Smith-Lemli-Opitz Syndrome 101

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Outline

• Review the discovery of Smith-Lemli-Opitz syndrome (SLOS) and its underlying cause
• Describe the clinical features of SLOS and recommended medical care
• Discuss the rationale behind various treatment approaches for SLOS
Origins

A newly recognized syndrome of multiple congenital anomalies

David W. Smith, M.D.,* Luc Lemli, M.D., and John M. Opitz, M.D.

Madison, Wis.

Smith et al., 1964. The Journal of Pediatrics. 64(2):210-217
Origins

Originally described as “RSH syndrome”

“The syndrome is presented with the hope that other cases will be recognized, allowing for the further definition of the condition and its etiology.”

Early Observations

• None of the individual characteristics were pathognomonic of the disorders
• None of the individual characteristics were obligatory
• The condition varied enormously in expressivity
• The occurrence in many races from unrelated parents indicated this was a relatively “common” disorder

Mechanism


Figure 4. Steps in Cholesterol Biosynthesis.
Cholesterol is synthesized from C-24(25) saturated and C-24(25) unsaturated intermediates (structures at left and right, respectively). The symbol X denotes the proposed block in cholesterol biosynthesis in the Smith–Lemli–Opitz syndrome — defective reduction of the C-7 double bond of 7-dehydrocholesterol or of any other intermediate with a C-7 double bond.
SLOS Today: Demographics

Prevalence:
• 1 out of every 20,000-60,000 live births
  • More common in individuals of northern or central European ancestry
  • Less common in individuals with Asian or African ancestry

Carrier frequency:
• Approximately 1 in 30 individuals

## SLOS Today: Clinical Features

<table>
<thead>
<tr>
<th>Category</th>
<th>Features</th>
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<tbody>
<tr>
<td>General</td>
<td>Slow growth, developmental delay, intellectual disability, low muscle tone, sleep issues, aggressive behaviors, autistic features</td>
</tr>
<tr>
<td>Skin</td>
<td>Sensitivity to light, eczema</td>
</tr>
<tr>
<td>Head</td>
<td>Small head size, small jaw, arched palate, cleft palate, holoprosencephaly</td>
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<tr>
<td>Eyes</td>
<td>Eyelid drooping, lazy eye, cataracts, underdeveloped optic nerve</td>
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<tr>
<td>Heart</td>
<td>Various heart malformations (septal defects, patent ductus arteriosis, AV canal), high blood pressure</td>
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<tr>
<td>Gastrointestinal Tract</td>
<td>Pyloric stenosis, Hirschsprung’s disease, intestinal malrotation, constipation, reflux, feeding issues, cholestatic liver disease</td>
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<tr>
<td>Kidney and Genitals</td>
<td>Underdeveloped genitals, undescended testicles, kidney malformations</td>
</tr>
<tr>
<td>Extremities</td>
<td>Shortened arms, 2,3 toe syndactyly, extra fingers or toes, short thumbs</td>
</tr>
</tbody>
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The Many Faces of SLOS
Underlying Cause

- Steroid Hormones
- Bile Acids
- Embryonic Development
- Cellular Membranes

Cholesterol
Genetic Cause

Cell
Each chromosome is composed of one large continuous DNA molecule.

Chromosomes

Gene
A gene is a segment of DNA that encodes a protein product.

Protein
A protein is a complex organic compound composed of hundreds or thousands of amino acids.

DNA
Nucleotides
- Adenine
- Thymine
- Guanine
- Cytosine

Greenwood Genetic Center
**Underlying Cause**

7-dehydrocholesterol

7-dehydrocholesterol reductase

Cholesterol

**DHCR7 Gene:** Provides instructions for the enzyme 7-dehydrocholesterol reductase
Underlying Cause

Cholesterol and Its Precursors

Diagnosis

Prenatal Ultrasound Findings:
• Poor growth
• Brain, heart, kidney, or limb malformations
• Underdeveloped male genitalia

Prenatal Laboratories:
• Low estriol
• Low hCG
• Low alpha fetoprotein
• Elevated equine sterols

Diagnosis

Clinical Features:
• Characteristic facial features
• 2,3 toe syndactyly
• Small head size
• Feeding and growth issues
• Developmental delays
• Underdeveloped genitals in males
• Cleft palate
• Extra fingers or toes

Laboratories:
• Serum 7-dehydrocholesterol
  • Typically elevated
• Serum cholesterol
  • Sometimes low, but may be normal
• Molecular testing of \textit{DHCR7} gene
Medical Care

At Diagnosis:
• Detailed history and physical examination
• Developmental assessment
• Ophthalmology exam
• Echocardiogram and ECG
• Brain imaging
• Kidney ultrasound
• Hearing evaluation
• Laboratories to look for signs of adrenal or liver issues
• Consultation with clinical geneticist
Medical Care

**Ongoing:**
- Detailed history and physical examination
- Developmental assessment
- Nutrition assessment with SLOS growth curves
- Laboratories (cholesterol, 7-dehydrocholesterol, 8-dehydrocholesterol, liver transaminases)
Treatment

• Therapy services
• Feeding tubes
• Cholesterol and/or bile acid therapy for liver disease
• Surgical repair for eye issues
• Polydactyly repair
• Tympanostomy tubes for frequent ear infections
• UV protective clothes and sunscreen
Cholesterol or Bile Acid Supplementation

7-dehydrocholesterol → Cholesterol

7-dehydrocholesterol reductase

Steroid Hormones
Bile Acids
Embryonic Development
Cellular Membranes
HMC-CoA Reductase Inhibitors

HMG-CoA

↓

HMG-CoA Reductase

Mevalonate

7-dehydrocholesterol

7-dehydrocholesterol reductase

Cholesterol

↑↑

8-dehydrocholesterol
Antioxidant Supplementation

Antioxidant Stress

7-dehydrocholesterol

8-dehydrocholesterol

7-dehydrocholesterol reductase

Cholesterol

↑↑↑↑

↑↑
Additional Therapies

- Prenatal cholesterol supplementation
- Stem cell therapy
- Gene therapy
Resources

• Smith-Lemli-Opitz Foundation
• Rare Disease Clinical Research Network (STAIR)
• Clinicaltrials.gov