2017 Alabama Newborn Screening Conference

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Newborn Screening for X-Linked Adrenoleukodystrophy (X-ALD)

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X-Linked Adrenoleukodystrophy (X-ALD)

- Affects nervous system white matter, adrenal cortex and testis
- Childhood cerebral, adult spastic paraparesis, and "Addison only" forms often co-occur in same family

X-Linked Adrenoleukodystrophy (X-ALD)

- Accumulation of saturated very long chain fatty acids (VLCFA) due to impaired peroxisomal VLCFA β-oxidation X-ALD results from mutations in the ABCD1 gene that codes for a peroxisomal membrane protein that is part of ATP Binding Cassette transporter superfamily

X-ALD History

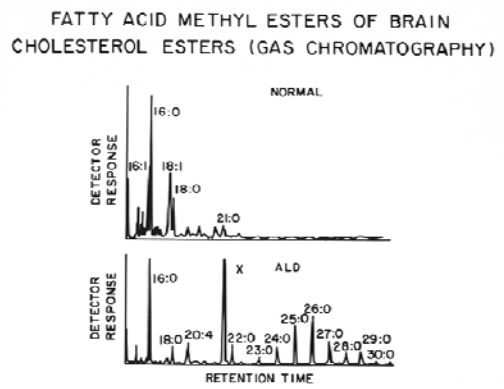
- 1923 Childhood form described by Siemerling and Creutzfeldt (Kiel)
- 1976 Very long chain fatty excess found in brain and adrenal cholesterol esters; Powers, Schaumburg, Kunihiko Suzuki, Masahiro Igarashi (Albert Einstein, NY)
- 1976 AMN recognized; Budka (Vienna), Griffin (NIH)

X-ALD History

- 1981 Plasma total lipid very long chain fatty acid assay; Ann Moser (KKI) Using this method screened mice at Jackson Labs & did not find any mice with increased plasma VLCFA
- 1981 Gene mapped to Xq28; Migeon (Hopkins)
- 1990 First successful bone marrow transplant; Aubourg (Paris)

X-ALD History

- **1993 ABCD1 Gene cloned; Aubourg, Mandel (Strasbourg)**
- **1997 Mouse model; Kirby Smith (Hopkins) normal plasma total lipid VLCFA, 5-fold increase total lipid C26:0 in all tissues, in 2006 we found increased C26:0 lysophosphatidyl choline in plasma and tissues, a new marker for evaluating therapies in the ABCD1 mouse**



X-ALD gene (ABCD1)

- **Maps to chromosome Xq28**
- **Codes for 745 amino acid peroxisomal membrane protein, ALD protein (ALDP or ABCD1) and belongs to the human protein family of ATP-binding cassette (ABC) transporters. ALDP is in the sub-family D, member 1 (ABCD1)**

X-ALD gene (ABCD1)

- **> 2475 mutations of which 748 are non-recurrent as of 7/12/17**
- **www.x-ald.nl**
- **No correlation with phenotype**
- **Mutation Analysis is essential for accurate heterozygote detection**

Boehm CD, et al., Accurate DNA-based diagnostic and carrier testing for X-linked adrenoleukodystrophy.
Mol Genet Metab. 1999; 66:128-36.

X-ALD Phenotypes and their Relative Frequency

- **Cerebral (35-40%)**
  Diffuse inflammatory demyelination, rapid progression.
  Childhood form (onset 4-8 years) most common

X-ALD Phenotypes and their Relative Frequency

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

X-ALD Phenotypes and their Relative Frequency

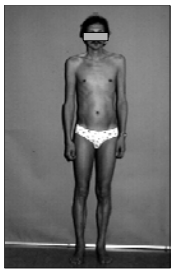
- **Addison Disease only (20-30% at onset)**
  Most develop AMN later

  Phenotypes frequently co-occur in same family
  > 50% of heterozygous women develop AMN in middle age or later

Adrenomyeloneuropathy

Clinical Findings

- **Spastic paraparesis**
- **Ataxia**
- **Sensory dysfunction**
- **Bladder dysfunction**
- **Distal muscle atrophy**
- **Dark skin**
- **Thin hair**
- **Adrenal insufficiency**



Childhood Cerebral Form of X-linked Adrenoleukodystrophy

- **35% of total X-ALD population**
- **Onset before 10 years: earliest 2.75 years, peak 7 years**
- **Initial symptoms resemble attention deficit-hyperactivity**
- **May respond to methylphenidate(ritalin) or other stimulants used for ADHD**
- **Progression to apparent vegetative state 1.9 +/- 2 Years**
  - **Range 0.5 to 10.5**

Childhood Cerebral Form of X-linked Adrenoleukodystrophy

- **Adrenal insufficiency 85% (often biochemical only)**
- **MRI abnormality precedes clinical findings**
- **65% parieto-occipital; 15% frontal; 15% projection fibers; 5% atypical**

Treatment Outcomes: Child Cerebral X-ALD

- **Disease Status Measures:**
  - **MRI Severity Rating (Loes Score, established by the neuroradiologist, Dan Loes)**

Loes Score	Clinical Guidelines
< 0.5	Normal, no neurological involvement
<8 or 9	Recommendation for HSCT or gene therapy
>8 or 9	Not usually recommended for HSCT or gene therapy

  - **Neurologic Function Score (NFS)**
  - **ALD-Disability Rating Scale (ALD-DRS)**

Outcomes, Early vs. Late Stage CCALD

- **At least 5 included outcome studies with N>6 that compare pre-post HCT outcomes between early vs. late stage CCALD with MRI Severity/Loes scores**

Outcomes, Early vs. Late Stage CCALD

Publication	Title	Journal	N
2004 Peters et al.	Cerebral X-ALD: the international hematopoietic cell transplantation experience from 1982 to 1999	Blood	94
2007 Beam et al.	Outcomes of unrelated umbilical cord blood transplantation for X-ALD	Biology of Blood & marrow transplantation	12
2011 Miller et al.	Outcomes after allogeneic HCT for childhood cerebral ALD: the largest single-institution cohort report	Blood	60
2013 McKinney et al.	Childhood cerebral X-linked ALD: Diffusion tensor imaging measurements for prediction of clinical outcome after HSCT	AJNeuroRadiol	8
2016 Bladowska et al.	The Role of MR Imaging in the Assessment of Clinical Outcomes in Children with X-ALD after Allogeneic HSCT	Pol J Radiol	7

Bone Marrow Transplantation stabilizes cerebral ALD when done in early stages

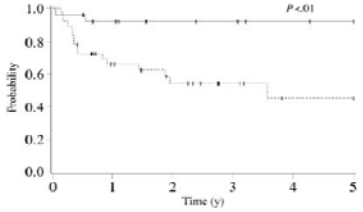


Figure 2. Kaplan-Meier estimate of survival for cerebral X-linked adrenoleukodystrophy following hematopoietic cell transplantation by number of neurologic deficits and MRI severity score before transplantation. Solid line indicates patients with 0 to 1 neurologic deficits and MRI severity score less than 9 (n = 25). Dashed line indicates patients with 2 or more neurologic deficits or MRI severity score 9 or greater (n = 37). Ticks on probability lines indicate dates of censoring at last follow-up.

Adrenal Insufficiency

- Untreated adrenal insufficiency can lead to death, about 80% of males with X-ALD have adrenal insufficiency, rare in X-ALD carriers
- One study (Polgreen et al, 2011) describes how diagnosis of adrenal insufficiency can help speed the diagnosis of X-ALD and improve outcomes
- HStemCellTransplant does not affect adrenal insufficiency

Adrenal Insufficiency

- Presymptomatic detection of adrenal insufficiency in X-ALD males will save lives

X-ALD Treatment Summary – Presymptomatic Identification

- Presymptomatic identification of adrenal insufficiency in X-ALD males
- HSCT improves outcomes, and treatment with a lower Loes score is associated with better outcomes Recommend MRI every 6 months from age of 1.5 years to 10 years, then annually

X-ALD Treatment Summary – Presymptomatic Identification

- Identification through family testing or newborn screening leads to improved survival in late childhood compared to detection after the development of neurological symptoms

Lorenzo's Oil

- 4:1 combination of glyceryl trioleate-glyceryl trierucate (mono-unsaturated)
- Reduces plasma very long chain fatty acid levels
- No beneficial effect in childhood or adult cerebral form.

Lorenzo's Oil

- In an open-label preventive study without control cohort the risk for cerebral disease was reduced by 60% in asymptomatic boys who normalized their VLCFA compared to those who did not normalize their VLCFA.
- Currently only available through FDA expanded access program in USA.

Purpose of ALD Newborn Screening

<u>Presymptomatic Diagnosis of Males with X-ALD to:</u>

1. Prevent overt adrenal insufficiency
2. Reduce the risk for childhood phenotype with Lorenzo's Oil diet
3. Improve prognosis of cerebral ALD by facilitating early hematopoietic stem cell and gene transplants
4. Improve success of future therapies

<u>Identification of 80% of X-ALD Heterozygotes to:</u>

1. Provide family screening for male X-ALD relatives.

<u>Diagnosis of Peroxisome Biogenesis Disorders and other peroxisomal VLCFA disorders :</u>

1. Prevent diagnostic odyssey, provide genetic counseling and early supportive therapy.

MINIMUM BIRTH FREQUENCY OF X-ALD IN THE UNITED STATES

	Male Population	Female Population	Total Population
Hemizygotes (a)	1:21,000		1:42,000
Heterozygotes (b) (calculated)		1:14,000	1:28,000
Hemizygotes + Heterozygotes			**1:16,800**

(a) Similar results in France and Canada
(b) 60% of heterozygotes develop symptoms in middle age or later

Bezman et al. Ann Neurology 2001.

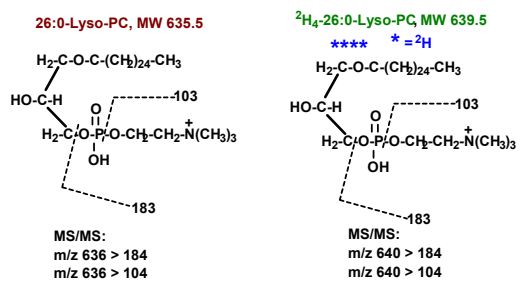
History of Development Newborn Screening Test for X-ALD

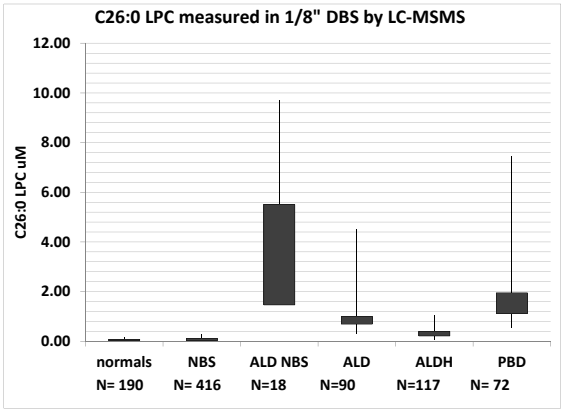
- 2004 Newborn Screening Meeting at NIH, X-ALD added to list of disorders, but no test available on newborn blood spots
- 2006 LC-MS/MS Assay for X-ALD newborn screening, Hubbard et al. Found 5 to 10-fold increase of C26:0 lyso phosphatidyl choline, C26:0 LPC in X-ALD dried blood spots
- 2008 D4-C26:0 LPC synthesized by Avanti
- 2009 Validation of LC-MS/MS assay for X-ALD newborn screening, Hubbard et al.
- 2013 X-ALD newborn screening pilot 5000 screened in MD

History of Development Newborn Screening Test for X-ALD

- December 2013, New York using the marker C26:0 LPC adds newborn screening for X-ALD; as of July 2017 and 820,000 screened, birth incidence of X-ALD is 1/15,472
- August 2015-Secretary's Advisory Committee voted to add X-ALD to the <u>R</u>ecommended <u>U</u>niform <u>S</u>creening <u>P</u>anel(RUSP)

MS/MS Fragmentation of 26:0 Lyso-PC





LC-MS/MS C26:0 lyso-PC Newborn Screening Test Identifies The Following Peroxisomal Disorders:

X-linked Adrenoleukodystrophy (ALD) – genetically inherited; affects 1 in 16,800 births, more severe in males; 3 phenotypes:

1) Childhood Cerebral phenotype: 35-40% of subjects appear normal at birth and at age 4 to 8 years symptoms occur, rapidly progressive to death in childhood

2) Adrenomyeloneuropathy (AMN) phenotype starting in 20s slowly progressive spinal cord disease

3) ALD with Addison's disease only, live with adrenal hormone therapy

Test also identifies: 80% of X-ALD Heterozygotes, Peroxisomal Biogenesis Disorders (PBDs) (Zellweger spectrum disorders) and Single Enzyme Defects of peroxisomal FA oxidation

Importance of Lobbying for X-ALD newborn screening by X-ALD family support groups!!

Lobbying in NY, MN,NJ, CT, GA, DC, MD, CA, TX IL, FL, PA, NE and MA has resulted in legislative approval to add X-ALD newborn screening. Lobbying continues in many other states.
8/27/15 Recommendation to add ALD Newborn Screening to RUSP

8/1/17 Update on X-ALD newborn screening

- **New York, thanks to Elisa Seeger and Aiden's Law, started screening at the end of December 2013**
- **Connecticut started screening in October 2015**
- **California started in September 2016 and screened 6 month's backlog as mandated.**
- **Minnesota and Pennsylvania added ALD to their newborn screening panels several months ago**
- **Georgia recently implemented and Washington, DC will start in the fall of 2017**

NY State NBS Program – "3-Tier" Screening for X-ALD

Tier - Screening Activity		Rate Definition		Rates
TIER 1	MS/MS for C26:0 LPC	Re-test rate (same specimen)	= 1509 of 820,000 *newborns*	=1.84%
TIER 2	HPLC & MS/MS for C26:0 LPC	Repeat rate (independent specimen)	= 74 borderline retest results, repeats requested of 820,000 *newborns* tested	= 0.009%
⇨ Mutation analysis – ABCD1 gene		Referral rate	=63 of 820,000 newborns	= 0.008%
	Confirmed Status:	*27 male with ABCD1 mutations (1/30,370)* *26 female carriers with ABCD1 mutations (1/31,538)* *All ALD (1/15,472)* *9 Other PBD/SED confirmed (1/91,000 screened)* *1 Aicardi-Goutieres syndrome confirmed*		

Total 820,000 newborns screened (Dec 30 2013 – June 30, 2017)

ALD Newborn Screening in NY using C26:0-LPC as marker (July 2017)

- **Referral rate: 1 in 13,016 births or 0.008% of infants screened**
- **Incidence of ALD: 1 in 30,370 males**
- **Incidence of ALD: 1 in 15,472 births**
- **Incidence of PBDs: 1 in 91,000 births**

Prediction of ALD is 1 in 17,000 to 1 in 20,000 births

ALD by the N*u*mbers (820,000 births)

Newborn Screening In Development

- **X-ALD Newborn Screening started recently in Georgia and is coming soon to Washington DC, New Jersey, Washington, Missouri, Nebraska and Illinois**

Newborn Screening In Development

- **CTX screening is proceeding in the Druze area of Israel (CTX is a treatable disease of bile acid metabolism)**

Newborn Screening In Development

- **Michael Gelb has begun a pilot study of combined anonymous screening for several inherited neurological disorders including CTX, MLD, NPA, NPC, and Krabbe, in 90,000 newborns born in the state of Washington**

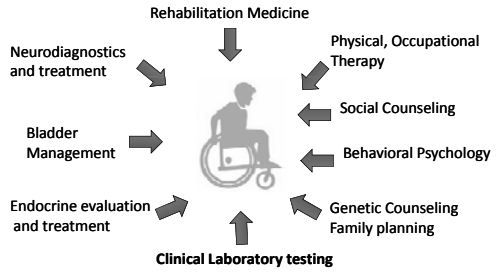
Current Therapies For X-ALD

1. **Assess adrenal function in newborn period and every 6 months; Adrenal hormone replacement if found to be deficient**
2. **Lorenzo's Oil therapy beginning at 6 months through 10 years (shown to be preventative of brain disease if very long chain fatty acids are normalized in blood)**

Current Therapies For X-ALD

3. **Follow with MRI every 6 months and if abnormal and progressive, refer for bone marrow transplantation if there is a matched sibling donor, or umbilical cell transplant if matched, or if no match, refer for ABCD1 gene therapy.**

Moser Center For Leukodystrophies at Kennedy Krieger Institute



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