Clinical Considerations: Newborn Screening for ALD

Paul Orchard, MD
University of Minnesota

National New Disorders Meeting
June 22, 2017
Discussion

• Phenotypes associated with ALD
• Diagnosis; implications for the family
• Monitoring of patients post diagnosis
• Current treatment; transplant outcomes
• Importance of newborn screening
Adrenoleukodystrophy

- Frequency \(\approx 1:20,000\) boys
- X-linked peroxisomal
- Defect in ABCD1 gene; many described mutations
- Defective metabolism of very long chain fatty acids (VLCFA)
- High plasma VLCFA; establishes the diagnosis

*Figure: Dr. Kemp, Emma Children’s Hospital, Amsterdam, Netherlands*
Diagnosis of ALD

- Very Long Chain Fatty Acid (VLCFA) accumulation in ALD esp. C24 and C26
- Defective gene (ABCD1) mapped to Xq2; >750 mutations described
- Other peroxisomal disorders can also have increased VLCFA

http://www.x-ald.nl/biochemistry-genetics/vlcfa/
### Phenotypes: ALD

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood Cerebral ALD (C-ALD)</td>
<td>30 - 35%</td>
</tr>
<tr>
<td>Age: 2.75-10 years; median age 7.2 years</td>
<td></td>
</tr>
<tr>
<td>Adolescent Cerebral ALD; 11-21 years</td>
<td>4 - 7%</td>
</tr>
<tr>
<td>Adrenomyeloneuropathy (AMN)</td>
<td>40 - 46%</td>
</tr>
<tr>
<td>Spinal cord disease (40% develop C-ALD)</td>
<td></td>
</tr>
<tr>
<td>Adult C-ALD alone</td>
<td>2 - 5%</td>
</tr>
<tr>
<td>Addisonian Disease alone</td>
<td>50%</td>
</tr>
<tr>
<td>Asymptomatic: Decreases with age</td>
<td>Rare &lt;40</td>
</tr>
</tbody>
</table>
Adrenomyeloneuropathy (AMN)

- Most frequent phenotype of ALD
- Symptom onset usually 20 - 30 yrs
- Slowly progressive motor disability. Stiffness, weakness in legs initially
- Leads to use of cane, then wheelchair
- Defects in spinal cord; non-inflammatory
- Also occurs to a lesser degree in women carriers

Kemp, Biochimica et Biophysica, 2012; (1822):1465-74
Adrenal Insufficiency (AI) in ALD

- VLCFA accumulate in adrenal glands
- IN ALD, production of cortisol and aldosterone can be impaired
- Chronic symptoms may include
  - Fatigue, weakness, weight loss, nausea
- Stress (infection, trauma) can cause
  - Severe N/V, dehydration, hypotension, hypoglycemia, low Na, high K
  - Deaths occur with common viral infections
Adrenal Insufficiency (AI)

Studies of AI in ALD:

- 49 asymptomatic pts (mean 4.5 yrs)
  - 39 (80%) showed adrenal dysfunction*
- 90 pts with cerebral ALD (mean 6.3 yrs)
  - 79 (88%) showed adrenal dysfunction**
  - 17 (22%) of these – AI first sign of ALD
- Transplantation does not reverse AI***

*Kemp, Biochimica et Biophysica, 2012; (1822):1465-74
***Petryk, Bone Marrow Transpl, 2012 (47): 1377-8
Cerebral ALD: MRI Findings

Occipital Disease  Gadolinium Enhancement
Cerebral ALD (CALD)

- Most lethal form of ALD
- Acute, neuroinflammatory process leading to demyelination in 35-40% of boys
- Peak age of onset of clinical disease is 7 years of age; MRI changes ~2 yrs earlier
- Occurs with other phenotypes
- Not clear what initiates disease
- Progressive and lethal; bone marrow transplantation is the only approved Rx
History Of Transplantation For Cerebral ALD

- Rationale based on transplant successes with LSD
- ALD known to be a peroxisomal disease, but thought to be an enzyme deficiency
- 1984; Moser - first report of HSCT for ALD; advanced patient; progressed, died
- 1990; Aubourg - reported disease stabilization in a patient with early cerebral ALD
- 1993; Aubourg cloned the gene, showing it is a transmembrane, non-secreted protein
- Allogeneic HCT now standard of care for early cALD (but why how does it work??)
What are the outcomes of transplantation for CALD?

1. Survival
2. Neurologic Outcomes
3. Neuropsychological Findings
### Phenotypes: ALD

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood Cerebral ALD (C-ALD)</td>
<td>30 - 35%</td>
</tr>
<tr>
<td>2.75-10 years; median age 7.2 years</td>
<td></td>
</tr>
<tr>
<td>Adolescent Cerebral ALD; 11-21 years</td>
<td>4 - 7%</td>
</tr>
<tr>
<td>Adrenomyeloneuropathy (AMN)</td>
<td>40 - 46%</td>
</tr>
<tr>
<td>Spinal cord disease (40% develop C-ALD)</td>
<td></td>
</tr>
<tr>
<td>Adult C-ALD alone</td>
<td>2 - 5%</td>
</tr>
<tr>
<td>Addisonian Disease alone</td>
<td>50%</td>
</tr>
<tr>
<td>Asymptomatic: Decreases with age</td>
<td>Rare &lt;40</td>
</tr>
</tbody>
</table>
Grading Radiographic Severity

Loes scoring: (0–34) Point system

- parieto-occipital WM
- antero-temporal WM
- frontal WM
- corpus callosum
- visual pathways
- auditory pathways
- pyramidal system
- basal ganglia
- anterior thalamus

Cerebral ALD: HCT Experience

- 2004; International experience (43 centers)
- 94 patients transplanted through 1999
- Numerous preparative regimens used
- Overall survival 56% over entire group
- Leading cause of death: disease progression
- Amount of disease at the time of BMT crucial

Survival Based On MRI Score

MRI score prior to transplant predicts survival

Minnesota Study: Overall Survival: All Transplanted ALD Patients (n=60)

76% (95% CI: 64-88%)

Survival by Graft Source; Early cALD (Loes Score <10; N=30)

Related Donor

Unrelated Donor

P = 0.28

Survival by pre-Transplant Loes Score (Early vs. Late Disease)

Could Modification of the Transplantation Approach Improve Outcomes in CALD?

1. Powers; 2005 – autopsy study
   Oxidative stress in brains of patients with ALD
2. Pujol; 2008 – murine data
   Confirmed oxidative stress in $ABCD1^-$ mice

Fourcade et al. Human Molecular Genetics. 2008 17(12):1762-1773
Advanced ALD; Modified Protocol (Loes Score >10; N=30)

Survival can be improved with transplant modification in advanced cALD

What about neurologic outcomes?
### Assessing Functional Outcome:

**Moser/Raymond NFS Scale**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hearing/auditory processing problems</td>
<td>1</td>
</tr>
<tr>
<td>Aphasia/apraxia</td>
<td>1</td>
</tr>
<tr>
<td>Loss of communication</td>
<td>3</td>
</tr>
<tr>
<td>Vision impairment/fields cut</td>
<td>1</td>
</tr>
<tr>
<td>Cortical blindness</td>
<td>2</td>
</tr>
<tr>
<td>Swallowing difficulty or other CNS dysfunction</td>
<td>2</td>
</tr>
<tr>
<td>Tube feeding</td>
<td>2</td>
</tr>
<tr>
<td>Running difficulties/hyperreflexia</td>
<td>1</td>
</tr>
<tr>
<td>Walking difficulties/spasticity/spastic gait (no assistance)</td>
<td>1</td>
</tr>
<tr>
<td>Spastic gait (needs assistance)</td>
<td>2</td>
</tr>
<tr>
<td>Wheelchair required</td>
<td>2</td>
</tr>
<tr>
<td>No voluntary movement</td>
<td>3</td>
</tr>
<tr>
<td>Episodes of incontinency</td>
<td>1</td>
</tr>
<tr>
<td>Total incontinency</td>
<td>2</td>
</tr>
<tr>
<td>Nonfebrile seizures</td>
<td>1</td>
</tr>
</tbody>
</table>

**Possible Total:** 25

*from Moser, Arch Neurol 2005;62:1073-1080*
Change In Neurologic Function Score (NFS) Based on Baseline Score, Loes Score

Δ NFS 1 yr. Post BMT

Baseline Functional Score

Baseline MRI (Loes) Score

n = 21
n = 32
n = 29
n = 24

fxn score 0
fxn score ≥ 1
Loes < 10
Loes ≥ 10

p < 0.01

Neurocognitive Assessments
Standard Risk cALD Patients

1. 139 cALD patients transplanted at Minnesota between 1991-2014
2. 62 patients had pre-BMT MRI scores <10 and pre-HCT neurocognitive testing (baseline group)
3. 33 had neurocognitive data obtained at least 2 years post HCT (long-term group)
4. Median age of all patients was 8 years
5. Testing included verbal reasoning, visual/perceptual reasoning, verbal reasoning, working memory and processing speed

Pierpont; JAMA Neurology, 2017; in press
Neurocognitive Functioning Pre-HCT Correlation: Increased MRI Severity

Pierpont; JAMA Neurology, 2017; in press
Effect Of Severity of Baseline MRI On Neurocognitive Functioning pre-HCT

<table>
<thead>
<tr>
<th>Testing</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal comprehension</td>
<td>0.008</td>
</tr>
<tr>
<td>Perceptual reasoning</td>
<td>0.001</td>
</tr>
<tr>
<td>Working memory</td>
<td>NS</td>
</tr>
<tr>
<td>Processing speed</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Conclusion: Despite being identified as being in a “standard risk” ALD group, significant deficits are observed, related to MRI based severity

*Pierpont; JAMA Neurology, 2017; in press*
Impairments at Most Recent Evaluation: Boys With Standard Risk cALD

<table>
<thead>
<tr>
<th></th>
<th>Pre-HCT MRI &lt;4</th>
<th>Pre-HCT MRI ≥4.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal comp</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per reasoning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working mem</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Processing spd</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal mem</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sustained attn</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual/motor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fine motor</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Black: Severe impairment
- Gray: Moderate impairment
- White: No impairment

Pierpont; JAMA Neurology, 2017; in press
### Predicted Outcome; Effect of Pre-HCT MRI On Neurocognitive Functioning post-HCT

<table>
<thead>
<tr>
<th>MRI Score</th>
<th>HCT</th>
<th>Verbal Comp</th>
<th>Percept Reason</th>
<th>Working Memory</th>
<th>Process Speed</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>pre</td>
<td>99</td>
<td>102</td>
<td>94</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>5 yr</td>
<td>93</td>
<td>102</td>
<td>93</td>
<td>86</td>
</tr>
<tr>
<td>7</td>
<td>pre</td>
<td>90</td>
<td>88</td>
<td>86</td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td>5 yr</td>
<td>65</td>
<td>63</td>
<td>79</td>
<td>46</td>
</tr>
</tbody>
</table>

Outcomes based on linear mixed model
Hypothetical 8 year old with cALD undergoing HCT

*Pierpont; JAMA Neurology, 2017; in press*
Predicted Outcome; Effect of Pre-HCT MRI On Neurocognitive Functioning post-HCT

<table>
<thead>
<tr>
<th>MRI Score</th>
<th>HCT</th>
<th>Verbal Comp</th>
<th>Percept Reason</th>
<th>Working Memory</th>
<th>Process Speed</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>pre</td>
<td>99</td>
<td>102</td>
<td>94</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>5 yr</td>
<td>93</td>
<td>102</td>
<td>93</td>
<td>86</td>
</tr>
<tr>
<td>7</td>
<td>pre</td>
<td>90</td>
<td>88</td>
<td>86</td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td>5 yr</td>
<td>65</td>
<td>63</td>
<td>79</td>
<td>46</td>
</tr>
</tbody>
</table>

Outcomes based on linear mixed model
Hypothetical 8 year old with cALD undergoing HCT

Pierpont; JAMA Neurology, 2017; in press
Summary: Neurocognitive Testing in “Standard-Risk” cALD and HCT

1. At baseline, as MRI scores increase, prior to HCT there is more impairment of verbal & visual reasoning and processing speed

2. Post transplant, patients with more advanced disease have a steeper decline in functioning

3. Two-thirds of all patients had severe impairment in $>1$ neurocognitive domain at the time of last testing

Implication: Even boys with “standard-risk” disease are at risk for long term deficits. Earliest diagnosis of cALD possible provides the best opportunity for good outcomes

Pierpont; JAMA Neurology, 2017; in press
Summary: NBS for ALD

1. **Newborn screening will save lives!**
2. Deaths due to adrenal insufficiency will be decreased.
3. Deaths and life-long disability will be decreased because of earlier transplantation.
4. With NBS, other boys at risk (brothers, cousins) will be identified as well.
5. For NBS to be effective, ongoing monitoring will be required to establish when intervention (hydrocortisone, BMT) will be necessary.
6. Can we identify CALD before demyelination occurs? May allow us to better preserve function.
Univ. of Minnesota

Brad Carlin
Jim Cloyd
Todd Defor
Reena Kartha
Maggie Kumbalek
Troy Lund
Brad Miller
Weston Miller
Gerald Raymond
Nicole Sando
Jakub Tolar
John Wagner
Chet Whitley

Imaging:
Alex Mckinney
Shalom Michaeli
Dave Nascene
Igor Nestrasil

Neuropsych:
Julie Eisengart
Rene Pierpont
Peg Semrud-Klikeman