Available online at www.sciencedirect.com
ScienceDirect
ELSEVIER
European Journal of Medical Genetics 51 (2008) 124–140
EUROPEAN JOURNAL OF MEDICAL GENETICS
http://www.elsevier.com/locate/ejmg

Short report

# Mild Smith-Lemli-Opitz syndrome: Further delineation of 5 Polish cases and review of the literature

A. Jezela-Stanek [a,*], E. Ciara [a], E.M. Malunowicz [b], L. Korniszewski [c], D. Piekutowska-Abramczuk [a], E. Popowska [a], M. Krajewska-Walasek [a]

[a] *Department of Medical Genetics, The Children's Memorial Health Institute, Warsaw, Poland*
[b] *Department of Laboratory Diagnostics, The Children's Memorial Health Institute, Warsaw, Poland*
[c] *Genetic Counselling Unit, Institute of Physiology and Pathology of Hearing, Warsaw, Poland*

Received 9 September 2007; accepted 23 November 2007
Available online 8 December 2007

**Abstract**

Smith-Lemli-Opitz syndrome (SLOS) is an autosomal recessive disorder caused by reduced activity of 7-dehydrocholesterol reductase, resulting in an increased concentrations of 7-dehydrocholesterol and 8-dehydrocholesterol in body fluids and tissues. Phenotypically it is characterized by wide range of abnormalities, from mild to lethal forms what causes difficulties in its clinical diagnostics. To further delineate the physical spectrum of the mild form of Smith-Lemli-Opitz syndrome, especially with regard to genotype-phenotype correlation, we describe 5 Polish patients with mild phenotype (one with novel mutation in *DHCR7* gene and four published before) and analyze 18 other cases from the literature. As the conclusion we give recommendation for tests toward SLOS in cases with ''idiopathic'' intellectual impairment and/or behavioral anomalies, as well as in biochemically doubtful but clinically fitting cases with overall gestalt and history of this syndrome.


*Keywords:* Smith-Lemli-Opitz syndrome; Mild phenotype; Cholesterol; 7-Dehydrocholesterol; *DHCR7* gene

* Corresponding author: Department of Medical Genetics, The Children's Memorial Health Institute, Aleja Dzieci Polskich 20, Warsaw, Poland.
*E-mail address:* jezela@gmail.com (A. Jezela-Stanek).

1769-7212/$ - see front matter © 2007 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmg.2007.11.004

## 1. Introduction

Smith-Lemli-Opitz syndrome (SLOS; MIM 270400) is an autosomal recessive disorder of cholesterol biosynthesis, characterized in the classical form by mental retardation, growth deficiency and such congenital anomalies as: microcephaly, cutaneous 2 and 3 toe syndactyly, external genital anomalies in males, and various central nervous system and internal malformations [14,25,31]. The typical facial appearance consists of a broad and high forehead, ptosis, epicanthal folds, short nose with broad nasal bridge, anteverted nares and micrognathia. The first report of the syndrome [31] has been followed by descriptions of over 700 patients, with different clinical characteristics, including — at the mildest end of the disease spectrum — isolated syndactyly of toes 2 and 3 as the only feature, as well as holoprosencephaly and multiple visceral anomalies resulting in death in utero, at the opposite end [6,13]. Therefore, historically, a clinical distinction was often made between the classic disorder (type I) and a more severe (type II) [7,13]. The SLOS phenotype has been conclusively redefined to include both mild cases with minor dysmorphic features and developmental delay [1,23,28] as well as severe ones, with congenital malformations and pre- or perinatal mortality [7,12,19].

The disorder is caused by mutations of the *DHCR7* gene coding for 3β-hydroxysterol $\Delta^7$-reductase (*DHCR7*), the enzyme that catalyses the conversion of 7-dehydrocholesterol (7DHC) to cholesterol [8,20,30,36,37]. The discovery of the biochemical marker and identification of the underlying molecular defect led to the introduction of reliable laboratory diagnostics to verify the phenotypical recognition of SLOS [34].

As a result of diminished *DHCR7* activity, 7DHC (and its epimer 8DHC) accumulates and a generalized cholesterol deficiency in all body tissues may develop. The plasma cholesterol concentration generally inversely correlates with severity, while a minor relationship is observed between severity and 7-dehydrocholesterol concentration [6,35,39,41].

Laboratory diagnostics of this syndrome is based on demonstration of elevated 7DHC levels, usually measured in plasma or amniotic fluid (as a prenatal test) [11], urinary 7DHPT/PT ratio [29] or molecular analyses of the *DHCR7* gene in DNA isolated from lymphocytes and chorionic or amniotic cells.

We describe five patients with minimal physical manifestations of SLOS. The diagnoses were proved by biochemical and molecular tests that revealed a novel mutation of the *DHCR7* gene in one patient, and analyze other mild cases presented thus far in the literature.

## 2. Patients

Clinical diagnoses of Smith-Lemli-Opitz syndrome were established in 5 patients (one female and four males; four probands and one sibling – Patient 1 and Patient 2; four of them – Patients 1–4 have been described previously by Ciara et al. [3], respectively Patients: 34, 35, 4, 22). On the basis of clinical features (mainly: facial features milder than in classical form), all of them were classified as mildly affected. In all cases, routine karyotyping (with 550 bands) was performed and yielded normal results: 46, XX in Patient 3 and 46, XY in Patients 1, 2, 4, 5.