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Case Report

Clinical Presentation and Diagnosis of Smith-Lemli-Opitz Syndrome: First Case Report from Sudan

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Abstract

Background: Smith-Lemli-Opitz syndrome (SLOS) is a congenital autosomal recessive disorder characterized by defective cholesterol metabolism, attributable to a deficiency of the enzyme 7-dehydrocholesterol reductase (*DHCR7*) caused by mutations in the *DHCR7* gene maps to chromosome 11q13. SLOS is linked to a wide variety of congenital anomalies, failure to thrive, dysmorphological features, and intellectual disabilities caused by cholesterol metabolic abnormalities.

Case Report: A 58-day-old Sudanese infant, the third offspring of parents in a consanguineous marriage, was brought to the hospital due to failure to thrive and delayed growth. Clinical examination revealed stunted growth, hypotonia, microcephaly, distinctive facial dysmorphism characterized by a broad nasal tip with anteverted nostrils and micrognathia, post-axial polydactyly in both upper and lower extremities, and ambiguous genitalia. A biochemical analysis revealed decreased plasma cholesterol levels alongside an increase in 7-dehydrocholesterol (7-DHC) concentration. The echocardiographic evaluation confirmed the presence of an atrial septal defect (ASD) while karyotyping demonstrated a normal male chromosomal pattern (46, XY). Based on these findings, a diagnosis of SLOS was made. Following thorough genetic counseling with the parents, the patient was referred to a pediatric tertiary care center for advanced management and continuous monitoring.

Conclusion: Clinical presentation of SLOS cases can widely vary, from minor dysmorphic features to severe congenital and mental anomalies which may lead to miscarriage, so a high index of suspicion is required to expedite referral and diagnosis using available, affordable, specific biochemical, genetic testing, especially in limited health resources areas, where expensive molecular investigations are not available. Early diagnosis and effective genetic counseling may help to minimize comorbidity and enhance the quality of life for the whole family.

Keywords: Smith-Lemli-Opitz syndrome, SLOS, ambiguous genitalia, chromosomal analysis

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1. Introduction

Smith-Lemli-Opitz syndrome (SLOS) is a metabolic syndrome combined with several congenital malformations and intellectual disability [1]. The prevalence of SLOS is estimated to range from 1 in 20,000 to 1 in 70,000 live births. Both males and females are equally affected [2].

The disorder is caused by an inborn error of cholesterol biosynthesis, attributable to mutations in the 7-dehydrocholesterol reductase (*DHCR7*) gene, located on chromosome 11q12-13, resulting in hypocholesterolemia and accumulation of 7-dehydrocholesterol (7-DHC) precursors [3]. It is inherited as an autosomal recessive genetic condition [4]. The carrier frequency of this genetic trait appears to be more prevalent among individuals of Caucasian ancestry, particularly those of Northern European origin, where it reaches approximately 1–2%. In contrast, it is quite rare among people of Asian or African descent [5].

The disorder is clinically characterized by failure to thrive, mental impairment, and multiple congenital anomalies, including dysmorphic faces, cleft palate, congenital heart disease, ambiguous genitalia, polydactyly, and second/third toe syndactyly. Mildly affected individuals (SLOS type I) may exhibit only subtle dysmorphic faces, learning disabilities, feeding difficulties, and failure to thrive, whereas, in the severe form of the disease (SLOS type II), patients suffer from fatal cardiac and brain malformations, microcephaly, cleft palate, multi-organ system failure, and complete sex reversal [6]. Miscarriage, stillbirth, and intrauterine fetal death often occur during the first trimester [7].

The diagnosis of SLOS relies on identifying distinctive dysmorphic features, clinical physical examination findings, and biochemical testing for serum cholesterol and its precursor levels. In mild presentation cases, confirmatory molecular analysis for the *DHCR7* gene mutation may be warranted to provide additional diagnostic certainty.

To our knowledge, this is the first documented case of SLOS in Sudan. The diagnostic approach in this report centered on identifying patients' unique dysmorphic traits, observing physical findings, utilizing available biochemical tests, and using the available chromosomal analysis as a screening test to rule out trisomy 13, 18, and other chromosomal syndromes and exclude the expensive and inaccessible molecular test. This highlights the importance of adopting such a diagnostic approach in regions with limited healthcare resources, where access to advanced molecular genetic technologies, such as DNA sequencers, is often lacking.

2. Case Presentation

A 58-day-old infant was delivered at the hospital following a term pregnancy complicated by antepartum hemorrhage during the first and second trimesters, which was managed conservatively. The infant exhibited immediate crying at birth, was placed with the mother, and breastfed. Concerns arose due to inadequate weight gain since birth, with the mother observing poor suckling, particularly during the second month, accompanied by regular bowel movements and an absence of vomiting or regurgitation. The infant is the third child of a 37-year-old healthy mother and a 40-year-old father, both first cousins with no familial history of similar conditions. They have two healthy older children and no record of prior miscarriages. The patient was referred to the Elite

Health Services Center for genetic diagnosis and counseling.

The examination showed significant growth retardation, with a weight of 1.5 kg (below the third percentile), a length of 46 cm (below the third percentile), and a head circumference of 30 cm (between the 50th and 97th percentile). The baby presented with dysmorphic features, including microcephaly, a broad nasal tip with anteverted nostrils, micrognathia, low-set ears, and post-axial polydactyly on hands and feet (Figure **1**). The genitalia were ambiguous, with an inguinal palpable left testis. Additionally, the baby displayed hypotonia, with normal eyes, skin, and back. Primitive reflexes were observed, except for the suckling reflex.

Investigations revealed mild macrocytic hypochromic anemia, normal arterial blood gases, random blood glucose, chest X-ray, and normal liver and renal function tests. The serum cholesterol level measured was low at 95 mg/dL, which falls below the normal 150–200 mg/dL range. Additionally, a significantly elevated plasma concentration of 7-DHC, recorded at 760 μmol/L, was observed, in contrast to the normal range of <2.5 μmol/L. This analysis was conducted using ultraviolet spectrophotometry at the Elite Health Services Center laboratory. Echocardiography revealed a small atrial septal defect (ASD). The left testis was found in the left inguinal canal on ultrasound, but the right testis could not be located, and no uterine structure was seen. Chromosomal analysis showed a normal male karyotype (46, XY; Figure **2**). Accordingly, a diagnosis of SLOS was established. After profound counseling, the patient was referred to the pediatric tertiary hospital to be followed collaboratively with a multidisciplinary team to optimize patient care.

3. Discussion

Since 1964, when David Smith, Luc Lemli, and John Opitz described the first true metabolic syndrome of multiple congenital malformations [6], SLOS has been classified as a rare genetic condition characterized by prenatal and postnatal growth retardation [8]. The clinical spectrum of SLOS manifestations is broad, including intrauterine growth retardation (IUGR), short stature, failure to thrive, distinctive craniofacial dysmorphic features, limb deformities, intellectual and behavioral disabilities, in addition to a variety of multi-organ congenital anomalies in the heart, genitalia, colon, and adrenal glands [9]. The impact of this wide range of disabilities results in significant morbidity for the affected child and exerts pressure on the entire family by diminishing the quality of life.

Previous studies reported the inverse correlation between the plasma cholesterol concentration and clinical severity score. Given its numerous functions, cholesterol has an essential role in myelin sheath synthesis and blood–brain barrier formation. Insufficient concentrations will affect the nervous system, leading to behavioral and intellectual impairments [11]. The relationship between severity score and 7-DHC concentration within SLOS patients with normal serum cholesterol concentrations, representing 10% of cases, showed minimal correlation [12]. As in the present case, genital ambiguity is a frequent feature of male SLOS patients, reported in 71% of cases. Patients may also present with hypospadias and micropenis to the complete absence of external virilization of genitalia due to the inability to synthesize cholesterol, the precursor of testosterone [13].

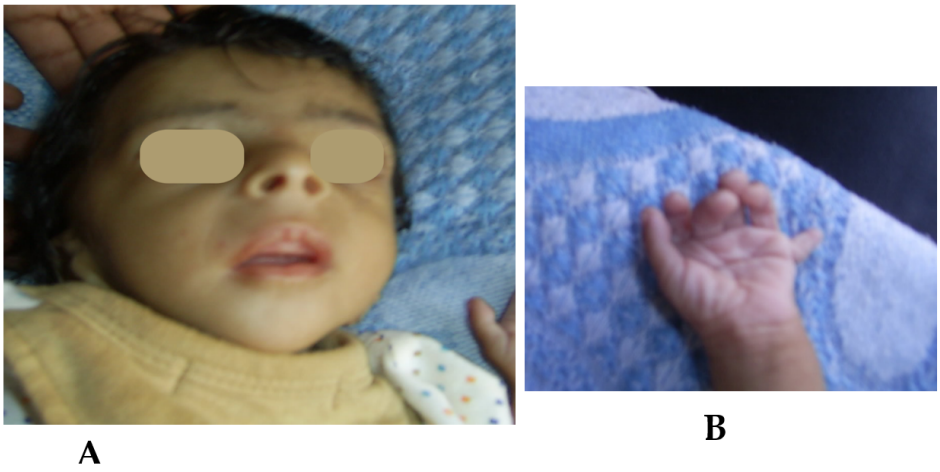

Figure 1: Dysmorphic features of a patient with SLOS: (A) microcephaly, a broad nasal tip with anteverted nostrils, micrognathia, and low-set ears; (B) post-axial polydactyly on hands.

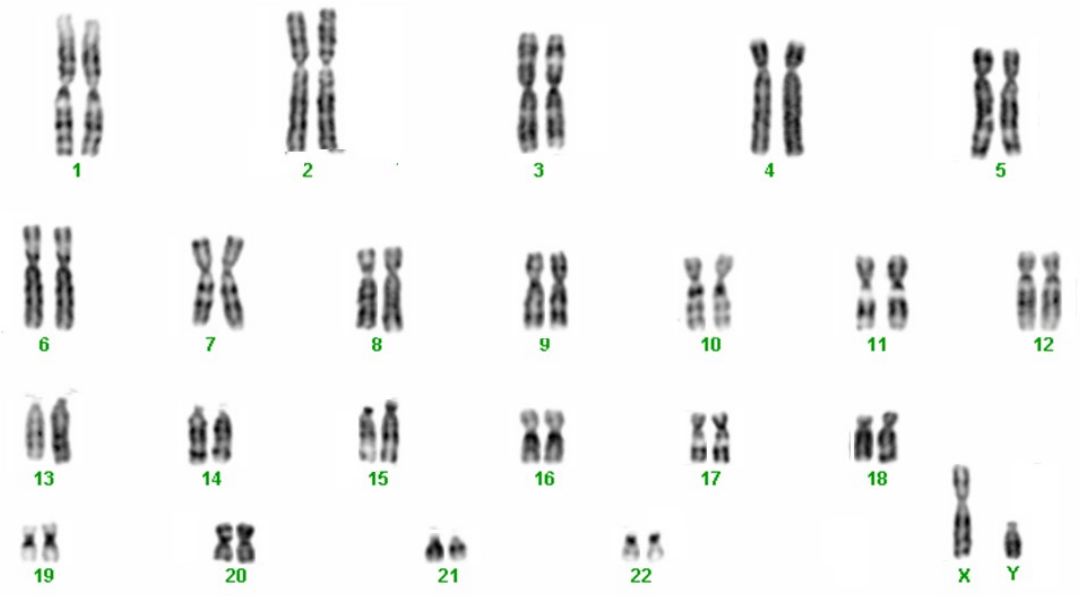

Figure 2: Normal male karyotype (46, XY).

SLOS is frequently reported in European populations and Western countries compared to Asia and Africa, which have lower prevalence and limited information [14]. A few cases of SLOS have been documented in Africa, particularly in South Africa and several North African nations such as Egypt and Morocco, where advanced genetic testing is more readily available. These cases typically reflect the universal presentation of SLOS, often showing similar clinical characteristics. However, due to underdiagnosis and limited reporting, the true prevalence of SLOS in Africa is likely underestimated [15, 16].

The disease is inherited as an autosomal recessive trait; therefore, it is expected to have a higher prevalence in populations characterized by elevated rates of consanguineous and intratribal marriages, as commonly observed in Sudan [17]. Nevertheless, very few, if any, documented cases of SLOS exist in this country. This intriguing observation raises the possibility of undetected cases, potentially stemming from

the absence of definitive confirmatory molecular tests and/or the inherent uncertainty associated with identifying the condition, particularly in individuals displaying mild manifestations of the disease.

Certain clinical traits of SLOS, such as cleft lip and cleft palate, cardiac defects, and polydactyly, overlap with features seen in other chromosomal and metabolic disorders. For example, trisomy 13 (Patau syndrome) and trisomy 18 (Edwards syndrome) can present with growth retardation and congenital anomalies that are similar to those found in SLOS. However, these trisomies are often characterized by specific pathognomonic features: Edwards syndrome is marked by a distinctive hand posture with overriding fingers, nail hypoplasia, a short hallux, and a short sternum. In contrast, the hallmark signs of Patau syndrome include orofacial clefts and holoprosencephaly, which can manifest as cyclops or cebocephaly. Recognizing these clinical distinctions can aid in differentiating these syndromes from SLOS. Additionally, congenital adrenal hyperplasia (CAH), particularly the salt-wasting form, may mimic some symptoms of SLOS, such as vomiting, developmental abnormalities, and failure to thrive. However, CAH is typically associated with electrolyte imbalances, which are not characteristic of SLOS [19].

We have diagnosed this infant based on a physical examination focusing on the dysmorphic features, supported by a biochemical test that revealed low plasma cholesterol and elevated 7-DHC concentration. Furthermore, we conducted a chromosomal analysis test, which proved a normal male karyotype, resolving the concern of ambiguous genitalia and excluding other possible differential diagnoses such as trisomy 18, trisomy 13, Williams syndrome, and Wolf-Hirschhorn syndrome. As in many developing countries with limited healthcare resources, confirmatory tests such as *DHCR7* gene molecular sequencing are not readily available in Sudan [20]. The confirmatory diagnostic test for SLOS identifies mutations in the *DHCR7* gene. Many authors have emphasized that SLOS can be rapidly recognized through clinical evaluation and biochemical testing, particularly in regions facing comparable limitations [21].

Despite resource constraints, heightening the awareness of treating physicians regarding SLOS, other inborn errors of metabolism, and dysmorphic children is essential. This heightened awareness will expedite referrals and diagnoses through feasible investigations, optimizing patient care. Assembling a multidisciplinary team of specialists, including pediatricians, geneticists, neurologists, and other specialists, to improve patient conditions is crucial to addressing the diverse clinical features of SLOS. Furthermore, providing families with comprehensive counseling on the disorder, expected complications, and family planning is imperative, given the significant genetic probability of a 25% risk for each future pregnancy [9]. Supplementation serves as a foundational aspect of treatment for SLOS. Dietary modifications that include cholesterol-rich foods are frequently recommended, as they can partially rectify cholesterol deficiencies and may enhance growth, development, and behavioral outcomes. Nevertheless, the prognosis for individuals with SLOS is contingent upon the severity of the condition. Typically, milder cases demonstrate a more favorable quality of life than severe cases, which may be linked to substantial morbidity and mortality [22].

4. Conclusion

The broad phenotypic spectrum of SLOS increases the need for a high index of suspicion to manage such disorders with significant clinical variability. Combining notorious congenital anomalies in the presence of low cholesterol concentration and elevated 7-DHC level with a normal karyotype supports the diagnosis of SLOS.

Declarations

Acknowledgments

None.

Ethical Considerations

The study was approved by the Ethical Committee at Al Neelain Stem Cell Center, Al Neelain University. The patient's father signed the informed consent forms and permitted us to document the case.

Competing Interests

The authors declare no conflict of interest.

Availability of Data and Material

Data sets are available upon request.

Funding

None.

Abbreviations and Symbols

SLOS: Smith-Lemli-Opitz syndrome

DHCR7: 7-dehydrocholesterol reductase

7-DHC: 7-dehydrocholesterol

ASD: Atrial septal defect

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