

Bandolier *Extra*

Evidence-based health care

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LORENZO'S OIL FOR ADRENOLEUKODYSTROPHY AND ADRENO MYELONEUROPATHY

Clinical bottom line

Lorenzo's oil has no value in patients with established symptoms. It may be of value of asymptomatic patients, and may delay onset of symptoms, but the extent of any effect is unclear. The problem is that the fatty acids in Lorenzo's oil do not replace the very long chain fatty acids in the brain because they do not cross the blood-brain barrier.

Background

Adrenoleukodystrophy (ALD) is a rare (incidence about 1 in 45,000), genetic disorder characterized by the breakdown or loss of the myelin sheath surrounding nerve cells in the brain and progressive dysfunction of the adrenal gland. ALD is one of a group of genetic disorders called the leukodystrophies that cause damage to the myelin sheath, the fatty covering — which acts as an insulator — on nerve fibers in the brain.

There are several forms of ALD. Onset of the classic childhood form, which is the most severe and affects only boys, may occur between ages 4 and 10. Features of this form may include visual loss, learning disabilities, seizures, dysarthria (poorly articulated speech), dysphagia (difficulty swallowing), deafness, disturbances of gait and coordination, fatigue, intermittent vomiting, melanoderma (increased skin pigmentation), and progressive dementia. The most common symptoms are usually behavioral changes such as abnormal withdrawal or aggression, poor memory, and poor school performance.

In the milder adult-onset form (also called adrenomyeloneuropathy, or AMN), which typically begins between ages 21 and 35, symptoms may include leg stiffness, progressive spastic paraparesis (stiffness, weakness and/or paralysis) of the lower extremities, and ataxia. Although adult-onset ALD progresses more slowly than the classic childhood form, it can also result in deterioration of brain function.

Another form of ALD is occasionally seen in women who are carriers of the disorder. Symptoms are mild and may include spastic paraparesis of the lower limbs, ataxia, hypertonia (excessive muscle tone), mild peripheral neuropathy, and urinary problems. Neonatal ALD affects both male and

female newborns. Symptoms may include mental retardation, facial abnormalities, seizures, retinal degeneration, hypotonia (low muscle tone), hepatomegaly (enlarged liver), and adrenal dysfunction. This form is usually quickly progressive.

Diagnosis usually involves the assay of very long chain fatty acids, hexacosanoic acid (C26:0), tetracosanoic acid (C24:0) and C22:0. Though not the sole marker for these heterogenous diseases, high levels in plasma are indicative. A comprehensive report [1] of many thousands of patients and others whose plasma fatty acids were tested over 16 years is instructive. Values of C26:0 are 2-4 times higher in affected patients. A good description of the genetics is to be found here <http://www.x-ald.nl/facts.htm>,

Lorenzo's oil

This is a mixture of glyceryl trioleate (C18:1) and glyceryl trierucate (C22:1). It is used to reduce the concentration of long chain fatty acids in the body, and the hope is that it also reduces demyelination and clinical progression.

Review

In this review Bandolier sought studies that examined the use of Lorenzo's oil for ALD or AMN, using PubMed (June 2002) and reference lists of papers and reviews. No randomised trials were expected. No pooling of information was thought likely. A description of the studies was sought to examine whether the use of Lorenzo's oil had any effect.

Results

The results of the review, with brief descriptions of the studies found, are in Table 1. The essence of these studies is that they are all (but one) open evaluations. The message seems to be the following:

- ◆ Lorenzo's oil rapidly reduces very long chain (C26:0) fatty acids in plasma to normal or near normal levels.
- ◆ Very long chain fatty acids in brain appear unaffected in postmortem studies.

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Reference	Design	Included patients	Outcomes	Results
Rizzo et al, 1989	Double-blind crossover of addition of erucic acid to oleic acid diet, for 2-19 months	12 newly diagnosed patients with ALD	Plasma fatty acids, clinical response	Plasma C26:0 returned to normal in 4 weeks 6/8 patients with moderate/advanced disease deteriorated. 2 mildly affected patients were clinically stable
Uziel et al, 1991	Open study with dietary erucic acid in 20 patients with ALD for up to 1 year	6 very severely affected 9 milder neurological symptoms 5 presymptomatic	Plasma fatty acids and clinical outcomes	Plasma C26:0 returned to normal in 4 weeks 6/8 patients with moderate/advanced disease deteriorated. 2 mildly affected patients were clinically stable
Aubourg et al, 1993	Open study, with full examination before start then 6, 12 and every 12 months thereafter over 18 to 48 months. Patients had a low fat diet with glycerol trioleate oil (1.7 g/kg) and glycerol trierucate (0.3 g/kg) daily. Vegetable and fish oils were also added daily to the diet.	14 men with AMN 5 symptomatic heterozygous women 5 boys with preclinical AMN	Plasma fatty acids, neurological, electrophysiological and clinical evaluations, including MRI if needed.	Plasma C26:0 fatty acids returned to normal. No encouraging data, but presymptomatic subjects still free of symptoms after 1 year.
Asano et al, 1994	Open study with retrospective controls. Patients had a mixture of glyceryl trioleate and glycerol trierucate, supplementing a low fat diet in which Lorenzo's oil provided about 20% of calories.	10 children and 1 adult with adrenoleukodystrophy 2 presymptomatic boys Controls were 10 childhood patients not treated, who had been examined by same physicians at about the same intervals	Plasma fatty acids and clinical outcomes	Plasma fatty acid changes over 1-24 months, with normalisation in some patients. Mean age of onset of neurological symptoms 7.4 years in 7 diet patients and 7_6 years in 10 controls. Suggestion that further progress slower.
Moser, 1995	Report of open studies in 53 patients who were neurologically asymptomatic when diet was started, and survey of others (Lecture report). Treatment with Lorenzo's oil for 12 months or longer. Uncontrolled.	53 neurologically asymptomatic adrenoleukodystrophy patients. Others referred to	Variety of neurological and clinical tests.	Plasma C26:0 levels normalised in 65%. Severe disability or death in 11% compared with 30-45% in US and Dutch series. Suggested that therapy may be helpful in asymptomatic patients, but not those already neurologically symptomatic.

Reference	Design	Included patients	Outcomes	Results
Korenke et al, 1995	Open therapy with fat restricted diet and addition of Lorenzo's oil as 20% of calories over 24 months. Patients with Addison's disease and neurological and endocrine asymptomatic patients as controls.	6 ALD 3 AMN (all with neurological symptoms) 2 Addison 5 asymptomatic neurological or endocrine	MRI, clinical tests, plasma fatty acids	All showed normalisation of C26:0 in 1-3 months 0/7 neurologically asymptomatic patients developed neurological symptoms. 6/9 AML/ALD had disease progression, and 3 died within 1 year of therapy start Thrombocytopenia common (75%)
Di Biase et al. 1998	Survey of Italian data 1985-1997	117 cases 68 subjects underwent dietary treatment	Various	Almost all of those with signs of cerebral involvement worsened or died. Patients with the milder form adrenomyeloneuropathy remained stable. 4/15 presymptomatic subjects developed neurological signs of the disease.
van Geel et al, 1999	Open study of Lorenzo's oil for at least 1 year or treatment, discontinuation, or end of observation period (mean 2.5 years)	2 asymptomatic 2 Addison only phenotype 13 AMN 3 symptomatic heterozygous women carriers	Neurological and endocrine consult every 3 months, with electrophysiology and MRI every 12 months	Plasma C26:0 were normal in 85% of patients. Disability increased in 11 patients and improved marginally in 2. Disability increased mildly but significantly in 16 patients with neurological symptoms
Restuccia et al, 1999.	Open study. Dietary treatment with low fat diet supplemented with 40 mg mixture of Lorenzo's oil daily. Treatment for up to 3 years	8 men with adult-onset ALD.	Clinical findings and nerve conduction studies	Plasma C26:0 in the normal range in all patients. EDSS scores worsened in 6/8 patients, unchanged in 2/8.
Moser et al, 2000	Survey of 372 patients with ALD, 256 treated with Lorenzo's oil	256 patients	Clinical findings and other outcomes	Normal baseline MRI: MRI worsened in 11/61 with good control and 6/79 with poor control of C26:0 plasma levels Abnormal baseline MRI: MRI worsened in 44/68 with good control and 20/48 with poor control
Suzuki et al, 2001	Survey, all treated with Lorenzo's oil, selected by parents. Many early symptoms appeared before treatment started	15 patients with childhood and adolescent ALD	Clinical findings and other outcomes	No apparent effect of Lorenzo's oil on rate of symptoms appearance.

- ◆ In patients with neurological symptoms, use of Lorenzo's oil is not associated with any reduction of symptoms or delay in disease progression.
- ◆ There is limited evidence that use of Lorenzo's oil in asymptomatic disease carriers may (repeat may) reduce the onset of symptoms.

Comment

This is a story of high hopes that a cure for an awful disease was at hand in Lorenzo's oil. It even spun off into a film of the same name. A side-effect was to make randomised trials impossible, so that a decade and more on we're still guessing whether this treatment has any benefit for anyone with this condition. It is not possible to say that it does. It is possible to say that it does not, at least for patients with established neurological symptoms.

Of course, that will be a gross oversimplification for what is a heterogeneous disease (or diseases). Informed neurologists will have a fair idea of what to do for the best. Lorenzo's oil is no silver bullet.

References

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Organisations

In the USA:

United Leukodystrophy Foundation
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In Europe

X-linked Adrenoleukodystrophy Database -
<http://www.x-ald.nl/>

Patient UK pages -
<http://www.patient.co.uk/illness/a/ald.htm>