Hypertrophic Cardiomyopathy Update 2011

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What is Hypertrophic Cardiomyopathy?

- Presence of left ventricular hypertrophy unexplained by the loading condition
Epidemiology of HCM

- Common monogenetic cardiac disease
- Inherited as autosomal dominant with variable penetrance and expression
- Prevalence is 0.2 %
- Incidence of sudden cardiac death (SCD) 1-2 % in children and adolescence and 0.5 to 1 % in adult

1. Maron BJ et al, J Am Coll Cardiol. 2003
2. Elliot PM et al, J Am Coll Cardiol. 2000
3. Elliot PM et al, Lancet. 2004
Clinical Presentation of HCM

- Asymptomatic
- Diastolic heart failure (Mild → refractory symptoms → brunt out stage)
- Arrhythmia
  - syncope
  - SDC
Genetics of HCM - 2011 Update

- 60% of cases, HCM is caused by mutations in genes coding for cardiac sarcomere proteins

- > 600 different sarcomeric gene mutations are reported, majority are missense

- < 5% of cases, mutations in genes encoding Z-disc proteins and proteins involved in Ca regulation

- Autosomal dominant, but with incomplete penetrance and variable clinical expression
Table 1. Currently Known Genes Implicated in HCM

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Frequency in Patients With HCM Phenotype</th>
<th>Associated Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarcomeric mutations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MYH7</td>
<td>β-myosin heavy chain</td>
<td>25%–35%</td>
<td>Variable</td>
</tr>
<tr>
<td>MYBPC3</td>
<td>Myosin-binding protein C</td>
<td>20%–30%</td>
<td>Variable, late onset</td>
</tr>
<tr>
<td>TNN2</td>
<td>Troponin T</td>
<td>3%–5%</td>
<td>Sudden death</td>
</tr>
<tr>
<td>TNNI3</td>
<td>Troponin I</td>
<td>&lt;5%</td>
<td>Extreme heterogeneity</td>
</tr>
<tr>
<td>TPM1</td>
<td>Tropomyosin 1α</td>
<td>&lt;5%</td>
<td>Variable prognosis, sudden death</td>
</tr>
<tr>
<td>MYL2</td>
<td>Regulatory myosin light chain 2</td>
<td>&lt;5%</td>
<td>Skeletal myopathy</td>
</tr>
<tr>
<td>MYL3</td>
<td>Essential myosin light chain 3</td>
<td>Rare</td>
<td>Skeletal myopathy</td>
</tr>
<tr>
<td>ACTC</td>
<td>α-Cardiac actin 1</td>
<td>Rare</td>
<td>Apical hypertrophy</td>
</tr>
<tr>
<td>TTN</td>
<td>Titin</td>
<td>Rare</td>
<td>Typical</td>
</tr>
<tr>
<td>TNNC1</td>
<td>Troponin C, slow skeletal and cardiac muscles</td>
<td>Rare</td>
<td>Typical</td>
</tr>
<tr>
<td>MYH6</td>
<td>α-Myosin heavy chain</td>
<td>Rare</td>
<td>Late onset</td>
</tr>
<tr>
<td>Nonsarcomeric mutations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSRNP3</td>
<td>Muscle LIM protein</td>
<td>Rare</td>
<td>Late onset</td>
</tr>
<tr>
<td>MYLK2</td>
<td>Myosin light chain kinase 2</td>
<td>Rare</td>
<td>Early onset</td>
</tr>
<tr>
<td>LDB3</td>
<td>LIM binding domain 3</td>
<td>Rare</td>
<td>Mainly sigmoidal</td>
</tr>
<tr>
<td>TCAP</td>
<td>Telothelin</td>
<td>Rare</td>
<td>Typical, variable</td>
</tr>
<tr>
<td>VCL</td>
<td>Vinculin/metavinculin</td>
<td>Rare</td>
<td>Obstructive midventricular hypertrophy</td>
</tr>
<tr>
<td>ACTN2</td>
<td>α-Actinin 2</td>
<td>Rare</td>
<td>Mainly sigmoidal</td>
</tr>
<tr>
<td>PLN</td>
<td>Phospholamban</td>
<td>Rare</td>
<td>Typical, variable</td>
</tr>
<tr>
<td>MYOZ2</td>
<td>Myозенин 2</td>
<td>Rare</td>
<td>Typical</td>
</tr>
<tr>
<td>JPH2</td>
<td>Junctophilin 2</td>
<td>Rare</td>
<td>Typical</td>
</tr>
</tbody>
</table>
Genes Mutations & Risk Stratification

- Role of genes and risk stratifications is controversial
- Early data suggested association:
  a) MHC mutations and ↑ mortality
  b) MYBPC mutations and later manifestation in life with milder form of the disease
  c) Troponin T mutations and less hypertrophy but more disarray, fibrosis and SCD
  d) ↑ CV events when positive genetic screening compared to negative test
  e) Multiple mutations and more severe phenotype and ↑ SDC

Role of Genetic Testing in 2011

Family studies showed heterogeneous expressions of the same mutation among individuals within the same family.

✓ No Role in Diagnosis
✓ No Role in ICD decision

- $A = B/C$
Role of Genetic Testing in 2011

Family Screening

Patient with unequivocal HCM
- Genetic testing

Not performed or no mutation identified
- Cardiac screening (ECG, echo) in first-degree relatives

A mutation is identified
- Predictive genetic testing in first-degree relatives

HCM is diagnosed
- Cardiac evaluation (clinical, ECG, imaging) and regular follow up
- Recommend cascade cardiac screening of offspring

No HCM diagnosed
- Continue regular cardiac follow up based on age recommendations

Guidelines for clinical and imaging follow-up, based on age
- < 10 years old
  - Optional unless there is malignant family history of SCD, competitive athlete, onset of symptoms or clinical suspicion of LVHH
- 10-21 years old
  - Every 12-18 months
- > 21 years old
  - At onset of symptoms or at least every 5 years

Mutation is present
- Cardiac evaluation and regular follow up based on age
- Recommend cascade genetic screening of offspring

Mutation is absent
- Stop examination and no follow up
- No screening of offspring

Desai MY et al, Circ Cardiovasc Imaging. 2011
1-Assessment of Morphology
- LV Geometry
- Evaluation of mitral valve and subvalvular apparatus
- Evaluation of myocardial perfusion
- Evaluation of myocardial fibrosis

2-Functional Assessment
- Evaluation of LV cavity obstruction
- Evaluation of systolic and diastolic LV function
# ECHO

## ADVANTAGE
- Assessment of LV thickness
- Mitral valve
- LVOT gradient
- Global and regional function

## LIMITATION
- Operator dependent
- Limited acoustic windows
- Suboptimal assessment of subvalvular apparatus
- Limited septal and temporal resolution
MRI

ADVANTAGE
- Gold standard to assess cardiac structure/LV mass
- Papillary muscle morphology
- Myocardial fibrosis
- Regional myocardial mechanics

LIMITATION
- Limited availability
- Device related contraindications
- Prognostic value of fibrous assessment is not well established
27 year old man with HCM

Desai MY et al, Circ Cardiovasc Imaging. 2011
35 year old man with HCM

Desai MY et al, Circ Cardiovasc Imaging. 2011
Fibrosis and HCM Facts

- Gadolinium-enhanced CMR provides an accurate method for detection of myocardial fibrosis ¹

- In HCM, fibrosis is patchy, midmyocardial and most commonly found in the regions of hypertrophy ²

- The pattern and amount of fibrosis correlates closely with histolopathology ²

Autopsy Correlation of Fibrosis With In Vivo LGE-CMR

O'Hanlon, R. et al. J Am Coll Cardiol 2010;56:867-874
Fibrosis and SCD in HCM - 2011

- Extent of fibrosis in patients aged < 40 years is associated with clinical markers of SCD, whereas in older patients, it is associated with progressive ventricular dysfunction.

- Studies demonstrated association between degree of fibrosis and ventricular arrhythmia.

- Emerging data demonstrates incremental prognostic values of myocardial fibrosis in predicting hard outcomes.

1) Moon JC et al, JACC. 2003
2) Kwon DH et al, JACC. 2009
3) Rubinshtein R, Circ Heart Fail. 2009
4) O’Hanlon R et al, JACC. 2010
5) Bruder O et al, JACC. 2010
Fibrosis in HCM Conclusion - 2011

- The long term clinical significance of fibrosis is uncertain
- Long term prospective studies are still needed
Sudden Cardiac Death in Hypertrophic Cardiomyopathy

Sudden Cardiac Death in HCM

- Nonsustained Ventricular Tachycardia
  - Rest
  - Exercise
- Role of Isolated Myofilament Mutation?
- Fibrosis or Scar
- Severity of LV Hypertrophy
- Abnormal Exercise Blood Pressure Response
- Outflow Obstruction
- Family History of Sudden Death
- Unexplained Syncope

Ommen S R, Gersh B J Eur Heart J 2009;eurheartj.ehp307
# Who Needs an ICD?

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Reassurance</td>
</tr>
<tr>
<td>1</td>
<td>Individualize (MRI?)</td>
</tr>
<tr>
<td>2 +</td>
<td>ICD</td>
</tr>
<tr>
<td>Prior SCD</td>
<td>ICD</td>
</tr>
<tr>
<td>Sustained VT</td>
<td>ICD</td>
</tr>
</tbody>
</table>
HCM

- Decrease obstructive Sx (dyspnea, CP, fatigue)
- Prevention of SCD
Symptomatic Obstructive HCM

- Beta-blockade
- Verapamil or Diltiazem
- Disopyramide

Drug-refractory symptoms

ACC/ESC Consensus Recommendation

Surgical Septal Myectomy

Special Circumstances (i.e., comorbidity)

Septal Ablation
Thank You