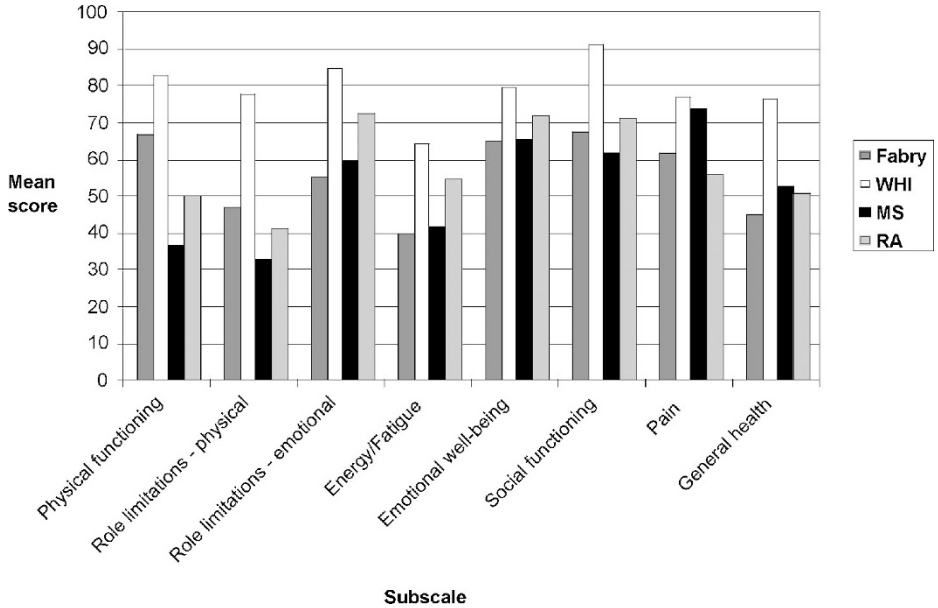

Fig. 2. Comparison of RAND-36 mean subscale scores between study subjects heterozygous for Fabry disease, the control group of the Women's Health Initiative (WHI), the group with multiple sclerosis (MS), and the group with rheumatoid arthritis (RA).

lower for women with Fabry disease ($P < 0.0001$; Table 1, Fig. 2). Moreover, when examining for clinically important differences, there was a moderate difference in score on the pain subscale, and large differences on the other seven subscales.

When compared to patients with Fabry disease, the patients with MS had significantly lower scores for physical functioning, role limitations due to physical health, and social functioning (Table 2, Fig. 2). Differences between the two groups were also clinically important in those domains – there was a large difference in physical functioning scores and a small difference in role limitations due to physical health and social functioning. Comparisons of patients with Fabry disease and MS did not reveal statistical or clinically important differences in emotional well-being, role limitations due to emotional health, or energy/fatigue. Subjects with Fabry disease scored significantly lower on the pain subscale and general health subscale than patients with MS. Clinically important differences between the two groups were small for those domains.

Table 3 shows comparisons between subjects with Fabry disease and patients with RA (Fig. 2). Patients with RA scored lower on the physical functioning and pain subscales. Clinical differences in these categories were moderate and small respectively. Subjects with Fabry disease had significantly lower scores than the patients with RA in the emotional well-being, role limitations due to emotional health, energy/fatigue, and general health domains. Clinically important differences for these domains were moderate for energy/fatigue and small for the other domains. Scores on role limitations due to physical functioning and social functioning were not statistically different between patients with Fabry disease and RA.

Several symptoms frequently associated with Fabry disease that would be expected to have an impact on quality of life are listed in Table 4. Only 19/190 subjects (10%) who completed the Fabry-specific portion of the questionnaire did not have symptoms of Fabry disease included in the table. Data from the comparison of study subjects who reported symptoms with those who did not

Table 1

Comparison of RAND-36 mean subscale scores for study subjects heterozygous for Fabry disease and the Women's Health Initiative control group

Health measures	Women's health initiative (N = 8102) Mean (SD)	Fabry heterozygotes (N = 202) Mean (SD)	*P*-value	CID[a] value
Physical functioning	82.9 (18.9)	67.1 (28.3)	<0.0001	0.84
Role limitations – Physical	78.3 (32.4)	47.0 (44.9)	<0.0001	0.97
Role limitations – emotional	85.3 (28.1)	55.4 (43.1)	<0.0001	1.06
Energy/fatigue	64.8 (18.7)	40.4 (25.3)	<0.0001	1.30
Emotional well-being	79.8 (13.9)	65.2 (20.5)	<0.0001	1.05
Social functioning	91.5 (16.4)	67.9 (27.8)	<0.0001	1.44
Pain	77.2 (21.9)	62.2 (27.6)	<0.0001	0.68
General health	76.5 (16.4)	45.1 (24.3)	<0.0001	1.91

[a]Clinically important differences were inferred by estimating effect sizes. A value of ≥0.80 indicates a large difference, 0.50–0.79 indicates a moderate difference, and 0.20–0.49 indicates a small HRQOL difference $[(\text{mean}_{WHI} - \text{mean}_{Fab})/ \text{SD}_{WHI}]$[12].

Table 2

Comparison of RAND-36 mean subscale scores for study subjects heterozygous for Fabry disease and the group with multiple sclerosis

Health measures	Multiple sclerosis (N = 179) Mean (SD)	Fabry heterozygotes (N = 202) Mean (SD)	*P*-value	CID[a] value
Physical functioning	36.7 (32.5)	67.1 (28.3)	<0.0001	−0.94
Role limitations – physical	32.9 (39.0)	47.0 (44.9)	0.002	−0.36
Role limitations – emotional	60.0 (42.3)	55.4 (43.1)	0.30	0.11
Energy/fatigue	42.2 (20.9)	40.4 (25.3)	0.45	0.09
Emotional well-being	65.6 (20.4)	65.2 (20.5)	0.85	0.02
Social functioning	61.7 (25.0)	67.9 (27.8)	0.03	−0.25
Pain	74.2 (25.5)	62.2 (27.6)	<0.0001	0.47
General health	53.3 (25.3)	45.1 (24.3)	0.01	0.32

[a]Clinically important differences were inferred by estimating effect sizes. A value of ≥0.80 indicates a large difference, 0.50–0.79 indicates a moderate difference, and 0.20–0.49 indicates a small HRQoL difference $[(\text{mean}_{WHI} - \text{mean}_{Fab})/ \text{SD}_{WHI}]$[12]. A negative sign by a CID value indicates that the HRQoL subscale for the comparison group is lower than for the study subjects with Fabry.

Table 3
Comparison of RAND-36 mean subscale scores for study subjects heterozygous for Fabry disease and the group with rheumatoid arthritis.

Health measures	Rheumatoid arthritis (N=679) Mean (SD)	Fabry heterozygotes (N=202) Mean (SD)	*P*-Value	CID[a] value
Physical functioning	50.8 (26.8)	67.1 (28.3)	<0.0001	−0.61
Role limitations – Physical	41.5 (42.3)	47.0 (44.9)	0.11	−0.13
Role limitations – emotional	72.8 (40.2)	55.4 (43.1)	<0.0001	0.43
Energy/fatigue	55.2 (20.5)	40.4 (25.3)	<0.0001	0.72
Emotional well-being	72.3 (18.9)	65.2 (20.5)	<0.0001	0.38
Social functioning	71.8 (25.9)	67.9 (27.8)	0.07	0.15
Pain	56.4 (22.4)	62.2 (27.6)	0.003	−0.26
General health	51.3 (20.2)	45.1 (24.3)	0.0003	0.31

[a]Clinically important differences were inferred by estimating effect sizes. A value of ≥0.80 indicates a large difference, 0.50–0.79 indicates a moderate difference, and 0.20–0.49 indicates a small HRQoL difference [$(\text{mean}_{WHI} - \text{mean}_{Fab})/ \text{SD}_{WHI}$][12]. A negative sign by a CID value indicates that the HRQoL subscale for the comparison group is lower than for the study subjects with Fabry.

Table 4
Manifestations of Fabry disease that have an impact on Health-Related Quality of Life

Fabry disease manifestations
General pain
Vertigo
Nausea and/or vomiting
Diarrhea and/or frequent bowel movements
Lack of sweating
Heat/cold intolerance
TIAs
Stroke
Left ventricular hypertrophy
Irregular heartbeat/rhythm disturbance
Heart valve abnormalities
Heart attack
Heart failure
Proteinuria
Abnormal kidney function
Kidney failure

are shown in Table 5. Symptoms were grouped into three categories based on the level of impact of the symptom on HRQoL. Symptoms that had a high impact on HRQoL showed statistically significant differences in means for 6–8 of the eight RAND-36 domains (acroparesthesia, nausea/vomiting, diarrhea, renal insufficiency, and TIAs). The medium impact category showed significance for 3–5 domains (stroke, arrhythmia, valve abnormalities, and renal failure). The low impact category was significant in 0–2 domains (left ventricular hypertrophy, heart failure, and proteinuria). Several symptoms included in Table 5 were uncommon in study participants, but would be expected to have an important impact on HRQoL if present. The impact of these complications is likely to be underestimated in this analysis. For example, kidney and heart failure were not frequent enough to be adequately assessed in this study.

DISCUSSION

Until recently, the medical community has considered the majority of women heterozygous for Fabry disease to be asymptomatic. Several clinical studies have shown that women may have serious health problems from Fabry disease. European investigators have examined the frequency of Fabry manifestations in 303 heterozygotes through the Fabry Outcomes Survey and discovered that 77% of women study subjects had neurological manifestations that included pain attacks and chronic pain.[4] A recent study of 61 heterozygous women found that 91% of study subjects had cardiac, renal, or cerebrovascular abnormalities.[5] In a study of 60 heterozygous women, 30% were found to have serious debilitating signs of Fabry disease.[7] A study of cardiac disease in 55 female patients documented a high rate of cardiac problems including left ventricular hypertrophy and valve abnormalities.[8] Another study of 20 women found many of the symptoms present in males including chronic and severe episodic pain as well as kidney, cerebrovascular, gastrointestinal, and cardiac disease.[9] These studies demonstrated that heterozygous women may have symptoms similar to men with Fabry disease and that a higher proportion of these women may manifest the disorder than previously thought.

Research studies that focus on the natural history of Fabry disease in affected men and women have also measured HRQoL in their study populations.[4,15,16] However, these studies gathered HRQoL data to obtain baseline information or to document a change in HRQoL after an intervention such as enzyme replacement therapy. Studies have been conducted comparing HRQoL between men with Fabry disease to a control group and to other groups with various disease types.[2,3] Another study compared HRQoL of boys with Fabry disease with controls.[17] Baehner et al.

Table 5
Percentage of study subjects reporting specific symptoms. Level of impact on HRQoL of women with symptoms of Fabry disease.

Level of impact	Symptom	Subjects with symptom N (%)	Physical functioning	Role Limitations - physical	Role limitations - emotional	Energy/ fatigue	Emotional well-being	Social functioning	Pain	General health
High (6–8 HRQoL domains)	Acroparesthesia	149 (80%)	SS	SS	SS	SS	SS	SS	SS	SS
	Nausea/vomiting	96 (52%)	NS	SS	SS	SS	SS	SS	SS	SS
	Diarrhea/frequent bowl movements	124 (66%)	SS	SS	SS	SS	SS	SS	SS	SS
	Transient ischemic attacks	36 (20%)	SS	SS	SS	SS	NS	SS	SS	NS
	Renal insufficiency	32 (17%)	SS	SS	NS	SS	SS	SS	SS	SS
Medium (3–5 HRQoL domains)	Stroke	14 (8%)	SS	SS	SS	SS	NS	NS	NS	NS
	Arrhythmia	81 (44%)	SS	SS	NS	SS	NS	NS	NS	NS
	Valve abnormalities	46 (25%)	SS	SS	NS	SS	NS	NS	NS	NS
	Kidney failure[a]	3 (2%)	SS	NS	NS	NS	NS	SS	SS	NS
Low (0–2 HRQoL domains)	Left ventricular hypertrophy	33 (18%)	SS	NS	NS	NS	NS	NS	NS	NS
	Heart failure[a]	1 (0.05%)	NS	NS	NS	NS	NS	NS	NS	NS
	Proteinuria	68 (38%)	SS	NS	NS	NS	NS	NS	NS	NS

[a]Number of women reporting symptom is low.
[b]SS = Statistically significant, $P < 0.05$; NS = not statistically significant, $P > 0.05$.

studied the HRQoL of 15 affected women before and after ERT and compared HRQoL scores with patients with rheumatoid arthritis and with the German general population.[18] These studies comparing HRQoL between study subjects and control populations found statistically significant differences in HRQoL domains. Our study also found significant differences between controls and study subjects and is the largest study to date that compares HRQoL of heterozygous women to controls and chronic disease populations.

It is paramount to assess the impact of Fabry disease on HRQoL in affected women to provide appropriate health care for this population and to monitor the success of treatment for prevention of serious complications. Nevertheless, non-specific signs of Fabry disease such as fatigue and pain are also common in the general population. In this study, women with Fabry disease reported significantly lower quality of life in all eight areas of functioning compared to healthy women. In all HRQoL domains, a moderate to large clinically important difference was observed between the women with Fabry disease and WHI control-arm population. In addition, comparisons revealed quality of life profiles for women with Fabry disease that resembled those of women with multiple sclerosis or rheumatoid arthritis. This implies that the burden of disease may be functionally important despite the nonspecific nature of many of the symptoms reported.

Using the Fabry-specific portion of the questionnaire and severity criteria that we defined, we determined the frequency of symptoms for this study population. Approximately 10% of our study population did not have symptoms included on the questionnaire. Many of the symptoms that were included (i.e., nausea/vomiting, diarrhea/frequent bowel movements) were not specific to Fabry disease; however, it is apparent that these symptoms can be a significant health burden to heterozygous women. Indeed, after comparing HRQoL scores between women who listed themselves as having a specific symptom to those who did not, we found that nausea/vomiting and diarrhea were among those that had the highest impact on the HRQoL of study subjects. Other symptoms that had the highest impact on HRQoL scores were acroparesthesia, renal insufficiency, and TIAs. While many of these symptoms are nonspecific, they were reported with very high frequency in this population while many of the health problems that are more specifically related to Fabry disease were relatively less common. These results highlight the need for additional studies to develop reliable methods for assessing disease severity and progression in affected women.

Chronic diseases such as MS and RA have many of the same nonspecific symptoms as Fabry disease. The presence of studies utilizing the RAND-36 to measure HRQoL presented the opportunity for comparing the HRQoL between our study subjects and people with MS or RA. Although the HRQoL of the women with Fabry disease was relatively similar to that reported in MS and RA, study subjects in the RA group indicated greater limitations in their physical functioning and lower quality of life due to the presence of pain. This seems to correlate well with symptoms of the disease in which joint mobility and pain are key features. Women who are obligate heterozygotes of Fabry disease had a significantly lower HRQoL regarding overall emotional health. The obligate heterozygotes also had lower energy and lower perception of general health

than the subjects with RA. The study by MacDermot et al. reported only one-third of their subjects to be happy, full of life, and energetic.[7] In our study, over one-third of women reported depression, anxiety, or both. Having to deal with the myriad of symptoms related to Fabry disease may negatively impact the quality of life of women heterozygous for the disease across multiple dimensions.

Limitations in mobility play a large role in MS and may help explain the lower scores in physical functioning for this population when compared to women heterozygous for Fabry disease. Social functioning was also significantly decreased in individuals with MS when compared to the obligate heterozygotes with Fabry disease. Interestingly, both the populations with MS and Fabry disease had similarly low scores in emotional aspects of HRQoL.

Certain limitations were inherent in the study design. The amount of time and resources available were prohibitive to the formation of our own control group. As a result, we selected a large historical control group of women that had used the same tool as this study to measure HRQoL. Even though women with Fabry disease had a mean age range of 34–44 years, their quality of life in all categories was much lower than older women in the WHI control population (50–70 years). Since the WHI population was recruited to be in a clinical trial, they probably do not adequately represent the general population of women. However, the much lower HRQoL scores for our 35–44-year-old study subjects contrasts substantially with the scores of the older WHI controls.

Lack of validation of heterozygote status and clinical signs of disease were also limitations in the study design. As stated earlier, the study was limited by amount of time and resources available; thus, verification of GLA mutations and clinical assessment for signs of disease were out of the scope of this study. However, obligate heterozygotes were identified by asking study subjects to list affected family members, so it is unlikely that this study included unaffected individuals. Furthermore, if some study subjects were not Fabry heterozygotes the differences in mean scores between controls and participants should reduce rather than increase the differences between the populations.

This study has some inherent selection bias since symptomatic female patients were more easily identified by the lysosomal disease centers than female relatives of male patients. Participants from the FSIG may also have been more likely to have symptoms than those who chose not to fill out the questionnaire. Thus, our study population may be enriched for symptomatic heterozygotes. As a result, this study design will not determine the percentage of women who manifest signs or symptoms of Fabry disease. We were unable to determine the differences between responders and non-responders. To help minimize selection bias, we included a raffle as an incentive for heterozygous women regardless of symptoms to fill out the questionnaire. Including a large study population with a wide range of HRQoL scores and Fabry symptoms enabled us to detect moderate to large CIDs between study subjects and controls. These findings do indicate that for women with symptoms this is a serious disorder that significantly impacts their quality of life.

HRQoL scores may be impacted by other factors besides coping with personal Fabry disease manifestations. Women who care for male relatives with Fabry disease may often be drained physically and emotionally from daily caregiving responsibilities. Caring for a person with extensive medical issues has been shown to have a negative effect on the quality of life of the caregiver and increases the risk for depression.[19] The lower scores in all subscales for the Fabry study subjects may well be impacted by the emotional and physical aspects of dealing with Fabry disease in another affected family member.

The Fabry-specific questionnaire was designed for the participant to assess the occurrence, frequency, and severity of Fabry disease manifestations. Self-reporting of personal medical information is subject to recall bias. Women who chose to complete the survey may have been more likely to label their medical problems as Fabry manifestations if they were familiar with these signs in other family members. It is also possible that some women may have indicated the presence of disease manifestations that they believed they had, but which had not been diagnosed by a physician. As an example, over one-third of study participants reported anxiety and/or depression. While we tried to minimize this last type of bias by asking participants to check "yes" to only those signs of disease that had been diagnosed by a doctor, women may have thought their feelings of depression and/or anxiety warranted recognition as a disease sign. However, as noted earlier, the MacDermot study also found that one-third of study subjects that were "depressed, anxious, tired, and frustrated some of the time."[7]

Women with mutations in the GLA gene have often been misdiagnosed with a variety of other disorders by their physicians, many of whom are not familiar with Fabry disease or believe that women are only carriers of the disease. Enzyme replacement therapy (ERT) is now available for individuals with Fabry disease; therefore, proper diagnosis and management is essential in both hemizygous males and heterozygous females. ERT trials have established the new therapy's efficacy in men.[16,20] Expert clinicians have recommended ERT for the treatment of women clinically identified with substantial signs and symptoms of Fabry disease.[21] Studies of ERT indicate that it improves the quality of life for patients with Fabry disease.[15,16] However these studies were done in populations that were predominantly male. To date there are no large studies of ERT in women with Fabry disease documenting long-term outcomes. Our study indicates that women who carry mutations in the α-gal A gene may have clinically important symptoms of Fabry disease that impact HRQoL and that require proper evaluation and treatment.

Existing protocols for the management of patients with Fabry disease are primarily based on research that included almost exclusively affected men.[21] Recent studies of heterozygous women have indicated that cardiac and cerebrovascular complications cause greater morbidity and mortality than the renal complications that are a primary cause of morbidity and mortality in affected men.[7,8,22] Future studies of heterozygous

women are needed to establish medical guidelines for initial evaluation and subsequent management of their symptoms. This study emphasizes the importance of evaluating women previously thought of as carriers for signs and symptoms of Fabry disease and of developing management protocols applicable to this population.

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