Smith-Lemli-Opitz syndrome: ultrasound and genetic findings.

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Objective

Mutations in the 7-dehydrocholesterol reductase gene (DHCR7) cause the Smith-Lemli-Opitz Syndrome (SLOS, OMIM # 270400), an autosomal recessive disorder with multiple malformation and cognitive impairment. These mutations results in elevation of the cholesterol precursor 7-dehydrocholesterol (7-DHC) and typically decreased cholesterol synthesis. Its incidence has been estimated to be 1/10000-1/70000 conceptions, but is strikingly different among various ethnic groups. The diagnosis is confirmed by high 7-DHC levels in plasma and tissues and/or by detection of biallelic mutations in the DHCR7 gene. The fetal phenotype of this syndrome has been poorly described in the literature, being our objective to demonstrate the enormous clinical variability that can present.

Methods

This is a case report.

Results

We describe a case of SLOS in a 39 years old patient, gravida III, para I, who came to our hospital for his first trimester ultrasound study. The fetus presented a crown-rump length of 74 mm (according to 13+4 weeks), nuchal translucency of 15 mm, severe congenital heart defect and omphalocele. The risk for trisomies 21, 18 and 13 obtained in the combined screening of the first trimester was 1/1, so the study of the fetal karyotype, Noonan phenotype and array-CGH was offered by invasive test. Amniocentesis was performed at 16+1 weeks. At this time, the fetus presented facial dysmorphism, choroid plexus cysts, fetal hydrops (pleural and pericardial perfusion, ascites and nuchal edema), severe cardiopathy (tetralogy of Fallot with pulmonary atresia), abdominal situs inversus, omphalocele, clenched hands with polydactyly, single umbilical artery and umbilical cord cyst. Given the severity of the alterations, the patient requested a legal interruption of the pregnancy. The result of karyotype was 46,XY, study Noonan syndrome negative and array CGH without alterations. Discarded these pathologies, we suspect an SLOS, so we requested study of mutations of the DHCR7 gene and determination of 7-DHC in amniotic fluid. The study of dehydrocholesterol levels in amniotic fluid was impossible because of lack of sample. The study of DHCR7 gene revealed the (c.1369C>T (p.Arg457Trp) alteration, which is described as a VOUS (variant of unknown significance) associated with SLOS in the database HGMD (CM154266). We offered genetic study to the parents, who refused it.

Conclusion

Ultrasonographic detection of multiple anomalies in association with normal karyotype is suggestive of Smith-Lemli-Opitz syndrome (SLOS), especially if it is accompanied by intrauterine growth restriction. Although SLOS presents frequently increased nuchal translucency, facial, limbs, and genital anomalies associated with growth and mental retardation, the wide phenotype variation is the most important aspect of this disorder. Major malformations from all the systems (brain, heart, kidneys, etc.) have been described. The finding of female genitalia with a male karyotype is highly suggestive of SLOS. Prenatal diagnosis can be done either by sterols profiling in amniotic fluid or chorionic villi, or by DHCR7 molecular analysis (as it happened in our case). Given that a normal karyotype should be established before initiating SLOS testing, this syndrome is typically undiagnosed until an advanced second trimester. A better knowledge of the aspects mentioned here could help the practitioners of fetal medicine units to diagnose more accurately SLOS during pregnancy.