X-linked adrenoleukodystrophy (X-ALD): women with ALD, long term outcome after HSCT, NBS

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I. Women with X-ALD
Clinical features of X-ALD: classical view

No genotype-phenotype correlation!
Clinical features of X-ALD: current view

Asymptomatic (screening)

Cerebral ALD – when?

Pre-symptomatic

Adrenal insufficiency

Myelopathy

Time (years)

Engelen et al, Current Neurol NeuroSci, 2014
For diagnosis in women: *ABCD1* gene mutation analysis
Women with X-ALD

**Myelopathy** (prominent fecal incontinence)

**Peripheral neuropathy** (clinically less relevant)

Symptomatic status highly age dependent

Women are patients!

Engelen et al, Brain, 2014
X-inactivation: specific for \textit{ABCD1}
Conclusion

Women are patients and not carriers

Probability of being symptomatic increases with age

Most frequent symptoms are incontinence and gait disorder
II. Long term follow-up after HSCT
Treatment for cerebral ALD
Cerebral ALD: Haematopoietic stem cell transplantation

Effective in early stage cerebral ALD

Transplants in UMCU/WKZ in Utrecht (Dr. Boelens)

Adults are also considered for treatment (France, Germany)

Aubourg et al, NEJM, 1990
Miller et al, Blood, 2011
Long term outcome after haematopoietic stem cell transplantation

Table 1  Summary of clinical characteristics of the five patients

<table>
<thead>
<tr>
<th>Transplantation</th>
<th>VLCFA pre-Tx</th>
<th>VLCFA post-Tx</th>
<th>Examination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C26:0</td>
<td>C26/C22</td>
<td>C26:0</td>
</tr>
<tr>
<td>Patient A</td>
<td>2.26</td>
<td>0.06</td>
<td>2.48</td>
</tr>
<tr>
<td>Patient B</td>
<td>2.56</td>
<td>0.08</td>
<td>1.6</td>
</tr>
<tr>
<td>Patient C1</td>
<td>n.a.</td>
<td>n.a.</td>
<td>0.77</td>
</tr>
<tr>
<td>Patient C2</td>
<td>5.17</td>
<td>0.07</td>
<td>1.7</td>
</tr>
<tr>
<td>Patient D</td>
<td>1.75</td>
<td>0.06</td>
<td>2.73</td>
</tr>
</tbody>
</table>

Does not prevent onset of myelopathy?!

Therefore no pre-symptomatic HSCT
III. The case for newborn screening (NBS)
Screen or not?

- Health benefit for the male neonate
  - Direct: HSCT for cerebral ALD, hydrocortisone
  - Indirect: shorter diagnostic Odyssey

- Reliable test
  - Available, implemented in parts of the U.S.A.

- Identification of other peroxisomal disorders

- No treatment for progressive myelopathy
Is X-ALD a candidate for newborn screening?

Screen female neonates or not?

- Health benefit for the female neonate
  - Direct: none
  - Indirect: shorter diagnostic Odyssey, reproductive choice
- No reliable test
  - Not all female neonates are identified
Some other peroxisomal diseases will be identified

- DBP, ACOX1, etc
- Zellweger spectrum disorders
- Shorter diagnostic Odyssey
- Supportive care: hydrocortisone, vitamin K
Experience in the U.S.

- Testing is feasible
- Implemented in N.Y. State in 2014, several other states will follow
What do you think?

- Each country will weigh benefits – problems in a different way

- Netherlands chose to screen boys only, implementation in progress

- Also helps research: do we really know natural history?
The Dutch cohort

- Find biomarkers to predict onset of cerebral ALD

- Define natural history, evaluate surrogate outcome measures like OCT

- Great need for treatments that stabilize the progressive myelopathy

- Newborn screening will reveal true incidence and allow unbiased natural history studies
Therefore, the disease becomes progressively more severe, often leading to a rapid, often fatal outcome. Caregivers, however, can be very long-chain fatty acids (VLCFA); ABCD1; magnetic resonance imaging (MRI); adrenocortical insufficiency.

Vernieuwingsimpuls 
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