Heterotaxy
Epidemiology in the era of prenatal diagnosis

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Fetal Heterotaxy

- definition
- prenatal incidence
- key features
  - cardiac findings
- intrauterine course
Normal body configuration „Lateralization“

Thoracal and abdominal organs are orientated to right or left side.
Definition of Heterotaxy*

Abnormal arrangement of thoracic and abdominal organs across the left-right axis of the body.

Associated with complex cardiac and extracardiac disease.

}* heteros“ = different  „taxis“ = arrangement
Idealized Heterotaxy Subsets

Left atrial Isomerism

Right atrial Isomerism
Incidence of Heterotaxy

- Incidence of heterotaxy 1-1.44/10,000 births
- 2-4.2% of all infants with congenital heart disease
- at least 6% of the cardiac defects detected in utero
- recurrence 5-10% of siblings

Typical findings on left atrial isomerism LAI

Bilateral left atria
- Abnormal sinus node and atrioventricular conduction
  → Bradycardia, AV-Block
- Anomalies of systemic veins (interrupted IVC)

Bilateral „left lungs“
Abdomen: Situs ambiguus
- Polysplenia
- Intestinal obstruction
- hypoplastic gallbladder 20%
- Biliary atresia 7%

Fig, from Anderson Ped. Cardiol. 3rd Ed.
Typical findings on right atrial isomerism

Bilateral right atrial appendages
- dual sinus nodes
  - Rhythm disturbances
  - Tachycardia
- Total anomalous pulmonary venous return

Bilateral right lungs

Situs ambiguus
- Intestinal obstruction
- Asplenia

Fig, from Anderson Ped. Cardiol. 3rd Ed.
Prenatal Epidemiology

165 Fetus with prenatal diagnosis of heterotaxy 1991-2011

Gestational age at first presentation:

LAI 23.35 ± 6.3  RAI 25.65 ± 7.18 wks
n= 111         n=54
## CHD and Heterotaxy

<table>
<thead>
<tr>
<th>Condition</th>
<th>Left isomerism</th>
<th>Right isomerism</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD in Heterotaxy</td>
<td>86.5%</td>
<td>98.1%</td>
</tr>
<tr>
<td>Total pulmonary venous connection</td>
<td>Rare 4.5%</td>
<td>31.5 % +/- obstruction</td>
</tr>
<tr>
<td>Partial pulmonary venous connection</td>
<td>9.9%</td>
<td>9.3%</td>
</tr>
<tr>
<td>AVSD unbalanced</td>
<td>71.2%</td>
<td>66.7%</td>
</tr>
<tr>
<td>DORV</td>
<td>22.5%</td>
<td>35.2%</td>
</tr>
<tr>
<td>Univentricular</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Ventriculoarterial connection</td>
<td>Discordant 11.7%</td>
<td>Discordant 35.2%*</td>
</tr>
<tr>
<td>Pulmonary atresia or stenosis</td>
<td>37.8%</td>
<td>63.8%*</td>
</tr>
<tr>
<td>Left sided obstructive lesion</td>
<td>11%</td>
<td>13%</td>
</tr>
</tbody>
</table>

* p<0.05
Heterotaxie Syndrom

Left atrial isomerism

- „better“ CHD
- 2/3 two ventricles
- biliary malformation**

Right atrial isomerism

- „worse“ CHD
- most single ventricle
- Total abnormal pulmonary venous return

"AV-Block" in Heterotaxy

<table>
<thead>
<tr>
<th></th>
<th>Left isomerism</th>
<th>Right isomerism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=111</td>
<td>N=54</td>
</tr>
<tr>
<td>AV-Block prenatal</td>
<td>n= 44</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>44 (40%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.001</td>
<td>p=0.002</td>
</tr>
<tr>
<td>Fetal hydrops n=38</td>
<td>33 (30%)</td>
<td>5 (9.4%)</td>
</tr>
<tr>
<td></td>
<td>p=0.002</td>
<td></td>
</tr>
<tr>
<td>Spontaneous IUFD</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Spontaneous IUFD with AV-Block</td>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>

fetal heart disease + AV-Block
high risk of fetal demise

Berg et al. 2006; Berg 2014
Table 2 Risk factors for fetal death (n = 19)

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Surviving patients (n = 15)</th>
<th>Non surviving patients (n = 4)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>First ventricular rate &lt;55 bpm (in utero)</td>
<td>2</td>
<td>1</td>
<td>0.530</td>
</tr>
<tr>
<td>Last ventricular rate &lt;55 bpm (in utero)</td>
<td>2</td>
<td>2</td>
<td>0.178</td>
</tr>
<tr>
<td><strong>Hydrops</strong></td>
<td><strong>3</strong></td>
<td><strong>4</strong></td>
<td><strong>0.009</strong></td>
</tr>
<tr>
<td>Cardiac dysfunction in utero</td>
<td>0</td>
<td>2</td>
<td><strong>0.035</strong></td>
</tr>
<tr>
<td>AV block in utero</td>
<td>5</td>
<td>2</td>
<td>0.603</td>
</tr>
</tbody>
</table>

Data in bold represents statistically significant data (p < 0.05)

AV atrioventricular
Counselling

Left atrial isomerism

• „better“ CHD
• 2/3 two ventricles
• biliary malformation?
• AV-Block → risk of IUFD

Right atrial isomerism

• „worse“ CHD
• most single ventricle
• Total abnormal pulmonary venous return

Parental decision?
Survival

RAI: Survival at birth: 72% incl TOP
93% intention to treat

LAI: Survival at birth: 59% incl TOP
89% intention to treat

P=0.022
"Fetal Outcome" of Heterotaxy

<table>
<thead>
<tr>
<th></th>
<th>n=</th>
<th>Interruption</th>
<th>Intrauterine death</th>
<th>Total survival</th>
<th>Survivors Excluding interruptions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Left Isomerism</strong></td>
<td>111</td>
<td>37</td>
<td>8</td>
<td>59%</td>
<td>89%</td>
</tr>
<tr>
<td>Our data</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lim 2005</strong></td>
<td>52</td>
<td>20</td>
<td>2</td>
<td>60%</td>
<td>96%</td>
</tr>
<tr>
<td><strong>Pepes 2009</strong></td>
<td>41</td>
<td>22</td>
<td>7</td>
<td>29%</td>
<td>63%</td>
</tr>
<tr>
<td><strong>Taketazu 2006</strong></td>
<td>48</td>
<td>13</td>
<td>2</td>
<td>73%</td>
<td>94%</td>
</tr>
<tr>
<td><strong>Right Isomerism</strong></td>
<td>54</td>
<td>12</td>
<td>3</td>
<td>72%</td>
<td>93%</td>
</tr>
<tr>
<td><strong>Lim</strong></td>
<td>31</td>
<td>7</td>
<td>1</td>
<td>74%</td>
<td>95%</td>
</tr>
<tr>
<td><strong>Taketazu 2006</strong></td>
<td>23</td>
<td>7</td>
<td>1</td>
<td>65%</td>
<td>93%</td>
</tr>
</tbody>
</table>

Berg et al. 2014; Pepes 2009; Taketazu 2006, Lim 2005
Summary

- The incidence of heterotaxy syndrome in utero is higher than postnatally

- Intrauterine fetal death is mostly related to fetal cardiac dysfunction and fetal AV-Block (LAI)

- the epidemiology of fetal heterotaxy is significantly influenced by a high rate of TOP in Western Countries
Summary

- LAI
  - „better“ CHD
  - relevant intrauterine mortality due to fetal AV-block and hydrops
  - associated with biliary atresia
  - postnatally LAI carries a significant better prognosis than RAI

- RAI is associated with
  - more complex CHD
  - favourable intrauterine course
  - relevant postnatal mortality