Adrenoleukodystrophy

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Professor Doug Brutlag — Genomics and Medicine
• Haberfeld and Spieler, 1910
• Paul Schilder, 1913
• “ALD-X” coined in 1970
Behavioral:
- ADHD
- Apathy
- Irritability

Neurological
- Hearing, vision problems – Poor handwriting
- Ataxia
- Spasticity
- Paralysis
- Seizures

Endocrine
- Adrenal insufficiency
Incidence

- Estimated between 1 : 20,000 and 1 : 100,000
- No apparent predilection for any one race
  - Afro-Americans
  - Native Americans
  - Hispanics
  - Jews
  - Chinese
  - Japanese
  - Maoris
Genetic s

- Mutation in ABVD1 gene (20kb)
  - Xq28
  - 480 identified point mutations
Homologous ATP-Binding Cassettes

ALD-related protein
- 66% amino acid identity with ALDP

PMP70 protein
- 38% amino acid identity with ALDP

PMP70-related protein (P70R)
- 27% amino acid identity with ALDP
endoplasmic reticulum

long chain fatty acids

elongation

very long-chain fatty acids (VLCFA)

ALDP

peroxisome
degradation

storage of VLCFA

mitochondrion

cell membrane
      - Added C26: 0 or C24: 0 (common VLCFAs that accumulate in patients with ALD-X) to cultured cells

   CONCLUSION: Excess VLCFA altered membrane structure, and this is likely the cause
2. Powers, *et al* study in 1980
   a. Morphological and cytochemical study done using MRI’s and MRS’s
     - Found that adrenal dysfunction in individuals with ALD-X is due to accumulation of abnormal lipids that contain VLCFAs

**CONCLUSION:** *Excess VLCFA is the cause of the adrenal insufficiency noted in patients with ALD-X*

**Why is the accumulation of VLCFA harmful?**
Why is the accumulation of VLCFAs harmful?

Remaining questions:

No studies have, as of yet, been able to associate axonopathy with VLCFAs. However, researchers believe that axonopathy is due to the VLCFAs’ disruption of axonal membranes, as was the case in adrenocortical cells.

→ A recent study by J. K. Ho, et al shows that incorporation of VLCFA in components of the multilamellar myelin membrane might indeed destabilize ALD myelin.
### Types of ALD

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<tr>
<th>Child-Onset ALD</th>
<th>Adult-onset ALD</th>
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<td><img src="image1" alt="Child-Onset ALD Image" /></td>
<td><img src="image2" alt="Adult-onset ALD Images" /></td>
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Cerebral demyelination seen in several regions of the brain, including the splenium of the corpus callosum, genu of the corpus callosum, brainstem, and other areas.

Neurocognitive defects may also be associated with these demyelinating processes.
MRI scan showing the progression of demyelination in the parieto-occipital white matter over a period of three years in a child.
Peripheral Nerve Demyelination

- Loss of axons and myelin throughout the:
  - Anterior corticospinal tract
  - Gracile tract
  - Dorsal spinocerebellar tract
- Little inflammatory response
Treatments
Classical Treatments

- Adrenal insufficiency therapy:

  Treat with steroid hormones
Classical Treatments

- **Bone Marrow Transplant**
  - Moser, *et al* 1984
  - Study done on a patient in the rapidly advancing stage of childhood X-ALD
  - Promising effects: VLCFA levels diminished 2 months after transplant
Novel Treatment

Gene Therapy

Dr. Aubourg, 2009

Able to correct 15% of a patient's hematopoietic stem cells

Drawbacks?
The end!
Please see notes for references