LORENZO’S OIL FOR ADRENOLEUKODYSTROPHY AND ADRENOMYELONEUROPATHY

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, hypotonia (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), heptomegaly (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), tetracosenoic 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.
<table>
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<th>Reference</th>
<th>Design</th>
<th>Included patients</th>
<th>Outcomes</th>
<th>Results</th>
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<tr>
<td>Rizzo et al, 1989</td>
<td>Double-blind crossover of addition of erucic acid to oleic acid diet, for 2-19 months</td>
<td>12 newly diagnosed patients with ALD</td>
<td>Plasma fatty acids, clinical response</td>
<td>Plasma C26:0 returned to normal in 4 weeks 6/8 patients with moderate/advanced disease deteriorated. 2 mildly affected patients were clinically stable</td>
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<tr>
<td>Uziel et al, 1991</td>
<td>Open study with dietary erucic acid in 20 patients with ALD for up to 1 year</td>
<td>6 very severely affected 9 milder neurological symptoms 5 presymptomatic</td>
<td>Plasma fatty acids and clinical outcomes</td>
<td>Plasma C26:0 returned to normal in 4 weeks 6/8 patients with moderate/advanced disease deteriorated. 2 mildly affected patients were clinically stable</td>
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<td>Aubourg et al, 1993</td>
<td>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.</td>
<td>14 men with AMN 5 symptomatic heterozygous women 5 boys with preclinical AMN</td>
<td>Plasma fatty acids, neurological, electrophysiological and clinical evaluations, including MRI if needed.</td>
<td>Plasma C26:0 fatty acids returned to normal. No encouraging data, but presymptomatic subjects still free of symptoms after 1 year.</td>
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<td>Asano et al, 1994</td>
<td>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.</td>
<td>10 children and 1 adult with adrenoleukodystrophy 2 presymptomatic boys</td>
<td>Plasma fatty acids and clinical outcomes</td>
<td>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.</td>
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<td>Moser, 1995</td>
<td>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.</td>
<td>53 neurologically asymptomatic adrenoleukodystrophy patients. Others referred to</td>
<td>Variety of neurological and clinical tests.</td>
<td>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.</td>
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<td>Korenke et al., 1995</td>
<td>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.</td>
<td>6 ALD, 3 AMN (all with neurological symptoms), 2 Addison, 5 asymptomatic neurological or endocrine</td>
<td>MRI, clinical tests, plasma fatty acids</td>
<td>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%).</td>
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<td>Di Biase et al., 1998</td>
<td>Survey of Italian data 1985-1997</td>
<td>117 cases, 68 subjects underwent dietary treatment</td>
<td>Various</td>
<td>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.</td>
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<td>van Geel et al., 1999</td>
<td>Open study of Lorenzo's oil for at least 1 year or treatment, discontinuation, or end of observation period (mean 2.5 years)</td>
<td>2 asymptomatic, 2 Addison only phenotype, 13 AMN, 3 symptomatic heterozygous women carriers</td>
<td>Neurological and endocrine consult every 3 months, with electrophysiology and MRI every 12 months</td>
<td>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.</td>
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<td>Restuccia et al., 1999</td>
<td>Open study. Dietary treatment with low fat diet supplemented with 40 mg mixture of Lorenzo’s oil daily. Treatment for up to 3 years</td>
<td>8 men with adult-onset ALD.</td>
<td>Clinical findings and nerve conduction studies</td>
<td>Plasma C26:0 in the normal range in all patients. EDSS scores worsened in 6/8 patients, unchanged in 2/8.</td>
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<tr>
<td>Moser et al., 2000</td>
<td>Survey of 372 patients with ALD, 256 treated with Lorenzo's oil</td>
<td>256 patients</td>
<td>Clinical findings and other outcomes</td>
<td>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.</td>
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<td>Suzuki et al., 2001</td>
<td>Survey, all treated with Lorenzo’s oil, selected by parents. Many early symptoms appeared before treatment started</td>
<td>15 patients with childhood and adolescent ALD</td>
<td>Clinical findings and other outcomes</td>
<td>No apparent effect of Lorenzo's oil on rate of symptoms appearance.</td>
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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


Organisations

In the USA:

United Leukodystrophy Foundation
2304 Highland Drive
Sycamore, IL 60178
ulf@tbcnet.com
http://www.ulf.org/
Tel: 815-895-3211 or 800-728-5483
Fax: 815-895-2432

In Europe

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

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