

# Smith-Lemli-Opitz syndrome

## Introduction

**Smith-Lemli-Opitz syndrome** (SLOS) is an **autosomal recessive inherited disease**, the manifestation of which is determined by a disorder of **cholesterol metabolism**. This syndrome was first described in 1964 by American pediatrician David Smith, Belgian pediatrician Luc Lemli and German-American geneticist John Opitz. However, this syndrome was properly clarified in the 1980s, when patients with this syndrome were found to have reduced cholesterol levels.

## Heredity

This disease, as already mentioned, is classified as an autosomal recessive inherited disease, which means that this disease (trait) is caused by the presence of a recessive allele in the autosomes. If an individual is a dominant homozygote, they are healthy, and heterozygotes are healthy carriers. In terms of Mendelian crossing, the risk probability can be expressed as follows:

P: Aa x Aa

g: A,a x A,a

F: AA, Aa, Aa, aa→25% risk of disease manifestation

This disease is caused by **a mutation of the DHCR7 gene**, which is located on the 11th chromosome.

## Molecular cause

The cause of this disease is a mutation **of the gene for 7-dehydrocholesterol reductase**, which is used in the last step of cholesterol synthesis, by catalyzing the reduction of the C7-C8 double bond of 7-dehydrocholesterol and cholesterol is formed. Deficiency of 7-dehydrocholesterol reductase leads to the accumulation of sterol precursors (7-dehydrocholesterol and 8-dehydrocholesterol), **which are toxic to the embryo**. Cholesterol plays an important role in embryogenesis, as it is the main component of cell membranes, a precursor of steroid hormones and is also responsible for the distribution of hedgehog proteins.

## Clinical manifestations

The clinical manifestations of SLOS vary in severity from barely perceptible abnormalities to death or miscarriage. Clinical features include **cleft palate, syndactyly of the second and third fingers, facial dysmorphism, microcephaly, malformations of the heart, lungs, liver, kidneys, adrenal glands, pancreas and brain**. Prenatal and postnatal growth retardation, intellectual disabilities and, in men, genital abnormalities ranging from mild hypospadias to double genitalia are also common. Those affected also have a wide spectrum of behavioral deviations (autism, aggressiveness, hyperactivity, frequent mood swings, outbursts of anger, destructiveness and self-harm, mental retardation, delayed speech development). Other manifestations are **insufficient production of steroid hormones, bile acids with subsequent low absorption of fats and fat-soluble vitamins**.

## Therapy

Treatment of SLOS is based on **cholesterol supplementation and reduction of pathological sterol metabolites**. Cholesterol treatment using ursodeoxycholic acid has been shown to improve condition and motor function in some patients. Treatment with 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors, which block cholesterol biosynthesis, which in children with SLOS leads to a surprising increase in cholesterol levels and improvement in clinical manifestations. Cholesterol delivery to the growing brain, reduction of pathological metabolites, and repair of damage done in embryonic life remain complex problems to solve.

## Occurrence

SLOS is the third most common inherited metabolic disorder in most countries after cystic fibrosis and phenylketonuria. It occurs with a frequency of 1:20,000 to 1:40,000 and is **more common in the European population** than in the Asian or African population. In the Czech Republic, the frequency is reported to be 1:10,000.

## Links

### External links

- Smith–Lemli–Opitz syndrome: pathogenesis, diagnosis and management (<http://www.nature.com/ejhg/journal/v16/n5/full/ejhg200810a.html>)
- Smithův-Lemliho-Opitzův syndrom - příznaky, projevy, symptomý (<http://www.priznaky-projevy.cz/geneticke-nemoci/582-smithuv-lemliho-opitzuv-syndrom-priznaky-projevy-symptomý>)
- Smith–Lemli–Opitz syndrome ([https://en.wikipedia.org/wiki/Smith%E2%80%93Lemli%E2%80%93Opitz\\_syndrome](https://en.wikipedia.org/wiki/Smith%E2%80%93Lemli%E2%80%93Opitz_syndrome))

## References

- HOFFMANN, GF, et al. *Hereditary metabolic disorders*. 1st edition. Prague: Grada, 2006. 416 pp. pp. 304-305. ISBN 80-247-0831-0 .

Category: Pediatrics Category: Genetics