Newborn Screening for X-linked Adrenoleukodystrophy (X-ALD): Preliminary Report from the Condition Review Workgroup (CRW)

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Alex R. Kemper, MD, MPH, MS
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Overview: X-Linked Adrenoleukodystrophy (X-ALD)

- Peroxisomal disorder affecting the adrenal cortex and the central nervous system (CNS)
- Broad phenotype spectrum ranging in onset and severity from childhood through adulthood
- Primarily affects males (across the spectrum). Female heterozygous carrier can develop symptom onset in adulthood
- Most common peroxisomal disorder
- Estimated X-ALD incidence in the U.S.:
  - 1 in 21,000 newborn males
  - 1 in 14,000 newborn females are carriers
Keywords: (“Adrenoleukodystrophy”[Mesh]) OR (“Adrenoleukodystrophy”[tiab]) OR (“Adrenoleukodystrophy/therapy”[Mesh]) OR (“X-ALD”[tiab]) OR (“very long-chain fatty acids”[All Fields]) OR (“VLCFA”[tiab]) OR (“Lorenzo’s oil”[Supplementary Concept]) OR (“Lorenzo’s oil”[tiab]) AND (“animals”[Mesh] NOT “humans”[mesh]) AND Limits: English.

Articles through PubMed, EMBASE, & CINAHL since database inception (1317)

Articles screened for relevance (987)

Articles assessed for initial eligibility (495)

Articles retained for data extraction & synthesis (170)

Screening by two independent reviewers
X-linked Adrenoleukodystrophy (ALD)

**Genetics:**
- ABCD1 = single causative gene of X-ALD, maps to Xq28. ABCD1 gene encodes adrenoleukodystrophy protein (ALDP), which facilitates transport of very long-chain fatty acids (VLCFA) into peroxisomes. ALDP deficiency impairs VLCFA beta-oxidations, leading to elongation of VLCFA.
- >600 mutations identified ([http://www.x-ald.nl](http://www.x-ald.nl)); most are unique
- No genotype-phenotype correlation, even within families

**Screening:**
Dried-blood spots – laboratory study conducted by Mayo Clinic (~100,000 samples), prospective screening in MD (~5,000 newborns)

**Diagnosis:**
ABLD1 mutation analysis, measurement of VLCFAs in plasma, MRI (“Loes Score”)

**Treatment(s):**
HSCT, adrenal hormone replacement therapy, N-acetyl-L-cysteine, Gene therapy
## X-ALD Phenotypes

<table>
<thead>
<tr>
<th></th>
<th>Cerebral ALD <em>(about 90% of CCALD have adrenal insufficiency [Addison’s disease]</em>)</th>
<th>Adrenomyeloneuropathy (AMN)</th>
<th>Addison Only (adrenal insufficiency)</th>
<th>Women with X-ALD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frequency (%)</strong></td>
<td><strong>CHILD (CCALD) 31 – 35</strong></td>
<td></td>
<td></td>
<td>unknown symptomatic</td>
</tr>
<tr>
<td></td>
<td><strong>ADOL (AdolALD) 4 – 7</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>ADULT (AALD) 2 – 5</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Onset Age (Yrs)</strong></td>
<td>2.5–10</td>
<td>&gt;21</td>
<td>&gt;18</td>
<td>&gt;2</td>
</tr>
<tr>
<td></td>
<td>10–21</td>
<td>&gt;21</td>
<td>&gt;18</td>
<td>Mostly &gt;40</td>
</tr>
<tr>
<td><strong>Progression</strong></td>
<td>Rapid</td>
<td>Slow <em>(if no cerebral involvement)</em></td>
<td>–</td>
<td>Slow</td>
</tr>
<tr>
<td><strong>Myelopathy</strong></td>
<td>–</td>
<td>+ / -</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Extensive</td>
<td>Some</td>
<td>–</td>
<td>Occasional-Rare</td>
</tr>
<tr>
<td><strong>White matter lesions on brain MRI</strong></td>
<td><strong>Extensive</strong></td>
<td>Some</td>
<td>–</td>
<td>Occasional-Rare</td>
</tr>
<tr>
<td><strong>Behavioral &amp; Cognitive Disorder</strong></td>
<td><strong>+</strong></td>
<td>− <em>(+ if cerebral involvement)</em></td>
<td>−</td>
<td>Very rare</td>
</tr>
<tr>
<td><strong>Peripheral Neuropathy</strong></td>
<td>−</td>
<td>rare</td>
<td>possible</td>
<td>Sensory-motor, axonal</td>
</tr>
<tr>
<td></td>
<td>Death within a few years after onset</td>
<td></td>
<td></td>
<td>+ / -</td>
</tr>
</tbody>
</table>
X-ALD Newborn Screening

• Measurement of C26:0 lysophosphatidylcholine (26:0-lyso-PC)

• Detected in dried-blood spots (DBS)

• Small pilot and validation studies suggest
  – low false-positive rates
  – High-throughput feasibility
  – Unknown sensitivity (false-negative rate)
  – Clinical validity with confirmation not established

• Primary Screening Methods:
  – Tandem mass spectrometry (MS/MS)
Current X-ALD Newborn Screening

- **NY, CT, and NJ** State Newborn Screening—legislation approved 2013
- **CA** – Proposed legislation to mandate NBS for ALD moving forward, April 2014
- **MD** – proposed to add ALD in 2014, pending funds and state lab changes
- Mayo Clinic Comparative Effectiveness of Screening study (100,000 NBS from CA), *final results pending.*

(State NBS for ALD data still being gathered)
X-ALD Newborn Screening

• What is the primary target of screening?
• What are the secondary targets?
• What would most help inform the Advisory Committee?

Proposal

– Screening: Summarize all cases detected

– Focus on expected outcomes from newborn screening: Cerebral ALD, Addison’s (in childhood), other peroxisomal disorders detected through newborn screening (Zellweger syndrome)? [SECONDARY TARGET]

– Exclude evaluating expected outcomes of early diagnosis of adult-onset conditions; will summarize guidelines/recommendations of care for early detected cases
Establishing the X-ALD Diagnosis

- **Definitive X-ALD diagnosis**
  - DNA diagnostic test for X-ALD involving non-nested genomic amplification of the ABDC1 gene, followed by sequencing and analysis with fluorescence.

- **Neuroimaging**
  - Brain MRI/(& Loes scale for MRI) – always abnormal in neurologically symptomatic males

- **Increased Very long-chain fatty acids**
  - Most important laboratory assay is VLCFA concentration in plasma

- **Clinical Diagnosis in CALD (Boys)** –
  - Symptoms of ADD, with signs of dementia and understanding of spoken language, progressive disturbance in behavior, coordination, handwriting, vision, other neurological disturbances.
  - Primary adrenocortical insufficiency (with additional diagnostic confirmation)
Management of Presymptomatic X-ALD

- Diagnosis X-ALD
  - Refer to endocrinologist
- MRI normal
  - Age 3-12 years
    - yes
      - Repeat MRI in 6 months
    - no
      - Repeat MRI in 12 months
  - no
    - Consider BMT *

Engelen et al. 2012. X-linked adrenoleukodystrophy: Clinical presentation and guidelines for diagnosis, follow-up and management. Orph J Rare Dis. 7
Management of Presymptomatic X-ALD

Follow-up flowchart for presymptomatic ALD

(Newborn screening) → Presymptomatic ALD patient → Prepare for HSCT

Follow-up every 6 months by MRI, neurological, neuropsychological and electrophysiological methods

+ Hormone replacement at the detection of adrenal insufficiency

Abnormal finding (+) → CCALD or AdoCALD (40%) HSCT

Abnormal finding (−) →

- adult AMN (25%) or ACALD → HSCT
- Follow-up cerebral involvements every 6 months → ACALD → HSCT

Prepare for HSCT

(option)

Familial analysis with genetic counseling Mutation & VLCFA

dietary therapy with Lorenzo’s oil

Follow-up VLCFA

Proband

Treatment Strategies

- **Hematopoietic Stem Cell Transplantation (HSCT)**
  - May reduce risk or progression of neurological degeneration in early stage CCALD

- **Adrenal Cortisol Replacement therapy**
  - Necessary for adrenocortical insufficiency “Addison’s disease” to prevent adrenal crisis
  - No effect on neurological symptoms

- **Gene Therapy for X-ALD**
  - 2 successful case studies in France (2 7 yr old boys, early CALD), cerebral disease progression halted after 14-16 mos

- **Lorenzo’s oil**
  - Aims to normalize Saturated VLCFA plasma levels, controversial and mixed results.
  - Efficacy and application studies continue.

- **Lovastatin in X-ALD**
  - Aims to lower VLCFA
  - Mixed findings, strongest study (Engemen, 2010, NEJM) show small VLCFA decrease in plasma, but not red and white blood cells
Survival Outcomes with Clinical Detection, with and without HCT

- Subjects: Boys with early stage CALD
  - N=283 non-transplanted
  - N=19 transplanted

- Mean age at symptom onset among 283 non-transplanted group was 7 years (SD 2 years).

- 131 (46%) patients died during the mean follow-up period of 5.9 years (5.3) at a mean age of 12.3 years (4.9), 5-year survival was 66%.

- The 5-year survival probability of 54% in the early stage group was significantly poorer (p=0.006) than the 5-year survival of 95% in the transplanted group with early stage cerebral disease.

Survival, CALD untreated (N=283 boys)

Figure 2: Kaplan-Meier estimate of survival for 283 boys with childhood cerebral X-linked adrenoleukodystrophy after development of neurological symptoms (cognitive, behavioural, or neurological symptoms)

Survival outcomes, CALD with (n=19) and without transplants (n=30)

Thank You!

Questions?

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Presentation Contact:

Alex R. Kemper, MD, MPH, MS
alex.kemper@duke.edu