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Individuals with Smith-Magenis syndrome display profound neurodevelopmental behavioral deficiencies and exhibit food-related behaviors equivalent to Prader-Willi syndrome

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ABSTRACT

Smith-Magenis syndrome (SMS) is a neurodevelopmental disorder associated with intellectual disability, sleep disturbances, early onset obesity and vast behavioral deficits. We used the Behavior Problems Inventory-01 to categorize the frequency and severity of behavioral abnormalities in a SMS cohort relative to individuals with intellectual disability of heterogeneous etiology. Self-injurious, stereotyped, and aggressive/destructive behavioral scores indicated that both frequency and severity were significantly higher among individuals with SMS relative to those with intellectual disability. Next, we categorized food behaviors in our SMS cohort across age using the Food Related Problems Questionnaire (FRPQ) and found that problems began to occur in SMS children as early as 5–11 years old, but children 12–18 years old and adults manifested the most severe problems. Furthermore, we evaluated the similarities of SMS adult food-related behaviors to those with intellectual disability and found that SMS adults had more severe behavioral problems. Many neurodevelopmental disorders exhibit syndromic obesity including SMS. Prader-Willi syndrome (PWS) is the most frequent neurodevelopmental disorder with syndromic obesity and has a well-established management and treatment plan. Using the FRPQ we found that SMS adults had similar scores relative to PWS adults. Both syndromes manifest weight gain early in development, and the FRPQ scores highlight specific areas in which behavioral similarities exist, including preoccupation with food, impaired satiety, and negative behavioral responses. SMS food-related behavior treatment paradigms are not as refined as PWS, suggesting that current PWS treatments for prevention of obesity may be beneficial for individuals with SMS.

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1. Introduction

Smith-Magenis syndrome (SMS) is a complex neurodevelopmental disorder caused by haploinsufficiency of *RAI1* due to either a deleterious point mutation or an interstitial deletion of chromosome band 17p11.2. SMS is routinely characterized by variable intellectual disability, sleep disturbances, craniofacial and skeletal changes, early onset obesity and a number of distinctive behavioral abnormalities including self-injury, aggression, and stereotypies (Elsea & Girirajan, 2008). Maladaptive behaviors are common among individuals with intellectual disability, but some neurodevelopmental disorders have a more severe manifestation than others. Maladaptive behaviors in SMS vary with age but are a key component for identifying the disorder; however, it is unclear how frequent and severe SMS behavioral problems are relative to disorders with intellectual disability (Edelman et al., 2007; Gropman, Elsea, Duncan, & Smith, 2007; Smith, Dykens, & Greenberg, 1998; Wolters et al., 2009).

In addition to specific behavioral hallmarks, hypotonia and feeding difficulties during infancy are very common among individuals with SMS (Gropman, Duncan, & Smith, 2006). Interestingly, 90% of individuals with SMS are at or above the 90th percentile for weight by age 14 (Burns et al., 2010). The transition in food-related behavioral patterns during infancy to the onset of obesity in early adolescence is not well understood. SMS mouse model work has demonstrated a similar feeding behavioral pattern where *Rai1* haploinsufficient ($Rai1^{+/-}$) mice throughout early development are similar in weight relative to wild-type littermates but transition to an obese phenotype in early adulthood (Burns et al., 2010). However, a recent study has shown that the growth rate and weight gain during early developmental stages significantly increased when $Rai1^{+/-}$ mice are fed either a high carbohydrate or a high fat diet, suggesting that dietary content early in development is important in obesity outcomes in SMS (Alaimo, Hahn, Mullegama, & Elsea, 2014). In addition, $Rai1^{+/-}$ mice also consume more food and have reduced satiation compared to wild type mice implicating a dysregulation of signaling systems underlying eating behavior (Burns et al., 2010).

Phenotypic food-related behaviors are found across a variety of neurodevelopmental disorders and cohorts of subjects with intellectual disability. One such neurodevelopmental disorder with phenotypic food-related behaviors is Prader-Willi syndrome (PWS). PWS is the leading known genetic cause of obesity and has a very similar phenotype to SMS including intellectual disability, comparable behavioral problems, early onset of obesity and hyperphagia. In early infancy, individuals with PWS have severe hypotonia and feeding difficulties, but by 6–10 years of age individuals are typically obese (Wollmann, Schultz, Grauer, & Ranke, 1998). Targeted interventions that consist of a strict diet of reduced fat, modified carbohydrates and limited access to food are extremely effective in limiting weight gain in these individuals, despite the juncture of time when the interventions are introduced (Bonfig, Dokoupil, & Schmidt, 2009; Schmidt, Pozza, Bonfig, Schwarz, & Dokoupil, 2008). Therefore, PWS weight management treatments provide a model for intervention, which may also discriminate, to SMS individuals; however, the degree of similarity between the food-related behavioral patterns observed in each disorder remains unclear.

Comparing phenotypically similar but genetically different neurodevelopmental syndromes may reveal a comprehensive understanding of the genetic basis of behavioral problems. Therefore, the aim of the present study was two-fold. The first aim was to discern the nature and extent of neurobehavioral deficits in SMS and to compare these deficits to a sample with intellectual disability using the Behavior Problems Inventory-01. The second aim was to compare food-related behavioral phenotypes using the Food Related Problems Questionnaire in adults with SMS relative to an adult sample with intellectual disability and to PWS to determine behavioral similarities between each disorder.

2. Materials and methods

2.1. Participants

Of the 100 respondents of the surveys 85% were female and either the biological or the adoptive parent (95%) of the SMS individual. All SMS individuals had a confirmed diagnosis of SMS and a chromosomal deletion (90%) was predominantly reported as the molecular finding. Additionally, 91% resided at home while 9% resided in a residential facility. Seventy-seven percent of the responders identified that their child has or had received special education services or remedial education. All 100 respondents completed the Food Related Problems Questionnaire (FRPQ) and 99 respondents completed The Behavioral Problems Inventory (BPI)-01. One respondent did not complete both surveys. On the BPI-01, participants with SMS, as described by their parent/caregiver, had a mean age of 13.5 years ($SD = 9.8$) ranging from 1.5 to 51 years, were 57% female, and 79% white of a non-Latino background. Individuals with SMS described on the FRQP were categorized by school age: 15 preschool age with a mean age of 3.2 years ($SD = 1.0$) ranging from 1.5 to 4 years; 36 primary school age with a mean age of 8.0 years ($SD = 1.9$) ranging from 5 to 11 years; 27 secondary school age with a mean age of 14.7 years ($SD = 1.8$) ranging from 11.8 to 18 years; and 22 adults with a mean age of 28.4 years ($SD = 9.3$) ranging from 20 to 51 years. Characteristics of participants are shown in Table 1 (Rojahn, Matson, Lott, Esbensen, & Smalls, 2001).

2.2. Procedure

All participants were recruited through the SMS outreach group Parents and Researchers Interested in SMS (PRISMS) via the organizations website, electronic mailing list, and Facebook group. The surveys were administered online via