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 delay, 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 nutrient for proper growth and development. It is unclear how much cholesterol may be passed from mother to fetus during pregnancy, and since the body makes most of its own cholesterol after birth, children with SLOS continue to have trouble with many areas of development throughout their lifetimes. The discovery of the abnormal cholesterol metabolism in SLOS has made possible not only a laboratory test for more precise diagnosis of SLOS, but also a rationale for potential treatment.
In 1993, scientists made the important discovery that children with SLOS have an inborn error of metabolism that prevents their making cholesterol in amounts sufficient for normal growth and development. At diagnosis, 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-DHC reductase” (DHCR7), which converts 7-DHC into cholesterol. SLOS children with 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 will 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 normal cholesterol and 7-DHC levels, probably have other genetic disorders that resemble 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 (an estimate 18% - 20% develop)
- 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-dehydrocholesterol test or sterol profile. It is a test that uses sophisticated instruments to measure cholesterol and at least 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 other conditions with 7-DHC elevations, although those conditions generally have different clinical features. 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.
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, both parents are carriers of an abnormal gene but show no physical 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 with SLOS patients. Almost all have feeding problems and “failure-to-thrive” 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 failure-to-thrive 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 SLOS children 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 common in SLOS. For those with severely delayed speech, frustration comes easily, and screaming or tantrums are often an outlet. Many patients show aggressiveness and 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 SLOS children 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 and can learn daily living skills. Independent living as adults, however, is unlikely.

Recurrent infections, including ear infections and pneumonia, are also common.
MANAGEMENT & 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, simvastatin drug trials and antioxidant 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.

Simvastatin Therapy: A placebo-controlled research study of simvastatin therapy showed a minimal biochemical shift in the 7-DHC to cholesterol ratio. There was also a difference in one of the behavioral scales used to track behavior over the course of the study, but this difference was small and unlikely to be of clinical benefit. All of the individuals in this study had mild or mild–classical SLOS and were screened ahead of time with the residual function of their DHCR7 protein to assure that the medication was safe in them. Even though the results of the study looked promising, at this point in time simvastatin cannot be recommended as a therapy. There is the potential of adverse results, even in mild to classical cases.

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.
In 1988, 37 families with SLOS children began a network to exchange experiences and information about Smith-Lemli-Opitz Syndrome. Since then, the group has grown to more than 800 families from around the world. In addition to informal networking and social media websites such as Facebook, the SLO/RSH Foundation sponsors every other year a national scientific and family medical conference where physicians, scientists, parents and caregivers from all over the world can learn from each other. The SLO/RSH Foundation also promotes and funds research into Smith-Lemli-Opitz Syndrome and strives to increase awareness about the syndrome.

Give today in support of families and to fund further research: smithlemliopitz.org/donations

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