Fabry Disease:
A Case-based Presentation

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James Clarke, Bruce Precious

Dalhousie University
Inspiring Minds
Objectives

- Recognise the **cardiac manifestations** of Fabry disease.

- Appropriately integrate Fabry disease in the **differential diagnosis** of hypertrophic and infiltrative cardiomyopathies.

- Identify the **other imaging features** of Fabry disease, including **cerebrovascular** and **renal** involvement.
Introduction

- Rare X-linked recessive genetic disorder
  - Men develop multisystem disease at an earlier age
  - Women can have a spectrum of involvement varying from asymptomatic carrier to severe disease

- Mutation GLA gene $\rightarrow$ deficiency $\alpha$-galactosidase A $\rightarrow$ accumulation glycosphingolipids in vascular endothelium and other tissues
  - Genetic testing available
  - Enzyme replacement therapy available since 2001

Epidemiology

- Prevalence up to 0.1 per 10 000 (possibly more prevalent since many patients are though to be under/misdiagnosed)
- Prevalence in men with unexplained left ventricular hypertrophy (LVH): $\geq$3% \(^1\)
- Prevalence in female with late onset LVH possibly up to 12% \(^2\)
Two patients with Fabry disease

<table>
<thead>
<tr>
<th>Cases</th>
<th>Short-axis cine MR in diastole</th>
<th>LGE MR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case #1: 68♀ with Fabry disease</td>
<td><img src="image1.png" alt="MRI Image" /></td>
<td><img src="image2.png" alt="MRI Image" /></td>
</tr>
<tr>
<td>Case #2: 60♂ with Fabry disease</td>
<td><img src="image3.png" alt="MRI Image" /></td>
<td><img src="image4.png" alt="MRI Image" /></td>
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</table>

What do they have in common? Concentric LV hypertrophy Inferolateral mesomyocardial delayed enhancement (arrow)
**Cardiac Involvement**

**Left ventricular hypertrophy (LVH)**
- LVH is the main cardiac finding in Fabry disease

**Case #3: 60♀ with Fabry disease**
- Short-axis cine MR image showing mild septal predominant LV hypertrophy

- Typical pattern → Concentric LVH

- But other patterns possible including:
  - Apical predominance
  - Asymmetrical septal hypertrophy
Cardiac Involvement

Case #4: 64♀ with Fabry disease

Short-axis cine MR image shows the septum to be at the upper limit of normal in thickness.

Mesomyocardial delayed enhancement is visualized in the basal inferoseptal segment (arrow).

Delayed myocardial enhancement:
- Although variable, predominance in Fabry disease has been described as:
  - Inferolateral wall
  - Basal-mid cavity level
  - Mesomyocardial
- This distribution is helpful to suggest FD in a patient with new LV hypertrophy.
Cardiac Involvement

Case #5: 51♂ with Fabry disease

CT MPR in the plane of the aortic valve shows calcification and thickening of the aortic valve leaflets

Case #6: 59♂ with Fabry disease

4 chamber cine MR showing thickening of the mitral leaflets

Valve involvement
- Thickening of the aortic and mitral valves leaflets (25.5%)
- Mitral valve prolapse (10.9%)

Right ventricle involvement
- Common
- Can progress to severe RV dysfunction

Arrhythmia
- Conduction system involvement → shortening of atrioventricular conduction → atrioventricular block
- Supraventricular and ventricular arrhythmias

Differential Diagnosis of Cardiac Fabry Disease

- Hypertrophic cardiomyopathy
- Sarcoidosis
- Myocarditis
- Other storage diseases
  - Amyloidosis
  - Iron overload
  - Other glycogen/lysosomal storage diseases
- Increased LV afterload
  - Hypertensive cardiomyopathy
  - Aortic stenosis
- Athlete heart
Diagnosis?

- Hypertrophic cardiomyopathy (HCM)
**Differential Diagnosis of Cardiac Fabry Disease**

**Hypertrophic cardiomyopathy**

Differentiation of Fabry disease from HCM is difficult.

- A few centers assess for Fabry disease by doing genetic testing for new cases of HCM.

<table>
<thead>
<tr>
<th></th>
<th><strong>HCM</strong></th>
<th><strong>Fabry disease</strong></th>
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<tbody>
<tr>
<td><strong>Hypertrophy</strong></td>
<td>- Asymmetric septal LVH most common distribution</td>
<td>- Most commonly concentric</td>
</tr>
<tr>
<td></td>
<td>- Minority have concentric form (~5%)</td>
<td>- Asymmetric septal hypertrophy can be seen</td>
</tr>
<tr>
<td><strong>Delayed enhancement</strong></td>
<td>- Typically in the septum or where wall thickening is predominant</td>
<td>- Predominance for the basal inferolateral LV wall</td>
</tr>
<tr>
<td></td>
<td>- When inferolateral LV wall involved, often other large areas are also involved</td>
<td></td>
</tr>
<tr>
<td><strong>LVOT obstruction</strong></td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>T1 mapping</strong></td>
<td>Common</td>
<td>Low native T1</td>
</tr>
</tbody>
</table>

*Cardiac T1 mapping is a MR technique that is not routinely performed at the moment in most centers. T1 mapping quantifies intrinsic pathologic processes involving the myocardium by using native T1 measures and post-contrast measures.*


Differential Diagnosis of Cardiac Fabry Disease

Case #8: 62♀ with LVEF of 30% and severe right ventricle dilatation on echocardiogram

Short-axis cine MR image shows LV wall thickening

LGE MR image shows mesomyocardial delayed enhancement involving the lateral and inferior wall of the LV
Diffuse LGE throughout the right ventricular wall is also seen

T2 weighted MR image shows edema in the same segments showing LGE

### Table: Sarcoidosis vs. Fabry disease

<table>
<thead>
<tr>
<th></th>
<th>Sarcoidosis</th>
<th>Fabry disease</th>
</tr>
</thead>
</table>
| **Hypertrophy**       | - Wall thickening during the inflammatory phase (inflammation, granulomatous infiltration)  
  - Focal wall thinning in chronic phase | Concentric LVH typical               |
| **Delayed enhancement**| Any pattern of non-ischemic LGE possible:  
  - Most common transmural or mesomyocardial, but subepicardial also seen | Predominance for mesomyocardial basal inferolateral LV wall |
| **Other**             | Evidence of extra-cardiac sarcoidosis                                        |                                      |
**Differential Diagnosis of Cardiac Fabry Disease**

**Case #9: 41  with chest pain, recent viral infection and mild elevation of troponins**

![Short-axis cine MR image](image1.png)

- Short-axis cine MR image shows **minimal LV wall thickening**

![LGE MR image](image2.png)

- LGE MR image shows **subepicardial delayed enhancement** involving the lateral and inferior wall

![T2 weighted MR image](image3.png)

- T2 weighted MR image shows **edema** in the same region

<table>
<thead>
<tr>
<th></th>
<th><strong>Myocarditis</strong></th>
<th><strong>Fabry disease</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertrophy</td>
<td><strong>Mild transient</strong> increase in wall thickness possible (acutely)</td>
<td>Concentric LVH typical LHV can sometime be subtle</td>
</tr>
</tbody>
</table>
| Delayed enhancement | 2 common patterns:  
- Mesomyocardial in septum  
- Subepicardial in the lateral wall | Predominance for mesomyocardial basal inferolateral LV wall |
| T2             | Transient increased T2 (acutely)                                               |                                           |
| Other          | Sometimes associated with **pericarditis**                                     |                                           |
| T1 mapping*    | High native T1                                                                 | Low native T1                              |
Differential Diagnosis of Cardiac Fabry Disease

Case #10: 64 with new heart failure → LVH and LVEF of 30% noted on echocardiogram

- Short-axis cine MR image shows concentric LV hypertrophy
- LGE MR image shows diffuse subendocardial delayed enhancement involving both left and right ventricles
- The blood pool is also darker than usual

<table>
<thead>
<tr>
<th>Other storages diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyloidosis</td>
</tr>
<tr>
<td>Typical pattern of diffuse subendocardial delayed enhancement (as seen in case #10)</td>
</tr>
<tr>
<td>Iron overload</td>
</tr>
<tr>
<td>T2* sequence to assess for myocardial iron overload</td>
</tr>
<tr>
<td>Other lysosomal/glycogen storage disease (e.g. Danons disease)</td>
</tr>
<tr>
<td>Non-cardiac signs and symptoms seen in these other diseases are most helpful to differentiate from Fabry disease</td>
</tr>
</tbody>
</table>

Most helpful findings to differentiate from Fabry disease
**Differential Diagnosis of Cardiac Fabry Disease**

**Case #11: 16σ hockey player**

- 4 chamber cine MR showing mild LV wall thickening
- No late gadolinium enhancement

**Left Ventricle**

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV End-Diastolic Volume</td>
<td>221.6 ml</td>
</tr>
<tr>
<td>LV End-Systolic Volume</td>
<td>88 ml</td>
</tr>
<tr>
<td>LV Ejection Fraction</td>
<td>60%</td>
</tr>
<tr>
<td>LV End-Diastolic Vol Index</td>
<td>120.7 ml/m²</td>
</tr>
<tr>
<td>LV End-Systolic Vol Index</td>
<td>48 ml/m²</td>
</tr>
<tr>
<td>Stroke Volume</td>
<td>133.6 ml</td>
</tr>
<tr>
<td>Cardiac Output</td>
<td>7.5 l/min</td>
</tr>
</tbody>
</table>

**Right Ventricle**

<table>
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<tr>
<th>Metric</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>RV End-Diastolic Volume</td>
<td>239.3 ml</td>
</tr>
<tr>
<td>RV End-Systolic Volume</td>
<td>87.2 ml</td>
</tr>
<tr>
<td>RV Ejection Fraction</td>
<td>64%</td>
</tr>
<tr>
<td>RV Stroke Volume</td>
<td>152 ml</td>
</tr>
</tbody>
</table>

**Physiologic adaptation:**

- Large end-diastolic volumes and stroke volumes

**Fabry disease**

<table>
<thead>
<tr>
<th>Hypertrophy</th>
<th>Overload cardiomyopathy</th>
<th>Fabry disease</th>
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<tbody>
<tr>
<td><strong>Hypertrophy</strong></td>
<td>Minimal LV wall thickening: usually less than 15 mm in σ and less than 12 mm in φ</td>
<td>Concentric mild LVH</td>
</tr>
<tr>
<td><strong>Delayed enhancement</strong></td>
<td>No LGE</td>
<td>Usually no LGE</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>Physiologic adaptation: - Large end-diastolic volumes and stroke volumes</td>
<td>Long standing systemic hypertension or aortic stenosis</td>
</tr>
</tbody>
</table>
Extra-cardiac Manifestations

- Cerebrovascular
- Peripheral nerves
- MSK
- Lung
- Renal
- Gastrointestinal
Neurovascular Involvement

Cerebrovascular involvement

- Signs and symptoms;
  - Headache, vertigo
  - Transient ischemic attacks, ischemic strokes
  - Vascular dementia
- High frequency of silent infarcts
  - Relative preference for posterior circulation described

- Fabry disease prevalence: Up to 4.9% of young patients with stroke*  
  [J Neurol Sci 2014; 344:5-19]

Case # 12: 37 with left side weakness

Axial T2 and Flair MR images show a small lesion in the anterolateral right thalamus (arrows)
Case #13: 51 with Fabry disease

Axial Flair MR images show:

- A large area of encephalomalacia in the right parietal lobe secondary to a remote infarct (yellow arrow)
- A more recent infarct in the right frontal lobe (blue arrow)
- Multiple white matter lesions in the cerebral hemispheres (green arrow)

Cerebrovascular involvement

- Large-vessel disease
  - Symptomatic stokes
- Small-vessel disease
  - Subcortical infarcts
  - Chronic white matter hyperintensities
    - Frequently asymptomatic
    - Involve subcortical and deep white matter
    - Symmetric
    - Increase with age

Fabry Disease
Axial T2 MR image show multiple hyperintense white matters lesions in the posterior fossa (yellow arrows)

Basilar artery ectasia (blue arrow) is also visualized

Multiple white matter lesions are seen in both cerebral hemispheres (green arrows)

**Cerebrovascular involvement**

- Large-vessel disease
  - Symptomatic strokes
- Small-vessel disease
  - Subcortical infarcts
  - **Chronic white matter hyperintensities**
    - Frequently asymptomatic
    - Involve subcortical and deep white matter
    - Symmetric
    - Increase with age

Case #14: 49\(\sigma\) with sudden deafness

Fabry Disease
Neurovascular Involvement

Case # 15 : 55♀ with Fabry disease
MR images show the basilar artery to be relatively increased in size (the basilar artery is usually smaller than the carotid arteries)

Case # 16 : 65♂ with Fabry disease
T1-W MR image shows mild hyperintensity in the R>L thalami

Cerebrovascular involvement
- Enlargement/dolichoectasia of the basilar artery
  - Frequently seen, more so with increased age and in men
- Pulvinar sign
  - Hyperintensity on T1-W MR of the postero-lateral thalami
  - Uni or bilateral
  - Thought to be related to subtle dystrophic calcifications
Differential Diagnostic of Neurovascular Fabry Disease

FD is included in the DDx of **multifocal white matter lesions** including:

- **Leukoaraiosis**
- **Multiple sclerosis (MS)**
  - At least 3 patients at our institution were initially thought to have MS before diagnosis of Fabry disease was made
- **Acute disseminated encephalomyelitis (ADEM)**
- **Progressive multifocal leukoencephalopathy (PML)**
- **Vasculopathies**
  - Vasculitis, Susac syndrome, CADASIL, arteriolosclerosis
- **Migraines**
Peripheral Nerves and MSK Involvement

**Peripheral neuropathy**
- Small nerve fiber damage
  - **Neuropathic pain** – hallmark of Fabry disease
  - Ongoing pain with exacerbations that are provoked by body temperature changes
  - Decreased cold sensation

**Musculoskeletal manifestations**
- Lymph node infiltration → lymphedema and infectious complications
- Osteoporosis/osteopenia
- Charcot foot
- Abnormally slender lower limbs
- Acute gout (renal failure related)
- Carpal tunnel syndrome
- Avascular necrosis
Lung Involvement

Case #17: 51 year-old male with Fabry disease with reduced forced expiratory volume in one second (FEV1)

Axial CT image shows bronchial wall thickening (arrow)

**Lung involvement**

- Obstructive lung disease more prevalent
- Small airway disease is secondary to hyperplasia of the bronchiolar smooth muscle cells
- Bronchial wall thickening can be seen on CT
Renal Involvement

**Kidney disease**
- Spectrum of severity:
  - Proteinuria → Endstage renal failure
  - Endstage failure typically reached after the 4th decade in men
- On sonography:
  - **Cysts** (cortical or parapelvic),
  - Small cysts in subcapsular location suggest Fabry disease
  - Increased echogenicity
  - Decreased cortical thickness

**Case #18:** 55 ♀ with Fabry disease and renal failure
US image of right kidney shows decreased cortical thickness

**Case #19:** 54 ♂ with Fabry disease and renal failure
US image of right kidney shows hyperechogenic kidney with cysts
Gastrointestinal Involvement

Case #20: 54\(\text{♂}\) with Fabry disease, presenting with abdominal pain and nausea

X-ray shows dilated colon with loss of haustral markings. On CT scan (not shown), there was no obstruction.

Case #21: 65\(\text{♂}\) with Fabry disease

Approximately 10% emptying at one hour, 38% emptying at 2 hour and 95% emptying at 4 hours, in keeping with slow initiation of gastric emptying.

 Delayed myocardial enhancement

- Autonomic system involvement may lead to intestinal dysmotility causing:
  - Gastroparesis
  - Pseudo-obstruction
  - Diverticular disease (duodenum, jejunum, colon)
  - Bacterial overgrowth
Conclusion

- Fabry disease is a rare X-linked recessive genetic disorder
  - Men develop multisystem disease at earlier age
  - Women can have a spectrum of involvement varying from asymptomatic carrier to severe disease

- When no family history available, the diagnosis may be challenging
  - Consider Fabry disease in patients with concentric left ventricular hypertrophy with typical LGE in a mesomyocardial inferolateral location
  - Consider Fabry disease in young patients with white matter hyperintensities or stroke with no apparent predisposing factors

- Enzyme replacement therapy is available → Early diagnosis is important
References