Fabry Anderson
Disease
Cardiac Involvement

The 3rd Saudi Heart Failure Group Conference - Jeddah
December 12-13, 2014

Bassam Mushannen, MD
Department of Cardiology
King Fahad Specialist Hospital - Dammam
Fabry Disease
Presentation Overview

X-linked inherited, lysosomal storage disease (LSD), with multi-systemic involvement, and progressive, life-threatening process affecting both males and females*  

Outlines:

- Inheritance and epidemiology
- Pathophysiology
- Clinical manifestation
  - Cardiac Involvement
- Diagnosis
- Treatment overview
- Summary & Screening Protocol
Inheritance and Epidemiology

- Estimated world-wide incidence:
  - 1:40,000 male births\(^1\),
  - 1:20,000 female births\(^2\)
- Maybe 1 in 3,100 males (newborn screening study)\(^3\)
- Pan-ethnic
- Most *males* have the “classic” form
- *Females* may be as severely affected as males\(^4\)
- FD commonly affects multiple generations.

\(^1\)Desnick et al 2001, *Metab Mol Bases Inherit Disease*;3733-74
\(^2\)Laney et al 2008, *J Genet Couns*;17:79-83
Globo\textsubscript{tri}aosylceramide (GL-3)

\textbf{Pathophysiology}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{globo_tri_aosylceramide_diagram.png}
\end{figure}

\begin{itemize}
\item Globo\textsubscript{tri}aosylceramide (GL-3)
\item \textbf{α-galactosidase}
\item \textbf{Galabiaosylceramide}
\end{itemize}

\textsuperscript{1}Desnick et al 2001, \textit{Metabolism Mol Bases Inherit Disease};3733-74
\textsuperscript{2}Brady et al 1967, \textit{NEJM};276:1163-7
Defect in the gene encoding α-galactosidase A (α-Gal A)\textsuperscript{1,2}

Deficient/ undetectable α-Gal A activity (FD) (often <1% residual enzyme activity in males)

Progressive, multisystemic lysosomal accumulation of GL-3

\begin{itemize}
  \item Normal lysosome
  \item GL-3-filled lysosome
\end{itemize}

\textsuperscript{1}Desnick et al 2001, \textit{Metab of Mol Bases Inherit Disease}\textsuperscript{3733-74}
\textsuperscript{2}Brady et al 1967, \textit{NEJM}\textsuperscript{276:1163-7}
Pathophysiology

Cells Affected by GL-3 Accumulation

- Vascular endothelial and smooth muscle cells
- Multiple renal cell types, including podocytes
- Cardiomyocytes, conduction system cells
- Neural cells
- Others

Cardiac GL-3 accumulation in vascular endothelial cells, and cardiomyocytes

Eng et al. Genet Med 2006;8:539-48

Image courtesy of B. Thurberg
Pediatric FD: Multi-organ Involvement
Boys and Girls

**Clinical Manifestations**

**Hypohidrosis**
- dry skin
- heat, cold, and exercise intolerance

**Cardiac**
- arrhythmias
- conduction abnormalities
- valvular dysfunction
- LVH

**GI dysmotility**
- abdominal cramping
- diarrhea
- bloating
- nausea

**Peripheral neuropathy**
- chronic burning pain
- severe episodic pain crises

**Renal**
- hyperfiltration
- microalbuminuria/proteinuria
- impaired urinary concentration ability
- GL-3 excretion

**Angiokeratoma**

**Cornea verticillata**

**Fatigue**

**Psychological issues**
- Growth retardation
- Hearing loss, tinnitus

Eng et al 2006, Genet Med;8:539-48
Early Signs and Symptoms

**Corneal Opacities**
Early Signs and Symptoms

**Angiokeratomas**

- Red-purple, non-blanching vascular skin lesions
- Most commonly in area from *umbilicus* to *thigh*;
- also often on *mucous membranes*


Clinical Manifestations
Pediatric FD
Cardiac Manifestations

- Involvement of SAN and conduction system
  - abnormal AV conduction (short P-R interval)
- Arrhythmias
- Valvular insufficiency (mild)
- LVH

2Kampmann et al. Z Kardiol 2002;91:786-95
Early Signs and Symptoms
Renal Manifestations, 19-year-old male

GL-3 accumulation in the kidney leads to irreversible damage

GL-3 accumulation in vascular endothelial cells (→), podocytes (→), mesangial cells (P)

Focal segmental glomerulosclerosis

Images courtesy of B. Thurberg
Early Signs and Symptoms
Renal Manifestations in **Two Girls**

Secondary damage occurs early, also in females

11-year-old girl 14-year-old girl

Hyaline-like material in the *media* of a small artery

Focal segmental glomerulosclerosis

Progression of Fabry Disease
Renal Complications

1. Progressive glomerulosclerosis
2. Tubular atrophy
3. Renal tissue fibrosis

(Overt) Proteinuria
Progressive decline in GFR
Hypertension
End-stage renal disease

References:
Progression of Fabry Disease

**Adult Male and Female Patients**

- **Cornea verticillata**
- **Hypohidrosis**
  - dry skin
  - heat, cold, and exercise intolerance
- **Cardiac complications**
  - arrhythmias
  - conduction abnormalities
  - valvular dysfunction
  - LVH
  - myocardial infarction
  - heart failure
  - sudden death
- **Peripheral neuropathy**
  - chronic burning pain
  - severe pain crises
  - paraesthesia
  - sensory abnormalities
- **GI dysmotility**
  - abdominal cramping
  - diarrhea
  - bloating
  - nausea
- **Renal complications**
  - decline in GFR
  - (overt) proteinuria
  - end-stage renal disease
- **Early stroke, TIAs**
- **Hearing loss, tinnitus**
- **Fatigue**
- **Psychological issues (e.g. depression)**
- **Angiokeratoma**

**Clinical Manifestations**
Cardiac Involvement In Fabry Disease

ECG  Echo  CMR

Johannes Fabry  William Anderson

1898
Progression of Fabry Disease
Cardiac Complications

- 13.9% of the females and 19.3% of males exhibited **cardiac involvement**;
  - mostly, LVH and **Arrhythmias**
- Events rate approximately the same in both genders
  - **males earlier**; 1st event at ~ 42 years vs. 48 years in females

<table>
<thead>
<tr>
<th>Event</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>Age at first event</td>
</tr>
<tr>
<td>Any cardiovascular events</td>
<td>19.3%</td>
<td>46</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2.4%</td>
<td>46</td>
</tr>
<tr>
<td>Significant cardiac procedure</td>
<td>7.7%</td>
<td>46</td>
</tr>
<tr>
<td><strong>Arrhythmia</strong></td>
<td><strong>11.3%</strong></td>
<td><strong>40.5</strong></td>
</tr>
<tr>
<td>Angina</td>
<td>3.4%</td>
<td>43</td>
</tr>
<tr>
<td><strong>Congestive heart failure</strong></td>
<td><strong>3.8%</strong></td>
<td><strong>45</strong></td>
</tr>
<tr>
<td>LVH (echo)</td>
<td><strong>21.6%</strong></td>
<td><strong>42</strong></td>
</tr>
</tbody>
</table>

Wilcox et al 2008; Mol Genet Metab; 93:112-28
Progression of Fabry Disease
Cardiac Complications

By age 45, 50% of males had a documented ARRHYTHMIA

(Kaplan Meier estimate of time to first cardiac arrhythmia)

Patients without arrhythmia (%)

Age

Female (n = 168)
Male (n = 279)

Schiffmann et al 2009, NDT; 24:2102-11
ECG

- Early Changes
- Late Changes
- Short P wave
- PR/ PQ Interval
- QRS duration
ECG: *Early* Fabry Disease

- Shortening of
  - P wave
  - PQ interval
  - QRS duration

- Prolongation of
  - QT/QTc interval
  - QTc dispersion
  - Tpeak-Tend dispersion

*Mehdi et al. Heart 2011;97:485-490*
ECG: *Early* Fabry Disease

- Shortening of
  - *P wave*
  - PQ interval
  - QRS duration

- Prolongation of
  - QT/ QTc interval
  - QTc dispersion
  - Tpeak-Tend dispersion

*Mehdi P et al. Heart 2011;97:485-490*
ECG: *Early*

- **Shortening of**
  - P wave
  - PQ interval
  - QRS duration

- **Prolongation of**
  - QT/QTc interval
  - **QTc dispersion**
    - max QTc interval - min QTc
  - **Tpeak-Tend dispersion**
    - max $T_p - T_e$ - min $T_p - T_e$.

**Life threatening Arrhythmias**
ECG: *Late* Changes

- PR interval prolongation
- Atrio-ventricular block
- LVH

**Arrhythmias & Sudden Cardiac Death:**
- 27–42% of males and 27% of females.
- Management of arrhythmias per standard guidelines.
Echo

- LVH
- Postero-lateral Fibrosis
- LV Diastolic Dysfunction
- Valvular Involvement
LVH in Fabry Disease

- Could be 1\textsuperscript{st} sign of cardiac involvement
- **Echo**: non-invasive tool
  - Diagnosis
  - follow-up
- Usually **NO**
  - systolic dysfunction
  - restrictive signs.
- ECG and Echo are not 100% sensitive → **Genetic testing**.
Chambers size, thickness and dimension:
Normal Values

<table>
<thead>
<tr>
<th></th>
<th>LV wall thickness (cm)</th>
<th>LA size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IVS</td>
<td>PW</td>
</tr>
<tr>
<td>Male</td>
<td>0.6-1.0</td>
<td>0.6-1.0</td>
</tr>
<tr>
<td>Female</td>
<td>0.6-.09</td>
<td>0.6-.09</td>
</tr>
</tbody>
</table>
Chambers size, thickness and dimension: Normal Values
Different LVH Types:

- CONCENTRIC LVH
- Symmetric (CH)

Images showing LAPS, SAPS, Apical 4, and Apical 2 views.
Different LVH Types:

**ECCENTRIC LVH**

Asymmetric

**Septal**

Hypertrophy

**(ASH)**
Different LVH Types:
ECCENTRIC LVH

Apical Hypertrophy (AH)
Prevalence of LVH in male and female FD

\textbf{Age}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{chart.png}
\caption{Prevalence of LVH in male and female FD by age.}
\end{figure}

\textit{Kampmann C et al. Int J Cardiol. 2008}
Prevalence of different types of **LV Morphometry** in men and women with FD

*Kampmann C et al. Int J Cardiol. 2008*
LVH –
Relationship of LV mass/relative wall thickness

LV Mass (g) = 0.8\{1.04\{([LVEDD + IVSd + PWd]^3 - LVEDD^3)\} + 0.6\}
Prevalence of different types of LV Morphometry in men and women with FD

Binary Sign

• Enhanced echo reflectivity of the endocardial border.
• Controversial
• Endomyocardial glycosphingolipid compartmentalization.
• Lacks sensitivity and specificity in Fabry’s cardiomyopathy.
Echo and **LV Endomyocardial biopsy** from 2 patients FD cardiomyopathy (A,D and B,E, respectively) and a patient HCM (C,F).

**Echo** → “Binary Sign” of LV endocardial border in 2 Fabry patients (A,B) reflecting GL3 compartmentalization.

**Biopsy**- thickened endocardium (End), enlarged & engulfed smooth muscle cells (SMC), subendocardial empty space (SES), and a prominent involvement of subendocardial myocardial layer (SL), - middle layer (ML) appears partially spared (D,E).

- The Echo pattern is absent in HCM (C), despite a similar thickening of the endocardium (F).
1. Sarcomeric Hypertrophic Cardiomyopathy (HCM)
2. Hypertensive Heart Disease
3. Athlete’s Heart
4. Cardiac Amyloidosis
5. Danon Disease (Lysosome-associated membrane protein-2 deficiency – LAMP-2 deficiency), GSD IIb
6. Friedreich Ataxia
7. Mucopolysaccharidoses (MPS)
8. Myocardial Oxalosis
9. Pompe Disease (Glycogen Storage Disease type IIa)
10. Niemann-Pick Disease
LV Diastolic Dysfunction
Tissue Doppler Imaging

- In early stages, subtle impairment in LV Fx detected by TDI and strain analysis.
- TDI abnormal prior to LVH.
- In heterozygous females, TDI abnormalities confirmed by EM Biopsy.
- TDI abnormalities seen early in posterolateral wall (late sign on Echo).

Sadick N et al. Heart Lung Circ. 2007
Strain & Strain Rate

- Assessment of regional and global wall motion and tissue deformation
- Systolic and diastolic function.
- May detect preclinical signs of diastolic dysfunction in absence of other signs of LVD.
- Early marker preceding measurable LVH.
- Early sign for early (ERT).

Hashimoto I et al. J Am Coll Cardiol.
The Tei Index is a sensitive indicator of diastolic dysfunction. It is defined as the sum of isovolumic contraction and relaxation time, divided by the LV ejection time.

For patients with familial dilated cardiomyopathy (FD):
- Increased Tei index
- Thinning of basal posterior wall
- Progression of cardiomyopathy
- Development of functional class III HF Sx
- Death

Kawano M et al. Am J Cardiol. 2007

Normal ≤ 0.39 ±0.05
Advanced Fabry Disease: Fibrosis and Thinning
**Tei Index**

- The sum of isovolumic contraction and relaxation time, divided by the LV ejection time.
- A sensitive indicator of diastolic dysfunction.

**Patients with FD:**
- *increased Tei index & thinning of basal posterior wall*
  - progression of cardiomyopathy
  - development of functional class III HF Sx
  - death

*Kawano M et al. Am J Cardiol.2007*

Normal ≤ 0.39 ±0.05
Echo: Basal Postero-lateral Fibrosis

Valvular Disease in FD

- Usually Mild
LGE on MRI
Posterolateral Segment
Progression of Fabry Disease
Cardiac Complications

- LVH
  - Diastolic dysfunction
  - Can progress to **heart failure**

References:

Progression of Fabry Disease to Major Clinical Events and Premature Death

Clinical status

MORBIDITY

Early clinical symptoms

Major clinical events

MORTALITY

Premature death

Age (yrs) 0 10 20 30 40 50 60

GL-3 accumulation // Progression of clinical disease

Clinical Manifestations
Life Expectancy

Clinical Manifestations

Deaths per 100 person-years of follow up

Age Category (years)

Males

Females

Common Misdiagnoses

- **Auto immune disease**
- **Connective tissue disorder**
  - RA
  - Juvenile arthritis
  - Rheumatic fever
  - Fibromyalgia / chronic fatigue syndrome
  - Raynaud’s syndrome
- **Neurological**
  - Multiple sclerosis
  - Chronic intermittent demyelinating polyneuropathy
  - Neurosis / malingering
- **Cardiovascular:**
  - Myocarditis
  - Vasculitis/ Petechiae
  - Growing pains
Diagnosis of Fabry Disease

- Several specialists before diagnosis\(^1\)
- Misdiagnoses and diagnostic delays are common → progressive, irreversible tissue damage
- Once suspected → confirmatory tests\(^2\):
  - \(\alpha\)-Gal A enzyme activity in leukocytes, plasma, dried blood spots (DBS)
  - Molecular genetic analysis

\(^1\)Desnick et al 2003, Intern Med; 138:338-46
\(^2\)Oqvist et al 2009; NDT; 24:1736-43
\(^3\)Wilcox et al 2008; Mol Genet Metab; 93:112-28
Definite Diagnosis

**α-Gal A Enzyme Assay, Genotyping**

- Measuring α-Gal A enzyme activity in **leukocytes** is the gold standard in **males**
- In **females**, α-Gal A enzyme activity maybe in normal to low normal range
- *When suspected* → **molecular genetic analysis** → determine diagnosis
  - Most families have “private” mutations
- **One new** index patient → ~ **5 patients** in that family →
  - Family screening and genetic counseling

Oqvist et al 2009; *NDT*; 24:1736-43
A considerable number of patients with one of the major signs/symptoms of Fabry disease can be identified by screening.

<table>
<thead>
<tr>
<th>Population</th>
<th>Prevalence of Fabry Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
</tr>
<tr>
<td>Dialysis</td>
<td>0.33%</td>
</tr>
<tr>
<td>Renal transplant</td>
<td>0.38%</td>
</tr>
<tr>
<td><strong>Left ventricular hypertrophy</strong></td>
<td><strong>0.9-3.9%</strong></td>
</tr>
<tr>
<td>Premature stroke</td>
<td>4.2%</td>
</tr>
</tbody>
</table>

Linthorst et al 2009; *J Med Genet*; in press
• Initiated in 2001, the Fabry Registry is the largest observational database of Fabry patients in the world
• Focus on key Fabry clinical events and assessments
• Scientific oversight by physician boards
• As of Dec. 2008, contains data from 3030 patients from 41 countries
• Goals of the Fabry Registry
  – Enhance the understanding of the variability, progression and natural history of Fabry disease
  – Assist with the development of patient monitoring recommendations and reports to help clinicians optimize care
  – Evaluate the long-term safety and effectiveness of ERT.
Treatment Options for Fabry Disease

**Symptom-Based**
- pain management,
- ACEI/ARBs, dialysis, kidney transplant, cardiac pacing, anti-depressants, hearing aids)

**Disease-Specific Therapy**
- Enzyme replacement therapy (ERT): *Agalsidase-β*

**Optimal care:**
- disease-specific and supportive treatment
- regular follow up with a multidisciplinary team experienced in FD.
Agalsidase beta ERT

**Composite:** Renal, Cardiac and CV events

Changes in Echo Parameters with 1, 2, and 3 years of Agalsidase-beta ERT for No fibrosis, Mild and Severe Fibrosis


<table>
<thead>
<tr>
<th>Table 3. Changes in Echocardiographic Data of the Fabry Subgroups of Fibrosis During 3 Years of ERT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrosis</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>LVEDD</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>PWT, mm</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Septum, mm</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>LV mass, g</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
Changes in Echo Parameters with 1, 2, and 3 years of Agalsidase-beta ERT for No fibrosis, Mild and Severe Fibrosis

Fabry Disease

Screening Protocol
Fabry’s Disease
Prevalence among patients with Chronic Kidney Disease and Left Ventricular Hypertrophy

Research Project
Department of Cardiovascular Disease
KFSH-D
28.4.2014
Prevalence of Fabry Disease among patients with Chronic Kidney Disease and Left Ventricular Hypertrophy

Total No. 400 pts.

- Chronic Kidney Disease (CKD) +/- Dialysis
- Kidney Transplant (Pre- & Post)

- Left Ventricular Hypertrophy
- Echo +/- EKG

Dried Blood Spot Test (DBST)

- Negative
- Positive in Female
- Positive in Male

- Confirming Gene Test
- Positive
- Offer ERT & FU

Regular FU
Summary

• FD a progressive, LSD, multi-organ, life-threatening disease affecting both males and females, *underdiagnosed*
• Females may be as severely affected as males
• Suspected:
  – 1) CKD/renal insufficiency, proteinuria, albuminuria;
  – 2) LVH of unknown etiology, arrhythmias;
  – 3) stroke of unknown etiology;
  – 4) neuropathic pain;
  – 5) GI distress;
  – 6) heat/cold intolerance;
  – 7) positive family history
  – 8) angiokeratoma and corneal whorling
• Testing:
  – enzyme activity assay in males and (additionally) DNA testing in females
• After confirmation → screening of *family*
• *Early diagnosis and treatment* critical to achieve best outcomes.
Thanks

End
Referrences


• Semithin (A) and ultrathin (B,C) sections from LV endomyocardial biopsy of the same patient of Figures 1A and 1D. In panel A, osmiophilic bodies intensely stained by Azur II seen in endocardium, subendocardial space, and in myocardium.

• In **subendocardial space**, they are localized in the region of empty spaces seen at H and E histology sections.

• In **myocardial tissue**, a gradient of storage material seen from subendocardial to inner layer.

• **Electron microscopy (B,C)**: osmiophilic bodies (GL3) organized in membrane-bounded bodies diffusely present in the context of the endocardium (End), occupying the subendocardial space as a free storage material and inside the myocytes (Myo).

• Arrows: membrane-bounded bodies at boundaries between a myocardiocyte and subendocardial space → release from cell to extracellular space.

*J Am Coll Cardiol. 2006.*