Heterozygous Fabry Disease Females Are Not Just “Carriers,” But Suffer From Significant Burden of Disease And Impaired Quality of Life

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Fabry Disease Background

**Inheritance:** “X-linked recessive disorder that affects males; females unaffected”

**Etiology:** deficiency of α-galactosidase

**Function:** degradation of glycosphingolipids

**Pathophysiology:** glycosphingolipid accumulation in tissues, especially the vascular endothelium
Clinical Manifestations of Fabry Disease

CNS / PNS (Cognitive function preserved)
- Stroke
- Acroparesthesias (“Burning sensation of the hands and feet”)
- Anhidrosis / hypohidrosis with subsequent heat intolerance
- Decreased vibration sense

Pulmonary
- Small-airway infiltration
- Abnormal gas exchange

Cardiac
- Microvascular myocardial ischemia
- Conduction abnormalities
- Valvular insufficiency
- Concentric, non-obstructive left ventricular hypertrophy

Renal
- Proteinuria / microalbuminuria
- Progressive loss of GFR \(\rightarrow\) renal failure

From Warnock, 2005
From Seino, 2005
From Whybra, 2001
Significance & Methods of Study

Women with α-galactosidase mutations were, until recently, thought to be “asymptomatic carriers”

Cedars-Sinai Medical Center is largest referral center for Fabry disease in the Southwestern United States

Retrospective chart review was conducted to quantify the degree of involvement and severity of symptoms in women

Categorical variables reported as percentages (proportions); continuous variables reported as mean (median) ± 95% C.I.
### Demographic Data of Cohort

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>N:</td>
<td>44 women</td>
</tr>
<tr>
<td>Age:</td>
<td>46.1 (48) ± 5.3 years</td>
</tr>
<tr>
<td>Age of symptom onset:</td>
<td>13.8 (10) ± 3.7 years</td>
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<tr>
<td>Age of diagnosis:</td>
<td>29.5 (27) ± 6.6 years</td>
</tr>
<tr>
<td>Acroparesthesias as first symptom:</td>
<td>76% (16 / 21)</td>
</tr>
<tr>
<td>Diagnosed because of family history:</td>
<td>76% (31 / 41)</td>
</tr>
<tr>
<td>Diagnosed because of symptoms:</td>
<td>24% (10 / 41)</td>
</tr>
<tr>
<td>All patients confirmed to be heterozygous for Fabry mutations</td>
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</tbody>
</table>
Neurologic Involvement in Fabry Heterozygotes

Stroke: 22% (8/36)

Peripheral neuropathy

- Acroparesthesias: 65% (26/40)
- Anhidrosis: 60% (25/42)
- Heat intolerance: 49% (19/39)
- Decreased vibration sense: 79% (33/42)
Pulmonary Involvement in Fabry Heterozygotes

Spirometry indicates small-medium airway disease
- ↓ $\text{FEF}_{25-75}$: 71.8% (76) ± 13.2 predicted

Abnormal noninvasive exercise testing
- ↓ maximum oxygen uptake: 78.5% (79.5) ± 9.8 predicted
- ↓ heart rate: 88.7% (88) ± 7.5 predicted
- ↓ diastolic blood pressure: 69% (18 / 26)
  25.3 (19) ± 6.3 mm Hg
Cardiac Involvement in Fabry Heterozygotes

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina</td>
<td>28%</td>
<td>(10 / 36)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>43%</td>
<td>(16 / 37)</td>
</tr>
<tr>
<td>Resting bradycardia</td>
<td>36%</td>
<td>(14 / 39)</td>
</tr>
<tr>
<td>Mitral and/or aortic insufficiency</td>
<td>58%</td>
<td>(18 / 31)</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>24%</td>
<td>(8 / 33)</td>
</tr>
</tbody>
</table>
Renal Involvement in Fabry Heterozygotes

- **End-stage Renal Disease**: 12.5% (5 / 40)

- **Reduced Creatinine Clearance**:
  - 90.4 (86.8) ± 21.7 mL/min/1.73 m²
  - CrCl < 90 mL/min/1.73 m²: 58% (21 / 36)
  - CrCl < 60 mL/min/1.73 m²: 19% (7 / 36)

- **Proteinuria / microalbuminuria**
  - 24-hr or random urine protein > 300 mg / 24 hr: 28% (5 / 18)
  - 24-hr or random urine microalbumin > 30 mg / 24 hr: 80% (8 / 10)
Impaired Quality of Life in Fabry Heterozygotes

- Fatigue: 59% (24 / 41)
- Exercise intolerance: 83% (33 / 40)
- Depression: 62% (21 / 34)
- Anxiety: 39% (13 / 33)

Physical Functionality Score on SF-36® survey:
62.2 ± 13.3 (normal 85.9 – 90.2)

- BMI > 25 (overweight): 68% (28 / 41)
- BMI > 30 (obese): 44% (18 / 41)
Impaired Quality of Life

The bar chart shows the SF-36 score for different domains of health: Physical functioning, Role physical, General health, Vitality, Social functioning, Role emotional, Mental health, Physical component summary, Mental component summary. The chart compares the cohort mean with the US female norms.
Fabry disease symptom comparison between ♂ and ♀

* = data gathered from CSMC Fabry ♂ cohort
** = data gathered from MacDermot, JMG 2001 and from Bierer, Respiration 2005
Conclusion I

**Heterozygous women with Fabry disease suffer from significant multisystem disease and reduction in quality of life**

- Women were thought to be asymptomatic but clearly not the case from this cohort; other studies in heterozygotes corroborate our findings
- Symptomatology is greater than expected for random complete inactivation of the normal X-chromosome and α-galactosidase gene
- Symptomatology is comparable than men with Fabry disease, with a few exceptions
- Fatigue and exercise intolerance reduced physical functionality and well-being. Depression and anxiety were also common in this cohort, possibly due to effects of chronic pain.
Conclusion II

**Heterozygous women with Fabry disease suffer a significant delay in diagnosis**

- Patient complaints consistent with disease (i.e. TIA, chest pain, palpitations, shortness of breath, or burning sensation of the hands and feet) should be fully evaluated, not disregarded.

- Prompt recognition of symptoms results in earlier diagnosis, onset of treatment, and prevention of disease progression / irreversible damage.
Heterozygous Fabry women are not just carriers, but have a significant burden of disease and impaired quality of life

Ymond Y. Wang, MD, Alicia Lelis, MS, James Mirocha, PhD, and William R. Wilcox, MD, PhD

Purpose: To determine if there is significant symptomatology in women with heterozygous α-galactosidase mutations. Methods: Data from medical records of the 44 heterozygous females followed at Cedars-Sinai Medical Center were compiled and analyzed for symptoms of Fabry disease. Quality of life data were also analyzed. Results: Seventy-six percent were referred due to an affected male relative; 76% reported acroparesthesias as their first symptom. A mean of 15.7 years elapsed from onset of first symptoms to the diagnosis. Quality of life, measured by the SF-36 survey, was globally reduced. Pain affected mood and enjoyment of life. Central/peripheral nervous, cardiopulmonary, and renal system manifestations of Fabry disease were present far above that predicted for random X-inactivation of the normal allele. Fatigue, present in 59%, was associated with reduced maximum oxygen consumption (P = 0.049); exercise intolerance, present in 83%, was associated with reduced maximal heart rate during exercise testing (P = 0.0089). Women diagnosed via family history experienced more angina (P = 0.035), decreased vibration sense (P = 0.026), and had a worse percentage predicted FEV_{1,0} (P = 0.037) compared to women diagnosed because of symptoms. Conclusions: This study indicates that the asymptomatic female carrier of Fabry disease is the exception, not the rule: heterozygotes suffer from significant multisystemic disease and reduced quality of life and must be monitored and treated accordingly. Genet Med 2007:9(1):34–45.

Key Words: Fabry disease, female, heterozygote, natural history, outcome, SF-36, symptom, quality of life
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The families that volunteered their time and their stories to make this study possible
Symptom comparison between ♀ because of family history versus symptoms

Neurologic
- Decreased vibration sense
  - FH: 87% (27 / 31)
  - Sx: 50% (5 / 10) $p = 0.026$, Fisher’s exact test

Cardiac
- Angina
  - FH: 39% (10 / 26)
  - Sx: 0% (0 / 10) $p = 0.035$, Fisher’s exact test
Symptom comparison between ♀ because of family history versus symptoms

Pulmonary
- % predicted $\text{FEF}_{25-75}$
  - FH: 63 ± 15%
  - Sx: 93 ± 13%  \( p = 0.037, \text{Wilcoxon rank-sum test} \)

Renal
- BUN
  - FH: 14.2 ± 1.9 mg/dL
  - Sx: 32 ± 15.8 mg/dL,  \( p = 0.023, \text{Wilcoxon rank-sum test} \)
- Serum creatinine
  - FH: 0.84 ± 0.16 mg/dL
  - Sx: 2.65 ± 2 mg/dL,  \( p = 0.071, \text{Wilcoxon rank-sum test} \)
- Creatinine clearance
  - FH: 87.7 ± 10.3 mL/min/1.73 m²
  - Sx: 60 ± 25 mL/min/1.73 m²,  \( p = 0.022, \text{Wilcoxon rank-sum test} \)
Correlation between subjective symptoms and abnormalities in exercise testing

$\text{VO}_2\text{max}, \% \text{ of predicted}$

- + Fatigue: $70.1 \pm 10.4\%$
- - Fatigue: $90.3 \pm 16.3\%, \ p = 0.049 \ (t\text{-test})$

Maximum HR, % of predicted

- + Exercise intolerance: $83.5 \pm 5.5\%$
- - Exercise intolerance: $113 \pm 31\%, \ p = 0.0089 \ (\text{Wilcoxon rank-sum test})$
## Other Fabry disease manifestations

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<tr>
<th>Condition</th>
<th>Percentage</th>
<th>Count</th>
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<tbody>
<tr>
<td>Angiokeratoma</td>
<td>22%</td>
<td>(9 / 41)</td>
</tr>
<tr>
<td>Abdominal Cramping</td>
<td>39%</td>
<td>(16 / 41)</td>
</tr>
<tr>
<td>Postprandial Diarrhea</td>
<td>43%</td>
<td>(18 / 42)</td>
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### Vestibular nerve involvement

- **Tinnitus:** 58% (22 / 38)
- **SHNL:** 37% (14 / 38)
Why do females have significant symptomatology?

Unlike all other sphingolipidoses, Fabry disease behaves as a dominant disorder.

Different organs have different thresholds for enzyme activity below which there is disease (less LVH, renal disease in women vs men).

In organs where prevalence of disease is comparable in women and men, perhaps α-galactosidase activity is required in all cells.