Adrenoleukodystrophy (ALD) and Lorenzo’s Oil: An Update

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1. Adrenoleukodystrophy: Biochemistry and management

2. The efficacy of Lorenzo’s Oil

3. Newborn Screening and Expanded Access: What does this mean for Lorenzo’s Oil
Peroxisomal Disorders

Assembly Disorders

- Zellweger Syndrome
- Neonatal Adrenoleukodystrophy
- Infantile Refsum
- Rhizomelic Chondrodysplasia Punctata

Single Peroxisomal Protein Disorders

- X-linked Adrenoleukodystrophy
- Acyl-CoA Oxidase Deficiency
- Multifunctional Enzyme Deficiency
- DHAP Alkyltransferase Deficiency
- Alkyl DHAP Synthetase Deficiency
- Glutaric aciduria type III
- Refsum Disease
- Hyperoxaluria type I
Adrenoleukodystrophy (ALD)

• X-linked disorder - Xq28
  – incidence 1:17,000, all races affected
• Peroxisomal ATPase Binding Cassette Protein (ABCD1)
• Defect in peroxisomal beta oxidation
• Accumulation of very long chain fatty acids (VLCFA)
• Affects myelin, adrenal cortex, Leydig cells of the testes
Fatty Acid Abnormality in Adrenoleukodystrophy

X-ALD (ABCD1) gene is approximately 20 kb long and consists of 10 exons.
# Statistics of X-ALD Mutations

## All X-ALD mutations in database

<table>
<thead>
<tr>
<th>Category</th>
<th>N</th>
<th>%</th>
<th>N</th>
<th>%</th>
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<tbody>
<tr>
<td>All X-ALD mutations in database</td>
<td>989</td>
<td>N/A</td>
<td>492</td>
<td>50%</td>
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<td>missense mutations</td>
<td>599</td>
<td>61%</td>
<td>254</td>
<td>52%</td>
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<tr>
<td>frame shift mutations</td>
<td>225</td>
<td>23%</td>
<td>134</td>
<td>27%</td>
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<tr>
<td>nonsense mutations</td>
<td>96</td>
<td>10%</td>
<td>56</td>
<td>11%</td>
</tr>
<tr>
<td>amino acid insertions/deletions</td>
<td>38</td>
<td>4%</td>
<td>31</td>
<td>6%</td>
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<tr>
<td>one or more exons deleted</td>
<td>31</td>
<td>3%</td>
<td>17</td>
<td>3%</td>
</tr>
</tbody>
</table>

78% of all ABCD1 point mutations are **transitions** (T>C, C>T, G>A, A>G)

22% of all ABCD1 point mutations are **transversions** (T>A or G, C>G or A, G>C or T, A>T or C)

75% of all ABCD1 mutations result in **absence** of ALDP

79% of all non-recurrent ABCD1 mutations result in **absence** of ALDP

[www.x-ald.nl](http://www.x-ald.nl) Stephan Kemp, PhD
• **Cerebral (35-40%)**
  – Diffuse inflammatory demyelination, rapid progression.
  – Childhood form (onset 4-8 years) most common

• **Adrenomyeloneuropathy (AMN) (40-45%)**
  – Distal axonopathy mainly in spinal cord.
  – Paraparesis in young adults, progress over decades

• **Addison Disease only (20-30% at onset)**
  – Most develop AMN later

• **Asymptomatic**

• >50% of heterozygous women develop AMN in middle age or later
Childhood Cerebral ALD

• Initial normal development
• Onset between 4-10 years
  – Earliest 2.75 years,
  – Peak 7 years
• Initial presentation often subtle
  – Attention, behavior, learning issues
  – May initially respond to stimulants
• Progresses rapidly to vegetative state
  – 1.9 years ± 2 years
• Adrenal insufficiency 85%
Thomas,  Oct. 2nd.

May we wait here?

She says she’s fine.

Well, I read five lines.

I’ve saved nine of Dave’s sneezes.
MRI in Childhood ALD

- 85% Parieto-occipital
- 15% Frontal
- Garland of contrast enhancement
- MRI abnormality precedes clinical findings
Pathology of Childhood ALD
MRI Progression

Fig 1. Axial FLAIR (A) and sagittal T1-weighted MRI after contrast administration (B) demonstrate a focal area of high signal in the splenium of the corpus callosum, which shows enhancement after contrast administration.

Fig 2. Axial FLAIR (A) and axial T1-weighted MRI after contrast administration (B) show progression of the corpus callosum lesion, as well as other lesions in the parietal white matter.
Adrenomyeloneuropathy

- Adult onset - mean age 25 years
- Spastic paraparesis, sensory involvement, bladder dysfunction
- Gradual progression
- Consistent with a normal life span, but cerebral disease occurs in approx. 20%.
Adrenomyeloneuropathy

Axonal disease resulting in loss of myelin and atrophy of the spinal cord
Adrenal insufficiency (Addison disease)

- Primary adrenocortical dysfunction
- May present acutely or chronically
- Hypoglycemia
- Difficulty fighting infections
- Dehydration
- Hyperpigmentation (elevation in ACTH)
- Rarely low Na, high K
- A leading cause of adrenal insufficiency in males
- Majority will develop neurologic manifestations
Plasma ACTH in X-ALD identified by VLCFA screen
Asymptomatic phenotype

- Asymptomatic boys with normal brain MRI
- Diagnosed by plasma VLCFA screening of relatives of known X-ALD patients
- Not identifiable in the past
- One of the most frequent phenotypes
  - Every boy identified in the newborn period will be in this category
Heterozygotes

- 20-50% of women who are carriers will have symptoms
- Spastic paraparesis, dysesthesias, bladder symptoms
- May be a function of age
- Rare - cerebral or adrenal disease
Neither the gene defect nor the biochemical abnormality predicts the phenotype. A genetic modifier has been postulated.
Diagnosis

- Elevation in VLCFA
  - Plasma/serum
  - Fibroblasts
  - Amniocytes
  - Other tissues
- Known heterozygotes have a 20% false negative rate using VLCFA
- DNA diagnosis is available
Newborn Screening for ALD

• **Advantages**
  – Identify and monitor individuals at risk for adrenal insufficiency
  – Monitor for early cerebral disease and refer when appropriate for therapy
  – Identify extended family members

• **Initial issues**
  – Technical/methodologic

• **Subsequent issue(s)**
  – Concerns about surveillance and management
Present status

• NY began screening on 12/30/2013
  – 503,432 newborns screened (12/2015)
    • 41 referrals with 15 males + 18 females with mutation
    • ~ 1 in 22,000

• CT, NJ, CA will begin when added to the Recommended Uniform Screening Panel (RUSP)

• The national advisory panel has voted to add ALD to the RUSP (Aug 2015)
  – Awaiting the Secretary’s signature

• Other states will likely follow the RUSP, but that will be decided locally
Current ALD Therapies

- Adrenal hormone replacement
  - Not to be overlooked
  - Life-saving and once instituted is life long
  - Stress dosing at times of illness and surgeries
- Hematopoietic stem cell transplant (HSCT)
  - Early cerebral disease
- Preventative therapy with Lorenzo’s oil
Hematopoietic Stem Cell Transplantation (Bone marrow transplantation)

- Effective in early cerebral disease
- Arrests disease progression through uncertain mechanism
- Significant morbidity and mortality to the procedure
  - Transplant related mortality 14%
- 92% survival for patients with mild neurological deficit (PIQ >80) and MRI score <9 (Peters et al Blood 104:881, 2004)
- Not indicated in asymptomatic boys
- Best candidates are routinely screenec individuals known to be at risk
- Development of gene therapy

Mahmood et al Lancet Neurology 2007
Role of VLCFA in pathogenesis

• Elevated, but are they involved in pathogenesis?

• Has implications as we discuss therapies to lower them
Accumulation of Saturated Very Long Chain Fatty Acids (SVLCFA)

- Extremely insoluble in water and alters properties of membranes
- Inclusion of C26:0 in model membrane perturbs structure and stability
- Impairs stability of axonal or myelin membranes
- In cell culture results in rise of oxidative stress markers
- Role as a trigger of immune response?
4:1 mixture of glyceryl trioleate (GTO) and trierucate (GTE, C22:1)

IND 032336

Competitive inhibitor for microsomal elongation of long chain fatty acids

Normalizes plasma levels of VLCFA within 4 weeks

Moderate thrombocytopenia

Ineffective in cerebral disease

Uncertain effectiveness in myelopathic forms
Effect on manifestations of ALD

- No effect on childhood cerebral disease
- Adrenomyeloneuropathy – no definitive answer
  - Cappa et al (1990) – cerebral demyelination in only 2/11 treated individuals
  - Kaplan et al (1993) – VEP did not improve despite therapy
  - Van Geel et al (1999) (n=22); varying phenotypes including heterozygotes. Generally progress
  - Aubourg et al (1993) (n=24); varying phenotypes including cerebral disease, boys, and heterozygotes; 9/14 men worsened.

- All of these studies were uncontrolled
- Small number of individuals studied with a wide range of ages, disability, and phenotype
- Limited information on compliance and effective reduction of VLCFA
- In spite of the poor design of the clinical evaluation, the lack of clear improvement led to the presumption that oil was ineffective in all forms of ALD.
Poulos et al (1994)
- Unable to detect any changes in the brain indicating that little erucic acid crossed the blood brain barrier
- Limited value in correcting the accumulation of saturated very long chain fatty acids in the brain

Rasmussen et al (1994)
- 4 treated, 7 untreated
- 1 out of 4 patients had decr VLCFA in brain
- Erucic acid was not detected in brain

Golovko and Murphy (2006)
- Showed that it did cross the blood brain barrier in rodents and was rapidly metabolized
X-ALD Lorenzo’s Oil Prevention Study in boys -- Rationale

• Saturated VLCFA (C26:0) excess
  – Principal biochemical abnormality
  – Contributes to pathogenesis
  – LO normalizes plasma VLCFA without serious adverse events

• Open trial
  – Placebo-controlled study not feasible
    • Disease severity
    • Concern about equipoise due to biochemical effect
ALD Lorenzo’s Oil Prevention Study

Study Group

• 89 boys with X-ALD
• Normal MRI and neurologic exam
• Age 6.9 ± 2.7 years
• Follow-up 6.7 ± 2.17 years
• All diagnosis confirmed at Kennedy Krieger
• All were offered LO and chose to participate in IRB approved protocol
### Table 2. Overall Clinical Outcome: 89-Member Study Group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Living</td>
<td>81 (91)</td>
</tr>
<tr>
<td>Deceased</td>
<td>8 (9)</td>
</tr>
<tr>
<td>Neurologically normal and normal MRI results</td>
<td>66 (74)</td>
</tr>
<tr>
<td>MRI abnormalities and neurologically normal</td>
<td>13 (15)</td>
</tr>
<tr>
<td>MRI and neurological abnormalities*</td>
<td>8 (9)</td>
</tr>
</tbody>
</table>

Abbreviation: MRI, magnetic resonance image.
*Two patients had missing MRI results and had developed neurological abnormalities.

Preventative Study Results

- Time weighted estimate of average plasma C26:0 over study period (LAUC) was significantly associated with risk reduction
  - 0.1 µg/ml reduction of plasma C26:0 LAUC reduces risk of cerebral X-ALD by 36%
  - Two-fold or greater reduction of risk feasible
- The most recent year of C26:0 observations did not show this significant association
- The association between the LAUC and the development of MRI abnormalities in asymptomatic patients with ALD suggests that long-term reduction of C26:0 levels reduces the risk of developing brain MRI abnormalities in asymptomatic boys with ALD

- **Substantial and prolonged lowering of C26:0 levels may be required to achieve significant reduction in risk of developing MRI abnormality**
Limitations of interpretation

• Follow-up period was relatively short
• Limited understanding of the factors that cause the profound differences between the inflammatory cerebral phenotype and the noninflammatory AMN phenotype
  – Over half of them never develop childhood cerebral disease and thus for unknown reasons appear resistant to this phenotype
Lorenzo’s oil
Present status

• Not FDA approved
  – Still an “investigational new drug”
  – IND 032336, sponsor G. Raymond, MD
• Placebo-controlled study in men and women with myelopathy
  – Study issues required early termination
• Presently available under two FDA protocols
  – Compassionate release
    • Limited number of individuals who had previously received oil
  – Expanded Access
Expanded Access

- IRB and FDA-approved protocol to make Lorenzo’s oil available
- Criteria
  - Males 18 months old through 18 years of age
  - Confirmed ALD with elevated VLCFA
  - Normal brain MRI within the past year
  - Able to be consented to participate in a research study
  - No medical contraindication to diet and oil
- Safety Monitoring is required
• Very long chain fatty acids
• Recent CBC and CMP
• Physical examination
• Recent normal brain MRI
• Nutrition assessment
• Consent, assent, and HIPAA
  – Properly signed and returned
• When all completed, an order for oil is placed and shipped directly to subject
Diet and Lorenzo’s oil

• Lorenzo’s oil is used to help the body make unsaturated VLCFA as opposed to saturated VLCFA.
• ALD diet from foods is low in total fat and saturated fats.
• Total calories of fat stay the same, but there is a shift to very long chain monounsaturated fatty acids.
• Supplementation of certain essential fatty acids (walnut oil), vitamins, and minerals.
Nutritional assessment

• Calculate the required daily calories for good growth
• Aim for 30-35% of calories to come from fat
  – 20% from LO, 5% Walnut oil, 10% from other dietary fats (3% saturated fats)
• Lorenzo’s oil is calculated to provide 20% of calories
  – Estimated caloric need per day x 0.2 = LO kcals (calories from LO)
  – Convert this LO kcal to ml
    • \( LO \text{ kcal} ÷ 8 = X \text{ ml LO per day} \)
• Calculate walnut oil dose
  – Estimated caloric need per day x 0.05 = walnut oil kcals
  – \( WO \text{ kcals} ÷ 8 = Y \text{ ml WO per day} \)
<table>
<thead>
<tr>
<th>Nutritional Assessment</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>Total calories</td>
<td>1200 kcal</td>
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<tr>
<td>Calories from fat</td>
<td>360 kcal</td>
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<tr>
<td>LO calories</td>
<td>240 kcal</td>
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<tr>
<td>Daily dose LO</td>
<td>30 ml</td>
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<tr>
<td>WO calories</td>
<td>60 kcal</td>
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<tr>
<td>WO dose</td>
<td>7.5 ml</td>
</tr>
<tr>
<td>Fat calories from diet</td>
<td>120 kcal</td>
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<tr>
<td>Saturated fat calories</td>
<td>36 kcal</td>
</tr>
<tr>
<td>~13 g fat and only 4 g saturated fats</td>
<td></td>
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</tbody>
</table>
Suggestions for usage

- Vitamin and Mineral Supplement (100% RDA)
  - Chewable for children
- Lorenzo’s Oil information
  - When starting, increase the dose gradually to total volume over a few weeks
  - While it may be taken all at once, increase tolerance by splitting it up over the day
  - Cannot cook with oil
  - May flavor (FlavorIt™, fat free Hershey’s™ chocolate sauce, fat free strawberry NesQuik™ and Tang™)
  - May mix with juice, fat free yogurt, pudding, ice cream, milkshake, cake frosting
- Walnut oil
  - Source of essential fatty acids
  - May be purchased at supermarkets, health food stores, or on the internet
Nutritional counseling

- Discuss and provide information on the assessment
- Educate
  - Types of fat
  - Changes in shopping, cooking, and eating out
  - Foods that may or may not be eaten
  - There are no “forbidden foods”, but foods high in saturated fats are not recommended
- May need to provide on-going counseling and monitoring
  - In most circumstances, weight loss is not desired
Required monitoring

• Every three months
  – VLCFA
  – Complete blood count with platelets
  – Comprehensive metabolic panel (AST/ALT)
• Yearly reassessment
  – General and neurologic exam
  – MRI
  – Nutritional re-assessment
• Results must be sent to Principal Investigator
Most common adverse reaction is a moderate reduction in platelet count
  – If <80,000, stop Lorenzo’s oil and substitute a fat that is low in saturated fats eg olive oil
  – In 2-4 weeks, repeat CBC and if normalized, restart oil
  – Similar steps may be taken for other laboratory abnormalities

Not tolerating the oil
  – Split dose throughout day
  – Mix in flavorings

Illness or hospitalization
  – Just omit the oil; no withdrawal
  – Report to PI

Change on MRI – contact the principal investigator
Summary

- ALD is a common X-linked metabolic disorder
- Diagnosis is made by elevations in VLCFA
- May present in childhood with adrenal insufficiency or cerebral disease
- Newborn screening will result in the determination of asymptomatic boys who require prospective monitoring
Summary

- Lorenzo’s oil is an investigational agent which can lower blood levels of VLCFA
- May have a preventative effect on the development of cerebral disease
- Presently available in the United States under an expanded access protocol
- Protocol requires baseline and continued monitoring for safety
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