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Behavior Phenotype in the RSH/Smith-Lemli-Opitz Syndrome

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The behavior phenotype of Smith-Lemli-Opitz syndrome (SLOS) was studied by assessing behavior, social, and communication abilities, sensory hyperreactivity, and the deficits associated with autistic disorder. Fifty-six SLOS subjects, age 0.3 to 32.3 years, were evaluated by multiple age-dependent questionnaires and telephone interviews. Of the 56 subjects, 50 (89%) had a history of repeated self-injury: 30 (54%) bit themselves; 27 (48%) head-banged; and 30 (54%) threw themselves backward in a highly characteristic upper body movement ("opisthokinesis"). Forty-seven of these subjects were also evaluated by direct observation and by direct interview of the parent or caregiver. Of 11 subjects 10 years or older, three (27%) had a stereotypic stretching motion of the upper body accompanied by hand flicking. Additional measures showed sensory hyperreactivity, temperament dysregulation, sleep disturbance, and social and communication deficits. Nine of 17 subjects (53%) met the diagnostic criteria for autistic disorder by the Autism Diagnostic Interview-Revised (ADI-R) algorithm questions [Lord et al., 1993, 1994]. Thus, SLOS is a metabolic disorder that can be associated with autism and other behavioral characteristics that define a distinctive and diagnostically important behavioral disorder.

KEY WORDS: Smith-Lemli-Opitz syndrome; behavior phenotype; cholesterol; 7-dehyrocholesterol; metabolic disorder; autism; Autism Diagnostic Interview (ADI); Sensory Profile; Screen for Social Interaction; temperament dysregulation; multiple congenital disorder; opisthokinesis, Temperament and Atypical Behavior Scale (TABS)

INTRODUCTION

Smith-Lemli-Opitz syndrome (RSH/SLO syndrome, SLOS, MIM #270400) is an autosomal recessive, multiple malformation/mental retardation syndrome [Smith et al., 1964] with an estimated variable incidence among individuals of European ancestry of 1 in 15,000 to 1 in 60,000 births [Lowry and Yong, 1980; Ryan et al., 1998; Opitz, 1999a; Bzdúch et al., 2000; Kelley and Hennekam, 2000] and a probable average carrier frequency of 1% [Kelley and Hennekam, 2000]. Principal abnormalities include a characteristic facial appearance, microcephaly, hypotonia, postnatal growth retardation, 2-3 toe syndactyly, and hypogenitalism. Less common are malformations of the brain, lung, heart, and gastrointestinal tract. In 1993, SLOS was shown to be caused by a defect of cholesterol biosynthesis at the level of the 7-dehydrocholesterol reductase [Irons et al., 1993; Tint et al., 1994]. This defect results in the impaired conversion of 7-dehydrocholesterol to cholesterol, causing an increased level of 7-dehydrocholesterol in blood and tissues, and, in most patients, associated decreased blood and tissue choles-

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terol levels. A major consequence of these biochemical abnormalities is the alteration of normal embryonic and fetal somatic development causing postnatal abnormalities of growth, learning, language, and behavior.

The level of cognitive ability in SLOS ranges from borderline intellectual functioning to profound mental retardation [Smith et al., 1964; Opitz et al., 1969; Lowry and Yong, 1980; Kelley, 1996]. Although SLOS is not a very rare disorder, the cognitive and communication profile of SLOS has not been studied systematically. The individuals may have severe language impairment [Tint et al., 1994; Kelley, 1996; Nwokoro and Mulvihill, 1997] with greater receptive than expressive language abilities [Kelley, 1996]. Nwokoro and Mulvihill [1997] described a sleep disturbance, and Ryan et al. [1998] studied 23 biochemically confirmed subjects age 6 months and older and found that 70% had a sleep cycle disturbance that usually did not respond to sedatives. Individuals with SLOS have also been described as "hyperactive" [Elias and Irons, 1995; Opitz, 1999b], and attention deficit hyperactivity disorder was diagnosed in one child, who was reported to have a positive clinical response to treatment with methylphenidate [Nowaczyk et al., 1998]. Ritualistic and repetitive behavior [Ryan et al., 1998], including trichotillomania [Nwokoro and Mulvihill, 1997], and autistic behavior [Opitz, 1999b] have also been described.

Although geneticists and developmental pediatricians have long recognized that certain genetic disorders, e.g., Down syndrome, have relatively specific behaviors, the formal study of syndrome-specific behavior is a relatively new discipline. Indeed, the term "behavioral phenotype" was first used in 1972 in a study describing the behavior profile of Cornelia de Lange syndrome [Nyhan, 1972]. Whereas the field of mental retardation research has traditionally classified individuals by their overall level of impairment, clinicians are increasingly aware that syndrome-specific behavior phenotyping and evaluation using both psychiatric and neuropsychological assessments often afford not only additional diagnostic criteria for the recognition of a clinical disorder but also a better understanding of the psychological and educational needs of individuals with a genetically determined disorder [Dykens, 1995].

Few syndromes have virtually pathognomonic individual behaviors such as the well-known "handwringing" of Rett syndrome. Rather, as noted by Dykens [1995], a behavior phenotype is not a set behavioral pattern but more "the heightened probability or likelihood that the people with a given syndrome will exhibit certain behavioral and developmental sequelae relative to those without the syndrome." Categorization of these behaviors into several domains and the development of reliable instruments for the assessment of the behaviors have increased the ability to delineate the basic elements of a behavior phenotype. Some of the domains most often assessed include: behavioral self-regulation; sensory hyperreactivity; social development; motor impairments; cognitive and adaptive functioning; psychiatric disorders/diagnoses; language and communication profile; and syndrome-specific behaviors.

The purpose of describing syndrome-specific behavior profiles is not just academic. Behavior phenotyping seeks to define better the behavioral and developmental needs of children with syndromes. Moreover, because of the genetic nature of many of these disorders, some of which are chromosomal microdeletion syndromes, researchers hope to be able to delineate the specific genes regulating the most characteristic behaviors and thereby understand the abnormal biochemistry, physiology, or central nervous system anatomy associated with and possibly contributing to the behaviors. In this respect, SLOS offers a unique opportunity to link behavior with biochemistry because it is a single gene disorder with a well-defined enzymatic deficiency and evidence of behavior modulation with biochemical treatment. One of the purposes of defining the behavior phenotype of SLOS in a rigorous manner is that there is a substantial number of SLOS patients whose physical phenotype is too mild to be recognized by most geneticists but whose behavior phenotype is nonetheless characteristic.

Treatment of SLOS with supplemental cholesterol began in 1993 after the discovery of the metabolic etiology of the disorder [Irons et al., 1993; Tint et al., 1994]. Ryan et al. [1998] did not find significant improvement in developmental ability after supplementation, although the length of time during which the subjects received supplementation was relatively short. But, they noted anecdotal reports by parents of cholesterol-associated improvement in behavior and alertness. Treatment with cholesterol was reported to decrease irritability [Elias and Irons, 1995; Nwokoro and Mulvihill, 1997], lead to a happier affect [Irons et al., 1995; Nwokoro and Mulvihill, 1997; Pauli et al., 1997; Opitz, 1999b], decrease hyperactivity, improve attention [Elias and Irons, 1995], and decrease self-injury [Irons et al., 1995; Ryan et al., 1998]. Other behaviors that decreased with supplementation were aggression [Nwokoro and Mulvihill, 1997; Ryan et al., 1998], temper outbursts, trichotillomania, and tactile defensiveness [Nwokoro and Mulvihill, 1997]. Individuals with SLOS have also been reported to be calmer [Pauli et al., 1997] and more sociable, including beginning to initiate hugs, after cholesterol supplementation [Nwokoro and Mulvihill, 1997; Pauli et al., 1997]. Other improvements noted after cholesterol supplementation were increases in alertness and activity in subjects who were abnormally passive [Irons et al., 1995; Ryan et al., 1998] and improved sleep patterns [Ryan et al., 1998]. The hearing of two subjects was reported to improve [Irons et al., 1995], and subjects were reported to become more verbal after supplementation [Pauli et al., 1997; Opitz, 1999b].

Prior to the design of our present study, the authors observed a number of characteristic neurodevelopmental abnormalities in patients with SLOS. SLOS patients were hypotonic and had poor suck from infancy. The more severely affected infants had little motion, interacted only slightly with their environment, and cried minimally. The mildly affected subjects were known to scream for hours, have a poor sleep pattern, and become more upset when touched or when a light was turned on. Language, motor, and cognitive mile-

stones were delayed, and attentional deficits, stereotypies, aggressive outbursts, temper tantrums, and self-injurious behavior were quite frequent. Individuals with SLOS became easily frustrated, screamed inappropriately, seemed nervous, high-strung, or tense, and had quick changes in mood. Other unusual behaviors included a sad affect and prolonged crying spells with no discernible precedents. They were frequently upset when things were out of place, disturbed by any change in routine, inflexible, self-restricting to unusual interests, and were more difficult to manage than unaffected children were. Parents reported to the authors that the majority of these behavioral difficulties decreased in intensity or subsided after initiation of cholesterol supplementation.

Because the frequent occurrence of many of these abnormal behaviors suggested to us a common behavior phenotype in SLOS patients, we designed a study to assess 1) behaviors that may have syndrome specificity, 2) sensory hyperreactivity, 3) anxiety and mood disorder symptoms, 4) social deficits and autism spectrum characteristics, and 5) other behavioral traits.

MATERIALS AND METHODS

This study was approved by the Johns Hopkins School of Medicine Institutional Review Board and the National Institutes of Health Institutional Review Board. Informed consent was obtained from all parents or legal guardians of the subjects in the study.

Subjects

Subjects with SLOS were recruited from two ongoing SLOS treatment protocols and through parents who contacted the authors for assistance with their children's care. There were 56 subjects (31 male and 25 female) age 3 months to 32.4 years (mean 7.8 ± 6.7 years) assessed over the period of 1.5 years. All subjects had a biochemical diagnosis of SLOS confirmed in our laboratory as previously described [Kelley, 1995]. All subjects were assessed by informant-completed, age-dependent behavioral measures and parental interviews. Forty-seven of the subjects (25 male and 22 female) age 3 months to 32.4 years (mean 8.2 ± 6.8 years), who could be seen at a clinic site, were examined and they and their parents or guardians (caretakers) were interviewed in person. The caretakers of nine subjects were interviewed by telephone and completed the questionnaires by mail. The measures and the ages at which these instruments can be administered, as well as the number of subjects for whom each measure was completed, are listed in Table I.

Of the 56 subjects in the study, 51 were receiving cholesterol supplementation. The other five were not on supplementation for the following reasons: three newly identified SLOS patients were entered into the study prior to the start of supplementation; and two patients with a clinical diagnosis of SLOS made more than 10 years earlier only recently had a biochemical diagnosis of SLOS and were entered into the study prior to starting supplementation.

Parental interview and direct assessment of the subject. One or both parents or legal guardians (informants) were asked if they had specific concerns about their children as well as whether or not their children manifested self-injury, aggression, or unusual motor movements. For the 47 subjects seen in person, attempts at social engagement were made and the subjects were observed for behavioral and physical signs.

Screen for Social Interaction (SSI). This informant-completed checklist measures basic social interaction skills [Ghuman et al., 1998]. Data for reliability and validity have been established for subjects age 30 to 60 months. In a previous study, SSI scores were able to differentiate between autistic disorder and other developmental disorders ($P < 0.0001$) when correlated with autism diagnoses using the ADI-R [Ghuman et al., 1998].

Nisonger Child Behavior Rating Form, Parent Version (Nisonger-CBRF). This informant-completed checklist measures a prosocial domain (calm and sociability subscales) as well as a problem behavior domain (conduct problem, insecurity/ anxiety, hyperactivity [overactivity and attention difficulties], self-injury, self-isolation/ rituals, and oversensitivity subscales) [Aman et al., 1996]. Behaviors present up to 2 months before assessment were rated. Sound psychometric properties were established for this scale by Aman et al. [1996], and normative data for 369 children with developmental disorders from age 3 to 16 years have been compiled by Tassé et al. [1996].

Infant Toddler Symptom Checklist. This measure consists of five age-specific informant-completed checklists that are used to identify sensory and regulatory disorders in infants [DeGangi et al., 1995]. Regu-

TABLE I. Behavioral, Communication, and Social Assessments: Domain Studied, Age of Normative Data, and the Number of Subjects for Each Assessment Method*

Measure/test	Domain	Normative data age	Subject #
Direct examination	SS	All ages	47
Screen social interaction	SD	30 to 60 months	13
Nisonger CBRF	B,M,SD	3 to 16 years	31
Infant-toddler symptom	B,SH	7 to 30 months	8
TABS temperament	B,SD,P	11 to 71 months	11
Sensory profile	SH,M	≥3 years	35
MacArthur gestures	L	≥8 months adapted	34
MacArthur sentences	L	≥16 months adapted	15
Autism diagnostic interview	PD,B,SD,L	≥18 months mental age	17
Parent global rating	B	All ages	51

*B, behavior; L, language/communication; M, motor; PD, psychiatric diagnostic; SD, social development; SH, sensory hyperreactivity; SS, syndrome-specific behavior.

lation is the ability of the child to integrate sensory input in the realms of emotion, environmental changes, and interaction with others. The measure was felt to be useful for differentiating normal from regulatory-disordered infants and toddlers and has been validated on a sample of 154 typical children and 67 regulatory-disordered subjects [DeGangi, 1991; DeGangi et al., 1995].

Temperament and Atypical Behavior Scale (TABS). This informant-completed checklist assesses present-state temperament and behavior in 11- to 71-month-old children [Bagnato et al., 1999]. Temperament in this measure refers to the behavior that a child exhibits in the realms of activity, excitability, and sleep. Comparison data include the study of Neisworth et al. [1999] of 621 typical children, and the study of Bagnato and Neisworth [1999] of 36 children with autism spectrum disorders, 12 with fragile-X syndrome, and 37 with developmental delay.

Sensory Profile. This informant-completed checklist measures symptoms in the domains of sensation (auditory, visual, olfactory/ gustatory, and tactile), activity level, body position, movement, emotional and social symptoms [Dunn, 1999a]. It has been shown to have good reliability and validity in typical children [Dunn and Westman, 1997]. Dunn [1999b] has shown that typical individuals age 10 years and older have results comparable with individuals in the norms for age 3 to 10 years. Thus, in this study, the data for those older than 10 years were grouped with subjects 3 to 10 years of age. Studies by Kientz and Dunn [1997] have also shown the Sensory Profile to discriminate between children with and without autism.

MacArthur Communicative Development Inventory (MacArthur CDI). This informant-completed checklist measures receptive and expressive language [Fenson, 1993]. The Word and Gestures (Gestures) form has normative data for chronological ages 8 to 16 months and the Words and Sentences (Sentences) form has normative data for chronological ages 16 to 30 months [Fenson, 1993; Fenson et al., 1994]. If the parent reported that the subject used at least two-word phrases, the Sentences form was completed rather than the Gestures form. The scoring method was adapted for a developmentally delayed population as described in the instrument's manual so that informants of all subjects age 8 months and older could complete the forms and the language ages up to 30 months could be calculated.

Autism Diagnostic Interview-Revised (ADI-R). The ADI-R is a semi-structured interview that can differentiate developmental deviation from developmental delay when administered to the primary caretaker of individuals with normal hearing and a mental age of 18 months or older [Lord et al., 1993, 1994]. The two interviewers in this study [JKG and ET] obtained independent primary reliability of greater than or equal to 90% with the ADI-R by meeting the research requirements of the instrument. In this current study, the algorithm questions were asked without the additional ADI-R questions. The reliability and validity of its use in this manner has yet to be established. The interview yields scores in the domains of Reciprocal Social Interactions, Communication (Nonverbal or Verbal for subjects using three-word phrases that sometimes include a verb), and Repetitive Behaviors and Stereotyped Patterns. The ADI-R social domain questions and most of the communication domain questions retrospectively measure features that were present at age 4.0 to 5.0 years, or at the present age if the child is 5.0 years or less. The repetitive and stereotypic behavior communication domain questions primarily assess whether certain behaviors have ever occurred. The ADI-R algorithm question criteria for autism corresponds very closely to the Diagnostic and Statistical Manual, fourth edition (DSM-IV) [APA, 1994] diagnostic criteria for autism.

Parenting Global Rating Form. Informants with children receiving cholesterol supplementation were asked to rank order their children's current behavioral response to treatment on a 10-point scale from 1 (terrible) to 10 (excellent).

RESULTS

Parental Interview and Visual Observation

Aggression and self-injurious behavior was frequently reported by the caretakers. Abnormal aggression occurred in 35 of 56 subjects (63%) in a repeated manner some time in the past or present. The parents reported that of the 56 subjects age 0.3 to 32.3 years, 50 (89%) had a history of the following repeated self-injury: 30 (54%) bit themselves and 27 (48%) banged their heads with their hands or on objects. Thirty-eight of the 56 subjects (68%) had repeated self-injury within the month prior to the study. In addition, 30 (54%) had engaged at some age in repeated forceful and rapid backward head and trunk arching and backward thrusting ("opisthokinesis") often resulting in the child's hitting an object. An additional seven subjects (13%) did not demonstrate the characteristic opisthokinesis but did arch their neck backward frequently, whereas 17 (30%) did neither. The opisthokinesis tended to occur when the subjects were under age 5 years and decreased over time.

In addition, upon visual observation, three children appeared to look for objects with hard corners to hit with their heads, and a fourth looked for firm objects to push her head against in a slower manner. Stereotypic stretching accompanied by brief and rapid hand movements was observed with 3 of 11 individuals (27%) who were 10.0 years and older. One of these three subjects was observed to also have a flicking motion of her feet at the same time as her hands flicked and another subject would at times stretch only one arm upward but would still have the characteristic hand-flicking. A parent of one of the three subjects stated that this stereotypic motion increased in frequency when their son was ill. This movement was neither observed nor reported to occur in younger subjects. Two subjects had myoclonic movements of the upper extremities.

Screen for Social Interaction (SSI)

This was completed for 13 SLOS children age 32 to 60 months. Their scores were compared with 14 age-matched typically developing children who were previ-

TABLE II. Screen for Social Interaction (SSI) for Groups of 30 to 60-Month-Old Children Who Are Unaffected, Have Autism, Developmental Disorder, or SLOS

	Unaffected (n = 14)	Autism (n = 14)	Developmental disorder (n = 13)	SLOS (n = 13)
Total SSI score (TSS)				
Mean and SD	131.3 ± 14.0	67.9 ± 18.4	93.7 ± 19.0	101.8 ± 22.3
Standard Error	3.7	4.9	5.3	6.2
Range	102–151	45–108	65–133	59–132
TSS percentile				
Mean and SD	66.0 ± 27.1	2.2 ± 7.3	10.1 ± 16.2	28.0 ± 32.7
Standard Error	7.2	1.9	4.3	9.1
Range	18–100	0–27	0–57	0–100

ously tested by Ghuman (unpublished data), to 14 children with autism (diagnosed by ADI-R) and to 13 children with other developmental disorders. A one-way analysis of variance was conducted on the Total SSI Scores. The independent variable was group (Typical versus Autism versus Developmental Disorder versus SLOS). There was a significant effect of group $F = (3, 50)\ 27.45$, $P < 0.001$. Post-hoc analyses using Tuckey Honestly Significantly Different (Tuckey HSD) tests [Tuckey, 1949] showed that all three groups performed significantly worse than the group with typical children (for all significant contrasts $P < 0.01$). The SLOS children performed significantly better than the autism subjects and at the same level as the Developmental Disorder group. But, when the Total SSI Scores were examined individually, 5 of the 13 SLOS subjects (38%) had SSI Total Scores at the 0 centile, which was below the mean centile score of 2 seen in a group of children with autism. The scores for the other eight subjects were at the following centiles: 8, 11, 28, 42, 54, 57, 64, and 100 (Table II).

Nisonger-CBRF

This measure that rates behavior that occurred within 2 months of assessment was completed for 31 subjects, age 3.1 to 12.3 years, and the results are summarized in Table III by the groupings (subscales) that were derived by factor analysis. On the "Hyperactive" subscale (which consists of questions regarding both overactivity and attention difficulties), only 1 of 31 subjects (3%) had a score that was equal to or greater than the 85th centile for a mixed group of subjects with developmental disorders [Tassé et al., 1996]. On the "Self-injury/stereotypic" subscale, 6 of 31 subjects (19%) had a score that was equal to or greater than the 85th centile. On this measure, the self-injurious behaviors occurred with 26 of 31 subjects (84%) when milder self-injury such as skin picking was included, and 14 of 31 (45%) had repeated self-biting that left toothmarks or broke the skin.

Infant-Toddler Symptom Checklist

This was completed for eight subjects, age 9 to 29 months. None of the four subjects age 22 months or younger had scores consistent with impairment, but all of the four subjects age 25 months or older had scores consistent with the presence of a regulatory disorder. Of the eight, five (63%) reported difficulties with sleep.

Temperament and Atypical Behavior Scale (TABS)

This was completed for 11 children, age 15 to 66 months. In Table IV, the Smith-Lemli-Opitz syndrome subjects' results are compared with previously published data on four groups of children: typical (without developmental delay); autism spectrum disorders; fragile-X; or developmentally delayed [Bagnato and Neisworth, 1999]. SLOS subjects overall had more dysfunction of temperament and self-regulation than subjects who were typical or had idiopathic developmental delay but less than subjects with autism spectrum disorders and fragile-X syndrome. Five of the seven questions in the TABS factor of "Dysregulation" address sleeping habits and the SLOS subjects had more dysregulation of sleep and less ability to self-soothe than typical, autism, fragile-X, and developmentally delayed subjects [Bagnato and Neisworth, 1999; Neisworth et al., 1999]. Of the 11 SLOS subjects, four (36%) had total scores greater than the mean seen in the subjects with fragile-X syndrome, and two (18%) had scores

TABLE III. Centile Scores * for 31 SLOS Subjects (18 Male, 13 Female) From the Nisonger Child Behavior Rating Form

	Less than 70th centile	70th to <85th centile	85th centile and above
Positive Behaviors			
Compliant/calm	25 (male 13, female 12)	4 (male 3, female 1)	2 (male 2, female 0)
Adaptive social	25 (male 16, female 9)	3 (male 1, female 2)	3 (male 1, female 2)
Problematic Behaviors			
Conduct	29 (male 17, female 12)	1 (male 1, female 0)	1 (male 0, female 1)
Insecure/anxious	26 (male 14, female 12)	4 (male 3, female 1)	1 (male 1, female 0)
Hyperactive	28 (male 16, female 12)	2 (male 1, female 1)	1 (male 1, female 0)
Self injury	13 (male 7, female 6)	12 (male 9, female 3)	6 (male 2, female 4)
Self isolative/ritualistic	24 (male 13, female 11)	5 (male 4, female 1)	2 (male 1, female 1)
Overly sensitive	25 (male 16, female 9)	5 (male 1, female 4)	1 (male 1, female 0)

*Centile scores are derived from 369 subjects with developmental disorders.

greater than the mean seen in subjects with autism. The TABS does not have questions regarding self-injury but does have two questions regarding stereotypic behavior. Three of 11 subjects (27%) were reported as "flaps hands over and over" and two of these three subjects (67%) "shakes head over and over." Six of 11 subjects (55%) were "disturbed by too much light, noise, touching." The parents of five subjects (45%) reported the behavior, "Stares at light." The subscale "Detached" has questions regarding interactions with objects in the environment, such as "plays with toys in a strange way," and questions regarding social behavior, such as "resists looking you in the eye." On this subscale, the mean of the group of children with SLOS (age 1.3–5.5 years) was shown to have the same standard score of zero that a population of subjects with autism spectrum disorders displayed (Table IV).

Sensory Profile

This was completed on 35 subjects, age 3.2 to 32.4 years, and compared with data sets for typical subjects, and subjects with autism, Asperger disorder, attention deficit hyperactivity disorder, and other disabilities [Dunn and Westman, 1997; Kientz and Dunn, 1997; Ermer and Dunn, 1998; Dunn, 1999b]. One way analysis of variance tests were conducted with post-hoc Tuckey HSD test analyses. The Sensory Profile showed that the subjects had auditory, oral, visual, and tactile processing difficulties (sensory hyperreactivity/ hypersensitivity) that was greater than 2 standard deviations from the mean observed with a group of typical subjects [Dunn and Westman, 1997]. By the Sensory Profile factor Visual Processing, a group of 30 SLOS subjects had statistically greater difficulties with these behaviors than typical subjects [Dunn and Westman, 1997], subjects with attention deficit hyperactivity disorder [Bennett and Dunn, 1996], Asperger disorder [Dunn, personal communication], autistic disorder [Kientz and Dunn, 1997], and other developmental disorders [Ermer and Dunn, 1998].

MacArthur Communicative Development Inventory

The MacArthur Gestures form was completed for 34 subjects, and the MacArthur Sentences form was completed for 15 subjects who had at least two-word phrases. Of the entire cohort of 49 subjects (mean age 8.2 ± 7.8 years; range 0.8–32.4 years), 21 (43%) had an expressive language age below 8 months, and 38 (78%) had an expressive language age of 30 months or less. As noted below, for both the Gestures and the Sentences forms, the SLOS subjects showed a marked impairment in receptive and expressive language skills but with substantially greater receptive than expressive ability.

MacArthur Gestures Form. Of 34 subjects (mean age 7.4 ± 8.2 years, range 0.8–29.9 years), 27 (79%) had receptive language ages of 16 months or below, and 31 (91%) had expressive language ages of 16 months or below, and 24 (71%) had no spoken language. Of these 34 subjects, six were between the chronological ages of 8 to 16 months for which the measure has normative data. Of those six, only one exceeded the 5th centile for receptive or expressive language, having a 40th centile score for receptive language age, but less than the 5th centile for expressive language. Three subjects reached the ceiling of the Gestures measure of greater than 16 months receptive and expressive language age despite not having two-word phrases. The scores of these subjects are summarized based on their receptive and expressive vocabulary ages in Table V.

MacArthur Sentences Form. This form was completed for 15 subjects (mean age 10.1 ± 6.6 years, range 3.7–32.4 years) who by report had at least two-word phrases. All subjects were older than the normative ages of 16 to 30 months for this test. Their results are grouped by their expressive vocabulary ages and sentence ages in Table VI.

ADI-R Algorithm Questions

Of 56 subjects, 26 had documented mental ages of 18 months or older. Of those 26, 17 subjects (age 3.3–32.4 years) with no hearing deficit were assessed by the ADI-R algorithm questions. Nine of the 17 subjects (53%) with a mental age of 18 months or greater met the ADI-R algorithm question criteria for the clinical diagnosis of autism that was established for the complete ADI-R interview. (Table VII).

Of the nine subjects who began cholesterol supplementation before the age of 5.0 years (# 7–9 and 11–16), two (22%) met the ADI-R algorithm criteria for autism at age 4.0 to 5.0 years. Of the remaining eight subjects (# 1–6 who began supplementation after the age of 5.0 years and subjects 10 and 17 who were older

TABLE IV. TABS Neurobehavioral Profiles for Four Diagnostic Groups: Raw Scores and Standard Scores (SS) for Autism Spectrum Disorder, Fragile X, Developmental Delay, and SLOS*

	Typical (n = 621)			Autism (n = 36)			Fragile X (n = 12)			Developmental delay (n = 37)			SLOS (n = 11)		
	Raw score			Raw score			Raw score			Raw score			Raw score		
Scales	M	SD	SS	M	SD	SS	M	SD	SS	M	SD	SS	M	SD	SS
TRI	2.9	(3.4)	100	20.2	(15.4)	<51	15.8	(26.3)	<51	7.5	(1.6)	80	12.6	(8.3)	56
Detached	0.6	(1.3)	55	9.9	(24.4)	0	6.0	(46.6)	7	2.7	(3.4)	35	7.0	(4.8)	0
Hypersensitive/active	1.6	(2.1)	55	6.3	(25.7)	27	7.3	(51.5)	22	3.3	(0.9)	43	4.0	(3.9)	39
Underreactive	0.4	(0.9)	54	2.6	(6.8)	25	2.1	(2.5)	30	0.8	(0.8)	52	2.1	(2.6)	31
Dysregulated	0.4	(0.8)	54	1.4	(4.5)	35	0.4	(0.2)	52	0.7	(1.2)	51	2.1	(2.3)	29

*M, Mean; SD, Standard Deviation.

TABLE V. MacArthur CDI Words and Gestures: Number of Subjects (*n*) and Chronologic Age (CA) of 34 SLOS Subjects Grouped by Their Receptive and Expressive Vocabulary Ages

	Receptive vocabulary age		
Expressive vocabulary age	Less than 8 months	8–16 months	Greater than 16 months
Less than 8 months			
Number of subjects	9	10	2
Mean chronological age	34.1 mo	51.7 mo	193.5 mo
Standard deviation	35.1 mo	37.0 mo	102.5 mo
8–16 months			
Number of subjects	3	4	3
Mean chronological age	99.3 mo	134.0 mo	146.7 mo
Standard deviation	143.5 mo	97.7 mo	180.5 mo
Greater than 16 months			
Number of subjects	Not possible on measure	1	2
Mean chronological age		68 mo	233.0 mo
Standard deviation			178.2 mo

than 5.0 years but had not yet started supplementation), seven (88%) met the ADI-R algorithm criteria for autism.

For the four subjects who had a chronological age of 5.0 years or younger, the ADI-R social domain questions and most of the communication questions were asked about their present condition. The other 13 subjects had a chronological age greater than 5.0 years, so these same questions were asked regarding their state between age 4.0 to 5.0 years. For all subjects, the questions regarding repetitive and stereotypic actions addressed whether the behaviors had occurred at any time.

All the subjects in this study who met the ADI-R algorithm criteria for autism also meet the DSM IV diagnostic criteria for autism.

Parenting Global Rating Form

This was completed by the parents of the 51 subjects on cholesterol. The parents of seven subjects (14%) said their children started taking cholesterol too young (early infancy) to compare the before- and after-cholesterol periods. The parents of six subjects (12%) said that there was no change in behavior following treatment with cholesterol. These subjects did continue to receive dietary supplementation, although at times it was at a lower dose than is usually given if the parents had difficulty with the subjects accepting the higher dose. For the remaining 38 subjects (75%), their before- and after-cholesterol periods could be assessed, so the parents rated how they felt the subjects' behavior and adjustment were presently compared prior to cholesterol supplementation. The mean score was 7.9 ± 1.7 on a scale of 1 (terrible) to 10 (excellent), indicating that they believed that cholesterol supplementation had a very positive effect on average.

DISCUSSION

As we have described here, individuals with RSH/SLOS manifest a characteristic behavioral profile of cognitive delay, sensory hyperreactivity, irritability, language impairment, sleep cycle disturbance, self-injurious behavior, syndrome specific motor movements, and autism spectrum behaviors. SLOS infants have been reported to be markedly irritable [Kelley, 1996] and often have prolonged, inconsolable screaming [Opitz, 1999b]. Although the subjects in our study did not show behavioral dysregulation when younger than 22 months while on cholesterol supplementation, which may have been due to a low level of interaction with their environment, they manifested marked dysregulation if age 25 months and older, based on the Infant-Toddler Symptom Checklist. This dysregulation was also seen on the TABS, which showed the SLOS group of subjects, age 11 to 66 months, to have statistically greater dysregulation than typical subjects and subjects with other developmental disorders including autism. The characteristic irritability of SLOS continues throughout life with aggression reported in both children and adults [Pauli et al., 1997; Ryan et al., 1998]. Similar to the results of Ryan et al. [1998] who

TABLE VI. MacArthur CDI Words and Sentences: Number of Subjects (*n*) and Chronologic Age (CA) of 15 SLOS Subjects Grouped by Their Sentence Age and Expressive Vocabulary Age*

	Sentence age		
Expressive vocabulary age	Less than 16 months	16–30 months	Greater than 30 months
Less than 16 months	*n* = 1 (CA = 64 mo)	*n* = 0	*n* = 0
16–30 months	*n* = 0	*n* = 7 (CA: M = 142.6 mo SD = 110.8 mo)	*n* = 0
Greater than 30 months	*n* = 0	*n* = 2 (CA: M = 70.5 mo SD = 2.12 mo)	*n* = 5 (CA: M = 121.4 mo SD = 22.3 mo)

**n,* Number of Subjects; CA, chronological age; M, mean; SD, standard deviation.

TABLE VII. Autism Diagnostic Interview: Revised (ADI-R) Algorithm Questions, Results for 17 Subjects With a Mental Age of 18 Months or Older*

Subject	Genotype	Age cholesterol was started (yr)	Age ADI-R obtained (yr)	Social domain T = 10	Communication N-C T = 8 V-C T = 7	Repetitive/ stereotypic behavior domain T = 3	ADI-R autism criteria achieved
1	XY	10.5	12.3	17	V9	7	Yes
2	XY Female	6.6	7.8	26	N14	7	Yes
3	XX	7.3	10.3	27	N18	8	Yes
4	XY	6.0	10.1	8	N7	4	No
5	XX	12.4	17.7	22	V13	6	Yes
6	XY	27.5	32.4	23	N14	4	Yes
7	XX	0.3	3.8	5	V5	5	No
8	XY	1.8	3.3	7	V3	4	No
9	XY	3.5	5.0	9	V4	8	No
10	XY	None	9.0	12	V13	6	Yes
11	XY	0.2	3.8	7	N6	6	No
12	XX	0.9	7.0	18	N12	8	Yes
13	XX	1.6	5.8	18	N9	3	Yes
14	XX	0.3	8.9	13	N5	7	No
15	XX	0.8	5.8	3	V0	1	No
16	XY	3.5	8.6	13	V6	11	No
17	XY	None	13.8	27	N10	17	Yes

*T, threshold for diagnosis of autism by ADI-R algorithm questions; N-C, nonverbal communication domain; V-C, verbal communication domain.

found that 12 of 23 (52%) of children and adults with SLOS had aggression, we found that 63% of subjects had aggression in the past or present from toddlerhood into adulthood. In addition to outwardly directed aggression, individuals with SLOS often have self-injurious behavior [Tint et al., 1994; Nwokoro and Mulvihill, 1997; Ryan et al., 1998; Opitz, 1999b]. For example, Ryan et al. [1998] found that 8 of 23 subjects (35%) had self-injury, although it is not clear whether Ryan et al., recorded self-injury that occurred in the past and/or the present. Upon interviewing the parents, we found that 89% of our subjects had a history of self-injury at some time and that 68% had self-injury within the prior month including less injurious behaviors such as skin picking. The Nisonger-CBRF scale measured a self-injury rate of 83% that occurred within the 2 months prior to assessment.

One of our study's limitations is the physical weakness and the health status of some of the subjects, particularly some of the infants and toddlers, which very likely affected their developmental, social, and emotional functioning. Another limitation is the dependence upon informant report rather than rigorous subject examination and testing of function. The informant-completion measures that have established validity and reliability are often for a relatively smaller age range. Thus, we were limited in our ability to assess features and compare functioning over the age spans of the subjects. For example, the developmental language function on the MacArthur Communicative Development Inventory forms spanned from only 8 to 30 months language ages. Because 2 of the 24 subjects on the Gestures form and 5 of the 15 subjects on the Sentences form exceeded the age ceiling for the measures, we were not able to more clearly define the language age other than to note that their vocabulary ages and sentences ages were greater than 16 or 30 months, respectively. Future studies will require prospective, longitudinal psychological, communication, motor, neurological, and psychiatric evaluations as well as the use of observational instruments such as the Autism Diagnostic Observation Schedule (ADOS-G) [Lord et al., 1999] in order to describe the present state of subjects with SLOS and to capture changes that occur following cholesterol supplementation.

Over half of the subjects demonstrated opisthokinesis. An additional 13% of the subjects who did not demonstrate the characteristic upper-body opisthokinesis nevertheless arched their neck backwards frequently. A stereotypic stretching accompanied by brief and rapid hand movements was observed in 27% of the individuals with SLOS who were 10.0 years and older. These movements have syndrome specificity (they occur in individuals with SLOS more frequently than in individuals with other developmental disorders) and may aid in the identification of individuals with SLOS.

We note with interest that on a recent neurology assessment at one of our outpatient clinics, a patient presented with autism associated with mild mental retardation and bilateral 2-3 toe syndactyly (which is a physical anomaly present in almost all individuals with SLOS). Based on these findings, he was tested for SLOS and was found to have mild but diagnostic abnormalities in his plasma sterol levels. Because SLOS is not a rare genetic disorder and because some SLOS patients have only subtle physical anomalies, there may be other undiagnosed cases of SLOS individuals presenting with autism spectrum disorders. Plasma sterol precursor analysis of these individuals or those with other characteristic behaviors of SLOS may help to determine the true incidence of SLOS, as well as possibly may even identify other new disorders of sterol biosynthesis in individuals with autism.

Of the subjects who began cholesterol supplementation before the age of 5.0 years, 22% met the ADI-R algorithm question criteria for autism. In contrast, of the subjects who began supplementation after age 5.0 years, 88% met the same criteria for autism. This

raises the question as to whether or not the behavioral, social, communicative, and cognitive abilities of SLOS individuals may be influenced by the age at which cholesterol is started. Information gathered from behavioral, cognitive, and communication studies as well as studies of the timing, amount, and type of cholesterol supplementation may increase our ability to maximize the therapeutic interventions for individuals with SLOS. Ryan et al. [1998] addressed the difficulty in demonstrating improvement in the trajectory of development after cholesterol supplementation and stated that it will be difficult to prove an effect of cholesterol without fully randomized trials.

Various studies estimate that between 10 and 25% of cases of autism are associated with a known medical condition such as fragile-X, tuberous sclerosis, or phenylketonuria, although autism tends to occur at a low frequency in these conditions [Rutter et al., 1996; Gillberg, 1999]. Our results now have added SLOS to the list of genetic disorders associated with autism.

Moreover, the recognition that a primary disorder of cholesterol biosynthesis is associated with autism may have broader relevance to the understanding of the biochemical basis of some forms of autism and other neuropsychiatric disabilities in children. SLOS may also serve as a prototype for understanding neuropsychiatric ontogeny of developmental problems such as severe non-verbal learning disability, social skill deficits, and other pervasive developmental disorders.

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