Brothers With Smith-Lemli-Opitz Syndrome

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KEY WORDS
Inherited metabolic error, autosomal recessive, developmental delays, cholesterol

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Conflicts of interest: None to report.

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J Pediatr Health Care. (2015) *29*, 97-103.

0891-5245/$36.00

Published online June 20, 2014.

http://dx.doi.org/10.1016/j.pedhc.2014.04.006

CASE PRESENTATION

Sibling A presented as a new patient to our pediatric practice at 28 months of age when his family moved into the community. Shortly after birth, he was diagnosed with Pierre-Robin–type cleft palate, hypospadias, cryptorchidism, and dysmorphic features. He underwent a genetic consultation at another academic center that did not reveal a syndromic diagnosis. The previous genetic evaluation consisted of normal peripheral blood chromosome studies, telomeric studies, and a fluorescence in situ hybridization study for microdeletion 15q11.2-13. The patient had a history of significant feeding problems in infancy leading to placement of a gastrostomy tube.

Upon his initial presentation to our clinic, physical examination revealed mildly dysmorphic features. The patient had mild microcephaly with a narrow forehead, pronounced eyelid ptosis, and epicanthal folds, but no cataracts. He had anteverted nares and moderate micrognathia. Palatal scarring was present from a repaired cleft palate. His ears were low set and slightly protuberant. He had hypoplastic thumbs bilaterally and two- to three-toe syndactyly bilaterally. Mild subglandular hypospadias was present. Surgical scars in the inguinal area were compatible with a previous bilateral orchiopexy. An area of repair was also noted where there had been a secondary urethral outlet, consistent with a partially repaired penoscrotal type of hypospadias. The boy's muscle mass was normal, although he was not yet walking. He spoke no words, but he was animated and interactive with the examiner. Because of concerns about an undiagnosed genetic condition and to establish care, the child was referred to the university medical center genetics clinic. His initial genetics clinic visit occurred one day after his mother delivered sibling B.

Sibling B was noted at birth to have features similar to those of his brother. Specifically, he had microcephaly, low-set ears, penoscrotal hypospadias, toe syndactyly, and micrognathia with mild craniofacial dysmorphism.

A genetics consultation suggested that this constellation of physical signs was characteristic of Smith-Lemli-Opitz syndrome (SLOS). Laboratory tests obtained at birth revealed a low total cholesterol level (24 mg/dl; normal, 115-169 mg/dl) and a markedly elevated 7-dehydrocholesterol level (86 μg/ml; normal, 0.16 ± 0.09 μg/ml). Because of poor feeding and a similar presentation in his brother, sibling B had a gastrostomy tube placed on day 5 of life. He subsequently was diagnosed with pyloric stenosis, which was repaired surgically at 5 weeks of age. A deoxyribonucleic acid (DNA) mutation analysis demonstrated two mutations consistent with the autosomal-recessive mechanism known to cause SLOS. He had a common mutation that involved an intron change (IVS8-1G-C) and a missense mutation (T93M) on the other allele.

Sibling B's diagnosis provided an answer to sibling A's history of developmental delays, feeding problems, and physical stigmata that were similar to those of sibling B (Table). Sibling A subsequently had a DNA mutational analysis that demonstrated the same abnormalities as the younger sibling. Sibling A also had a low serum total cholesterol level (77 mg/dL) and an elevated 7-dehydrocholesterol (7DHC) level (104 μg/ml) when it was checked as part of the expanded genetics evaluation.

CASE STUDY QUESTIONS

1. What is Smith-Lemli-Opitz syndrome?
2. What other syndromes would be in the differential diagnosis for a child with SLOS stigmata?
3. How is SLOS managed?
4. What is the primary care provider's role in caring for children with SLOS?

CASE STUDY ANSWERS

Smith-Lemli-Optiz Syndrome

1. What is Smith-Lemli-Optiz syndrome?

SLOS is an autosomal-recessive syndrome associated with multiple congenital anomalies, intellectual impairment, growth delay, and behavior problems. Smith, Lemli, and Opitz (1964) first described a genetic association of multiple congenital anomalies and mental retardation. Irons and colleagues (1994) determined that these patients had low levels of plasma cholesterol and elevated sterol precursors. Subsequent research discovered that SLOS was caused by a gene mutation for DHCR7 mapped to chromosome 11q12-13 (Moebius, Fitzky, Lee, Paik, & Glossmann, 1998; Waterham et al., 1998). SLOS is a more common inborn error of metabolism than was previously thought. It occurs in 1 in 20,000 to 40,000 births (Lowry & Yong, 1980; Opitz, 1994). SLOS occurs equally in males and females, and the carrier frequency is 1% to 2%, making it second to phenylketonuria as the most common treatable autosomal-recessive inherited error of metabolism causing mental retardation.

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Enzyme DRCR7 is responsible for the formation of cholesterol by reducing the 7-9 double bond of 7DHC, the final step in the synthesis of cholesterol (Figure 1). It is present in the plasma of healthy persons in trace quantities (Steiner, 2013). The inability to convert 7DHC to cholesterol results in low cholesterol levels and the accumulation of cholesterol precursors (7DHC and 8DHC). The abnormal cholesterol and noncholesterol sterol profiles are caused by deficient activity of 7DHC delta7-reductase (DHCR7), which converts 7DHC to cholesterol in the last step of the cholesterol biosynthesis pathway (Chan et al., 2009).

Cholesterol is a major constituent of cell membranes and myelin and is essential for the synthesis of steroid hormones and bile acids. It is postulated that the low plasma cholesterol levels found in patients with SLOS cause limited cholesterol availability to the central nervous system, creating suboptimal neural growth that results in mental retardation. As in other errors of metabolism, the extent of cholesterol deficiency correlates with the severity of the clinical presentation (Tint et al., 1994). Secondary biochemical abnormalities may develop as a result of cholesterol deficiency. For example, bile acid deficiency can cause fat malabsorption and fat-soluble vitamin deficiency, leading to failure to thrive, night blindness, immune system dysfunction, rickets, and osteomalacia. Cholestatic liver disease may develop.

Clinical indications for DHCR7 measurements include developmental delay of unknown cause plus any of the following: facial features suggestive of SLOS, syndactyly of the second and third toes, hand anomalies, genital anomalies, intrauterine growth