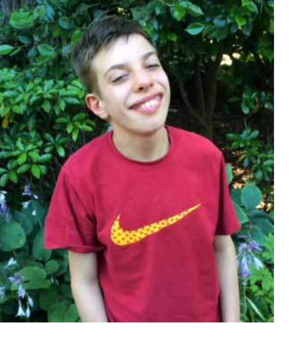
Smith-Lemli-Opitz FOUNDATION

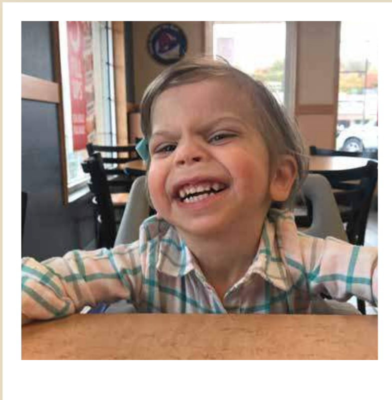
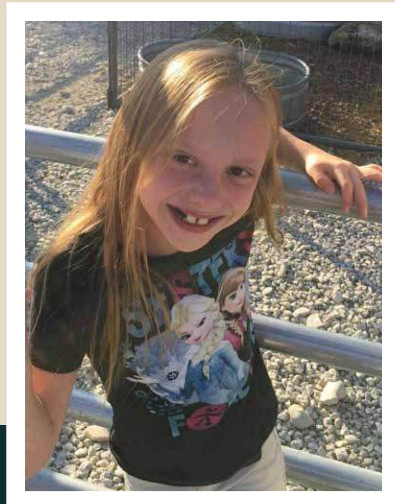
SLOS INFORMATIONAL GUIDE

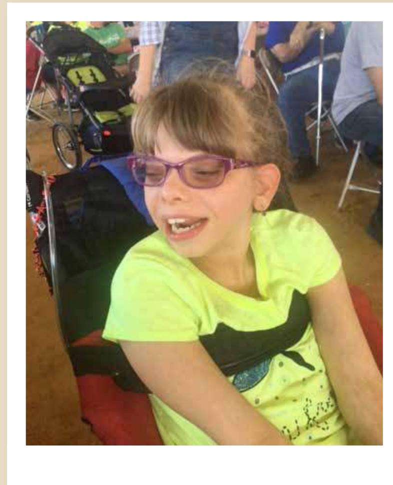
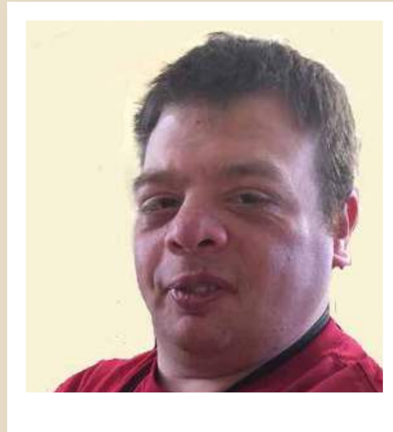
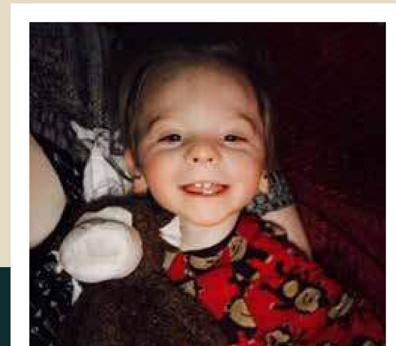
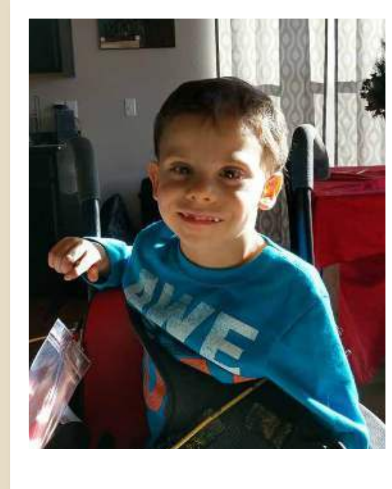






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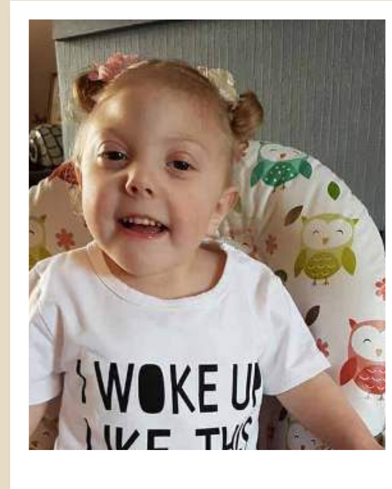
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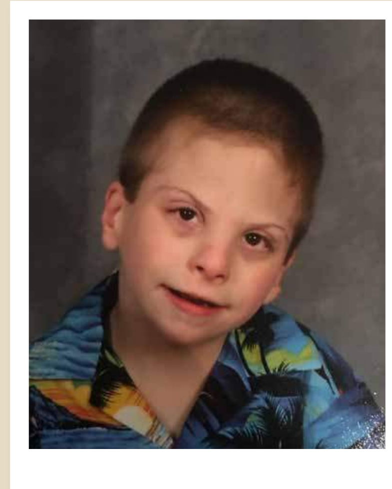
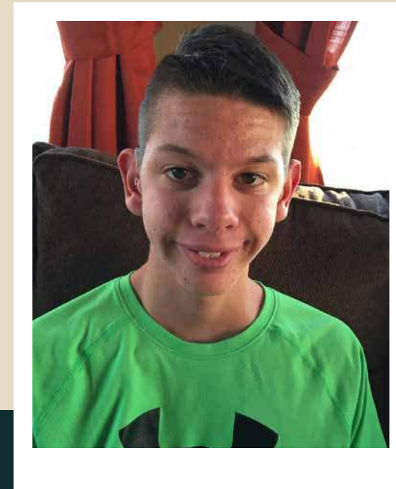
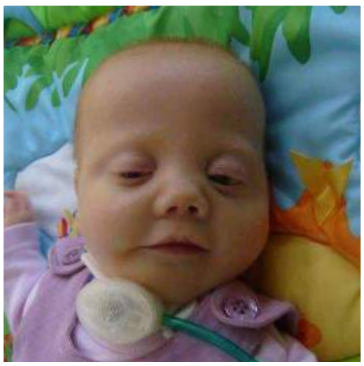





Smith-Lemli-Opitz Syndrome

Smith-Lemli-Opitz syndrome is a genetic disorder that affects the development of children both before and after birth. The syndrome was first described in 1964 in three boys with poor growth, developmental delays, and a common pattern of congenital malformations including cleft palate, genital malformations, and polydactyly (extra fingers and toes). Initially referred to as the “RSH syndrome” after the initials of the first three patients, the syndrome is now better known for the names of the three geneticists who first described it: Smith-Lemli-Opitz syndrome (SLOS). Although SLOS had been known as a genetic disorder, the cause was not known until 1993, when scientists and clinicians discovered that children with SLOS are unable to produce sufficient amounts of cholesterol, an essential chemical for proper growth and development. It is unclear how much cholesterol may be passed from mother to fetus during pregnancy, however unlike other nutrients or molecules essential for fetal development, the mother cannot supply sufficient cholesterol to the developing baby. The discovery of abnormal cholesterol metabolism in SLOS has made possible the development of a laboratory test for diagnosis, and served as a rationale for potential treatment.

Biochemistry

Children with SLOS typically, but not always, have cholesterol levels below normal ("normal" is typically greater than 100 mg/dl, though this varies with age and may vary from one laboratory to another), and abnormally high levels of a precursor of cholesterol, 7-dehydrocholesterol (7-DHC). The deficiency of cholesterol, an essential building block of all cell membranes and the white matter of the brain, is caused by abnormally low levels of the enzyme 7-dehydrocholesterol reductase (DHCR7), which converts 7-DHC into cholesterol. Children with SLOS who have the lowest cholesterol levels tend to have the most severe forms of the disorder, and those with major internal issues often die at birth or in their early years. With proper diagnosis and treatment, however, many with SLOS live well into adulthood. Although about 10% of children with SLOS have near normal cholesterol levels, essentially all have increased levels of 7-DHC. The few individuals who carry a clinical diagnosis of SLOS, but have normal cholesterol and 7-DHC levels, probably have a genetic disorder that resembles SLOS.

Physical Characteristics and Diagnosis

In addition to growth retardation and developmental delay, many different malformations have been described in SLOS.

Most Common Defects:

- Microcephaly (small head)
- Syndactyly of the second and third toes (fused toes)
- Bitemporal narrowing (reduced distance between temples)
- Ptosis (drooping eyelids)
- Epicanthal folds (skin folds of the upper eyelid)
- Short and upturned nose
- High-arched, narrow, hard palate
- Cleft palate
- Cataracts
- Brain malformations including agenesis of the corpus callosum and in very severe cases major malformation of the front part of the brain (holoprosencephaly)
- Cerebellar hypoplasia
- Renal, pulmonary, liver and eye abnormalities
- Low-set and posteriorly rotated ears
- Micrognathia (small chin)
- Polydactyly of hands or feet
- Short, proximally placed thumb
- Abnormal palmar creases (usually single)
- Hypospadias (genital malformation in boys)
- Undescended testicles in boys
- Ambiguous or female-like male genitalia
- Congenital heart defects
- Pyloric stenosis
- Hirschsprung disease

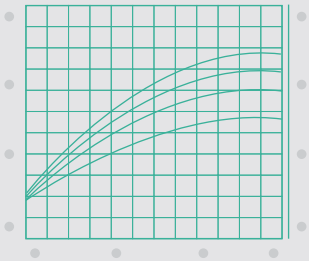
Some children will have only one or two minor malformations, such as webbing of the toes and cleft soft palate, whereas others will have almost all of the defects listed above. Because of the possibility of internal malformations, patients with SLOS should be evaluated carefully, especially for heart and kidney defects. Often, children with SLOS resemble one another more than they do others in their families.

In most cases, but not all, a standard blood cholesterol test will show low cholesterol levels. However, to confirm the diagnosis of SLOS, another blood test is needed. This test is called the 7-DHC test or sterol profile. It is a test that uses sophisticated instruments to measure cholesterol and the precursor 7-DHC along with usually a number of other sterols. The elevated level of 7-DHC confirms the diagnosis of SLOS. There are a few conditions associated with 7-DHC elevation, although those conditions generally have different clinical features. Some drugs may also increase 7-DHC. In addition, after biochemical testing, molecular testing (a.k.a. DNA mutation testing or sequencing) is indicated to confirm diagnosis and allow identification of carriers within the family.

SLOS GROWTH CHARTS

Growth and development of children with SLOS can be delayed and affected by the spectrum of disease severity, with decreased weight gain and final height. Medical specialists have developed SLOS-specific growth charts to improve the care of individuals with SLOS. With exception to the extremes of growth, there is limited evidence to suggest that failure to attain optimal growth, in mild to moderate degrees, leads to damaging consequences for the individual. Just like with the normal growth curves, a crossing of percentiles can be a sign of an intercurrent illness.

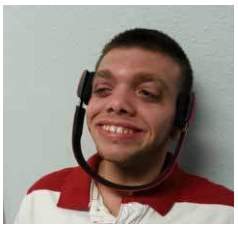
Many of our families download and bring the SLOS growth charts to their pediatricians to help them understand the decreased growth of our children.



► **SmithLemliOpitz.org/SLOSGrowthCharts**

Genetics

SLOS of all degrees of severity is inherited as an autosomal recessive disorder, like cystic fibrosis and sickle cell disease. In autosomal recessive diseases, each parent is a carrier of one abnormal gene and shows no physical or metabolic evidence of the disorder because the paired normal gene is protective. However, if a child inherits the abnormal SLOS gene from each parent, then SLOS will occur. There is a 1 in 4 chance that a child will inherit only the abnormal SLOS gene from each parent. Following the discovery of the gene mutation on the long arm of chromosome 11, molecular testing or DNA testing is now available to aid in carrier determination and future pregnancy testing. SLOS is one of the most common autosomal recessive disorders. Estimates of the incidence vary, but most studies in Europe, the United States, and Canada have found an incidence of 1 in 20,000 births. In some regions, the disorder may occur as often as 1 in 10,000 births.




Natural History

Certain behaviors and attributes are common in patients with SLOS. Almost all have feeding problems, constipation, and poor growth to some degree. Common feeding problems include trouble sucking and swallowing because of weakness, cleft palate, reflux, persistent vomiting, and pyloric stenosis. Other causes of poor growth may be internal malformations such as heart and kidney defects, Hirschsprung disease, or, more rarely, chronic liver disease. However, even children who are vigorous and feed well do not grow normally and tend to be small as children and adults.

In addition to feeding problems, many children with SLOS have severe sleep disorders, some requiring medication. Lack of sleep can increase irritability, lack of focus, and behavioral issues; therefore, it may be necessary for families to consult with a sleep specialist to help improve the child's quality of sleep.

Behavior issues are also very common in SLOS. For those with severely delayed speech, frustration comes easily, and screaming or tantrums are often an outlet. Many patients show aggressive or self-injurious behaviors, including biting, hitting, scratching, or more seriously, head banging. In up to 75% of cases, a secondary diagnosis of autism is made. Given the frequency of behavior issues and overall hypersensitivity, it is highly recommended that families consult with a behavioral specialist on an ongoing basis.

Almost all children with SLOS are born with minor anatomical variations in brain structure and have various degrees of slow development and intellectual disability. Although not all children with SLOS learn to walk and talk, many acquire good communication (often with the help of electronic devices) and can learn daily living skills. Independent living as adults, however, is uncommon.

Recurrent infections, including ear infections and pneumonia, are also common.

Management and Treatment

The major medical problems of children with SLOS are in the areas of feeding, growth, and development. In addition, there may be other serious medical problems caused by one or more malformations, such as heart or kidney defects. The care of these problems often require the combined efforts of geneticists and specialists.

Even for more mildly affected children, feeding problems are common and require careful management. Special attention must be paid to the frequent problem of limited formula tolerance because of the prevalence of functionally small stomachs and poor gastrointestinal motility in children with SLOS. Some patients with SLOS have feeding problems severe enough to require placement of feeding tubes. Consultation with a registered dietician may be necessary, and use of special formulas is often helpful. That children with SLOS have a limited potential for growth is also important to recognize. A special SLOS growth chart has been developed and can be downloaded at SmithLemliOpitz.org. Pyloric stenosis, caused by a thickening and spasm of the stomach outlet, is also common in the first weeks or months and often requires surgical correction. Severe liver disease is a rare problem in some of the most severely affected children and may require treatment with special medications.

There is no cure for SLOS and treatment is mostly symptomatic. Three potential treatment options have been or are currently being investigated: cholesterol supplementation, antioxidant supplementation, and cholic acid supplementation.

Cholesterol Supplementation

With the discovery that SLOS is caused by a metabolic error in cholesterol production, dietary cholesterol supplementation has been proposed as an intervention since the 1990's. With the more recent discovery that the accumulation of the cholesterol precursors 7-DHC and 8-DHC can also lead to medical concerns, cholesterol treatment, given both to raise cholesterol levels as well as lower production of precursors, may prove to be important. This may be particularly relevant in more severely affected patients who have very low cholesterol levels. However, dietary cholesterol does not cross the blood-brain-barrier and there is no good evidence that dietary cholesterol will improve behavior or developmental outcomes.

Most specialists, however, believe that cholesterol supplementation may result in better growth and overall health of the patient. Cholesterol supplementation is either achieved by consuming foods that are naturally high in cholesterol (such as egg yolks), or in the form of a synthetic cholesterol compounded by a pharmacy. Any cholesterol supplementation should be recommended and monitored by your child's physician.

More clinical studies are needed to determine the benefits and possible risks of cholesterol supplementation as an intervention.

Antioxidant Supplementation

A trial using antioxidant supplementation was started in 2008, following studies in an SLOS animal model which showed that abnormalities in eye function could be improved with antioxidant treatment. It was then discovered that the precursors 7-DHC and 8-DHC are "oxidized" and turned into substances called oxysterols which are toxic to the brain and the eye. A research protocol was developed to give antioxidants in the form of vitamins, in hopes of reducing the formation of oxysterols and thus protecting the brain and eye from oxysterol toxic side effects. So far there have been no negative side effects of the vitamins and some improvements in special vision tests have been noted, but further studies are needed to determine the overall efficacy of this treatment as a therapy.

Cholic Acid Supplementation

Bile acids are made from cholesterol, so a patient with very low cholesterol levels cannot make a sufficient amount of bile acids. Therefore, patients with severe SLOS have a bile acid deficiency. Bile acids are essential for the absorption of nutrients in the intestines, particularly fats and fat-soluble vitamins. Without sufficient bile acids present in the gut, patients cannot properly absorb cholesterol and other nutrients. Bile acids (including one called Cholic acid) were used in the early 1990s to treat patients with SLOS. The bile acids were tolerated well and seemed to help cholesterol levels improve on treatment. But in the late 1990s, Cholic acid stopped being manufactured and was not available until recently. A new pharmaceutical company is manufacturing Cholic acid again, called Cholbam, making it available for patients with SLOS. A pilot study was conducted at Children's Hospital Colorado, and Cholic acid was well tolerated and had minimal side effects. There was a modest improvement in cholesterol and precursor levels in the short study time.

Smith-Lemli-Opitz FOUNDATION

OUR MISSION

The SLO Foundation works worldwide to improve the quality of life for people with Smith-Lemli-Opitz syndrome through education, family support, awareness, and financial support for research into the disorder.

OUR STORY

In 1990, 37 families living with SLOS founded the Smith-Lemli-Opitz Foundation. They wanted to help the estimated tens of thousands of individuals around the world living with undiagnosed SLOS and families facing significant challenges including surgeries, therapies, a revolving door of doctor appointments, and countless unanswered questions. Since then, the Foundation has grown into a network of professionals, supporters, and more than 1,000 families from around the world who share experiences and information about Smith-Lemli-Opitz syndrome.

Supporting families is important to the Foundation's mission. The Foundation fulfills this mission by providing informal networking and social media interfaces to connect families with a caring community, a free lifetime membership to the Foundation and its network, and national SLOS scientific and family medical conferences held every other year. During these conferences, physicians, scientists, parents, and caregivers from around the world collaborate and learn from each other.

Through **SmithLemliOpitz.org**, parents find answers to their questions, information to help them learn about the syndrome, available treatments, family support programs, and SLOS research studies and therapeutic trials. All these resources can help the growth and development of their children and empower them on their journey of raising a child with SLOS.

The Smith-Lemli-Opitz Foundation continues to raise awareness of the syndrome and funds research to improve treatments with the hope of someday finding a cure for Smith-Lemli-Opitz syndrome.

Give today to support families and fund further research:

SmithLemliOpitz.org/ways-to-give

Smith-Lemli-Opitz
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Phone: (701) 367-1976
Email: Info@SmithLemliOpitz.org
Website: SmithLemliOpitz.org

YOUR INFORMATION (PLEASE PRINT)

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In Memory of | In Honor of (CIRCLE ONE)

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Who would you like us to notify of this dedication?

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