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COMMENTARY

Smith–Lemli–Opitz Syndrome (SLOS) and the Fetus

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Smith–Lemli–Opitz syndrome (SLOS) is an autosomal recessive congenital malformation syndrome due to dehydrocholesterol reductase deficiency. It was described about half-century ago by Smith et al. [1]. Both its biochemical profile with low cholesterol and high 7-dehydrocholesterol concentrations and cloning of the sterol delta 7-dehydrocholesterol reductase (DHCR7) gene, which catalyzes the conversion of 7-dehydrocholesterol to cholesterol in the final step of cholesterol biosynthesis, were discovered two decades ago [2, 3].

The clinical presentation of SLOS ranges from subtle physical anomalies with behavioral and learning problems to microcephaly, cardiac defects, cleft palate, and intellectual disabilities to perinatally lethal multiple malformations. The second and third toe syndactyly and facial dysmorphism, including short nose with anteverted nares are typical malformations. The characteristic craniofacial appearance is independent from clinical or biochemical severity [4]. A number of neurodevelopmental problems are a consistent part of the syndrome, and the most common brain abnormalities affect midline structures, such as the corpus callosum, intraventricular septum, and cerebellar vermis [5]. In a series of 10 fetuses examined at autopsy with molecularly proven SLOS, the fetal phenotype of SLOS includes characteristic facial dysmorphism, even in the young fetus. Genital abnormalities are rare in 46, XX subjects, but ambiguous genitalia, hypospadias, and cryptorchidism are well described in affected males. Gonadal differentiation appears histologically normal and in agreement with the chromosomal sex, contrary to what has been previously stated. Some additional anomalies include ulnar hypoplasia, vertebral segmentation anomalies, congenital pulmonary adenomatoid malformation, fused lungs, gastroschisis, tetra-amelia, and hypothalamic hamartoma, which overlaps with the malformation found in Pallister–Hall syndrome [6].

Prenatal diagnosis of SLOS may be indicated in pregnancies of known parental carriers or when ultrasound findings of growth restriction, cleft palate, and genital abnormalities are noted. An affected pregnancy may be signaled by low maternal serum estriol. However, with the advent of directly testing fetal DNA in the maternal circulation for aneuploidy, maternal serum screening has less utilization. Prenatal diagnosis is accomplished by sterol profiling in amniotic fluid or chorionic villi, and detection of biallelic mutations in the *DHCR7* gene. There are 192 disease-causing mutations of the *DHCR7* gene reported in the Human Gene Mutation Database (https://portal.biobase-international.com/hgmd) accessed on 21 March 2016, including 167 missense/nonsense mutations, six splicing mutations, eight small deletions, three small insertions, one small indel, and seven gross deletions. All of these mutations cause SLOS, except one of the missense mutations in exon 9 (p.G344D, c.1031G > A) causing holoprosencephaly due to reduced enzyme activity [7] and one of the splicing mutations in intron 5 (IVS5 + 3 A > T, c.412 + 3A > T) resulting in insufficient enzyme activity during embryogenesis due to inducing a large splicing change, but remaining sufficient *DHCR7* activity once cholesterol synthetic rates decrease postnatally [8]. This unique example underscores the adjunctive use of fibroblast and molecular testing in ambiguous cases of SLOS, and may provide insight into the potential efficacy of therapeutic interventions altering postnatal cholesterol biosynthesis [9]. The majority of the SLOS cases are

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Table 1 *DHCR7* mutation testing in fetus

Case number	Mutations
1	Compound heterozygous IVS8-1G > C and p.T289I
2	Compound heterozygous IVS8-1G > C and p.W151*
3	Compound heterozygous IVS8-1G > C and p.F302L
4	Compound heterozygous p.R228 W and p.V326L
5	Compound heterozygous IVS8-1G > C and p.Y408H
6	Compound heterozygous IVS8-1G > C and p.R242H
7	Compound heterozygous p.M1 V and p.R446Q
8	Heterozygous IVS8
9	Heterozygous IVS8

Indications for testing include low maternal serum estriol, previously affected child, and abnormal fetal ultrasound findings

caused by the five most common mutations. The most common mutation is the splice site mutation IVS8-1G > C (c.964-1G > C) having a frequency of 29 % in SLOS alleles and leading to an insertion of 134 bp between exons 8 and 9. Other frequently observed mutations are p.R404C (c.1210C < A), p.W151* (c.452G > A), p.T93M (c.278C > T) and p.V326L (c.976G > T), having a frequency of 11, 8, 8, and 7 %, respectively [10]. By targeted testing of common mutations, there were nine *DHCR7* mutation positive fetal cases found in our laboratory as shown in Table 1. Seven of them were compound heterozygous mutations, while two of them were heterozygous mutations. The most common mutation IVS8-1G > C was found in seven out of nine cases. As DNA sequencing has become routine, full sequencing with >96 % detection has replaced targeted mutation analysis. Deletion analysis would be recommended if only one pathogenic allele was identified. Identification of mutations in *DHCR7* in affected pregnancies has allowed carrier detection and future preimplantation and prenatal diagnosis.

Lack of cholesterol and accumulation of cholesterol precursors including 7- and 8- dehydrocholesterol during embryogenesis causes the disease phenotype in SLOS. Accumulation of cholesterol precursors might lead to a preference for other additional sterol pathways, such as diversion of the sterol precursor farnesyl-PP toward long-chain isoprenoids [11]. In addition, various distribution patterns of cholesterol, 7-dehydrocholesterol, and oxysterol metabolite of 7-dehydrocholesterol in the brain regions might explain pathophysiology in the brain of SLOS patients [12]. There is a clear correlation between genotype and phenotype when comparing the SLOS patients' clinically described severity scores with their biochemical data and genotypes [13]. However, a wide range of phenotype and clinical severity can be found in patients with the same genotype. Modifying factors, apart from the *DHCR7* genotype, may influence phenotype and disease severity. Disease severity varies significantly depending on whether the apolipoprotein E (*apoE*) alleles ε2, ε3, or ε4 were carried by the respective patient's mother. Lower concentration of cholesterol and higher disease severity scores were found in patients having the maternal apo ε2 genotype [14]. Maternal ATP-binding cassette transporter A1 (*ABCA1*) genotype also modifies disease severity in SLOS. The rare maternal p.1587Lys allele in the *ABCA1* gene was associated with milder phenotypes. Therefore, modifying placental cholesterol transfer pathways may be an approach for prenatal therapy of SLOS [15].

Since the clinical phenotype of SLOS is due to lack of cholesterol during embryogenesis, therapy is needed at the fetal stage, such as cholesterol substitution, HMG-CoA reductase inhibitors to cross the blood–brain barrier, and antioxidant supplementation to inhibit the formation of the toxic precursors including 7- and 8- dehydrocholesterol derived oxysterols. How to implement these measures prenatally awaits realization.

Compliance with Ethical Standards

Conflict of interest None.

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