How to Differentiate Patients with LV Hypertrophic Disorders

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1. To make an accurate diagnosis in patients with clinically unexplained left ventricular hypertrophy (LVH) is often difficult.

2. Most of the patients have been diagnosed as having hypertrophic cardiomyopathy.

3. Correct diagnosis becomes important, because specific treatment is now available for some of the disorders.

4. Fabry disease is one of the disorders for which a specific treatment has been developed.
Fabry Disease

1. In cardiology, Fabry disease including cardiac variant have been classified as one of the specific cardiomyopathies.

2. It has been reported that the disease may be more common than previously believed.

3. Enzyme replacement therapy (ERT), a specific and effective therapy, is now available for the disease.

4. It becomes very important for cardiologists to differentiate Fabry disease at early stage.
Fabry Disease

1. Deficiency of the lysosomal hydrolase $\alpha$-galactosidase A ($\alpha$-gal A)

2. Defect leads to the systemic accumulation of glycolipids, especially ceramidetrihexoside.

3. X–linked, panethnic disorder: frequency of $\sim$1/40,000 males in the USA

4. Manifestations due to accumulation of glycolipids mainly in vascular endothelial cells
   Angiokeratoma, Acroparesthesias, Hypohidrosis, Corneal opacities.
   Dysfunction of the kidney, brain, and heart.
Atypical Variant of Fabry Disease (Cardiac Fabry Disease)

1. First reported in 1989
2. Manifestations limited to the heart
3. Patients have LVH due to deposition of glycolipids in the cardiomyocytes.
Overview

1. Incidence
2. Clinical Features
3. ERT and the heart
1603 male patients referred to the cardiology section of Kagoshima University Hospital

Echocardiogram (≥13 mm)

230 patients identified with LVH

Measurement of plasma α-gal A activity

7 patients diagnosed with Fabry disease

Assessment of clinical manifestations
Evaluation of endomyocardial–biopsy findings
Gene analysis of the α–gal A gene

Plasma $\alpha$–Gal A Activity in Male Patients With LVH

### Characteristics of 7 Patients Diagnosed With Fabry Disease

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>66</td>
<td>69</td>
<td>62</td>
<td>62</td>
<td>55</td>
<td>70</td>
</tr>
<tr>
<td>Plasma α-gal A (nmol/hr/ml)</td>
<td>1.2</td>
<td>0.6</td>
<td>1.2</td>
<td>0.6</td>
<td>0.4</td>
<td>0.7</td>
</tr>
<tr>
<td>LV wall thickness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVSth (mm)</td>
<td>20</td>
<td>20</td>
<td>13</td>
<td>13</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>LVPWth (mm)</td>
<td>20</td>
<td>17</td>
<td>13</td>
<td>12</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>Hypertension</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Albuminuria</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Cerebrovascular damage</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Angiokeratoma</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Acroparesthesias</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hypohidrosis</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Corneal opacities</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>
1. Seven unrelated patients with atypical variant of Fabry disease, whose manifestations were limited to the heart, were found among 230 men with LVH (3% incidence rate).

2. We designated these cardiac variants as “cardiac Fabry disease.”

3. Fabry disease should be considered as a cause of unexplained LVH.
153 consecutive male patients who had been given a diagnosis of HCM at St. George’s Hospital in UK

Measurement of plasma $\alpha$-gal A activity

\[ \downarrow \]

Patients given a diagnosis of Fabry disease

\[ \downarrow \]

Assessment of clinical manifestations and echocardiographic findings

Plasma α-gal A Activity in 153 Male Patients With HCM in UK

Plasma α-gal A activity (nmol/hr/ml)

7.4±2.7 (n= 147)

0.4±0.3 (n= 6)
### Prevalence of Fabry Disease in Kagoshima and in UK

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Kagoshima</th>
<th>UK</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVH</td>
<td>230</td>
<td>93</td>
</tr>
<tr>
<td>HCM</td>
<td>153</td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Fabry disease</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>
# Prevalence of Fabry Disease in Patients With HCM in Germany

## Subjects:
250 consecutive patients with HCM in Germany

## Methods:
Right ventricular endomyocardial biopsy

<table>
<thead>
<tr>
<th></th>
<th>No. of patients</th>
<th>Fabry disease</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>154</td>
<td>17</td>
<td>11.0%</td>
</tr>
<tr>
<td>Female</td>
<td>96</td>
<td>4</td>
<td>4.2%</td>
</tr>
<tr>
<td>Total</td>
<td>250</td>
<td>21</td>
<td>8.4%</td>
</tr>
</tbody>
</table>

Beer et al., Eur Heart J 2000; 21 suppl: 424
## Prevalence of Fabry Disease in Patients With HCM in Italy

**Subjects:** 96 consecutive patients with HCM in Italy

**Methods:** Endomyocardial-biopsy Pathological examination

<table>
<thead>
<tr>
<th></th>
<th>No. of patients</th>
<th>Fabry disease</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>62</td>
<td>2</td>
<td>3.3%</td>
</tr>
<tr>
<td>Female</td>
<td>34</td>
<td>4</td>
<td>12.0%</td>
</tr>
<tr>
<td>Total</td>
<td>96</td>
<td>6</td>
<td>6.3%</td>
</tr>
</tbody>
</table>

Chimenti et al., Circulation 2004; 110: 1047–1053.
1. Fabry disease may present with a several percent incidence rate in patients with unexplained LVH among different ethnic population.

2. A multicenter study for screening of cardiac Fabry disease among patients with LVH in Korea is now underway.

3. Plasma $\alpha$-gal A activities should be evaluated for patients with unexplained LVH.
Overview

1. Incidence
2. Clinical Features
3. ERT and the heart
Subjects:

11 male patients with cardiac Fabry disease

Age at diagnosis; 46 – 73 (yr)
Mean; 56 (yr)

Methods:

1) Echocardiogram
2) Cardiac catheterization
3) ECG, Holter ECG
# Cardiac Findings at Diagnosis

<table>
<thead>
<tr>
<th>Echocardiogram</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVH (≥13 mm)</td>
<td>11 / 11 (100%)</td>
</tr>
<tr>
<td>LV dilatation (≥58 mm)</td>
<td>2 / 11 (19%)</td>
</tr>
<tr>
<td>LV asynergy</td>
<td>8 / 11 (73%)</td>
</tr>
<tr>
<td>Deteriorated FS (27% ≥)</td>
<td>6 / 11</td>
</tr>
<tr>
<td></td>
<td>(55%)</td>
</tr>
</tbody>
</table>

<p>| Cardiac catheterization                |                 |
| Elevated LV EDP (≥13 mmHg)            | 9 / 10 (90%)    |</p>
<table>
<thead>
<tr>
<th>ECG Findings at Diagnosis</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Permanent pace maker</td>
<td>2 / 11 (18%)</td>
</tr>
<tr>
<td>Atrioventricular block</td>
<td>4 / 11 (36%)</td>
</tr>
<tr>
<td>Intraventricular conduction delay</td>
<td>7 / 9 (78%)</td>
</tr>
<tr>
<td>LV high voltage</td>
<td>4 / 9 (44%)</td>
</tr>
<tr>
<td>Abnormal Q wave</td>
<td>4 / 9 (44%)</td>
</tr>
</tbody>
</table>
Time Course of the Disease

1. Attenuation of LVH
   Thinning of basal posterior wall

2. Worsening of LV dysfunction
   Severe diastolic and systolic dysfunction

3. Worsening of conduction delay and/or VPC
   Attenuation of LV high voltage

Onset of heart failure and/or fatal arrhythmia
29 yr, Male

Mild LVH
43 yr, Male

Mimicking HCM
52 yr, Male

Mimicking HCM
51 yr, Male

Mimicking dilated phase of HCM
77 yr, Male

Mimicking dilated phase of HCM
77 yr, Male
## Clinical Characteristics of Autopsied Patients

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of death (yr)</td>
<td>66</td>
<td>68</td>
<td>63</td>
<td>66</td>
<td>64</td>
</tr>
<tr>
<td>Cause of death</td>
<td>Ventricular fibrillation</td>
<td>Heart failure</td>
<td>Heart failure</td>
<td>Heart failure</td>
<td>Heart failure</td>
</tr>
<tr>
<td>Plasma $\alpha$-gal A (nmol/hr/ml)</td>
<td>1.2</td>
<td>1.2</td>
<td>1.3</td>
<td>1.0</td>
<td>0.4</td>
</tr>
<tr>
<td>IVSth (mm)</td>
<td>20</td>
<td>17</td>
<td>16</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>LVPWth (mm)</td>
<td>20</td>
<td>14</td>
<td>16</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Coronary angiogram</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Albuminuria</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.2</td>
<td>0.9</td>
<td>0.9</td>
<td>1.1</td>
<td>-</td>
</tr>
<tr>
<td>Angiokeratoma</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Acroparesthesia</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hypohidrosis</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Corneal opacity</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Pathological Findings of the Heart

Case 2

Case 3

H.E. staining

T.B. staining

staining

staining

staining

staining
Electron Microscopy

Low magnification

High magnification
Significance of Asymmetric Basal Posterior Wall Thinning in Patients with Cardiac Fabry’s Disease.

Kawano, Takenaka et al., Am J Cardiol 2007; 99.

To evaluate whether disappearance of basal posterior hypertrophy and elevation of Tei index can be predictors of cardiac death.
Event–free Rate:
Disappearance of Basal Posterior Hypertrophy
and Cardiac Death

IVS/PW >1.3
Cardiac death

67.2 ± 2.2 yr
71.9 ± 1.7 yr

Kawano, Takenaka, et al. (p<0.05)
Am J Cardiol 2007, 99.
Event-free Rate:
Tei index >0.60 and Cardiac Death

- Tei index >0.60: 66.8 ± 2.5 yr
- Cardiac death: 71.9 ± 1.7 yr

(p<0.05)

Kawano, Takenaka, et al.
Am J Cardiol 2007, 99.
Disappearance of basal posterior hypertrophy and elevated Tei index is a characteristic echocardiographic finding which precedes cardiac death in patients with cardiac Fabry disease.
Female carriers (Heterozygote) –

1. Fabry disease is an \( X \)-linked disorder.

2. Female carriers have 2 \( X \) chromosomes, one is normal and the other is mutated.

3. At the cellular level, female carriers have two populations of cells, one with normal and the other with mutant enzymatic activity resulting from the random inactivation of one \( X \) chromosome in each cell early in embryogenesis.
Female carriers (Heterozygote) –

1. Theoretically, 50% of the cells are normal and the remaining 50% are diseased in female carriers.

2. Female carriers may have attenuated form of the disease. They usually are asymptomatic, although rarely can be as severely affected as males.
Endomyocardial–Biopsy Specimen

Male
(hemizygote, X’Y)

All cells are Fabry

Female
(heterozygote, X’X)

Normal cells
Fabry cells
56 yr, Female

Looks like normal
61 yr, Female

Mimicking HCM
78 yr, Female

Mimicking dilated phase of HCM
Overview

1. Incidence
2. Clinical Features
3. ERT and the heart
Treatment for Fabry Disease

1. Enzyme Replacement Therapy (ERT)
   - Approved in Europe (2001)
   - Approved in USA (2003)
   - Approved in Japan (2004)
   - Approved in Korea (2004)

2. Gene Therapy
   - Experimental studies using retroviral, adeno-associated viral, or lentiviral vectors.
Improvement of cardiac function during enzyme replacement therapy in patients with Fabry disease: A prospective strain rate imaging study

Weidemann et al., Circulation 2003; 108.
# Echocardiographic and MRI Findings Before and After ERT

16 patients (Age 42±3 yr)

<table>
<thead>
<tr>
<th>Metric</th>
<th>Before ERT</th>
<th>After ERT (12 months)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DcT (µs)</td>
<td>242±11</td>
<td>258±12</td>
<td>n.s.</td>
</tr>
<tr>
<td>E/A</td>
<td>1.3±0.2</td>
<td>1.4±0.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>EF (%)</td>
<td>62±1</td>
<td>64±1</td>
<td>n.s.</td>
</tr>
<tr>
<td>LVPWth (mm)</td>
<td>13.8±0.6</td>
<td>11.8±0.6</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>LV mass (g)</td>
<td>201±18</td>
<td>180±21</td>
<td>p&lt;0.05</td>
</tr>
</tbody>
</table>
LV Radial Function
Before and After 6 and 12 Months of ERT

Weidemann et al., Circulation 2003; 108.
Impact of enzyme replacement therapy on cardiac morphology and function and late enhancement in Fabry’s cardiomyopathy

Beer et al., Am J Cardiol 2006; 97.
Efficacy of ERT: Changes of LV mass

Fibrosis (+)

n.s.

211 ± 58 g
195 ± 64 g

Fibrosis (-)

p < 0.01

160 ± 23 g
145 ± 28 g

First studies have done for patients with preserved global LV function and have shown efficacy of ERT to reduce LVH and improve regional LV function.
Enzyme Replacement Therapy Questions need to be clarified

1. Who should be treated?
   All hemizygotes and heterozygotes?

2. When should ERT be started?
   Is ERT effective for patients with deteriorated LV function?

3. How long should ERT be continued?
   For life-long?
Specific and effective therapy is now available for patients with Fabry disease, so it is very important to diagnose patients with the disease at early stage.
Can cardiologists suspect Fabry disease, especially cardiac variant of the disease, by routine non-invasive cardiac examinations?
1. It is not easy to differentiate Fabry disease from the other unexplained LVH by routine non-invasive examinations such as ECG, echocardiogram and MRI.

2. At present, plasma $\alpha$-galactosidase A activities should be evaluated for patients with unexplained LVH.

3. We wish to find out some specific findings which can lead to suspect Fabry disease by routine examinations.
Cardiac Findings at Diagnosis

1. Left ventricular hypertrophy
2. LV dysfunction
diastolic and/or systolic dysfunction
3. ECG abnormalities
   atrioventricular block,
intraventricular conduction delay,
LV high voltage,
abnormal Q wave,
VPC
28 yr, Male

Looks like normal
81 yr, Male

Mimicking dilated phase of HCM
81 yr, Male
57 yr, Female

Mimicking HCM
Event–free Rate:
Disappearance of Basal Posterior Hypertrophy and NYHA III Heart Failure

<table>
<thead>
<tr>
<th>Event</th>
<th>Event</th>
<th>Event</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>VS/PW &gt;1.3</td>
<td>NYHA III</td>
<td>VS/PW &gt;1.3</td>
<td>NYHA III</td>
</tr>
<tr>
<td>67.2 ±2.2 yr</td>
<td>71.2 ±2.1 yr</td>
<td>67.2 ±2.2 yr</td>
<td>71.2 ±2.1 yr</td>
</tr>
</tbody>
</table>

NYHA III heart failure (p<0.05)

Event–free Rate:
Tei index >0.60 and NYHA III Heart Failure

Tei index >0.60 66.8 ±2.5 yr
NYHA III 71.2 ±2.1 yr

Safety and efficacy of recombinant human α-galactosidase A replacement therapy in Fabry’s Disease.

Efficacy of ERT

Mean Capillary Endothelium Scores

α-gal A vs Placebo

Baseline vs Week 20

Kidney Skin Heart

Fabry’s disease cardiomyopathy: Echocardiographic detection of endomyocardial glycosphingolipid compartmentalization

Pieroni et al., J Am Coll Cardiol 2006; 47.
Echocardiographic binary appearance of LV endocardial border, reflecting endomyocardial glycosphingolipids compartmentalization, represents a sensitive and specific diagnostic hallmark of Fabry’s disease cardiomyopathy.

Pieroni et al., J Am Coll Cardiol 2006; 47.