Epidemiology (Relevance to Screening) and the Natural Course of Fabry Disease

Raphael Schiffmann, M.D., M.H.Sc.
Institute of Metabolic Disease
Baylor Research Institute
Dallas, Texas, USA
Disclosure of Interests

Research support, travel expenses, honoraria

• Amicus Therapeutics
• Protalix Biotherapeutics
• Shire, Inc.
Classic Epidemiology (Based on Enzyme activity)

- The prevalence 1:17,000 to 1:117,000 in Caucasian males.
- 1:40,000 males and females
- 1:15,000 in Nova Scotia, Canada (founder effect, West et al 2002)
- About 350 missense mutations
- About 50% are relatively mild

Main reference: Human Gene Mutation Database at the Institute of Medical Genetics in Cardiff
Newborn Screening for Fabry Disease
(DNA Sequencing-Based)

- (Spada et al 2006, Chien et al 2012) 1:4,600, with a 7:1 ratio of patients with the late-onset:classic phenotypes – *All pathogenic?*
- 1:7057 in Japan and 1:2996 in Taiwan
- Taiwan: 1:875 males and 1:399 females had the IVS4+919G→A mutation (Chien et al 2012) – 10% residual enzyme activity but not all are symptomatic
Is It Fabry Disease?

1. Residual enzyme activity ranges from 0% about 30% of mean normal value.

2. α–Galactosidase A deficiency is a genetic risk factor for a number of organ ailments (e.g. stroke, kidney and heart disease, small-fiber neuropathy)

3. Fabry complications are non-specific in nature – Difficulty to decide if a GLA variant is the cause

4. Newly identified GLA gene variants have higher residual enzyme activity. But are they clinically significant?
The Effect of Enzyme Activity

Enzyme Activity % of Normal

- Benign GLA variants – e.g. D313Y, S126G, R118C? IVS0-10C>T, IVS4-16A>G, IVS6-22C>T – risk depends only on other factors
- GLA variants conditional on other risk factors + ethnicity – e.g. A143T, N215S, R112H, P60L
- GLA disease variants less risk factors-dependent – missense and nonsense
Is It Fabry Disease?

- Blood/urine Gb₃ or lyso-Gb₃ cannot be used as diagnostic tools
  1. Can be normal in Fabry disease
  2. Can be abnormal in non-Fabry heart disease
  3. Can be increased in other LSD e.g. Gaucher (J. Aerts)

- Zebra bodies are non-specific (GM2, N-P, Silicon nephropathy) and may not be present
- Gb₃ in organ/tissue has to be elevated also IHC anti-Gb₃
<table>
<thead>
<tr>
<th>TYPE</th>
<th>% of NORMAL White Blood Cells α-GAL*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemizygotes – classic forms (males)</td>
<td>Usually less than 1%</td>
</tr>
<tr>
<td>Milder Variants (male patients with symptoms limited to few organ systems)</td>
<td>≈5-30%</td>
</tr>
<tr>
<td>Heterozygotes (females)</td>
<td>Very low-100%</td>
</tr>
</tbody>
</table>

• α-GAL levels can vary considerably depending on the tissue or cell type assayed

Lyonization Illustration

2:1 female/male ratio

Normal (left), Mosaic (right)
Conclusions/recommendations

• The potential causality of GLA variants should depend ultimately on elevation of globotriaosylceramide with appropriate lipid profile in tissue extracts as determined by mass spectrometry.

• Even in accepted Fabry mutations, we do not know whether and how disease will be expressed.

• Do we have treatment proven to meaningfully change the natural history if initiated in childhood?
True Natural History: Probability of developing renal syndromes

Branton et al. 2002
Kaplan-Meier estimates of time to first renal, cardiac, stroke, or death

Schiffmann et al. NDT 2009
eGFR By Age For Male and Female Patients

Non-ESRD Males: GFR slope = -2.93 ml/min/1.73m²/year

Non-ESRD Females: GFR slope = -1.02 ml/min/1.73m²/year

ESRD Males: GFR slope = -3.85 ml/min/1.73m²/year
ESRD Females: GFR slope = -305 ml/min/1.72m²/year

Schiffmann et al NDT 2009
### Yearly Decline based on Estimated GFR Slopes (ml/min/1.73m² per year)

<table>
<thead>
<tr>
<th>Urinary protein</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.1</td>
<td><img src="image1" alt="Graph" /></td>
<td>eGFR Slope (SEM) = -0.6 (2.6) N=7</td>
</tr>
<tr>
<td>≥ 0.1 to &lt; 1</td>
<td><img src="image2" alt="Graph" /></td>
<td>eGFR Slope (SEM) = -2.2 (2.2) N=17</td>
</tr>
<tr>
<td>≥ 1</td>
<td><img src="image3" alt="Graph" /></td>
<td>eGFR Slope (SEM) = -4.6 (2.3) N=5</td>
</tr>
</tbody>
</table>

**Schiffmann et al. NDT 2009**
Onset of CRI by Residual $\alpha$-gal A Activity

$p = 0.01$

Branton et al. 2001, 2002
Incidence of Stroke in Fabry Disease (US Population)

Stroke risk 2-fold increased (at least) on ERT compared to non-ERT

Germain et al 2015

Sims et al, Stroke, 2009
Effects of ERT on Events retrospective

Incidence of stroke, haemodialysis or death in 40 subjects treated with enzyme-replacement therapy (ERT) for a period of at least 5 years (ERT group).

At recruitment 211 adults and seven children were on ERT (range of treatment duration, 0 to 9.7 and 0 to 4.2 years respectively).

Weidemann et al J Int Med 2013

Anderson et al JIMD 2014
Estimated glomerular filtration rate (eGFR) slopes (A), left ventricular posterior wall thickness (LPWT) slopes (B), and interventricular septum thickness (IVST) slopes (C).

Patients with a UPCR ≤0.5 g/g and <50% sclerotic glomeruli were classified as low renal involvement (LRI);
Patients with UPCR >0.5 g/g or ≥50% sclerotic glomeruli at baseline were classified as high renal involvement (HRI)
Natural History of Hearing Loss in Fabry Disease

A  PTA$_{.5,.1,.2}$ male FD patients

B  PTA$_{8,.10,.12}$ male FD patients

C  PTA$_{.5,.1,.2}$ female FD patients

D  PTA$_{8,.10,.12}$ female FD patients

Suntjens et al 2015 JIMD
Conclusions

• **Screening for Fabry disease:** define which GLA variant is significant and what does it mean to diagnose Fabry patients pre-clinically

• **Natural history:** Organ/system specific may be the best approach
Thank You!