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Behavior and Sleep Disturbance in Smith-Magenis Syndrome

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Abstract

Purpose of review: To provide an update of the most recent studies on Smith-Magenis syndrome (SMS) with a focus on the unique pattern of behavioral and sleep disturbances associated with the condition.

Recent findings: The recent literature on SMS has focused on the characteristic severe behavioral and sleep disturbances. A better understanding of the underlying pathophysiological mechanisms and common clinical course has helped further characterize SMS, while much is left to be discovered in regard to effective treatment/management.

Summary: SMS is a difficult to manage genetic condition defined by pervasive and progressive behavioral and sleep disturbances with a unique pattern that can often be easily discerned from other neurodevelopmental disorders. Common behavioral features include maladaptive/self-injurious, aggressive, stereotypic, and the newly appreciated food seeking behaviors associated with SMS. In addition, there is a sleep disturbance defined by an altered circadian rhythm with frequent nighttime waking and daytime sleepiness, causing patients and families significant distress. Small studies have suggested some treatment/management approaches to the behavioral and sleep disturbances, however, a lot remains to be discovered.

Keywords

Smith-Magenis syndrome; 17p11.2 deletion; RAI1; self-injurious behaviors; sleep disturbance

Introduction

Smith-Magenis syndrome (SMS) (OMIM #182290) is an autosomal dominant genetic condition characterized most notably by distinctive physical features, developmental delays, behavioral abnormalities, and sleep disturbance. Less commonly, patients may also present with seizures, hearing loss, renal anomalies, ocular anomalies, and cleft lip and/or palate. Weight management is also a concern, with >90% of individuals being overweight or obese after 10 years of age.

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Conflicts of interest

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SMS is typically the result of haploinsufficiency of *retinoic acid induced 1* (*RAI1)* due to a ~3.7 Mb interstitial deletion of chromosome 17p11.2, including *RAI1*; however, ~10% of cases may also be secondary to pathogenic variants in the gene itself [1]. Haploinsufficiency of RAI1 is known to cause most of the SMS features, including the neurocognitive, behavioral, and sleep phenotype; however, there are some differences in patients with SMS secondary to pathogenic *RAI1* variants compared to those with the more expansive 17p11.2 deletion. For example, patients with *RAI1* variants generally have less severe cognitive impairment and a lower incidence of hypotonia, short stature, hearing loss, and congenital heart defects but are more likely to exhibit some of the abnormal behavioral patterns common to SMS [2,3]. While most cases are the result of de novo genomic events caused by non-allelic homologous recombination errors during meiosis, there are rare reports of recurrence in families secondary to maternal mosaicism [4], complex familial chromosomal rearrangements [5,6], and one reported case of a maternally inherited *RAI1* pathogenic variant [1].

With advances in genetic testing and increased accessibility, the majority of cases are diagnosed during infancy through early childhood, although symptoms may be present from birth [7]. While most have normal growth parameters at birth, failure to thrive with decelerated weight gain typically ensues with associated feeding difficulties and gastroesophageal reflux [8]. Most will also have mild hypotonia, hyporeflexia, and a generalized gestalt of complacency similar to that seen in Down syndrome [9]. With such non-specific early findings, SMS will not typically be suspected until some of the behavioral and sleep abnormalities that are unique to the condition become more apparent with age [9].

This review seeks to provide an update on the most recent studies regarding the unique behavioral and sleep patterns observed in SMS. The behavioral abnormalities will focus on the maladaptive/self-injurious, aggressive, stereotypic, and food seeking behaviors common to SMS, whereas discussion of sleep disturbance will focus on the abnormal melatonin secretion pattern and possible treatments, as the underlying pathophysiological mechanism is better understood.

Behavior Disturbance

Patients with SMS typically do not exhibit behavioral problems until at least 18 months of age [9]. In fact, many are described as being very well-behaved babies with infrequent crying early in life. The behavioral problems will then generally progress with age with particular escalation coinciding with the major life stages: 18–24 months, school age, and onset of puberty [10]. The behavior disturbances may, in part, be related to neurocognitive impairment like speech delay, leading to more frequent and severe temper tantrums, but are notably far more severe than that observed in comparable disorders with developmental delays. The behavioral phenotype of SMS includes a complex mixture of maladaptive/self-injurious, aggressive, stereotypic, and food seeking behaviors, which recent studies have been able to further characterize.

The maladaptive and self-injurious behaviors in SMS are a major concern for caregivers, as these actions can result in serious physical injury. Symptoms can begin as early as 18

months with head-banging and later manifest as frequent outbursts, severe temper tantrums, disobedience, self-injury, aggression towards others, and destruction of property [11]. These maladaptive behaviors typically progress with age due to a widening gap between intellect and emotional development, resulting in particularly difficult to control behaviors in adolescents and adults [12]. Predictors of such maladaptive behaviors have been described, with the most notable being the degree of sleep disturbance, environmental contingencies, change-related anxiety, and level of impulsivity [13,14**].

The self-injurious behaviors specifically, have a very unique pattern that helps distinguish it from other similar neurodevelopmental disorders. Huisman et al. [15*] compared the self-injurious behaviors in 12 different genetic conditions including SMS, and identified some notable similarities and differences between them. For example, common influencing factors leading to self-injurious behaviors for SMS and most other conditions include the presence of interpersonal behavioral characteristics like stereotypy, repetitive behavior, impulsivity, hyperactivity, and anxiety, as well as environmental factors like seeking adult attention, ignoring others, demand avoidance, solitude, change of routine, change to environment, and institutionalization. However, the self-injurious behaviors in SMS are unique in that it has a particularly early onset usually before 2 years of age, a very high prevalence comparable to Lesch-Nyhan syndrome of >90%, and involvement of several body parts, including the very characteristic onychotillomania (53.5%), polyembolokoilamania (32.3%), and trichotillomania (20.2%) [15*,16**,17**]. Polyembolokoilamania, or insertion of objects into bodily orifices, in SMS most commonly involves the ears, but may also include the nose, vagina, and rectum and may be mistaken for sexual abuse [18]. Additional methods of self-injury reported in individuals with SMS include head-hitting (self and/or with objects) (79.8%), body hitting (self and/or with objects) (66.7%), self-biting (57%), skin-picking (46.5%), self-pinching (29.3%), and self-induced vomiting (10.1%) [16**].

Individuals with SMS also have a tendency towards aggression and property destruction with a reported prevalence of 77% in one study and particularly high in those with hearing and/or vision loss [17**]. This is in contrast to control patients with idiopathic autism spectrum disorder (ASD) who had a prevalence of 44% of property destruction [17**]. Physical aggression is also a common feature of SMS with a prevalence of 68–87%, although not considered to be significantly more prevalent than that observed in contrasting neurodevelopmentally delayed children [17**,19]. Similar to the self-injurious behaviors, episodes of physical aggression in SMS are highly associated with environmental contingencies [19]. Furthermore, aggression is often directed towards close relatives, can be verbal or physical, and interestingly, is not always impulsive and can even be planned [20**].

Another classical feature of SMS includes the very stereotypic behaviors that often lead medical providers to the eventual diagnosis. Most commonly observed is a spasmodic crossing of both arms across the upper-body and squeezing often referred to as “self-hugging” or clasping both hands and tensing both arms at the sides or in front of the body. Episodes typically last seconds and occur in flurries during times of excitement and are generally positive behaviors. There is also a tendency to put their hands in their mouth which can lead to self-mutilation of the hand/fingers. On the less destructive spectrum, patients

may also lick their fingers and mechanically turn the pages of a book, referred to as “lick and flip,” which more recent studies suggest is not quite as prevalent in SMS as initially suggested [10]. Other common stereotypies include yelling (86%), clapping hands (70%), teeth grinding (54–62%), bouncing around (46%), body rocking (43%), spinning/twirling objects (40%), and grimacing (30%) [16**,21].

More recent literature has found SMS patients to have significant food-related behaviors, comparable to those seen in Prader-Willi syndrome (PWS). Similar to PWS, these food-related behaviors lead to childhood/adolescent onset obesity with greater than 90% of SMS adolescents and adults being above the 90th percentile for weight [22]. In a study comparing SMS and PWS food-related behaviors, the total scores on the Food Related Problems Questionnaire (FRPQ) were similar for the two conditions and statistically higher than controls with idiopathic intellectual disability. Both SMS and PWS patients reported high food-related behavior scores relating to preoccupation, composite negative behavior, and taking/storing food. SMS patients, however, scored higher in inappropriate response to food frequency and lower in impaired satiety when compared to PWS [16**]. Studies have shown that *RAI1* haploinsufficiency down regulates brain-derived neurotrophic factor (BDNF) [22,23]; low levels of BDNF have previously been associated with obesity and hyperphagia [24,25*]. This may explain some the food seeking behaviors seen in SMS patients, although additional research examining this connection is necessary.

Sleep Disturbance

The second major characteristic of SMS is severe sleep disturbance. Recent studies have attributed the sleep disturbance in SMS to a primary disturbance of the circadian clock, with RAI1 functioning as a positive regulator of *Circadian Locomotor Output Cycles Kaput* (*CLOCK*) transcription, a key component of the mammalian circadian oscillator [25*]. Dysregulation of *CLOCK* results in further dysregulation of other circadian clock components, including *PER1*, *PER2*, *CRY*, *BMAL1,* and others [26, 27]. This disconnect has more specifically been localized to the hypothalamus when compared to peripheral tissues in the mouse model, indicating an asynchronized rhythmicity [28].

Additionally, disrupted melatonin secretion has been noted with moderate to high levels of daytime salivary melatonin observed in SMS patients [29,30**]. Barboni et al. [31*] proposed this to be the result of impaired pupillary light responses with an altered sustained response to light of a specific wavelength, causing defective melatonin production suppression during the day.

Finally, facial anatomy, hypotonia, and obesity-related ventilatory problems are often overlooked as contributing factors to the sleeping difficulties in SMS, for which non-invasive ventilation has been shown to effectively manage, when indicated [32]. Thus, evaluation for obstructive sleep apnea with a polysomnogram may be warranted in patients.

Clinically, the sleep disturbances in SMS manifest as fragmented sleep cycles with a reduction in total sleep time that has been documented as early as six months of age and persistent throughout life [7,26,33,34**]. Sleep complaints include frequent nighttime

awakenings, parasomnias, and excessive daytime sleepiness [34**]. The daytime sleepiness is particularly notable in SMS because of the dual contribution of lack of nighttime sleep and elevated daytime melatonin [35]. In comparison to other neurodevelopmental disorders, SMS patients have significantly higher levels of sleep disordered breathing, daytime sleepiness/drowsiness, severe night waking, and severe early morning waking.

Treatment

The treatment/management of SMS is challenging with a few basic guidelines put forth and a lot left to be determined. No general consensus has been reached for treatment of behaviors, although most suggest a multimodal patient-centered approach of which several considerations must be made. Because SMS patients have decreased sensitivity to pain, severe medical conditions may go undiagnosed and exacerbate behavioral disturbances [20**]. Thus, causes of physical pain relating to an undiagnosed medical condition like dental infections, ear infections, or gastrointestinal pain should always be ruled out during episodes of increased behavioral disturbance. Subclinical seizures may also go undiagnosed and misinterpreted as inattention and worsening behaviors. Furthermore, hearing loss and delays in expressive language, common to SMS, can increase anxiety and frustration and thus, predispose patients to more severe behavioral problems. Early hearing evaluations and initiation of language/speech therapy and assistive communication are considered high priority [20**,36*]. Use of psychotropic medication is often required, as well, for the management of inattention and hyperactivity, although no single regimen has shown consistent or long-term efficacy in SMS patients [37, 38]. Given the high distractibility and lack of flexibility, patients tend to do best when placed in a small class with a stable environment and daily routine. Patients also may benefit from focused parent training and cognitive behavioral therapy (CBT), but no specific management strategies for the maladaptive behaviors have been described for SMS. In a series of studies, Wilde et al. [39–41] found relative to Down syndrome patients, SMS patients have greater executive functioning deficits, suggesting that interventions focusing on everyday activities like working memory may be beneficial. Social motivations also differed, with SMS characterized by comparatively frequent social initiations when adult attention is low and stronger preference for familiar adults, which may be particularly demanding for caregivers and, in part, explain the reported high levels of caregiver stress [42]. Nonetheless, the behavior profile of SMS patients differs from other neurodevelopmental disorders and as such may require a different treatment approach.

A key factor in managing the behavioral problems observed in SMS is to ameliorate the sleep disturbance through various treatment approaches. Recent theory has focused on reestablishing the circadian rhythm via administration of exogenous melatonin before bed and sometimes beta-adrenergic antagonists in the morning to block endogenous melatonin secretion. Early studies suggested efficacy of such strategies with reported normalized sleeping habits, improved behavior, and improved quality of life for patients and their families [43–47]. In another case, ramelteon at night and amphetamine-dextroamphetamine salt led to a decreased CSHQ (Children Sleep Habits Questionnaire) score and Vanderbilt ADHD parent rating scale in a 7 year old patient [48]. However, most of these reports are anecdotal and no large well-controlled treatment trials have been reported to date. As such,

no standard of care for the pharmaceutical management of the sleep disturbances in SMS have been put forth, and it is generally recommended that a patient-centered approach is utilized. Current therapies in the clinical trial phase include the use of melatonin, bright lights, and tasimelteon.

Interestingly, a recent study, Huang et al [49] showed that at least in the mouse model, normalizing the *Rai1* level 3–4 weeks after birth corrected the expression of genes related to neural developmental pathways and reversed the social interaction deficit as illustrated by the tube test. In contrast, *Rai1* reactivation 7–8 weeks after birth was not found to be beneficial. Thus, with future advancements, reversibility of the SMS neurobehavioral phenotype may be possible in humans if implemented during this critical period.

Conclusion:

SMS is a rare genetic condition most notably characterized by a common pattern of severe behavioral and sleep disturbances. The recent literature on SMS has further defined these characteristics along with a better understanding of their underlying pathophysiological mechanisms. Additionally, an association to abnormal food related behaviors has been established. Nonetheless, much remains to be learned about SMS, particularly in regard to treatment/management, as families continue to report difficulty in controlling the behavior and sleep disturbances.

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Key Points :

- Behavioral and sleep disturbances in Smith-Magenis syndrome are pervasive and progressive with age into adulthood
- Common behavioral features include maladaptive/self-injurious, aggressive, stereotypic, and the newly appreciated food seeking behaviors
- Sleep disturbance in SMS is defined by frequent nighttime waking and daytime sleepiness, likely, in part, due to abnormal melatonin secretion and a dysregulation of the molecular circadian clock.
- The use of exogenous melatonin and beta-adrenergic antagonists has shown some efficacy in a few small reports; however, a well-formulated study has yet to establish this as a standard of care.
- Smith-Magenis syndrome has significant differences compared to other neurodevelopmental disorders and as such may require a different treatment/ management approach.