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Neurodevelopment of Children Under Three Years with Smith-Magenis Syndrome

Pamela L. Wolters, Ph.D.^{*,§}, Andrea L. Gropman, M.D.^{†,#}, Staci C. Martin, Ph.D.^{*,§}, Michaele R. Smith, PT, M.Ed.[□], Hanna L. Hildenbrand, M.S., OTRL[□], Carmen C. Brewer, Ph.D.[¶], and Ann C.M. Smith, M.A., D.Sc. (Hon)^{‡,#}

^{*}Medical Illness Counseling Center, Chevy Chase, MD

[†]Dept of Neurology, Children's National Medical Center, Washington, D.C.

[‡]Kelly Government Solutions, Rockville, M.D.

[§]Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD

[□]Rehabilitation Medicine Department, National Institutes of Health, Bethesda, MD

[¶]Otolaryngology Branch, National Institute on Deafness and Other Communication Disorders, National Institutes of Health, Bethesda, MD

[#]Office of the Clinical Director, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD

Abstract

Systematic data regarding early neurodevelopmental functioning in Smith-Magenis syndrome is limited. Eleven children with Smith-Magenis syndrome less than three years of age (mean = 19 months; range 5–34) received prospective multidisciplinary assessments using standardized measures. The total sample scored in the moderately to severely delayed range in cognitive functioning, expressive language, and motor skills, and exhibited generalized hypotonia, oral-motor abnormalities, and middle ear dysfunction. Socialization skills were average and significantly higher than daily living, communication, and motor abilities, which were below average. Mean behavior ratings were in the non-autistic range. Exploratory analyses revealed the toddler subgroup scored significantly lower than the infant subgroup in cognition, expressive language, and adaptive behavior suggesting that the toddlers were more delayed than the infants relative to their respective peers. Infants aged approximately one year or younger exhibited cognitive, language, and motor skills that ranged from average to delayed but age-appropriate social skills and minimal maladaptive behaviors. At ages two to three years, the toddlers consistently exhibited cognitive, expressive language, adaptive behavior, and motor delays and mildly to moderately autistic behaviors. Combining age groups in studies may mask developmental and behavioral differences. Increased knowledge of these early neurodevelopmental characteristics should facilitate diagnosis and appropriate intervention.

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Corresponding Author: Pamela L. Wolters, Ph.D., 9030 Old Georgetown Road, Building 82, Room 109, Bethesda, MD 20892-8200., Phone: 301-496-0561; Fax: 301-402-1734; woltersp@mail.nih.gov.

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Introduction

Smith-Magenis syndrome (SMS) is a genetic disorder associated with a distinct phenotype of physical features and neurobehavioral abnormalities due to an interstitial deletion of chromosome 17p11.2 [1] or mutations in the *RAI1* gene [2]. Since first described in 1982 [3], more than 500 persons with SMS have been identified worldwide [4]. The minimum prevalence of this genetic disorder is estimated to be approximately one in every 25,000 births [5]. Clinical recognition of the complex physical, developmental, and behavioral features is important for diagnosis. SMS usually is confirmed by detecting the deletion cytogenetically and/or by fluorescence in situ hybridization (FISH[5]) with genomic probes that contain *RAI1* [6]. Despite advances in cytogenetic techniques, however, the diagnosis of SMS may be delayed or even missed from lack of clinical awareness of the syndrome and overlap of some identifying characteristics with other genetic disorders [7].

The characteristic physical features of children and adults with SMS include minor facial dysmorphism, such as brachycephaly, midface hypoplasia, prominent broad forehead, upslanting palpebral fissures, epicanthal folds, broad nasal bridge, and “tented” upper lip [8]. Hearing impairment, ocular abnormalities, short stature, brachydactyly, and scoliosis also are common [1,5,9].

The neurobehavioral features associated with SMS, described primarily from studies of older children and adults, include mental retardation generally in the mildly to severely delayed range [1,9–14]. Specific cognitive profiles include relative weaknesses in sequential processing, arithmetic, and visual-motor skills and relative strengths in long-term memory, fund of information, and visual-perceptual abilities [11,14].

Most children with SMS exhibit deficits in speech and language skills [1,4,15]. Reports suggest that expressive language is more impaired than receptive language [9,16,17], but limited objective data has been published supporting this assertion. Studies also describe pragmatic language deficits [18] and aberrant voice quality. Otolaryngological abnormalities and oral sensory motor deficits are common and may impact speech [4,15].

Common behavioral problems include deficits in all domains of adaptive behavior [11,14] with daily living skills and communication significantly more impaired than socialization [13]. The majority of children with SMS engage in moderate to severe maladaptive behavior [13,17,19,20], including aggression, temper tantrums, hyperactivity, and stereotypies, such as self-hugging. Furthermore, self-injurious behaviors, such as head-banging, hitting self, hand biting, skin picking, and onychotillomania, are frequent [9,13,17,19,20]. Parent reports [5,9,21] and wrist actigraphy [7,22,23] have documented substantial sleep disturbances that are associated with an inverted circadian rhythm of melatonin [24,25] and maladaptive behavior [17,19]. These behavioral difficulties are considered the most distinctive and problematic characteristic of the syndrome [17,19,26,27].

To date, no systematic evaluation of a group of children with SMS less than three years of age has been reported. A few prospective studies that included infants did not present the infant data separately [9,12,20]. Currently, the main sources of information regarding the development and behavior of infants and young children with SMS are case reports of very small samples [1,10,29–32] based primarily on subjective descriptions, retrospective observations, and chart reviews [1,10,30,32]. These case reports describe global developmental delays, including motor and speech deficits [7,10,15,29–32], but age appropriate social skills [30]. Observations also include decreased overall sleep [22], lethargy, and placid behavior [7,30] in infants, and stereotypic and self-injurious behavioral problems that begin to appear around 18 to 24 months of age [4,5,7,17,29,32]. Systematic, prospective studies of young children using a comprehensive battery of standardized measures are needed to validate these

observations, further define the early neurodevelopmental characteristics of SMS, and address longitudinal changes in development. Such information will facilitate earlier clinical diagnosis, effective educational and treatment interventions, and more appropriate management of this disorder, which may lead to improved developmental outcomes [33].

This study presents objective cross-sectional data collected prospectively from comprehensive multidisciplinary assessments of 11 children with SMS, ages 5 to 35 months, to further delineate the early neurodevelopmental profile of this disorder. Preliminary cross-sectional analyses were conducted to explore the neurodevelopmental characteristics of a younger “infant” subgroup and an older “toddler” subgroup.

Methods

Participants

Children with a confirmed diagnosis of SMS, less than three years of age, who were enrolled on a longitudinal protocol to assess the natural history of this syndrome, were eligible for the study. All children had a visible interstitial deletion of 17p11.2 documented cytogenetically and/or by FISH. The Institutional Review Board approved the protocol. All parents gave written informed consent for their child’s participation.

Procedures

Neurological exam—A pediatric neurologist/geneticist conducted a neurological evaluation on all the children, except one infant and one toddler due to scheduling conflicts. Information obtained from this evaluation included parental report of birth and developmental history, and data regarding cranial nerve function with specific attention to oral motor abilities, neuromotor status, and deep tendon reflexes.

Psychological assessment—A psychologist administered an age-appropriate assessment battery to each child in a quiet room during one to several sessions that consisted of the following scales:

The Bayley Scales of Infant Development-Mental II [34] assesses the developmental functioning of children from birth to 42 months of age. This test yields a Mental Developmental Index, which is a composite standard score reflecting a child’s cognitive, language, motor, and social development relative to the normative group.

The Preschool Language Scale-3 [35] evaluates the receptive and expressive language function of children from birth to 83 months of age. It yields standard scores in total language, auditory comprehension (receptive language), and expressive communication (expressive language).

The Vineland Adaptive Behavior Scales [36] is a semi-structured parent interview that assesses the everyday behavioral functioning of children, ages birth through 18 years. The scale yields standard scores in the domains of communication, daily living skills, socialization, and motor function, and an overall Adaptive Behavior Composite.

The Childhood Autism Rating Scale [37] is a behavioral measure used to identify children with autism. The psychologist rates the child’s behavior based on observations during the test session and from parent report of behaviors not directly observed. Fifteen items are rated from 1 (*normal*) to 4 (*severely abnormal*) including half-point ratings (1.5, 2.5, 3.5), which are summed for the total score. The child’s behavior is classified as non-autistic (total scores < 30), mildly to moderately autistic (30 – 36.5), and severely autistic (37 – 60).

Fine and Gross Motor Evaluation—An occupational therapist assessed the fine motor function and a physical therapist evaluated the gross motor function of four infants and four toddlers on this study. Three children did not complete the motor evaluation because of non-compliance (2 toddlers) or scheduling difficulties (1 infant).

The Peabody Developmental Motor Scales-1st [38] and 2nd edition [39] are two versions of a standardized test that assess the motor skills of children from birth to 72 (2nd edition) or 83 (1st edition) months. Three children evaluated prior to the year 2000 were administered the 1st edition (1 infant, 2 toddlers) and the other five children were assessed with the 2nd edition. Both tests are divided into fine and gross motor scales that assess similar skills and yield gross and fine motor standard scores.

Statistical Analysis

The developmental scales (Bayley, Preschool Language, Peabody Motor, and Vineland) yield standard scores (mean = 100, standard deviation = 15) at all ages of the normative sample, allowing comparisons of children's functioning to their same-aged peers. Furthermore, standard scores can be compared between domains to examine strengths and weaknesses and between different ages to explore the progression of developmental delays over time.

Due to the small sample size in this study, we used non-parametric statistics to evaluate differences between scores. To compare various domain standard scores within tests to identify possible strengths and weaknesses, we used the Wilcoxon signed rank test for measures with two domain scores and the Friedman two-way analysis of variance (ANOVA) for measures with more than two domain scores [40]. If significant differences were found with the Friedman two-way test, post hoc analyses were done to determine which scores were different. One-tailed tests were used when the directionality of the differences was predicted in advance based on previous published reports and clinical observations. Specifically, we hypothesized that expressive language would be more impaired than receptive language [9,16,17] and socialization skills would be better developed than the other adaptive behavior domains [13]. To explore the progression of developmental delays in young children with SMS, we conducted preliminary cross-sectional analyses of standard scores between the infant and toddler subgroups using the exact test method of the Wilcoxon rank sum test [41]. Due to the multiple comparisons and small sample, all analyses of the infant and toddler subgroups are considered exploratory and were performed to generate hypotheses regarding the early neurodevelopment characteristics of SMS.

Results

Participants

Table 1 summarizes the characteristics of the total sample as well as the infant and toddler subgroups. The total sample consisted of 11 children with SMS with a mean age of 19.4 months (median age = 21.1 months; range 5.5 – 34.8). Due to developmental differences between younger and older children under three years of age, the sample was divided into two subgroups for further exploratory analyses. Children from birth to less than 18 months of age were classified as infants while children from 18 months to less than 36 months of age were classified as toddlers. Eighteen months was chosen as the cutoff for the two subgroups because of the significant developmental changes that typically occur around this age, including the transition to walking and talking, and the emerging behavioral changes in children with SMS that have been observed around this time [4,7]. Of the 11 children in the sample, five were classified as infants (mean age = 10.4 months; range = 5.5 – 16.6) and six were classified as toddlers (mean age = 26.8 months; range = 21.1 – 34.8).

All the children were born full-term except for one patient who was a twin delivered at 34 weeks gestation, and none experienced any major birth complications. They all received early intervention services, although the amount and type varied widely from an infant having one general developmental intervention session every other week to a toddler getting both physical and occupational therapy three times a week and speech therapy five times a week. The toddlers received a significantly greater number of therapy sessions per week (mean = 5.7; median = 5.0) than the infants (mean = 2.2; median = 1.5; $p < .05$) yet the amount of therapy was not associated with developmental test scores (all $ps > .05$).

Audiological evaluations, completed the same week as the neurodevelopmental testing, identified middle ear dysfunction in all five infants and five of the six toddlers that was evidenced by flat tympanograms and associated with ventilation tubes and/or middle ear effusion. One toddler was found to have a high frequency sensorineural hearing loss, but he participated fully in the evaluation. Speech detection in a quiet testing situation was adequate, ranging from normal to mildly reduced, for all children except one nine-month old infant who had moderately reduced hearing for speech. Since developmental testing of young infants is dependent primarily on demonstration and observation, the hearing problems of this infant did not appear to interfere with the assessment of his functioning. Thus, the developmental test results are considered valid for all the children.

Neurodevelopmental Functioning of the Total Sample

Cognitive Function—The developmental assessment scores for the total sample of 11 young children with SMS are listed in Table 2. On the Bayley Scales, the mean Mental Developmental Index of 66.6 is over 2 standard deviations below the normative mean of 100, which indicates severe delays in overall cognitive functioning (see Table 3). Six children scored in the severely delayed range, three were mildly-moderately delayed, and two were in the lower end of normal limits.

Language Function—Mean language scores ranged from mild delays in receptive skills (78.7) to moderate delays in expressive skills (72.2). Expressive language scores were lower than receptive language scores in all but two children, who were the youngest infants both less than 8 months old. There was a trend for lower expressive versus receptive language scores, but this discrepancy was not significant ($p = .0654$, one-tailed) in the total sample.

Neurologic Function and Motor Skills—All nine children who received a neurological exam exhibited mild or moderate generalized hypotonia that impacted their motor development. Seven of the nine (77.7%) children had normal deep tendon reflexes (DTRs) while two children exhibited depressed rather than exaggerated DTRs. Three children demonstrated fine motor tremor. By parent report, achievement of gross motor milestones was mildly to moderately delayed in the majority of children. Independent ambulation was achieved at a mean age of 19.7 months (median = 18 months; range = 14 – 30). As assessed by the neurologist, all children exhibited oral-motor dysfunction, ranging from mild to severe, with the majority being moderately impaired. Specific areas of dysfunction included poor tongue mobility and low oral motor tone resulting in open mouth posture, excessive drooling, feeding difficulties, and speech problems.

The mean fine (75.3) and gross (71.0) motor scores indicated moderate delays in the total sample of eight children evaluated with the Peabody Motor tests. All patients except one had slightly lower scores on the gross motor than fine motor scale. A non-significant trend of more impaired gross motor than fine motor skills ($p = .0782$, two tailed) was found in this smaller cohort.

Adaptive and Maladaptive Behavior—The Vineland Scales mean Adaptive Behavior Composite for the total sample (76.3) was in the mildly delayed range. There was a significant difference between scores from the four behavioral domains ($F_{r}=17.54$; $p \leq .001$). Post hoc tests revealed that socialization scores were significantly higher than daily living, communication, and motor scores (all p s $< .05$, one-tailed), as hypothesized. The daily living, communication, and motor scores were not significantly different from each other. The mean score was within normal limits for socialization skills but delayed for the other three domains.

For all 11 children, the Childhood Autism Rating Scale mean total score of 27.2 (median = 28.5; range = 18.5 – 38.5) was in the non-autistic category. The mean item scores for the total sample ranged from the normal to mildly abnormal range with imitation, body use, verbal communication, intellectual response, and general impressions being in the mildly abnormal range (see Table 4).

Preliminary Neurodevelopmental Characteristics of the Infant and Toddler Subgroups

In a preliminary manner, we explored the progression of developmental delays in SMS during early childhood by comparing the cross-sectional assessment scores between the infant and toddler subgroups. We also examined possible strengths and weaknesses in specific areas of development separately for the infants and toddlers by comparing scores from the different domains of the language and motor tests as well as the behavioral scales within each age group.

Cognitive Function—The Bayley Scales Mental Developmental Index scores of the toddler group were significantly lower than those of the infant group ($p \leq .05$; two-tailed), suggesting that the cognitive function of the toddlers is more delayed relative to their peers than the infants are compared to their peers. The mean Mental Developmental Index was mildly delayed (78.0) in the infant subgroup and severely delayed (57.2) in the toddler subgroup.

Language—The toddlers had significantly lower standard scores than the infants in expressive language ($p < .05$, two-tailed) but not receptive language. The mean expressive language score was mildly delayed (83.8) for the infant subgroup and severely delayed (60.6) for the toddler subgroup. The mean receptive language score was mildly delayed (83.0) for the infants and moderately delayed (74.4) for the toddlers.

In the infant subgroup, individual scores in both language domains varied from average to delayed. The infants did not exhibit a consistent receptive-expressive pattern or significant discrepancy between receptive and expressive language scores. However, in the toddler subgroup, all expressive language scores were severely delayed and significantly lower than receptive language scores ($p < .05$; one-tailed) with the receptive-expressive discrepancy ranging from 8 to 24 points.

Motor Skills—For the eight children evaluated with the Peabody Motor tests, the toddler subgroup had slightly, but not significantly, lower standard scores than the infant subgroup in both the fine and gross motor domains. The mean fine and gross motor scores were mildly to moderately delayed (81.0 and 74.5, respectively) for the infants and severely delayed (69.5 and 67.5, respectively) for the toddlers.

In the infant subgroup, no significant difference was found between the fine and gross motor scores but only four infants received a motor evaluation. Although all these infants had slightly lower gross motor compared to fine motor scores, the discrepancies ranged from only 4 to 9 points. Two infants exhibited fine and gross motor skills that were within normal limits and the other two exhibited delays in both these domains.

In the toddler subgroup, no significant difference was found between the gross and fine motor scores but only four toddlers received the motor evaluation. Three toddlers had slightly lower gross motor scores by 4 to 6 points, and all four were delayed in both domains.

Adaptive and Maladaptive Behavior—The standard scores of the toddler subgroup were significantly lower than those of the infant subgroup on the four Vineland domains and Adaptive Behavior Composite ($ps < .05$; two-tailed). For the infant subgroup, all mean domain scores were within normal limits while in the toddler subgroup, all mean domain scores were in the moderately to severely delayed range.

The infant subgroup had a significant difference between the Vineland domain scores ($F = 11.94$; $p < .01$) with socialization significantly higher than motor skills ($p < .05$; one-tailed). The toddler subgroup also had a significant difference between the Vineland domains ($F = 10.71$; $p < .05$) with higher scores on socialization than daily living skills ($ps < .05$, one-tailed). The other domains were not significantly different from one another in either subgroup.

On the Childhood Autism Rating Scale, the total scores of the toddlers were higher, indicating more severe autistic-like behaviors, than those of the infants ($p = .052$, two-tailed). The mean total score was in the mildly to moderately autistic range (30.9) for the toddler subgroup and in the non-autistic range (22.7) for the infant subgroup. On individual items, the toddler subgroup had mildly to moderately abnormal ratings in five areas in which the infant subgroup had normal ratings (imitation, emotional response, object use, verbal communication, and general impressions).

For the infant subgroup, all the Childhood Autism Rating Scale mean scores were in the normal range except for two mildly abnormal mean scores in body use and intellectual response. For the toddler subgroup, the mean scores were in the normal range for eight items, while six (imitation, emotional response, body use, object use, intellectual response, and general impressions) were mildly abnormal and one (verbal communication) was moderately abnormal.

Discussion

This is the first study to report on the neurodevelopment of a group of young children with SMS based on a prospective multidisciplinary assessment conducted systematically using objective, standardized measures and procedures. Neurodevelopmental test results indicated that the total sample of 11 children with SMS less than three years of age exhibited significant developmental delays in cognitive, language, and motor functioning. As a group, parents reported that socialization skills were within normal limits and significantly higher than communication, daily living and motor scores, which were delayed. In addition, psychologists' ratings indicated that maladaptive behaviors (e.g., self-injurious and stereotypies) were present in this young sample but in the non-autistic range overall. Additional evaluations indicated that all children displayed oral motor abnormalities, hypotonia, and middle ear dysfunction. These objective data validate the observations and information presented in earlier case studies obtained with smaller samples and less systematic methods [7,10,29,32]. The current results expand on previous findings by describing the specific ranges of functioning of a sample of young children with SMS in relation to the normative group of typically developing children and by identifying strengths and weaknesses among different developmental domains.

This study also explored the neurodevelopmental characteristics of the infants and toddlers separately to begin investigating the early clinical manifestations of SMS that may be somewhat different between these young age groups. Based on the preliminary cross-sectional analyses comparing developmental assessment scores between the infants and toddlers, a

consistent pattern emerged: the toddler subgroup had significantly lower standard scores on standardized measures of cognitive, expressive language, and behavioral functioning and slightly lower motor scores than the infant subgroup. This pattern suggests that the toddlers are more delayed compared to their same-aged peers than the infants are relative to their peers. The functioning of the four infants near one year of age or younger generally varied from the normal to mildly/moderately delayed range while the six toddlers, from two to three years of age, primarily scored in the moderate to severely delayed range.

Although estimating longitudinal patterns of development based on cross-sectional analysis of a small sample must be considered very tentative, it suggests that the developmental delays seen in SMS may progress from infancy to toddlerhood. Even such a preliminary finding is important for clinicians who may diagnose and monitor these young children, and it supports the need for early developmental evaluations and intervention services in infancy before delays may become more pronounced. This information also is useful for researchers since previous studies often combined infants and young children into one group and reported the developmental results collectively. Possible differences in the neurodevelopmental profile of infants and toddlers found in the current study emphasize the importance of reporting on various age groups separately, even in children less than 3 years of age, and conducting longitudinal research to investigate changes in development over time.

Since the phenotypic features of young children with SMS are often subtle and not well defined, SMS typically is not diagnosed until mid-childhood when the features become more apparent [4,7,30]. To increase the clinical awareness of SMS in early childhood and facilitate earlier diagnosis and plan interventions, preliminary findings regarding the salient neurodevelopmental characteristics of the infants and toddlers are summarized below.

Cognitive

Although mild to moderate mental retardation is found in the majority of school-age children with SMS [9,13], this study documented cognitive delays in all children by two to three years of age and in some children younger than 18 months. Early cognitive delays should prompt a referral for a developmental evaluation to identify specific strengths and weaknesses and initiate interventions.

Speech and Language

The test results from this study indicate that language is a vulnerable domain of functioning in young children with SMS with a trend toward poorer expressive skills. Observations during the test sessions indicated that all but one infant exhibited some vocalizations, but babbling and verbal imitation of sounds were limited. At two to three years of age when children typically use speech as a primary means of communication, the toddlers with SMS rarely used spoken words to communicate. All six toddlers primarily displayed limited vocalizations that included grunts, gurgles, and squeals, and some babbling, thus exhibiting severe impairments in verbal imitation and speech production as indicated by their test scores. Several toddlers used nonverbal communication such as gestures and simple hand signs to communicate their needs. Such expressive language deficits are likely related to the oral sensory motor dysfunction observed in SMS [15].

Expressive language delays also are common in autism [42] and other genetic syndromes [43,44] so should serve as an early warning sign and generate a referral for genetic testing to aid in the differential diagnosis. Young children with SMS also need to be referred for speech and language assessment and therapy early in life to promote development and minimize deficits. Middle ear dysfunction was common in this study and in some other genetic syndromes [43,45]. Since persistent and untreated middle ear abnormalities can cause hearing loss and

impact language development [46], audiological and otological assessment and treatment are essential.

Neurologic and Motor findings

Mild to moderate generalized hypotonia and motor delays, with a trend toward lower gross motor compared to fine motor function, were early and consistent findings in these young children with SMS. It is important to note that the presentation of hypotonia appears to be clinically different than what is typically seen in other young children exhibiting cognitive delay and low muscle tone who tend to have hyperreflexia with central hypotonia. In addition, all children exhibited mild to severe oral-motor dysfunction, which affects speech and feeding skills. Such motor deficits have been reported in other genetic disorders as well [44,47–49]. Health care professionals noticing such early motor dysfunction should refer for physical, occupational, and speech therapy as well as genetic testing.

Behavior

The significant strength found in the children's socialization skills has been described previously in SMS based on retrospective chart reviews in infants [30] and the use of objective measures in older children [13]. The mean scores of all the adaptive behavior domains were within normal limits for the infant subgroup and delayed for the toddler subgroup.

Maladaptive autistic-like behaviors were very minimal in the infants and more prominent in the toddlers. These preliminary data suggest that maladaptive behaviors are more apparent during the second to third year of life, which is consistent with other published reports [4,5, 17,29,30]. Testing observations and parent descriptions of behavior included a few mild repetitive motor movements (e.g., back arching, body rocking, head/hand shaking) in all infants except one nine-month old. Only the two infants who were older than one year demonstrated self-injurious behaviors (e.g., mild hitting/biting self). All the toddlers between 18 and 36 months, however, exhibited both repetitive (e.g., tilting head, body rocking, rubbing surfaces, excessive mouthing of objects/fingers, playing with thread and shoelaces, flipping pages, hugging body) and self-injurious (e.g., hitting/biting self, banging head, pulling hair) behaviors. In addition, parents of the older infants and toddlers reported refusal of solid foods and less sensitivity to pain. Although not assessed in this study, sleep disturbances also have been documented in SMS by one year of age [7,22].

Age-appropriate social skills combined with the lack of maladaptive behaviors in the young infants with SMS may prevent early diagnosis since their behavior may appear similar to normally developing babies. Infants with SMS often are suspected to have Down syndrome [4], another genetic disorder that displays well-developed socialization abilities, hypotonia, expressive language delays [50] and a dysmorphic facial appearance [7]. As toddlers, some of the maladaptive behaviors as well as expressive language deficits are similar to those seen in autism [13], but children with SMS display generally age-appropriate social skills. Thus, awareness of the neurobehavioral aspects of SMS in infants and young children and how they are similar and different from other syndromes is important for purposes of early diagnosis and intervention.

Limitations

The results of this study should be considered preliminary due to the small sample, particularly between the ages of one to two years. However, the diagnosis of SMS in infancy is so rare that the patient population from which to obtain children is very small. These data also were collected on a natural history study designed to describe development without controlling for factors that may impact functioning such as socioeconomic status, parental characteristics, and level of intervention services. Additional limitations include the cross-sectional design and

multiple comparisons of the infant and toddler subgroups that were performed without statistical adjustment due to the exploratory nature of the analyses; thus, all significant findings about these age groups should be considered tentative. However, this is the largest published study of children with SMS younger than three years of age assessed prospectively with standardized measures. Despite dividing the sample into two smaller age groups, administering the same standardized measures to both the infants and toddlers allows the scores to be compared, and these preliminary findings can help guide future research and improve the clinical awareness of SMS in young children. Systematic longitudinal studies beginning in infancy are sorely needed to examine the changes in various developmental domains over time. The children in this study are being assessed periodically and the longitudinal data will be analyzed in the future.

Summary

This study systematically evaluated a group of children with SMS less than three years of age to provide a better understanding of the early neurodevelopmental characteristics of the disorder. Given the significant and pervasive developmental and behavioral impairments identified in these young children, a multidisciplinary team approach is critical for the appropriate management of SMS that includes comprehensive assessments and early intervention services. In addition, parents would benefit from training in sign language and behavior modification to help prevent and manage the developmental and behavioral challenges characteristic of SMS. Therefore, early diagnosis and intervention, facilitated by a better understanding of the specific neurodevelopmental features of infants and young children with SMS, are important first steps in managing the multidisciplinary and complex needs of this syndrome. Future studies need to report on different age groups separately so specific characteristics are not masked by overall effects and collect longitudinal data to investigate developmental changes throughout childhood.

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Table 1

Demographic Characteristics of the Sample

	Total Sample	Age Group	
		Infant [*]	Toddler [†]
Mean age (months)	19.4	10.4	26.8
Median age (months)	21.1	9.4	25.1
Age range (months)	5.5 – 34.8	5.5 – 16.6	21.1 – 34.8
Gender (male/female)	3/8	1/4	2/4
Race (Caucasian/Hispanic)	10/1	5/0	5/1
Median parent education (years)	15.3	14.0	15.8
Parent education range (years)	10.5 – 17.0	12.0 – 16.0	10.5 – 17.0

* Children < 18 months classified as infants.

† Children from 18 to < 36 months classified as toddlers.

Table 2

Scores on the Developmental and Behavioral Scales for the Total Sample and the Infant and Toddler Subgroups*

Measures	Total Sample (N = 11)	Age Groups	
	Mean (Mdn [†] , range)	Infant (n = 5) Mean (Mdn, range)	Toddler (n = 6) Mean (Mdn, range)
Bayley Mental Scale			
Mental Developmental Index	66.6 (63.0, 42 – 89)	78.0 (82.0, 63 – 89)	57.2 (54.0, 42 – 84)
Preschool Language Scale [‡]			
Auditory Comprehension	78.7 (77.0, 59 – 104)	83.0 (77.0, 75 – 104)	74.4 (77.0, 59 – 89)
Expressive Language	72.2 (65.0, 51 – 111)	83.8 (71.0, 65 – 111)	60.6 (63.0, 51 – 65)
Peabody Developmental Motor Scales [§]			
Fine Motor	75.3 (70.0, 69 – 97)	81.0 (79.0, 69 – 97)	69.5 (69.5, 69 – 70)
Gross Motor	71.0 (65.0, 61 – 91)	74.5 (73.0, 61 – 91)	67.5 (65.0, 64 – 76)
Vineland Adaptive Behavior Scales			
Communication	80.1 (80.0, 60 – 104)	91.4 (90.0, 74 – 104)	70.7 (69.5, 60 – 82)
Daily Living	78.6 (73.0, 52 – 106)	92.6 (95.0, 69 – 106)	67.0 (70.0, 52 – 75)
Socialization	86.4 (82.0, 63 – 108)	98.6 (103.0, 78 – 108)	76.2 (78.0, 63 – 87)
Motor	76.6 (75.0, 54 – 84)	85.0 (87.0, 67 – 94)	69.7 (70.0, 54 – 84)
Composite Score	76.3 (71.0, 53 – 101)	89.2 (94.0, 66 – 101)	65.5 (68.5, 53 – 72)
Childhood Autism Rating Scale			
Total Score	27.2 (28.5, 18.5 – 38.5)	22.7 (20.5, 19 – 33)	30.9 (30.0, 25 – 39)

* All scales yield standard scores (mean = 100, SD = 15) except the Childhood Autism Rating Scale (total score < 30 = no autistic behaviors, 30 – 37 = mild-moderate autistic behaviors, and > 37 = severe autistic behaviors).

[†] Mdn = Median

[‡] n = 5 on the Preschool Language Scale-3 for the toddler subgroup; one toddler primarily spoke Spanish and was not administered the language scale so on this test N = 10.

[§] n = 4 on the Peabody Developmental Motor Scales for each the infant and toddler subgroups so on this test N = 8.

Table 3

Descriptive Classifications of Standard Scores from the Developmental Scales*

Classification	Relation to Normative Mean	Range of Standard Scores
Within Normal Limits	Within ± 1 SD [†]	85 – 115
Mildly Delayed	From 1 – 1.5 SDs below	77 – 84
Moderately Delayed	From 1.5 – 2 SDs below	70 – 76
Severely Delayed	2 + SDs below	≤ 69

* This table consolidates the descriptive classifications of standard scores from the four developmental scales (Bayley Scales Infant Development-II, Preshool Language Scale-3, Peabody Developmental Motor Scales, Vineland Adaptive Behavior Scales) used in this study in relation to the normal curve.

[†] SD = Standard Deviation

Table 4

Item Scores on the Childhood Autism Rating Scale for the Total Sample and Infant and Toddler Subgroups*

Items	Age Groups		
	Total Sample (N = 11) Mean (Mdn [†] , Range)	Infant (n = 5) Mean (Mdn, Range)	Toddler (n = 6) Mean (Mdn, Range)
Relating to People	1.5 (1.5, 1.0 – 2.5)	1.4 (1.0, 1.0 – 2.5)	1.5 (1.5, 1.0 – 2.5)
Imitation	2.5 (2.5, 1.0 – 3.5)	1.9 (2.0, 1.0 – 2.5)	2.9 (3.0, 2.0 – 3.5)
Emotional Response	1.8 (2.0, 1.0 – 3.0)	1.5 (1.5, 1.0 – 2.5)	2.1 (2.0, 1.0 – 3.0)
Body Use	2.3 (2.0, 1.5 – 3.0)	2.3 (2.0, 1.5 – 3.0)	2.3 (2.25, 2.0 – 3.0)
Object Use	1.7 (1.5, 1.0 – 3.0)	1.3 (1.0, 1.0 – 2.5)	2.0 (2.0, 1.5 – 3.0)
Adaptation to Change	1.4 (1.0, 1.0 – 2.5)	1.0 (1.0, 1.0 – 1.0)	1.7 (1.5, 1.0 – 2.5)
Visual Response	1.4 (1.0, 1.0 – 2.5)	1.3 (1.0, 1.0 – 2.0)	1.5 (1.25, 1.0 – 2.5)
Listening Response	1.6 (1.5, 1.0 – 3.0)	1.3 (1.5, 1.0 – 1.5)	1.9 (2.0, 1.0 – 3.0)
Taste, Smell Touch Response	1.7 (2.0, 1.0 – 2.5)	1.7 (2.0, 1.0 – 2.5)	1.8 (2.0, 1.0 – 2.0)
Fear or Nervousness	1.2 (1.0, 1.0 – 2.0)	1.0 (1.0, 1.0 – 1.0)	1.3 (1.0, 1.0 – 2.0)
Verbal Communication	2.6 (2.5, 1.0 – 4.0)	1.6 (1.5, 1.0 – 2.5)	3.3 (3.5, 2.5 – 4.0)
Nonverbal Communication	1.6 (1.5, 1.0 – 3.0)	1.6 (1.5, 1.0 – 2.0)	1.6 (1.25, 1.0 – 3.0)
Activity Level	1.6 (1.5, 1.0 – 2.0)	1.2 (1.0, 1.0 – 2.0)	1.8 (2.0, 1.5 – 2.0)
Intellectual Response	2.5 (2.5, 1.5 – 3.0)	2.0 (2.0, 1.5 – 2.5)	2.9 (3.0, 2.5 – 3.0)
General Impressions	2.0 (2.0, 1.0 – 3.0)	1.6 (1.5, 1.0 – 2.5)	2.3 (2.25, 2.0 – 3.0)

* Item scores range from 1.0 – 4.0 (1 = normal, 2 = mildly abnormal, 3 = moderately abnormal, 4 = severely abnormal).

[†] Mdn = Median