Paediatric cardiomyopathy: new developments and insights
WHO definition (1996): “Diseases of the myocardium associated with cardiac dysfunction”

- Dilated cardiomyopathy
- Hypertrophic cardiomyopathy
- Restrictive cardiomyopathy
- Unclassified: Arrhythmogenic RV dysplasia, LV non-compaction
Dilated cardiomyopathy: overview

- Characterised by dilatation and impaired ventricular contraction
- May be familial, genetic, post-viral, drug or toxin induced, metabolic, mitochondrial, connective tissue associated or due to HIV
- Anomalous coronary origin from a pulmonary artery must be excluded
- Histology non-specific
- Usually presents with heart failure
- Accompanying diastolic dysfunction may include impaired ventricular relaxation and non-compliance
Dilated cardiomyopathy: echocardiogram
Dilated cardiomyopathy

Genetic mutations

- Up to 25% of dilated CM is caused by genetic mutations.
- 1st gene identified was dystrophin (X-linked CM); others include actin, desmin and lamin A/C (dominant and recessive).
- Actin, desmin and dystrophin are cytoskeletal proteins with roles in force transmission, cytoskeletal stability, calcium homeostasis, myocyte differentiation, myofibrillogenesis.
- Lamin is a nuclear protein; commonest mutation and is associated with conducting system disease.
- Dystrophin, desmin and lamin mutations can be associated with skeletal muscle disease.
Dilated cardiomyopathy: viral disease

- Common pathogenic viruses include adenovirus, enterovirus, CMV, influenza
- About 20% of subjects with dilated CM have virus by PCR
- In subjects with myocarditis, 35-40% viral yield
- Mechanisms of damage are both acute (dystrophin cleavage) and delayed (lymphocytic infiltrate)
- Adenovirus typically causes little lymphocytic infiltrate
Myocarditis: mouse model

Acute myocarditis

- Viral infection
- Myocyte necrosis
- Macrophage activation
- Infiltrating mononuclear cells
- Cytokines
- Nitric oxide
- Natural killer cells

4 days

Viraemia

Subacute myocarditis

- Cytotoxic T lymphocytes
- B lymphocytes
- Neutralising antibodies

14 days

Viral clearing

Chronic myocarditis

- Fibrosis
- Dilatation
- Death

Viral absence
Myocarditis – histologic variation

Diffuse mononuclear infiltrate

Focal mononuclear infiltrate

Myocardial oedema – no infiltrate

Myocardial fibrosis and hypertrophy
Dilated cardiomyopathy investigations

- ECG, CXR, cardiac ultrasound
- Serum carnitine, pyruvate, lactate, urine metabolic screen
- Viral PCR and culture of available tissues/fluids
- Metabolic consults; consider liver and skeletal muscle biopsy
- Screen first degree relatives
- Genotype and skeletal muscle biopsy if no improvement
Mitochondrial diseases
typical organ involvement

Brain: seizures, dementia, infarcts, leukoencephalopathy
Eye: optic atrophy, pigmentary degeneration, cataracts
Ear: deafness
Muscle: skeletal myopathy
Heart: cardiomyopathy (HCM, DCM), conduction defects
Kidney: tubular dysfunction
Liver: hepatic dysfunction, bile stasis
Bone marrow: pancytopaenia, specific cell line failure
Blood, urine, CSF: increased lactate
Mitochondrial diseases
Respiratory chain Complex 1 deficiency cardiomyopathy

Muscle

Liver

Heart
Dilated cardiomyopathy
Drug therapy

- Diuretics: provide symptomatic relief
- Digoxin: small effect on symptoms and heart failure admissions; no benefit with respect to mortality
- ACE inhibitors: Reduce both hospitalisation and mortality; higher doses more effective; greatest effect in mild CHF
- Beta-blockers: good evidence for reduction in mortality and improvement in ventricular function
Hypertrophic cardiomyopathy

- Primary cardiac disorder with a heterogeneous expression and diverse clinical course
- Characterised by left ventricular hypertrophy in the absence of dilatation, or conditions capable of producing LVH
- Non-obstructive in around 75% of cases
- Prevalence in the general population is around 0.2%
Hypertrophic cardiomyopathy:

**echocardiogram**
Hypertrophic cardiomyopathy
morphological characteristics

- Distribution of hypertrophy is usually asymmetric
- Any pattern possible but anterior ventricular septum predominantly involved
- Spontaneous LV remodeling with increase in wall thickness during adolescence, and a decrease in wall thickness with aging
Hypertrophic cardiomyopathy

- Mendelian trait with autosomal dominant inheritance
- Mutations involve genes that encode for sarcomeric proteins
- 10 different proteins implicated and >200 described mutations (allelic heterogeneity)
- Around 50% of cases represent spontaneous mutations
- Hypertrophy may be secondary to altered sensitivity to calcium and impaired contractility
Hypertrophic cardiomyopathy
contractile protein mutations
Paediatric HCM
aetiological considerations

- Contractile protein abnormality
- Syndromes: Noonan, Beckwith-Wiedemann, LEOPARD, Friedreich’s ataxia
- Metabolic: Carnitine deficiency, Fatty acid oxidation defects, Glycogen storage disease, MPS, Mannosidosis, Fucosidosis, lipodystrophy
- Mitochondrial myopathies
- Neonatal hyperinsulinaemia
Causes of sudden cardiac death in young people


- Hypertrophic cardiomyopathy (36%)
- Congenital coronary anomalies (19%)
- Mildly increased cardiac mass (10%)
- Ruptured aorta 5%
- Tunneled LAD 5%
- Aortic stenosis 4%
- Myocarditis 3%
- ARVC 3%
- MVP 2%
- CAD 2%
- Other 6%
Mortality in HCM
Maron et al; Circulation 2000

Age at Death or Most Recent Evaluation (years)

% Mortality

- Stroke
- Heart Failure
- Sudden
Hypertrophic cardiomyopathy
substrate for SCD

- Disorganised cellular architecture
- Abnormal intramural coronary arteries with thickened walls and narrow lumens
- Replacement fibrosis adjacent to intramural vessels

Maron BJ; Lancet 1997
Adult hypertrophic cardiomyopathy
risk factors for sudden death

Cardiac arrest/sustained VT
Family history of sudden death
Recurrent syncope
Multiple-repetitive NSVT
Exercise hypotension
Massive LVH
Malignant genotype?
Coronary bridging?

- Implantable defibrillator
- Medical therapy (?)
Relation of wall thickness to sudden death

Spirito P et al, NEJM 2000

Incidence of Sudden Death (per 1000 person - yr)

Maximal Left-Ventricular-Wall Thickness (mm)

- $\leq 15$ mm: 0
- 16 - 19 mm: 2.6
- 20 - 24 mm: 7.4
- 25 - 29 mm: 11.0
- $\geq 30$ mm: 18.2
HCM - age related penetrance

Nimura et al; NEJM 1998

- Cardiac beta-myosin heavy chain
- Cardiac troponin T
- Cardiac myosin-binding protein C
Myocardial bridging
Hypertrophic cardiomyopathy: myocardial bridging
Hypertrophic cardiomyopathy:
myocardial bridging
Restrictive cardiomyopathy

- Basic defect unknown
- Diastolic dysfunction with normal wall thickness and systolic function
- Primary: endomyocardial fibrosis, Loeffler’s, and primary RCM
- Infiltrative: Irradiation, sarcoid, amyloid
- Metabolic: Glycogen storage disease, Fabry’s disease, haemachromatosis
- Mixed HCM and RCM may be due to Troponin I mutation
- Relentless downhill course
Restrictive cardiomyopathy:
echocardiogram
Arrhythmogenic right ventricular dysplasia

- Progressive fibro-fatty replacement of right ventricular myocardium with relative septal sparing
- May be autosomal dominant with incomplete penetrance or autosomal recessive
- Presentation with arrhythmias and sudden death is common, particularly in adolescents and young adults
Initial reports suggested a 3-5% mortality per year in adults with HCM being followed at tertiary care institutions.

In 1989, Spirito et al (NEJM) pointed out that of 3404 subjects with HCM in a total of 78 published studies, 73% were from two referral institutions!

More recent population based data suggests that the outcome for most subjects is good, with 10 year survival rates of 85% reported.
10 year cohort of Australian children aged 0-10 years at presentation, with primary cardiomyopathy

- Site visits to paediatric cardiology centres and hospitals
- All available data reviewed including clinical details and follow-up, lab results, all cardiac imaging
- Cases sought from regional paediatricians and adult cardiologists, transplant centres and coroners’ courts
- Available cardiac histology reviewed centrally
# NACCS - epidemiology

## Incidence per 100,000 at risk/year

<table>
<thead>
<tr>
<th>Type of CM</th>
<th>0-&lt;1 year</th>
<th>1-&lt;2 years</th>
<th>2-&lt;5 years</th>
<th>5-10 years</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dilated CM</td>
<td>4.76</td>
<td>1.14</td>
<td>0.24</td>
<td>0.13</td>
<td>0.73</td>
</tr>
<tr>
<td>Hypertrophic CM</td>
<td>1.89</td>
<td>0.36</td>
<td>0.13</td>
<td>0.10</td>
<td>0.32</td>
</tr>
<tr>
<td>Restrictive CM</td>
<td>0</td>
<td>0.04</td>
<td>0.05</td>
<td>0.02</td>
<td>0.03</td>
</tr>
<tr>
<td>Unclassified CM</td>
<td>1.18</td>
<td>0.20</td>
<td>0.05</td>
<td>0.02</td>
<td>0.17</td>
</tr>
<tr>
<td>Total</td>
<td>7.84</td>
<td>1.73</td>
<td>0.47</td>
<td>0.28</td>
<td>1.24</td>
</tr>
</tbody>
</table>
Cumulative frequency histogram of age at presentation
Racial differences

- Indigenous children had a higher incidence of dilated CM than remaining subjects (relative risk 2.67; 95% CI 1.42, 4.63)

- Sudden death was the presenting symptom in 11 (3.5%) cases including 4.9% of dilated CM cases, and 4.8% of unclassified CM cases

- Indigenous children had a higher rate of death as the presenting symptom 16.7% vs 2.6%; p=0.02)
Proportion of DCM subjects with known/likely aetiology

% Myocarditis  Viral  Familial  Consang  Metabolic

- Myocarditis
- Viral
- Familial
- Consang
- Metabolic
Prevalence of lymphocytic myocarditis among DCM subjects

<table>
<thead>
<tr>
<th>Time from presentation</th>
<th>0 – 7 days</th>
<th>1 – 4 weeks</th>
<th>4 – 8 weeks</th>
<th>&gt;8 weeks</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytic myocarditis</td>
<td>22</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>Total</td>
<td>44</td>
<td>10</td>
<td>8</td>
<td>8</td>
<td>70</td>
</tr>
<tr>
<td>Proportion (%)</td>
<td>50</td>
<td>20</td>
<td>12.5</td>
<td>0</td>
<td>37</td>
</tr>
</tbody>
</table>

p = 0.009 Kruskall-Wallis
A probable or definite viral aetiology was identified in 59 of 184 (32.1%) subjects, including

- 30 of 44 (68.2%) subjects with available histology within 1 week of presentation

- 8 of 9 subjects who presented with sudden death
Dilated cardiomyopathy: risk factors for death/transplant

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presentation above 5 years</td>
<td>5.6</td>
<td>2.6, 12.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Familial cardiomyopathy</td>
<td>2.9</td>
<td>1.5, 5.6.2</td>
<td>0.001</td>
</tr>
<tr>
<td>F.S. Z score at presentation*</td>
<td>0.75</td>
<td>0.65, 0.87</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Change in F.S. Z score*</td>
<td>0.68</td>
<td>0.58, 0.79</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* Per unit Z score
DCM: survival according to patient characteristics

A

Proportion surviving

Years from presentation

No. at risk 175 126 108 92 77 60 48 37 26 15 8

B

Proportion surviving

Years from presentation

No. at risk 159 120 104 89 74 58 47 36 25 14 7

C

Proportion surviving

Years from presentation

No. at risk 149 114 98 83 68 52 41 32 22 12 6

D

Proportion surviving

Years from presentation

No. at risk 26 20 17 14 13 10 9 6 5 2 1

No familial cardiomyopathy

Familial cardiomyopathy

Presenting age 0-5 years

Presenting age >5 years

No Lymphocytic myocarditis

Lymphocytic myocarditis

No

Yes

No

Yes
<table>
<thead>
<tr>
<th></th>
<th>Adult</th>
<th>Pediatric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>5-10%</td>
<td>30-40%</td>
</tr>
<tr>
<td>Non-viral etiology</td>
<td>35%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Chronic symptoms</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Potential for recovery</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Speed of recovery</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Progression to end-stage CM</td>
<td>30-40%</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>
Proportion of HCM subjects with known/likely aetiology

- Noonan
- Other syndrome
- Familial
- Consang
- Metabolic
## Hypertrophic cardiomyopathy: risk factors for death/transplant

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presentation below 1 year</td>
<td>6.16</td>
<td>1.44, 26.3</td>
<td>0.014</td>
</tr>
<tr>
<td>Concentric LVH</td>
<td>8.01</td>
<td>1.33, 48.2</td>
<td>0.02</td>
</tr>
<tr>
<td>Increase in post wall Z score*</td>
<td>1.36</td>
<td>1.03, 1.81</td>
<td>0.03</td>
</tr>
<tr>
<td>Fractional shortening Z at presentation*</td>
<td>1.32</td>
<td>1.08, 1.60</td>
<td>0.006</td>
</tr>
</tbody>
</table>

* Per unit Z score
HCM: freedom from death and LV myectomy

Survival

Surgery
Left ventricular non-compaction

- Poorly characterised
- Persistance of foetal spongiform myocardium
- Mitochondrial basis
- Can be associated with restrictive or dilated physiology
- Undulating phenotype
- 9.2% of all paediatric cardiomyopathy cases
Paediatric cardiomyopathies: conclusions

- Heterogenous group of disorders with genetic, infectious, mitochondrial and metabolic aetiologies
- Behaviour can be predicted by morphological and functional characteristics, and underlying patient characteristics
- Sudden death may occur at presentation and during follow-up
- Require a multidisciplinary approach to diagnosis and management
- If aetiology is unclear, remaining first degree family members should be screened periodically
Paediatric cardiomyopathy
underutilised investigations

- Post mortem with light and electron microscopy of the heart
- Genetic testing and DNA storage
- Viral PCR of the myocardium
- Respiratory chain enzyme assay