Prevalence of symptoms in female Fabry disease patients: a case-control survey

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Abstract

Background Fabry disease (FD) is an X-linked lysosomal storage disorder, caused by a deficiency of α-galactosidase A. Several studies demonstrated that heterozygotes have symptoms such as acroparesthesia, abdominal pain and chronic fatigue. However, as these symptoms are aspecific and relatively common in the general population, it is important to compare the prevalence of these symptoms with an appropriate control group. The aim of this study was to explore the prevalence of signs and symptoms in FD females in comparison to a control group.

Methods FD females and age-matched controls were approached to complete a questionnaire. This questionnaire was developed by the Dutch Fabry patient organisation (Fabry Support en Informatie Groep Nederland, FSIGN) with input from Fabry expert-physicians from the AMC. We compared the prevalence symptoms using Pearson’s chi-square test. Bonferroni correction was used to correct for multiple comparisons.

Results A total of 63 heterozygotes and 52 controls completed the questionnaire. Many symptoms were also common in controls. Yet, fatigue, palpitations, pains in hands and feet, joint pain, dizziness, loss of libido and proteinuria during pregnancy were more common in Fabry females (all p<0.001).

Conclusion In addition to acroparesthesia - fatigue, palpitations, dizziness, proteinuria during pregnancy, libido loss and joint pain are more prevalent in FD females as compared to a control group. Although, these symptoms are present in a significant proportion of normal controls they deserve further attention by treating physicians to better understand their significance, treatment and relationship with FD.

Introduction

Fabry disease (FD) is a lysosomal storage disorder, caused by a deficiency of the lysosomal enzyme alpha-galactosidase A (Desnick et al. 2001). Accumulation of globotriaosylceramide in vascular cells leads to multiple organ disease, characterised by acroparesthesia, angiokeratoma, progressive renal failure, cardiac complications and stroke. Unlike most lysosomal storage disorders, the inheritance of FD is X-linked and therefore in general heterozygotes have a mosaic state.

Following the availability of enzyme replacement therapy (ERT) in 2001, a number of Fabry cohort studies and post-marketing registry studies have been reported in the literature, describing the natural history of FD in males (Germain et al. 2003; Macdermot et al. 2001a, b;
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symptoms in FD females and an age matched control group.
Based on personal experience of a group of FD females
certain symptoms were added to the questionnaire. The
purpose of this study was to explore the prevalence of
symptoms in FD females compared to controls by use of a
questionnaire.

Methods
Participants and recruitment
Participants for the study were recruited from the Academic
Medical Centre, the national referral center for patients with
Fabry disease in the Netherlands. We asked all FD females,
aged 12 years and older, diagnosed by mutation analysis
(n=81) to participate. We sent a letter explaining the aim of
the study including two questionnaires.

FD females were asked to fill out one questionnaire
marked “P”) and to give one questionnaire to a non-Fabry
female friend, neighbour or relative (marked “C”), with
approximately the same age. All questionnaires were ana-
lysed anonymously. This study was judged by the Ethical
Committee of the AMC, Amsterdam as being a non-
interventional study, which does not require formal approval
under Dutch law and is considered to cause no harm to the
study subjects.

Questionnaire
The questionnaire was developed by two members (ES and
AS) of the Dutch Fabry patient organisation (FSIGN) in
close collaboration with Fabry expert-physicians (SMR
and CEH) from the AMC. During a meeting organised
and attended by FD females only (n=20), the content of the
questionnaire was discussed. Based on personal experience
of the attendees, additional symptoms were added that were
so far not considered to be part of Fabry symptomatology
(see Results, Table 4).

The questionnaire contained general questions on health,
sports, smoking, employment and sleeping difficulty (12
questions). Furthermore women were asked on the presence
of cardiopulmonary, gastrointestinal, musculoskeletal, neu-
ropsychological, urogenital symptoms and pregnancy out-
come (54 questions). Participants were asked to respond
yes/no to the presence of these symptoms during the last
three months.

Statistical analysis
All statistical analyses were performed using SPSS version
16.0. Pearson’s chi-square test was used to compare the
frequency of symptoms in FD females with the frequency
in control females. The Fisher’s exact test was used when
one or more of the cells in the 2×2 contingency table had an
expected frequency of five or less.

Multiple testing may result in false positive results sim-
ply due to chance. Therefore, the significance level was
adjusted in accordance with the Bonferroni correction
(Bland and Altman 1995). To determine the significance
level, a p-value of 0.05 was divided by the number of
comparisons done (n=66; p=0.0008) (Bland and Altman
1995) and was subsequently set at p<0.001. In addition,
odds ratios were calculated, but here we used a 95% confi-
dence interval.

Results
A total of 62 FD females completed the questionnaire
(response rate of 77%). In addition 53 female controls
participated in the study. The mean age of the FD females
was 39 years versus 42 years in controls (p=0.67; Table 1).
Pearson’s chi-square test was used to compare the frequency
of symptoms in FD females with the frequency in
control females. The results of these analyses are men-
tioned in Tables 1, 2 and 3. There was no difference in
Table 1: Characteristics of FD females and controls

|                                    | Fabry | Control | OR (95% CI) | p valuea |
|------------------------------------|-------|---------|-------------|----------|
| Age                                | 39.3 (±17.5) | 41.7 (±16.7) | NA         | 0.67b    |
| Employed                           | 29/52 (56%) | 31/44 (71%) | 0.53 (0.23-1.23) | 0.14    |
| Doing sports                       | 31/62 (50%) | 36/53 (68%) | 0.47 (0.22-1.01) | 0.052   |
| Smoking                            | 8/62 (13%) | 10/52 (19%) | 0.62 (0.23-1.71) | 0.36    |
| Drinking alcohol                   | 30/61 (49%) | 33/52 (64%) | 0.58 (0.26-1.19) | 0.13    |
| Not sleeping well *                | 32/61 (53%) | 14/53 (26%) | 3.07 (1.39-6.78) | 0.005   |
| Not well rested when awake *       | 37/60 (62%) | 16/52 (33%) | 3.62 (1.65-7.94) | 0.002   |
| Perceived health status as not good| 26/61 (42%) | 3/52 (8%) | 12.1 (3.40-43.3) | ≤0.001  |
| Medication                         | 40/62 (65%) | 16/52 (31%) | 4.09 (1.86-8.98) | ≤0.001  |
| Paramedic treatment *              | 16/62 (26%) | 7/53 (13%) | 2.29 (0.86-6.08) | 0.09    |
| In treatment specialist / general practitioner | 31/60 (52%) | 10/53 (19%) | 4.60 (1.96-10.8) | <0.001  |
| Health problems *                  | 40/60 (67%) | 18/51 (35%) | 3.67 (1.67-8.05) | 0.001   |

Data are number (%). OR = odds ratio. * p<0.05. Bold: significant after Bonferroni correction. NA: not applicable. a according to Pearson chi-square test, b according to t-test.

employment status, smoking, alcohol use and sports participation (Table 1).

Perceived health status was significantly decreased in FD females as 26 patients reported not feeling healthy compared to three controls (42% versus 8% respectively; p<0.001, OR 12.1). Significantly more patients with FD were prescribed medication, including enzyme replacement therapy (65% versus 31% respectively, p<0.001, OR 4.09; Table 1). In total 28 FD females were treated with ERT (45%).

Cardiopulmonary symptoms

Palpitations were reported significantly more often in FD females (48% versus 13% in controls, p<0.001, OR 5.96). Almost half of the patients reported to have shortness of breath, although there was no significant difference after Bonferroni correction (Table 2).

Gastrointestinal (GI) symptoms

GI symptoms were reported often by both FD females and control females, see Table 2. FD females frequently reported nausea, swallowing difficulties, abdominal pain, diarrhoea and constipation. Abdominal pain was reported by 60% of the FD females. Diarrhoea and constipation were present in 41% and 34% respectively. These symptoms were also common in controls (in 30%, 19% and 9% respectively). After adjustment of the p-value with the Bonferroni correction, there were no significant differences in gastrointestinal symptoms between the two groups (nausea: p=0.01; swallowing difficulties: p=0.01; abdominal pain: p=0.002; diarrhoea: p=0.01 and constipation: p=0.002). Any GI symptom was mentioned by 51 of the 62 Fabry females versus 27 of the 53 controls (82% versus 51%, p<0.001, Pearson chi square test).

Musculoskeletal symptoms

The results on the neuromuscular symptoms are summarised in Table 2. Joint pain was present in 36 FD females which was significantly more compared to 13 control females (58% versus 25%, p<0.001, OR 4.15). In addition pain in hands and feet was reported significantly more frequent in FD females (58% versus 11%, p<0.001, OR 10.9 and 39% versus 9% respectively, p<0.001, OR 6.2).

Neuropsychological symptoms

Dizziness was reported more frequently by FD females (60% versus 19%, p<0.001, OR 6.36). Fatigue was reported by almost all patients (n=55), but also by many controls (n=30), yet it was significantly more common in FD females (89% versus 57%, p<0.001, OR 6.02). No differences were found in other neuropsychological symptoms (see Table 2).

Menstrual cycle

The prevalence of premenstrual, menstrual symptoms and menarche was not different between Fabry females and controls (p=0.59, p=0.42 and p=0.72 respectively; see Table 2).

Pregnancy related outcome

Thirty-two females with Fabry disease had a history of pregnancy and 35 controls (in total 89 pregnancies in Fabry females, 78 in controls; miscarriages not included). The results are summarised in Table 3. Proteinuria during pregnancy was reported by nearly one third of Fabry females (34% versus 0%, p<0.001) as well as hypertension during pregnancy in FD females, although the latter was not significantly different (34% versus 14%, p=0.05). There were
Table 2 Prevalence of symptoms in FD females and controls

| Symptom                        | Fabry          | Control    | OR (95% CI)    | p value<sup>a</sup> |
|--------------------------------|----------------|------------|----------------|--------------------|
| **Cardiopulmonary symptoms**   |                |            |                |                    |
| Palpitations                   | 29/63 (48%)    | 7/53 (13%) | 5.96 (2.32-15.3) | ≤0.001             |
| Skipped heartbeat <sup>*</sup> | 20/60 (33%)    | 6/53 (11%) | 3.92 (1.43-10.7) | 0.006              |
| Chest pain <sup>*</sup>        | 18/62 (29%)    | 5/51 (10%) | 3.76 (1.29-11.0) | 0.01               |
| Shortness of breath <sup>*</sup> | 30/62 (48%) | 10/53 (19%) | 4.03 (1.72-9.43) | 0.01               |
| **Gastrointestinal symptoms**  |                |            |                |                    |
| Regurgitation                  | 23/61 (38%)    | 16/52 (31%) | 1.36 (0.62-2.98) | 0.44               |
| Reflux                         | 18/62 (29%)    | 11/52 (21%) | 1.52 (0.64-3.61) | 0.34               |
| Nausea <sup>*</sup>            | 27/62 (44%)    | 11/53 (21%) | 2.95 (1.28-6.77) | 0.01               |
| Swallowing difficulties <sup>*</sup> | 19/61 (31%) | 6/51 (11%) | 3.54 (1.29-9.71) | 0.01               |
| Hiccup                         | 25/58 (43%)    | 18/51 (35%) | 1.39 (0.64-3.01) | 0.40               |
| Abdominal pain <sup>*</sup>    | 37/62 (60%)    | 16/53 (30%) | 3.42 (1.58-7.43) | 0.002              |
| Diarrhoea <sup>*</sup>         | 25/61 (41%)    | 10/53 (19%) | 2.99 (1.27-7.03) | 0.01               |
| Constipation <sup>*</sup>      | 21/61 (34%)    | 5/53 (9%)  | 5.04 (1.74-14.6) | 0.002              |
| Flatulence                     | 34/62 (55%)    | 25/53 (47%) | 1.36 (0.65-2.84) | 0.41               |
| **Musculoskeletal symptoms**   |                |            |                |                    |
| Myalgia <sup>*</sup>           | 35/62 (57%)    | 19/53 (36%) | 2.32 (1.09-4.93) | 0.03               |
| Muscle cramps <sup>*</sup>     | 25/62 (40%)    | 8/53 (15%) | 3.80 (1.53-9.42) | 0.003              |
| Back ache <sup>*</sup>         | 38/61 (62%)    | 17/53 (32%) | 3.50 (1.61-7.60) | 0.001              |
| Joint pain                     | 36/62 (58%)    | 13/52 (25%) | 4.15 (1.86-9.29) | ≤0.001             |
| **Neuropsychological symptoms**|                |            |                |                    |
| Loss of strength <sup>*</sup>  | 28/62 (45%)    | 8/53 (15%) | 4.63 (1.88-11.4) | 0.001              |
| Numbness                       | 8/61 (13%)     | 8/53 (15%) | 0.85 (0.30-2.44) | 0.56               |
| Fatigue                        | 55/62 (89%)    | 30/53 (57%) | 6.02 (2.32-15.7) | ≤0.001             |
| Dizziness                      | 37/62 (60%)    | 10/53 (19%) | 6.36 (2.71-15.0) | ≤0.001             |
| Headache                       | 36/62 (60%)    | 24/53 (45%) | 1.67 (0.80-3.59) | 0.12               |
| Depressed mood                 | 34/62 (55%)    | 20/51 (39%) | 1.88 (0.89-3.99) | 0.19               |
| **Urogenital symptoms**        |                |            |                |                    |
| Urinary incontinence           | 16/62 (26%)    | 12/53 (23%) | 1.19 (0.50-2.80) | 0.69               |
| Dysuria <sup>#</sup>           | 3/62 (4.8%)    | 1/53 (1.9) | 2.64 (0.27-26.2) | 0.62               |
| Premenstrual symptoms          | 26/40 (65%)    | 20/34 (29%) | 1.30 (0.51-3.34) | 0.59               |
| Menstrual symptoms             | 24/35 (67%)    | 23/31 (74%) | 0.76 (0.26-2.22) | 0.42               |
| Menarche at 12-15 years        | 44/62 (71%)    | 36/53 (68%) | NA              | 0.72               |
| Fertility problems <sup>#</sup>| 5/40 (13%)     | 1/39 (2.6%) | 5.43 (0.60-48.8) | 0.20               |
| **Loss of libido**             | 27/48 (60%)    | 9/31 (23%) | 3.67 (1.38-9.75) | <0.001             |
| **Dermatological symptoms**    |                |            |                |                    |
| Dry skin <sup>*</sup>          | 42/61 (68%)    | 25/53 (47%) | 2.48 (1.15-5.32) | 0.03               |
| Acne                           | 10/61 (16%)    | 6/53 (11%) | 1.54 (0.52-4.55) | 0.44               |
| Eczema                         | 11/62 (18%)    | 7/53 (13%) | 1.42 (0.51-3.96) | 0.50               |
| Vitiligo                       | 6/62 (10%)     | 5/53 (9%)  | 1.03 (0.21-3.58) | 0.97               |
| Urticaria <sup>#</sup>         | 3/61 (4.9%)    | 2/52 (3.8%) | 1.29 (0.21-8.05) | 1.00               |
| Other symptoms                 |                |            |                |                    |
| Hypohidrosis <sup>*</sup>      | 17/59 (29%)    | 5/51 (10%) | 3.72 (1.26-11.0) | 0.01               |
| Spontaneous tear in molar      | 13/60 (22%)    | 10/49 (20%) | 1.08 (0.43-2.73) | 0.87               |
| Allergy                        | 10/62 (16%)    | 9/53 (17%) | 0.94 (0.35-2.52) | 0.90               |
| Snoring                        | 20/62 (32%)    | 31/53 (56%) | 0.34 (0.16-0.73) | 0.30               |
| Gum disease <sup>*</sup>       | 16/62 (26%)    | 6/53 (11%) | 2.72 (0.98-7.58) | 0.05               |

Data are number (%). OR = odds ratio. Bold: significant after Bonferroni correction. <sup>*</sup> p<0.05.

<sup>a</sup>according to Pearson chi-square test. <sup>#</sup> Fisher’s exact test because of small sample size.
no significant differences in frequency of pre-eclampsia (9.4% versus 0%, p = 0.10), miscarriages (25% versus 11%, p = 0.15), fertility problems (13% versus 2.6%, p = 0.20) and premature delivery in FD females and controls (19% versus 6%, p = 0.14). In addition, intrauterine death did not occur more often in the studied group (3% versus 3%, p = 1.0).

Other symptoms

Loss of libido was also reported significantly more common by FD females than controls (60% vs. 23%, p < 0.001, OR 3.67). Loss of libido was not significantly related to fatigue in both FD females (p = 0.38) and non-FD females (p = 0.06). Twenty-nine percent (17/59) of the FD females had hypohidrosis (versus 10% in controls 5/51, p = 0.01) (see Table 2). Table 4 shows the frequency of occurrence of symptoms suggested specifically by Fabry females to be included in the questionnaire.

Discussion

In this exploratory study we compared the prevalence of both classical FD related symptoms as well as a variety of other complaints in a large cohort of FD females with prevalence of these symptoms in a well matched control group. This study confirms that some previously described symptoms are significantly more common in Fabry females. Pain in hands and feet, acroparesthesia, are indeed a common symptom in FD females. The prevalence of acroparesthesia in the current study is higher than previously reported by us in a smaller cohort (Vedder et al. 2007), and is in agreement with the overall prevalence of 61% (range 23-90%) in several other studies (see Tables 2 and 5). Palpitations were also significantly more common in FD females. Fatigue was the most commonly reported symptom (89%), as was also reported by Mac Dermot et al. (Macdermot et al. ...
| Study                  | From   | Patients n | AP   | HH   | Diarrhoea | Constipation | Abdominal pain | Cardiovascular symptoms | Angina | Palpitations | Fatigue | Vertigo | Tinnitus | Depression |
|-----------------------|--------|------------|------|------|-----------|--------------|-----------------|-------------------------|--------|-------------|---------|---------|----------|------------|
| Macdermot et al. 2001 | UK     | 60         | 42/60| 20/60| 35/60     |              | 32/60          | 40/60                   | 15/60  |             |         |         |          |            |
| Whybra et al. 2001    | Germany| 20         | 18/20| 10/20| 2/20      |              | 8/38           | 11/38                   | 6/11   | 5/11        |         |         |          |            |
| Galanos 2002          | Australia| 38      | 20/38| 4/38  | 4/38      | 8/38         | 20%             | 29%                     |         |             |         |         |          |            |
| Guffon 2003           | France | 11         | 8/11 | 3/11  | 73%       |              | 6/11           | 55%                     | 45%    |             |         |         |          |            |
| Gupta et al. 2005     | USA    | 57         | 42/57| 18/57 | 26/57     |              | 9/36           | 24/51                   | 22/38  | 21/34       |         |         |          |            |
| Wang et al. 2007      | USA    | 51         | 26/40| 25/42 | 18/42     |              | 6/11           | 55%                     | 60%    |             |         |         |          |            |
| Vedder et al. 2007    | NL     | 39         | 9/39 | 5/39  | 23%       |              | 9/36           | 24/51                   | 22/38  | 21/34       |         |         |          |            |
| Kobayashi et al. 2008 | Japan  | 36         | 18/36| 6/36  | 50%       |              | 6/11           | 55%                     | 55%    |             |         |         |          |            |
| Overall prevalence    |        | 183/301    | 73/233| 57/168| 44/99     | 2/20          | 17/74          | 19/76                   | 64/111 | 6/11        |         |         |          |            |
| This study; FD        | NL     | 62         | 36/62| 51/62 | 25/61     | 21/61         | 18/62          | 29/61                   | 55/62  | 37/62       |         |         |          |            |
| This study; controls  | NL     | 53         | 6/53 | 27/53 | 10/53     | 5/53          | 16/53          | 5/51                    | 30/53  | 10/53       |         |         |          |            |

| Study                  | From   | Patients n | AP   | HH   | Diarrhoea | Constipation | Abdominal pain | Cardiovascular symptoms | Angina | Palpitations | Fatigue | Vertigo | Tinnitus | Depression |
|-----------------------|--------|------------|------|------|-----------|--------------|-----------------|-------------------------|--------|-------------|---------|---------|----------|------------|
| Macdermot et al. 2001 | UK     | 60         | 42/60| 20/60| 35/60     |              | 32/60          | 40/60                   | 15/60  |             |         |         |          |            |
| Whybra et al. 2001    | Germany| 20         | 18/20| 10/20| 2/20      |              | 8/38           | 11/38                   | 6/11   | 5/11        |         |         |          |            |
| Galanos 2002          | Australia| 38      | 20/38| 4/38  | 4/38      | 8/38         | 20%             | 29%                     |         |             |         |         |          |            |
| Guffon 2003           | France | 11         | 8/11 | 3/11  | 73%       |              | 6/11           | 55%                     | 45%    |             |         |         |          |            |
| Gupta et al. 2005     | USA    | 57         | 42/57| 18/57 | 26/57     |              | 9/36           | 24/51                   | 22/38  | 21/34       |         |         |          |            |
| Wang et al. 2007      | USA    | 51         | 26/40| 25/42 | 18/42     |              | 6/11           | 55%                     | 60%    |             |         |         |          |            |
| Vedder et al. 2007    | NL     | 39         | 9/39 | 5/39  | 23%       |              | 9/36           | 24/51                   | 22/38  | 21/34       |         |         |          |            |
| Kobayashi et al. 2008 | Japan  | 36         | 18/36| 6/36  | 50%       |              | 6/11           | 55%                     | 55%    |             |         |         |          |            |
| Overall prevalence    |        | 183/301    | 73/233| 57/168| 44/99     | 2/20          | 17/74          | 19/76                   | 64/111 | 6/11        |         |         |          |            |
| This study; FD        | NL     | 62         | 36/62| 51/62 | 25/61     | 21/61         | 18/62          | 29/61                   | 55/62  | 37/62       |         |         |          |            |
| This study; controls  | NL     | 53         | 6/53 | 27/53 | 10/53     | 5/53          | 16/53          | 5/51                    | 30/53  | 10/53       |         |         |          |            |

**Table 5** Overview of prevalence of symptoms in cohort studies of FD females
Although, as may be expected, a substantial proportion of normal controls also experienced chronic fatigue (57%), this was significantly more prevalent in the FD females. In addition to the more common FD attributed symptoms, this study also confirms a higher prevalence of symptoms of joint pain and dizziness in FD females as compared to controls.

A high prevalence of gastro-intestinal symptoms was observed (any GI symptom was mentioned by 82% of the Fabry females, versus 51% in controls). However, none of these individual symptoms were significantly more prevalent in the Fabry disease group with a threshold of p<0.001 following the Bonferroni correction for multiple comparisons. Nevertheless, five of the nine gastro-intestinal symptoms that were included in the questionnaire were more common in FD females with a p-value of <0.05, with odds ratios ranging from 3 to 5 (Table 2). We feel therefore that it is unlikely that this is completely due to chance and suggests that the gastro-intestinal tract is indeed affected in FD females. In other studies the overall prevalence of gastro-intestinal symptoms in FD females was 34% (range 11-58%). In one large cohort study the prevalence of GI symptoms was 58%, and consisted of complaints of bloating, indigestion and abdominal cramps (Macdermot et al. 2001a, b). A previous smaller study by our group revealed only a prevalence of 12% in the female Fabry patients (Vedder et al. 2007). The differences in prevalence between that study and the current one could be due to difference in methods used (questionnaire versus physicians’ interpretation). The fact that we also observed a high prevalence of gastro-intestinal symptoms in controls (51%) emphasises the need to include a control group, especially when evaluating the prevalence of non-specific symptoms.

This study has identified several potentially FD related symptoms that were previously not recognised. This may be relevant for both FD females and their treating physicians. First, our results indicate that there is a high prevalence of proteinuria during pregnancy in FD females. It cannot be made clear from this study whether these patients had proteinuria before pregnancy, which was subsequently revealed during pregnancy or that Fabry females are more prone to develop proteinuria during pregnancy. However, this finding deserves further study. So far, only case-studies on uneventful pregnancies have been reported (Bouwman et al. 2010; Germain et al. 2010; Kalkum et al. 2009; Parent et al. 2010; Politei 2010; Wendt et al. 2005). The prevalence of hypertension during pregnancy and pre-eclampsia was slightly increased in Fabry females, although not to a statistically significant level in this relatively small group. Its exact pathophysiological mechanism remains unclear. We suggest that complications during pregnancy and pregnancy outcome should be studied in a larger cohort of FD females.

In the current study, we found a high prevalence of loss of libido. This may well be caused by the presence of a chronic medical condition (Simon 2010) and therefore not necessarily be Fabry-specific. Nevertheless it is important for physicians treating FD females to acknowledge presence of this symptom.

A limitation of the current study is that we used a non-validated questionnaire specifically developed for this study. Though a variety of symptoms were evaluated, this questionnaire might not have covered all possible signs and symptoms. Another limitation of the study is the way controls were selected, as this was a patient selected group of friends, neighbours or relatives, and controls were not randomly selected. However, this approach also has advantages, as it generates a control group which is similar in several important respects, such as socioeconomic status and education. In addition, the groups did not differ in age and the controls included in the study were not only healthy individuals. We decided not to stratify for age and treatment with ERT, to prevent additional testing. However, these are important confounders. In general we found that patients treated with ERT had more symptoms and were generally older than patients not on ERT (data not shown). Finally, we confirm that fatigue, palpitations, pains in hands and feet, dizziness and joint pain are more prevalent in FD females as compared to a control group. Although, these symptoms are present in a significant proportion of normal controls they deserve further attention by treating physicians and researchers to better understand their significance, treatment and possible relationship with FD.

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On request a translated version of the questionnaire can be obtained through the Dutch Fabry patient organisation (Fabry Support en Informatie Groep Nederland, FSIGN, FSIGN@fabry.nl)

Conflicts of interest G.E.L., C.E.M.H., and F.A.W. have received reimbursement of travel expenses and honoraria for lectures on the management of lysosomal storage diseases, including Fabry disease, from Genzyme Corporation and Shire HGT, pharmaceutical companies producing enzyme replacement therapy for Fabry disease. G.E.L., and C.E.M.H. donated all honoraria to the Gaucher Foundation, an organization that support research in lysosomal storage diseases. The other authors declare no conflicts of interest.

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