Pediatric Pulmonary Hypertension

The Netherlands experience

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Beatrix Children’s Hospital
University Medical Center Groningen
The Netherlands

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The Netherlands

Total Population: 16,577,612

Children (0-18yrs) 3,927,975

University Medical Centers 8
National Network for Pediatric Pulmonary Hypertension

The Netherlands registry

- Epidemiology
- Clinical presentation and characteristics
- Outcome
- Predictors of Outcome
- Treatment patterns and treatment effects
Epidemiology of Pediatric Pulmonary Hypertension in the Netherlands period 1991-2005

• 2 registries
  – Institutional Pediatric Cardiology databases (EPCC)
  – Dutch National Hospitalisation Registry (ICD-9)

• 1991 – 2006

• medical files
  – patient characteristics, diagnostic work up, diagnosis, outcome

• classification
  – Dana Point

Pediatric pulmonary hypertension in the Netherlands: period 1991-2005

Annual Incidence Ratio's

Significant decline in PAH-CHD over time: first 5 years vs last 5 years (p=0.02)
National Network for Pediatric Pulmonary Hypertension

All children suspected for P(A)H (DanaPoint class1/(3)/4/5) are referred to expert center

National Referral Center Groningen
Standarized Diagnostic work up
Treatment initiation
Standarized follow up

National Network for Pediatric Pulmonary Hypertension
The Netherlands
registry

• Epidemiology
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**Table 1.** Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>All patients n = 63</th>
<th>IPAH n = 29</th>
<th>PAH-CHD n = 23</th>
<th>PAH-CTD n = 2</th>
<th>PH-RSH n = 8</th>
<th>CTE-PH n = 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at presentation at referral center</td>
<td>6.8 (1.1; 17.4)</td>
<td>5.0 (0.04; 15.6)</td>
<td>6.9 (0.06; 17.4)</td>
<td>8.9 (4.6; 7.1)</td>
<td>0.8 (0.6; 13.9)</td>
<td>15.7</td>
</tr>
<tr>
<td>Sex male</td>
<td>24 (38)</td>
<td>13 (45)</td>
<td>6 (26)</td>
<td>1 (50)</td>
<td>4 (50)</td>
<td>0</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea Exercise induced</td>
<td>62 (98)</td>
<td>39 (44)</td>
<td>23 (37)</td>
<td>2 (3)</td>
<td>8 (13)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Dyspnea At rest</td>
<td>16 (25)</td>
<td>4 (6)</td>
<td>6 (10)</td>
<td>1 (2)</td>
<td>5 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Chest pain</td>
<td>2 (3)</td>
<td>2 (3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Syncope</td>
<td>8 (13)</td>
<td>7 (11)</td>
<td>1 (2)*</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TrG02 (%)</td>
<td>91 ± 7</td>
<td>94 ± 5</td>
<td>89 ± 7*</td>
<td>87</td>
<td>88 ± 9</td>
<td>96</td>
</tr>
</tbody>
</table>

**Hemodynamics**

<table>
<thead>
<tr>
<th></th>
<th>All patients n = 63</th>
<th>IPAH n = 29</th>
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<th>PAH-CTD n = 2</th>
<th>PH-RSH n = 8</th>
<th>CTE-PH n = 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>nRAP (mm Hg)</td>
<td>7 ± 4</td>
<td>7 ± 4</td>
<td>7 ± 4</td>
<td>8</td>
<td>7 ± 3</td>
<td>4</td>
</tr>
<tr>
<td>nPAP (mm Hg)</td>
<td>52 ± 20</td>
<td>55 ± 17</td>
<td>54 ± 20</td>
<td>61</td>
<td>25 ± 5*</td>
<td>75</td>
</tr>
<tr>
<td>nPAP/minSAP</td>
<td>0.98 ± 0.28</td>
<td>0.90 ± 0.3</td>
<td>0.95 ± 0.12</td>
<td>1.10</td>
<td>0.55 ± 0.22*</td>
<td>0.96</td>
</tr>
<tr>
<td>CI (L/min/m2)</td>
<td>2.8 ± 1.1</td>
<td>2.8 ± 0.8</td>
<td>2.8 ± 1.5</td>
<td>3.6</td>
<td>2.9 ± 0.4</td>
<td>2.3</td>
</tr>
<tr>
<td>Qp/QsCI</td>
<td>1.2 ± 0.9</td>
<td>0.97 ± 0.2</td>
<td>1.4 ± 1.0</td>
<td>0.80</td>
<td>1.1 ± 0.1</td>
<td>1.24</td>
</tr>
<tr>
<td>PVR (RI, m2)</td>
<td>18.4 ± 13.4</td>
<td>19.9 ± 12.3</td>
<td>20.1 ± 15.1</td>
<td>19.5</td>
<td>4.2 ± 1.3*</td>
<td>14.3</td>
</tr>
<tr>
<td>PVR/SA</td>
<td>0.95 ± 0.6</td>
<td>1.00 ± 0.6</td>
<td>1.02 ± 0.65</td>
<td>1.40</td>
<td>0.33 ± 0.21</td>
<td>0.75</td>
</tr>
</tbody>
</table>

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**Genetic Abnormalities in Pediatric Pulmonary Hypertension**

n=27 (43%)
National Network for Pediatric Pulmonary Hypertension
The Netherlands registry

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Survival
Dutch National Registry for Pediatric PAH

A. all patients (n=52).
1, 3, 5 and 7 year survival rates: 87%, 78%, 73% and 70%.

Van Loon, Am J Cardiol, in press
Survival
Dutch National Registry for Pediatric PAH

B. iPAH and PAH-CHD.
1,3,5 and 7 year survival rates:
iPAH 86%, 71%, 66% and 66%
PAH-CHD 87%, 87%, 81% and 75%

Van Loon, Am J Cardiol, in press

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**WHO functional class in pediatric PAH**

![Image of survival curve with WHO classifications and survival data]

- Rosenzweig JACC 2005

**Biomarkers in pediatric PAH**

- **NT-pro-BNP**
  - Correlated with WHO-class and 6MWD
  - Correlated with treatment effect (n=30)

![Graph showing correlation between WHO-classification and Log N-terminal pro-BNP (pg/ml)]

- van Albada et al., Pediatr Res 2008
Biomarkers in pediatric PAH

n=30

**NT-pro-BNP**
**uric acid**
**norepinephrine**

Correlated with hemodynamics mPAP, PVR and CI

NT-pro-BNP > 605 pg/ml

Uric acid > 0.32 mmol/l

Norepinephrine > 1.0 nmol/l

Biomarkers, predictive value survival in pediatric PAH

ROC curves

van Albada et al., Pediatr Res 2008
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Second generation anti-PAH drugs

- Calcium channel blockers 8
- 2nd generation anti-PAH drugs 37
  - Monotherapy 22
  - Combination therapy (2 drugs) 13
  - Combination therapy (3 drugs) 3

  - Bosentan 33
  - Beraprost 1
  - Sildenafil 11
  - Epoprostenol 9
Follow up variables during antiproliferative treatment

- WHO FC
- 6MWD
- NT-proBNP

Time of diagnosis in relation to the availability of second generation anti-PAH drugs

**Cohort 1**, patients who were diagnosed before and died before second generation drugs were available to the patient (n=7)

**Cohort 2**, patients for whom second generation drugs were not available at time of diagnosis, but became available during the disease course (“prevalent” cases, n=21)

**Cohort 3**, patients for whom second generation drugs were available at time of diagnosis (“incident” cases, n=24).
Survival
Dutch National Registry for Pediatric PAH

C. cohorts 1, 2 and 3
1, 3, 5 and 7 year survival rates:
100%, 100%, 100% and 95% (cohort 2, incident cases)
88%, 70%, 51% and 51% (cohort 3, prevalent cases)
43%, 29%, 29% and 29% (cohort 1)

Survival in era of 2nd generation anti-PAH drugs vs predicted (NIH)

Van Loon et al, Am J Cardiol, in press
Survival
Dutch National Registry for Pediatric PAH
in the era of 2nd generation anti-PAH drugs
vs predicted (NIH)

Prevalent cases

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO class</td>
<td>2.74 (1.21 – 6.23)</td>
<td>0.016</td>
</tr>
<tr>
<td>Syst blood pressure</td>
<td>0.43 (0.21 – 0.88)</td>
<td>0.022</td>
</tr>
<tr>
<td>mPAP/mSAP</td>
<td>2.43 (1.16 – 5.10)</td>
<td>0.019</td>
</tr>
<tr>
<td>NT-pro-BNP</td>
<td>2.90 (1.11 – 7.60)</td>
<td>0.030</td>
</tr>
<tr>
<td>Uric acid</td>
<td>3.28 (1.36 – 7.90)</td>
<td>0.008</td>
</tr>
<tr>
<td>Cardiac index</td>
<td>0.31 (0.12 – 0.81)</td>
<td>0.018</td>
</tr>
<tr>
<td>Diagnosis iPAH vs PAH-CHD</td>
<td>0.78 (0.24 – 2.53)</td>
<td>0.680</td>
</tr>
<tr>
<td>Cohort 2 vs 3 (when corrected for Dx)</td>
<td>5.32 (1.63 – 17.3)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Van Loon et al, Am J Cardiol, in press
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Conclusions

Epidemiology
• Incidence and prevalence rates for iPAH are lower in children compared to those reported in adults
• Incidence and prevalence rates for PAH-CHD are higher in children compared to those reported in adults

Clinical presentation and characteristics
• Pediatric PAH often has a complex presentation with multiple associated conditions
• Pediatric PAH is frequently associated with unspecified syndromal anomalies

Outcome
• Survival in iPAH (untreated) seems similar in children and adults
• Survival in PAH-CHD is worse in children compared to adults, but is importantly affected by cardiac diagnosis

Predictors of Outcome
• Predictors of prognosis in pediatric PAH include WHO-functional class, 6MWD, hemodynamics (cardiac index, PAP/SAP) and biomarkers (NT-proBNP, uric acid, epinephrine)
Conclusions

Treatment effects

• Survival of pediatric PAH seemed improved since the introduction of second generation drugs, however only in selected patients who already survived before drugs became available (prevalent), not in “incident” cases…

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• Marc Roofthoof, MD
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• Beatrijs Bartelds, MD
• Sira Baars
• Ria Stam
Bosentan patients with PAH-CHD long term follow-up

Van Loon et al, Am Heart J 2007
Persistence of beneficial bosentan effect in PAH-CHD

definition:
death, requirement additional therapy, treatment discontinuation, 6MWD decline

v Loon et al, Am Heart J. 2007