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Smith-Magenis Syndrome: Genetic Basis and Clinical Implications

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Smith-Magenis syndrome (SMS) is a neurobehavioral disorder associated with deletions and mutations of the RAI1 *gene on chromosome 17p11.2. Clinical features of the syndrome include intellectual disability, sleep disturbance, craniofacial differences, and a distinctive profile of stereotypic and self-injurious behaviors. Although the functional role of* RAI1 *and neighboring genes is not completely understood, disruption of these genes is thought to contribute to specific clinical features of the disorder. Maladaptive behaviors in people with SMS appear to reflect a complex interplay between physiology and environment that may be further compounded by an underlying developmental asynchrony. Management requires a multidisciplinary approach and involves treatment for sleep disturbance, speech and occupational therapies, medical monitoring, educational and behavioral interventions, and family support.*

KEYWORDS Smith-Magenis syndrome, deletion 17p11.2, self-injury, intellectual disability, sleep disturbance, dual diagnosis

Since the first reports of individuals with Chromosome 17p11.2 deletions (Greenberg et al., 1991; Smith et al., 1986; Stratton et al., 1986), hundreds of articles have been published describing a broad range of physical, behavioral, and cognitive findings in Smith-Magenis syndrome (SMS; Edelman et al., 2007; Greenberg et al., 1996; Smith et al., 2006). Initially thought to be directly correlated with the deletion of 15 or more contiguous genes, Slager, Newton, Vlangos, Finucane, & Elsea (2003) later discovered that the clinical features

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of SMS are primarily due to disruption of a single gene, called *RAI1*, which is found within the 17p11.2 region. This allowed the delineation of a molecularly related and clinically similar subtype of SMS due to mutations in *RAI1*. Whether due to a 17p11.2 deletion or an *RAI1* mutation, SMS is a multisystem disorder with significant disabling effects on behavior and cognition.

MOLECULAR BASIS

Approximately 90% of people with SMS have deletions of the chromosomal region 17p11.2 that encompasses the retinoic acid induced 1 (*RAI1*) gene. Although there is some variability in deletion size, most people with SMS are missing a segment containing several dozen neighboring genes, including *RAI1,* on one of their two copies of chromosome 17 (Bi et al., 2002; Vlangos, Yim, & Elsea, 2003). Genes within this deleted region include *SREBF1,* which is involved in cholesterol metabolism (Smith et al., 2002); *MYO15,* which is associated with sensorineural deafness (Liburd et al., 2001); and *COPS3* (Potocki et al., 2000), which is thought to play a role in melatonin metabolism and the regulation of circadian rhythms. *PMP22* (King, Waldrop, Lupski, & Shaffer, 1998), whose gene product is essential for peripheral nerve functioning, is located just distal to the chromosomal region commonly deleted in people with SMS. Although an exact mechanism has yet to be elucidated, abnormalities in the expression of these and other genes may contribute to specific clinical features of SMS, including elevated cholesterol levels, peripheral neuropathy, hearing loss, and abnormal sleep patterns.

Up to 10% of people with SMS do not have a chromosomal deletion but rather a mutation (alteration) of the *RAI1* genetic code (Edelman et al., 2007; Vlangos et al., 2003). The protein normally produced by *RAI1* is thought to function as a transcription factor (i.e., a protein that binds to DNA to alter gene expression). *RAI1* thus serves like a master switch for multiple genes involved in growth and neurobehavioral regulation, explaining the diverse range of symptoms seen in SMS. This also explains the significant clinical overlap between people with multigene deletions of 17p11.2 and those with small, targeted mutations of *RAI1*. With minor differences, both groups exhibit the characteristic physical and neurobehavioral symptoms of SMS. In both groups, core diagnostic features such as intellectual disability, disordered sleep patterns, behavioral and neurological abnormalities, and craniofacial and skeletal differences appear to be correlated with haploinsufficiency (lack of a second functional copy) of *RAI1* (Girirajan et al., 2006). Although *RAI1* has been shown to be responsible for most SMS features, other genes in the 17p11.2 region contribute to the variability and severity of symptoms (Edelman et al., 2007; Girirajan et al., 2006). Short stature, hypotonia,

speech and motor delay, hearing loss, ear infections, and structural organ defects are primarily seen in people who have chromosomal deletions, suggesting that *RAI1* plays only a minor role in causing these clinical symptoms. By contrast, individuals with *RAI1* mutations have higher intellectual functioning and are more likely to exhibit obesity and somatic overgrowth (>90th percentile for height and weight) compared with those with deletions. Insights gained from further research on genotype-phenotype correlations may lead to the development of targeted interventions for specific SMS symptoms.

DIAGNOSIS

The diagnosis of SMS is based upon initial clinical suspicion of the disorder, followed by molecular confirmation of the chromosomal deletion or gene mutation. Diagnosis is often delayed due to the lack of obvious physical and behavioral findings in infants and young children. The presence of distinctive behavioral features, such as onychotillomania (mutilation of finger- and toenails) and polyembolokoilamania (insertion of foreign objects into body orifices) should prompt consideration of the diagnosis in older children and adults. DNA testing, typically using highly accurate fluorescence in situ hybridization (FISH) probes encompassing *RAI1*, confirms the diagnosis in those with deletions of the 17p11.2 chromosomal region. Additional analyses may be required to make the diagnosis in those who have *RAI1* mutations (Vlangos et al., 2003).

SMS deletions and mutations almost always occur de novo, with no prior family history of the condition and a low chance of happening again in future generations. Chromosomally normal parents of a child with SMS have less than a 1% chance of a recurrence. Individuals with SMS theoretically have a 50% chance of passing the deletion or mutation to their offspring; however, reproduction among adults with SMS has not been reported, likely due to societal constraints and the impact of cognitive and behavioral symptoms on social relationships.

SMS is thought to occur once in every 25,000 live births; however, the condition is likely underdiagnosed due to a lack of awareness and low clinical detection outside the medical genetics community. Using a conservative estimate of 1–2% for the prevalence of intellectual disabilities in the general population, approximately 1 in 200 individuals with such disabilities has SMS as the underlying cause. Among dually diagnosed populations having intellectual disabilities and comorbid psychiatric symptoms, the prevalence is likely to be much higher. Although SMS is not common, it is among the most recognizable genetic causes of intellectual disabilities due to its distinctive profile of physical and behavioral symptoms.

CLINICAL FINDINGS

SMS is a complex medical disorder affecting multiple organ systems. It is associated with characteristic facial differences that include underdeveloped cheekbones, a prominent jaw, and a downturned mouth (Allanson, Greenberg, & Smith, 1999). Although the facial features are recognizable to those familiar with the syndrome, they can be subtle (Figure 1), and many children and adults with SMS do not appear physically unusual compared with their peers. Progressive prognathism (prominent lower jaw) and coarsening of the facial appearance with age increase the clinical recognition of SMS in older children and adults (Allanson et al., 1999).

Structural abnormalities have been described affecting skeletal, cardiac, urogenital, endocrine, and immune systems, although these rarely cause significant morbidity (Greenberg et al., 1996). Hypercholesterolemia is present in over half of children and adults with SMS and may be a useful biochemical marker of the syndrome (Smith et al., 2002). Short stature is common among people with deletions of 17p11.2, although height appears to be unaffected in those with *RAI1* mutations (Girirajan, 2006). Vertebral anomalies, particularly scoliosis, are present in over half of children and adults, sometimes requiring surgical intervention (Greenberg et al., 1996).

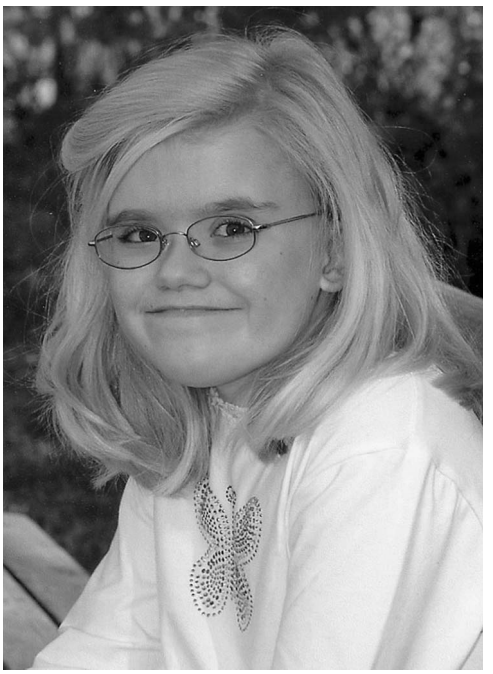

FIGURE 1 Smith-Magenis syndrome is associated with a characteristic but subtle facial appearance.

A majority of individuals with 17p11.2 deletions exhibit symptoms of peripheral neuropathy and have a decreased sensitivity to pain (Greenberg et al., 1996). Hands and fingers tend to be short with dry, leathery skin, further limiting fine motor abilities. Onychotillomania, a common behavioral manifestation of SMS, is likely related to abnormal or decreased sensation in the extremities associated with peripheral neuropathy (Finucane, Dirrgl, & Simon, 2001). Other common sensory impairments include mixed hearing loss and myopia, occasionally associated with retinal detachments (Finucane, Jaeger, Kurtz, Weinstein, & Scott, 1993). Otolaryngologic symptoms, particularly chronic otitis media, velopharyngeal insufficiency, and vocal cord polyps, are common and impact speech acquisition and intelligibility (Di Cicco et al., 2001; Solomon, McCullagh, Krasnewich, & Smith, 2002). Life span appears to approach normal for most people with SMS, as several individuals in their 60s and 70s have now been identified; mortality in this disorder is likely related to the presence or absence of congenital structural anomalies and to the quality of health monitoring. Published health care guidelines have been developed to promote anticipatory medical management for individuals with SMS throughout the life span (Smith et al., 2006).

DEVELOPMENTAL COURSE

Newborns with SMS have birth weights within the normal range and generally present with hypotonia. There is significant clinical overlap with Down syndrome in the newborn period, and the diagnosis of SMS is sometimes detected after negative genetic testing for trisomy 21 (Allanson et al., 1999; Gropman, Duncan, & Smith, 2006). A number of adults have been diagnosed late in life with SMS after living for decades with a misdiagnosis of Down syndrome. Infants with SMS tend to be lethargic and frequently have feeding difficulties. Hypotonia leads to motor delays in young children with 17p11.2 deletions, but the majority are ambulatory by age 3. Older children and adults typically walk with an awkward, lurching gait, possibly related to peripheral neuropathy. Hypotonia does not appear to be a prominent clinical symptom in people who have SMS due to an *RAI1* mutation (Girirajan et al., 2006).

Speech acquisition is delayed, likely compounded by oral-motor incoordination and hearing impairment. Most individuals with SMS eventually speak, although intelligibility may be limited by articulation errors (Gropman et al., 2006; Solomon et al., 2002). Verbal dyspraxia is so severe in some children with SMS that they never acquire speech, despite good receptive language abilities and relatively high IQs. Expressive language problems can exacerbate behavioral difficulties, and alternative methods of communication, including manual sign language, are recommended (Gropman et al., 2006).

Individuals with SMS exhibit a wide range of cognitive impairments, with most functioning in the mild to moderate range of intellectual disability

(Dykens, Finucane, & Gayley, 1997; Madduri et al., 2006). The cognitive profile of school-age students with SMS is characterized by relative strengths in long-term memory and perceptual closure with significant weaknesses in sequential processing and short-term memory (Dykens et al., 1997). Reading tends to be a relative strength for many children with SMS, in contrast to poor math skills. Intellectual functioning is generally consistent with adaptive behavior, although children with SMS have a particular strength in socialization (Madduri et al., 2006; Martin, Wolters, & Smith, 2006). Madduri et al. noted deficits in daily living skills that could be related to peripheral nerve dysfunction and poor fine motor abilities. Despite relatively mild cognitive deficits in many children with SMS, school performance is disproportionately affected by maladaptive behaviors and psychiatric comorbidity. Aggressive, impulsive, and self-injurious behaviors limit academic and functional attainment in children and adults with SMS (Gropman et al., 2006; Udwin, Webber, & Horn, 2001).

Abnormal sleep patterns, characterized by shortened sleep cycles, frequent nighttime awakenings, and excessive daytime sleepiness, further complicate the neurobehavioral profile of SMS (Potocki et al., 2000; Smith, Dykens, & Greenberg, 1998b). Starting in early childhood and persisting into the adult years, severe sleep disturbance poses a major management challenge for caregivers while also exacerbating other maladaptive behaviors in these individuals. Among the sleep-related abnormalities described in SMS are an inverted circadian rhythm of melatonin, diminished REM sleep, and a reduction in 24-hr and night sleep compared to children without SMS (De Leersnyder et al., 2001; Greenberg et al., 1996; Potocki et al., 2000). Abnormally low nocturnal melatonin production is associated with frequent nighttime awakenings and early wake-up; excessive daytime melatonin secretion is common along with sleepiness, irritability, and "sleep attacks," in which the person may quickly fall into a profound sleep state. As expected, nighttime sleep disturbance appears to correlate with maladaptive behavior in people with SMS (Dykens & Smith, 1998).

BEHAVIORAL PROFILE

A characteristic pattern of stereotypic and self-injurious behaviors (SIB) distinguishes SMS from many other genetic syndromes (Dykens & Smith, 1998; Finucane, Dirrgl, & Simon, 2001; Martin et al., 2006). An unusual "self-hugging" stereotypy has been described in SMS that may be unique to this condition (Finucane, Konar, Haas-Givler, Kurtz, & Scott, 1994). Dykens and Smith also cite hand and object mouthing, teeth grinding, and repetitive page turning (the "lick and flip" behavior) as common associated findings. Maladaptive behaviors, particularly aggression, attention seeking, prolonged outbursts, and self-injury begin in early childhood and pose a significant

challenge throughout life. Self-injury in SMS appears to directly correlate with cognitive functioning as opposed to the inverse relationship between level of functioning and prevalence of SIB generally observed in people with intellectual disabilities (Finucane, Dirrgl, & Simon, 2001). With increasing age and ability levels, people with SMS add to their repertoire of self-injury from among a small number of specific behaviors. Head banging and face slapping are among the most commonly reported types of SIB in this population. Over half of children and adults with SMS engage in onychotillomania, picking at finger- and/ or toenails to the point of bleeding and often removing the nail completely (Finucane, Dirrgl, & Simon, 2001; Greenberg et al., 1991). Polyembolokoilamania sometimes requires surgical removal of beads, food, and other items from the ears or nose. Self-insertion of objects in the vagina can be mistaken for sexual abuse in females with SMS. Although not exclusively seen in this disorder, the presence of onychotillomania and/or polyembolokoilamania in a person with intellectual disability signals a high likelihood of SMS. By contrast, these two distinct behaviors are seen to a much lesser extent among people without SMS (Dykens & Smith, 1998).

Personality and motivation in people with SMS have not been well researched, although descriptive reports suggest a consistent pattern of attention-seeking and reactive behaviors (Beall, 2007; Dykens & Smith, 1998; Haas-Givler, 1994; Taylor & Oliver, 2008; Willekens, De Cock, & Fryns, 2000). Children with SMS tend to be adult oriented, with a sometimes insatiable need for individual attention. They often compete with peers and siblings for adult attention and may react with aggression and/or self-injury when attention is withdrawn (Taylor & Oliver, 2008). Prolonged tantrums lasting hours, with self-injury, property destruction, and physical aggression, are common through adolescence and into adulthood. Behavioral outbursts are generally precipitated by a need for attention, an unexpected change in routine, or a lack of clear expectations or structure.

It is important to balance the description of maladaptive behaviors in SMS with a discussion of the positive personality attributes associated with this condition. Many individuals with SMS have an engaging and endearing personality along with a well-developed sense of humor (Haas-Givler, 1994). Although they crave adult attention, they are generally appreciative when attention is given and respond well to positive reinforcement. Parents and teachers have described children with SMS as "eager to please," "communicative," and "affectionate." Most adapt readily to structure and routine. Students with SMS are generally popular among their peers despite the significant management problems they can present. Teachers report that these students seem to endear themselves to staff because of their affectionate natures and happy outbursts of excitability (Finucane et al., 1994). In particular, the self-hugging stereotypy is perceived by caretakers as a positive personality trait, partially offsetting the negative reactions

FIGURE 2 A self-hugging stereotypy that occurs in response to happiness and positive excitement may be a unique aspect of the Smith-Magenis syndrome clinical phenotype.

otherwise engendered by people who display aggression and self-injury. For a condition associated with many uniquely difficult behaviors, self-hugging is among the more benign and appealing aspects of the behavioral phenotype (Figure 2).

PSYCHOPATHOLOGY

Maladaptive behaviors occur at a higher rate among children and adults with SMS than they do in people with other genetic syndromes or nonspecific developmental disorders (Dykens & Smith, 1998). Not surprisingly, people with SMS usually meet criteria for one or more comorbid psychiatric conditions in addition to a diagnosis of intellectual disability (Levitas, Dykens, Finucane, & Kates, 2007). Attention-deficit/hyperactivity disorder is commonly diagnosed in childhood, as is Oppositional Defiant Disorder. Some children with SMS exhibit autistic behaviors and are diagnosed with a Pervasive Developmental Disorder, although they rarely meet full criteria for Autistic Disorder. Obsessive compulsive symptoms are frequently observed and result in behavioral decompensation (e.g., aggression, agitation, extreme

anxiety) when a routine is changed or something doesn't go exactly as expected. Mood lability is prominent through adulthood and may be diagnosed as bipolar disorder (Levitas et al., 2007).

It is not uncommon for parents and some professionals to be confused about the concurrent diagnosis of several psychiatric disorders in a person with a known genetic diagnosis of SMS (Finucane, 2005). They may erroneously interpret these multiple diagnoses as being independent of each other and unrelated. Psychiatric disorders in people with SMS should be viewed as distinct symptom constellations for which SMS is the underlying etiology. A diagnosis of SMS answers important questions about the cause of a person's disability, its genetic implications, associated physical and behavioral symptoms, and potential treatments. Likewise, comorbid psychiatric diagnoses can help determine eligibility for educational and counseling services while providing direction for pharmaceutical interventions and nonmedical treatment approaches (e.g., Applied Behavior Analysis (ABA) therapy for children with autism).

DEVELOPMENTAL AND BEHAVIORAL CONSIDERATIONS

Maladaptive behaviors in people with SMS appear to have their roots in innate personality and processing differences, including physiological impulses, the need for an inordinate amount of attention, poor understanding of time and sequence, attentional deficits, low tolerance for frustration, and poor impulse control. Genetically driven differences influence behaviors that are then reinforced by the responses they generate in the environment, resulting in a complex mix of learned and innate behaviors. Taylor and Oliver (2008) observed that aggression and self-injury in children with SMS were evoked by low levels of adult attention and subsequently reinforced when attention was increased following the behaviors. Peripheral neuropathy may help to explain why people with SMS can engage in self-mutilatory behavior such as onychotillomania with no apparent discomfort. Once this behavior occurs, the person with SMS quickly learns that pulling out finger- and toenails results in a more immediate and reinforcing response (i.e., attention) than previously displayed behaviors. Therefore, a complex interplay between physiology and environment serves to maintain this and perhaps other forms of SIB in people with SMS (Finucane, Dirrgl, & Simon, 2001).

Developmental asynchrony, specifically between intellectual functioning and emotional maturity, may also contribute to maladaptive behaviors in people with SMS. It has been observed that gifted children with very high IQs can at the same time be socially and emotionally immature compared with their same-age peers (Silverman, 1997). We have noted a parallel phenomenon in children and adults with SMS (Finucane, 2008). Overall adaptive behavior in SMS appears to be consistent with intellectual level (Madduri et al., 2006; Martin et al., 2006), although adults with SMS require a higher

degree of support than might be predicted based on their cognitive level (Gropman et al., 2006; Udwin et al., 2001). We have observed that although academic achievement in this population generally falls within the 6- to 8-year-old range, the emotional reactions of people with SMS are more consistent with a 1- to 3-year-old development level. Such emotional reactivity is not necessarily captured on assessments of adaptive behavior and remains to be researched. Many aspects of the SMS behavioral profile could equally describe the development of typical toddlers, including a low tolerance for frustration, negativity, mood lability, a need to do things for themselves, attention seeking, tantrums, anxiety about separation from loved ones, resistance to changes in routine, and relentless question asking. Behavioral outbursts in adults with SMS look very much like the "temper tantrums" seen in very young children, with a person throwing herself to the floor, kicking and crying. Such behavior seems incongruous with the intellectual skills of these adults, many of whom can read, socialize well, and have a good general fund of knowledge. Some of the more unusual behaviors observed in SMS may also have their roots in normal early childhood development. It is not uncommon for typical toddlers to insert objects into their noses or ears. In people with SMS, polyembolokoilamania has a later onset, generally starting in late childhood and persisting through adulthood. Another very common behavior in children and adults with SMS is the self-hug or "spasmodic upper body squeeze" (Finucane et al., 1994). This midline, ticlike gesture takes the form of self-hugging or hand squeezing and usually occurs in response to happiness and positive excitement. A similar behavior can be observed among very young typical children when they are excited (Figure 3).

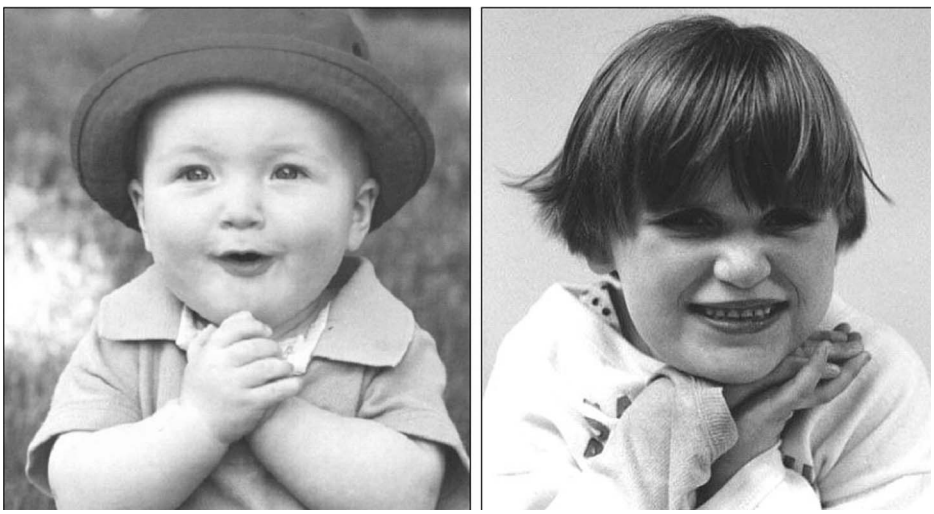

FIGURE 3 On the left, a typical young child engaged in an excitable hand-clasping posture; at right, a 7-year-old girl with Smith-Magenis syndrome exhibiting the self-hugging stereotypy.

Our experience suggests that developmental asynchrony is common among people with SMS and is a major underlying contributor to maladaptive behavior in this population. With age, the gap between intellectual attainment and emotional development appears to widen for many people with SMS, and this disparity poses significant behavioral and programmatic challenges. Behavioral and educational plans that ignore a person's "inner toddler" often do not succeed, but strategies that neglect the person's chronological age and academic abilities do not promote growth and learning. A combined approach that incorporates fundamental practices of early childhood education, age progressed to match the interests and skills of the older child or adult with SMS, can be very effective when working with this population (Finucane, 2008). Pending research on developmental trajectories in SMS may provide additional insights into behavioral and emotional functioning as well as potential intervention strategies.

INTERVENTIONS

Once the diagnosis of SMS is confirmed, children and adults with this condition require lifelong health monitoring in addition to behavioral, educational, and social supports (Gropman et al., 2006; Smith et al., 2006). Medical recommendations include imaging studies to check for structural abnormalities of the heart, urogenital organs, and spine; fasting cholesterol studies; and ophthalmologic and audiologic evaluations to identify potential sensory impairments. Babies and young children with SMS should be referred as soon as possible for early intervention services, particularly speech/language therapy, to optimize oral-motor abilities and functional communication. School-age children in the United States generally qualify for an individualized education program, which should include a comprehensive behavior support plan, to maximize academic and social attainment. Adults with SMS benefit from structured day programs and typically live at home or in supervised residential settings with varying degrees of personal independence.

Of the many clinical symptoms associated with SMS, maladaptive behaviors pose the most significant management challenge. A comprehensive behavior support plan for home and school should be considered as soon as problem behaviors arise, typically starting in early elementary school. A structured school program with one-to-one support and curricula matched to the known cognitive and behavioral profile of SMS can be effective in addressing the needs of these students. After-school programs and respite care are also essential to decrease the daily stress on families. The combination of intellectual disability, severe behavioral abnormalities, and sleep disturbance takes a significant toll on parents and siblings. Parents report high rates of depression and anxiety (Kozachek, Foster, Kanotra, Stern, & Elsea,

2008), and family stress is significantly higher in families of people with SMS than it is in those of children with nonspecific developmental disabilities (Hodapp, Fidler, & Smith, 1998). Family support services and resources should be included as essential components of a holistic management plan for people with SMS.

In addition to environmental supports, psychotropic medications are often prescribed to address behavioral and psychiatric symptoms, and polypharmacy is typical. To date, there are no published controlled studies of medication trials in people with SMS, and reports of medication use are anecdotal. A database of adverse effects and medication efficacy has been established by the national support group PRISMS (Parents and Researchers Interested in Smith-Magenis Syndrome, Sterling, VA, USA, www.prisms.org), and a review of the data is in progress (Gropman et al., 2006). Use of psychotropics is targeted to specific behaviors, as there is no medication that addresses every area of behavioral concern. Unfortunately, there is no particular pharmaceutical regimen that works well for all people with SMS, and behavior in some individuals is better managed without medications. Anecdotally, mood stabilizers such as valproate and lithium have been relatively useful for reducing mood swings in people with SMS. Some individuals respond well to a combination of mood stabilizers and antipsychotic medications, such as risperidone, although weight gain can be problematic (Gropman et al., 2006; Niederhofer, 2007). Given the lack of controlled medication trials for behavioral symptoms in SMS, psychotropic medications, when indicated, should be prescribed after careful evaluation by a psychiatric professional with input from family members and caregivers most familiar with the individual.

Abnormal sleep patterns adversely affect behavior in people with SMS and should be addressed as part of the behavior support plan. Despite evidence for an inverted circadian rhythm of melatonin, there have been no well-controlled melatonin treatment trials for sleep disturbance in this disorder. Anecdotal reports of the use of exogenous melatonin to normalize sleep patterns in SMS have been inconclusive, although many parents report dramatic improvement. Lack of therapeutic effect in some cases could be related to inconsistency in product formulation; in the United States, melatonin is not federally regulated and dosages may be inexact. In an uncontrolled study, De Leersnyder et al. (2003) combined a daytime dose of acebutolol (a B_1-adrenergic antagonist) to suppress melatonin secretion with an evening dose of melatonin in an attempt to restore the circadian rhythm of melatonin in 10 children with SMS. The researchers reported normalization of nighttime melatonin secretion, with improved sleep and disappearance of nocturnal awakenings. A corresponding subjective improvement in daytime behaviors was also reported by parents of the children studied. Although these results are encouraging, double-blind controlled studies are needed to fully evaluate the effect of melatonin treatment on sleep disturbance in people with SMS.

Despite many challenges, children and adults with SMS have much potential. In recent years, awareness has steadily increased, allowing earlier detection and an improved prognosis for those affected. Significant advances have been made over the past decade in our understanding of sleep disturbance and other behavioral abnormalities in people with SMS. International support organizations have been established to provide practical resources for families and encourage syndrome-specific research. In the coming years, the ongoing elucidation of genotype-phenotype correlations holds the promise of effective, targeted treatments for the disorder's many complex behavioral and somatic symptoms.

REFERENCES

Allanson, J., Greenberg, F., & Smith, A. C. M. (1999). The face of Smith-Magenis syndrome: A subjective and objective study. *Journal of Medical Genetics*, *36*, 394–397.

Beall, M. (2007). Behavior management in SMS. *Spectrum*, *11*(2), 12–15.

Bi, W., Yan, J., Stankiewicz, P., Park, S. S., Walz, K., Boerkoel, C. F., et al. (2002).Genes in a refined Smith-Magenis syndrome critical deletion interval on chromosome 17p11.2 and the syntenic region of the mouse. *Genome Research*, *12*, 713–728.

De Leersnyder, H., Bresson, J. L., de Blois, M. C., Souberbielle, J. C., Mogenet, A., Delhotal-Landes, B., et al. (2003). Beta 1-adrenergic antagonists and melatonin reset the clock and restore sleep in a circadian disorder, Smith-Magenis syndrome. *Journal of Medical Genetics*, *40*, 74–78.

De Leersnyder, H., De Blois, M. C., Claustrat, B., Romana, S., Albrecht, U., Von Kleist-Retzow, J. C., et al. (2001). Inversion of the circadian rhythm of melatonin in the Smith-Magenis syndrome. *Journal of Pediatrics*, *139*, 111–116.

Di Cicco, M., Padoan, R., Felisati, G., Dilani, D., Moretti, E., Guerneri, S., et al. (2001). Otorhinolaringologic manifestation of Smith-Magenis syndrome. *International Journal of Pediatric Otorhinolaryngology*, *59*, 147–50.

Dykens, E. M., Finucane, B. M., & Gayley, C. (1997). Brief report: Cognitive and behavioral profiles in persons with Smith-Magenis syndrome. *Journal of Autism and Developmental Disabilities*, *27*, 203–211.

Dykens, E. M., & Smith, A. C. (1998). Distinctiveness and correlates of maladaptive behaviour in children and adolescents with Smith-Magenis syndrome. *Journal of Intellectual Disability Research*, *42*, 481–489.

Edelman, E. A., Girirajan, S., Finucane, B., Patel, P. I., Lupski, J. R., Smith, A. C., et al. (2007). Gender, genotype, and phenotype differences in Smith-Magenis syndrome: A meta-analysis of 105 cases. *Clinical Genetics*, *71*, 540–550.

Finucane, B. (2005). What's in a name? Symptoms versus causes in the diagnostic age. *Exceptional Parent*, *35*, 26–28.

Finucane, B. (2008). Embracing the inner toddler in people with Smith-Magenis syndrome. *Spectrum*, *12*(3), 1.

Finucane, B., Dirrgl, K., & Simon, E. W. (2001). Characterization of self-injurious behaviors in children and adults with Smith-Magenis syndrome. *American Journal on Mental Retardation*, *106*, 52–58.

Finucane, B. M., Jaeger, E. R., Kurtz, M. B., Weinstein, M., & Scott, C. I. (1993). Eye abnormalities in the Smith-Magenis contiguous gene deletion syndrome. *American Journal of Medical Genetics*, *45*, 443–446.

Finucane, B. M., Konar, D., Haas-Givler, B., Kurtz, M. B., & Scott, C. I. (1994). The spasmodic upper-body squeeze: A characteristic behavior in Smith-Magenis syndrome. *Developmental Medicine and Child Neurology*, *36*, 78–83.

Girirajan, S., Vlangos, C. N., Szomju, B. B., Edelman, E., Trevors, C. D., Dupuis, L., et al. (2006). Genotype-phenotype correlation in Smith-Magenis syndrome: Evidence that multiple genes in 17p11.2 contribute to the clinical spectrum. *Genetics in Medicine*, *8*, 417–427.

Greenberg, F., Guzzetta, V., Montes de Oca-Luna, R., Magenis, R. E., Smith, A. C. M., Richter, S. F., et al. (1991). Molecular analysis of the Smith-Magenis syndrome: A possible contiguous gene deletion syndrome associated with del(17)(p11.2). *American Journal of Human Genetics*, *49*, 1207–1218.

Greenberg, F., Lewis, R.A., Potocki, L., Glaze, D., Parke, J., Killian, J., et al. (1996). Multi-disciplinary clinical study of Smith-Magenis syndrome (deletion 17p11.2). *American Journal of Medical Genetics*, *62*, 247–254.

Gropman, A. L., Duncan, W. C., & Smith, A. C. M. (2006). Neurologic and developmental features of the Smith-Magenis syndrome (del 17p11.2). *Pediatric Neurology*, *34*, 337–350.

Haas-Givler, B. (1994). Observations on the behavioral and personality characteristics of children with Smith-Magenis syndrome. *Spectrum*, *1*(2), 1.

Hodapp, R. M., Fidler, D. J., & Smith, A. C. M. (1998). Stress and coping in families of children with Smith-Magenis syndrome. *Journal of Intellectual Disability Research*, *42*, 331–340.

King, P. H., Waldrop, R., Lupski, J. R., & Shaffer, L. G. (1998). Charcot-Marie-Tooth phenotype produced by a duplicated PMP22 gene as part of a 17p trisomy-translocation to the X chromosome. *Clinical Genetics*, *54*, 413–416.

Kozachek, S., Foster, R. H., Kanotra, S., Stern, M., & Elsea, S. H. (2008). Smith-Magenis syndrome caregiver study: Results and recommendations. *Spectrum*, *12*(3), 1.

Levitas, A., Dykens, E., Finucane, B., & Kates, W. R. (2007). Behavioral phenotypes of genetic disorders. In R. Fletcher, E. Loschen, C. Stavrakaki, & M. First (Eds.), *Diagnostic manual—intellectual disability: A textbook of diagnosis of mental disorders in* p*ersons with intellectual disability* (pp. 42–43). Kingston, NY: NADD Press.

Liburd, N., Ghosh, M., Riazuddin, S., Naz, S., Khan, S., Ahmed, Z., et al. (2001). Novel mutations of MYO15A associated with profound deafness in consanguineous families and moderately severe hearing loss in a patient with Smith-Magenis syndrome. *Human Genetics*, *109*, 535–541.

Madduri, N., Peters, S. U., Voigt, R. G., Llorente, A. M., Lupski, J. R., & Potocki, L. (2006). Cognitive and adaptive behavior profiles in Smith-Magenis syndrome. *Journal of Developmental and Behavioral Pediatrics*, *27*, 188–192.

Martin, S. C., Wolters, P. L., & Smith A. C. (2006). Adaptive and maladaptive behavior in children with Smith-Magenis syndrome. *Journal of Autism and Developmental Disorders*, *36*, 541–52.

Niederhofer, H. (2007). Efficacy of risperidone treatment in Smith-Magenis syndrome (del 17pll.2). *Psychiatrica Danubina*, *19*, 189–192.

Potocki, L., Glaze, D., Tan, D. X., Park, S. S., Kashork, C. D., Shaffer, L. G., et al. (2000). Circadian rhythm abnormalities of melatonin in Smith-Magenis syndrome. *Journal of Medical Genetics*, *37*, 428–433.

Silverman, L. K. (1997). The construct of asynchronous development. *Peabody Journal of Education*, *72*, 36–58.

Slager, R. E., Newton, T. L., Vlangos, C. N., Finucane, B., & Elsea, S. H. (2003). Mutations in *RAI1* associated with Smith-Magenis syndrome. *Nature Genetics*, *33*, 466–468.

Smith, A. C. M., Allanson, J., Elsea, S. H., Finucane, B., Haas-Givler, B., Gropman, A., et al. (2006). Smith-Magenis syndrome. *Gene Reviews*. Retrieved October 13, 2008, from http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=sms

Smith, A. C., Dykens, E., & Greenberg, F. (1998a). Behavioral phenotype of Smith-Magenis syndrome (del17p11.2). *American Journal of Medical Genetics*, *181*, 179–185.

Smith, A. C. M., Dykens, E., & Greenberg, F. (1998b). Sleep disturbance in Smith-Magenis syndrome (del 17p11.2). *American Journal of Medical Genetics (Neuropsychiatric Genetics)*, *81*, 186–191.

Smith, A. C., Gropman, A. L., Bailey-Wilson, J. E., Goker-Alpan, O., Elsea, S. H., Blancato, J., et al. (2002). Hypercholesterolemia in children with Smith-Magenis syndrome: del (17) (p11.2p11.2). *Genetics in Medicine*, *4*, 118–125.

Smith, A. C., McGavran, L., Robinson, J., Waldstein, G., Macfarlane, J., Zonona, J., et al. (1986). Interstitial deletion of (17) (p11.2p11.2) in nine patients. *American Journal of Medical Genetics*, *24*, 393–414.

Solomon, B., McCullagh, L., Krasnewich, D., & Smith, A. C. M. (2002). Oral motor, speech and voice functions in Smith-Magenis syndrome children: A research update. *American Journal of Human Genetics*, *71*, 271.

Stratton, R. F., Dobyns, W. B., Greenberg, F., DeSana, J. B., Moore, C., Fidone, G., et al. (1986). Interstitial deletion of (17) (p11.2p11.2): Report of six additional patients with a new chromosome deletion syndrome. *American Journal of Medical Genetics*, *24*, 421–432.

Taylor, L., & Oliver, C. (2008). The behavioural phenotype of Smith-Magenis syndrome: Evidence for a gene-environment interaction [Electronic version ahead of print]. *Journal of Intellectual Disability Research, 6*. Retrieved October 13, 2008, from http://www3.interscience.wiley.com/journal/120118375/tocgroup

Udwin, O., Webber, C., & Horn, I. (2001). Abilities and attainment in Smith-Magenis syndrome. *Developmental Medicine and Child Neurology*, *43*, 823–828.

Vlangos, C. N., Yim, D. K., & Elsea, S. H. (2003). Refinement of the Smith-Magenis syndrome critical region to approximately 950kb and assessment of 17p11.2 deletions. Are all deletions created equally? *Molecular Genetics and Metabolism*, *79*, 134–141.

Willekens, D., De Cock, P., & Fryns, J. P. (2000). Three young children with Smith-Magenis syndrome: their distinct, recognisable behavioural phenotype as the most important clinical symptoms. *Genetic Counseling*, *11*, 103–110.