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Review Article

Neurologic and Developmental Features of the Smith-Magenis Syndrome (del 17p11.2)

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The Smith-Magenis syndrome is a rare, complex multisystemic disorder featuring, mental retardation and multiple congenital anomalies caused by a heterozygous interstitial deletion of chromosome 17p11.2. The phenotype of Smith-Magenis syndrome is characterized by a distinct pattern of features including infantile hypotonia, generalized complacency and lethargy in infancy, minor skeletal (brachycephaly, brachydactyly) and craniofacial features, ocular abnormalities, middle ear and laryngeal abnormalities including hoarse voice, as well as marked early expressive speech and language delays, psychomotor and growth retardation, and a 24-hour sleep disturbance. A striking neurobehavioral pattern of stereotypies, hyperactivity, polyembolokoilamania, onychotillomania, maladaptive and self-injurious and aggressive behavior is observed with increasing age. The diagnosis of Smith-Magenis syndrome is based upon the clinical recognition of a constellation of physical, developmental, and behavioral features in combination with a sleep disorder characterized by inverted circadian rhythm of melatonin secretion. Many of the features of Smith-Magenis syndrome are subtle in infancy and early childhood, and become more recognizable with advancing age. Infants are described as looking "cherubic" with a Down syndrome–like appearance, whereas with age the facial appearance is that of relative prognathism. Early diagnosis requires awareness of the often subtle clinical and neurobehavioral phenotype of the infant period. Speech delay with or without hearing loss is common. Most children are diagnosed in mid-childhood when the features of the disorder are most recognizable and striking. While improvements in cytogenetic analysis help to bring cases to clinical recognition at an earlier age, this review seeks to increase clinical awareness about Smith-Magenis syndrome by presenting the salient features observed at different ages including descriptions of the neurologic and behavioral features. Detailed review of the circadian rhythm disturbance unique to Smith-Magenis syndrome is presented. Suggestions for management of the behavioral and sleep difficulties are discussed in the context of the authors' personal experience in the setting of an ongoing Smith-Magenis syndrome natural history study.

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Introduction

The Smith-Magenis syndrome is a clinically recognizable, probable contiguous gene syndrome comprising multiple congenital anomalies and mental retardation [1]. It is caused by an interstitial deletion of chromosome 17p11.2 (Fig 1), first described by Smith et al. in 1982, with the full clinical spectrum delineated in additional patients in 1986 [2]. Smith-Magenis syndrome occurs in all ethnic groups with an overall frequency estimated to be 1/25,000 [3]. The diagnosis of Smith-Magenis syndrome is based upon clinical recognition of a unique phenotype involving physical, developmental, and behavioral aspects. The diagnosis is confirmed cytogenetically or by

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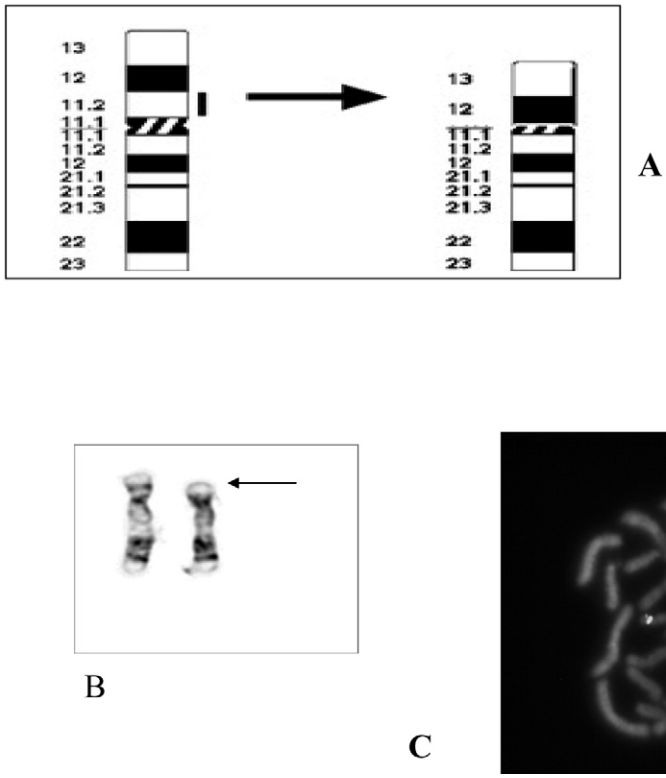


Figure 1. Smith-Magenis syndrome (SMS) deletion 17p.11.2. Schematic diagram (A) and partial G-banded karyotype (B) from male with Smith-Magenis syndrome (46,XY, del 17 (p11.2p11.2); arrows point to deleted 17 chromosome. Normal chromosome 17 (left) and deleted 17 (right). (C) Metaphase fluorescence in situ hybridization FISH analysis using RA11 FISH probe for Smith-Magenis syndrome critical region. Partial karyotype courtesy of Jeanne Meck, PhD, Director of Cytogenetics Laboratory, Georgetown University, Washington, DC. FISH analysis courtesy of Jan Blancato, PhD, Georgetown University Medical Center, Washington, DC.

fluorescence in situ hybridization in the majority of cases. In addition, a small cohort of patients with the Smith-Magenis syndrome phenotype, but without a detectable deletion by fluorescence in situ hybridization, was recently found to harbor a frame shift mutation of the *RAI1* gene (Retinoic acid induced-1) [4-6] contained in the critical region, which encodes a novel gene of unknown function believed to play a role in neuronal differentiation [6], and possibly responsible for the major features of the syndrome [7,8].

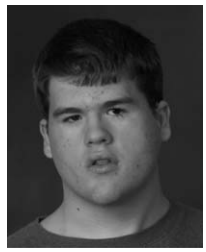
Patients with Smith-Magenis syndrome present with a clinically recognizable craniofacial appearance that includes brachycephaly, midface hypoplasia, a prominent forehead, upslanting palpebral fissures, epicanthal folds, synophyrs, and age-dependent development of relative prognathism due to persisting midfacial hypoplasia (Table 1). The facial appearance may be quite subtle in infancy, thus diagnosis may not be apparent [9]. Other common features of Smith-Magenis syndrome include short stature, brachydactyly, ophthalmologic problems (myopia, strabismus, microcornea, retinal detachment), hearing loss, infantile hypotonia, mental retardation, maladaptive behaviors, expressive language delay, oral motor dysfunction, peripheral neuropathy, and sleep disorder partially attributed to inversion of the circadian rhythm of melatonin secretion [10-12]. Behavioral problems, including self-injury, tantrums, and stereotypies are observed in the majority of patients with Smith-Magenis syndrome and represent a major challenge for parents, caregivers, and professionals [13-15].

Despite increased clinical awareness of Smith-Magenis syndrome as well as improved cytogenetic technologies, many children are not definitively diagnosed until early childhood or even school age [9,16]. The majority of children with Smith-Magenis syndrome have been identified in the last decade owing to improved cytogenetic techniques and the availability of fluorescence in situ hybridization probes specific for the Smith-Magenis syndrome critical region [7,17-20,21].

With few exceptions, the deletion in Smith-Magenis syndrome occurs de novo [22,23], thus imparting a low recurrence risk. However, parental cytogenetic analysis is recommended in new cases. There is no evidence to suggest either a parental age contribution, or skewed sex distribution in deletion cases, and random parental origin for the 17p deletion has been demonstrated, thus suggesting that genomic imprinting is not a factor [3,24]. The mechanism of the deletion in Smith-Magenis syndrome is due to homologous recombination of a flanking repeat gene cluster, leading to mismatch pairing [25].

While the molecular cause of Smith-Magenis syndrome is uncertain, it is believed to be due to a contiguous gene syndrome where haploinsufficiency of multiple genes in

Table 1. Clinical and behavioral aspects of Smith-Magenis syndrome across the age span

	Infancy	Toddler/Early Childhood	School Age	Adolescence to Adulthood
		 		 
Clinical features	Brachycephaly Mild facial dysmorphism Broad, square-shape face Upslanting palpebral fissures "Cherubic" appearance "Down syndrome–like" appearance Mid-face hypoplasia Cupid-bow mouth with tented upper lip Open mouth posture Eye problems: strabismus; microcornea; pigmented flecking of iris Short broad hands and feet Central nervous system: mildly enlarged ventricles	Recognizable facial appearance with mid-face hypoplasia; rosy cheeks Frequent/chronic otitis media Hearing loss (predominantly conductive) Vision problems (myopia) Fair hair and coloring compared with family Short stature Hoarse voice Unusual gait/toe walking High cholesterol	Characteristic facies with persisting midface hypoplasia, relative prognathia, heavy brows extending laterally; Hoarse voice Progressive myopia Hearing loss (conductive vs sensorineural) Short stature Scoliosis Broad-based flapping gait	Coarser facial appearance with deep-set eyes, relative prognathia, heavy brows, synophyrs Progressive myopia Hearing loss (conductive and/or sensorineural) Females: premature adrenarche; irregular menses; hygiene concerns Tendency to obesity Hoarse voice Short stature (5–10%) Scoliosis Broad-based flapping gait
Neuro-develop-mental	Feeding difficulties (major oral-sensorimotor dysfunction Failure to thrive Generalized hypotonia Alert and responsive Hypotonia (low muscle tone) Hyporeflexia Social skills—age-appropriate Delayed gross/fine motor skills	Developmental delays; Gross/fine motor delays Marked speech delay (expressive > receptive) Decreased pain sensitivity Pes planus (flat) or pes cavus (high arch) Delayed potty training Sensory Integration issues	Cognitive delays weaknesses: sequential processing and short-term memory strengths: long-term memory and perceptual closure Visual learners, Pes planus or pes cavus, Bedwetting, sensory integration issues	Cognitive delays Excellent long-term memory Reports of exercise intolerance Poor adaptive function
Behavior	Diminished vocalizations and crying "Quiet good babies" Complacent Parent perception of "good sleeper" Decreased total sleep for age Lethargic	Stereotypic behaviors: self-hugging lick and flip behaviors Self-abusive behaviors head banging; hitting: self wrist bitting; skin picking Sleep disturbance: short sleep cycle; early risers (5:30–6:30 am); frequent night awakenings and daytime naps Engaging personality Affinity for electronic toys, buttons, etc.	Attention-seeking behaviors Adult-oriented Frequent outbursts/tantrums Sudden mood shifts Yes/No game Impulsivity/aggression Hyperactivity Attention deficits Chronic sleep disturbance: short sleep cycle; early risers (4:30–6:30 am); frequent night awakenings and daytime sleepiness Stereotypic behaviors Self-injurious behaviors: Hitting self, nail biting or pulling; object insertion (older ages) Very communicative Excellent long-term memory Affinity for computers or electronics	Chronic sleep disturbance; decreased total sleep time; increased naps with age* (parental reports) Major behavioral outbursts or rage behaviors, property destruction, attention seeking Aggressive/explosive outbursts Impulsive, disobedient Mood shifts (rapid) without major provocation Attention deficits Argumentative Self-injurious behaviors (hitting self/objects; nail yanking; object insertion) Mouthing of objects, bruxism Lick and flip of pages in a book, Self-hug, upper body Spasmodic squeeze Body rocking Spinning and twirling of objects Very communicative Excellent long-term memory Affinity for computers and electronics

* Adapted from Smith ACM, as presented at the Smith-Magenis syndrome parent conference (SIRIUS) Heidelberg, Germany, November 13, 2004. Behavioral data adapted from Dykens and Smith [13].

the critical region contributes collectively to the phenotype [26].

We have been engaged in a natural history study of the Smith-Magenis syndrome initiated at the National Institutes of Health from 1997. Research collaborators consist of an interdisciplinary team of physicians and allied health professionals (medical genetics, psychology, developmental pediatrics, child neurology, audiology, speech and language, occupational and physical therapy, radiology, ophthalmology, and sleep physiology). The study has several aims. One aim is to characterize the physical, biochemical, developmental, and neurobehavioral aspects of Smith-Magenis syndrome from infancy to adulthood and develop diagnostic criteria for early clinical recognition and diagnosis.

Another aim of the natural history study is to follow the clinical, neurologic, and neurobehavioral features of Smith-Magenis syndrome throughout the lifespan and to determine intervention and management strategies for the neurodevelopmental delays and maladaptive behaviors. A major aspect of the research is to document indices of abnormal sleep physiology [11,12]. It is anticipated that such findings will assist in the design of rational interventions to address this complex aspect of the disorder. Additionally, the study also seeks to understand phenotypic variability of Smith-Magenis syndrome as related to deletion size and other genetic modifiers.

Clinical Manifestations of Smith-Magenis Syndrome

Diagnostic Criteria

The diagnosis of Smith-Magenis syndrome is based upon clinical recognition of the unique phenotype, with diagnostic confirmation of an interstitial deletion of 17p11.2 or mutation in the *RAI1* gene. Those features which are observed consistently in the majority of individuals with Smith-Magenis syndrome are referenced in Table 1.

Neurologic and Neurobehavioral Features of Smith-Magenis Syndrome

The neurologic phenotype of Smith-Magenis syndrome is variable depending upon the age of initial clinical presentation. These developmentally dependent phenotypes are described in the next several sections.

Smith-Magenis Syndrome in Infancy

Infants with Smith-Magenis syndrome may have mild dysmorphic features and developmental delays; however, because of agreeable temperament and social skills, diagnosis is often not made at this age. To discern whether a recognizable Smith-Magenis syndrome infant phenotype exists, we conducted a prospective analysis and retrospective chart review of the initial 19 children with cytogenetically confirmed Smith-Magenis syndrome. These children were evaluated at the National Institutes of Health from 1997 to 2001 as part of a multidisciplinary institutional review board approved study of the natural history and molecular genetic features of Smith-Magenis syndrome. Subjects were recruited through physician referral or parent self-referral through PRISMS (parent support group).

Table 2. Demographics of infants with Smith-Magenis syndrome studied at the National Institutes of Health

	Group I: Diagnosed <18 Months of Age	Group 2: Diagnosed >18 Months of Age
n	10 (M/F)	9 (M/F)
Mean age at diagnosis	9 mo (range 2 day-17 mo)	5.4 yr (range 22 mo-12 yr)
Birth year	1991–1997	1980–1991

Among this initial National Institutes of Health group of 19 children (11 female, 8 male), two groups of patients with confirmed diagnosis of Smith-Magenis syndrome were identified (Table 2): Group 1 consisted of 10 infants and children who were diagnosed at a mean age of 9 months (range 2 days to 17 months). Group 2 consisted of nine older children in whom the diagnosis was made at a mean age of 5.4 years (range 22 months to 12 years). Gestational and pregnancy histories were notable for decreased fetal movement in 9 (50%).

Infantile characteristics were ascertained by parent questionnaire, interview, and examinations. In addition, in all children older than 24 months at the time of the study, either a retrospective chart and photographic review, or a prospective detailed neurologic examination was conducted. In the five children who were younger than 24 months of age at the time of the review, parental interviews, direct evaluation, and detailed examinations were conducted. The comprehensive evaluation included craniofacial measurements, neurologic and behavioral assessments, dysmorphology examination, developmental and cognitive testing, and videotaping in which five behaviors were assessed including task-oriented behavior, interpersonal and social behavior, affective behavior, sensorimotor and communicative behaviors. All children had a speech and language evaluation as well as audiology and otolaryngology evaluations. Some children underwent nerve conduction velocity and electromyographic testing.

Based on these studies, a clinically recognizable infant Smith-Magenis syndrome phenotype emerged that added to previous published clinical series (Table 3). Infants with Smith-Magenis syndrome display normal growth with birth weight, length, and head circumference generally in the normal range at birth. By age 1 year, however, evidence of decline in height velocity and often poor weight gain may lead to concern for failure to thrive that may persist into early childhood [27]. Even as infants, the facial phenotype of Smith-Magenis syndrome was ob-

Table 3. Characteristics of the infant phenotype of Smith-Magenis syndrome

Decreased fetal movement by history	9/19
Hypotonia	19/19
Hyporeflexia	17/19
Increased daytime sleepiness and napping; perceived to be "good sleepers"	19/19
Oromotor dysfunction	19/19
Delayed gross motor skills (2–24 months behind)	19/19
Delayed fine motor skills	19/19
Marked speech delay (Expressive language <Receptive language)	19/19
Near or age-appropriate social skills	16/19
Major behavioral problems documented in first 18 mo (Average age onset of behavioral abnormalities 18–24 mo)	0/19
Sleep disorder	19/19
Cherubic facial appearance that is perceived as dysmorphic	19/19

served to be quite distinctive, with an overall facial shape that is broad and square. With age, the mid-face hypoplasia persists, yielding to an appearance of relative prognathism (Table 1). There is phenotypic overlap with Down syndrome early in life. Both Smith-Magenis syndrome and Down syndrome share upslanting palpebral fissures, brachycephaly, flat mid face, and short, broad nose. Facial depth in Smith-Magenis syndrome is less than that in Down syndrome, and total facial height as well as ear size is greater in Smith-Magenis syndrome compared with Down syndrome [28].

Neurobehavioral features of the Smith-Magenis syndrome infant included hypotonia, lethargy, increased sleepiness, and daytime napping [29]. Often, the infants needed to be awakened for feedings. In most cases, there were no behavioral problems in the first 18 months of life, and in fact, many of these infants were felt to be "perfect babies".

Recent objective sleep data derived from actigraphy indicate a sleep disturbance in infancy that continues into later childhood and beyond [30]. Data on three infants under 1 year of age indicate fragmented sleep with reduced 24-hour total sleep time as early as 6 months of age. Because of their relatively quiet behavior pattern during sleep, these infants can be described as "quiet babies sleeping poorly".

The incidence of crying, babbling, and vocalizing was markedly decreased for age in virtually all infants with Smith-Magenis syndrome, despite normal hearing [31]. These observations apparently led to parent reports of hypersomnolence and lethargy in infants, because infants were often not "signaling" parents upon waking.

Motor delays were evident in all infants and children, with gross motor delays of 2-24 months; however, social-emotional function was within the normal range or only slightly delayed [9,27]. All infants with Smith-Magenis syndrome displayed oral motor dysfunction including poor feeding in some, manifest by poor tongue protrusion, lingual weakness, weak bilabial seal, open mouth posture, soft cry, and excessive drooling [31]. Despite motor and speech delays, the majority (16/19 or 84%) exhibited age-appropriate social skills (Table 3).

Other features of the neurologic examination in infants with Smith-Magenis syndrome include reduced reflexes in 84% in the absence of abnormal electromyographic or nerve conduction velocities and a 6-8 Hz postural tremor in the upper, distal extremities. Once ambulatory, pes planus or cavus was observed in two thirds of the initial study (n = 19) population. Infants with Smith-Magenis syndrome manifested some decreased sensation to pain, but nerve conduction velocities measured in six infants were normal.

The most common diagnosis entertained in infancy is Down syndrome, prompting request for karyotype in the majority of children during infancy. Among the 19 Smith-Magenis syndrome children in our initial National Institutes of Health study, 30% were thought to have Down syndrome; other diagnoses included Angelman syndrome (n = 1), Cornelia de Lange's syndrome (n = 1), and Prader-Willi syndrome (n = 1). Karyotypes were obtained in two children with cleft palate and one child with polydactyly. Overall, only six children were described as looking dysmorphic. Other diagnoses considered after the first year of life were atypical Prader-Willi syndrome and Fragile X, autism, and pervasive developmental delay. Despite early karyotypes, the diagnosis was made on the first karyotype in 8 of 10 children in Group 1 compared with only 4 of 9 children in Group 2. All 19 children were diagnosed by the third karyotype. Those Group 1 children diagnosed in early infancy were born between 1991 and 1997, whereas those in Group 2 with a mean age of 5.4 years (Group 2) at diagnosis were born between 1980 and 1991.

Based on our assessment, we found that several distinctive features characterize the infantile phenotype of Smith-Magenis syndrome [9,27,29,32] (Table 3).

Smith-Magenis Syndrome in Childhood (Age 18 Months to 12 Years)

While the clinical and neurobehavioral features of Smith-Magenis syndrome in infancy may be overlooked, the more classic physical and neurobehavioral aspects of Smith-Magenis syndrome come to be appreciated during childhood. Sleep disturbance is manifest, and is often the most pervasive feature of the disorder that may aid in diagnostic suspicion. Some degree of developmental delay or mental retardation, or both, is observed in all patients with Smith-Magenis syndrome. A more distinctive neurobehavioral pattern emerges during the toddler years and continues into childhood, characterized by maladaptive, self-injurious, and stereotypic behaviors that have been well described [2,13,15,33-35]. Self-injurious behaviors begin to emerge around 18 months of age, with head-banging being rather frequent. Overall, the prevalence of self-injurious behaviors is 96% [13] and has been demon-

Table 4. Self injurious behaviors in Smith-Magenis syndrome [41]

	Dykens and Smith [13]	Finucane et al. [15]	
	n = 35 Mean = 9 yr (%)	n = 15 Mean = 6.46 yr (%)	n = 14 Mean = 25.01 yr (%)
Self-injurious behavior	92	93	100
Bites self	77	87	
Hits/slaps self	71	40	86
Head banging		47	64
Hits self against surface	40	NN	NN
Pulls hair or skin	31	NN	NN
Hits self with object	20	NN	NN
Skin picking/scratching	29	33	86
Object insertion	25		
Ears	NN	20	43
Nose	NN	7	29
Rectum	NN	0	7
Vagina	NN	11	30

Abbreviation:
NN = Not noted or differentiated

strated to correlate directly with age and level of intellectual functioning [15]. In our experience, this represents frustration related to inability to communicate. In addition, somatic disturbances, such as gastrointestinal problems may be contributory but are often overlooked. Onychotillomania (nail yanking) and polyembolokoilamania (bodily insertions beyond mouthing objects) appear to be unique behaviors in this disorder, and thus may help facilitate the diagnosis [15]. Generally, these latter two behaviors do not become major issues until adolescence or older ages (Table 4).

Clinically, many of the children with Smith-Magenis syndrome have been given the diagnosis of autism/pervasive developmental disorder because of abnormalities of language and stereotypic behaviors [29]. Although children with Smith-Magenis syndrome share behaviors observed in autistic children (self-injurious behaviors, delayed verbal language), scores on scales of childhood autism (Childhood Autism Rating Scale) demonstrate differences between the two groups. Typically children with Smith-Magenis syndrome fall at the low end of the mild classification for autism on the Childhood Autism Rating Scale [36]. Sensory aversions are typical in this group, presenting as both tactile and auditory aversions. Early data derived using the Sensory Profile Caregiver Questionnaire [37] for an initial group of 21 Smith-Magenis syndrome children (ages 3-10 years) examined at the National Institutes of Health demonstrate significant problems in modulating responses to sensory input and difficulties in the ability to perform sustained activity and meet performance demands [38]. In addition to hypersensitivity to sound, oral motor dysfunction, and decreased response to pain, there is also evidence of vestibular dysfunction and suggested difficulties with depth perception (climbing down stairs), affecting balance and gravitational security.

Significant speech/language delay, with or without associated hearing loss, occurs in over 90% of individuals with Smith-Magenis syndrome [31,39]. In general, expressive language delays are out of proportion to receptive language skills, especially during early childhood [1,14,29]. Toddlers and school-age children with Smith-Magenis syndrome manifest delayed expressive language skills into early childhood. Thus, the clinician evaluating a dysmorphic child with absent age-appropriate vocalizations should consider testing for Smith-Magenis syndrome.

Children with Smith-Magenis syndrome overall demonstrate significant delays in adaptive behavior, including communication and socialization skills as well as their daily living skills. While delays in communication and daily living skills tend to be consistent with cognitive functioning, socialization skills were significantly higher than cognitive functioning, suggesting potential strengths in this area [36]. In addition, it has been observed that adults with Smith-Magenis syndrome remain more dependent on caregivers and require a higher degree of support than might be predicted based on their cognitive level of functioning as described below [40] (A.C.M. Smith, personal experience).

In general, children (and adults) with Smith-Magenis syndrome have difficulties modulating both bodily functions (eating/sleep) and behaviors, especially those that involve integration of sensory stimuli [13]. This difficulty is clinically manifest by delayed toilet training, persisting nighttime enuresis, impulsivity and aggression, oversensitivity to touch or decreased pain tolerance, difficulty with transitions, and clumsiness.

The relationship between self-abusive behaviors and decreased pain sensitivity (i.e., peripheral neuropathy) has not been determined and is a topic of further interest and study in our research at the National Institutes of Health.

Many believe that the early behavioral problems, including head banging, self-biting, and self-hitting, are in part related to the general frustrations experienced with poor expressive language skills [1,14]. The sleep disturbance and self-abusive behaviors also appear to escalate with age, often at expected developmental life stages, specifically at 18-24 months, at school age, and with pubertal onset.

Adolescents and Adults With Smith-Magenis Syndrome

Little has been detailed about the adolescent or adult with Smith-Magenis syndrome [40]. Cognitive function in Smith-Magenis syndrome appears to be preserved into adulthood without any evidence for degeneration or progressive dementia. In addition, the number and severity of maladaptive behaviors may increase with cognitive ability and age [15]. There is no published evidence of neuromotor deterioration, and the majority of adolescents and adults with Smith-Magenis syndrome appear to have less issues with balance and incoordination as they mature. However, two patients developed strokes associated with loss of milestones (Smith and Gropman, personal observations). In at least one of these cases, cardiac embolus was the etiology.

Typical behavioral problems observed in this age group include stereotypies, mood instability, attentional disorders, and anxiety.

When compared with age- and sex-matched subjects with Prader-Willi syndrome or mixed mental retardation, the majority of subjects with Smith-Magenis syndrome (89%) demonstrate significantly elevated maladaptive behavior scores compared with their counterparts. In addition, 12 characteristic behaviors differentiate Smith-Magenis syndrome from either Prader-Willi syndrome or mixed mental retardation with 100% accuracy. Specifically, those with Smith-Magenis syndrome demonstrated significantly higher rates of temper tantrums (94%), disobedience (97%), attention-seeking (100%), property destruction (86%), impulsivity (86%), aggression (57%), hyperactivity (94%), distractibility (89%), toileting difficulties (80%), sleep disturbance (94%), and nail-biting behaviors (72%). Self-injurious behaviors were observed in 92% of the Smith-Magenis syndrome study group, including biting or hitting self (71-77%), onychotillomania (29%), and polyembolokoilamania (25%) (Table 4). Stereotypic behaviors were demonstrated by all Smith-Magenis syndrome subjects including mouthing objects or hands in mouth (54-69%), teeth grinding (54%), "lick-and flip" behavior (51%), self-hug or upper body spasmodic squeeze (46%), body rocking (43%), and spinning or twirling objects (40%) [13].

Individuals with Smith-Magenis syndrome also differed from their counterparts in terms of regulation of basic bodily functions (sleeping, modulating activity and affect, eating, and toileting), and in social and repetitive behaviors [13]. Patients with Smith-Magenis syndrome slept less, were more hyperactive, and were more emotionally labile. Enuresis and encopresis were singularly frequent in Smith-Magenis syndrome compared with Prader-Willi syndrome and mixed mentally retarded subjects. Socially, those with Smith-Magenis syndrome demand more attention than their counterparts. Adolescents and adults with Smith-Magenis syndrome exhibit obsessive thinking, primarily about specific topics, and anxiety manifest as repetitive behaviors. In the authors' experience, flight reactions without an apparent trigger or provocation have been observed in teenagers and adults.

Central and Peripheral Neurologic System Involvement in Smith-Magenis Syndrome

Individuals with Smith-Magenis syndrome present features of both central and peripheral nervous system dysfunction [1,29]. Cognitive functioning in Smith-Magenis syndrome ranges from borderline to profound mental retardation [41]. Epileptic seizures occur in 11-30% of individuals with Smith-Magenis syndrome [1,3,29]. Electroencephalographic abnormalities have been documented in approximately 25% of patients in the absence of a clinical history of seizures in one series [1,29]. There is no single seizure type or electroencephalographic pattern that is characteristic of Smith-Magenis syndrome, although complex partial seizures appear more frequent (authors' personal experience). An isolated case of infantile spasms was reported in a 9-month-old female with Smith-Magenis syndrome [42]. Recognition and treatment of seizures is important as it may improve attention, behavior, sleep, and overall cognitive functioning. The prognosis depends on the type of seizure and response to antiepileptics. Adverse side effects of medications have been reported with high frequency in Smith-Magenis syndrome (Gropman and Smith, unpublished observations, 1997); these include excessive lethargy, paradoxical hyperactivity, and irritability. There are at least two teenage females with Smith-Magenis syndrome who appear to have significant catemenial seizures.

Nonspecific central nervous system structural abnormalities documented by neuroimaging may be observed in over half of affected individuals, with an increased frequency of ventriculomegaly reported [1]. However, there is no other specific neuroimaging finding associated with Smith-Magenis syndrome. Computed tomographic scans performed in 25 patients with Smith-Magenis syndrome demonstrated ventriculomegaly in 9, enlargement of the cisterna magna in 2, and partial absence of the cerebellar vermis in 1 [1]. Similar findings were observed among a group of 10 children who had undergone previous magnetic resonance imaging: 5 had ventriculomegaly; 2 had enlarged posterior fossa; and 3 had normal scans [9]. Recent studies employing magnetic resonance imaging volume-based morphometrics and positron emission tomography have reported significant bilateral decrease of

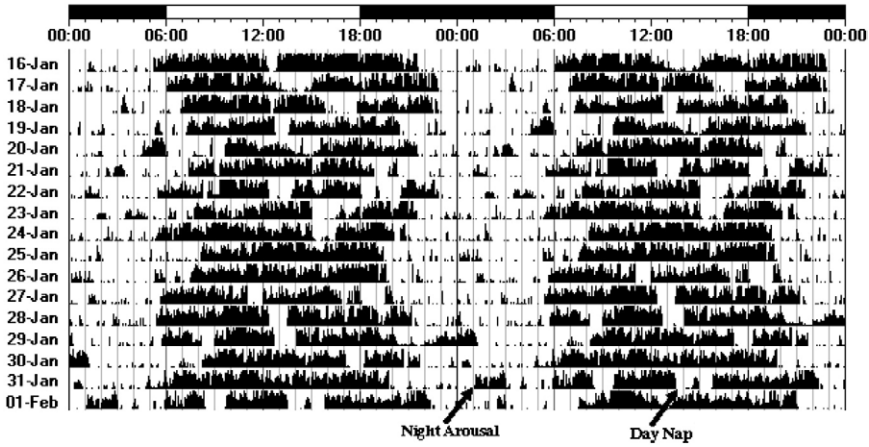


Figure 2. Seventeen days of continuous wrist activity are depicted from a male 5 years of age with fluorescence in situ hybridization–confirmed Smith-Magenis syndrome. The clock time (48 hours) is indicated at the top of the panel; consecutive days are plotted beneath each other as indicated on the left margin. In addition, consecutive days are plotted adjacent to each other on the same horizontal line in order to view the nighttime transition from one day to the next. The bars at the top identify the approximate hours of day and night. Vertical black bars indicate minute-to-minute activity counts. Rest is indicated by the absence of the vertical bars. Note that most rest occurs during the night, and most activity occurs during the day. However, this pattern is often interrupted by episodes of night waking, and daytime naps. The arrows at the bottom identify one (of many) episodes of night arousal (left) and daytime nap (right).

gray matter concentration in the insular and lenticular nucleus in Smith-Magenis syndrome children [43]. In addition, a significant hypoperfusion was evident in the same regions. The only known neuropathologic study on a patient with Smith-Magenis syndrome in whom the entire 17p11.2 band was deleted, demonstrated microcephaly and foreshortened frontal lobes with neuronal depletion; a small choroid plexus hemangioma was also observed in the lateral ventricle [2].

Clinical signs of peripheral neuropathy are reported in approximately 75% of patients with Smith-Magenis syndrome [1,9]. Individuals with Smith-Magenis syndrome have a characteristic appearance of the legs and feet that is often observed in peripheral nerve syndromes or neuropathies. Decreased sensitivity to pain is common. Because of their relative insensitivity to pain, individuals with Smith-Magenis syndrome may cause injury to themselves by object insertion, persistent skin picking, biting, or hitting oneself or striking hard surfaces during uncontrolled rages [44]. During early infancy and childhood, signs of peripheral nervous system involvement include hypotonia (100%) with hyporeflexia (84%) and decreased sensitivity to pain [29], although these could be caused by central abnormality. Marked pes planus or cavus deformities and unusual gait (flapping feet) are generally observed in childhood. Children with Smith-Magenis syndrome tend to toe walk despite absence of tightened heel cords.

Peroneal motor nerve conduction velocities are generally normal in childhood. Delayed motor nerve conduction velocities due to biopsy-confirmed segmental demyelination and remyelination, similar to that observed in hereditary neuropathy with liability to pressure palsy [1,2] occur rarely in patients with contiguous deletion of the PMP22 gene, located at 17p12 (distal to the Smith-Magenis syndrome critical region) [45,46]. Signs of a nonprogressive peripheral neuropathy nonetheless are present in individuals with Smith-Magenis syndrome. It is unclear whether other genes in the critical region are responsible.

Sleep Disturbance in Smith-Magenis Syndrome

Sleep disturbance occurs in all cases of Smith-Magenis syndrome [1,47], from infancy into adulthood. In infants the sleep disturbance is manifest by excessive daytime lethargy as well as decreased 24-hour sleep. Older toddlers and children manifest fragmented and shortened total sleep cycles, frequent and prolonged nocturnal awakenings, early morning awakening, excessive daytime sleepiness, daytime napping, snoring, and enuresis [1,12,47]. The decreased nocturnal sleep, early awakenings, and daytime naps extends into adolescence [12]. Although other neurologic dysfunction may contribute, an abnormal pattern of melatonin in which daytime levels are high and nighttime levels are low [11,12] (i.e., opposite the normal pattern) may be associated with some of these abnormal sleep features.

Sleep Methodologies in Smith-Magenis Syndrome

Three methods have been used to quantify the sleep of patients with Smith-Magenis syndrome: clinical polysomnography, actigraphy, and subjective questionnaires or diaries. Each has relative advantages and disadvantages, and the findings drawn from the use of each method should be considered in view of their strengths and weaknesses. Polysomnography is the gold standard used to evaluate sleep and sleep disorders. The use of standard tests that rely on polysomnography, such as sleep apnea evaluations and multiple sleep latency tests can be clinically important, and the test results can be compared with normal standards. Further, sleep stages (e.g., rapid eye movement, delta sleep) can only be measured using the electroencephalogram from polysomnographic recordings. However, in individuals with Smith-Magenis syndrome who frequently have sensory (especially involving head and face) and settling issues, the use of polysomnography to estimate sleep amounts may be suspect, particularly if the electrodes and clinical setting are uncomfortable to the patient and disturb sleep. It is often difficult to record a

representative night of sleep if only one or two nights are evaluated and the patient is uncomfortable. A second objective method for estimating sleep is wrist actigraphy (Fig 2). Wrist actigraphy provides an estimate of sleep based on the wrist motion. The disadvantages of this method are that it does not measure electroencephalographic activity, but physical motion. A second disadvantage of actigraphy is that it sometimes produces an overestimate of sleep. Actigraphy is less invasive than the polysomnography and is therefore more tolerable to patients at all ages. The device can be worn for a prolonged period of time (6 weeks or more) in the home setting, and can provide a continuous estimate of the activity-rest cycle during the study period. It therefore can provide objective information regarding the dynamics of home sleep in the context of behavioral and developmental changes.

Questionnaires and sleep diaries have been demonstrated to be quite useful in describing core features of sleep disturbance in Smith-Magenis syndrome [1,47]. This information can be used to evaluate treatment effects on sleep. In the absence of more objective measures, sleep diaries can be a simple method for clinicians and parents to quantify and evaluate sleep changes during treatments and behavioral interventions. The disadvantage of the sleep diary and questionnaires is that parents are often unaware of when and for how long their children are awake during the night, which is a great disadvantage in studying a syndrome like Smith-Magenis syndrome. Such information can only be obtained by continuous observation, or by polysomnographic and actigraphic methods.

Polysomnographic Findings

Reduced sleep time has been documented by polysomnography in virtually all Smith-Magenis syndrome patients studied [1,11,12]. The reduced total sleep time is variably related to difficulty falling asleep, staying asleep, or waking early, thus highlighting increased variability of sleep homeostasis in these individuals. For example, 29% of 24 patients had reduced sleep secondary to frequent awakening [1]. Reduced sleep in the remaining 71% might be associated with difficulty falling asleep, or waking up early. Interestingly, polysomnography of 23 patients with Smith-Magenis syndrome (age range 2.7-31 years) indicated reduced total sleep time in 43% of the group, but no relationship between total sleep time and age or sex [11]. In contrast to this latter point, recent actigraphy data suggest that estimated sleep varies with age [30,48]. The functional consequence of reduced nighttime sleep is an increased sleep debt that consequently increases daytime sleepiness. The Multiple Sleep Latency Test is an objective measure used to quantify excessive daytime sleepiness. Not surprisingly, individuals with Smith-Magenis syndrome have an abnormally reduced latency to fall asleep during the daytime [11], a finding that is consistent with increased daytime napping in Smith-Magenis syndrome.

Specific sleep stage abnormalities in Smith-Magenis syndrome with respect to rapid eye movement and slow wave sleep have been identified with polysomnography. Fifty percent of patients with Smith-Magenis syndrome manifest abnormalities of rapid eye movement sleep [3,11,12]. Forty-three percent [11] and 50% [1] of the populations had reduced rapid eye movement sleep, and in another study, rapid eye movement sleep was disrupted by arousals in all children [12]. As was the case with total sleep time, rapid eye movement sleep percentage did not correlate with age [11] and was reduced in patients with Smith-Magenis syndrome (age range 4-17 years) [12].

Actigraphy Findings

Sleep estimates from wrist actigraphy support persistent sleep disturbance in Smith-Magenis syndrome that extends from infancy into late childhood (Fig 3). Wrist activity was recorded continuously from individuals in the home for 4-6 weeks; these data are then used to estimate 24-hour sleep, as well as night sleep between 7 pm and 7 am. Preliminary data collected from 12 individuals with fluorescence in situ hybridization–confirmed Smith-Magenis syndrome indicate that reduced sleep begins at infancy (<1 year) with reduced 24-hour sleep compared with healthy control subjects. The pattern continues with preschool (3 years), early school (5 years), and later school children (6-8 years) who sleep 1-2 hours less per 24 hours than healthy age-matched control children. Reduced 24-hour sleep stems largely from the reduction of night sleep in each of the age groups. The sleep debt is compensated for by daytime napping (Fig 2). In contrast to polysomnographic studies in which no relationship between age and sleep amounts were observed, home-based 24-hour and night estimated sleep declines in Smith-Magenis syndrome from infancy to 8 years. Thus, the decline in total sleep that occurs from infancy to later childhood seems to be present in Smith-Magenis syndrome as in control subjects. However, with less sleep in Smith-Magenis syndrome, the Smith-Magenis syndrome curve is shifted to the right (Fig 4). Actigraphy appears to be a useful technique to estimate sleep in Smith-Magenis syndrome and would appear to have applications beyond assessment of developmental changes. One clear application would be to objectively measure sleep changes that occur during the course of Smith-Magenis syndrome treatment trials.

Inverted Circadian Pattern of Melatonin in Smith-Magenis Syndrome

In mammals, levels of plasma melatonin begin to increase in the evening and continue to be elevated at night as a consequence of noradrenalin stimulation of B receptors located on pinealocyte cells on the pineal organ. Melatonin levels decline at dawn and are low or undetectable during the daytime. As described below, this night-

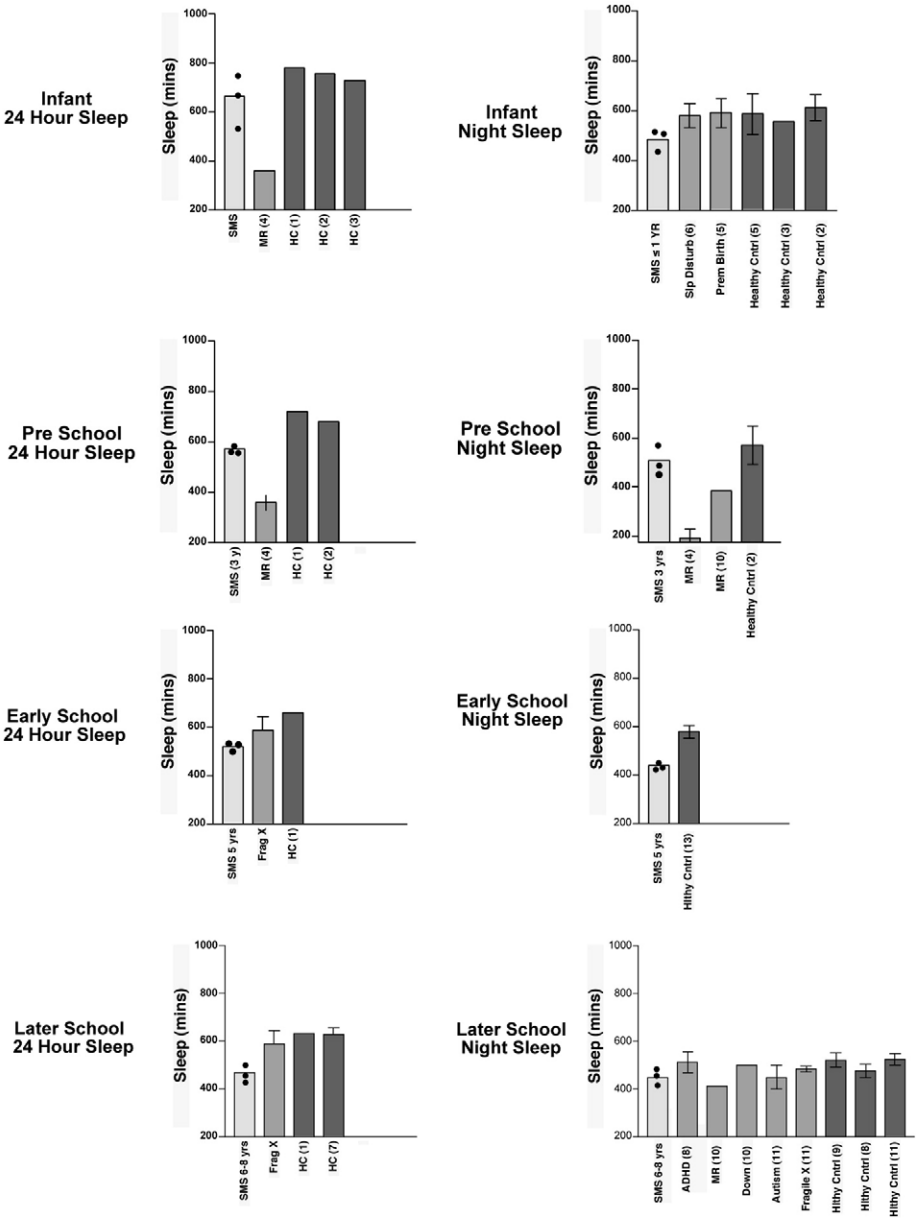


Figure 3. Twenty-four hour actigraphy estimated sleep (left) and nighttime sleep (right) are illustrated in children with Smith-Magenis syndrome (SMS) (light gray), in comparison with other patient groups (gray) and healthy children (dark gray). The different populations are identified beneath the bar graphs. Four age groups are arranged from top to bottom: infants (<1 year, row one), preschool (3 years, row two), early school (5 years, row three), and later school (6-8 years, row four). Note the lower estimated 24-hour and night sleep in children with Smith-Magenis syndrome especially compared with healthy control subjects of the same age. Children with Smith-Magenis syndrome often have less sleep than other children with developmental disabilities although some children with more severe mental retardation (MR) appear to have more sever sleep problems. Also note the decrease in the total 24-hour estimated sleep in children with Smith-Magenis syndrome from 1 year to 8 years of age. The numbers in parentheses indicate the cited studies from which the comparison data were drawn: [50-62]. The estimated sleep from the comparison child groups was derived from actigraphy, video, sleep logs, or electroencephalography.

time rise and daytime decline is conserved across the plant and animal kingdoms—with the exception of Smith-Magenis syndrome.

The inverted circadian rhythm of melatonin secretion (Fig 5) in which daytime levels are elevated, whereas nighttime levels of melatonin are virtually nondetectable has been described for both the major urinary metabolite of melatonin, 6 sulphatoxymelatonin [11] as well as plasma melatonin levels [12]. The inverted melatonin pattern supports the view that the sleep disturbance observed in Smith-Magenis syndrome could be due to abnormalities in the production, secretion, distribution, or metabolism of melatonin [11]. Attempts to correct the disturbed sleep in Smith-Magenis syndrome by a) treatment with nighttime melatonin and/or b) treatment with beta-blockers to prevent the daytime elevation of melatonin, have had limited success [49]. These uncontrolled

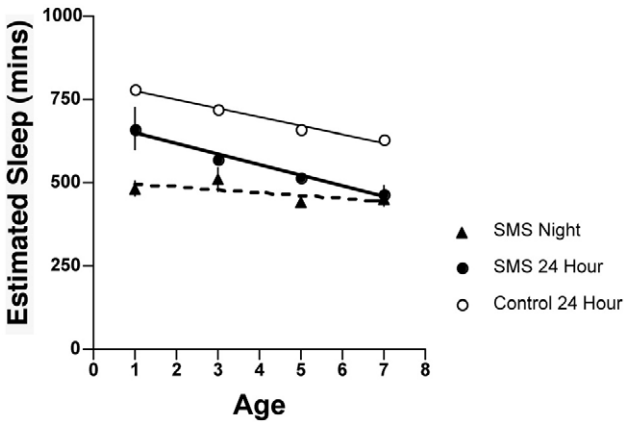


Figure 4. Comparison of actigrpahy-estimated night and total 24-hour sleep in Smith-Magenis syndrome (SMS) and healthy control subjects. Patients with Smith-Magenis syndrome range in age from <1 year to 7 years. control data are from Roffwarg et al. [50]. Both 24-hour sleep as well as nighttime sleep are reduced in Smith-Magenis syndrome relative to healthy control subjects.

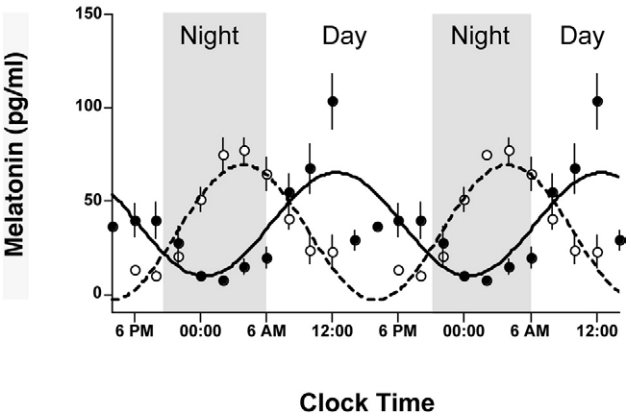


Figure 5. The inverted pattern of plasma melatonin is depicted in eight children with Smith-Magenis syndrome (solid line, filled circles) compared with 15 healthy control subjects (dotted line, open circles). The lines represent the best-fit sine curves to each data set based on minimal least-squares criteria. The peak of the 24-hour curve is at night(~3-4am) in healthy control subjects; the peak occurs during the day (noon) in patients with Smith-Magenis syndrome. The data are redrawn from Figure 2 of De Leersnyder [12].

trials were successful in raising nighttime melatonin and reducing daytime melatonin, as well as reducing daytime tantrums. Objective evaluation of treatment effects on sleep is required as well as a double-blind trial that controls for parent bias.

Sleep, Smith-Magenis Syndrome, and Circadian Rhythms

As mentioned earlier, the 24-hour pattern of melatonin is inverted in individuals with Smith-Magenis syndrome: levels are high during the daytime and low at night. This highly unusual pattern is uniquely present in Smith-Magenis syndrome patients; the inverted pattern of melatonin is not without consequence.

In mammals, 24-hour rhythms in sleep, behavior, and hormone levels are controlled by a central clock in the suprachiasmatic nucleus of the hypothalamus. Lesions of the suprachiasmatic nucleus abolish these 24-hour rhythms, indicating that this clock provides the 24-hour signal to systems that directly produce sleep, behavior, and hormones. In fact, the signal provided by the central clock to the pineal gland to produce melatonin is so strong that in humans, the pattern of melatonin is often used as a surrogate biologic marker for the timing of the clock itself. The fact that the pattern of melatonin is inverted in Smith-Magenis syndrome might suggest that the central clock is inverted. If this hypothesis were correct, all 24-hour rhythms of sleep, behavior, and hormones would also be inverted. This does not appear to be the case. Twenty-four hour rhythms of cortisol and growth hormone are not inverted in patients with Smith-Magenis syndrome. Growth hormone peaked after nighttime sleep onset, and cortisol levels increased from an evening low to a morning high [12]. In addition, the 24-hour rhythm in body temperature, a second surrogate biologic marker of the central clock, was not inverted in Smith-Magenis syndrome [48]. Thus, the inverted melatonin rhythm is not driven by an inverted central clock, but by inverted regulatory elements that more directly control the release of the hormone by the pineal gland.

Sleep Hygiene in Patients and Families Living With Smith-Magenis Syndrome

Persons with Smith-Magenis syndrome have decreased nocturnal sleep and sleep debt, manifest by increased daytime sleepiness. This increased daytime sleepiness may partially be reduced by properly scheduled naps. Naps during midday (12:00-15:00) are more beneficial than late day naps which interfere with capacity to fall asleep at scheduled bedtime. In addition, abnormally high daytime melatonin levels will lead to daytime sleepiness and potentiate the requirement for daytime naps. Clinical signs of increased sleep requirement include napping at unscheduled times, increased nap duration, and the need to awaken a child from a nap or in the morning. Increased sleep debt also is a likely contributor to the behavioral disturbances observed in Smith-Magenis syndrome.

Management of Smith-Magenis Syndrome

Accurate assessment of the cognitive and developmental status of individuals with Smith-Magenis syndrome is difficult and often complicated by the presence of maladaptive behaviors and marked speech delay which makes traditional cognitive test batteries inappropriate in these patients owing to difficulty with interpretation and assurance of validity.

Speech and language evaluations in the infant with Smith-Magenis syndrome should be pursued early to assess for speech and language delays and feeding difficulties, to optimize functional communication and oral motor abilities, and to develop intervention strategies. The early use of sign language and a total communication approach reduces maladaptive behaviors by improving communication [3].

Development of a behavioral treatment plan should be considered as soon as problem behaviors arise. A search for organic causes of behavior should be explored including gastrointestinal disorders (gastroesophageal reflux, constipation), otitis media, or other organ or joint pain. The use of medications to control behaviors has had mixed results in this population [16], and this is an active area of interest. Adverse reactions to some medications have also been reported. Unpublished medication history data on 12 children with Smith-Magenis syndrome ages 3-16 years yield a median number of five medication trials; only two children were not on medication therapy, and one of these was enrolled in a strict behavior-modification program (Allen and Smith, 1997, unpublished).

Older stimulant drugs, in our experience, are not particularly useful in controlling behavior nor increasing attention span in patients with Smith-Magenis syndrome (Allen and Smith, unpublished observations, 1997). However, there is not enough experience with the newer preparations of this class of medications to deduce efficacy. Nevertheless, preliminary experience with atomoxetine would indicate that this should not be a first-line strategy for children with Smith-Magenis syndrome owing to increased incidence of psychotic behaviors (Gropman, unpublished observation). A compilation of a comprehensive review of medications used in Smith-Magenis syndrome, adverse effects, and efficacy is in progress (Allen, Smith, and Gropman, unpublished, 2005).

Typical behavioral problems observed in Smith-Magenis syndrome are effectively controlled with mood-stabilizing agents such as lithium and valproic acid as well as the antipsychotic rispirodone that acts on the dopamine receptor. Low dosage of risperidone may reduce aggression and impulsivity. In addition, in some patients with anxiety, selective serotonin reuptake inhibitors appear helpful. A propensity towards weight gain in adolescents with Smith-Magenis syndrome makes medication selection particularly tricky. For example, valproic acid and risperidone, and some of the newer mood-stabilizing agents are not first-line choices in Smith-Magenis syndrome patients because of problems with excessive rapid weight gain and alterations of lipid profiles.

Symptomatic treatments for aggression and self-injurious behavior including beta-blockers, particularly for individuals with rage attacks or chronic states of overarousal, mood stabilizers such as lithium, neuroleptics, and selective serotonin reuptake inhibitors such as fluoxetine have all been tried with variable results. A pilot uncontrolled trial using the beta-blocker acebutolol suggests that there may be some benefit derived as a result of secondary effects of inhibition of melatonin [12,49].

Stimulants alone generally are not adequate for patients with Smith-Magenis syndrome, as they do not medicate the co-morbid mood disorders. Polypharmacy is typical in children with Smith-Magenis syndrome, as a single drug generally is inadequate to control all symptoms. Therefore the cumulative potential side effects should be monitored. With any trial, tracking sleep patterns and mood is important to judge efficacy.

A careful neurologic evaluation in all patients with Smith-Magenis syndrome ideally should occur at diagnosis and thereafter, the frequency should be based on clinical indices. Electroencephalography should be obtained in all affected individuals who have clinical seizures to guide the choice of antiepileptic treatment. For those without overt seizures, electroencephalography may be helpful to rule out subclinical events in which treatment may improve attention or behavior, especially those with autism spectrum features. Neuroimaging should be accomplished in accordance with clinical findings, such as seizures, abnormalities of cranial circumference, motor asymmetries or abnormalities, and oral motor dysfunction to rule out an anatomic basis.

Change in behavior or attention warrant reevaluation of both seizures and possible medication effects. Electromyography may be of benefit in individual situations, especially in the setting of clinical evidence of peripheral neuropathy.

With regard to sleep management, there have been no well-controlled treatment trials to date for Smith-Magenis syndrome. However, due to the presence of elevated daytime melatonin levels with low nocturnal levels, De Leersnyder et al. [12,49] used the daytime B_1-adrenergic antagonist acebutolol (10 mg/kg administered at 8:00 am) to reduce daytime melatonin secretion, combined with an evening oral dose of control-release melatonin (6 mg at 8 pm) in an attempt to restore normal nocturnal plasma melatonin levels. Although this uncontrolled trial demonstrated improved circadian rhythm of melatonin secretion and possibly improved behavior in nine children with Smith-Magenis syndrome, the results may have been biased as a result of high parental expectations. Objective measures were lacking.

Anecdotal single case reports of therapeutic benefit from melatonin in Smith-Magenis syndrome exist [47], as do an equivalent number of reports with no benefits. The time of its administration is important, because melatonin can have phase shifting properties when taken at different times. Low dosages (i.e., 0.5-2.5 mg) are preferred, because higher dosages (5-10 mg) can result in increased daytime levels of melatonin and increased daytime sleepiness. A double-blind controlled trial is required to fully evaluate the effect of melatonin treatment in improving the quality of sleep in Smith-Magenis syndrome.

Conclusions and Perspectives

Although the phenotype of Smith-Magenis syndrome was first recognized in 1982, our knowledge of the disorder continues to accumulate. Advances in the fields of cytogenetics and molecular genetics will enable more efficient diagnosis as well as identification of the genes involved in the Smith-Magenis syndrome critical region and their contribution to aspects of the phenotype. However, the greater challenges are the timely diagnosis and understanding of the phenotype across the lifespan as well as the daily management of many of the problems unique to Smith-Magenis syndrome.

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