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Cognitive and Adaptive Behavior Profiles in Smith-Magenis Syndrome

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ABSTRACT. Smith-Magenis syndrome (SMS) is a multiple congenital anomalies and mental retardation syndrome associated with an interstitial deletion of chromosome 17 band p11.2. The incidence of this microdeletion syndrome is estimated to be 1 in 25,000 individuals. Persons with SMS have a distinctive neurobehavioral phenotype that is characterized by aggressive and self-injurious behaviors and significant sleep disturbances. From December 1990 through September 1999, 58 persons with SMS were enrolled in a 5-day multidisciplinary clinical protocol. Developmental assessments consisting of cognitive level and adaptive behavior were completed in 57 persons. Most patients functioned in the mild-to-moderate range of mental retardation. In addition, we report that patients with SMS have low adaptive functioning with relative strengths in socialization and relative weakness in daily living skills. These data were analyzed in light of the molecular extent of the microdeletion within 17p11.2. We found that the level of cognitive and adaptive functioning does depend on deletion size, and that a small percentage of SMS patients have cognitive function in the borderline range. *J Dev Behav Pediatr 27:188–192, 2006.* Index terms: *chromosome 17, microdeletion syndrome, mental retardation, adaptive behavior.*

Smith-Magenis syndrome (SMS) comprises a constellation of various physical, behavioral, and cognitive features. Initially reported in 1986,[1,2] the incidence of SMS is now estimated to be 1 of 25,000.[3,4] Although most SMS patients harbor a common 3.7-Mb interstitial deletion of 17p11.2,[5,6] 9 individuals with SMS and mutations in *RAI1* (retinoic acid–induced 1)—a gene within the SMS critical region—have been identified (Fig. 1).[7–9]

Distinct physical characteristics in SMS involve multiple organ systems. Specific craniofacial anomalies include brachycephaly, broad face, midface hypoplasia, prognathism, and an everted upper lip.[10,11] Skeletal findings include short hands, short stature, and scoliosis.[10,12] Ophthalmologic manifestations are also present in most patients, specifically, strabismus, myopia, and iris abnormalities.[13,14] Hearing loss is documented in nearly 70% of patients and may be sensorineural, conductive, or mixed.[6] Electroencephalographic abnormalities are observed in approximately 50% of patients, whereas only 20% are affected with a seizure disorder.[6,15] Structural abnormalities of the cardiac and genitourinary/renal systems can occur in deletion patients but have not been described in patients with *RAI1* mutations.[7–9]

The neurobehavioral abnormalities in SMS are among the most striking features of this disorder and are present in patients having both deletion and *RAI1* point mutations.[3,7–10,16,17] Individuals with SMS demonstrate an array of disruptive behaviors, including hyperactivity, distractibility, temper tantrums, and attention-seeking behavior. Self-injurious and aggressive behaviors are also features of SMS and include biting, headbanging, skin picking, and slapping.[3,10,17,18] The most striking self-injurious behaviors associated with SMS are onychotillomania (picking/pulling fingers and toenails) and polyembolokoilamania (insertion of foreign objects into various body orifices).[3] A positive

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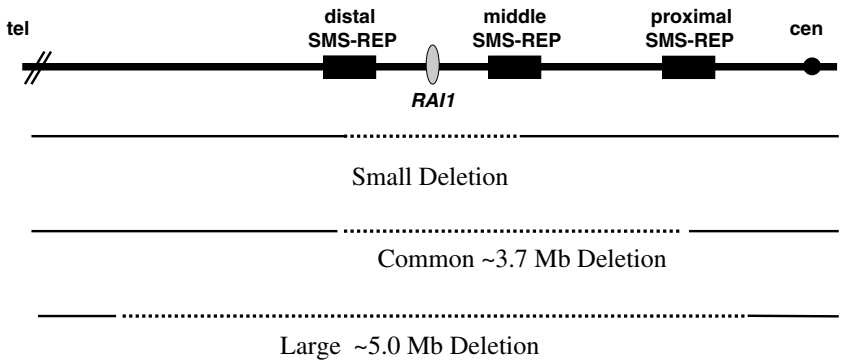

FIGURE 1. Diagram of the proximal short arm of chromosome 17. The centromere, telomere, SMS-REPs, and *RAI1* gene are shown. The common deletion, which is observed in approximately 75% of SMS deletion patients, is approximately 3.7 Mb. Approximately 15% of SMS deletion patients have deletion sizes either larger or smaller than 3.7 Mb. Not all of these are of the same size as depicted in this figure, yet all SMS deletions encompass *RAI1*. Cen indicates centromere; tel, telomere.

behavior that seems unique to SMS is an expression of happiness referred to as self-hugging or the ''spasmodic upper body squeeze.''[19]

All patients with SMS demonstrate significant sleep disturbances. Families report prolonged nocturnal awakening and increased daytime sleepiness.[3] Objective abnormalities include abnormal sleep stage distribution, decreased sleep time, and an abnormal circadian rhythm of melatonin.[16,20] Although the literature supports that sleep disturbances are generally associated with behavior difficulties,[21] objective data regarding SMS, sleep, and behavior correlates are lacking.

Few reports in the medical literature describe the cognitive abilities in SMS. Furthermore, these reports are limited by sample size and lack of molecular data. Initial SMS cohort studies of 29 patients documented moderate mental retardation (MR) in most patients.[10] Dykens et al[22] examined 10 patients with SMS (deletion 17p11.2) and confirmed a mean intelligence quotient (IQ) in the moderate MR range. A larger cohort of SMS deletion patients (19 adults and 29 children) reported by Udwin et al[23] also noted that most patients tested in the moderate MR range.

Fifty-eight patients with SMS were admitted to the General Clinical Research Center at Texas Children's Hospital for clinical assessment. Cognitive and adaptive profiles were completed for 57 subjects. These data are analyzed in light of the molecular extent of the microdeletion within 17p11.2.

METHODS

Patient Ascertainment

From December 1990 to September 1999, 58 persons with Smith-Magenis syndrome (SMS) (57% female; mean age, 9 years; age range, 1 year 6 months to 31 years) were enrolled in the multidisciplinary clinical study of SMS through the General Clinical Research Center at Texas Children's Hospital under a protocol approved by the Baylor College of Medicine Institutional Review Board. All 58 patients were ascertained by abnormal chromosome analysis with del(17)(p11.2p11.2), which was performed for developmental delay and/or mental retardation (MR). Informed consent was obtained from the parent or legal guardian of the patient.

Cytogenetic and Molecular Analysis

Each patient had an interstitial deletion within 17p11.2 detected by G-banded chromosome analysis. The deletion size was determined by fluorescent in situ hybridization and pulsed-field gel electrophoresis and was reported previously.[6] Of the 51 patients in whom the molecular extent of the deletion could be determined, 76% harbored the same-sized (common) deletion.[6] The deletion size of the patient who could not complete the study was undetermined.

Cognitive Assessment

The Cognitive Adaptive Test/Clinical Linguistic and Auditory Milestone Scale[24] was administered by a developmental pediatrician to determine a developmental quotient (DQ) in visual-motor problem-solving (Cognitive Adaptive Test DQ) and language skills (Clinical Linguistic Auditory Milestone Scale DQ) in individuals whose developmental age was less than 3 years. Gross motor development was assessed with the Revised Gesell Developmental Schedules gross motor portion.[25] Psychoeducational testing was administered by a clinical psychologist and included determination of cognitive ability by McCarthy Scales of Children's Abilities (MSCA),[26] Stanford-Binet Intelligence Scales, Fourth Edition (SBIS-IV),[27] Wechsler Intelligence Scales for Children III (WISC-III),[28] or Wechsler Adult Intelligence Scales–Revised (WAIS-R).[29] Intelligence testing was determined based on developmental age. If the developmental age of the patient was below 2 years, a Bayley Scale of Infant Development, Second Edition (BSID-II)[30] was administered

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Table 1. IQ or DQ Score Distribution

	n	Mean	SD	Min	Max
IQ/DQ	55	50.33	12.91	19	78
Verbal IQ	44	54.52	10.49	44	84
Performance IQ	44	53.89	10.14	38	76

(n = 12/57). The primary caregivers (parent or guardian) were administered the Vineland Adaptive Behavior Scale, Interview Edition (VABS)[31] by a clinical psychologist through a semistructured interview. The VABS identifies capability among specific areas of adaptability.

RESULTS

Fifty-seven Smith-Magenis syndrome (SMS) patients completed the neurodevelopmental and cognitive evaluations and/or adaptive behavioral assessments. Fifty-four percent were female (n = 31/57). The age range was 1 year 6 months to 29 years, with median of 8.5 years.

Neurodevelopmental Assessment

Fifty-eight patients underwent a comprehensive history and physical examination by a developmental pediatrician and a clinical geneticist, including investigation of behavior problems and developmental history. Fifty-seven were able to complete the formal developmental and/or adaptive behavior assessments. Language delays were reported in 84% (n = 48/57). Children with visual-motor problem-solving delays comprised 72% (n = 41/57). In the area of gross motor skills, 61% (n = 35/57) of the children exhibited delays based on parent history or observation by the physician.

Intellectual Assessment

Participants were evaluated using standardized measures to assess cognitive/developmental skills. The Bayley Scale of Infant Development, Second Edition (BSID-II) was used to assess cognitive skills in children who were either between the ages of birth and 2½ years or those who were unable to complete a more age-appropriate measure. Twelve children received the BSID-II. The MCSA was used for 13 children who were too old to complete the BSID-II but were too young to complete the Wechsler Intelligence Scales for Children III (WISC-III). The SBIS-IV was used for 7 children who were too old to complete the MCSA but who were too low-functioning to complete the WISC-III. The WISC-III was completed for 20 children, and the WAIS-R was completed for the 4 adults who participated in the study. Standard intelligence quotient (IQ) scores are used when possible. For children who received an intelligence test beyond the normative age range of the test, a developmental quotient (DQ) was calculated. Chronological age was used as a covariate in all analyses.

Table 1 reflects the distribution of IQ/DQ scores for the sample. The average IQ score fell within the moderate range of mental retardation (MR), with scores ranging between the profound range of MR and the borderline range. For those participants (n = 44) who received the MCSA, SBIS-IV, WISC-III, or the WAIS-R, a repeated measures analysis of variance was used to assess any differences between Verbal IQ and Performance IQ. The results did not reveal any statistically significant differences ($p = .598$).

Adaptive Behavior Assessment

The parents of 50 participants were interviewed using the standardized administration of the Vineland Adaptive Behavior Scale, Interview Edition (VABS), which assesses the ability of a child to perform activities of daily living required for personal and social competence. For children younger than 6 years, it yields standard scores in 4 domains, including communication, daily living skills, socialization, and motor skills. For children older than 6 years, the motor skills domain is not assessed.

Table 2 reflects the scores of children from the VABS. Generally, children were found to be functioning in the moderate deficits range of the low adaptive level. Repeated measures analyses of variance were conducted to determine whether there were significant differences in Vineland standard scores across the domains of communication, daily living skills, and socialization. A main effect of domain was observed ($F_{2,48} = 17.75$, $p < .001$). A Bonferroni post hoc test was subsequently conducted, and daily living skills were a relative weakness compared with communication and socialization skills. A second analysis was conducted using only 22 children who were younger than 6 years to consider the motor skills domain of adaptive behavior. A main effect for domain was found ($F_{3,19} = 7.66$, $p < .001$). Results of a Bonferroni post hoc test revealed that the domains of daily living skills and motor skills were relative weaknesses compared with the domains of communication and socialization.

Deletion Size, Cognitive Skills, and Adaptive Behavior

Molecular analyses were performed to determine the size of the deletion of 17p11.2. The deletion size was determined for 51 participants and is published.[6,32,33] Two participants did not complete evaluations for cognitive and adaptive behavior and were subsequently excluded from analyses. The psychologists who were conducting the assessments were blinded to deletion size. One child who was found to have a complex chromosomal rearrangement resulting in deletion 17p11.2 was eliminated from the

Table 2. Standard Scores from the Vineland Adaptive Behavior Scales, Interview Edition

Subtest	n	Mean	SD	Min	Max
Communication	50	54.12	15.74	<20	73
Daily living skills	50	47.58	17.10	<20	76
Socialization	50	56.73	15.82	<20	89
Adaptive behavior composite	50	48.30	13.58	<20	73

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Table 3. IQ or DQ Scores by Deletion Size

Deletion Size	n	Mean	SD	Min	Max
A. IQ or DQ scores					
Common	37	52.62	13.03	21	78
Small	6	51.67	4.76	48	61
Large	5	30.60	10.50	19	44
B. Vineland composite scores					
Common	37	48.00	14.36	20	73
Small	6	50.00	10.43	34	60
Large	5	41.80	14.77	20	57

DQ indicates developmental quotient.

statistical analysis. Table 3A reflects the IQ/DQ scores of participants as broken down by deletion size. Data were normally distributed. The results revealed that children with large deletions were significantly more likely to have lower IQ scores compared with those with small deletions or common deletions ($F_{2,47} = 7.89$, $p = .001$, adjusted $R^2 = .22$). When examining differences in VABS scores (Table 3B), the results revealed that individuals with large deletions were significantly more likely to have lower adaptive behavior composite scores than those with either small or common deletions ($F_{2,47} = 4.67$, $p = .01$, adjusted $R^2 = .48$).

DISCUSSION

Our study represents the first report of the cognitive and adaptive behavior profiles of a cohort of 57 Smith-Magenis syndrome (SMS) patients with deletion 17p11.2 in the context of their deletion size. The findings extend previous research and provide important information regarding the prognosis of patients as a result of their deletion size. First, our results demonstrate that, although the clinical phenotype can be variable in SMS, at least some of these phenotypic differences (e.g., cognition and adaptive function) are related to differences in the size of chromosomal deletion of the patient.

Specifically, in this study, individuals with deletions larger than the 3.7-Mb common deletion had lower levels of cognition (in the severe-to-profound range of mental retardation [MR]) compared with individuals with either small or common deletions. Interestingly, 1 of these 5 patients (Patient 1153) has an uncommon but recurrent 5-Mb deletion.[32] It is important to note that these differences are completely independent of chronological age. Similar differences were noted for adaptive behavior, with individuals with larger deletions exhibiting significantly lower scores compared with individuals with small or common deletions. Thus, our results indicate that overall, individuals with larger deletions, including 1 patient who has the uncommon but recurrent 5-Mb deletion,[32] have a more severe phenotype and a poorer prognosis compared with their counterparts. These data demonstrate the need for further analysis of SMS patients with common-sized deletions in comparison with those patients with either larger or smaller deletions or patients with SMS due to *RAI1* point mutations, to determine the significance of these findings with regard to prognosis and defining future expectations. Although maladaptive behaviors were not examined in this study, previous studies have found attention-seeking behavior, hostility, and impulsivity in patients with SMS.[21] These behaviors can be more common in individuals with severe to profound MR. It therefore will be important to determine whether individuals with SMS who have larger deletions also exhibit higher levels of problem behaviors. Since there have been abnormalities in sleep associated with behavior problems,[21] a correlation with severity of impulsivity, hyperactivity, and inattention in SMS patients would also be warranted in future studies of SMS patients.

As is consistent with previous research, our findings demonstrate that most individuals with SMS are functioning in the moderate range of MR.[10,23] In addition, our study is the first to report borderline cognition in 4 individuals with SMS (all 4 of whom had a common deletion). Strengths and weaknesses in specific subtests could not be examined because a number of different instruments were used to assess cognition in the present study. No overall differences were found in the verbal and nonverbal reasoning abilities of participants in this study. In future research, it will be important to examine subtest strengths and weaknesses in a population of SMS children that is matched for chronological and developmental age to ascertain how the profiles of children with SMS differ from those children with other genetic disorders such as Prader-Willi syndrome, fragile X syndrome, and Williams syndrome.

Regarding the adaptive behavior profiles of the patients in this study, individuals with SMS have relative strengths in the areas of communication and socialization compared with self-help skills or motor skills. These findings were in contrast to a previous study by Dykens et al, who did not demonstrate any differences across the domains of adaptive behavior.[22] It is possible that some of the problematic behaviors (e.g., nocturnal enuresis and encopresis) that have been reported in previous studies of SMS[21] are adversely impacting their activities of daily living. Previous reports show that adults with SMS continue to live either in their parents' homes or residential facilities, and of those in residential facilities, most depend on the staff for personal care.[23]

Our study provides some support for earlier findings of moderate MR in SMS[10,23] and complements these findings with data on adaptive functioning in individuals with SMS. Although the common mechanism of SMS yields a deletion of 17p11.2, recent reports suggest that *RAI1* haploinsufficiency due to deletion or point mutation is sufficient to cause the cognitive and neurobehavioral impairments in this disorder in both humans[7–9] and mice.[34,35] Further clinical investigation of individuals with *RAI1* point mutations is required to determine if there is a difference between the cognitive and behavioral profiles of patients with deletion versus *RAI1* point mutations.

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