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Smith-Lemli-Opitz Syndrome in Trisomy 13: How Does the Mix Work?

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BACKGROUND: Trisomy 13 and Smith-Lemli-Opitz syndrome (SLOS) are both well-recognized multiple congenital anomaly/mental retardation syndromes. **CASE:** In this report we describe a male newborn with trisomy 13 who also has features of SLOS, such as 2/3 toe syndactyly and a shawl-like scrotum. Biochemical analysis was consistent with SLOS, and limited molecular analysis revealed 1 mutation in the *DHCR7* gene. **CONCLUSIONS:** The challenges in establishing the diagnosis of SLOS in this patient are presented and the unique coexistence of the 2 major malformation syndromes is discussed. Given the overlapping phenotype of the 2 syndromes, our report should encourage further research on cholesterol biosynthesis in patients with trisomy 13. *Birth Defects Research (Part A) 73:569–571, 2005.* © 2005 Wiley-Liss, Inc.

Key words: SLOS; trisomy 13; neonate; shawl-like scrotum; syndactyly

INTRODUCTION

Trisomy 13 and Smith-Lemli-Opitz syndrome (SLOS) are both well-recognized multiple congenital anomaly/mental retardation syndromes. A number of clinical features are shared by the 2 disorders. We report a newborn boy with trisomy 13 with a biochemical profile suggestive of SLOS. The unique clinical profile of this patient is reviewed. To the best of our knowledge, this is the first time such an association has been reported.

CASE

This patient was the first child of his unrelated 20-year-old Jamaican/Portuguese mother and 24-year-old Haitian father. A prenatal ultrasound scan at 19 weeks of gestation revealed increased nuchal thickness. A subsequent ultrasound scan at 30 weeks of gestation was significant only for decreased abdominal circumference. The parents declined amniocentesis and a maternal serum triple screen. There was no report of teratogenic exposures, and the family history was unremarkable.

The delivery was vaginal and spontaneous at 37 weeks of gestation. Apgar scores were 8 and 9, at 1 and 5 min; respectively. The neonatal birth weight was 2.7 kg (between the 5th and 10th centile), length was 45 cm (below the 3rd centile), and head circumference was 32 cm (below the 3rd centile) with a wide-open anterior fontanel. Dysmorphic features included a prominent and broad nasal bridge, right anotia, and left microtia (Fig. 1A and B). Bilateral microphthalmia and corneal clouding were noted. There was bilateral postaxial polydactyly of hands and feet and bilateral 2/3 toe syndactyly (Fig. 2). His scrotum was shawl-like and the right testicle was undescended (Fig. 3). Magnetic resonance imaging of the brain showed that it was undersulcated, with prominent Sylvian fissures in addition to delayed myelination. An echocardiogram revealed the presence of a patent foramen ovale, a moderate-sized patent ductus arteriosus and a secundum atrial septal defect.

Although trisomy 13 was suspected, the combination of microcephaly, polydactyly, and 2/3 toe syndactyly was also suggestive of SLOS. Trisomy 13 was confirmed at 72 hr of age on peripheral blood in all cells analyzed. On the basis of the karyotype result, the parents elected to withhold active respiratory support. The patient developed multiple prolonged apneic episodes and died at 6 days of age. The family declined autopsy of the child. Subsequent to our patient's death, he was found to have elevated 7-dehydrocholesterol (7-DHC) at 0.4 mg/dl (normal: 0.036 ± 0.02 mg/dl) and 8-dehydrocholesterol (8-DHC) at 0.32 mg/dl (normal: 0.062 ± 0.036 mg/dl) and low cholesterol at 45 mg/dl. These results suggested a diagnosis of SLOS. Because no tissue was available as a source of DNA after the patient's death, we sought to identify the carrier status of both parents for SLOS by using molecular techniques. A previously unreported missense mutation, G70S,

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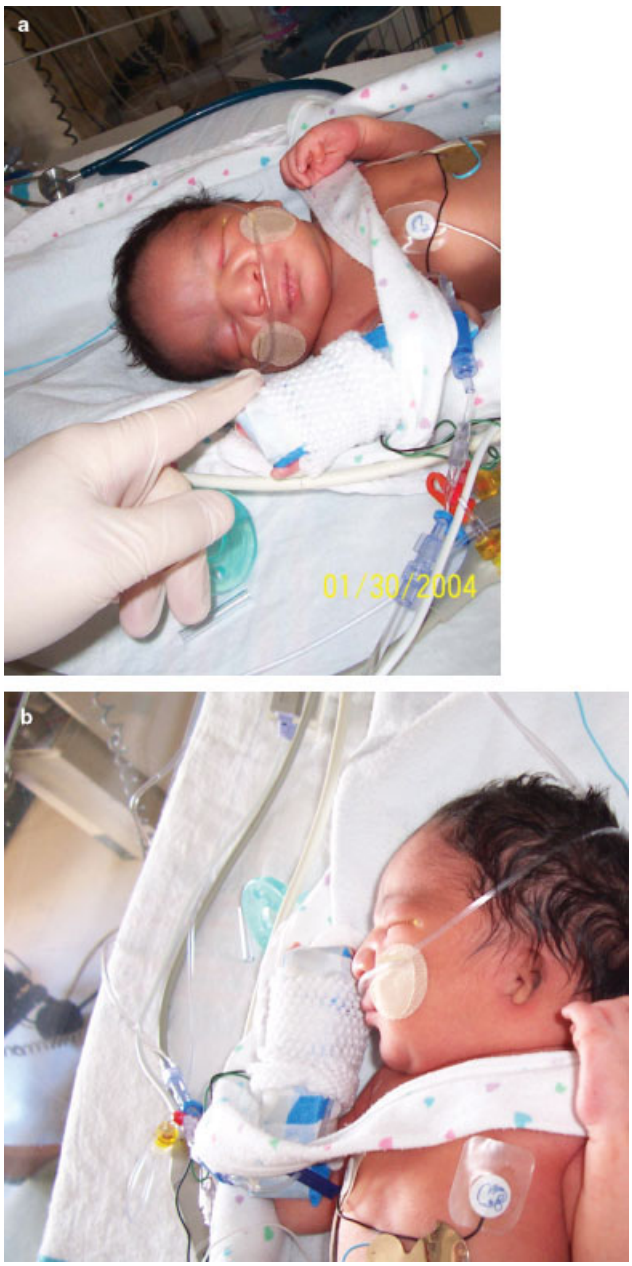

Figure 1. Front view (**A**) and profile (**B**) of the patient at 1 day of age, depicting the prominent and broad nasal bridge and left microtia. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

was identified in the father's *DHCR7* gene, confirming his possible carrier status. Analysis of the maternal *DHCR7* gene, however, only identified 2 polymorphisms: T77T and G424G, of uncertain clinical significance.

DISCUSSION

The incidence at birth of SLOS and trisomy 13 is 1 in 20,000–40,000 and 1 in 13,000, respectively (Gardner and Sutherland, 1996; Lowry and Yong, 1980). The coexistence of both conditions is therefore rare and, to the best of our knowledge, has not been reported previously. Confirmation of SLOS in our patient, despite his classical biochemical derangement, was challenged by several facts. First, both disorders are associated with microcephaly, polydactyly, small size at birth, cryptorchidism, and delayed myelination (Moraine et al., 1972; Pfeiffer and Santelmann, 1977; Castilla et al., 1998; Gross and Bombard, 1998; Ryan et al., 1998; Dar and Gross, 2000; Patterson, 2002; Kiesler and Ricer, 2003); thus, it was difficult to diagnose SLOS on clinical grounds in our patient. Second, lack of DNA from our patient left us no option but to test both parents for mutations in *DHCR7*. Although we were only able to demonstrate a previously unreported mutation in the father, the possibility exists that the mother also has a pathogenic mutation that we could not detect. Third, a maternal serum triple screen, which can be associated with low estriol when the fetus has SLOS (Rossiter et al., 1995; Palomaki et al., 2002), was declined by the parents. Lastly, confirmation of SLOS at autopsy was not possible as it was also declined by the parents. For these reasons, the diagnosis of SLOS, even though we believe it is likely, could not be unequivocally proven. This uncertainty was discussed with the parents and we offered them the option of prenatal diagnosis of SLOS and trisomy 13 in future pregnancies by

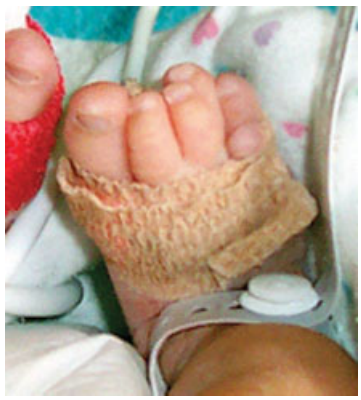

Figure 2. The right foot of the patient, showing 2/3 toe syndactyly and polydactyl. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

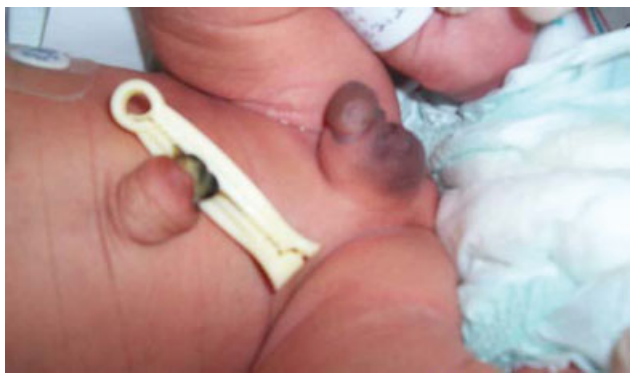

Figure 3. The genitalia of the patient showing a shawl-like appearance of the scrotum. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

measuring the level of 7DHC in the amniotic fluid and cytogenetic analysis of amniocytes, respectively.

Syndactyly has been seen in trisomy 13 only when triploidy or other chromosomal aberrations were present (James et al., 1969; Phelan et al., 2001). A shawl-like scrotum has not been reported in association with trisomy 13. The latter 2 abnormalities, i.e., syndactyly and shawl-like scrotum, are features of SLOS. Although shawl-like scrotum has been reported only in a few clinical descriptions of SLOS, 2/3 toe syndactyly is considered to be the most consistent feature of the syndrome (Itokazu et al., 1992; Aalfs et al., 1996; Ryan et al., 1998; Kelley and Hennekam, 2000). We believe the diagnosis of SLOS may be responsible for these 2 unusual findings in our patient. Although the gene responsible for SLOS is on a different chromosome (*DHCR7* on 11q12–13), we were interested in reviewing the sterol metabolites in other patients with trisomy 13, given the number of similar features shared by the 2 disorders. We found 1 neonate in our institution with trisomy 13 whose sterol metabolites were fully investigated as part of his diagnostic evaluation. All the sterol metabolites were within the normal range (unpublished results). This does suggest that the association we observed in our patient was a coincidence. Nevertheless, we believe this patient represents a rare opportunity to observe the overlapping effect of 2 major malformation syndromes. Future research in the field of human development may provide a more comprehensive insight into this interaction at a molecular level. Should cholesterol biosynthesis be altered in trisomy 13, this may shed further light on the pathoetiology of the trisomy 13 malformation picture and may have clinical implications for long-term survivors of trisomy 13.

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