Familial Aggregation of Dilated Cardiomyopathy in Patients with Peripartum Cardiomyopathy

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PPCM Aetiology

- Multifactorial
  - Environmental
  - Inflammatory
  - Genetic

- Case reports of Familial Disease Across the globe
- Anectodal observations suggest those with familial disease never fully recover
- Hypotheses of abnormal signal pathways may be genetically influenced
- FDCM; Lamin A/C mutation most virulent
Aims

- Measure prevalence of - IDC

Also

- Reduced fractional shortening
- $\pm$ LV dilatation

- Measure prevalence of LMNA abnormalities in PPCM patients

Among 1º relatives of patients with PCM
PPCM – Familial Study (South Africa)

**METHODS (Family Echo Screening)**
- Screening of 1° Relatives – Clinical & Echo
- “Screened Positive” = Objective LV systolic dysfunction in absence of other clinically plausible reason

**METHODS (LMNA Gene Screen)**
- Consenting PPCM patients underwent genetic screening for LMNA abnormalities

**RESULTS (Family Echo Screening)**
- 18 Families successfully screened
- Total of 31 relatives screened → mean 1.9 per proband
- 58% screened relatives were male.

- Subset of 9 probands with HHFP also underwent family screening
# PPCM/DCM – Entry Criteria

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 16 and ≤ 40 years</td>
<td>Significant organic valvular heart disease</td>
</tr>
<tr>
<td>Symptomatic CHF*</td>
<td>Systolic BP&gt;160mmHg and/or diastolic BP&gt;100mmHg</td>
</tr>
<tr>
<td>No other identifiable cause for heart failure</td>
<td>Severe anaemia (haemoglobin concentration &lt;9gm/dL)</td>
</tr>
<tr>
<td>Left ventricular EF≤45% by transthoracic echocardiography</td>
<td>Other clinical conditions accounting for the raised inflammatory markers#</td>
</tr>
</tbody>
</table>

*Symptoms of congestive heart failure (CHF) that developed in the last month of pregnancy or during the first 5 months postpartum | BP; Blood Pressure

#NB. For the purposes of this study, this meant HIV-seropositivity was considered an exclusion factor.
Participant Flow - From Recruitment to Diagnosis

Total PPCM Patients Approached for Family Screening
- 51

Patients Diagnosed with PPCM but:
- Found to have chronic/essential HT
- 7

Patients Diagnosed with PPCM but:
- Found to have PIH in index pregnancy
- 2

Patients Diagnosed with PPCM with:
- No other potential cause for HF
- ≥ One 1° relative successfully screened
- 21 Families

Patients Diagnosed with PPCM with:
- No other potential cause for HF
- ≥ One 1° relative successfully screened
- Exclusion criteria among all relatives screened
- 3 families

Patients Diagnosed with PPCM with:
- No other potential cause for HF
- ≥ One 1° relative successfully screened
- Any other CVD*
- 8 families

Patients Diagnosed with PPCM with:
- No other potential cause for HF
- ≥ One 1° relative with any other CVD*
- 1 Family

Possible Familial Disease
- 1 Family

No Familial Disease
- 8 Families

Confirmed Familial Disease
- 4 Families

Possible Familial Disease
- 3 Families

No Familial Disease
- 11 Families

≥ One 1° relative with any other CVD*
- 4 Families

≥ One 1° relative with any other CVD*
- 3 Families

≥ One 1° relative with any other CVD*
- 2 Families

≥ One 1° relative with any other CVD*
- 8 Families

Possible Familial Disease
- 1 Family

≥ One 1° relative with any other CVD*
- 4 Families

≥ One 1° relative with any other CVD*
- 3 Families

≥ One 1° relative with any other CVD*
- 2 Families

≥ One 1° relative with any other CVD*
- 8 Families

≥ One 1° relative with any other CVD*
- 1 Family
PPCM – Familial Study (South Africa)

- 18 index PPCM patients with at least one 1° relative screened for DCM.
- 4 index cases (22%) had confirmed familial disease (i.e. DCM on echocardiography),
- Additional 3 (17%) had possible familial disease (i.e., early echocardiographic signs of DCM).
- None of the HHFP cases had confirmed familial DCM, but one (11%) had possible familial disease; and displayed autosomal dominance.
### Bio-demographic profile of PPCM probands and their first degree relatives screened

*Standard deviation (± SD); Inter-quartile range (IQR)*

<table>
<thead>
<tr>
<th></th>
<th>PROBANDS (N=18)</th>
<th>1ST DEGREE RELATIVES (N=44)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>29 ± 7</td>
<td>26 ± 13</td>
<td>0.282</td>
</tr>
<tr>
<td><strong>Parity</strong></td>
<td>2 (IQR 1-2)</td>
<td>1 ± 1.6</td>
<td>0.0003</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>27 ± 6</td>
<td>28 ± 7</td>
<td>0.622</td>
</tr>
<tr>
<td><strong>Pulse rate</strong></td>
<td>94 ± 19</td>
<td>74 ± 13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Blood pressure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean systolic (mmHg)</td>
<td>108 ± 18</td>
<td>116 ± 13</td>
<td>0.065</td>
</tr>
<tr>
<td>Mean diastolic (mmHg)</td>
<td>70 ± 10</td>
<td>73 ± 9</td>
<td>0.341</td>
</tr>
</tbody>
</table>

### Heart failure symptomatology in screened first degree relatives of PPCM patients

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Prevalence among probands (N=18)</th>
<th>Prevalence among 1st degree relatives (N=44)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnoea (NYHA FC II or greater)</td>
<td>100%</td>
<td>2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dizziness</td>
<td>33%</td>
<td>11%</td>
<td>0.367</td>
</tr>
<tr>
<td>Palpitations</td>
<td>44%</td>
<td>11%</td>
<td>0.045</td>
</tr>
<tr>
<td>Chest pain</td>
<td>28%</td>
<td>16%</td>
<td>0.970</td>
</tr>
<tr>
<td>Lower limb swelling</td>
<td>61%</td>
<td>5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other (eg. Abdominal pain)</td>
<td>50%</td>
<td>5%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
## Summary of Key Abnormal Echo Findings Among 1st Degree Relatives of PPCM Patients

<table>
<thead>
<tr>
<th>Echo-cardiographic measurement</th>
<th>Relatives (N=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dilated LV in diastole</td>
<td>18%</td>
</tr>
<tr>
<td>Dilated LA in diastole</td>
<td>9%</td>
</tr>
<tr>
<td>Reduced ejection fraction</td>
<td>7%</td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td>5%</td>
</tr>
<tr>
<td>Tricuspid regurgitation</td>
<td>12%</td>
</tr>
</tbody>
</table>

[LV Left ventricle; LA Left atrium]
Figure 1. Pedigree of Index Case (Arrowed) with Peripartum Cardiomyopathy with Familial Disease (Family I)

(DCM, dilated cardiomyopathy)

Legend

<table>
<thead>
<tr>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

- Not screened, or no known features of DCM
- Screened Normal
- Affected with DCM
- Possibly affected from verbal history
- Deceased

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I:1
I:2
II:1
II:2
N
II:3
40yrs
II:4
53yrs
Screened; found affected but asymptomatic. All other clinical parameters were normal. Chose conservative management. One year later developed symptoms of DCM.

II:5
Died: Non-cardiac illness

II:6

III:1
22yrs
Presented postpartum

III:2

III:3
40yrs

III:4
33yrs
Admits previous fainting twice in crowded places; told BP low

III:5

IV:1
4yrs

IV:2

IV:3

IV:4

IV:5
3yrs

NB. Dotted lines imply partners that never married.
Figure 2. Pedigree of Index Case (Arrowed) with Peripartum Cardiomyopathy with Familial Disease (Family II)

II:12 28yrs
Palpitations for years; occasional lightheadedness.
Screened: Echocardiogram normal.
Wolf-Parkinson-White syndrome found
24-hour Holter: no concerning arrhythmias.
Accessory pathway ablated in February 2009.

I:1 60yrs
Had "heart problem", then CVA. Died shortly after CVA

I:2 39yrs
DCM on screening
Admits to symptoms

II:1 60yrs
Had "heart problem", then CVA. Died shortly after CVA

II:2 38yrs

II:3 39yrs
DCM on screening
Admits to symptoms

II:4 30yrs
Developed HF 3.4 years after 1st childbirth. Her HF worsened 2 weeks after 2nd childbirth. Later had CVA then died one year after 2nd childbirth.

II:5 28yrs
Palpitations for years; occasional lightheadedness. Wolf-Parkinson-White syndrome found
24-hour Holter: no concerning arrhythmias.
Accessory pathway ablated in February 2009.

II:6 23yrs
Asymptomatic after 1st childbirth.
Symptomatic 1 month after 2nd childbirth. PPCM diagnosed

II:7 22yrs
Screened: found asymptomatic CM
Echocardiogram: LV non-dilated, EF 42.6%
ECG: normal, PR interval 132ms
24-hour Holter: no concerning arrhythmias

LEGEND

- Males
- Females
- Not screened, or no known features of DCM
- Screened Normal
- Affected with DCM
- Reduced Ejection Fraction
- Arrhythmia detected on screening
- Possibly affected from verbal history
- Deceased
PPCM Familial Study - Limitations

- Inaccessible Relatives
  - Incomplete picture
  - Potential for volunteer bias

- Cross-sectional study
  - Variable penetrance
  - Ideally; follow-up for all
  - Exclusive entry criteria

But.......  
Can only result in underestimation of existing phenomenon
Results of LMNA Screen in PPCM

• Genetic screening successfully conducted in 38 PPCM patients

• Abnormalities in 6 of the 12 exons; most within intronic region of exon

• Amidst these 6 exons, a total of 9 variations were observed; →78% intronic (all known SNPs)
  →22% synonymous (SNPs)

• NB. No novel mutation in our PPCM cohort
Key aetio-pathogenic factors implicated in PPCM and their impact on management

**Predisposing Factors**

**CLINICAL**
- Most present 1st 3 months postpartum
- Previous PCM
- Autoimmune abnormalities → Viral-induced → Microchimerism
- Lactation?

**BIOCHEMICAL**
- Oxidative stress/inflammation/apoptosis
- Excess abnormal Prolactin (16kDa)

**Familial dilated cardiomyopathy (22%-39%)**

**Clinical Features**
- CCF (Acute or Subacute)
- Dilated LV; Bedside & imaging
- Hypotension
- Arrhythmia

**Complications**
- Thromboembolism; cerebral/pulmonary/digital infarcts
- Ischaemic Organ Failure;
  - Renal failure/ ischaemic hepatitis
- Prolonged heart failure (50-75%)
- Death (15-30%)

**Targets for Intervention**
- Treat as per standard for IDCM

1° PREVENTION
- Detailed family history & echo screening
- Discourage lactation in those at risk
- Bromocriptine; Dual benefit → Block 16kDa prolactin → May improve haemodynamics & oxidative stress, ± cardioprotection

2° PREVENTION
- Early accurate diagnosis (by exclusion)
- Early Rx of HF & PPCM complications
- Vigilant follow-up & dose optimisation
- Avoid undue lipid-lowering

Abnormal ECG
Conclusions

• Over a third of PPCM cases bear familial DCM, supporting that PPCM is part of spectrum of familial DCM.

• HHFP appear at far lower risk of familial disease, larger studies still needed to better quantify this risk.

• Detailed family history and routine family screening may be as much merited in PPCM as it is in DCM.

• LMNA mutations appear of little importance in PPCM, but larger studies needed