Behavioral Phenotype of Smith-Magenis Syndrome (del 17p11.2)

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Smith-Magenis syndrome (SMS) is a distinct and clinically recognizable multiple congenital anomaly (MCA) and mental retardation syndrome caused by an interstitial deletion of chromosome 17p11.2. The phenotype of SMS has been well described and includes: a characteristic pattern of physical features; a hoarse, deep voice; speech delay with or without associated hearing loss; signs of peripheral neuropathy; variable levels of mental retardation; and neurobehavioral problems. Although self-injury and sleep disturbance are major problems in SMS, studies are limited on the behavioral phenotype of SMS. This report reviews the current state of knowledge about SMS and presents new data based on syndrome-specific observations by the authors' longitudinal experience working with SMS, specifically related to the behavioral aspects of SMS. This information should have relevance for parents, clinicians, geneticists, and educators involved in the care of individuals with SMS.

KEY WORDS: SMS; chromosome 17; behavioral phenotype; sleep disturbance; multiple congenital anomaly (MCA); mental retardation syndrome

INTRODUCTION

Recent technological advances arising from the Human Genome project have stimulated renewed interest in research that focuses on the behavioral phenotypes of microdeletion syndromes. Smith-Magenis syndrome is a distinct and clinically recognizable multiple congenital anomaly (MCA) and mental retardation syndrome caused by an interstitial deletion of chromosome 17p11.2. Since the initial report of two male infants with interstitial deletion of chromosome 17p11.2, additional cases have been reported, further delineating the distinct and clinically recognizable phenotype, which has come to be referred to as the Smith-Magenis syndrome (SMS). More than 100 cases of SMS have been identified worldwide, representing a diversity of ethnic backgrounds [Smith et al., 1982, 1986; Patil and Bartley, 1984; Stratton et al., 1986; Popp et al., 1987; Lockwood et al., 1988; Colley et al., 1990; Hamill et al., 1991; Allen et al., 1991; de Rijk-van Andel et al., 1991; Greenberg et al., 1991, 1996; Moncla et al., 1991; Massuno et al., 1992; Finucane et al., 1993a,b; Fisher et al., 1993; Meinecke, 1993; Al-Quadah et al., 1994; Fan and Farrell, 1994; Barnicoat et al., 1996; Brown et al., 1996; Behjati et al., 1997; Van Haneghan et al., 1997].

The phenotype of SMS has been well described and includes a characteristic pattern of physical features, developmental delay, clinical signs of peripheral neuropathy, and neurobehavioral problems including sleep disturbance and self-injurious behaviors. Behavioral problems, some distinctive in SMS, represent the major management problem for both parents and professionals working with this syndrome. However, systematic study of the cognitive and behavioral phenotype of SMS has been fairly limited [Finucane et al., 1994; Greenberg et al., 1996; Dykens et al., 1997] compared to the rigorous information generated from extensive clinical and molecular studies of SMS [Chen et al., 1995; Elsea et al., 1995; Greenberg et al., 1991, 1996; Moncla, 1993; Patel et al., 1990; Smith et al., 1986; Stratton et al., 1986].

The paper reviews the current state of knowledge about SMS and presents new data based on syndrome-specific observations and the authors' longitudinal experience working with SMS over the past 15 years, specifically as it relates to the behavioral aspects of SMS. This information should have relevance for parents, clinicians, geneticists and educators involved in the care of individuals with SMS.

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Prevalence of SMS

The vast majority of persons with SMS has been identified in the last 5 years as a result of improved cytogenetic banding techniques. The incidence of SMS is estimated to be 1/25,000 births [Greenberg et al., 1991]; however, this reflects a probable underascertainment. The diagnosis of SMS is generally confirmed cytogenetically, with detectable deletions of 17p11.2 ranging from 2 to 9 megabases. Moderate quality and 450-550 band resolution is generally adequate for detection of the deletions of 17p11 [Behjati et al., 1997]. One reported case of del 17p11.2 was detected prenatally [Fan and Farell, 1994]. The availability of a fluorescence in situ hybridization (FISH) probe specific for SMS has proven beneficial in equivocal cases [Elsea et al., 1996; Juyal et al., 1995a,b]. Previously normal cytogenetic studies in a patient whose phenotype is suggestive of SMS warrant repeat studies accompanied by FISH analysis.

The cause for the deletion remains unknown. Virtually all cases occur de novo, suggesting a low recurrence risk for parents. However, Zori et al. [1993] reported the first and only case of vertical transmission of the del 17p11.2 from mother to daughter; the mother was confirmed to be mosaic for the deletion. Consequently, parental chromosomes are recommended. The random parental origin of the 17p deletion in 15 patients with SMS suggests that imprinting does not play a role in the expression of SMS phenotype [Greenberg et al., 1991].

Clinical Phenotype of SMS

The largest and most recent series of SMS patients (n = 27) was evaluated as part of a multidisciplinary clinical, cytogenetic, and molecular approach to SMS [Greenberg et al., 1996]. Common features (Table I) seen in over two-thirds of SMS individuals include: brachycephaly with a characteristic craniofacial appearance; ocular abnormalities; short stature; brachydactyly; a hoarse, deep voice; history of infantile hypotonia and failure to thrive; speech delay with or without associated hearing loss; signs of peripheral neuropathy; behavioral problems including sleep disturbance and self-injurious behaviors; and variable degree of mental retardation.

The facial appearance (Fig. 1) is characterized by midface hypoplasia, prominent forehead, upslanting palpebral fissures, epicanthal folds, broad nasal bridge, downturned mouth with cupid’s bow, ear anomalies, and relative prognathism. Anthropometric Z-scale pattern profiles were recently compiled by Allanson et al. (unpublished observations) on 32 individuals with SMS (ranging in age from 9 months to 33 years) who attended the First International Conference on SMS. The facial pattern profile supported past subjective impressions, with mandibular dimensions consistently exceeding the maxillary counterparts. Craniofacial widths were greater than depths and heights.

Several features appear to be age-dependent, including the prominent forehead, prognathism, brachycephaly, hoarse voice, and ophthalmologic findings, specifically high myopia with and without retinal detachment [Finucane et al., 1993a; Chen et al., 1996].

Clinical signs of peripheral neuropathy are seen in approximately 75% of SMS [Greenberg et al., 1996], including decreased deep tendon reflexes, decreased sensitivity to pain or temperature, pes cavus or planus. However, peroneal motor nerve conduction velocities (when available) have been normal in all but one case. Molecular studies of SMS patients show that PMP-22, the gene for CMT1A, which causes hereditary neuropathy with liability to pressure palsy (HNPP) when deleted, is usually not deleted in SMS patients [Greenberg et al., 1991; Chevillard et al., 1993; Moncla et al., 1993]. Peripheral neuropathy has been noted in SMS patients even when PMP-22 is not deleted.

Comprehensive ophthalmologic evaluations on persons with SMS reveal a high frequency of eye abnormalities, including: iris anomalies, microcornea, myopia and strabismus, “apparent” telecanthus, cataracts, and myopia [Chen et al., 1996; Finucane, 1993a]. A high incidence of microcornea (50%), a new finding not previously described, was found in their series. The heterochromic irides or “brushfield-like” spots that several authors have noted in irides are best described as Wolfflin-Kruckmann spots [Chen et al., 1996]. The relatively high frequency of retinal detachment (3/10) in

| Characteristic facial appearance | Cardiac defects | Cardiac defects |
| Variable degree of mental retardation | Renal abnormalities | Cardiac defects |
| Speech delay | Low thyroxine levels | Cardiac defects |
| Ocular abnormalities | Low immunoglobulins | Cardiac defects |
| Brachycephaly | Seizures by history | Cardiac defects |
| Hoarse deep voice | Abn. EEG w/o seizure history | Cardiac defects |
| Brachydactyly | Forearm abnormalities | Cardiac defects |
| Short stature/FTT | Cleft lip/palate | Cardiac defects |
| Sleep disorder | 9 | Cardiac defects |
| Signs of peripheral neuropathy | 75 | Cardiac defects |
| Hearing loss | 75 | Cardiac defects |
| Self-abusive behavior | 67 | Cardiac defects |
| Scoliosis | 65 | Cardiac defects |
| Infantile hypotonia | 51 | Cardiac defects |

*Greenberg et al. [1996] (multidisciplinary study of 27 SMS patients.)
patients with high myopia reported by Finucane et al. [1993a] was not found in Chen's series [1996].

Although the first two males reported with del 17p11.2 had multiple major anomalies including cardiac defects, facial clefts; and urogenital anomalies, these findings have not held up in the larger series of reported SMS patients. Variable findings seen in SMS cases include: cardiac defects (37%); renal abnormali-

Fig. 1. Female with SMS at ages 6 months (A), 3 years (B), and 15 years (C) respectively. Note the “doll-like” appearance, downturned mouth, and prominent cheeks. In addition, redundant skin folds (with almost constriction-like bands) are present on the arms.
ties, especially duplication of collecting system (35%); thyroid abnormalities (29%); low immunoglobulins (23%); seizures (11-30%); abnormal EEG without seizures (21%); forearm abnormalities (16%); and facial clefts (9%).

Newborn and Early Infancy

The diagnosis of SMS in the neonate and young infant is often difficult, since the facial appearance is not highly dysmorphic, but rather subtle. Facial features are characterized by a “cherubic,” almost “doll-like” facial appearance, with prominent “pudgy” cheeks often with a flushed (“rosy”) appearance, flat midface, upslanting palpebral fissures, and a down-turned mouth (Fig. 1A). The shape of the mouth and upper lip is the most characteristic with fleshy upper lip with a cupid bow or tented appearance. As infants, they are very sociable, with appealing smiles; many have been described as “beautiful” babies, especially when smiling. A history of infantile hypotonia and failure to thrive is common in infancy. Several mothers suspect a problem in early infancy, but are often reassured by their child’s primary care provider, given their child’s alertness and social smiles. Failure to note the mild dysmorphic features in these children until they are older often delays the diagnosis of SMS.

Several findings not previously described in SMS are worthy of mention. Many of the infants also have redundant fat folds, especially on their arms and legs, which some describe as resembling the “Michelin” man (Fig. 1A and B). Infants with SMS are often described by their mothers as being “a perfect baby” that “never cries.” With further questioning, several parents report a need to wake their child for feedings. Although sleep studies during infancy are not available, these parental reports are consistent with early signs of sleep disturbance in infants with SMS.

In several cases, a diagnosis of Down syndrome was initially suspected due to generalized hypotonia, flat midface, and upslanting palpebral fissures, especially when congenital heart disease is also present. Often cytogenetic studies are recommended in the newborn period to rule out Down syndrome, and these studies are often reported as “normal” without the del 17p11.2 detected, delaying diagnosis.

Molecular Aspects of SMS

Molecular evaluation of patients with SMS strongly suggests that it is a contiguous gene syndrome. Molecular and phenotypic analysis of SMS began in earnest in 1991, with the mapping of Charcot-Marie-Tooth disease, CMT1A, a dominantly inherited peripheral neuropathy, to a large DNA duplication, distal to the SMS region [Lupski et al., 1991; Patel et al., 1990]. Using RFLP analysis, Greenberg et al. [1991] demonstrated five markers deleted on chromosome 17 in all of the 31 patients with SMS (six previously reported and 25 new patients). Recent studies identified a common deletion interval between EW301 (D17S58) and cC117 in the majority of patients with SMS [Juyal et al., 1996]. To date, 12 genes have been localized to the SMS region of 17p11.2 (Table II). The role of each of these in SMS is not yet known; however, intensive work to narrow the SMS critical region (SMSCR) continues.

One of these, the sterol regulatory element binding protein (SREBF1) is intriguing in light of at least one report of elevated LDL in 11 of 13 SMS patients [Fincane et al. 1996]. This has not been the experience of other groups (Lupski et al., personal communication) and warrants further investigation.

Cognitive and Behavioral Characteristics

While the physical features of SMS have remained fairly consistent since the syndromes original description in the 1980s, there have been relatively few systematic studies focusing on the cognitive and behavioral phenotype of SMS. And yet, the psychological and behavioral aspects of SMS are perhaps the most characteristic features of the syndrome.

All individuals with SMS have some degree of cognitive delay. On average, they show moderate levels of mental retardation with speech and language delays. IQ scores measured on 27 SMS patients ranged between 20 and 78 [Greenberg et al., 1996], with most falling in the moderate range of 40–54. Dykens et al. [1997] found specific cognitive profiles in 10 SMS subjects. Relative weaknesses were seen in sequential processing and short-term memory and relative strengths were found in long-term memory and perceptual closure.

Speech delay with or without associated hearing loss occurs in 96% of cases. Receptive language skills are generally higher than expressive language. The hoarse voice can be a diagnostic marker for the syndrome. The use of sign language as an adjunct to speech therapy has had a major effect on overall speech development and probably helps decrease a child’s frustration associated with expressive language problems. Speech therapy with early use of sign language should be part of the management plans for all children with SMS.

Behavioral problems are salient in SMS, including aggression, temper tantrums, impulsivity, outbursts, repetitive behaviors, attention deficits, and attention-
seeking behaviors [Dykens et al., 1997; Greenberg et al., 1996; Smith et al., 1986]. These problems are observed in more than 60-80% of cases of SMS and represent the major management problem for both parents and professionals working with this syndrome.

Self-injurious behaviors. Self-injurious behaviors are also problematic in SMS and include head banging, wrist biting, skin picking, and two behaviors which may prove unique to SMS, onychotillomania (pulling out fingernails and toenails) and polymembokolamania (object insertion). Some of these behaviors appear to be age-related, including head banging and wrist biting, which often begin as early as the second year of life, and onychotillomania, which is uncommon under age 5–6 years [Greenberg et al., 1991].

In general, SMS patients exhibit a relative insensitivity to pain and consequently, may cause injury to themselves by persistent picking or biting or during uncontrolled rages. Indeed, the authors are aware of at least two cases in which parents have been reported to social services for suspicion of child abuse, which actually stemmed from self-inflicted injuries by the child with SMS. PRIMS1 has also received calls from parents who have reported that their child has punched his/her fist through the wall, door and/or window glass during a rage.

Dykens et al. [1994] also described another salient behavior which may prove to be unique to SMS, the spasmodic upper-body squeeze, or “self-hug.” This behavior was observed with increased frequency in 11 patients with SMS, especially when they were happy or pleased. Two types of self-hugging were described: an upper body movement versus clasping the hands at chest or chin level and squeezing, often with interlocked fingers. More frequent among the young children and adolescents than adults, these movements appear involuntary, with a tic-like quality. In addition to hugging themselves, individuals with SMS often hug others repetitively and with force. We are aware of several instances in which a family pet (e.g., cat, hamster, etc.,) was actually “hugged” to death. Clinical observations by Dykens et al. [1997] also noted a high frequency of a previously undescribed stereotypic behavior involving hand licking and page flipping (lick and flip).

Psychotropic Management of Behavior

Although children with SMS have some degree of control over their behaviors, it is important to recognize that many of the negative behaviors seen in SMS have their origins in internally driven impulses. Most of the patients with SMS have been tried on a number of medications to control behavior. In the multidisciplinary study conducted by Greenberg et al. [1996], the most common medications tried among 27 SMS patients were: methylphenidate, pemoline, and thioridazine. In most cases, the stimulant drugs were not particularly helpful in controlling behavior or increasing attention span. Thoridazine caused excessive sedation in some. Several SMS patients, both with and without seizures, tried on carbamazepine showed some improvement behaviorally; however, some showed only transient improvement. Adverse reactions to some medications have also been reported. Recent use of SSRIs (serotonin reuptake inhibitors) has shown considerable improvement with respect to behavioral outbursts and sleep for at least three individuals with SMS (Smith, ACM and Allen AJ, unpublished experience).

Classroom behaviors. Unfortunately, research into the specific educational strategies and interventions beneficial to SMS has lagged behind current molecular understanding of SMS. Little has been written in this area except by Haas-Givler and Finucane [1995] and Haas-Givler [1994]. Most of the published information appears in Spectrum, the official newsletter for PRISMS. Typically the child with SMS demonstrates some degree of ongoing and severe behavioral problems at home and/or in the classroom. In addition to the self-injurious behaviors, problems with attention-seeking, hyperactivity, explosive outbursts, and aggressive behaviors are frequently seen.

Children with SMS are inherently distractible and tend to do better in smaller, calmer, and more focused classroom settings. Ideally, they seem to do best when there are no more than five to seven other children in a classroom, with one teacher and one teacher’s aide [Haas-Givler et al., 1996]. With a class size above this ratio, the competition for teacher attention becomes greater, and the possibility of behavioral problems increases. Instructional strategies that recognize the SMS child’s weaknesses in sequential processing (e.g., counting, mathematical tasks and/or multistep tasks) and take advantage of their strengths in visual reasoning tasks are the most effective [Dykens et al., 1997]. They tend to be visual learners and can benefit greatly from the use of pictures, etc. to illustrate multistep tasks, classroom schedules, etc.

Children with SMS are very adult-oriented, with a sometimes insatiable need for individualized attention from the teacher (and other adults); when this is denied, aggression toward others, behavioral outbursts, tantrums, and self-injurious behavior frequently result. Transitioning from one activity to another and changes in routine, at home or in the classroom, often precipitate behavioral outbursts. They respond positively to consistency, structure and routine, especially with visual cues.

Several positive attributes of behavior in SMS warrant emphasis. Individuals with SMS have engaging and endearing personalities (impish smile, self-hugging, good eye contact), are eager to please, and often have a well-developed sense of humor. They enjoy and thrive on adult attention. In the classroom, they are able to learn, remember and recall all the names of fellow teachers and other students. A unique fascination with electronics, including computers, VCRs, tape recorders, is a positive “skill” with potential for opening up new avenues for educational instruction using computer-assisted technology.

PRISMS is the parent support group for parents & researchers interested in Smith-Magenis syndrome. (URL http://www.kumc.edu/gee/support/smith-ma.html)
Sleep Behaviors in SMS

Significant symptoms of sleep disturbance are very common in SMS and have a major impact on not only the SMS child but for his/her parents and other family members, many of whom also become sleep-deprived themselves. Greenberg et al. [1996] documented sleep abnormalities in 75% of 27 SMS patients, including difficulties falling asleep, frequent and prolonged nighttime awakenings, and excessive daytime sleepiness. Abnormalities of REM sleep have been seen in over half of those studied with polysomnography; 12 had reduced REM sleep; one, increased REM sleep, and two, absent REM sleep [Greenberg et al., 1996, 1991].

In a recent study of sleep behaviors in 39 individuals with SMS, we found a significant relationship between increased age and a steady decline in the total hours of sleep needed at night, earlier bedtimes, shorter nap lengths, and increased frequency of naps (Smith et al., 1998). The most frequent problems during bedtime and nighttime periods were bedtime ritual (74%), use of sleep medications (59%), bedwetting (79%), snoring (69%), and awakening during the night either to go to the bathroom (54%) or to get a drink (54%). Other medical problems found with relatively high frequencies for this population included: frequent ear infections (87%); constipation (58%); gait disturbance and/or signs of peripheral neuropathy (> 50%). Problems with enuresis may be related to increased fluid intake, medications and/or underlying urinary tract problems, including hypotonic bladder, which has been seen in a few SMS cases. Whether the constipation is related to generalized hypotonia and/or dietary intake also remains unclear.

Therapeutic management of the sleep disorder in SMS remains a challenge for the physician and parents. Preliminary studies by Potacki et al. [1997] documented abnormally elevated urinary 6-sulphatoxymelatonin (aMT6s) during a 24-hour sleep study in five of six SMS patients studied. Reversal of the normal pattern highs to daylight hours versus nighttime hours was found. The biochemical finding of aberrant melatonin levels skewed to daytime highs, is also supported by anecdotal parental reports and unpublished data on general improvement of sleep patterns with the administration of melatonin (over the counter; Smith ACM et al., 1998). The REM sleep abnormalities, abnormal melatonin levels, and sleep cycle disturbances are suggestive of an underlying biological clock problem in SMS. Further research is needed to answer this question.

The sleep disorder in SMS is particularly stressful on the parents and family members. Parents, especially the mothers, report that they become sleep-deprived themselves and have difficulty falling asleep and staying asleep, due to their child’s frequent nightly awakenings (SMS parental “phenotype”). Independently, parents have implemented similar solutions to “SMS-proof” their child’s room to minimize self-injury and maximize sleep cycle, thereby providing some degree of assurance that their child will not wake and wander about and/or injure themselves (Smith et al., 1998). Removing all small objects, toys, lamps, etc. from the bedroom, installing a door peephole to look in, an outside locking “door,” and window “black-out” curtains have all been tried with some success.

There is currently no universal treatment that works for all SMS patients. Current research efforts to identify effective treatment modalities is needed. While some medications may offer some or limited benefit to behavioral management (e.g., carbamazepin), others may cause greater problems. Until we understand the underlying biochemistry affected in SMS, and have identified the gene(s) responsible for the condition, treatment will continue to be on an individualized basis.

Psychosocial Support Issues

Since the original description of SMS in the early 1980s, additional cases continue to be identified. The distinct constellation of behavioral dysfunction and sleep disturbances have a significant impact on the parents, siblings, and relatives of individuals with SMS. For the parents and family members of the newly diagnosed child with SMS, the search for information on SMS is often a formidable task. Since public and professional awareness about SMS and its implications for families is not widespread, SMS families are forced to become “experts” themselves. Support groups, like PRISMS, provide families with up to date information, as well as emotional and peer support, enabling them to better care for their child.

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