

# Lorenzo's oil in X-linked Adrenoleukodystrophy

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# Adrenoleukodystrophy (ALD)

X-linked disorder - Xq28

incidence 1:17,000, all races affected

Peroxisomal ATPase Binding Cassette Protein (ABCD1)

Defect in peroxisomal beta oxidation

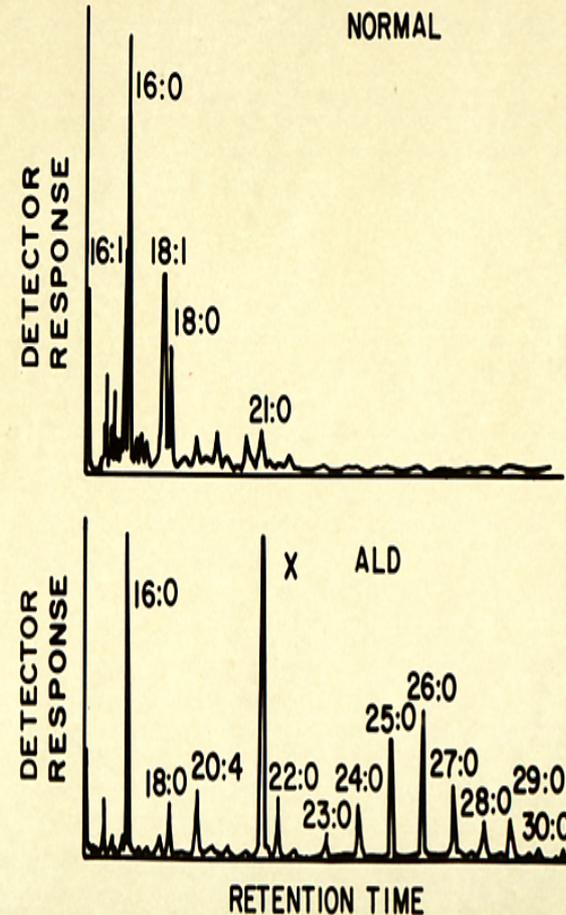
Accumulation of very long chain fatty acids (VLCFA)

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

## FATTY ACID METHYL ESTERS OF BRAIN CHOLESTEROL ESTERS (GAS CHROMATOGRAPHY)

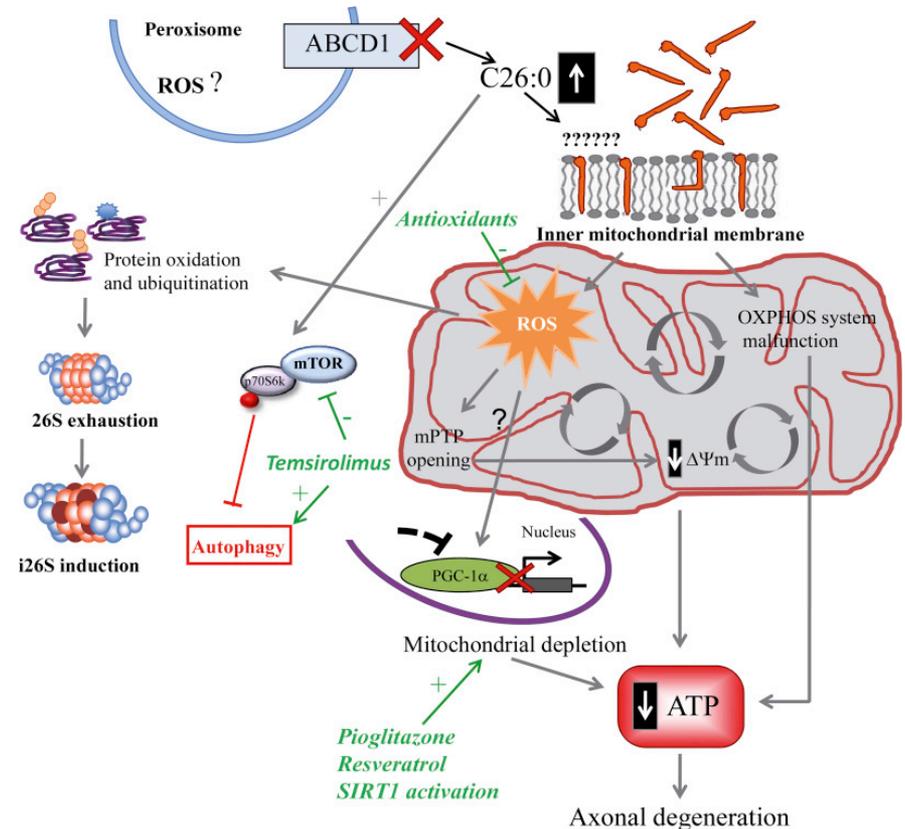


# Role of VLCFA in pathogenesis

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

# Role of VLCFA in pathogenesis

- Extremely insoluble in water and alters properties of membranes
  - Viscosity of red cell membranes is increased
  - Inclusion of C26:0 in model membrane perturbs structure and stability
  - Impair stability of axonal or myelin membranes
- Role of reactive oxygen species
  - Exogenously added C26:0 resulted in increase in ROS and protein damage
  - ALD fibroblasts responded more acutely to C26: than did control cells
  - Impaired anti-oxidant response consistent with GSH depletion
  - Increase in oxidative stress in animal models
  - Antioxidant therapy improves performance in mice
- Oxidative stress as trigger for inflammation
- Endovascular Dysfunction

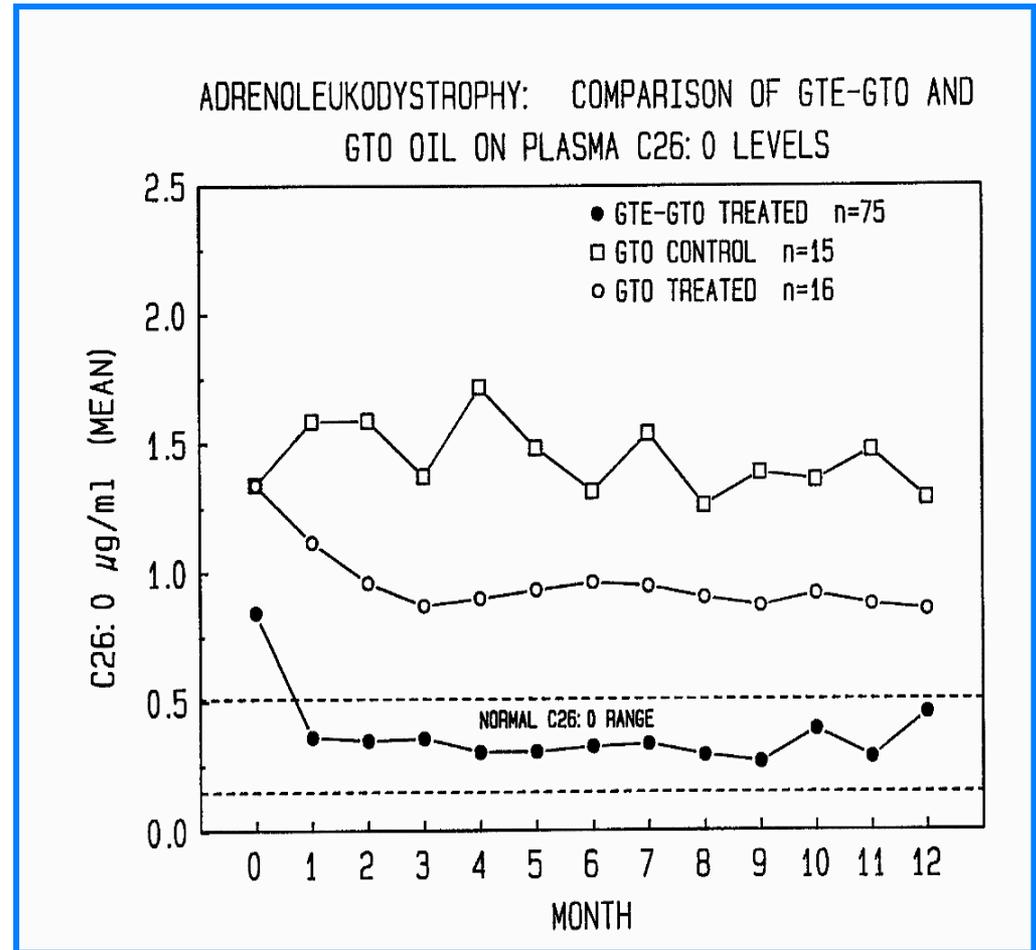


# Early dietary experience

- Adrenoleukodystrophy: Evidence that abnormal very long chain fatty acids of brain cholesterol esters are of exogenous origin (Kishimoto et al 1980)
- Adrenoleukodystrophy: Effects of Dietary Restriction of Very Long Chain Fatty Acids and of Administration of Carnitine and Clofibrate on Clinical Status and Plasma Fatty Acids (Brown et al 1982)
- Adrenoleukodystrophy: Oleic acid lowers fibroblast saturated C22-C26 (Rizzo et al 1986)
- A new dietary therapy for adrenoleukodystrophy: biochemical and preliminary clinical results in 36 patients. (Moser et al 1987)
- Dietary erucic acid therapy for X-linked adrenoleukodystrophy (Rizzo et al 1989)

# Diet and the use of Lorenzo's Oil

- **4:1 mixture of glyceryl trioleate (GTO) and trierucate (GTE, C22:1)**
- **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.
  - Van Geel et al (2001) Evolution of phenotypes in adult male patients with X-linked adrenoleukodystrophy
    - Ignored treatment in evaluating progression
- 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

# 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 more frequent phenotypes

# 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  $6.9 \pm 2.7$  years
- Follow-up  $6.7 \pm 2.17$  years
- All diagnosis confirmed at Kennedy Krieger
- All were offered LO and chose to participate in IRB approved protocol

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**Table 2. Overall Clinical Outcome: 89-Member Study Group**

<b>Characteristic</b>	<b>No. (%)</b>
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)

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Abbreviation: MRI, magnetic resonance image.

\*Two patients had missing MRI results and had developed neurological abnormalities.

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

# Preventative Study Results

- Time weighted estimate of average plasma C26:0 over study period (LAUC) was significantly associated with risk reduction
  - 0.1  $\mu\text{g/ml}$  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 status

- Not FDA approved
  - “investigational new drug”
  - IND 032336, sponsor G. Raymond, MD
- Placebo-controlled study in men and women with myelopathy
  - Study issues required early termination
- Expanded access was terminated
  - No funding
  - Increasing demand
  - Lack of effective lowering of VLCFA in majority of participants

# Importation for personal use

- Agents required for care of an individual which are not available in the United States
  - Previous examples Vigabatrin, felbamate, etc
- WEP Clinical [www.wepclinical.com](http://www.wepclinical.com)
- Purchases Nutricia's product in the UK
- Ships it to the individual's physician
- Prescribing physician is responsible for determining if appropriate and monitoring
- Estimated cost is 12,000 dollars per year
- Unlikely to be covered by insurance

# 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
- *Nutricia Learning Center*
  - *<https://www.nutricialearningcenter.com/en/metabolics/webinar/ald-and-lorenzos-oil-an-update/>*

# 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
    - $LO\ kcal \div 7.73 = X\ ml\ LO\ per\ day$
- Calculate walnut oil dose
  - Estimated caloric need per day x 0.05 = walnut oil kcals
  - $WO\ kcals \div 8 = Y\ ml\ WO\ per\ day$

# Example – Nutritional Assessment

- Total calories 1200 kcal
- Calories from fat 360 kcal
- LO calories 240 kcal
- Daily dose LO 31 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

# Suggested 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
- Change on MRI – proceed to evaluation for BMT

# Future

- Still a question as to whether VLCFA reduction is of benefit
- Other monounsaturated fatty acids that could serve?
- Other modalities to reduce VLCFA?  
ELOV1 inhibitors?