Adrenoleukodystrophies

Diane E. Mosqueda
Lorenzo was diagnosed with Adrenoleukodystrophy (ALD) in 1984, aged 6. Doctors told his parents that the neurological disease would swiftly deprive him of all his faculties and lead to his death within a maximum of two years.

Overview of Adrenoleukodystrophy (ALD)

- **Definition:**
  - is an rare inherited disorder that leads to progressive brain damage, failure of the adrenal glands and eventually death. ALD is one disease in a group of inherited disorders called leukodystrophies.
Pathophysiology:

- Adrenoleukodystrophy progressively damages the myelin,
- An essential protein, called a transporter protein, is missing.
- This protein is needed to carry an enzyme which is used to break down very long-chain fatty acids found in the normal diet.
- Lack of this protein can give rise to a build-up of very long-chain fatty acids, (VLCFA) in the body which can damage the brain and the adrenal glands.
Adrenoleukodystrophy (ALD)

- Prevalence of the disease:
  - It affects approximately 1 in 20,000 people from all races.
  - The minimum frequency of hemizygotes (affected males) identified in the US is 1:21,000 and that of hemizygotes plus heterozygotes (carrier females) 1:16,800
Overview of Adrenoleukodystrophy (ALD)

Three major categories of disease:
1. Childhood cerebral form: appears in mid-childhood (ages 4–8).
2. Adrenomyelopathy: occurs in men in their 20s or later in life
3. Impaired adrenal gland function (called Addison disease or Addison-like phenotype)

Overview of Adrenoleukodystrophy (ALD)

- Symptoms:
- Childhood cerebral type:
  - Adrenal problems, changes in muscle tone, especially muscle spasms and spasticity, crossed eyes (strabismus) decreased understanding of verbal communication, deterioration of handwriting, difficulty at school hearing loss, hyperactivity, progressive nervous system deterioration, coma, decreased fine motor control or paralysis.
Overview of Adrenoleukodystrophy (ALD)

- Symptoms:
- Adrenomyelopathy:
  - Adrenal problems
  - Difficulty controlling urination
  - Possible worsening muscle weakness or leg stiffness
  - Problems with thinking speed and visual memory
- Adrenal Gland failure (Addison type):
  - Coma
  - Decreased appetite
  - Increased skin pigmentation
  - Loss of weight, muscle mass (wasting)
  - Muscle weakness
  - Vomiting
Adrenoleukodystrophy (ALD)

- **Diagnosis:** is based on clinical findings
  - Blood levels show elevated very-long-chain fatty acids (Very-long-chain fatty acid test) (99% in males with X-ALD).
  - Blood levels of plasma ACTH concentration will be elevated and impaired rise of plasma cortisol concentration in response to administered ACTH.
  - Chromosome study shows ABCD1 gene mutations (molecular genetic testing of the ABCD1 gene is available).
  - MRI of the head shows damage to the white matter of the brain.
  - Prenatal diagnosis of X-linked adrenoleukodystrophy is also available; it is done from CVS or amniocentesis.
Adrenoleukodystrophy (ALD)

- Plasma very long chain fatty acid (VLCFA) values in X–ALD

<table>
<thead>
<tr>
<th>VLCFA</th>
<th>NORMAL</th>
<th>MALES WITH X–ALD</th>
<th>FEMALE CARRIERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>C26:0ug/ml2</td>
<td>0.23+0.09</td>
<td>1.30+0.45</td>
<td>0.68+0.29</td>
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<tr>
<td>C24:0/Css:0#</td>
<td>0.84+0.10</td>
<td>1.71+0.23</td>
<td>1.30+0.19</td>
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<tr>
<td>C26:0/C22:03</td>
<td>0.01+0.004</td>
<td>0.07+0.03</td>
<td>0.04+0.02</td>
</tr>
</tbody>
</table>

Treatments:
- Adrenal dysfunction is treated with steroids (cortisol)
- Eating a diet in very-long-chain fatty acids and taking special oils can lower the blood levels of very-long-chain fatty acids.
- Lorenzo’s oil, (no cure and may not help all patients) is a combination of glycercyl trierucate and glycercyl trioleate in a 1:4 (glycerol trierucate:glycerol trioleate): 1.7 g/kg of glycerol trioleate and 0.3 g/kg of eruucic acid
- Bone marrow transplant (experimental treatment)
- Lovastatin Medication: has shown to reduce plasma concentrations of very long chain fatty acids (esp C26:0, hexacosanoic acid)
Adrenoleukodystrophy (ALD)

- Prognosis:
  - The childhood form of the X-linked adrenoleukodystrophy is a progressive disease that lead to a long-term coma (vegetative state) about 2 years after neurological symptoms develop. The child can live in this condition for as long as 10 years until death occurs.
  - The other forms of this disease are milder

- Possible complications:
  - Adrenal crisis
  - Vegetative state
Genetic Inheritance of ALD

- X-linked genetic trait:
  - It affects mostly males
  - Females who are carriers can have milder forms of the disease.

- The biochemical phenotype of elevated plasma concentration of VLCFA has nearly 100% penetrance in males.

- Although the variation in clinical phenotypes is great, neurologic manifestations are present in nearly all males by adulthood.
Molecular Basis for ALD

- ABCD1 (ALDP) maps to Xq28 and is partially deleted and therefore mutated in the X-linked disorder adrenoleukodystrophy (ALD;300100).
- ABCD1 is a member of the ATP-binding cassette (ABC) transporter super family. The super family contains membrane proteins that translocate a wide variety of substrates across extra- and intracellular membranes, including metabolic products, lipids and sterols, and drugs.
Molecular Basis for ALD

Gene structure:
- ALD gene extends over 21 kb and contains 10 exons.

Gene Function:
- ABCD1 expresses a half transporter which is located in the peroxisomes.
- When mutated, ABCD1 results in the condition ALD with an elevation in very long chain fatty acids.
- ABCD1 is 1 of 4 related peroxisomal transporters that are found in the human genome.
# Molecular Basis for ALD

<table>
<thead>
<tr>
<th>GENESYMBOL</th>
<th>CHROMOSOMAL LOCUS</th>
<th>PROTEIN NAME</th>
<th>LOCUS SPECIFIC</th>
<th>HGMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCD1</td>
<td>Xq28</td>
<td>ATP- binding cassette sub-family D member 1</td>
<td>X-linked Adrenoleukodystrophy database ABCD1 @ LOVD</td>
<td>ABCD1</td>
</tr>
</tbody>
</table>

93% of individuals have inherited the ABCD1 mutation from one parent and 7% of individuals have de novo mutations.

Offspring:
- Affected males transmit the ABCD 1 mutation to all of their daughters and none of their sons.
- Carrier females have a 50% chance of transmitting the ABCD1 mutation in each pregnancy. Males who inherit the mutation will be affected and females who inherit the mutation are carriers and will usually not be seriously affected.
Affected males:

Carrier detection: Measurement of plasma concentrations of VLCFA is performed first, if abnormal, the female is a carrier. Because 20% of female carriers have normal plasma concentration of VLCFA, molecular genetic testing should be used to test those females with a normal concentration if the disease causing ABCD1 mutation has been identified in the family.
Gene Therapies for ALD

- A pilot study of two patients receiving gene therapy combined with blood–stem–cell therapy, and stating that the combination” may be a useful tool for treating” ALD (2009).
- Stem cells are harvested from the patient’s soft bone tissue and then a correcting gene is introduced using inactivated AIDs virus cells.
- These cells are used because they are the only ones which can penetrate into the heart of the stem cells.
Summary

- Adrenoleukodystrophy
- Lorenzo lyrics

Once upon a time I made a lion roar –
he was sleeping in the sunbeams on the old zoo floor.
I had gone to see the park where my papa used to play,
it's called called Villa Borghese and it's on the way
to East Africa.

Down on Grand Comoro Island, where I grew past four,
I could swim and fish and snorkel on the ocean floor,
and the wind laughed, and the wind laughed through the trees as if to say,
here's a child who'll want the world to go his way
in East Africa, in East Africa.

Suddenly for me the world turned upside down –
far from my friends the lions and the dolphins came this awful sound.

Dark shadows, sounds of thunder raging over me,
came this monster called 'A-dre-no-leu-ko-dys-tro-phy'
Where's my East Africa?

Well they said, they said, they said (the ones who know it all)
they said from now on for you there will be no more standing tall,
so I took my parents' hands, I lifted my head to say
I'll just have to be a hero, there's no other way!

Back to East Africa
Back to East Africa
Back to East Africa
Come with me I'm going back, going back to East Africa

http://www.youtube.com/watch?v=PHETbKt-Dzo&feature=player_embedded
References