Smith-Lemli-Opitz syndrome (SLOS, RSH/SLO syndrome, MIM 270400) is an autosomal recessive multiple malformation/mental retardation syndrome initially described by Smith et al. [1964] that is due to a defect in cholesterol biosynthesis. The behavioral phenotype of Smith-Lemli-Opitz syndrome demonstrates cognitive abilities from borderline intellectual functioning to profound mental retardation, sensory hyperreactivity, irritability, language impairment, sleep cycle disturbance, self-injurious behavior, and autism spectrum behaviors. In a recent study of 28 subjects, 14 subjects (50%) with SLOS also exhibited the behavior of throwing themselves backward in a characteristic upper body movement (“opisthokinesis”) and 2 adolescents had a stretching motion of the upper body accompanied by hand flapping [Tierney et al., 1999]. In that same study, 6 of 13 subjects (46%) met the Autism Diagnostic Interview-Revised (ADI-R) algorithm criteria [Lord et al. [1993] Infant Mental Health 14:234-252; Lord et al. [1994] J Autism Dev Disord 24:659-685] and the Diagnostic and Statistical Manual (APA [1994] DSM-IV) diagnostic criteria for autistic disorder. Smith-Lemli-Opitz syndrome is a metabolic disorder that is associated with autism.

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INTRODUCTION

Smith-Lemli-Opitz syndrome (SLOS, RSH/SLO syndrome, MIM 270400) is an autosomal recessive multiple malformation/mental retardation syndrome [Smith et al., 1964] with an estimated variable incidence of one in 20,000 to one in 80,000 births in Norm America [Lowry and Yong, 1980; Ryan et al., 1998; Kelley and Hennekam, 2000] and a probable average carrier frequency of% among individuais of European ancestry [Kelley and Hennekam, 2000]. Principal abnormalities include a characteristic facial appearance, microcephaly, hypo-tonia, postnatal growth retardation, 2-3 toe syndactyly, and hypogonitalism. 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 7-dehydrocholesterol reductase [Irons et al., 1993; Tint et al., 1994]. This defect impairs the conversion of 7-dehydrocholesterol (7-DHC) to cholesterol, causing an increased level of 7DHC in blood and tissues, and, in most patients, decreased blood and tissue cholesterol levels. A major consequence of these abnormalities is the alteration of normal embryonic and fetal brain development and function with characteristic abnormalities of brain development, growth, learning, language, and behavior. For example, the level of cognitive abilities ranges from borderline normal intelligence to profound mental retardation [Opitz et al., 1969; Lowry and Yong, 1980; Kelley, 1996].

Although geneticists and developmental pediatricians have long recognized that Down syndrome and certain other genetic disorders have relatively specific behaviors, the formal study of syndrome-specific behavior is a relatively new discipline. In-deed, the term "behavioral phenotype" was first used in a study describing the behavioral 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 have increasingly become aware that syndrome-specific behavioral phenotyping and evaluation using both psychiatric and neuropsychological assessments often affords not only additional diagnostic criteria for the recognition of a clinical disorder, but also a superior 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 "hand-wringing" of Rett syndrome. Rather, there is usually much Variation in the expression of all behaviors, including those most identified with the syndrome. As noted by Dykens [1995], a behavioral 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

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The algorithmic questions of the Autism Diagnostic Interview-Revised (ADI-R) [Lord et al., 1993; Lord et al., 1994] were used in the Tierney et al. study [1999] for parents who could be interviewed in person. The ADI-R Social Domain and a portion of the Communication Domain as well as the corresponding sections on the Diagnostic and Statistical Manual, 4th edition (DSM-IV) [APA, 1994] autism diagnostic criteria were used to gather information prospectively if the child was 5.0 years or younger but retrospectively if the subject was older than 5.0 years. The ADI-R Repetitive and Stereotyped Behavior

In a study of 28 subjects, 14 (50%) had engaged, at some age, in repeated forceful and rapid backward head and trunk arching and backward thrusting (opisthokinesis) often resulting in head banging.

The behavioral phenotype of SLOS continues throughout the life span. With aggression reported in children [Ryan et al., 1998] and adults [Pauli et al., 1997; Ryan et al., 1998; Nwokoro et al., in preparation], Ryan et al. [1998] found that 12 of 23 (52%) of children and adults with SLOS had aggression.

Sleep
Insomnia has been noted [Nwokoro and Mulvihil, 1997] and Ryan et al. [1998] found that 70% of die subjects had a sleep cycle disturbance that usually did not respond to sedatives.

Self-Injurious Behavior
Individuals with SLOS often have self-injurious behavior [Nwokoro et al., 1994; Tint et al., 1994; Opitz, 1999]. In one study, 8 of 23 (35%) of the subjects had self-injury [Ryan et al., 1998] (although the report did not state whether the self-injury referred to the past as well as the present). In a study of 28 subjects [Tierney et al., 1999], aged 0.3 to 32.3 years, 20 (71%) had, at some time, the following repeated self-injury: 15 (54%) bit themselves and 10 (36%) banged their heads on objects.

Possible Syndrome-Specific Motor Movements
In a study of 28 subjects [Tierney et al., 1999], 14 (50%) had engaged, at some age, in repeated forceful and rapid backward head and trunk arching and backward thrusting (opisthokinesis) often resulting in head banging. An additional two subjects (7%) did not demonstrate the characteristic opisthokinesis but did arch their neck backward frequently while 12 (43%) did neither. The opisthokinesis often occurred suddenly and could result in the child hitting an object. A Stereotypic stretching accompanied by brief and rapid hand movements was observed in two adolescents with SLOS. Myoclonic movements of the upper extremities were observed in two subjects.
Sensory Hyperreactivity / Hypersensitivity

Tactile hypersensitivity [Nwokoro and Mulvihill, 1997; Ryan et al., 1998], auditory hypersensitivity [Nwokoro and Mulvihill, 1997], ritualistic behavior [Ryan et al., 1998], and autistic behavior [Opitz, 1999] have previously been reported in individuals with SLOS. In a recent study [Tierney et al., 1999], the Sensory Profile [Dunn and Westman, 1997; Dunn 1999a] showed that the subjects had statistically greater sensory hyperreactivity compared to the groups of subjects who were typical or had attention deficit hyperactivity disorder, Asperger disorder, autism, and other developmental disorders [Dunn and Westman, 1997; Kientz and Dunn, 1997; Ermer and Dunn, 1998; Dunn, 1999b].

Autism Disorder Spectrum

Autistic behavior [Opitz, 1999] has been reported. In a group of 23 subjects studied by Ryan et al. [1998], 12 (52%) had ritualistic behavior such as playing the same video cassette repeatedly and having obsessions about placement of objects. Of 28 subjects [Tierney et al., 1999], 11 of 13 subjects (46%) had a mental age of 18 months or greater met the ADI-R algorithm question criteria for the clinical diagnosis of autism and had decreased with supplementation were more sociable, less irritable [Elias and Irons, 1995], and subjects were reported to become more verbal with supplementation [Opitz et al., 1999]. Parents also reported to Tierney et al. [1999] that, following supplementation, they noticed an improve-

Of note, 6 of 13 subjects (46%) met the ADI-R algorithm questions and DSM-IV diagnostic criteria for the diagnosis of autism.

DISCUSSION

Current studies in progress are examining various aspects of the behavioral phenotype and are looking at the timing of the initiation of cholesterol supplementation, the dosages used, and the source of cholesterol supplementation in order to optimize therapeutic interventions for individuals with SLOS. There is a need for prospective studies using the diagnostic instruments described here as well as observational instruments such as the Autism Diagnostic Observation Schedule [ADOS-G] [Lord et al., 1999]. Also needed are longitudinal psychological, communication, motor, neurologic, and psychiatric evaluations to describe the present state and capture changes that occur with cholesterol supplementation over time.

Also important to note is that on a recent neurology assessment at one of the site's outpatient clinic, a patient presented with autism associated with mild mental retardation and bilateral 2-3 toe syndactyly. Based on these findings, he was referred for SLOS biochemical testing which was positive. Because it is possible that some individuals with SLOS may present only with mental retardation, mild dysmorphism, and autism, plasma sterol precursor analysis of individuals with autism who have 2-3 toe syndactyly with mild or no facial dysmorphism or those with other characteristic behaviors of SLOS may help to determine the true incidence of SLOS or may even identify new disorders of sterol biosynthesis.

REFERENCES


