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Normal IQ is possible in Smith-Lemli-Opitz syndrome

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Abstract

Children with Smith-Lemli-Opitz syndrome (SLOS) are typically reported to have moderate to severe intellectual disability. This study aims to determine whether normal cognitive function is possible in this population and to describe clinical, biochemical and molecular characteristics of children with SLOS and normal intelligent quotient (IQ). The study included children with SLOS who underwent cognitive testing in four centers. All children with at least one IQ composite score above 80 were included in the study. Six girls, three boys with SLOS were found to have normal or low-normal IQ in a cohort of 145 children with SLOS. Major/multiple organ anomalies and low serum cholesterol levels were uncommon. No correlation with IQ and genotype was evident and no specific developmental profile were observed. Thus, normal or low-normal cognitive function is possible in SLOS. Further studies are needed to elucidate factors contributing to normal or low-normal cognitive function in children with SLOS.

Keywords

development; IQ; Smith-Lemli-Opitz

1 | INTRODUCTION

Smith-Lemli-Opitz syndrome (SLOS, OMIM #270400) is an autosomal recessive neurodevelopmental disorder characterized by multiple congenital anomalies and facultative

intellectual disability. It is caused by mutations in the *DHCR7* gene encoding 7-dehydrocholesterol reductase (7DHCR), the enzyme that catalyzes the final step in cholesterol biosynthesis (Battaile, Battaile, Merkens, Maslen, & Steiner, 2001; Wassif et al., 1998; Waterham et al., 1998). Reduced activity of 7DHCR typically leads to low levels of cholesterol, but markedly increased levels of precursor 7DHC and its isomer, 8DHC in blood and tissues.

Typical SLOS manifestations include intellectual disability, growth retardation, minor craniofacial anomalies, microcephaly, 2–3 toe syndactyly, and various malformations (DeBarber, Eroglu, Merkens, Pappu, & Steiner, 2011; Nowaczyk and Irons, 2012). Expressivity varies widely; severe forms can result in fetal or neonatal death, while mild cases may have subtle phenotypes. Most individuals reported with SLOS have moderate to severe intellectual disability. A strong correlation of biochemical parameters and severity score with development has been reported previously (Cunniff, Kratz, Moser, Natowicz, & Kelley 1997; Kratz and Kelley, 1999; Ryan et al., 1998; Sikora et al., 2004).

Normal to low-normal cognitive functioning in SLOS has been reported very rarely (Ryan et al., 1998; Mueller et al., 2003). After identifying a child with average intelligence at OHSU, we collaborated with other centers to find additional subjects and aimed to describe the characteristics of SLOS subjects with normal cognitive function.

2 | METHODS

Our study included subjects with SLOS who have been followed at four research centers, Oregon Health & Science University, Portland, OR; Children's Hospital, Aurora, CO; Kennedy Krieger Institute and *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, NIH Baltimore and Bethesda, MD; and McMaster University, Hamilton, ON, Canada. Subjects who had cognitive evaluation with at least one composite Intelligence Quotient (IQ) score above 80 were identified. Demographic, clinical, biochemical, molecular data, and IQ scores for this group of subjects were obtained by chart review. The modified Bialer scoring system of Kelley and Hennekam (2000) was used to document phenotypic severity. Clinical severity score under 20 indicates mild phenotype, 20–50 classical phenotype, and over 50 severe phenotype. Stanford Binet 4 (SB4), Stanford Binet 5 (SB5), Wechsler Intelligence Scale for Children-4th Edition (WISC-IV) and Wechsler Preschool and Primary Scale of Intelligence-3rd Edition (WPPSI-III) were used to measure cognitive functions of subjects.

3 | RESULTS

Nine subjects (6.2%) were identified with at least one composite IQ score above 80 among 145 subjects with SLOS (Table 1). The median age at diagnosis was 24 months (2 weeks–14 years). The median cholesterol level of subjects at diagnosis was 128 mg/dl (range: 85–181), median 7DHC level was 2.8 mg/dl (range: 2–5.2). Clinical severity scores were consistent with mild phenotype (range: 5–10). No specific mutation patterns were observed. Subject 9, in addition, had an inversion of chromosome 9 (inv [9][p22q22.3]) and duplication of the short arm of chromosome X (dup[X] [22.31]).

Table 2 documents IQ scores of subjects. Scores were derived from administration of SB4 in three subjects, SB5 in 3, WISC-IV in 2, and WPPSI-III in one. Full scale and factor IQ scores were calculated for each participant. Subjects tended to demonstrate relative strengths in verbal measures of IQ and working memory abilities, based on higher scores on tests of verbal reasoning and simple attention than visual-spatial reasoning.

4 | DISCUSSION

SLOS is commonly reported as a multiple malformation/intellectual disability syndrome. However, intellectual disability appears to occur across a range, with mild intellectual disability with IQ of 50–70 previously detected in 1 in 10 children (Ryan et al., 1998; Kelley and Hennekam, 2000). Current findings suggest that significant intellectual disability may not be universal in SLOS.

Factors determining variation in intellectual functioning in SLOS are unclear, though cholesterol's role in brain development and activity, as well as accumulation of potentially toxic cholesterol precursors, 7-DHC, and its isomer 8-DHC are implicated. Cholesterol is essential for brain development, myelination, neuronal signaling and survival (Orth and Bellosta, 2012). It is also essential for processing and signaling of sonic hedgehog, a morphogen involved in midline development (Porter et al., 1996; Maity, Fuse, & Beachy, 2005; Stottmann et al., 2011). Thus, severity of cholesterol depletion in the brain is expected to affect the degree of neuronal dysfunction and somatic malformations including brain abnormalities such as microcephaly, holoprosencephaly, and corpus callosum agenesis. In support of this, Lee, Conley, Gropman, Porter, and Baker (2013) found significant correlations between brain anomaly severity score and other measures of SLOS severity such as somatic severity score, 7-DHC and total cholesterol levels. Lee, Yoshida, et al. (2013) measured midsagittal corpus callosum (CC) length and area in individuals with SLOS and mild to severe developmental delay, and found that shorter CC length and smaller area correlated with lower developmental quotient in gross motor and language domains. CC length and area negatively correlated with serum sterol precursors and severity score, and positively correlated with total cholesterol.

The phenotypic variations in SLOS can be explained, in part, by different mutations in the *DHCR7* gene. At present, more than 100 pathogenic mutations are known. Based on a topology model of DHCR7 protein, two null alleles or two mutations in loop 8–9 generally cause a more severe phenotype and the highest 7DHC/total sterol ratios (Waterham and Hennekam, 2012). Individuals with one or two mutations in loop 1–2, one mutation in the N terminus have a milder phenotype. Although there appears to be a correlation between certain genotypes and clinical severity, individuals with the same *DHCR7* genotype can have marked differences in severity scores and plasma 7DHC levels indicating influence of other yet unidentified factors or genes.

Cholesterol supply during embryogenesis is likely to be the most important factor affecting SLOS phenotype (Cunniff et al., 1997). Although most of the cholesterol is synthesized endogenously in the growing embryo (Pitkin, Connor, & Lin, 1972), there is evidence that the fetus depends largely on maternal cholesterol, predominantly by transport of lipoproteins

from the mother (Baardman et al., 2013). Witsch-Baumgartner et al. (2004) showed that maternal apolipoproteinE (ApoE) genotype is associated with variability of SLOS phenotype. The maternal ApoE₂ genotypes were associated with a severe SLOS phenotype, whereas ApoE genotypes without the ApoE₂ allele were associated with a milder phenotype. The correlation of maternal ApoE genotype with disease severity persisted after stratification for *DHCR7* genotype. Furthermore, Lanthaler, Steichen-Gersdorf, Kollerits, Zschocke, and Witsch-Baumgartner (2013) reported that maternal ABCA1 genotype is an additional genetic modifier in SLOS. The p.Arg1587Lys polymorphism in maternal *ABCA1* gene was associated with milder clinical phenotypes. These studies show that modification of placental cholesterol transfer pathways may be an approach for prenatal therapy of SLOS.

Cholesterol supplementation is widely recommended for treatment of SLOS; however, cholesterol does not cross the blood-brain barrier (Dietschy and Turley, 2001), thus, does not improve developmental progress of affected individuals (Sikora et al., 2004). Statins, which do cross the blood-brain barrier, are being tested in SLOS (Haas et al., 2007). Simvastatin has been shown to decrease 7-DHC levels and increase cholesterol in fibroblasts from patients with SLOS when there was at least some activity of 7DHCR (Wassif et al., 2005). However, whether statins affects cognitive development remains unknown. Determining the factors affecting the SLOS phenotype could shed light on pathophysiology and potential therapeutic strategies.

The nine children identified in the current study had at least one IQ composite score in the normal or near normal range, with relative strengths in verbal and working memory abilities. However, they had other IQ composite standard scores below 80. Thus, many of these children have cognitive and learning impairments that likely necessitate attention in school and at home.

There are several limitations to the study. The sample size is relatively small (though large for such a rare disorder), limiting analysis of associations between cognitive profiles and other phenotypic and genotypic indicators; however, SLOS is a rare disease and children with higher cognitive skills are more likely underdiagnosed. The IQ scores were obtained over a 10-year period and various IQ tests were utilized, resulting in possible influence of method variance and differences in interpretation. Longitudinal data are not available; therefore it is not known whether these children preserve their normal cognitive skills.

In conclusion, normal IQ is possible in children with SLOS and may be more prevalent than previously recognized. As physical findings in SLOS may be subtle and easily overlooked, these findings raise the possibility that children with little or no cognitive impairment are not evaluated for potential diagnosis of SLOS. Future investigations to better understand the range of cognitive function in SLOS and the factors that modify the clinical phenotype are needed.

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Demographic, clinical, biochemical, and genetic characteristics of subjects with Smith-Lemli-Opitz syndrome and normal IQ

TABLE 1

Patient	Sex	Age ^I	Cholesterol (mg/dL)	7-DHC ^I (mg/dL)	Clinical severity score	Mutation
#1	F	24 months	91	3.2	10	IVS8-1G>C/V466
#2	F	28 months	96	3.4	5	S192F/Y462H
#3	F	6 months	128	2.4	5	IVS8-1G>C, Q65Q, T77T, G424G
#4	M	2 weeks	85	2	10	IVS8-1G>C/S169L
#5	F	9 years	NA	NA	5	IVS8-1G>C/R450L
#6	F	6 months	NA	NA	5	Q98X/T154M
#7	M	11 months	142	2.4	10	Q98X/M1V
#8	F	4 years	141	3.9	5	c.1396G>A/c.964-1G>C
#9	M	14 years	181	5.2	5	c.452G>C/c.91C>T

F: female; M: male.
^I at diagnosis.

TABLE 2

IQ scores of subjects with Smith-Lemli-Opitz syndrome

SB5	Age (year)	FSIQ	VIQ	NVIQ	FR	K	QR	VS	WM
#1	4	75	83	69	62	63	83	103	83
#2	6	83	93	74	76	91	89	79	91
#7	7	80	67	95	88	83	78	82	83
SB4		FSIQ	VR	AVR	QR	STM	TC		
#4	8		81	77	86	74	75		
#5	10		73	84	NA	67	70		
#6	14.5		82	74	72	60	68		
WISC-IV		FSIQ	VCI	PIQ	PSI	PRI		WMI	
#9	14		85		100	90		86	
#3	7	99	95	102				100	
WPPSI-III		FSIQ	VCI	PIQ	PSI				
#8	5	87	86	90	56				

SB5: Stanford Binet 5; FSIQ: full scale IQ; VIQ: verbal IQ; NVIQ: nonverbal IQ; FR: fluid reasoning; K: knowledge; QR: quantitative reasoning; VS: visual-spatial; WM: working memory; SB4: Stanford Binet 4; VR: verbal reasoning; AVR: abstract-visual reasoning; STM: short term memory; TC: total composite; WISC-IV: Wechsler Intelligence Scale for Children-4th edition; VCI: Verbal comprehension IQ; PIQ: performance IQ; PSI: processing speed IQ; PRI: perceptual reasoning index; WMI: working memory IQ; WPPSI-III: Wechsler Preschool and Primary Scale of Intelligence-3rd edition.