VLCFA levels in cells from ALD patients and the X-ALD knockout mouse can be significantly reduced by treatment with 4-phenylbutyrate.

Lorenzo’s Oil—six years later

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In late 1992 a major motion picture entitled Lorenzo’s Oil was released by Universal Studios. The film was remarkable in several ways; it dramatized the true story of a boy, Lorenzo Odone, stricken with a rare lipid storage disease, adrenoleukodystrophy (ALD), and of his parents’ refusal to accept the then-accepted medical doctrine that there was no cure.

Drawing upon several disparate strands of chemical and biochemical research, the Odones eventually contacted Croda Universal Ltd. in the United Kingdom with an idea for a dietary treatment for Lorenzo’s ALD. This was worked upon by a small group of lipid chemists including the late Don Suddaby, who also played a cameo role in the film (INFORM 4:403-408).

The result of this work was a dietary lipid containing highly purified glyceryl trioleate and glyceryl trierucate, which is now known as Lorenzo’s Oil.

The film ended with a message of hope for ALD sufferers, their parents, and also, possibly, for people with other similar diseases. During the past decade, and particularly in the past five years, great strides have been made in understanding the disease.

This article presents the background and most relevant recent developments in treating ALD.

The ALD defect

The ALD defect is a rare X-linked genetic disorder affecting male children and young adults. There are several phenotypes of the disease, the commonest being childhood cerebral ALD with a mean age of onset of 7 years. This phenotype is also the most severe with progressive neurological symptoms leading to early death, usually from opportunistic infection.

The disease is characterized by central nervous system demyelination, probably caused by the accumulation of very long chain saturated fatty acids (VLCFA) such as tetracosanoic acid (C24:0) and hexacosanoic acid (C26:0) in the brain and other tissues.

All the cerebral forms of ALD are associated with an aggressive inflammatory response mounted by both cytokines and the immune system. The breakdown of the blood–brain barrier in ALD closely resembles that of multiple sclerosis and was first observed in 1923 by Siemerling and Creutzfeld.

It is now known that ALD is caused by a single-gene defect. This gene is located on the Xq28 chromosome, close to the region of the gene responsible for red-green color blindness. Color blindness often has been observed in ALD boys. The gene encodes a protein, the exact function of which is not known but is thought to be “involved in” the transport of VLCFA or in the production of active intermediates in the β-oxidation pathway. Regardless of the exact mechanism by which the ALD gene mutation affects this pathway, it is known that there is an impaired ability to form the co-enzyme A ester of VLCFA. This, in turn, probably results from the low activity of the enzyme lignoceryl-CoA ligase.

Dietary management of ALD

One strategy to treat metabolic diseases that are caused by the accumulation of an exogenous toxin or toxic metabolite is to restrict the dietary intake of the offending metabolite. This has been successful in several diseases such as phenylketonuria (PKU) and Refsum’s disease. Refsum’s disease is another lipid-storage disease that results from the inability to metabolize phytanic acid. Accumulation of phytanic acid causes mild to severe neurological symptoms such as optic neuritis. If the diet is restricted in phytanic acid, then a marked improvement in the symptoms and outcome results.

Unfortunately, restriction of the diet in the case of ALD is not effective since the VLCFA which cause demyelination come from both endogenous synthesis and diet. The problem is how to interfere with the biosynthetic pathway to prevent formation of saturated VLCFA.

The groundbreaking studies from Dr. Bill Rizzo’s laboratory in Richmond, Virginia, are the basis of all current dietary therapies for ALD. Rizzo observed that the addition of monoenoic fatty acids, particularly oleic acid, to cultured ALD fibroblasts resulted in a reduction of C26:0 in these cells. Despite the success of the laboratory experiments, in vivo studies were disappointing. Serum levels of C26:0 fell markedly in four months on a diet rich in C18:1 triglyceride; however, oleic acid did not reduce serum VLCFA levels to normal. What these studies did show—for the first time—was
that competitive inhibition of saturated fatty acid elongase was a distinct possibility. The oleic acid was competing for the elongase, and the VLCFA produced were unsaturated and not cytotoxic.

The question being asked at this time (1986) was “if C18:1 could effectively reduce the production of C24:0 and C26:0 from lower molecular weight homologs, could a cocktail of monoenoic fatty acids, C18:1/C20:1/C22:1, intervene more effectively than C18:1 alone?”

Production of the required triglyceride containing no VLCFA but only C18:1/C20:1/C22:1 was achieved at my laboratory at Croda Universal in Hull, England, during 1986. It was this lipid that was administered by Augusto Odone to his sister-in-law (Dierdre Murphy), who was ALD heterozygous with elevated VLCFA but without neurological involvement. Her high levels of serum C26:0 fell dramatically, with the predicted 30%. These data along with other data from European and Japanese sources would indicate that Lorenzo’s Oil is of benefit, particularly in asymptomatic boys.

A much larger study is currently being carried out in the United States and at several European centers involving some 260 patients. This study is due to finish in about one year. In addition, a number of smaller studies are being attempted using combination therapy. These include combining Lorenzo’s Oil with anti-inflammatory drugs such as pentoxyfilline, thalidomide or γ-globulin. These combination therapy trials were expected to be completed at the end of 1998 with results to be published later.

One combination therapy trial that has finished was the unsuccessful treatment of eight symptomatic patients with Lorenzo’s Oil and β-interferon for one year. All of the patients showed rapidly progressive neurological symptoms, and the therapy was halted in four patients after six months.

Several other therapies are in development such as bone marrow transplantation (BMT) and gene therapy. BMT has been successful in a small number of cases where the neurological deficit is mild. It also appears that normalisation of VLCFA with Lorenzo’s Oil prior to transplantation is beneficial.

In November 1998 an exciting development in pharmacological gene therapy for ALD was reported from the Johns Hopkins School of Medicine. Researchers have published a paper showing that VLCFA levels in cells from ALD patients and the X-ALD knockout mouse can be significantly reduced by treatment with 4-phenylbutyrate. This results from increased β-oxidation, increased expression of the peroxisomal protein ALDRP, and induction of peroxisomal proliferation. The in vitro experiment has been confirmed in vivo in the knockout mouse. After six weeks of dietary 4-phenylbutyrate treatment, C24:0/C26:0 levels in brain and adrenal glands were returned almost to normal.

It is suggested that 4-phenylbutyrate therapy should be examined clinically in ALD patients.

Conclusion
Dietary therapy using a mixture of glyceryl trioleate and glyceryl trierucate appears beneficial in treating asymptomatic ALD patients. The results with symptomatic ALD patients and the related adult phenotype adrenomyeloneuropathy (AMN) have been disappointing. Combination therapies using the lipid with immunosuppressive drugs are currently being investigated.

Another approach at the early stage of development is to increase the transfer of long-chain monounsaturated fatty acids across the blood–brain barrier. The potential use of gene therapy or glial transplantation techniques represents a major hope for the future. Lorenzo Odone is now 20 years old and is cared for at home by his parents, Michaela and Augusto Odone.

References and recommended reading


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