UNDERSTANDING ADRENOLEUKODYSTROPHY

What is Adrenoleukodystrophy?

Adrenoleukodystrophy (AD-REENO-LOOKO- DISTRO-FEE) or **ALD** is an inherited metabolic disorder that affects how the body breaks down fatty acids, the building blocks of fats. The prevalence of ALD is 1 in 20 000 to 50 000 people worldwide.

Peroxisomes are structures inside of our cells that digest fatty acids through the process of beta oxidation. In ALD, the peroxisomes are unable to break down very long chain fatty acids (VLCFA) using beta oxidation. These VLCFAs build up in the blood and eventually accumulate in the brain, spinal cord, testes and the adrenal glands.

How does ALD affect the body?

Adrenal Glands

In patients with ALD, VLCFAs build up and reduce hormone production by the adrenal gland. The adrenal glands sit on top of each of the two kidneys. They are responsible for releasing several hormones needed by the body. These hormones include:

- **Cortisol** (helps us respond to stress)
- **Androgens** (growth, sex drive in women, hair growth)
- **Aldosterone** (kidney function)
- **Epinephrine and norepinephrine** (help us respond to stress, heart function)

When the body doesn't make enough of these hormones, it is referred to as **adrenal insufficiency**. Symptoms of this include weakness, increased colouring of the skin, lack of appetite, weight loss, depression and anxiety.

Eventually, the adrenal gland can become so plugged-up with VLCFAs that it stops making the hormones altogether. This is referred to as **adrenal crisis** and is an emergency situation.

Symptoms of an **adrenal crisis** include:

- Abdominal pain
- Confusion
- Dizziness
- Profound weakness and fatigue
- Fast heart rate and breathing rate
- Nausea and Vomiting
- Excessive sweating on face and hands
- Shaking chills
- Headache
- fever

Nervous system

Nerves are fibres that carry signals to and from the brain and spinal cord and parts of the body. Each nerve is covered in insulation, called the **myelin sheath**. Myelin is like the plastic coating around an electrical cord. Myelin is largely made up of fat. In ALD, the myelin sheath around nerves gets eaten away, eventually causing the nerve to "short-circuit". It is not clear whether the mechanism for breakdown of the myelin sheath is related to the build up of VLCFAs or just another symptom of the disease. The destruction of the myelin sheath leads to neurological problems, either in the brain or in the spinal cord, or sometimes, in both the brain and spinal cord.

How do people get adrenoleukodystrophy?

Adrenoleukodystrophy is an inborn error of metabolism. It is genetic. This means that the person has the disorder from the time they are conceived. At conception, the baby receives two sets of genetic material, one from the mother, and one from the father. This genetic material, called **DNA,** acts as a recipe for the baby's development.

DNA includes information about the baby's eye and hair colour, and even whether the baby will be right or left-handed. DNA comes in units called **genes**. Each pair of genes gives directions to a certain part of the body.

DNA also determines the sex of the baby. Females have two X chromosomes and males have one X and one Y chromosome.

XY

XX

In adrenoleukodystrophy, there is a problem with the gene that gives information on how the body breaks down fatty acids. This gene is carried on the **X chromosome** which is passed to the child from the mother. ALD is therefore an X-linked disorder.

The parents of people with ALD are usually unaffected. The rare exception to this is when a man with ALD has children with a woman who carries the gene that causes ALD (i.e. she is a "carrier").

If a woman who carries the ALD gene has a baby boy, there is:
- a 50% chance that he will have the disorder
- a 50% chance that he will be unaffected

If a woman who carries the ALD gene has a baby girl, there is:
- a 50% chance that she will be a carrier of the gene for ALD
- a 50% chance that she will be unaffected

If a man with ALD has:
- a baby boy, he will be unaffected (because he will get his X chromosome from his mother and his Y chromosome from his father)
- a baby girl, she will be a carrier (because she will get one X chromosome from her mother and the other from her affected father)

What are the symptoms of adrenoleukodystrophy?

ALD is caused by mutations, or changes in a gene called **ABCD1**. A phenotype is a set of symptoms associated with a gene. In both males and females* with the ABCD1 gene, phenotypes can range from:

- no symptoms
- adrenal insufficiency only
- severe brain disease beginning with behavioural changes; can start in childhood or adulthood
- spinal cord involvement causing numbness and tingling, weakness and problems with walking

Generally, once symptoms begin, they get worse over time.

*Females have a milder form of the disease because they have two X chromosomes. One will be linked to the ABCD1 gene and one will be normal.

It is important to note that newborn or neonatal ALD is genetically unrelated to the ALD discussed in this pamphlet. These babies don't make peroxisomes at all. They usually die of an early disease and are very severely neurologically affected.

How is adrenoleukodystrophy treated?

1. Steroids

Adrenal insufficiency is treated with supplemental steroids such as cortisone (glucocorticoid) and fludrocortisone (mineralocorticoid). The physician decides which steroids are needed based on blood tests. These medications are available by prescription only and require careful monitoring by a physician.

2. Physiotherapy, occupational therapy and psychological support

These services can help the person to better manage the effects of ALD on the body and to cope better with a chronic condition.

3. Energy conservation

People with ALD tend to tire easily. It is important for them to pace themselves and to alternate between rest and periods of activity to conserve energy. Sleep is very important. Symptoms may increase when the person is fatigued.

4. Illness and Emergency management

<u>For patients with ALD and adrenal insufficiency (i.e. on daily steroid replacement)</u>

Patients with adrenoleukodystrophy need to increase their steroid doses under certain circumstances to avoid adrenal insufficiency:

- Coughs, colds and other minor illnesses that do not involve a fever don't usually need extra steroid cover.
- **Double** normal daily dose for:
  - a temperature of more than 37.5 Celsius (99.5 Fahrenheit).
  - an injury such as cuts requiring stitches or a broken bone
- **Triple** normal daily dose for:
  - a temperature of more than 39 Celsius (102 Fahrenheit)
  - Vomiting and/or diarrhea
  - Severe injury or fracture

If hospitalized for any of the above, patients with ALD require:
-Solucortef 75 mg every 8 hours by intramuscular or subcutaneous injection or by IV
-or subcutaneous Depo-Medrol 20 mg every 8 hours

<u>Patients with ALD without adrenal insufficiency (i.e. not on daily steroid replacement)</u>

These patients need steroid replacement (i.e. Solucortef 75 mg every 8 hours by intramuscular or subcutaneous injection or by IV or subcutaneous Depo-Medrol 20 mg every 8 hours) in these circumstances:
-severe vomiting/diarrhea
-fractures or other severe injuries
-loss of consciousness
-general anesthetic
-major seizure

5. Restriction of fat intake and Lorenzo's Oil

In very limited number of patients, restriction of fat intake to no more than 30% of daily diet and Lorenzo's oil, a mixture of unsaturated fatty acids, might help to slow the progression of the disease by stabilizing the VLCFA levels in the body.

6. Stem cell transplant

Stem cell transplant may cure a limited number of ALD patients with **early** brain involvement by stopping the demyelination that causes neurological problems. However, stem cell transplant is a risky procedure and is therefore is just reserved for those with brain involvement, not for those with just spinal cord involvement. The brain involvement must be detected at an early stage to be halted by stem cell transplant. If the brain involvement is advanced, stem cell transplantation can actually worsen the progression. Therefore, regular monitoring with brain scans are important to determine if a person with ALD is a candidate for stem cell transplant.

7. Gene therapy

Gene therapy is a new approach to stem cell transplantation. The transplant is done using the person's own cells, instead of those from a donor. Cells are removed from the person with ALD and the correct genetic sequence is inserted into them. The cells are then re-introduced into the person. These new cells are capable of breaking down the fatty acids and the symptoms either stay the same or get better. This is a very promising treatment for the future but is still in the research stages at this time.

How is adrenoleukodystrophy diagnosed?

People often know that there is a family history of this disease. If one member of the family is diagnosed, this may lead to other members being tested to see if they have the disease or are carrying the gene that causes it.

Tests for diagnosis include:

- **Blood test** to look for high VLCFAs
- **blood test** to look for the gene that causes ALD

If the blood tests indicate high levels of VLCFAs or the presence of the gene that causes ALD, an MRI (brain scan) will be done to see if the brain is affected. The person will also have an ACTH stimulation test to see how well the adrenal glands are working.

How is adrenoleukodystrophy monitored?

It is important to closely monitor any changes to the brain, testes and to adrenal gland function that may result from the buildup of VLCFAs. The person with ALD should be followed by a metabolic physician to have yearly **MRI** (magnetic resonance imaging) and **MRS** (magnetic resonance spectrometry) scans of the head to look for damage to the white matter of the brain (a specific type of brain tissue), ACTH stimulation tests are done to check adrenal gland function if the person hasn't been diagnosed with adrenal insufficiency. Blood tests are done to check the hormone levels of males with ALD.

Regular visits to the metabolic clinic are needed to consult with the team. Referrals can be made to other specialists to closely monitor the effects of ALD on the body.

How can family and friends help?

Recognize and accept that the person with ALD may have physical limitations and may tire easily. Become familiar with how they are affected by the disorder. Be sure to know and be able to recognize the signs and symptoms of an adrenal crisis. Don't make assumptions about their level of physical or mental functioning. Learn as much about ALD as you can and help to explain it to others. This not only increases awareness of the disorder, it helps the person affected to have a break from explaining it over and over again.

Helpful Resources

The Adult Metabolic Diseases Clinic
Vancouver General Hospital
Gordon & Leslie Diamond Health Care Centre
2775 Laurel Street, 4th level
(604) 875-5965

National Institute for Neurological Disorders and Stroke
Office of communication and public liason
PO Box 5801
Bethesda, Maryland 20892
Web site:
http://www.ninds.nih.gov/patients/disorder/adrenoleukodystrophy/adrenoleuko.htm

http://www.aldlife.org/