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BEHAVIORAL PHENOTYPE OF RSH/SMITH-LEMLI-OPITZ SYNDROME

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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, sieep 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 flicking [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 ofone 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 ofl% among individuais ofEuropean ancestry [Kelley and Hennekam, 2000]. Principal abnormalities include a characteristic facial appearance, microcephaly, hypo-tonia, 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 ofthe 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 af-fords 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 detennined disorder [Dykens, 1995]. Few syndromes have virtually pathognomonic individual behaviors such äs the well-known "hand-wringing" ofRett 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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and the development of assessment instruments for them have increased the ability to delineate the basic elements ofa behavioral phenotype. Some of the domains most often assessed include:

Behavioral self-regulation
Sensory hyperreactivity
Social development
Motor impairments
Cognitive and adaptive function-ing
Psychiatric disorders/diagnoses
Language and communication profile
Syndrome-specific behaviors

The purpose of describing syndrome-specific behavioral profiles is not just academic. Rather, behavioral phenotyping seeks to define better the behavioral and developmental needs of children with these syndromes. Moreover, because of the genetic nature of these disorders, most of which are chromosomal microdeletion syndromes, re-searchers hope to be able to delineate the specific genes regulating the most characteristic behaviors and thereby under-stand the abnormal biochemistry, physiology, or central nervous System (CNS) anatomy associated with and possibly contributing to the behaviors. In this re-spect, 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 behavioral modulation with biochemical treatment. One of the purposes of defining the behavioral phenotype of SLOS in a rigorous manner is that there are a significant number of SLOS patients whose physical phenotype is too mild to be recognized by most geneticists, but whose behavioral phenotype is nonetheless characteristic.

The behavioral phenotypic characteristics discussed in this review are from studies in which all subjects had biochemically confirmed SLOS. Also, a significant portion of this review will be based on a recent study on the behavioral phenotype of SLOS performed by Tierney and colleagues [1999]. In this study, a total of 28 subjects aged 3 months to 32.0 years were assessed by informant-completed age-dependent behavioral measures and parental Interviews. Subjects who were able to travel to be seen at a clinic site were examined and they and their parents or guardians were inter-viewed in person. The remaining subjects •were interviewed by telephone and the completed questionnaires were retumed by mail. Of the 28 subjects in the study, 27 were on cholesterol supplementation and l subject was newly diagnosed wich SLOS by a clinician at one of the research sites and was entered into the study prior to the start ofsupplementation.

The algorithm 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.

Domain recorded behavior that occurred in both the past and the present. The Sensory Profile [Dunn 1999a] was used as a prospective instrument and thus described the patients' present state.

RESULTS

Communication and Language

Severe language impairment has been described [Tint et al., 1994; KeUey, 1996; Nwokoro and MulvihiU, 1997] with greater receptive than expressive language abilities [KeUey, 1996].

Activity Level and Attention

Individuals with SLOS have been described as "hyperactive" [Elias and Irons, 1995; Opitz, 1999]. 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].

Irritability and Affect

SLOS infants are markedly irritable [KeUey, 1996] and often have prolonged, inconsolable screaming [Opitz, 1999]. Children and adults with SLOS often have a sad affect, experience prolonged crying spells with no discernible antecedents, and can be unreasonably impatient. They become easily frustrated, scream inappropriately, seem nervous, high-strung, or tense, and have quick changes in mood [Nwokoro et al., in preparation].

Aggression

Ryan et al. [1998] described behavioral characteristics derived from a questionnaire completed for 23 subjects, age 6 months through adulthood. The characteristic irritability 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 MulvihiU, 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] (al-though the report did not state whether the self-injury referred to the past as well as the present). In a study of28 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 ob-served in two adolescents with SLOS. Myoclonic movements of the upper extremities were observed m 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 cypical 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 of23 subjects studied by Ryan et al. [1998], 12 (52%) had ritualistic behavior such äs 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%) with a mental age of 18 months or greater met the ADI-R algorithm question criteria for the clinical diagnosis of autism and had Symptoms and signs consistent •with the DSM-IV criteria for autism between the ages of 4.0 to 5.0 years (by recall if older than age 5.0 years).

Changes Following Cholesterol Supplementation

Ryan et al. [1998] addressed the difficulty in demonstrating improvement m the trajectory of development after cholesterol supplementation and stated that it will be difficult to prove an effect without fully randomized trials. Ryan et al. [1998] did not see a dramatic improvement in developmental ability after supplementation in the patients seen in their series but they noted anecdotal re-ports by parents of improvement in behavior and alertness. Treatment with cholesterol has been reported to decrease irritability [Elias and Irons, 1995; Nwokoro and Mulvihill, 1997] and to lead to a happier affect [Irons et al., 1995; Nwokoro and Mulvihill, 1997; Opitz, 1999]. The SLOS patients have been reported to have decreased hyperactivity [Elias and Irons, 1995] and an improved attention span after cholesterol treatment is begun [Elias and Irons, 1995]. Self-injurious behavior also decreased •with supplementation [Irons et al., 1995]. Other behaviors that decreased with supplementation were aggressive behaviors, temper outbursts, trichotillomania, and tactile defensiveness [Nwokoro and Mulvihill, 1997]. Individuals with SLOS have also been reported to be more sociable, including initiating hugs, after supplementation [Nwokoro and Mulvihill, 1997]. They become more alert and active and demand more attention at home and at school, when previously they had been passive [Irons et al., 1995; 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 with supplementation [Opitz, 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.

ment in articulation, length of sentence, and duration of conversations. Sleep patterns are reported to improve after supplementation [Ryan et al., 1998; Nwokoro et al., in preparation], and parents have reported that the frequency of opisthokinesis decreased after supplementation [Tierney et al., 1999].

DISCUSSION

Current studies in progress are examining various aspects of the behavioral phenotype and are looking ac 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 dysmorphia, and autism, plasma sterol precursor analysis of individuals with autism who have 2-3 toe syndactyly with mild or no facial dysmorphology 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.

As we have described here, Smith-Lemli-Opitz syndrome (SLOS) presents with a characteristic behavioral profile of cognitive delay, sensory hyperreacrivity, irritability, language impairment, sleep cycle disturbance, self-injurious behavior, syndrome specific motor movements, and aurism spectrum behaviors. Of note, 6 of 13 subjects (46%) met the ADI-R algorithm questions and DSM-IV diagnostic criteria for the diagnosis of autism [Tierney et al., 1999]. Various studies estimate that between 10% and 25% of cases of autism spectrum disorders have a known medical condition such äs fragile-X, tuberous sclerosis, or phenylketonuria, although autism tends to occur at a low frequency in most of these conditions [Rutter et al., 1996; Gillberg, 1999]. These findings presented in this review suggest that SLOS is another genetic disorder associated with autism. •

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