

Smith-Magenis syndrome

Author: Doctor H el ene De Leersnyder¹, Professor Arnold Munnich

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¹D epartement de G en etique m edicale, H opital Necker Enfants malades, 149 Rue de S evres, 75743 Paris Cedex 15, France. deleers@club-internet.fr

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Abstract

Smith-Magenis syndrome (SMS) is caused by interstitial deletions of chromosome 17p11.2. The incidence is estimated to be 1/25,000. Common features include characteristic craniofacial appearance, brachydactyly, short stature, and infantile hypotonia. Mental retardation with speech delay is a constant feature associated with hyperactivity, attention deficit and self-injurious behaviors. Major sleep disturbances and behavioral problems could be partly related to an inverted, diurnal melatonin release. Other features include hoarse deep voice, congenital heart defects, renal anomalies, ORL and ophthalmologic abnormalities, scoliosis, signs of peripheral neuropathy. Deletions ranging from 2 to 9 megabases (mainly 4-5 Mb) are detectable cytogenetically and diagnosis is confirmed by FISH analysis. Multiple genes have been mapped to the 17p11.2 SMS critical region, but the role of each of these is not yet known; haploinsufficiency for several genes is likely to account for the phenotype. Early behavioral and educational therapies, speech/language therapy are necessary to provide support and treatment for developmental deficits. Regarding the inverted rhythm of melatonin, beta-adrenergic antagonists and melatonin improve inappropriate behavior and restore sleep.

Keywords

Smith-Magenis syndrome; microdeletion syndrome; chromosome 17p11.2; mental retardation; behavioral phenotype; sleep disturbance; melatonin.

Disease name and synonyms

Smith-Magenis syndrome (SMS)

Diagnostic criteria / Definition

The diagnosis is based on clinical examination.

The SMS is characterized by:

- mental retardation with speech delay;
- specific behavioral phenotype and major sleep disturbances;

- mild dysmorphism.

The diagnosis is confirmed on high-resolution karyotype with detectable deletion of 17p11.2 and by FISH on chromosome 17.

Differential diagnosis

At the onset, SMS may be mistaken for other mental retardation syndromes, most notably fragile X syndrome, developmental delay

associated with telomeric deletions, syndromes associated with mental retardation and dysmorphism, autism. Recently, mutations in *RAI1* (*Retinoic Acid-Induced gene 1*) were shown in individuals who have phenotypic features consistent with SMS, with no 17p11.2 deletions.

Incidence

Due to recent delineation, most persons with SMS have been identified in the last 8 years. The incidence of SMS is estimated to be 1/ 25 000 births.

Clinical description

Common features of SMS include:

- history of infantile hypotonia and failure to thrive;
- brachycephaly, midface hypoplasia, broad nasal bridge, down-turned mouth with cupid bow, relative prognathism;
- brachydactyly, ocular abnormality, short stature, hoarse deep voice;
- other features include: congenital heart defects (52%), otolaryngologic abnormalities (94%), hearing impairment (68%), cleft lip and/or palate, signs of peripheral neuropathy (75%), seizures (26%), eye abnormalities (85%), scoliosis (65%), renal or genital anomalies (35%);
- endocrine and immunologic abnormalities include low thyroxin levels (29%), low immunoglobulin levels (23%), hypercholesterolemia (57%);
- mental retardation (IQ scores ranged between 40 and 60) with speech delay is a constant feature associated with self-injurious behavior, temper tantrums, spasmodic upper body squeeze, insensitivity to pain;
- hyperactivity and attention deficit cause severe behavioral problems at home and at school;
- major sleep disturbances include early sleep onset (8-9 pm), instability of sleep (1 -3 long awakenings per night), early sleep offset (4-5 am);
- abnormalities in the circadian rhythm of plasma, urinary melatonin and urinary 6-sulfatoxymelatonin. Sleep disturbances and behavioral problems may be partly related to inappropriate diurnal melatonin release.

Management including treatment

• Clinical management should start as soon as the diagnosis is made. Referral for physical, occupational and speech therapies is necessary to provide support and treatment for developmental deficits.

• Behavioral therapies play an integral role in the behavioral management of SMS. Family psychological and social support are absolutely necessary.

• Educational intervention along schooling should take into account the very specific SMS behavior disorder.

• Management strategies that improve speech/language pathology should be started as early as possible.

• Corrective lenses for myopia and treatment for strabismus are recommended.

• Pharmacological or surgical intervention should be offered for cardiac, renal, neurological, or musculoskeletal anomalies.

• Most patients with SMS have been tried on a number of medications that control behavior and have shown mixed responses; adverse reactions to some medications have also been reported. The most commonly used medications were neuroleptics, hypnotics, mental stimulants, tricyclic antidepressants, antipsychotics, carbamazepine, and serotonin re-uptake inhibitors.

• Regarding the inverted rhythm of melatonin in SMS, use of beta-adrenergic antagonists in the morning improves inappropriate behavior with increased concentration; acebutolol or propranolol are used in a single morning dose of 10mg/kg/day. Beta-adrenergic antagonists associated with melatonin therapy in the evening restore sleep and reset the circadian clock; melatonin or CR melatonin are used in a single evening dose of 6 mg/kg/day. No side effects of these treatments were reported.

Etiology

Most persons with SMS have a large, common deletion of about 4 MB (2 to 9 Mb) mapping to chromosome 17p11.2, but many other affected individuals have smaller or larger, atypical deletions. Size of deletion does not correlate with clinical features or severity of the disorder. However, very large deletions can induce more severe manifestations. All cases occur *de novo* on either parental chromosome. Few cases with *de novo* duplications of the same region were observed, suggesting that the deletion and its reciprocal duplication of chromosome 17p11.2 result from unequal meiotic crossovers mediated through nonallelic homologous recombination that occurs via both interchromosomal and intrachromosomal exchange events between the proximal and distal SMS repeats.

Diagnostic methods

Smith-magenis syndrome is a clinically recognizable multiple congenital anomaly and mental retardation syndrome caused by

interstitial deletion of chromosome 17p11.2. Deletions ranging from 2 to 9 megabases are detectable cytogenetically and diagnosis is confirmed by FISH analysis.

Antenatal diagnosis and genetic counseling

The condition is sporadic. Neither recurrence in families, nor germinal mosaicism have been hitherto reported.

Unresolved questions

The mechanism of the inverted rhythm of melatonin, which partly accounts for disturbed circadian behavior, is unknown.

SMS is regarded as a contiguous gene syndrome and it is of interest to identify possible SMS candidate genes that are developmentally-regulated or play a role in mental and behavioral development. Transcription factors could play a role as they have a more global effect on development and are often dosage-sensitive. A single gene, *RAI1* could possibly account for most features when other deleted genes may modify the overall phenotype.

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