

Smith–Lemli–Opitz syndrome: a treatable inherited error of metabolism causing mental retardation

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Abstract

SMITH–LEMLI–OPITZ SYNDROME, a syndrome of multiple malformations and mental retardation that for years was relegated to the atlases of genetic esoterica, was recently found to be a relatively common inborn error of metabolism. The underlying defect is absent or deficient activity of 7-dehydrocholesterol- Δ^7 -reductase, the enzyme catalysing the final step of cholesterol synthesis. The discovery of the biochemical defect causing Smith–Lemli–Opitz syndrome has resulted in the development of a diagnostic test and a potentially beneficial treatment (dietary cholesterol supplementation). Infants and young children with the syndrome have shown marked improvement in growth, behaviour and general health after receiving cholesterol therapy; older children and adults have shown some improvement in development and intellectual functioning. Despite the excitement these developments have elicited among geneticists and biochemists, this syndrome remains relatively unknown to many primary care physicians. Increased awareness of Smith–Lemli–Opitz syndrome is needed to identify affected patients so that they and their families can benefit from appropriate treatment and genetic counselling.

Smith–Lemli–Opitz syndrome (SLOS) appears to be the second most common treatable recessive inherited error of metabolism causing mental retardation, after phenylketonuria. Its incidence is estimated to be between 1 in 40 000 and 1 in 20 000 births.^{1,2} SLOS is caused by a defect in cholesterol synthesis and presents with characteristic dysmorphic facial features, mental retardation, multiple congenital anomalies and failure to thrive.^{3–10} It was first described in 1964⁶ and, until recently, was of limited clinical interest to primary care physicians because no diagnostic test or treatment was available.

In 1994 the discovery of the underlying defect that affects cholesterol synthesis led to the development of a biochemical diagnostic test for SLOS.^{3,7} With increasing use of this diagnostic test, it became apparent that the syndrome presents with a wide spectrum of clinical severity and that patients at either end of the clinical spectrum are often missed — mildly affected patients because of their very subtle physical findings and more severely affected patients because death or pregnancy termination occurred before the diagnosis was considered.^{5,8–10}

Despite the exciting research developments, we believe that this relatively common genetic disease remains unknown to primary care physicians.^{1,11} Because dietary therapy with cholesterol supplementation has been shown to have a considerable positive impact on the clinical course of this disease, increased physician awareness is needed to ensure that patients and their families receive appropriate diagnosis, treatment and genetic counselling.

Clinical features

SLOS is characterized by dysmorphic facial features, microcephaly, growth retardation, multiple internal anomalies, cutaneous syndactyly of the second and third toes, and genital malformations.^{1–10} Patients with SLOS have a broad and high forehead, bilateral ptosis, epicanthal folds, a broad nasal bridge, a short nose with an-



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teverted nares and micrognathia. The ears are low set and small, and midline cleft palate is common. On occasion, newborns with SLOS have been mistakenly thought to have Down syndrome. However, the facial features may be subtle and difficult to recognize in both newborns and adults. The characteristic malformation of the feet (Fig. 1) is present in about 80% of patients with confirmed SLOS,⁵ but it may be very subtle.⁹ Polydactyly of feet and hands, oligodactyly of hands, short thumbs, hypoplastic thenar eminences and club feet are also common. The genital malformations observed in affected males include hypospadias, undescended testes and micropenis. The ease of detecting abnormalities of male external genitalia has led to a clinical diagnosis in more males with SLOS than in females with SLOS.^{10,12-15} Other malformations involving the brain, and respiratory, genitourinary and gastrointestinal systems have been reported in patients with more severe forms of SLOS.¹⁰ Overall there are no clinical features that are pathognomonic for the syndrome, and therefore it may be difficult to diagnose the condition on the basis of clinical findings alone; however, there are features that should prompt physicians to consider SLOS in the differential diagnosis of mental retardation (Table 1).

Patients with severe forms of the syndrome present with life-threatening congenital malformations of the central nervous system and heart, cystic kidney dysplasia and ambiguous genitalia and have an associated high neonatal mortality.¹⁰ Those with mild forms may present with mental deficits alone or accompanied by isolated cataracts, cleft palate or syndactyly.^{2,9,16} SLOS also has been diagnosed in mentally retarded adults (personal observation).¹⁷⁻²⁰ Since the discovery of the biochemical defect associated with the syndrome, the clinical spectrum of this disease has expanded, and an increasing number of patients with subtle clinical findings are being reported.^{5,9}

In children with SLOS, feeding difficulties constitute a major problem during infancy, and supplemental enteral tube feeding may be required. However, despite adequate energy intake, failure to thrive frequently persists during infancy and childhood. Global developmental delay appears

to occur universally among affected patients, who consequently require extensive care for their activities of daily living. Speech does not develop in most, but comprehension may be surprisingly good. Behavioural difficulties such as hyperactivity, frequent temper tantrums, violent outbursts, destruction of property and self-mutilation are common in children and adults and may cause a severe strain on family members (personal observation).¹⁶⁻²⁰ Children with SLOS and minimal clinical findings had been diagnosed with autism or pervasive developmental disorder (Dr. Richard I. Kelley, Kennedy Krieger Institute, Baltimore; personal communication, 1999). Skin photosensitivity with marked reaction to sunlight is frequently observed.⁵

Secondary biochemical abnormalities may develop as a result of the cholesterol deficiency; these include deficiencies of steroid hormones and of bile acids.²¹⁻²³ Bile acid deficiency can lead to fat malabsorption and fat-soluble vitamin deficiency, with resultant failure to thrive. Cholestatic liver disease in a number of patients with severe SLOS has been reported, and it can occur as part of the initial presentation in neonates.²¹

Genetics and epidemiology

SLOS is an autosomal recessive disease, which implies that both parents of affected patients are obligate carriers. Thus, the parents have a 1-in-4 risk of recurrence with each subsequent pregnancy. The syndrome appears to be most common in the Caucasian population of North European origin, with infrequent reports in people of African or Japanese origin.^{24,25} In the Caucasian population, the carrier frequency is estimated to be 1 in 70 people.²⁴ Because of the high carrier rate, genetic counselling for more distant family members should be offered as well.

Recently the gene for 7-dehydrocholesterol- Δ^7 -reductase was mapped to chromosome 11q12-13, and mutations in this gene were found in a number of patients with SLOS.²⁶⁻²⁸ Future studies should prospectively determine



Fig. 1: Cutaneous Y-syndactyly of the second and third toes and "fork-toe" appearance characteristic of Smith-Lemli-Opitz syndrome (SLOS).

Table 1: Clinical indications for 7-dehydrocholesterol measurement in diagnostic testing for Smith-Lemli-Opitz syndrome (SLOS)
Developmental delay of unknown cause and any of the following:
Facial features suggestive of SLOS
Syndactyly of the second and third toes
Hand anomalies
Genital anomalies
Intrauterine growth retardation and low birth weight
Failure to thrive
Feeding difficulties necessitating enteral tube feeding
Cleft palate
Autistic features
Family history of SLOS
Ambiguous genitalia or male-sex reversal
Clinical diagnosis of Down syndrome, but normal chromosomes
Abnormally low unconjugated estriol level detected through maternal serum screening
Previous clinical diagnosis of SLOS



the incidence of SLOS, and mutation analysis is hoped to allow more accurate carrier testing in the future.

Biomedical defect and diagnosis

The inherited biochemical defect is a deficiency of 7-dehydrocholesterol- Δ^7 -reductase, the catalyst in the last step of cholesterol synthesis: the conversion of 7-dehydrocholesterol (7-DHC) to cholesterol.²⁶⁻²⁹ Because of this enzymatic defect, there is a generalized cholesterol deficiency and an accumulation of 7-DHC in all body tissues. Cholesterol is a major constituent of cell membranes and myelin and is necessary for the synthesis of steroid hormones and bile acids. The severity of the clinical presentation and mortality of SLOS correlates well with the extent of the cholesterol deficiency.³⁰ Secondary deficiencies of steroid hormones may be present in most patients with severe disease.²³

In any child or adult with idiopathic mental retardation, a genetic consultation should be considered and, if indi-

cated, diagnostic testing should be performed (Fig. 2).³¹ The diagnosis is based on the demonstration of elevated levels of 7-DHC in plasma or amniotic fluid. The immediate precursor of cholesterol, 7-DHC is present only in trace amounts in normal plasma.^{3,7,8,29,30} It is detected and quantified by means of gas chromatography-mass spectrometry, which is available in many tertiary care centres. SLOS is frequently associated with subnormal plasma cholesterol levels; however, a plasma cholesterol level should not be used to confirm or exclude the diagnosis, because about 10% of affected patients have normal cholesterol levels. For patients whose disease has been diagnosed on the basis of clinical features alone, measurement of the plasma 7-DHC level is required for confirmation, because some patients with physical characteristics of SLOS do not have the disease and would not benefit from cholesterol therapy.⁵ Elevated levels of 7-DHC have also been observed in adults who are being treated with high doses of haloperidol but who do not have SLOS (unpublished data).

Prenatal diagnosis and screening

Families in whom a patient with SLOS has been identified should be aware of the 25% recurrence rate and the availability of prenatal diagnosis. Before the biochemical defect was discovered, ultrasonography was used to detect characteristic birth defects in pregnancies at risk for SLOS.^{32,33} Increased nuchal-fold thickness at 13 to 14 weeks' gestation may be the first ultrasonographic sign that the fetus has SLOS.³³ A detailed ultrasound examination at 18 to 20 weeks' gestation may detect some of the severe malformations, but it does not detect subtle abnormalities of the face, hands and feet.

Prenatal diagnosis is now based on the detection of 7-DHC and a related compound, 8-DHC, in amniotic fluid any time after 13 weeks' gestation.³⁴⁻³⁷ A carrier couple may want to consider a number of reproductive choices such as termination of an affected pregnancy, adoption or artificial insemination. If a couple wishes to continue with an affected pregnancy, maternal cholesterol supplementation has been reported;³⁷ however, there is limited follow-up regarding the efficacy of this treatment.

SLOS should also be considered whenever a low unconjugated estriol (uE3) level is detected as part of triple-marker maternal serum screening for Down's syndrome and open spina bifida. Because steroid hormones such as uE3 are derived from cholesterol and because cholesterol synthesis is diminished in fetuses with SLOS, mothers with affected fetuses have abnormally low uE3 levels.³⁸ Screening for SLOS in families who are not known to be at increased risk (i.e., no family history of the disease) may become part of maternal serum screening. A prospective multicentre study is under way that will evaluate the clinical utility of screening for SLOS as part of maternal serum screening (Dr. Richard I. Kelley, Kennedy Krieger Institute, Baltimore: personal communication, 1998). New non-

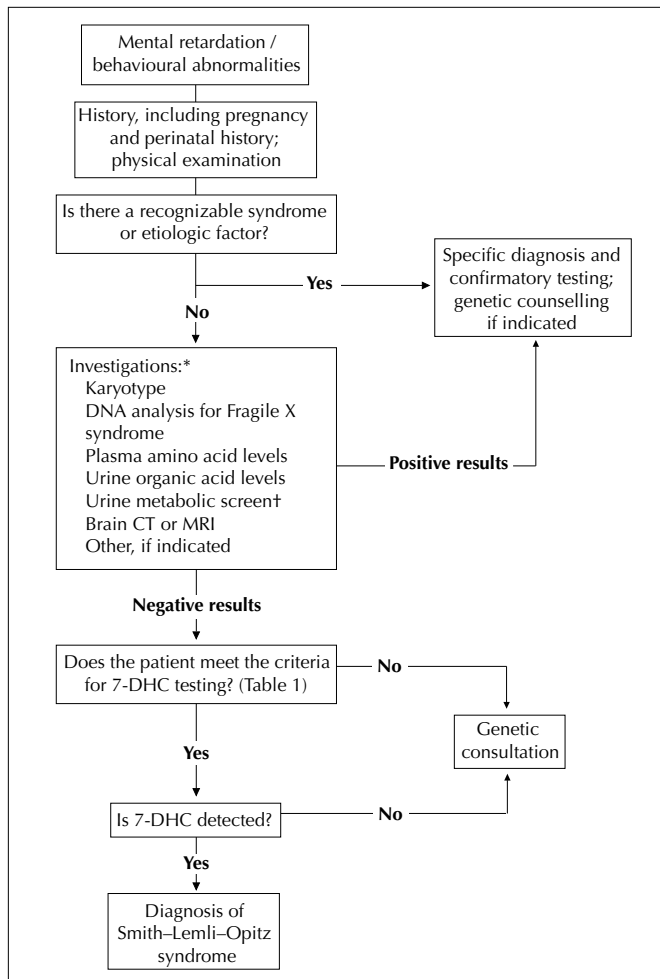


Fig. 2: Diagnostic approach to mental retardation. *Investigations based on recommendations of Curry and associates.³¹ †Urine metabolic screen may include qualitative detection of reducing substances, ketones, thiosulfite, branched chain amino acids, tyrosine, disulfides and other tests.



invasive tests to screen for SLOS using maternal urine are currently being developed.

Treatment

The goal of treatment is to provide enough dietary cholesterol to return the plasma cholesterol level to normal. The usual starting dose is 40–50 mg/kg daily, with increases based on somatic growth requirements. Dietary cholesterol can be given either in a natural form (e.g., eggs, cream) or as purified food-grade cholesterol. Because of feeding difficulties in infants and younger children who have SLOS, and because the diet is usually un-

palatable to older children, enteral tube feeding is often required.

Dietary cholesterol supplementation can restore a normal growth pattern in children and adolescents with SLOS, alleviate behavioural abnormalities and improve general health (e.g., fewer infections, improved gut motility, onset of puberty).^{4,39,40} Furthermore, cholesterol supplementation appears to be effective in old and young patients alike; therefore, delays in diagnosing SLOS should not deter initiation of treatment. Behavioural changes typically occur before any changes in the plasma cholesterol level; this has also been observed in adults with SLOS who have received cholesterol therapy.³⁹ However, a significant

Clinical reports

The following cases illustrate the difficulty in diagnosing SLOS based on clinical features alone and the potential benefits of cholesterol supplementation. The second report is a composite based on several cases managed by us and other colleagues (Dr. Annette S.J. Feigenbaum, Hospital for Sick Children, Toronto: personal communication, 1998); the cases described in the third report have been reported previously.⁹

Report 1

This girl was born at term to a 29-year-old woman. Results of maternal serum screening at 16 weeks' gestation were negative for Down syndrome and open neural tube defects; the unconjugated estriol level was 1.00 nmol/L, or 0.27 multiples of the mean. Ultrasound examination at 18 weeks' gestation was reported as normal. Intrauterine growth retardation was noted at 36 weeks, and labour was induced at 38 weeks because of lack of interim growth.

Birth weight and length were appropriate for gestational age (10th percentile), but there was relative microcephaly (third percentile). The baby had facial features typical of SLOS: small chin, cleft palate, abnormally shaped skull, abnormal hands and syndactyly of the second and third toes (Fig. 1). The external genitalia were normal and female in appearance. A genetic consultation was requested because of suspected Down syndrome.

The baby had a normal female kary-

otype. The plasma cholesterol level was less than 1.10 mmol/L and the plasma 7-DHC level 200 nmol/L, thereby confirming the clinical diagnosis of SLOS. Cholesterol supplementation was started, but difficulties with oral feeding led to the placement of a percutaneous gastric tube at 2 months of age. At 10 months, the girl was below the third percentile for head circumference, weight and length, but her rate of growth had increased. She was cooing, laughing, rolling and smiling responsively with good eye contact.

Report 2

This 15-year-old boy was born fol-

lowing an uncomplicated pregnancy and delivery. Growth parameters were normal, but he had a cleft palate, small chin, hypospadias and undescended testes. Chromosomal analysis demonstrated a normal male karyotype. Feeding problems soon after birth resulted in the need for nasogastric tube feeding. A clinical diagnosis of SLOS was made at the age of 20 months based on the following features: microcephaly, long and narrow skull, bilateral epicanthal folds, broad nasal bridge, cleft palate, bilateral ptosis and bilateral cutaneous syndactyly of the second and third toes.

The child underwent surgical correction of his congenital malformations without complications. His general

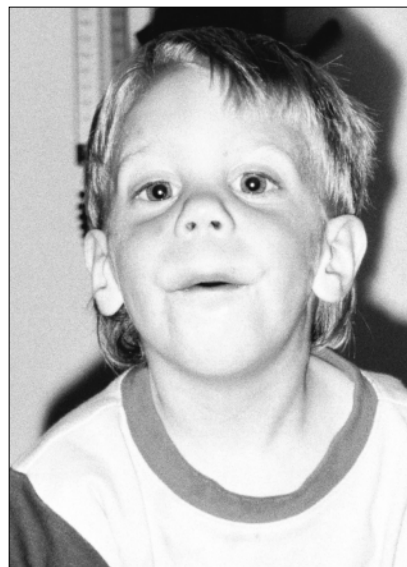
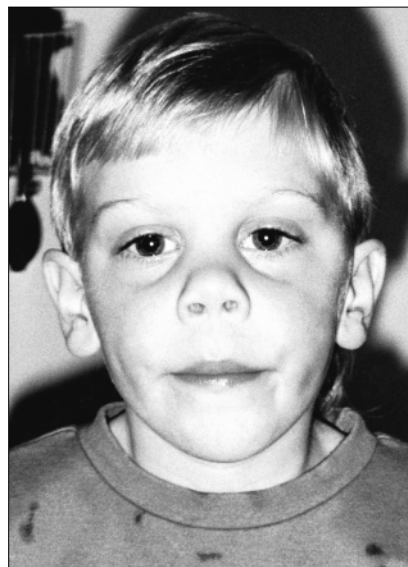


Fig. 3: Two brothers with facial features typical of SLOS: ptosis, epicanthal folds, small chin and short nose. The facial features are more pronounced in the younger brother (right).



placebo effect cannot be excluded. No complications of cholesterol therapy in children or adults have been reported to date.^{4,39,40}

Dietary therapy is monitored by growth parameters (i.e., body weight and length, and head circumference), behavioural and neurologic assessments, and biochemical testing (i.e., plasma cholesterol and 7-DHC levels). A multidisciplinary team approach is helpful in providing optimal care for children with SLOS and for their families.

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health was good thereafter, except for recurrent upper and lower respiratory tract infections. Hearing and visual acuity were normal. He had marked developmental delay and required assistance with most activities of daily living. He also had major behavioural difficulties, including self-mutilation and sexual aggression.

The clinical diagnosis was confirmed biochemically at age 15 years: the plasma 7-DHC level was 375 mmol/L and the plasma cholesterol level 1.56 mmol/L. Cholesterol therapy (50 mg/kg daily) was administered through a gastrostomy tube. Within a year a marked improvement in behaviour was reported by the parents.



Fig. 4: A cousin of the 2 brothers at 5 years of age. Facial changes are subtle; however, retrognathia and low-set ears are noticeable.

Report 3

Two similarly affected brothers were referred at the ages of 21 and 31 months for a genetic consultation because of developmental delay. Both were born at term following uncomplicated pregnancies; their birth weights were at the 10th percentile. Both had neonatal feeding difficulties associated with vomiting and poor weight gain, and the younger brother required nasogastric tube feeding. The younger brother also had congenital club feet and coarctation of the aorta. Both boys had recurrent ear infections.

The older boy did not walk unaided until the age of 18 months, and at 30 months he still had no speech and was not toilet-trained. He reacted with temper tantrums and screaming when presented with new or stressful situations. The younger brother's gross motor milestones were within normal limits; however, his fine motor and speech development were significantly delayed. Multiple investigations, including a work-up for metabolic conditions, a CT scan of the head and chromosome analysis yielded normal findings in both boys.

At the time of the genetic consultation the similarities of their facial features were striking: bilateral ptosis, epicanthal folds, short upturned noses and generalized hypotonia (Fig. 3). The older brother's growth parameters were within normal limits; the younger boy's weight was under the third percentile. Both brothers had minimal syndactyly of the second and third toes, which, combined with the characteristic facial features, led to the consideration of SLOS.

The plasma cholesterol level of the

older boy was 2.23 mmol/L and the plasma 7-DHC level 134 mmol/L; his younger brother's plasma cholesterol level was 2.42 mmol/L and the 7-DHC level 183 mmol/L. The clinical diagnosis of SLOS was confirmed in both brothers. A high cholesterol diet and cholesterol supplementation were started. Within 7 months the boys showed steady improvement in growth, were walking and running unsupported and had started to speak. The older brother was using 3-word sentences.

Shortly after SLOS was diagnosed in the brothers, their uncle (the father's brother) contacted us to request testing in one of his 4 daughters. The girl was 11 years old with significant developmental delay: she was able to read and write at the level of senior kindergarten. Attention deficit hyperactivity disorder had been diagnosed at the age of 6 and was treated medically. She was born following a normal pregnancy; her birth weight was at the third percentile. Her infancy was marked by significant feeding difficulties and failure to thrive. Multiple investigations throughout childhood failed to find the cause of her health problems.

On examination, she had subtle facial features that may be considered normal (Fig. 4) and mild hand and toe abnormalities; the syndactyly of the second and third toes was so subtle that it was only detectable from the plantar surface of the foot. Her weight and head circumference were at the third percentile and her height was at the 10th percentile. The plasma cholesterol level was 2.30 mmol/L and the plasma 7-DHC level 48 mmol/L, which confirmed the diagnosis of SLOS.



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