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CASE REPORT

Keeping you on your toes: Smith–Lemli–Opitz Syndrome is an easily missed cause of developmental delays

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Abstract

Smith-Lemli-Opitz syndrome (SLOS) is a relatively common genetic cause of developmental delay and may only present in conjunction with 2,3 toe syndactyly. This case series illustrates a milder phenotype of SLOS, where the predominant findings are neurocognitive in the presence of 2,3 toe syndactyly.

KEYWORDS

7-Dehydrocholesterol, biochemical genetics, diagnosis, metabolism, smith–lemli–opitz syndrome

1 | INTRODUCTION

Smith–Lemli–Opitz syndrome (OMIM # 270400) is one of several inborn errors of metabolism (IEMs) that can present with developmental delay and is not detected by newborn screening or a urine metabolic screen. It is an autosomal recessive disorder caused by bi-allelic pathogenic variants in the *DHCR7* gene located on the long arm of chromosome 11 (Chr 11q13.4). *DHCR7* encodes for the enzyme 7-dehydrocholesterol reductase (EC1.3.1.21), which catalyzes the reduction of the delta-7 bond in sterols (7-dehydrocholesterol and 7-dehydrodesmosterol). These sterols are final intermediates in the pathway of cholesterol biosynthesis. Deficiency of this enzyme leads to the accumulation of 7DHC (with or without 8-dehydrocholesterol) and normal to decreased cholesterol levels.[1]

Estimated incidence rates of SLOS are between 1:20,000 and 1:60,000.[2] Surprisingly, Lazarin and colleagues estimate that the carrier frequency of *DHCR7* variants to be approximately 1:54 in the Northern European population[3]; which is higher than expected based on the above incidence data. This may be in keeping with the reported 80% prenatal mortality rate,[4] which is suggestive of an even higher disease burden.

Simone Coupe and Ashley Hertzog contributed equally to this work as first co-authors.

2 | CASE 1

A three-year-old boy was referred for investigation of developmental delay, especially expressive language development, and poor growth. He was the second child born to Caucasian, non-consanguineous parents after an unremarkable pregnancy. At birth, he weighed 3.2 kg and was 51 cm long, with a head circumference of 35.5 cm. He had a history of poor weight gain and feeding difficulties with recurrent abdominal discomfort and abnormal stools in his first year of life. At 12 months of age, a urine metabolic screen (comprising organic acid, amino acid, purine and pyrimidine, and creatine and guanidinoacetate analyses) showed no significant abnormalities. At 3 years of age, he had significantly delayed receptive and expressive language (with only 12 single words) and could only follow single-step instructions. He made good eye contact and was able to engage in reciprocal play. From a gross motor perspective, he crawled at 7 months and walked at 18 months of age. A chromosomal microarray was normal.

On examination, his weight, height, and head circumference were on the 5th, 30th, and 10th centiles, respectively. He had subtle, distinctive facial features (anteverted nares, a tented upper lip (Figure 1A), slightly posteriorly rotated ears, bilateral 2,3 toe syndactyly (Figure 1B), and pes planus. Examinations of the cardiovascular, respiratory and abdominal systems and external genitalia were normal.

Biochemical genetic investigations showed an elevated plasma 7-dehydrocholesterol (7DHC) of 264 μmol/L (reference range: <38.3) and cholesterol level at the lower limit of the normal range, 1.8 mmol/L (research reference range specific for SLOS patients: 1.8–5.2) consistent with Smith–Lemli–Opitz syndrome (SLOS).

Sanger sequencing of the *DHCR7* gene showed compound heterozygosity (in *trans*) for two pathogenic variants, (NM_001360.2:c.866C > T (p.Thr289Ile) and NM_001360.2:c.964-1G > C (p.Gly322Lysfs*136)). Parental segregation confirmed that the NM_001360.2:c.866C > T variant was paternally inherited and the NM_001360.2:c.964-1G > C variant was maternally inherited (Figure 2).

Treatment with cholesterol powder supplementation was initially commenced at 115 mg/kg/day. The patient is now 4.5 years of age, and his cholesterol supplementation has been increased to 180 mg/kg/day. There has been some improvement in his general development, most notably with his expressive language. Overall, he has a good sleep pattern and does not display aggressive behavior. However, he gets angry when frustrated and exhibits teeth grinding. He currently undergoes speech and occupational therapy. A renal ultrasound was normal.

3 | CASE 2

Case 2, the older sister of case 1 was also diagnosed with SLOS (7DHC 148 μmol/L (reference range: <38.3) and cholesterol 2.9 mmol/L (research reference range specific for SLOS patients: 1.8–5.2) at 6 years of age subsequent to her younger brother. It is presumed that she has the same pathogenic variants as her brother; however, molecular confirmation is unavailable at this time.

At 2 years of age, she was diagnosed with autism spectrum disorder, which evolved into a broader global developmental delay phenotype. In particular, she has significant expressive and receptive language delay, behavioral disturbances and a disturbed sleep pattern with frequent overnight awakening. She attends specialized support classes in a mainstream school and is making progress with her learning.

Clinical examination showed short stature (5th centile), small head circumference (2nd centile), subtle distinctive facial features including ptosis, a long philtrum, low set ears (Figure 1C), and 2,3 toe syndactyly. A renal ultrasound showed bilateral small kidneys for age (<5th centile).

Cholesterol powder supplementation was commenced at 190 mg/kg/day. She attends a combination of mainstream and special education classes. She receives fortnightly speech and occupational therapy and is making developmental progress, but still has difficulty with word articulation. Targeted dietary interventions have been commenced to assist with her restrictive eating.

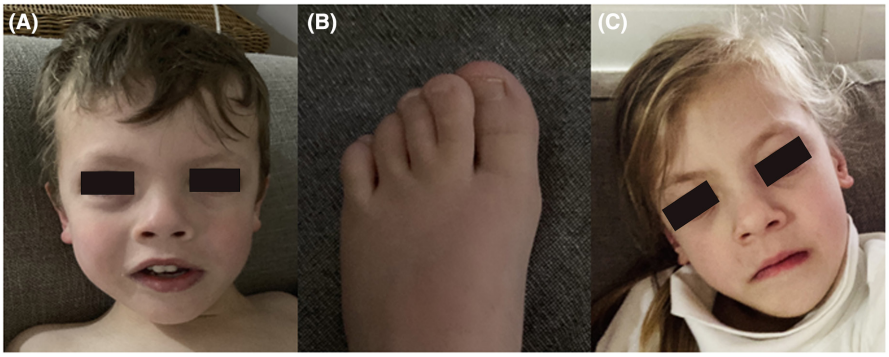

FIGURE 1 Phenotypic features, including distinctive facial findings, in Smith–Lemli–Opitz syndrome: (1A) Case 1 with anteverted nares and a tented upper lip, (1B) Case 1 with 2,3 toe syndactyly, (1C) Case 2 with ptosis, long philtrum, and low set ears

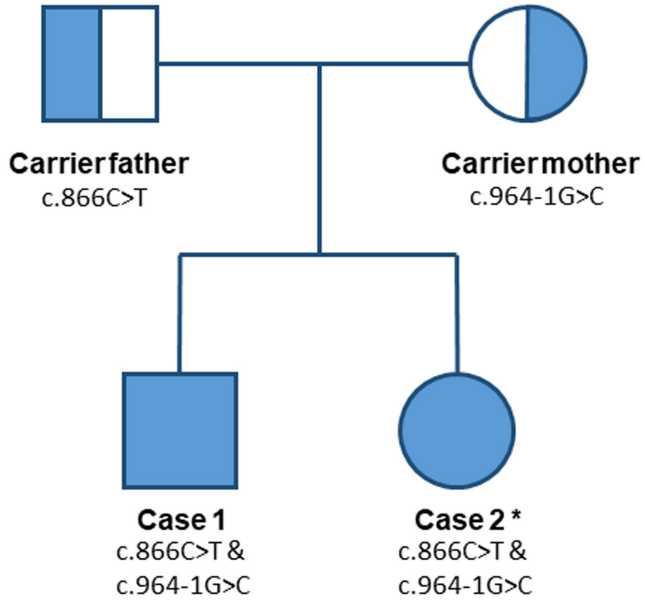

FIGURE 2 Familial pedigree depicting autosomal recessive inheritance of the DHCR7 variants. Case 1 and Case 2 (both with clinical and biochemical features consistent with SLOS) inherited an affected allele from each parent. *Genotype assumed, but not molecularly confirmed

4 | DISCUSSION

The clinical spectrum of SLOS is broad, ranging from the prenatal mortality to subtle distinctive facial features and 2,3 toe syndactyly.[5] Congenital anomalies including microcephaly, growth restriction, structural heart defects, and genitourinary abnormalities are prevalent in the vast majority of severe patients. The two cases discussed in this report illustrate a milder phenotype where the predominate findings are neurocognitive (autistic features, developmental delays, sleep issues, and behavioral disturbances) in the presence of 2,3 toe syndactyly (Figure 1). Donoghue and colleagues reported 18 patients with SLOS of varying clinical severity, noting that patients with milder phenotypes have higher presenting cholesterol levels (typically at the lower end of the normal range).[6] In keeping with this, the presenting cholesterol levels of Cases 1 and 2 were within the reference range. However, it is important to note that Case 1's cholesterol level was borderline low; this may have led to an earlier diagnosis due to increased neurocognitive abnormalities when compared to his sister. It may be that without the diagnosis in Case 1, Case 2 may have had an even longer diagnostic odyssey. This also highlights the intra-familial variability of clinical manifestations as previously reported.[7]

Despite the high level of phenotypic variability, 2,3 toe syndactyly appears to be an almost ubiquitous finding.[7] In patients presenting with developmental delay, a thorough physical examination should be performed for the observation of 2,3 toe syndactyly, in turn prompting the analysis of 7DHC levels in plasma.

However, it is also important to consider that the causes of 2,3 toe syndactyly are broad. Mild 2,3 toe syndactyly is a common anatomical variant. More significant 2,3 toe syndactyly that occurs in isolation, also known as syndactyly type I-a (with an estimated incidence of 1:2000), is typically non-syndromic and is more common than SLOS.[8,9] There are other syndromic causes of 2,3 toe syndactyly (such as Scott craniodigital syndrome, Timothy syndrome); however, these disorders often have other distinctive clinical features, are less common than SLOS, and would require molecular testing for diagnosis.[10] Other cholesterol biosynthetic defects (including squalene synthase deficiency) are also in the differential diagnoses and can be biochemically diagnosed, but are exceedingly rare.[11]

As with many rare genetic metabolic disorders, there is a lack of evidence regarding optimal management strategies.[12] Despite the limited evidence for the efficacy of cholesterol supplementation, early diagnosis is beneficial. An early diagnosis will shorten the diagnostic odyssey, provide closure to families, allow for early interventional allied health therapies, and restore parental reproductive confidence. Therefore, SLOS should be considered in patients presenting with developmental delay in conjunction with the finding of 2,3 toe syndactyly. Furthermore, it is recommended that plasma 7DHC analysis be a first tier investigation for these patients as this specialized biochemical genetic testing is faster and more cost effective than molecular genetic investigations.

AUTHOR CONTRIBUTIONS

Simone Coupe involved in performing literature review, submission of ethics approval, performing laboratory investigations, and drafting of manuscript. Ashley Hertzog involved in planning of project, performing literature review, laboratory diagnostic expertise and result review, drafting and editing of manuscript. Carolyn Foran involved in performing literature review, submission of ethics approval, performing laboratory investigations, drafting of manuscript, and submission process. Adviye Ayper Tolun involved in laboratory diagnostic expertise and result review, provision of resources, drafting and editing manuscript. Megan Suthern involved in clinical management of patients, drafting and editing of manuscript. Clara Chung involved in clinical management of patients, clinical genetics expertise, drafting and editing of manuscript. Carolyn Ellaway involved in clinical management of patients, clinical genetic and metabolic expertise, editing manuscript, correspondence with journal

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CONFLICT OF INTEREST

No authors have any conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ETHICAL APPROVAL

This project received ethics approval from the Sydney Children's Hospital Network Human Research Ethics Committee (Project Number CCR2021/20), and signed consent was obtained.

CONSENT

Written informed consent was obtained from the patients' parents to publish this report in accordance with the journal's patient consent policy.

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