AN UNCOMMON CAUSE OF HEART FAILURE WITH NORMAL EJECTION FRACTION

Presented by Dr. Chu Hei Yu (TMH)
DIFFERENTIALS

- Valvular heart disease
- High output heart failure
- Pericardial diseases
- Cardiomyopathies
  - Restrictive cardiomyopathy
  - Hypertrophic cardiomyopathy
- Right heart failure
  - PH
  - RV infarct
- ARVC
Patient with heart failure

Echocardiogram shows preserved left ventricular ejection fraction (LVEF) with increased LV wall thickness

Hypertensive heart disease (patient has history of uncontrolled hypertension)

Infiltrative restrictive cardiomyopathy

Hypertrophic cardiomyopathy (patient has LVOT gradient, SAM of mitral valve, or asymmetric septal hypertrophy)

High output heart failure (patient has increased cardiac output, arteriovenous shunts, liver disease, hyperthyroid, myeloproliferative disorders)

Restrictive cardiomyopathy (RCM) (patient has normal LV chamber volumes, biatrial enlargement, increased LV filling pressures)

Constrictive pericarditis (patient has thickened pericardium, respirophasic discordance in LV-RV pressure and in mitral tricuspid inflow velocities)

Amyloidosis
Glycogen storage diseases such as Fabry disease
Endomyocardial fibrosis
Radiation heart disease
Iron overload cardiomyopathy
Idiopathic RCM

RESTRICTIVE CARDIOMYOPATHY

- HFpEF and predominant diastolic dysfunction due to stiff and thickened myocardium

- Echo features:
  - Normal LV size or hypertrophic LV
  - Preserved LV systolic function
  - Dilated biatria due to increased LVEDP
  - Diastolic dysfunction
DIASTOLIC DYSFUNCTION

- Mitral annular tissue doppler (E’)
- Speed of myocardial relaxation
- Mitral inflow pattern
CAUSES OF RCM

• Acquired causes:
  • Amyloidosis
  • Scleroderma
  • Carcinoid heart disease
  • Endomyocardial fibrosis
    • Hypereosinophilic syndrome
    • Drugs (Serotonin, methylsergide, ergotamine, anthracycline)
    • Radiation
  • Radiation

• Congenital causes:
  • Haemochromatosis
  • Anderson-Fabry disease
  • Glycogen storage disease (e.g. Gaucher’s disease)
ECHO FEATURES OF SPECIFIC RCM

- Fabry disease
  - Endocardial hyperechoic layer
  - Aortic and mitral valve thickening
- Hypereosinophilic syndrome
  - Acute necrotic stage; intermediate phase characterised by thrombus formation at damaged myocardium; fibrotic stage
  - Thrombus in apex despite absence of RWMA
- Amyloidosis
  - Sparkling appearance
  - Valves thickening
  - Apical sparing on global longitudinal strain
INTEGRATION WITH OTHER INFORMATION

• Systemic disease

• ECG findings

• Family history

  • X-linked lysosomal storage disease for Fabry

  • Autosomal dominant for HCM
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HYPERTROPHIC CARDIOMYOPATHY

- Hypertrophic cardiomyopathy
  - LV wall thickness of > 15mm
  - Absence of other pathology causing LVH (hypertension, aortic stenosis, subaortic membrane)
  - Not mandatory for diagnosis: Asymmetric septal hypertrophy, systolic anterior motion of mitral valve, dynamic LVOT obstruction
CASE HISTORY

- 65/F
- Unremarkable past health
- Strong family history of sudden deaths in her family including 3 of her maternal uncles and her maternal grandfather
- 2 brothers diagnosed with Fabry disease in Australia
- NYHA class II symptoms

ECG:
CASE HISTORY

- Echocardiogram:
  - Dilated LA. Concentric LVH. IVSd: 1.55cm.
  - Satisfactory LV systolic function. (EF 67% by Simpson). No RWMA
  - E’ 0.03m/s; E/A 1.00; E/E’ 32.37
  - Systolic anterior movement of mitral valve with moderate posteriorly directed MR
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CASE HISTORY

• Cardiac MRI
  • Normal LVEF with concentric LVH.
  • No late Gadolinium enhancement suggestive of myocardial fibrosis
CASE HISTORY

- Differential diagnosis of LVH:
FABRY DISEASE

- Commonest lysosomal storage disorder
- Estimated prevalence 1:8500 to 1:117000 male births
- X-linked inborn error
- Over 1000 genetic mutations have been identified
- Deficiency of enzyme alpha-galactosidase A (GAL-A)
- Resulting in lysosomal accumulation of glycolipids, primarily globotriasosylceramide (Gb3)
FABRY DISEASE

- Accumulation in skin -> Telangiectasias and angiokeratomas
- Accumulation in dorsal root ganglia -> Neuropathic pain
- Accumulation in renal cells -> Proteinuria, CKD
- Accumulation in vascular endothelial cells -> Stroke, coronary artery disease
- Accumulation in autonomic ganglia of bowel and mesenteric blood vessels -> Intestinal dysmotility
- Accumulation in cornea -> vortex keratopathy
- Accumulation in cardiac tissue cells -> Left ventricular hypertrophy, restrictive cardiomyopathy, conduction defects
FABRY DISEASE

• Wide spectrum of clinical manifestations depending on level of enzyme activity

• Classic Fabry disease
  • Predominantly in male
  • Begin in childhood or adolescence
  • Neurologic symptoms in second decade of life
  • Renal manifestations in third decade
  • Cardiac manifestations in fifth decade
FABRY DISEASE

- Atypical presentation
  - Cardiac variant
    - Fifth to eighth decade of life
    - Predominantly affects the heart
  - Renal variant
FABRY DISEASE

• Diagnostic process
  • Measure leukocyte alpha-Gal A activity level
    • In female heterozygous tend to be less accurate
  • Genetic testing
  • Plasma lysoGb3 level
CASE HISTORY

• Blood tests:
  - GLA 1.55umol/L/h (ref: 4.75 +/- 1.8); Partial alpha-galactosidase A deficiency
  - Abnormally high Lyso-Gb3 of 3.095ng/mL (normal range < 0.8)
<table>
<thead>
<tr>
<th>Table 3 Consensus criteria for initiation of ERT</th>
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<td><strong>No signs or symptoms</strong></td>
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*consistent with FD and not fully explained by other pathology; †according to international guidelines of kidney disease, KDIGO criteria; §in ml/min/1.73 m² corrected for age (>40 years: -1 ml/min/1.73 m²/year); ¶sinus bradycardia, AF, repolarization disorders; ERT = enzyme replacement therapy; GFR = glomerular filtration rate; MWT = maximal wall thickness; CNS = central nervous system; WMLs = white matter lesions; TIA = transient ischemic attack; GI = gastrointestinal.
ENDOMYOCARDIAL BIOPSY

- Biopsy result: Perinuclear vacuoles with marked reduction and displacement of the residual myofibrils to the periphery, consistent with Fabry’s disease
TREATMENT

• Treatment:
  • Enzyme replacement therapy (recombinant human alpha-Gal A)
    • IV infusion every 2 weeks
    • Agalsidase Alfa (Replagal), Agalsidase Beta (Fabrazyme)
  • Oral chaperone therapy - Migalastat
    • Stabilizes mutant alpha-GLA A enzymes, helping it function properly
    • Only patients with amenable mutation benefit from it
TREATMENT EFFICACY

• Effects on ERT:
  
  • Under-powered randomised controlled trials
  
  • 15 adult males with Fabry disease randomised into placebo group and ERT group
  
  • Significant reduction in left ventricular mass measured by MRI after 6 months of treatment (mean decrease of 11.5g in ERT group as opposed to increase of 21.8g in placebo)
  
  • Mean 20% reduction of myocardial Gb3 content in patients receiving ERT (assessed by endomyocardial biopsy) as compared to 10% in patients receiving placebo
  
TREATMENT EFFICACY

<table>
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<tr>
<th>Fibrosis</th>
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<th>1 Year</th>
<th>2 Years</th>
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<tr>
<td></td>
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<td>LVEDD</td>
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<tr>
<td>No</td>
<td>48 ± 4</td>
<td>49 ± 4</td>
<td>49 ± 6</td>
<td>49 ± 4</td>
<td>0.89*</td>
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<tr>
<td>Mild</td>
<td>49 ± 5</td>
<td>48 ± 5</td>
<td>47 ± 5</td>
<td>48 ± 6</td>
<td>0.99†</td>
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<tr>
<td>Severe</td>
<td>51 ± 12</td>
<td>49 ± 5</td>
<td>47 ± 3</td>
<td>49 ± 6</td>
<td>0.69†</td>
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<tr>
<td>No</td>
<td>13.0 ± 1.2</td>
<td>11.7 ± 1.6</td>
<td>11.3 ± 1.8</td>
<td>11.5 ± 1.6</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Mild</td>
<td>14.4 ± 2.2</td>
<td>13.1 ± 2.4</td>
<td>13.3 ± 2.4</td>
<td>12.9 ± 1.8</td>
<td>0.21†</td>
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<td>Severe</td>
<td>14.7 ± 2.7</td>
<td>13.3 ± 2.3</td>
<td>13.4 ± 2.5</td>
<td>12.8 ± 2.3</td>
<td>0.17†</td>
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<tr>
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<td>13.5 ± 1.4</td>
<td>12.1 ± 1.0</td>
<td>11.9 ± 1.2</td>
<td>12.0 ± 1.4</td>
<td>&lt;0.01*</td>
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<tr>
<td>Mild</td>
<td>14.4 ± 1.8</td>
<td>13.3 ± 1.9</td>
<td>13.4 ± 1.9</td>
<td>13.4 ± 1.4</td>
<td>0.20†</td>
</tr>
<tr>
<td>Severe</td>
<td>14.9 ± 3.0</td>
<td>14.3 ± 2.7</td>
<td>14.3 ± 2.6</td>
<td>14.1 ± 2.0</td>
<td>0.01†</td>
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<td>LV mass, g</td>
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<tr>
<td>No</td>
<td>238 ± 42</td>
<td>213 ± 46</td>
<td>201 ± 65</td>
<td>202 ± 46</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Mild</td>
<td>275 ± 62</td>
<td>244 ± 60</td>
<td>234 ± 47</td>
<td>244 ± 65</td>
<td>0.31†</td>
</tr>
<tr>
<td>Severe</td>
<td>303 ± 84</td>
<td>255 ± 58</td>
<td>246 ± 70</td>
<td>247 ± 45</td>
<td>0.24†</td>
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TREATMENT EFFICACY

• Migalastat
  • ATTRACT study
  • 18 month randomised controlled study on effects of migalastat on renal function.
  • Effects of heart also studied.
  • 57 patients with preliminary cell based assay confirmed responsiveness to migalastat and receiving ERT randomised to migalastat vs ERT group
  • LV mass index decreased significantly with migalastat treatment (-6.6g/m2)

STRAIGHTFORWARD DIAGNOSIS?

- 65/F

- Unremarkable past health

- Strong family history of sudden deaths in her family including 3 of her maternal uncles and her maternal grandfather

- NYHA class II symptoms

ECG:
CASE HISTORY

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  - E’ 0.03m/s; E/A 1.00; E/E’ 32.37 (Grade II/III diastolic dysfunction)
  - Systolic anterior movement of mitral valve with moderate posteriorly directed MR
  - Increased LVOT gradient (LVOT Vmax 2.72m/s; PG 29.6mmHg)
Fabry:
- Enzyme replacement therapy

HCM:
- Betablockers, verapamil, diltiazem
- Surgical myectomy
- Ablation
- ICD
HYPERTROPHIC CARDIOMYOPATHY VS FABRY DISEASE

• Prevalence of Fabry disease in patients with HCM?
  
  • 79 men with HCM -> check plasma alpha-galactosidase A level. -> 6 patients (7.6%) have low alpha galactosidase A level. Confirmed to have alpha galactosidase A gene mutation in genetic studies


  • 1386 patients with HCM (63.9% male with mean age of 57.9 years) -> rapid mutation screening of alpha galactosidase A gene -> 7 (0.5%) patients identified, 3 of them were men. 4 had concentric LVH, 3 had asymmetric septal hypertrophy

HYPERTROPHIC CARDIOMYOPATHY VS FABRY DISEASE

- ECG findings:
  - Fabry: Shortened PR interval in young age, heart block in older age

- History:
  - Signs and symptoms of classical Fabry

- Family history:
  - Pedigree
SUMMARY

• Differentials of heart failure with preserved ejection fraction

• Diagnosis of restrictive cardiomyopathy, hypertrophic cardiomyopathy and constrictive pericarditis

• Classical Fabry disease characteristics

• Be aware of atypical features in HCM patients that may point to Fabry
REFERENCES


MCQ

• Question 1:

• Which of the following is not required to make a diagnosis of hypertrophic cardiomyopathy?

A. Asymmetric septal hypertrophy
B. LV wall thickness > 15mm
C. LVOT gradient of > 30mmHg
D. A and C
MCQ

• Question 2:

• Which of the following tests would confirm the diagnosis of Fabry patient in a male patient with suspected Fabry disease?

  A. Genetic testing to search for disease causing mutation of GLA gene
  B. Alpha galactosidase A leukocyte activity
  C. Globotriasosylsphingosine (lysoGb3) level
  D. Endomyocardial biopsy