Nutricia Metabolics Webinar Series

# Adrenoleukodystrophy (ALD) and Lorenzo's Oil: An Update

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# Outline

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

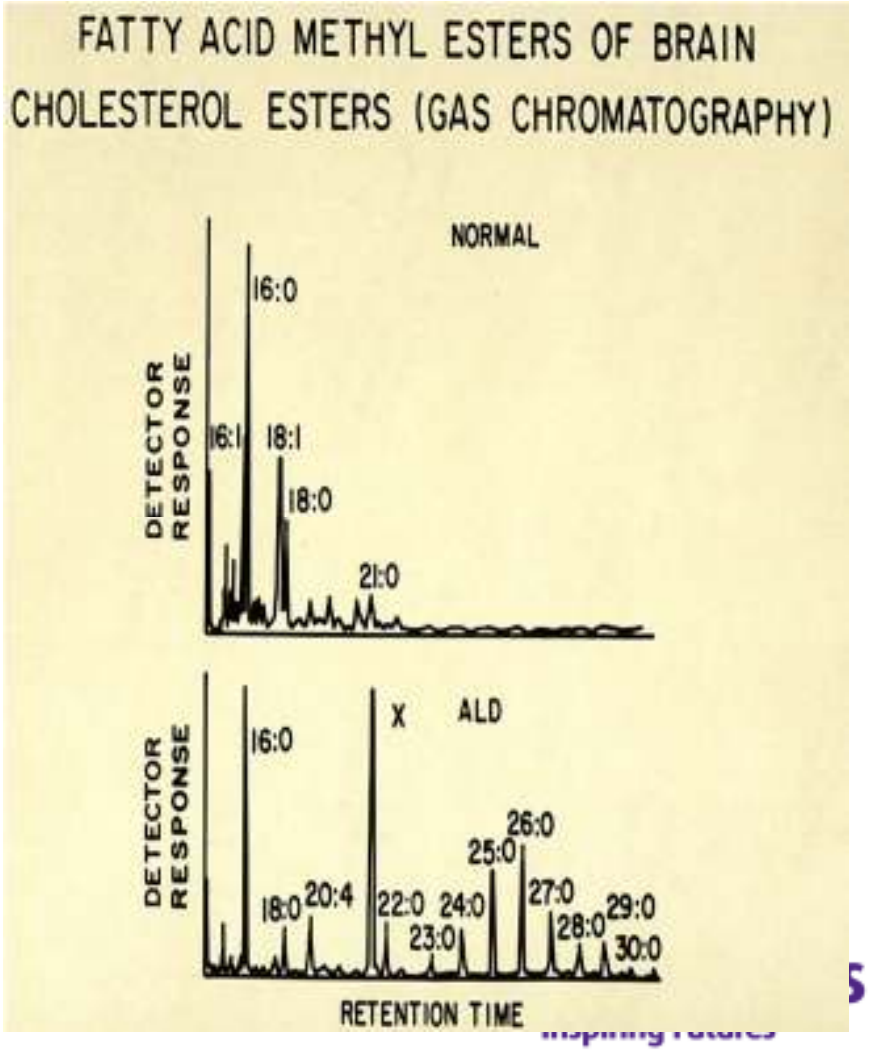
- **X-linked Adrenoleukodystrophy**
- **Acyl-CoA Oxidase Deficiency**
- **Multifunctional Enzyme Deficiency**
- **DHAP Alkyltransferase Deficiency**
- **Alkyl DHAP Synthetase Deficiency**
- **Glutaric aciduria type III**
- **Refsum Disease**
- **Hyperoxaluria type I**

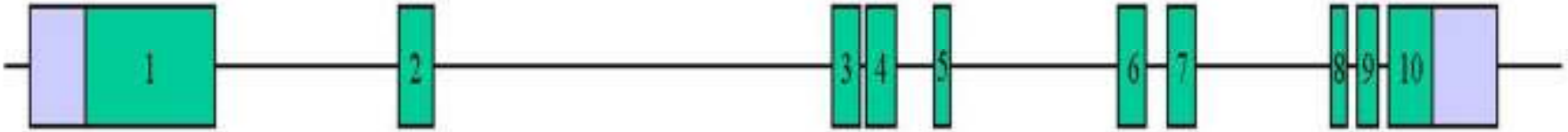
# Adrenoleukodystrophy (ALD)

- 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

Igarashi M, Schaumburg HH, Powers J, Kishimoto Y, Kolodny E, Suzuki K. Journal of Neurochemistry 26:851-860, 1976






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

# Statistics of X-ALD Mutations

## Statistics of X-ALD mutations

| | All mutations | | Non-recurrent | |
|---|---|---|---|---|
| | N | % | N | % |
| All X-ALD mutations in database | **989** | N/A | **492** | 50 % |
| missense mutations | 599 | 61 % | 254 | 52 % |
| frame shift mutations | 225 | 23 % | 134 | 27 % |
| nonsense mutations | 96 | 10 % | 56 | 11 % |
| amino acid insertions/deletions | 38 | 4 % | 31 | 6 % |
| one or more exons deleted | 31 | 3 % | 17 | 3 % |

| | |
|---|---|
| 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 |

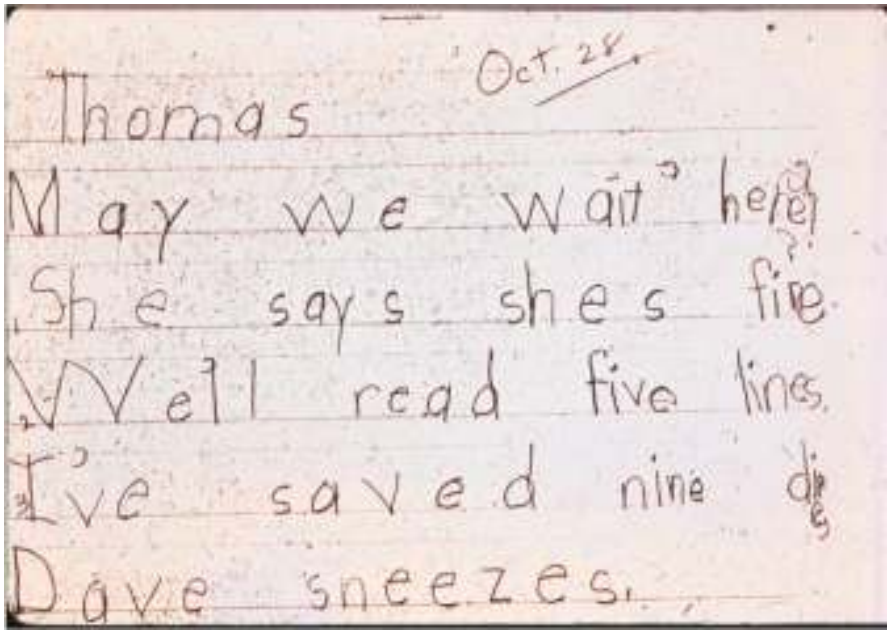
www.x-ald.nl Stephan Kemp, PhD

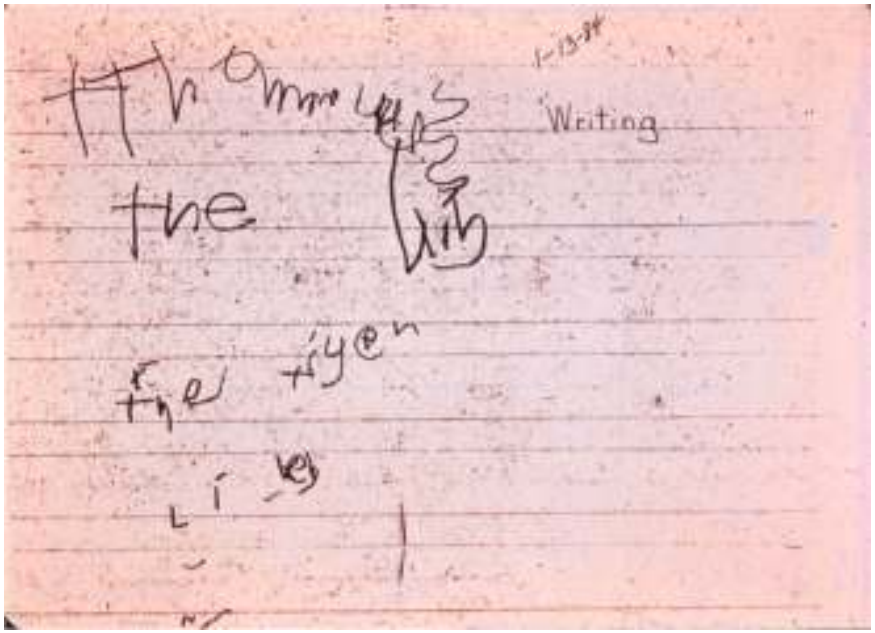
# X-ALD Phenotypes and their Relative Frequency

- **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

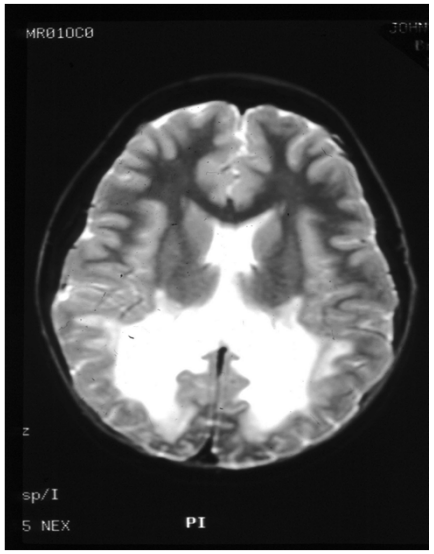
- Initial normal development
- Onset between 4-10 years
  - Earliest 2.75 years,
  - Peak 7 years
- Initial presentation often subtle
  - Attention, behavior, learning issues
  - May initially respond to stimulants
- Progresses rapidly to vegetative state
  - 1.9 years ± 2 years
- Adrenal insufficiency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

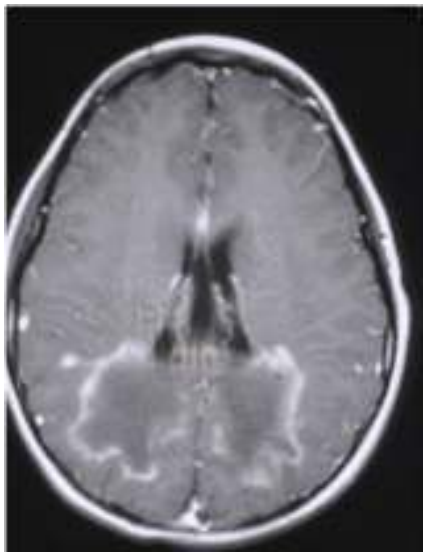

Oct. 28
Thomas
May we wait here?
She says she's five.
Well read five lines.
I've saved nine dies
Dave sneezes.


Writing

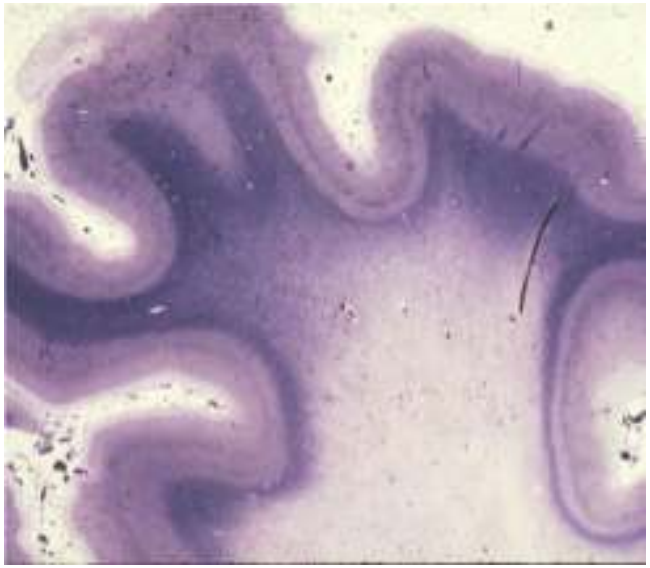
# MRI in Childhood ALD

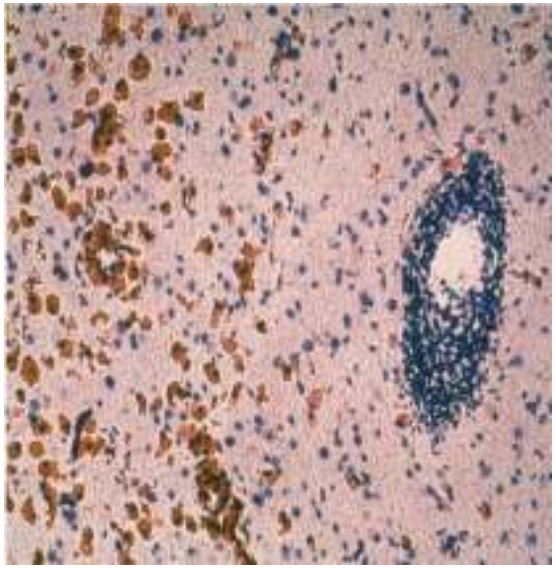
- 85% Parieto-occipital
- 15% Frontal
- Garland of contrast enhancement
- MRI abnormality precedes clinical findings

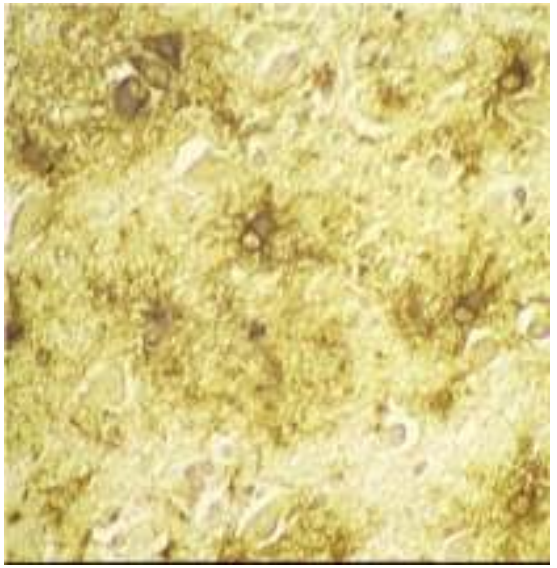


# Pathology of Childhood ALD







# MRI Progression

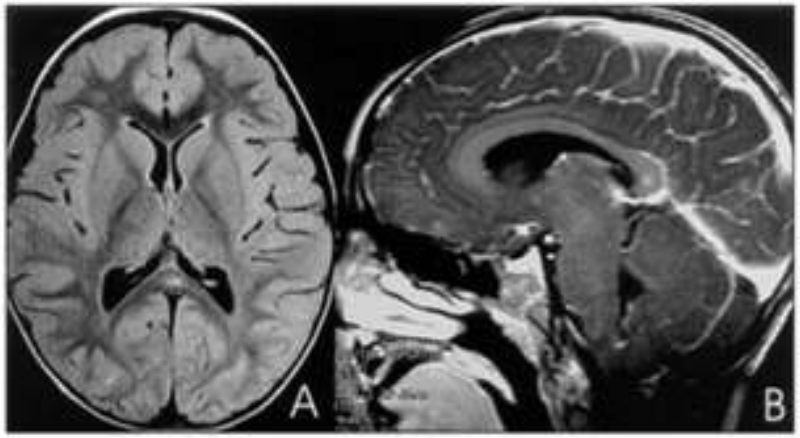



*Fig 1. Axial FLAIR (A) and sagital T1-weighted MRI after contrast administration (B) demonstrate a focal area of high signal in the splenium of corpus calosum, which shows enhancement after contrast administration.*

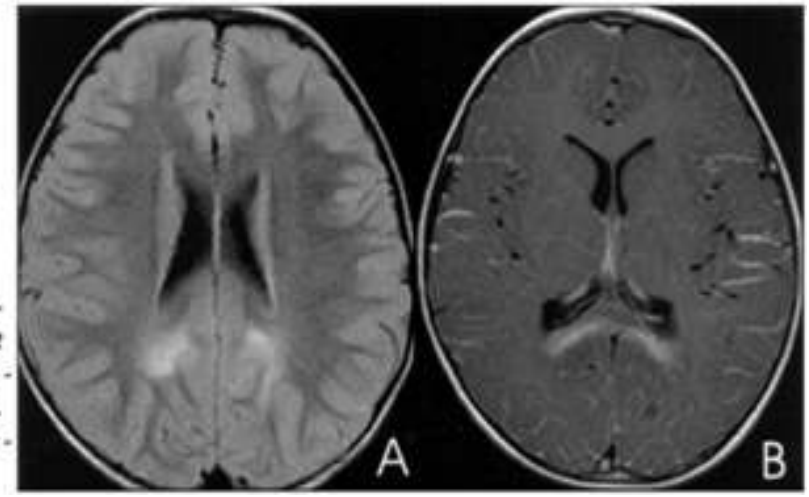
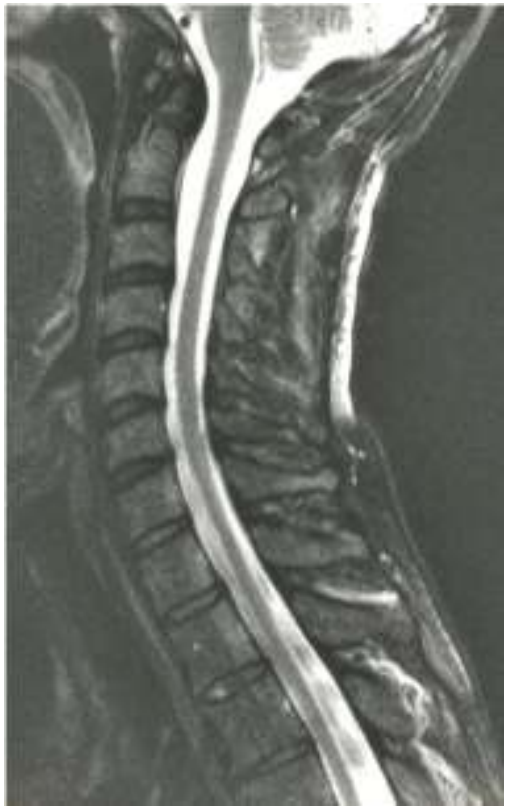


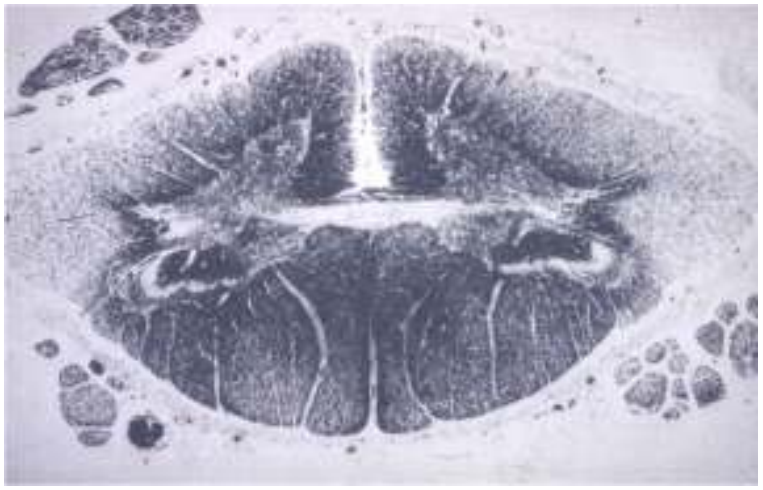

*Fig 2. Axial FLAIR (A) and axial T1-weighted MRI after contrast administration (B) show progres - sion of the corpus calosum lesion, as well as other lesions in the pari - etal white matter.*

# 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



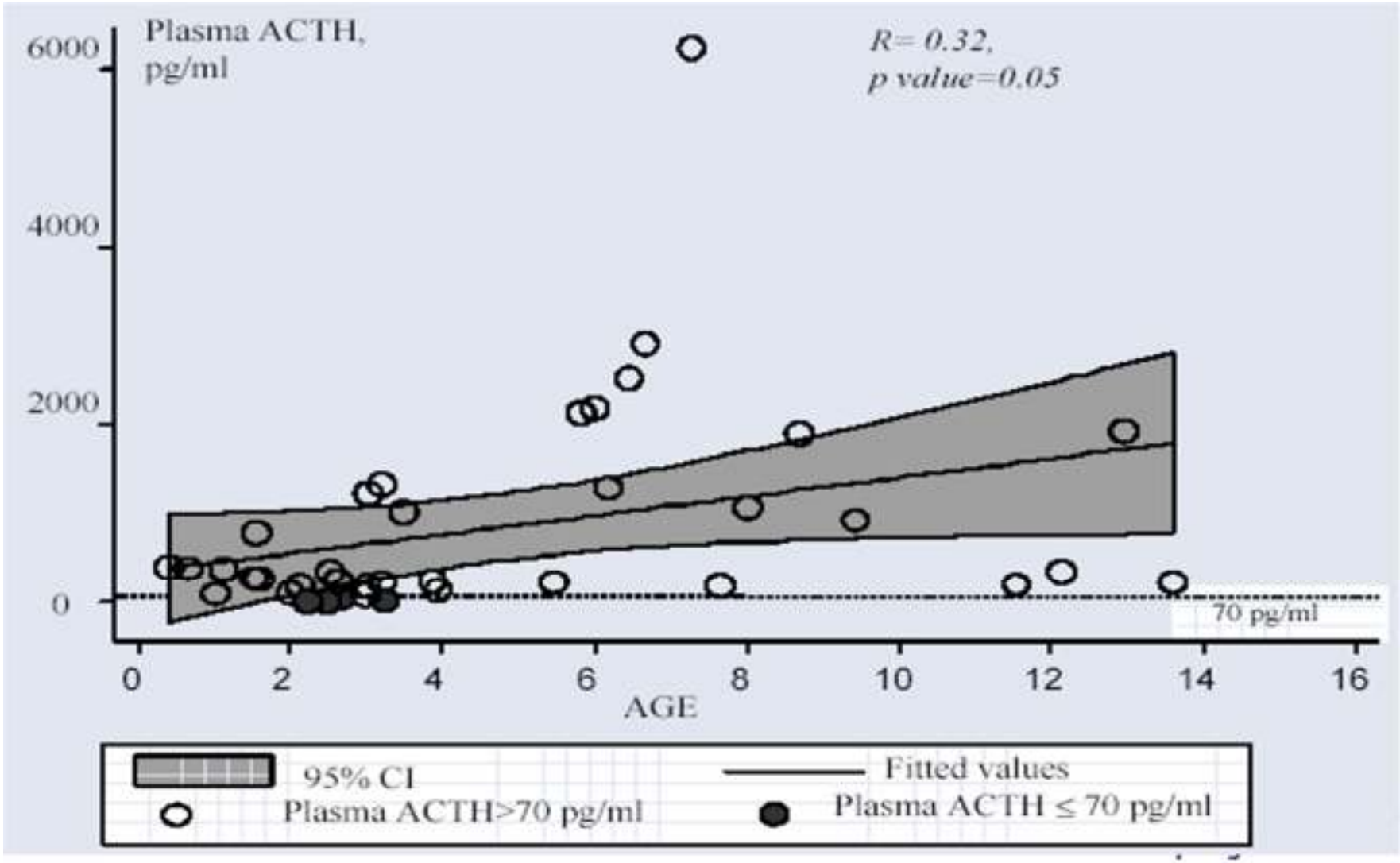


Axonal disease resulting in loss of myelin and atrophy of the spinal cord

# 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

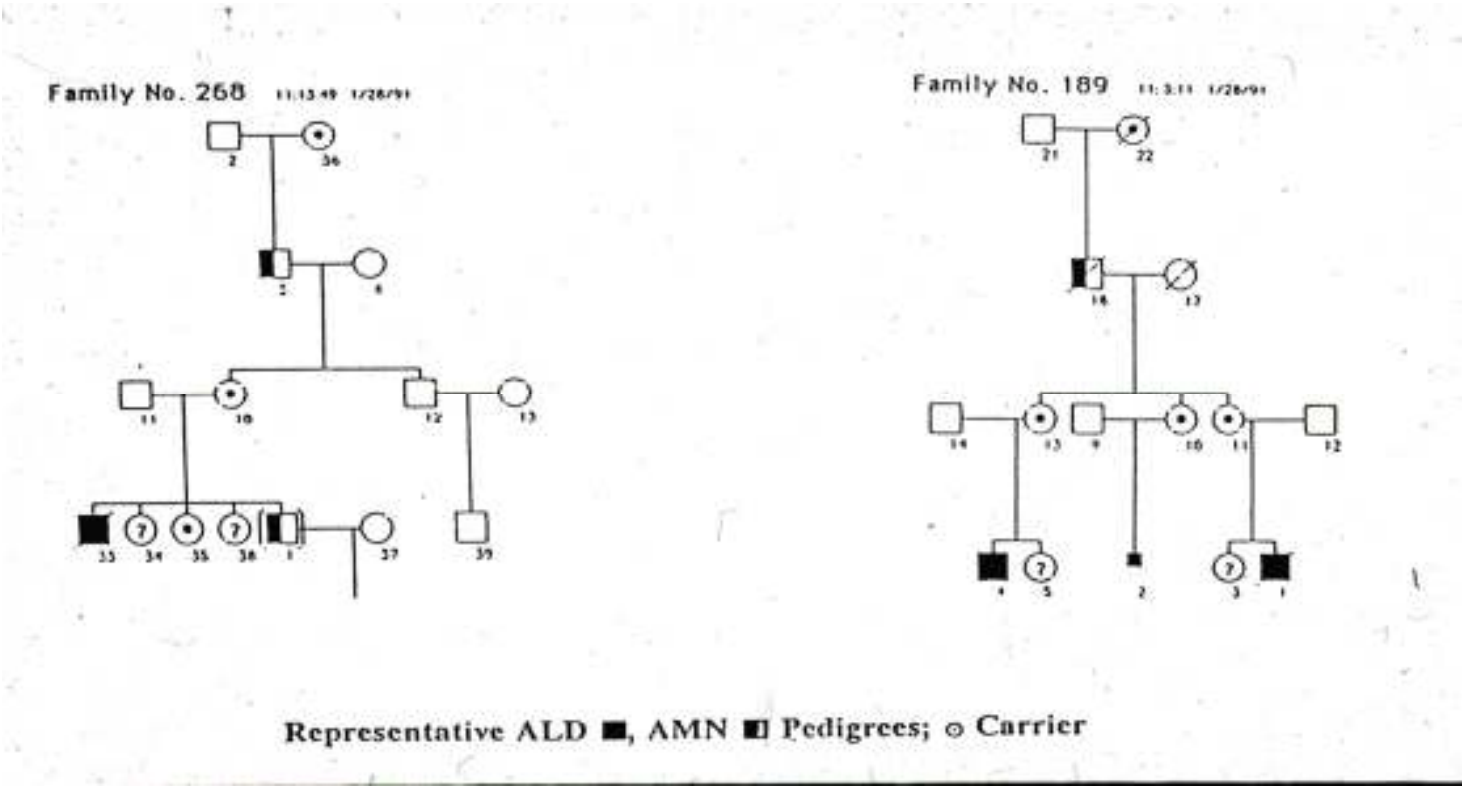


# Asymptomatic phenotype

- 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

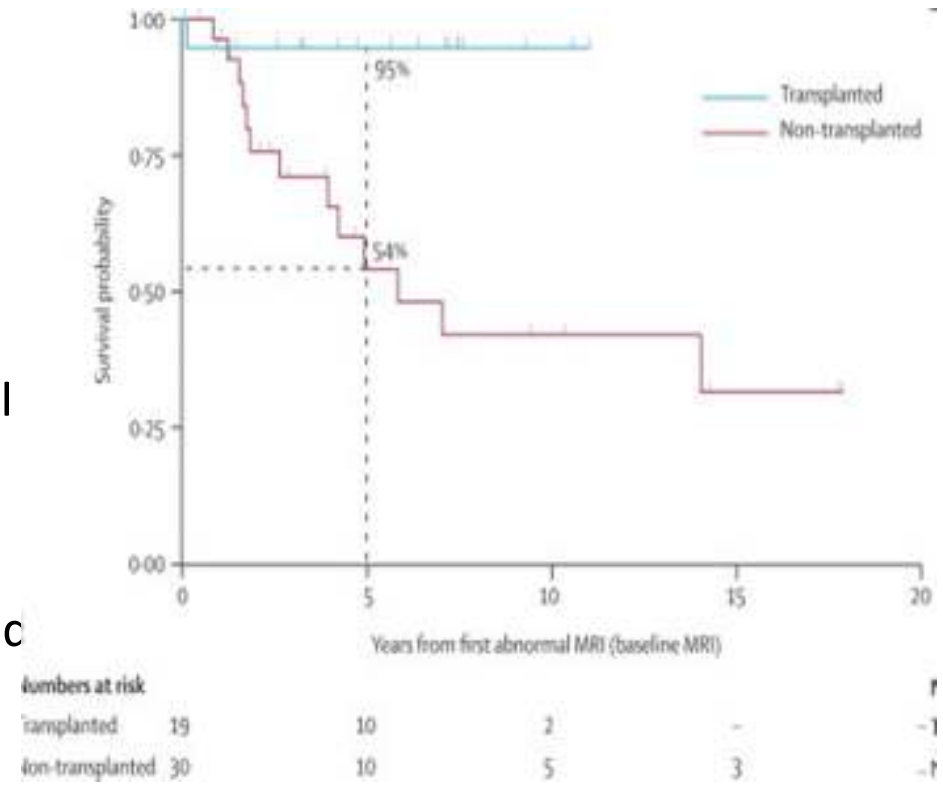
- NY began screening on 12/30/2013
  - 503,432 newborns screened (12/2015)
    - 41 referrals with 15 males + 18 females with mutation
    - ~ 1 in 22, 000
- CT, NJ, CA will begin when added to the Recommended Uniform Screening Panel (RUSP)
- The national advisory panel has voted to add ALD to the RUSP (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 screened individuals known to be at risk
- Development of gene therapy



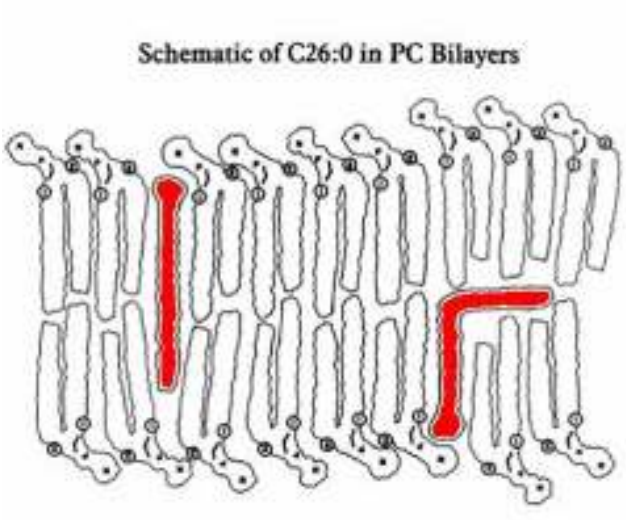

*Mahmood et al Lancet Neurology 2007*

# Role of VLCFA in pathogenesis

- Elevated, but are they involved in pathogenesis?
- Has implications as we discuss therapies to lower them

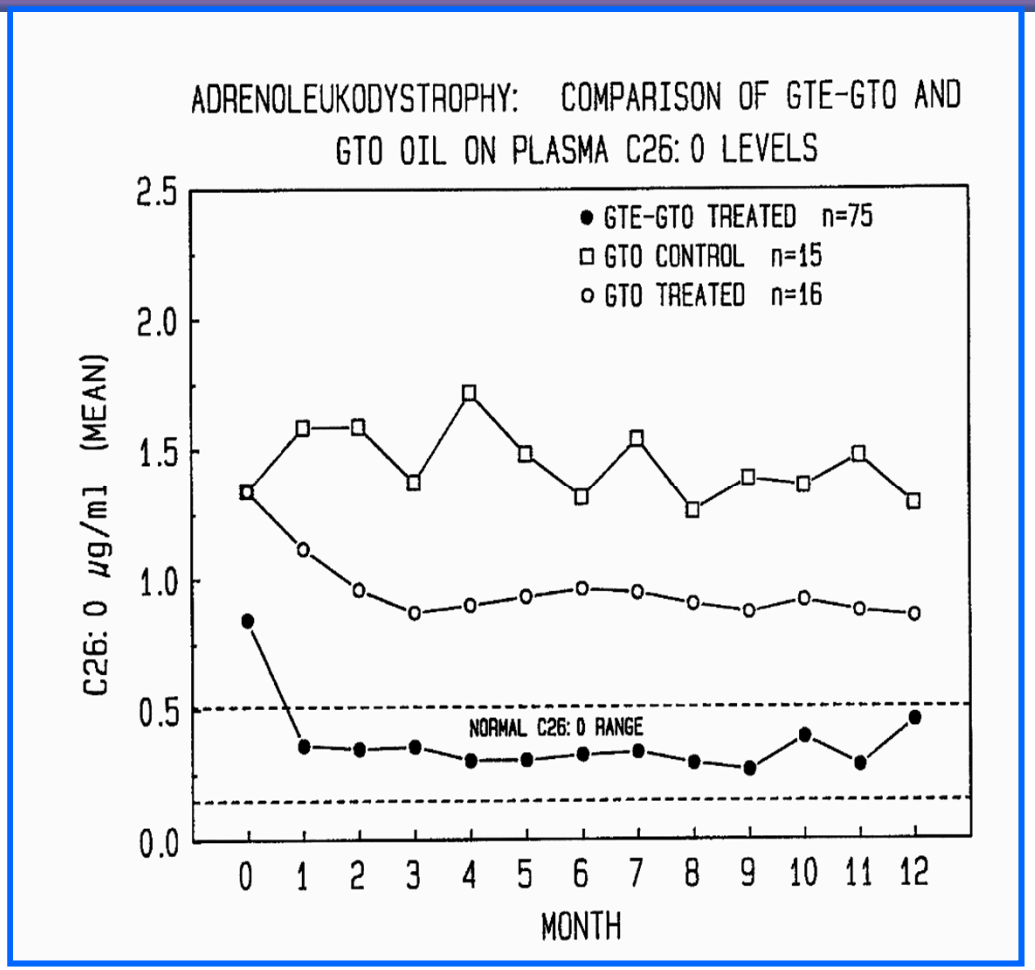
# Accumulation of Saturated Very Long Chain Fatty Acids (SVLCFA)

- 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?



# Lorenzo's Oil

- **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.

# Erucic acid entry into brain

- 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**

| Characteristic | No. (%) |
|---|---|
| Living | 81 (91) |
| Deceased | 8 (9) |
| Neurologically normal and normal MRI results | 66 (74) |
| MRI abnormalities and neurologically normal | 13 (15) |
| MRI and neurological abnormalities* | 8 (9) |

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

Moser, H. W. et al. Arch Neurol 2005;62:1073-1080.



ARCHIVES OF NEUROLOGY

# 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

- **<u>Substantial and prolonged lowering of C26:0 levels may be required to achieve significant reduction in risk of developing MRI abnormality</u>**

# 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

# Expanded Access Requirements Baseline

- 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 kcal* $\div \ 8 \ = X \ ml \ LO \ per \ day$
- Calculate walnut oil dose
  - Estimated caloric need per day x 0.05 = walnut oil kcals
  - *WO kcals ÷8 = Y ml WO per day*

# Example – Nutritional Assessment

- Total calories 1200 kcal
- Calories from fat 360 kcal
- LO calories 240 kcal
- Daily dose LO 30 ml
- WO calories 60 kcal
- WO dose 7.5 ml
- Fat calories from diet 120 kcal
- Saturated fat calories 36 kcal
- ~13 g fat and only 4 g saturated fats

# 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

# In the event of…

- 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

# Contact Information

To contact Dr. Raymond, please email him at:

**gvraymon@umn.edu**

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