Smith–Magenis Syndrome

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Smith–Magenis syndrome (SMS) is a complex neurobehavioural disorder caused by haploinsufficiency of the RAI1 gene on chromosome 17p11.2. Key clinical features include intellectual disability, self-injurious behaviours, sleep disturbance and craniofacial and skeletal anomalies. Diagnostic strategies are focused towards identification of a 17p11.2 microdeletion encompassing RAI1 or a mutation of RAI1. G-banding and fluorescent in situ hybridization are classical methods used to detect the SMS deletions, whereas multiplex ligation-dependent probe amplification, comparative genomic hybridization and real-time quantitative PCR (polymerase chain reaction) are the newer technologies. Most SMS features are due to RAI1 haploinsufficiency, whereas variability and severity are modified by other genes in the 17p11.2 region. The functional role for RAI1 is not completely understood, but it is likely involved in transcription and functions in several different biological pathways. Management of SMS is a multidisciplinary approach and involves treatment for sleep disturbance, speech and occupational therapies, minor medical interventions and management of behaviours.

Synonyms: SMS, del(17)(p11.2), del(17)(p11.2p11.2), RAI1 mutation

Introduction

Smith–Magenis syndrome (SMS; OMIM # 182290, *607642) is a complex disorder characterized by variable developmental disabilities, sleep disturbance, craniofacial and skeletal anomalies and self-injurious and attention-seeking behaviours (Elsea and Girirajan, 2008; Smith et al., 1986). SMS is generally a sporadic condition caused by either a 17p11.2 deletion encompassing the retinoic acid induced 1 (RAI1) gene or a mutation of RAI1 (Slager et al., 2003; Smith et al., 1986; Vlangos et al., 2003). All SMS patients with a 17p11.2 deletion are deleted for RAI1, and mutations in RAI1 likely result in a truncated and/or non-functional protein, thus resulting in haploinsufficiency (Girirajan et al., 2005; Slager et al., 2003). The incidence of SMS is estimated to be approximately 1/25 000 live births; however, it is thought to be under-diagnosed (Greenberg et al., 1991). Although SMS is not common, its distinct physical and behavioural profile makes it one of the most recognizable genetic causes of intellectual disabilities.

Clinical Features of Smith–Magenis Syndrome

SMS is a multisystem disorder with significant disabling effects on behaviour and cognition (Table 1). Structural abnormalities have been described affecting skeletal, cardiac, urogenital, endocrine and immune systems, although these rarely cause significant morbidity (Greenberg et al., 1996). Common sensory impairments include mixed hearing loss and myopia, occasionally associated with retinal detachments (Finucane et al., 1993). Otolaryngologic symptoms, particularly chronic otitis media, velopharyngeal insufficiency and vocal cord polyps, are present in most people with SMS. Hypercholesterolaemia 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). A majority of individuals with 17p11.2 deletions also exhibit peripheral neuropathy and have a decreased sensitivity to pain (Greenberg et al., 1996). Onychotillomania (picking off of finger- and toenails), a common behavioural manifestation of SMS, is likely related to abnormal sensation in the extremities caused by peripheral neuropathy (Finucane et al., 2001). Scoliosis and other vertebral anomalies are found in over half of people with SMS, sometimes requiring surgical intervention. Most adults with 17p11.2 deletions have mild to moderate short stature, although height is generally unaffected in those with RAI1 mutations. Life expectancy appears to be normal for most people with SMS, as several individuals in their 60s and 70s have now been identified; mortality in this disorder is likely
determined by the presence or absence of congenital structural anomalies, as well as the quality of anticipatory health monitoring. See also: Birth Defects: Overview; Microdeletion Syndromes

SMS is associated with a characteristic pattern of facial dysmorphia, which includes a down-turned mouth, malar hypoplasia and relative prognathism (Figure 1). These facial features can be subtle in young children, delaying diagnosis. Progressive prognathism and coarsening of the facial appearance with age increase the clinical recognition of SMS in older children and adults (Allanson et al., 1999). Birth weight in SMS is typically normal, but infants tend to be hypotonic and excessively sleepy. In the newborn period, there is significant clinical overlap with Down syndrome, and the diagnosis of SMS is sometimes detected after negative cytogenetic testing for trisomy 21. Hypotonia leads to motor delays in young children with SMS, but the vast majority are ambulatory by age 3. Older children and adults typically walk with an awkward, lurching gait due to peripheral neuropathy. Speech development is delayed, likely compounded by oral-motor incoordination and chronic otitis media. As they age, most children with SMS acquire speech, although intelligibility in some is severely limited by articulation errors (Solomon et al., 2002).

See also: Down Syndrome

Individuals with SMS exhibit a wide range of cognitive impairments, with most functioning in the mild to moderate range of intellectual disability. The cognitive profile of school-aged 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). As students with SMS age, educational planning may be complicated by developmental asynchrony (i.e. a significant gap between intellectual attainment and emotional development) (Finucane, 2008). Co-morbid psychiatric conditions, such as attention deficit disorders, autism and obsessive compulsive disorder, are frequently associated with SMS (Levitas et al., 2007). Maladaptive behaviours, particularly aggression, attention-seeking, prolonged outbursts and self-injury, occur in early childhood and pose a significant challenge throughout life. A characteristic repertoire of self-injurious behaviours, including head-banging, onychotillomania and polyembolokoilomania (insertion of foreign objects into body orifices) has been described (Finucane et al., 2001). A unique ‘self-hugging’ behaviour is seen in most children and many adults with SMS and may be a pathognomonic feature of the syndrome (Finucane et al., 1994). See also: Intellectual Disability: Genetics

Table 1 Clinical manifestations of Smith–Magenis syndrome

<table>
<thead>
<tr>
<th>Neurological/behavioural</th>
<th>Craniofacial/skeletal</th>
<th>Otolaryngological</th>
<th>Ocular</th>
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<td>Chronic ear infections</td>
<td>Myopia</td>
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<td>Speech delay</td>
<td>Midface hypoplasia</td>
<td>Hearing loss</td>
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<td>Hypotonia</td>
<td>Tented upper lip</td>
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<td>- Head-banging</td>
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<td>- Skin-picking</td>
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Figure 1 Smith–Magenis syndrome. (a) Typical SMS infant phenotype with ‘tented’ upper lip and depressed nasal bridge. Reproduced with permission from Lorna Harris. (b) Male, age 19 years, with SMS. Note, although recognizable, the characteristic facial features associated with SMS are often subtle. Reproduced from Genetic Causes of Developmental Disabilities Brochure, with permission. © Genetic Services at Elwyn.
Complicating the behavioural phenotype of SMS is a severe sleep disturbance characterized by shortened sleep cycles, frequent night-time awakenings, and excessive daytime sleepiness (Smith et al., 1998). Starting in early childhood, sleep disturbance poses a major management challenge for caregivers while also exacerbating other maladaptive behaviours in these children. Among the sleep-related abnormalities described in SMS are an inverted circadian rhythm of melatonin, diminished rapid eye movement (REM) sleep and a reduction in 24 h and night sleep as compared to children without SMS (Greenberg et al., 1996; Potocki et al., 2000). Laboratory evidence of elevated daytime and decreased nocturnal melatonin secretion are consistent with the clinical phenotype and offer potential approaches to treatment (De Leersnyder et al., 2003).

The combination of intellectual disability, severe behavioural abnormalities and sleep disturbance takes its toll on the families of people with SMS. Parents report high rates of depression and anxiety (Kozachek et al., 2008), and family stress is significantly higher in SMS families than it is in those of children with nonspecific developmental disabilities (Hodapp et al., 1998). Holistic management of SMS includes the need for family support services and resources.

**Molecular Aspects of Smith–Magenis Syndrome**

**Mechanism of SMS deletions**

Approximately 90% of all reported cases with SMS have a 17p11.2 deletion encompassing the RAI1 gene, whereas the remaining 10% have a mutation in the RAI1 gene. Approximately 65% of all SMS patients have a common 3.7 Mb deletion, while approximately 25% have larger, smaller or atypical 17p11.2 deletions (Vlangos et al., 2003). The remaining 10% of SMS patients have mutations in RAI1 (Elsea and Girirajan, 2008). Chromosome microdeletions like del(17)(p11.2) result from aberrant chromosomal recombination and are sponsored by repeat elements in the susceptible region of the genome. Chen et al. (1997) identified three copies of a low-copy number repeat (LCRs) flanking the SMS common deletion region (Figure 2) (Chen et al., 1997). The chromosome 17p11.2 deletions result from both nonhomologous mechanisms and nonallelic homologous recombination mediated either by SMS-repeat cluster or low-copy repeats during maternal or paternal gametogenesis (Lee et al., 2006). These repeats (proximal, middle and distal SMS-REPs) form substrates for inter- and intra-chromosomal recombination (Chen et al., 1997). Unequal meiotic crossovers mediated through nonallelic homologous recombination (NAHR) occur between the proximal and distal SMS-REPs in approximately 70% of SMS deletion cases resulting in a ‘common deletion’ (Figure 2) (Shaw et al., 2002). Similarly, ‘uncommon deletions’ (seen in approximately 25% of deletion cases) are either due to alternate LCRs, such as AT-rich repeats or Alu elements acting as homologous recombination substrates, or other nonhomologous mechanisms (Shaw and Lupski, 2004, 2005; Shaw et al., 2004; Vlangos et al., 2003). No imprinting or parent-of-origin bias for the SMS deletion has been identified (Juyal et al., 1996). See also: Evolution of Imprinting: Imprinted Gene Function in Human Disease; Microdeletions and Microduplications: Mechanism; Relevance of Copy Number Variation to Human Genetic Disease

**Retinoic acid induced 1 (RAI1): The primary gene for SMS**

Analysis of different sized SMS deletions revealed a common region of overlap or a ‘critical interval’ of
approximately 1.5 Mb within 17p11.2 (Figure 2). A contiguous physical and transcription map of the ‘critical interval’ identified > 15 genes (Lucas et al., 2001). Sequencing of candidate genes within the ‘critical interval’ in patients with SMS clinical features but without a 17p11.2 deletion identified frame-shift mutations in the retinoic acid induced 1 (RAI1) gene (Slager et al., 2003). Since then, > 15 mutations have been identified in RAI1, including nonsense mutations, single to multiple nucleotide deletions and/or insertions, and missense mutations (Figure 3) (Bi et al., 2006; Bi et al., 2004; Elsea and Girirajan, 2008; Girirajan et al., 2005, 2006). In addition, numerous single nucleotide polymorphisms including a variable polyglutamine repeat have been identified (Bi et al., 2006; Girirajan et al., 2006; Seranski et al., 2001). See also: Mutation; Mutations and the Genetic Code; Spectrum of Mutations in the Human Genome Inferred by Single Nucleotide Polymorphisms

The primary transcript for RAI1 (GenBank AY172136, AJ271790; NM_030665.3; NP_109590.3; OMIM*607642) is formed by six exons generating an approximately 8.5 kb messenger ribonucleic acid (mRNA) and a 1906 amino acid protein (Figure 3) (Toulouse et al., 2003). The RAI1 protein contains a bipartite nuclear localization signal, polyglutamine and polyserine tracts, and a C-terminal plant homeodomain (PHD)/zinc-finger domain (Toulouse et al., 2003). These latter domains suggest that RAI1 functions as a transcription factor. Further, amino acid sequence motifs representing these four domains of the RAI1 protein are similar to the transcription factor stromelysin-1 platelet derived growth factor-responsive element binding protein, TCF20 (Seranski et al., 2001; Slager et al., 2003). Thus, RAI1 likely functions in the transcriptional machinery for multiple genes involved in growth and neurobehavioural regulation, explaining the pleiotropic effects seen in this disorder. See also: Short DNA Sequence Repeats; Transcription Factors; Transcription Factors and Human Disorders

Genotype–phenotype correlation

Haploinsufficiency leading to functional abrogation of RAI1 is responsible for the major diagnostic features of SMS including variable intellectual disability, sleep disorder, behavioural and neurological abnormalities and craniofacial and skeletal abnormalities (Girirajan et al., 2006). Recently, the phenotypic role of RAI1 and the contributions of other genes in the 17p11.2 region towards SMS phenotype were evaluated by a genotype–phenotype correlation (Edelman et al., 2007; Girirajan et al., 2006). Whereas RAI1 was shown to be responsible for most SMS features, other genes in the 17p11.2 region contribute to the variability and severity of the phenotype in 17p11.2 deletion cases (Table 1) (Girirajan et al., 2006). Short stature, hypotonia, speech and motor delay, hearing loss, frequent ear infections and cardiac and renal defects are associated with patients with deletions, suggesting a minor role for RAI1 in these clinical features (Girirajan et al., 2006). Thus, other genes in 17p11.2 likely contribute to these findings in 17p11.2 deletion cases. In addition, patients with RAI1 mutations may have less severe motor delay and higher functioning. They are also more likely to exhibit overeating/obesity and overgrowth phenotypes (>90th percentile for weight and height), polyembolokoilamania, self-hugging, muscle cramping and dry skin compared to patients with deletions. However, all RAI1 mutation cases so far described are phenotypically quite similar, and a bias in ascertainment must be considered; thus, the full spectrum of phenotypic effects of RAI1 mutation are not yet known. See also: Genotype-Phenotype Relationships; Haploinsufficiency

Phenotypes in cases with small deletions are similar to those with RAI1 mutations. Edelman et al. (2007) also reported that individuals with small deletions are less likely to show brachycephaly, dental anomalies, iris-abnormalities, head-banging and hyperactivity (Edelman et al., 2007). Incidence of behavioural features are considerably lower in patients with large and atypical deletions, most likely due to the severe, movement-limiting phenotypes including severe intellectual disability and significant motor delays (Girirajan et al., 2006). Potential gender differences are also seen in SMS, with females more likely to report myopia, eating/appetite disorders, cold extremities and problems with communication and language compared to males (Edelman et al., 2007).

Diagnostic Approach

Diagnosis of SMS is based upon initial clinical suspicion of the disorder, followed by a molecular confirmation of the chromosomal/gene defect. Clinical recognition of the disorder is typically delayed due to the lack of obvious facial dysmorphia in infants and young children. The presence of distinct behavioural features, such as onychotillomania and self-hugging, prompts consideration of the diagnosis in older children and adults. Suspected cases of SMS should first have high-resolution chromosomes followed by
fluorescent in situ hybridization (FISH) for 17p11.2 deletion. Alternative methods for identifying the 17p11.2 deletion include multiplex ligation-dependent probe amplification (MLPA) or real-time quantitative polymerase chain reaction (PCR) for the RAI1 gene and array comparative genomic hybridization (aCGH) (Girirajan et al., 2007; Truong et al., 2008). All methods must include probes that represent the RAI1 gene. Owing to phenotypic overlap, other disorders should also be considered on a case-by-case basis, including Prader–Willi syndrome (9q-syndrome).

See also: Comparative Genomic Hybridization; Comparative Genomic Hybridization in the Study of Human Disease; Fluorescence In Situ Hybridization; Identification of Disease Genes by CGH Microarrays; Karyotype Interpretation; Polymerase Chain Reaction (PCR); Polymerase Chain Reaction (PCR): Specialized Reactions

Recurrence of SMS in siblings is rare but has been described (Hicks et al., 2008). Cases of parental mosaicism, with or without phenotypic effect, range from approximately 3% to 5%. Chromosomally normal parents of a child with SMS have less than 1% chance for a future recurrence; this risk is increased over that of couples in the general population because of the potential for germline mosaicism. Highly accurate prenatal testing using FISH analysis is available for at-risk pregnancies. See also: Mosaicism; Prenatal Diagnosis

Although FISH and G-banding are classically used for SMS diagnosis in a clinical cytogenetic laboratory, MLPA and qPCR are newer, cost-efficient methodologies for rapid, high-throughput diagnosis that require only deoxynucleic acid (DNA) for analysis (Truong et al., 2008). Further, MLPA and real-time qPCR can identify smaller deletions at a higher resolution, usually missed by FISH or G-banding, such as exonic deletions involving RAI1 (Figure 2) (Girirajan et al., 2007). Chromosome microarray studies (CGH) will also identify 17p11.2 deletions. Individuals in whom no 17p11.2 deletion can be found should have the RAI1 gene sequenced to detect heterozygous nucleotide variations (Figure 3). Upon detection of a nucleotide change, parental samples are evaluated to confirm the mutation is de novo. So far, only one case of SMS with an inherited RAI1 nucleotide change has been reported; however, parental mosaicism for an RAI1 mutation has been documented in more than one family (Elsea unpublished results) (Bi et al., 2006). Thus, evaluation of all parents of SMS cases with RAI1 mutations for familial mutations or mosaicism is critical, as the presence of an inherited mutation or mosaicism in the parent of a child with SMS would greatly alter the recurrence risks. Further, the identification of familial, population-specific, 'novel' single nucleotide polymorphisms (SNPs) complicates diagnosis.

See also: Mutations in Human Genetic Disease

Therapeutic Strategies/Management

Once the diagnosis of SMS is confirmed, children and adults with this condition require lifelong health monitoring in addition to behavioural, educational and social support. Published healthcare guidelines promote anticipatory medical management for individuals with SMS throughout the lifespan (Smith et al., 2006). Recommended studies at diagnosis include echocardiography, renal ultrasound and spine radiographs to rule out structural cardiac, urogenital and vertebral anomalies; a fasting lipid profile to detect hypercholesterolaemia; and ophthalmologic and audiologic evaluations to check for potential sensory impairments. Infants and toddlers 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. An individualized education programme, including a comprehensive behaviour support plan, is essential to maximize academic and social attainment in school-aged children. As adults, individuals with SMS benefit from structured day programmes 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 behaviours pose the most significant management challenge. Although cognition is often only mildly affected, aggressive, impulsive and self-injurious behaviours limit academic and functional abilities in children and adults with this disorder. A comprehensive behaviour support plan for home and school should be considered as soon as problem behaviours arise, typically starting in early elementary school. A structured school programme with one-to-one support and curricula matched to the known cognitive and behavioural profile of SMS can be highly effective in meeting the needs of these students. After-school and respite care is also essential to decrease the daily stress on families of children with SMS.

In addition to environmental supports, psychotropic medications are often prescribed to manage behaviour in children and adults, and polypharmacy is typical. Reports of medication use in people with SMS are anecdotal, and to date, there are no published controlled studies of medication trials in this disorder. A database of adverse effects and medication efficacy has been compiled by the national support group PRISMS (Parents and Researchers Interested in Smith–Magenis Syndrome, Reston, VA, USA, www.prisms.org) and a review of the data is in progress (Gropman et al., 2006). Medication use should be targeted to specific behaviours, as there is no medication that addresses every area of behavioural concern. Unfortunately, there is no particular medication that works well for all people with SMS, and behaviour in some individuals is better managed without medications. Anecdotally, mood-stabilizing medications such as valproate and lithium have been relatively successful in reducing mood swings in people with SMS. Some individuals respond well to a combination of mood stabilizers and antipsychotic medications, such as rispiridone, although weight gain can be problematic (Gropman et al., 2006). Because of the lack of controlled medication trials for behavioural symptoms in SMS, medication should be prescribed very carefully by
a psychiatric professional with input from family members and caregivers most familiar with the individual.

Abnormal sleep patterns in people with SMS adversely affect behaviour and should be addressed as part of the behaviour support plan. Despite evidence for an inverted circadian rhythm of melatonin, to date there have been no well-controlled melatonin treatment trials for sleep disturbance in this disorder. Anecdotal case 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 regulated by the FDA (Food and Drug Administration) and dosages may be inexact. In an uncontrolled 2003 study, De Leersnyder et al., combined a daytime dose of acebutolol (a B1-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 (De Leersnyder et al., 2003). The researchers reported normalization of night-time melatonin secretion, with improved sleep and disappearance of nocturnal awakenings. A corresponding subjective improvement in daytime behaviours 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. See also: Adrenergic Receptors

Despite their many challenges, children and adults with SMS have much potential. Beginning with the original published descriptions of the condition (Smith et al., 1986; Smith et al., 1982), 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 behavioural 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 behavioural and somatic symptoms.

References


Further Reading

Reviews


Book Chapters


Useful web sites


Gene Clinics – http://www.geneclinics.org

PRISMS – Parents and Researchers Interested in Smith-Magenis Syndrome: http://www.prisms.org

The Smith-Magenis Syndrome Foundation: http://www.smith-magenis.co.uk/