Sotos Syndrome

Sotos syndrome was described by Sotos in 1964 and is relatively common among overgrowth syndromes. It is also known as cerebral gigantism.

GENETICS/BASIC DEFECTS

1. Inheritance: genetically heterogeneous
   a. Sporadic in majority of cases (>98%)
   b. Autosomal dominant inheritance reported in a few families
   c. Autosomal recessive inheritances postulated in some families

2. Discovery of human NSD1 gene
   a. Report of a patient with Sotos syndrome who had t(5;8)(q35;q24.1)
   b. Discovery of a partial genomic sequence homologous to mouse Nsd1 near the breakpoint by constructing a BAC/PAC/cosmid contig covering the breakpoint
   c. Human NSD1 gene was subsequently isolated and characterized.

3. Molecular defect
   a. The major cause of Sotos syndrome: haploinsufficiency of the NSD1 gene at 5q35, because the majority of patients had either a common microdeletion including NSD1 or a truncated type of point mutation in NSD1
   b. NSD1 gene mutations and deletions
      i. Japanese patients (66%)
         a) Point mutations (48.5%)
         b) Deletions (18.2%)
      ii. British patients (78%)
         a) Point mutations (70%)
         b) Large deletions (8%)
   c. Size of the deletion correlates with severity of the phenotype.

4. No satisfactory explanation for the overgrowth

CLINICAL FEATURES

1. Prenatal and postnatal overgrowth (major clinical features)
   a. Large for gestational age at birth
   b. Excessive growth velocity particularly in the first 3 to 4 years
   c. Advanced bone age by 2 to 4 years over chronological age during childhood
   d. Large hands and feet
   e. Excessive heights in some adult patients

2. Performance
   a. Developmental retardation
   b. Mental deficiency of varying degree
   c. Lack of fine motor control
   d. Difficulties in neonatal adaptation and/or feeding

3. Characteristic craniofacial appearance
   a. Dolichocephalic large head
   b. Prominent forehead
   c. Ocular hypertelorism
   d. Down slanting of the palpebral fissures
   e. High-arched palate
   f. Premature teeth eruptions
   g. Pointed chin (prominent mandible)

4. CNS manifestations
   a. Hypotonia
   b. Seizures
   c. Clumsy gait
   d. Mildly enlarged ventricles
   e. Increased subarachnoid spaces
   f. Agenesis/hypoplasia of the corpus callosum
   g. Agenesis of the septal pellucidum
   h. Hypoplasia/atrophy of the cerebellar vermis
   i. Large cisternal magna
   j. Abnormal Sylvian fissure

5. Neoplasms (3.9%)
   a. Benign tumors
      i. Multiple hemangiommas
      ii. Osteochondroma
      iii. Large hairy nevus
      iv. Giant cell granulomas of the mandible
   b. Malignant tumors
      i. Wilms tumor
      ii. Neuroblastoma
      iii. Hepatocellular carcinoma
      iv. Epidermoid carcinoma of the vagina
      v. Small-cell carcinoma of the lung

6. Other features
   a. Strabismus
   b. Lax joints
   c. Pes planus
   d. Kyphoscoliosis
   e. Asymmetric leg length
   f. Syndactyly
   g. Congenital heart defects
      i. Septal defects
      ii. Persistent ductus arteriosus
      iii. Ebstein malformation
   h. Functional megacolon
   i. Urinary anomalies
      i. Hypoplastic kidney
      ii. Hydronephrosis
      iii. Vesicoureteric reflux
   j. Recurrent hernias
   k. Abnormal dermatoglyphics

7. Social and behavioral difficulties
   a. Emotional immaturity
   b. Poor motor control
c. Temper tantrums
d. Good social skills in some patients

8. Weaver syndrome: the major differential diagnosis
a. Seen less commonly than Sotos syndrome
b. Caused by NSD1 mutations in a significant number of patients
c. Cardinal features
i. Accelerated growth
ii. Distinctive facies with micrognathia and a deep horizontal chin crease
iii. Advanced bone age
iv. Developmental delay
d. Additional features
i. A hoarse low-pitched cry
ii. Metaphyseal flaring of the femurs
iii. Deep-set nails
iv. Prominent finger pads
v. Camptodactyly

DIAGNOSTIC INVESTIGATIONS

1. Glucose intolerance (14%)
2. Radiography: advanced bone age
3. CNS lesions by CAT scan and/or MRI of the brain
   a. Ventricles
     i. Ventriculomegaly
     ii. Prominent trigone of the lateral ventricles
     iii. Prominent occipital horn
   b. Extracerebral fluid
     i. Increased supratentorial space
     ii. Increased posterior fossa space
   c. Midline anomalies
     i. Persistent cavitum septum pellucidum
     ii. Persistent cavitum vergae
     iii. Cavitum velum interpositum
     iv. Macrociesterna magna
     v. Agenesis of corpus callosum
     vi. Hypoplasia (thinning) of corpus callosum
   d. Periventricular leukomalacia
   e. Macrocerebellum
   f. Open operculum
4. DNA analysis
   a. Deletion of NSD1 gene by FISH analysis
   b. Mutations of NSD1 gene
     i. Sequencing of entire coding region
     ii. Sequencing of select exons
     iii. Mutation analysis

GENETIC COUNSELING

1. Recurrence risk
   a. Patient’s sib: not increased unless a parent is affected
   b. Patient’s offspring: 50%
2. Prenatal diagnosis of fetuses at risk for Sotos syndrome
   a. Ultrasonography in the third trimester
     i. Macrocephaly
     ii. Ventriculomegaly
     iii. Hypoplasia of the corpus callosum
     iv. An enlarged cisterna magna
   b. Prenatal diagnosis possible by molecular mutation analysis of fetal DNA obtained from amniocytes or CVS of previously identified disease-causing NSD1 gene: available on a clinical basis
3. Management: No specific therapy exists

REFERENCES


Fig. 1. A child with Sotos syndrome showing excessive growth, a large dolichocephalic head, prominent forehead, down slanting palpebral fissures, and a pointed chin.

Fig. 2. The radiograph of the hand from a 20-month-old showing advanced bone age (3 years).

Fig. 3. A 5-year-old girl with Sotos syndrome showing gigantism, large head, prominent forehead, large hands and feet, and MRI findings of enlarged subarachnoid spaces, mild ventriculomegaly, thinning of the corpus callosum, and mild polymicrogyria.

Fig. 3. A 5-year-old girl with Sotos syndrome showing gigantism, large head, prominent forehead, large hands and feet, and MRI findings of enlarged subarachnoid spaces, mild ventriculomegaly, thinning of the corpus callosum, and mild polymicrogyria.
Fig. 4. An adult with Sotos-like syndrome showing excessive height (compared with other family members), prominent forehead, hypertelorism, a pointed chin, and large hands and feet (compared to normal adult). Chromosome analysis by FISH showed duplication of 4p15.2 and 4q32. Both parents have normal chromosomes.