Surgery in Congenital Hyperinsulinism — less may be more

Winfried Barthlen
congenital hyperinsulinism

- very rare (1:40.000)
- uncontrolled insulin secretion
- life threatening hypoglycemia

symptoms

- unconsciousness, apathia, fits,
- severe neurological damage
Genetics

Saint-Martin 2011, Senniappan 2012

Genes involved in hyperinsulinism:

- ABCC8
- KCNJ11
- GCK
- GLUD1
- HADH
- HNF1A
- HNF4A
- UCP2
- SLC16A1

45% of cases
10% of cases
CHI forms

- focal

- normal islets
  - green circle

- pathological islets
  - red circle

- segmental mosaic

- diffuse
Focal CHI:
- paternal mutation in ABCC8 or KCNJ11
- maternal loss of heterozygosity (LOH) only in the focal lesion

Josip, 6 months

$^{18}$F- DOPA- PET/CT

Einmündung der V. mesenterica sup. in den Confluens

craniale Begrenzung des oberen Fokusareals
frozen sections during surgery

Josip: n = 29
Josip, 6 Monate
Ashton from Malaysia, 17 months old

pat...
choledochal duct - gastroduodenal, hepatic, lienal artery
venous confluens
# personal series *focal* CHI

<table>
<thead>
<tr>
<th></th>
<th>Charité Berlin 2004-2008</th>
<th>Greifswald 2010 - today</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>focal</td>
<td>22</td>
<td>20</td>
</tr>
<tr>
<td>focal lesion visible and palpable</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>cured</td>
<td>19 (86%)</td>
<td>19 (95%)</td>
</tr>
<tr>
<td>2nd surgery</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>3rd surgery</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>laparoscopy</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Roux-en-Y</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>complications</td>
<td>1 pseudocyst</td>
<td>1 pulmonary embolism (factor V Leiden mutation), 1 adhesion ileus, 1 NEC</td>
</tr>
</tbody>
</table>
Asyraf from Malaysia, 6 months
three surgeries August 2013
CHI forms

- focal
- segmental mosaic
- diffuse

normal islets

pathological islets
Persisting hypoglycemia
(< 50 mg/dL or < 2.8 mmol/L)

Laboratory
simultaneous blood taking for blood glucose, insulin, β-hydroxybutyrat, fatty acids

Differential diagnoses
- transient hypoglycemia of the newborn
- diabetes mellitus of the mother
- hypopituitarism, cortisol deficiency
- etc.

Diagnosis: congenital hyperinsulinism
hypoglycemia and normal or elevated insulin levels, low β-hydroxybutyrate, free fatty acids, glucose demand >8mg/kg/min; glucagon testing: rise in blood glucose > 30 mg/dL,

Genetics
ABCC8, KCNJ11, GK, GLUD1, HADH, SLC16A1, HNF4A, UCP2

Long term therapy
(for years)

18F-DOPA-PET/CT
focal CHI

Long term therapy
(for years)
unresponsive?

lap. pancreatic biopsy
lap. restrictive pancreatic resection

selective surgical resection of the focal lesion

Arnoux 2011
sub- or near-total resection is still recommended and widely performed!
subtotal pancreatectomy: long term results:

**diabetes**
- 19% postop
- 42% at 8 yrs
- **91% at 14 yrs**

n=58
1984-2006
Hopital Necker Paris

Beltrand, de Lonlay et al
*Diabetes Care 2012*
Morphological Mosaicism of the Pancreatic Islets: A Novel Anatomopathological Form of Persistent Hyperinsulinemic Hypoglycemia of Infancy

C. Sempoux, C. Capito, C. Bellanné-Chantelot, V. Verkarre, P. de Lonlay, Y. Aigrain, C. Fekete, Y. Guiot, and J. Rahier

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Birth weight</th>
<th>Age at presentation</th>
<th>Pancre DZx treatment</th>
<th>Localization (PVS or 18F-PET)</th>
<th>Surgery</th>
<th>Follow-up</th>
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<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>45</td>
<td>3</td>
<td>6.5</td>
<td>Inconclusive (PVS)</td>
<td>Partial tail</td>
<td>Recurrence controlled by low-dose DZx Cured</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>73</td>
<td>3</td>
<td>10</td>
<td>Focal-corpus (PVS) and tail</td>
<td>Partial corpus</td>
<td>Cured</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>94</td>
<td>8</td>
<td>10</td>
<td>Focal (PVS)</td>
<td>Partial corpus</td>
<td>Cured</td>
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<tr>
<td>4</td>
<td>F</td>
<td>91</td>
<td>5</td>
<td>12</td>
<td>Diffuse (PVS)</td>
<td>Partial corpus</td>
<td>Cured</td>
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<tr>
<td>5</td>
<td>F</td>
<td>61</td>
<td>6</td>
<td>15</td>
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<td>Partial tail</td>
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<tr>
<td>6</td>
<td>F</td>
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<tr>
<td>7</td>
<td>M</td>
<td>73</td>
<td>4</td>
<td>15</td>
<td>Inconclusive (PVS)</td>
<td>Tail (PVS)</td>
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<tr>
<td>8</td>
<td>M</td>
<td>48</td>
<td>5</td>
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<tr>
<td>9</td>
<td>M</td>
<td>7</td>
<td>9</td>
<td>10</td>
<td>Focal tail (PVS)</td>
<td>Partial tail</td>
<td>Recurrence controlled by low-dose DZx Cured</td>
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<tr>
<td>10</td>
<td>M</td>
<td>43</td>
<td>5.5</td>
<td>15</td>
<td>Focal tail (PVS)</td>
<td>Partial tail</td>
<td>Recurrence controlled by low-dose DZx Cured</td>
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<tr>
<td>11</td>
<td>F</td>
<td>51</td>
<td>6</td>
<td>15</td>
<td>Focal DZx Transient sensitivity</td>
<td>Partial corpus</td>
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<td>12</td>
<td>F</td>
<td>85</td>
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<td>18</td>
<td>Focal-corpus (PVS) and tail</td>
<td>Partial corpus</td>
<td>Cured</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>48</td>
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<td>14</td>
<td>F</td>
<td>90</td>
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<tr>
<td>16</td>
<td>M</td>
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<td>7</td>
<td>Inconclusive (PVS)</td>
<td>Partial corpus</td>
<td>Cured</td>
<td></td>
</tr>
</tbody>
</table>

Cases 4, 6, and 13 were not tested for ABCC8, KCNJ11, and GCK mutations. Mutations in the GAD gene have been ruled out in patients 1, 10, 14, and 1. Dazoxomic: F: female, M: male, P: postoperative.
Jolina, 15 months medically unresponsive

laparoscopic biopsies: segmental mosaic CHI

http://www.wix.com/dianasula2/jolinas-welt
Laparoscopic pancreatic tail resection
restrictive surgery in *segmental mosaic* CHI

<table>
<thead>
<tr>
<th>pat</th>
<th>age at diagnosis (months)</th>
<th>mutation</th>
<th>medication before surgery</th>
<th>response to medication</th>
<th>age at surgery (months)</th>
<th>medication after surgery</th>
<th>time follow-up (september 2013)</th>
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<tr>
<td>JB</td>
<td>6</td>
<td>none</td>
<td>diazoxide 7mg/kg/d</td>
<td>unsatisfactory</td>
<td>15</td>
<td>none</td>
<td>31</td>
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<td>LH</td>
<td>5</td>
<td>none</td>
<td>diazoxide 7.5mg/kg/d</td>
<td>insufficient</td>
<td>15</td>
<td>diazoxide 7.1mg/kg/d</td>
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<tr>
<td>FS</td>
<td>3</td>
<td>none</td>
<td>diazoxide 22mg/kg/d and octreotide 15μg/kg/d</td>
<td>insufficient</td>
<td>18</td>
<td>diazoxide 8.8mg/kg/d</td>
<td>25</td>
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<tr>
<td>HB</td>
<td>3</td>
<td>ABCC8 compund heterozygous</td>
<td>octreotide 17 μg/kg/d and glucagon 11 μg/kg/h</td>
<td>insufficient</td>
<td>10</td>
<td>lanreotide 60mg/month</td>
<td>9</td>
</tr>
</tbody>
</table>

complications n=0
Results *segmental mosaic* CHI

- nothing: n=1
- Low-dose diazoxide or octreotide: n=3

23 / 16.10.2013
CHI forms

focal
diffuse
segmental mosaic

normal islets
pathological islets
Yildirim, 21 Monate

- Homozygous KCNJ11
- Octreotide $111 \mu g/kg/d$ (15-50$\mu g/kg/d$)
- Laparoscopic biopsies: diffuse cHI
<table>
<thead>
<tr>
<th>pat</th>
<th>age at diagnosis (months)</th>
<th>mutation</th>
<th>medication before surgery</th>
<th>response to medication</th>
<th>age at surgery (months)</th>
<th>medication after surgery</th>
<th>time follow-up (september 2013)</th>
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<tr>
<td>BY</td>
<td>neonatal</td>
<td>KCNJ11 homozygous</td>
<td>octreotide 111 µg/kg/d</td>
<td>insufficient</td>
<td>21</td>
<td>none</td>
<td>29</td>
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<td>DI</td>
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<td>ABCC8 heterozygous dominant</td>
<td>octreotide 90 µg/kg/d</td>
<td>unsatisfactory</td>
<td>14</td>
<td>lanreotide 60mg/month</td>
<td>25</td>
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<tr>
<td>AN</td>
<td>neonatal</td>
<td>none</td>
<td>diazoxide 7.9 mg/kg/d</td>
<td>unsatisfactory</td>
<td>360 (30 years)</td>
<td>none</td>
<td>23</td>
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<tr>
<td>EC</td>
<td>neonatal</td>
<td>none</td>
<td>diazoxide 5 mg/kg/d</td>
<td>insufficient</td>
<td>20</td>
<td>none</td>
<td>22</td>
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<tr>
<td>CN</td>
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<td>none</td>
<td>diazoxide 6.6 mg/kg/d</td>
<td>insufficient</td>
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<td>lanreotide 60mg/month</td>
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<td>RP</td>
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<td>ABCC8 compound heterozygous</td>
<td>diazoxide 8.5 mg/kg/d</td>
<td>insufficient</td>
<td>7</td>
<td>lanreotide 60mg/month</td>
<td>16</td>
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<tr>
<td>SB</td>
<td>neonatal</td>
<td>ABCC8 heterozygous dominant</td>
<td>diazoxide 5mg/kg/d</td>
<td>unsatisfactory</td>
<td>132 (11 years)</td>
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<td>15</td>
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<td>AK</td>
<td>neonatal</td>
<td>ABCC8 compound heterozygous</td>
<td>octreotide 20 µg/kg/d + iv glucose 7.6 mg/kg/min</td>
<td>insufficient</td>
<td>2</td>
<td>subtotal resection</td>
<td>8/1</td>
</tr>
<tr>
<td>Elizabeth P</td>
<td>neonatal</td>
<td>ABCC8 heterozygous</td>
<td>octreotide 8 µg/kg/d</td>
<td>unsatisfactory</td>
<td>5</td>
<td>octreotide 5 µg/kg/d</td>
<td>8</td>
</tr>
<tr>
<td>Elias P</td>
<td>neonatal</td>
<td>ABCC8 heterozygous</td>
<td>octreotide 8 µg/kg/d</td>
<td>unsatisfactory</td>
<td>5</td>
<td>none</td>
<td>8</td>
</tr>
</tbody>
</table>

Restrictive surgery in **diffuse** CHI

complication n=1 (hematoma)
Results *diffuse* CHI

- nothing: n=5
- octreotide or lanreotide: n=4
- n=1
Dizygotic twins from Argentina
same mutation: ABCC8 p.G716C (c.2146G>T)
same surgery: laparoscopic pancreatic tail resection

Elizabeth
still on octreotide

Elias
nothing

diffuse ≠ diffuse
Rapid functional evaluation of beta-cells by extracellular recording of membrane potential oscillations with microelectrode arrays

Pharmacology Tübingen, Germany

pancreas slice of child Eloise from Guatemala

Glucose 10mM

Fraction of plateau phase (FOPP) = percentage of time with spike activity = 48%

200 µm
K$_{ATP}$ channel modulators

- diazoxide 150 µM
- tolbutamide 400 µM

Isolated islet of Eloise

Electrode with islet

Electrode without

Glucose 10mM

5 µV

3 min
Surgery in Congenital Hyperinsulinism - less *is* more!

- cure in *focal* CHI: 95%
- weaning of medication in *non-focal* CHI: 43%
- reducing the risk of diabetes
referral area for CHI surgery
n=34
since 2010
from abroad 44%
Greetings from Germany!
5th Congenital Hyperinsulinism Family Conference
September 17-18, 2013
NH Milano 2 Hotel
Segrate, Italy

Tuesday, September 17, 2013