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

Alex R. Kemper, MD, MPH, MS
May 12, 2015
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
Systematic Evidence Review: Published Literature – Through ~November 2014

Figure 1. Preliminary PRISMA Diagram of Published Literature Search

- **Keywords:** (“Adrenoleukodystrophy”[Mesh]) OR (“Adrenoleukodystrophy”[tiab]) (“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 (pending final exclusions)
- Screening by two independent reviewers
NBS for X-ALD Condition Review Focus

• Primary target of review: childhood forms detected at screening
  – Cerebral ALD – symptomatic and asymptomatic [later-onset] at birth
  – Adrenal insufficiency/Addison’s only

• Secondary screening targets – counts of female carriers detected, other disorders (Zellweger’s, other peroxisomal disorders)

• Exclude evaluating expected outcomes of early diagnosis of adult-onset conditions (AMN, female heterozygote ALD)
**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, Steroid/Adrenal hormone replacement therapy, Gene therapy
**X-ALD Phenotype Spectrum**

<table>
<thead>
<tr>
<th></th>
<th>CHILDHOOD</th>
<th>ADULT</th>
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<tbody>
<tr>
<td><strong>Cerebral ALD (CALD)</strong></td>
<td><em>(about 90% of C-CALD also have adrenal insufficiency)</em></td>
<td>Adrenomyelo-neuropathy (AMN)</td>
</tr>
<tr>
<td>Onset Age (Yrs)</td>
<td>2.5–10 10–21 &gt;21</td>
<td>&gt;2</td>
</tr>
<tr>
<td>Frequency (%)</td>
<td>CHILD 31 – 35 ADOL 4 – 7 ADULT 2 – 5 <em>(prevalence decreases with age)</em></td>
<td>40 - 46 unknown symptomatic</td>
</tr>
<tr>
<td>Progression</td>
<td>Rapid</td>
<td>Slow Slow</td>
</tr>
<tr>
<td>Myelopathy</td>
<td>Extensive Some Possible</td>
<td>+ +</td>
</tr>
<tr>
<td>Brain MRI - White matter lesions</td>
<td>Extensive</td>
<td>Some Occasional-Rare</td>
</tr>
<tr>
<td>Behavioral &amp; Cognitive Disorder</td>
<td>Extensive Some Possible</td>
<td>− <em>(+ if cerebral involvement)</em></td>
</tr>
<tr>
<td>Peripheral Neuropathy</td>
<td>Rare Possible</td>
<td>Sensory-motor, axonal + / -</td>
</tr>
<tr>
<td>Life Expectancy (untreated)</td>
<td>Death within a few years after onset</td>
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</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
  - Unclear sensitivity (false-negative rate)
- Primary Screening Methods:
  - Tandem mass spectrometry (MS/MS)
Current X-ALD Newborn Screening

• Legislative Approval:
  – NY, CT, and NJ State Newborn Screening–2013
  – NY NBS – Live screening since December 2013

• States considering X-ALD screening:
  – 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 updates ongoing)
NY State NBS Program: “3-Tier” Screen for X-ALD

Dates: Dec 30, 2013 to present, >300,000 newborns screened

<table>
<thead>
<tr>
<th>Tier - Screening Activity</th>
<th>Rate Definition</th>
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<tbody>
<tr>
<td>TIER 1</td>
<td>MS/MS for C26:0 LPC</td>
</tr>
<tr>
<td>TIER 2</td>
<td>HPLC &amp; MS/MS for C26:0 LPC</td>
</tr>
</tbody>
</table>

> Mutation analysis of ABCD1 gene, in-house
⇒ Referral also for confirmatory testing

(screening results removed; manuscript is in preparation)
NY NBS Short-term Follow Up Algorithm: Tier 3 & Referral

Establishing the X-ALD Diagnosis

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

• **X-ALD diagnosis – ABCD1 mutations**
  – *DNA diagnostic test for X-ALD involving non-nested genomic amplification of the ABDC1 gene, followed by sequencing and analysis with fluorescence.*

  ➢ *affected X-ALD newborns may have known gene mutations from mutation analysis, OR gene deletions and other abnormalities which require further genetic analysis – gene mutation analysis alone may not ID all cases*
Establishing the X-ALD Diagnosis (cont’)

• **Clinical Assessment**
  
  – **Neuroimaging** - *Brain MRI/(& Loes severity scale for MRI)* – always abnormal in neurologically symptomatic males
  
  – **Clinical Symptoms - Child Cerebral ALD (Boys)**
    
    - *ADD symptoms, signs of dementia, difficulties understanding spoken language, progressive disturbance in behavior, coordination, handwriting, vision, other neurological disturbances.*
    
    - *Primary adrenocortical insufficiency co-occurs in ~90% of Cerebral ALD (with additional diagnostic confirmation)*
  
  – **Asymptomatic**
    
    - *May show ABCD1 mutations, but be asymptomatic in infancy and require follow-up and monitoring*
Management of Presymptomatic X-ALD

• Ongoing follow up care for early detected, presymptomatic X-ALD patients to monitor for disease progression

• Management protocols of follow up care for X-ALD patients established

• Brain magnetic resonance imaging (MRI) has been found to be a reliable marker for disease progression/cerebral involvement

• Loes Score – MRI disease severity rating established to inform progression and need for transplant

• Referral to endocrinologist specialists to monitor adrenal function
Primary Treatment Strategies

• **Hematopoietic Stem Cell Transplantation (HSCT)**
  – *May reduce risk or progression of neurological degeneration in early stage CALD*

• **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**
  – *Not standard care, Experimental*
  – *2 successful case studies in France (2 7 yr old boys, early CALD), cerebral disease progression halted after 14-16 mos*
# 5-year Survival for Childhood Cerebral X-ALD, With and Without Transplant

<table>
<thead>
<tr>
<th>C-CALD (Historical Controls)</th>
<th>No Transplant (n=283)</th>
<th>Transplant ---</th>
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<tbody>
<tr>
<td>5-year survival</td>
<td>66%</td>
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<tr>
<td>Deaths by 5 years</td>
<td>46% (12.3 years)</td>
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<thead>
<tr>
<th>C-CALD (Early stage)</th>
<th>No Transplant (n=30)</th>
<th>Transplant (n=19)</th>
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</thead>
<tbody>
<tr>
<td>5-year survival</td>
<td>54%</td>
<td>95% **&lt;br&gt;**p=0.006</td>
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Decision Modeling Population Level Outcomes

• Decision Modeling… *in progress*
  – Technical Expert Panel (TEP) assembled
  – 3 expert panel meetings scheduled
## Decision Modeling Population Level Outcomes

<table>
<thead>
<tr>
<th>TEP</th>
<th>Date</th>
<th>Objectives</th>
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<tbody>
<tr>
<td>TEP 1</td>
<td>14 APR 2015</td>
<td>1. Determine natural history and epidemiology with usual clinical detection</td>
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<td>2. Discuss screening and diagnostic confirmation process</td>
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<td>3. Identify key outcomes of X-ALD</td>
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<td>4. Identify standard treatments and treatment effectiveness</td>
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<td>5. Review initial draft of decision tree model for X-ALD</td>
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<tr>
<td>TEP 2</td>
<td>14 MAY 2015</td>
<td>• Review updated model structure</td>
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<tr>
<td></td>
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<td>• Review probability inputs</td>
</tr>
<tr>
<td>TEP 3</td>
<td>11 JUN 2015</td>
<td>• Review preliminary results</td>
</tr>
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Decision Modeling Population Level Outcomes (cont.)

Next Steps:

- Develop/refine Decision Model Structure
- Translate key parameter inputs from evidence review
- Project population outcomes
Public Health System Impact Assessment for X-ALD

Association of Public Health Laboratories
PHSI Background

- The Secretary of HHS Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) makes recommendations to the Secretary, HHS, about what conditions should be included in the RUSP

- These recommendations are based on
  - The certainty of net benefit
  - The feasibility and readiness of implementing comprehensive screening

- Feasibility and readiness is based, in part, on an assessment of the public health system impact
Aims/Goals

• Inform the ACHDNC
• Opportunity to
  – Understand the “real world” barriers and facilitators related to screening
  – Identify research gaps
  – Conduct a needs assessment
  – Evaluate opportunity costs
  – Share practices that can ultimately improve implementation
Guiding Philosophy

• All states can provide useful information about public health impact
• We need to provide useful, high-quality data to the ACHDNC within a short period of time
• We cannot burden state public health officials
• We need to provide information to states to facilitate the process
• This is a critical opportunity to assure that the ACHDNC is aware of issues at the state level
Progress

• Key informant interviews with state NBS programs that are screening or have mandates to screen

• Development of Fact Sheet for X-ALD Screening Methods

• Development of X-ALD public health system impact assessment survey
Next Steps

• Distribute survey to NBS program directors in all 50 states, DC and PR via email

• Period to complete: May 13 to June 17, 2015

• Educational X-ALD webinar on May 14 at 2 pm ET

• Report to ACHDNC: July/August 2015
Thank You!

Questions?

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