

## Case Report

# Smith-Lemli-Opitz-syndrome

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Smith-Lemli-Opitz syndrome is an autosomal recessively inherited disorder. A severe defect in cholesterol biosynthesis has been identified leading to abnormally low plasma cholesterol levels and elevated levels of the cholesterol precursor 7-dehydrocholesterol, the result of deficiency of 7-dehydrocholesterol reductase. We describe one such child with Smith-Lemli-Opitz syndrome. This child had clinical features similar to Smith-Lemli-Opitz syndrome like facial dysmorphism and cardiac and renal anomalies with failure to thrive.

**Key words:** Atrial septal defect, cholesterol, hydronephrosis, polydactyly, smith lemli opitz syndrome

a 4½-month-old boy with clinical and biochemical profile suggestive of Smith-Lemli-Opitz syndrome.

### Case Report

A 4½-month-old male child, born of a non-consanguineous marriage, was referred in view of failure to thrive. He was born at 7½ months gestation by caesarean section in view of oligohydramnios, had a weak cry at birth, and had a birth weight of 2.1 kg. He required neonatal intensive care unit (NICU) stay for 7 days. Antenatal ultrasound (USG) was suggestive of a right hydronephrosis. Mother had hypothyroidism and was on thyroid supplements for past 5 years. At 4½ months of age, the child had only achieved partial head holding. He was on exclusive breast feeds and was immunized until date. Physical examination revealed failure to thrive (weight = 3.6 kg, <5<sup>th</sup> centile; length = 57 cm, <5<sup>th</sup> centile), microcephaly, hypertelorism, prominent forehead, large and low-set ears, bulbous nose, long philtrum, micrognathia [Figures 1 and 2], right postaxial polydactyly, long fingers [Figure 3], left lower limb oligodactyly [Figure 4], and deep sacral dimple. Genital examination was within normal limits. Other systems were normal. On investigation, hemoglobin was 6.7 gm/dL and white cell count was 30,800/cu.mm (73% polymorphs, 25% lymphocytes). Urine showed proteinuria (albumin 2+) with uncountable pus cells. Blood urea nitrogen was 14 mg/dL and creatinine was 0.7 mg/dL. USG abdomen showed right-sided hydronephrosis and a dilated pelvicalyceal system on the left side. Echocardiography revealed moderate-sized ostium secundum atrial septal defect (ASD) with left-to-right shunt and mild pulmonary hypertension. In view of renal and cardiac anomalies with dysmorphic features, he was suspected to have Smith-Lemli-Opitz syndrome and serum cholesterol levels were

### Introduction

Smith-Lemli-Opitz syndrome is an autosomal recessively inherited disorder<sup>[1]</sup> with equal preponderance in males and females. The disease incidence is very rare in African and Asian nations. A severe defect in cholesterol biosynthesis has been identified leading to abnormally low plasma cholesterol levels and elevated levels of the cholesterol precursor 7-dehydrocholesterol (7-DHC), the result of deficiency of 7-dehydrocholesterol reductase (DHCR7). The DHCR7 gene is localized to chromosome 11q11-13.<sup>[1]</sup> The clinical manifestations are the result of the reduced cholesterol, which is needed in many important biological processes and the accumulation of the toxic precursors of cholesterol as described above. We describe

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**Figure 1: Microcephaly, large and low-set ears, bulbous nose, retromicrognathia**



**Figure 2: Large forehead, hypertelorism, large and prominent philtrum**



**Figures 3: Polydactyly of right upper limb**



**Figures 4: Oligodactyly of left lower limb**

done, which were low (94 mg/dL [Normal = 150-250 mg/dL]). He was advised genetic testing but could not do the same due to non-affordability.

## Discussion

Prevalence of Smith-Lemli-Opitz syndrome has been estimated to be 1 in 20000.<sup>[1]</sup> Smith-Lemli-Opitz syndrome, first described in 1964, has been described in only one patient from India.<sup>[2,3]</sup>

The abnormality in cholesterol biosynthesis appears to explain much of the clinical phenotype of these children. The abnormalities include growth failure in form of moderately small at birth with subsequent failure to thrive; moderate-to-severe mental deficiency with

variably altered muscle tone (10% have IQ of 50-70); microcephaly with narrow frontal area; slanted or low-set ears; ptosis of eyelids; broad nasal tip with anteverted nares; micrognathia; simian crease; syndactyly of second and third toes; and post-axial polydactyly of hand and less often feet. Genitourinary abnormalities may include hypospadias, cryptorchidism, micropenis, bifid scrotum, upper tract anomalies, ureteropelvic junction obstruction, hydronephrosis, renal cystic dysplasia, renal duplication, renal agenesis, and reflux in 57% patients. Cardiac defects are seen in 50%, particularly endocardial cushion defect, hypoplastic left heart, ASD, patent ductus arteriosus, and membranous ventricular septal defect.<sup>[1]</sup> Similarly, our patient had facial dysmorphism with cardiac and renal anomalies and delayed milestones. Patients may have seizures, central nervous system malformations, eye abnormalities, cleft palate, macrostomia, bifid tongue, sensorineural hearing loss, hypoplasia of

thymus, adrenal enlargement, inguinal hernia, hepatic dysfunction, deep sacral dimple, rectal atresia, pyloric stenosis, cholestatic liver disease, malrotation of the gut, diaphragmatic hernia, anal stenosis, Hirschsprung's disease, and short neck occasionally.<sup>[1]</sup> Our patient did have deep sacral dimple.

These babies are often born in a breech presentation. Stillbirths and early neonatal deaths are not uncommon. Of those who survive, 20% die during the first year. Death might be due to pneumonia in most of them. Affected children are sociable, have better receptive than expressive language, and may be mechanically adept. Behavioral characteristics of autism and self-injurious and aggressive behavior are common.<sup>[1,3]</sup>

Treatment in form of dietary trials are under way in view of cholesterol deficiency being the major reason for the various manifestations of the syndrome. Cholesterol supplementation in the food is being evaluated as this would lead to decreased precursors of cholesterol, i.e., 7-DHC by feed-back inhibition. Doses of cholesterol from 20-300 mg/kg/day have been tried in some of the studies.<sup>[4,5]</sup> 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) have recently been studied as potential therapy for Smith-Lemli-Opitz syndrome. Statins would be expected to lower 7-DHC

concentrations. Interestingly, in contrast to the effects in healthy individuals, statins do not appear to lower plasma cholesterol levels in many of those with Smith-Lemli-Opitz syndrome. Prenatal diagnosis can be done at 16 weeks of gestation on an affected fetus on the basis of reduced amniotic fluid cholesterol and elevated 7-dehydrocholesterol with undetectable amniotic fluid unconjugated estriol.<sup>[4]</sup>

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