Smith-Magenis Syndrome

Smith-Magenis syndrome (SMS) is a complex multiple congenital anomalies and mental retardation syndrome caused by an interstitial deletion of chromosome 17p11.2.

GENETICS/BASIC DEFECTS
1. Inheritance
   a. Autosomal dominant inheritance in virtually all cases of SMS occurring de novo
   b. Rare familial chromosome complex rearrangements leading to del(17)(p11.2) and SMS
2. Caused by an interstitial deletion of 17p11.2
   a. A common deletion size observed in the majority of patients, derived from nonallelic homologous recombination between low-copy repeat gene clusters during either maternal or paternal gametogenesis
   b. Either smaller or larger sized deletions in about 20–25% of patients
3. Considered a contiguous gene syndrome
   a. Haploinsufficiency of multiple functionally unrelated genes located in close proximity is responsible for the phenotype
   b. Deletion of a common interval spanning an estimated 4–5 Mb in majority of patients
4. Sterol regulatory element binding protein 1 (SREBP1) has been mapped to 17p11.2 within the SMS critical region. Therefore, the patients are hemizygous for the gene encoding SREBP1 leading to hypercholesterolemia.
5. Rare non-deletion cases
   a. Report of additional patients without a microdeletion, each harbors a mutation in RAI1, which maps within the SMS critical region
   b. MYO15 clearly associated with a specific phenotypic feature (sensorineural hearing impairment) in a patient with SMS who harbored a recessive mutation on the nondeleted allele

CLINICAL FEATURES
1. Infantile hypotonia
2. Feeding difficulties
3. Failure to thrive
4. Developmental delay
5. Distinctive craniofacial features
   a. Brachycephaly
   b. Broad square-shaped face
   c. Prominent forehead
   d. Synophrys
   e. Epicanthal folds
   f. Upslanted palpebral fissures
   g. Deep-set eyes
   h. Broad nasal bridge
   i. Marked mid-facial hypoplasia
   j. Short full-tipped nose with reduced nasal height
   k. Micrognathia in infancy changing to relative prognathia with age
   l. Distinctive appearance of the mouth, with fleshy everted upper lip with a “tented” appearance
6. Otolaryngologic anomalies
   a. Speech delay
   b. Hoarse voice
   c. Velophalangeal insufficiency
   d. Tracheobronchial problems
7. Ocular anomalies
   a. Iris anomalies
   b. Microcornia
   c. Retinal detachment
8. Skeletal abnormalities
   a. Short stature
   b. Scoliosis
   c. Brachydactyly
   d. Flat feet
9. Characteristic neurobehavioral phenotype
   a. Mental retardation (most patients in moderate range)
   b. Speech delay
   c. Signs of peripheral neuropathy
   d. Inattention
   e. Hyperactivity
   f. Maladaptive behaviors including frequent outbursts and temper tantrums
   g. Attention seeking
   h. Attention deficit
   i. Impulsivity
   j. Distractability
   k. Disobedience
   l. Aggression
   m. Toileting difficulties
   n. Decreased sensitivity to pain
   o. Self-injurious behaviors
      i. Self-hitting
      ii. Self-biting
      iii. Skin picking
   iv. Inserting foreign objects into body orifices
   v. Yanking finger nails and/or toenails (onychotillomania)
p. Stereotypic behaviors
   i. Specific to SMS
      a) Spasmodic upper-body squeeze or “self hug”
      b) Hang licking and page flipping (“lick and flip”)
   ii. Additional stereotypies
      a) Mouthing objects or insertion of hand in mouth
      b) Teeth grinding
10. Other features
   a. Cardiac defects
   b. Renal and urinary tract abnormalities
   c. Thyroid function abnormalities
   d. Cleft lip/palate
   e. Hearing loss
   f. Seizures
   g. Immune function abnormalities, especially low IgA

**DIAGNOSTIC INVESTIGATIONS**

1. Cytogenetic studies for detection of an interstitial deletion of 17p11.2
   a. G-banded karyotype: may not detect small deletion especially when the indication of cytogenetic study is other than SMS
   b. Molecular cytogenetic analysis by FISH using a DNA probe specific for the SMS critical region

2. Molecular genetic testing of RAI1, the only gene known to account for the majority of features in SMS: available on a clinical basis

3. Blood chemistry
   a. Hypercholesterolemia
   b. Hypertriglyceridemia
   c. Qualitative immunoglobulins
   d. Thyroid function tests

4. Renal ultrasound for possible renal and urologic anomalies

5. Echocardiogram for possible cardiac defects

6. Radiography of the spine for scoliosis and other vertebral anomalies

7. EEG for clinical seizures

8. MRI and PET imaging
   a. A significant decrease of grey matter concentration in the insula and lenticular nuclei
   b. A significant hypoperfusion in the same regions

**GENETIC COUNSELING**

1. Recurrence risk
   a. Patient’s sib
      i. <1% if parental chromosome analysis is normal, taking account of possible presence of parental germline mosaicism
      ii. An increased risk, provided a parent carries a chromosome rearrangement and dependent upon the specific chromosome rearrangement
   b. Patient’s offspring
      i. Unlikely to have offspring due to severe phenotype
      ii. Theoretically, a 50% risk of having offspring with SMS

2. Prenatal diagnosis: available for pregnancies at risk using a combination of routine cytogenetic studies and FISH
   a. Amniocentesis
   b. CVS

3. Management
   a. Early childhood intervention programs
   b. Special education
      i. Speech and language
      ii. Physical and occupational
      iii. Sensory integration
   c. Vocational training in later years
   d. Psychotropic medications to increase attention and decrease hyperactivity
   e. Behavioral modification
   f. Administration of β1-adrenergic antagonist and melatonin helps to manage hyperactivity, enhances cognitive performance, and reduces sleep disorders
   g. Psychosocial support for the family

**REFERENCES**


Fig. 1. An infant with Smith-Magenis syndrome showing prominent forehead, broad square-shaped face, synophrys, short full-tipped nose, and fleshy everted upper lip with a “tented” appearance. Chromosome analysis showed an interstitial deletion of 17p11.2.