

Sotos syndrome

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Abstract

Sotos syndrome (OMIM 117550) is an overgrowth syndrome characterized by three major features namely distinctive facial gestalt, macrocephaly and variable degree of learning difficulties. Other features are childhood overgrowth, advanced bone age, cardiac and genitourinary anomalies, neonatal jaundice and hypotonia, seizures and scoliosis, all fairly found in this condition. Tumours are rare.

Sotos syndrome is a relatively common condition but, the exact estimated birth incidence is unknown. Mutations and deletions of NSD1, a histone methyltransferase implicated in transcriptional regulation, is responsible for at least 75% of Sotos cases. This gene, recently discovered, is located at chromosome 5q35. The large majority of NSD1 abnormalities are de novo and there are a few familial cases. The recurrence risk for normal parents is very low (<1%).

Keywords

Overgrowth, macrocephaly, NSD1 gene, locus 5q35

Disease name/Synonyms

Sotos syndrome (OMIM 117550)

Cerebral Gigantism syndrome

Excluded diseases

Sotos syndrome belongs to a group of overgrowth syndromes that have some clinical features in common such as pre- and/or postnatal overgrowth or advanced bone age. Many of them are easily excluded by other major clinical features. The entities that have been mentioned in the nosology of the Sotos syndrome for a general differential diagnosis are:

- [Weaver syndrome](#)
- [Beckwith-Wiedemann syndrome](#)
- [Perlman syndrome](#)
- [Simpson-Golabi-Behmel syndrome](#)
- [Bannayan-Zonana syndrome, PTEN mutations](#)
- [Fragile \(X\) syndrome](#)
- [Neurofibromatosis I](#)
- [Marshall syndrome](#)
- [Marfan syndrome](#)
- [Homocystinuria](#)
- [Acromegaly](#)

The basic nosology is between the syndromes of Sotos and Weaver [Opitz 1998].

Definition

Sotos syndrome is a childhood overgrowth condition, first described in 1964 by Sotos *et al* [Sotos 1964], though the first patient described may have been reported in 1931 [Schlesinger 1931]. The four major diagnostic criteria were established in 1994 by Cole and Hughes [Cole and Hughes 1994], based on the systematic assessment of 41 typical cases: overgrowth, characteristic facial appearance, advanced bone age and learning difficulties. These clinical criteria remained the cornerstone for the diagnosis of Sotos until 2002. The recent identification of *NSD1* mutations and deletions [Kurotaki 2002, Douglas 2003, Rio 2003, Turkmen 2003] has allowed re-evaluation of the features of this condition. In 2004, Tatton-Brown and Rahman studied the clinical features of 105 Sotos cases with *NSD1* abnormalities. They re-defined Sotos syndrome as a condition characterized by macrocephaly, distinctive craniofacial features and learning difficulties. Childhood overgrowth, advanced bone age, cardiac and genitourinary anomalies, neonatal jaundice and hypotonia, seizures and scoliosis are fairly common in this syndrome [Tatton-Brown 2004].

Prevalence

Sotos syndrome is probably one of the most common overgrowth conditions, after the Beckwith-Wiedemann syndrome. The exact birth prevalence remains unknown. Hundreds of cases are reported. The literature on Sotos syndrome, before the identification of the *NSD1* gene responsibility, has to be read carefully since it is mixed with publications that evidently do not deal with the Sotos syndrome. The systematic *NSD1* gene screening in provisional diagnosis of Sotos syndrome will probably help to define its prevalence.

Clinical description

For forty years, the diagnosis of Sotos syndrome has been based on the subjective evaluation of clinical features. However, although the combination of craniofacial features may be distinctive, the other components are non-specific. This lack of specific clinical features was often the center of nosologic discussion [Cole 1994, Opitz 1998]. Recently, Tatton-Brown and Rahman reported the clinical features of a series of more than one hundred Sotos syndrome cases with proven abnormalities in *NSD1* [Tatton-Brown 2004].

Generally, pregnancy is described as normal; however, toxemia or pre-eclampsia is

mentioned in several cases [Opitz 1998]. Mean gestational age is normal (39 weeks) but the infants are large for gestational age. According to Cole and Hughes [1994] birth length, weight, and occipito-frontal circumference (OFC) are respectively 3.2, 1.0, and 1.8 standard deviations above the mean. Length is likely more increased than weight. Indeed, the birth weight of 76% of the 107 Sotos cases reported by Tatton-Brown was less than the 98th centile and the mean birth weight centile was 75th-91st [Tatton-Brown 2004]. In the neonatal period, many infants experience early feeding difficulties (40% required tube feeding [Cole 1994]), variable degree of congenital hypotonia, hypoglycaemia and jaundice by hyperbilirubinemia. Throughout childhood, the advance growth is particularly pronounced in the first year of life, after which it stabilizes with a height consistently above the 97th centile between age 2 and 6 years. Growth in height and weight tends to normalize at puberty, probably because of the epiphyseal fusion. Final height is in the majority of cases within the high normal range [Agwu 1999], particularly in females, in whom the growth pattern correlates well with the presence of advanced bone age and early puberty. Macrocephaly and large hands and feet are also consistent features [Sotos 1964]. Craniostenosis by premature fusion of lambdoid, sagittal and coronal sutures has been reported [Opitz 1998]. The reported incidence of advanced bone age varies from 74% to 100% of cases, and this variability is probably related to the frequency, timing and method of assessment. Bone age is often described as dysharmonic with the phalangeal age being in advance in comparison with the carpal age. X-rays of the hand are also useful for metacarpophalangeal profiles, which have been reported to produce specific patterns in Sotos syndrome [Dijkstra 1994].

The overall craniofacial features are distinctive, especially between one and six years of age. In infancy, the face is round with disproportionate prominence of forehead and become longer in adolescence, with prominence of the pointed chin. Macrodolichocephaly, receding hairline, apparent hypertelorism with down slanting palpebral fissures, prominent jaw, malar flushing, anteverted nostrils, mild micrognathia, high arched palate and large ears are commonly identified. Occipito-frontal circumference (OFC) is between the 98th and 99.6th centile in infancy, childhood and adulthood. It is below the 91st centile in only 7% of the series of Tatton-Brown [2004] and 51% had an OFC greater than the 99.6th percentile.

Most patients have non progressive neurologic dysfunction manifested by clumsiness and poor coordination (96% in the series of Tatton-Brown [2004]). Cole and Hughes [1994] reported a mean DQ/IQ of 78 with a range 40-129 (n=23). Delay in expressive language and motor development during the infancy is particularly common. The degree of learning disability appears extremely variable. Delay in walking until after 15 months of age and speech delay until after 2.5 years are usual. Seizures are found in about 50% of patients, but in about half the cases, they are febrile. Attention deficit and placid behaviour may also be a component [Cohen 2003, Sarimski 2003]. Dilatation of the cerebral ventricles is common. Other neurological abnormalities include absent corpus callosum, prominent cortical sulci, cavum septum pellucidum and cavum velum interpositi [Cohen 2003]. Minor neuroimaging anomalies are considered to be specific for Sotos syndrome: in 90%, there is prominence of the trigone, in 75% prominence of the occipital horns and ventriculomegaly in 63% [Schaefer 1991, Aoki 1998]. Brisk deep tendon reflexes (sometimes even with a few beats of clonus) are often observed.

Scoliosis is present in 43% of the Sotos cases [Tatton-Brown 2004] and genu valga or vara, congenitally dislocated hips and propensity to fracturing with minimal trauma are reported [Opitz 1998]. Finger nails are usually deep and brittle. The incidence of congenital heart defects in Sotos syndrome is approximately 8% in the series of Cole and Hughes [1994] but 24% in the series of Tatton-Brown [2004]. The most common defects are septal defects and patent ductus arteriosus. One patient is reported with Wolff-Parkinson-White Pattern [Sharma 2003]. Recurrent upper respiratory infections, otitis media are frequent, leading to some degree of conductive hearing loss. Constipation is common and may request investigation. Genitourinary anomalies include renal anatomical anomalies (bifid, duplex or absent kidneys, vesico-ureteric reflux, pelvo-ureteric junction obstruction) cystic kidneys and genital anomalies as hypospadias and cryptorchidism [Cole 1996] and are present in 19% of children with *NSD1* abnormalities [Tatton-Brown 2004].

Overgrowth syndromes are often associated with neoplasias (Beckwith-Wiedemann syndrome with over-expression of *IG-2* and Simpson-Golabi-Behmel with *GPC3* mutations) and initial reports suggested a frequency of 7% in Sotos syndrome [Witt 1985]. In a survey of 224 patients with Sotos syndrome, the malignancy risk found was lower than 2.2% [Hersch 1992]. Cohen reviewed the reported neoplasias

critically and suggested a tumour frequency of about 3.9% (more than in the population) [Cohen 1999]. Sotos cases with *NSD1* anomalies have been reported with small cell lung cancer [Tatton-Brown 2004], ganglioglioma [Deardorff 2004], neuroblastoma in two cases [Nagai 2003, Turkmen 2003], and with acute myelocytic leukaemia [Al-Mulla 2004]. In the series of Tatton-Brown, 3 sacrococcygeal teratomas, 1 presacral ganglioneuroma 1 neuroblastoma and 1 acute lymphocytic leukaemia occurred in childhood in confirmed *NSD1* positive cases. Thus, the risk of tumours in childhood appears low and the relative risk of sacrococgygeal teratomas and neuroblastoma may be increased [Tatton-Brown 2004].

Laboratory findings

No biochemical or endocrinological marker has been documented in patients with Sotos syndrome and/ or *NSD1* anomalie, especially endocrine and paracrine systems [Visser 2004, De Boer 2004].

Etiology

Although most cases are sporadic, autosomal dominant inheritance has been reported in a few cases [Winship 1985].

The report of a child with Sotos syndrome and a t(5;8)(q35;q24.1) translocation [Imaizumi 2002], has led to the identification of *NSD1* gene which was disrupted by the 5q35 breakpoint (Nuclear receptor SET domain containing protein) [Kurotaki 2002]. *NSD1* intragenic mutations cause ~ 75% of Sotos syndromes cases in UK, France, Germany and USA, whereas microdeletions encompassing *NSD1* cause ~ 10% of cases [Douglas 2003, Rio 2003, Turkmen 2003, Raca 2003]. In contrast, *NSD1* microdeletions are the primary cause of Sotos syndrome in Japan, accounting for over 50% [Kurotaki 2003]. *NSD1* abnormalities rarely occur in other childhood overgrowth phenotypes [Douglas 2003, Rio 2003, Turkem 2003]. Current researches are focused on the identification of hotspots for *NSD1* mutations or micro deletions and to establish a genotype-phenotype correlation [Kurotaki 2002, Douglas 2003, Rio 2003, Nagai 2003].

The functions of *NSD1* have not been fully established. The gene contains 23 exons and encodes a protein of 2696 amino acids. This protein is a transcriptional intermediary factor and may act as either a nuclear receptor co-repressor or co-activator by interacting with the holo- or apoforms respectively, of the ligand binding domain of different subsets of nuclear hormone receptors. *NSD1* expression in human

tissue has been detected in foetal/adult brain, kidney, skeletal, muscle, spleen, lung and thymus [Kurotaki 2001]. The protein contains multiples functional domains, including the SET (Su[VAR]3-9,E[Z], trithorax) domain, which was initially identified in *Drosophila* genes involved in chromatin-mediated regulation during development and a SET associated Cys-rich (SAC) domain adjacent to the SET domain. The combination of SAC and SET domains is present in proteins that function as histone-methyltransferase suggesting that *NSD1* may be involved in histone modification and the establishment and maintenance of chromatin states. *NSD1* contains also five plant homeodomains (PHD). The PHD domain is a zinc finger-like motif that occurs predominantly in proteins that functions at the chromatin level. *NSD1* contains two PWWP (Proline-tryptophane-tryptophane-proline) domains. Their role has not been established but they are presumably involved in protein-protein interactions. Finally, *NSD1* contains two distinct nuclear receptor (NR) interaction domains [Kurotaki 2001]. Rare cases of Sotos syndrome have been reported in association with other chromosomal abnormalities: apparently balanced t(3;6)(p21;p21), deletion 15q12 [Schrandt 1990], 45,XY,t(15q;15q) robertsonian translocation [Wajntal 1991]. 25 % of Sotos patients do not have any *NSD1* anomalies suggesting a genetic heterogeneity. In these patients, the involvement of *NSD2* and *NSD3* genes has been excluded by sequencing [Douglas 2004].

Diagnosis methods

Diagnosis is based on clinical exam and radiographic bone age. The cardinal features are pre- and postnatal accelerated somatic growth, characteristic facial appearance advanced bone age and learning difficulties. The clinical diagnosis can be confirmed by FISH analysis to look for *NSD1* deletion and DNA analysis to look for *NSD1* mutations.

In patients without *NSD1* anomalies, cytogenetic studies are necessary.

Genetic counselling

Sotos syndrome is caused by hemizygous mutations in an autosomal non-imprinted gene. The mental difficulties in Sotos syndrome are usually in the mild/moderate range, and are not sufficient to account for the extreme paucity of familial Sotos cases. It has been suggested that this lack of family cases is associated with an underlying defect in fertility associated with *NSD1* mutations. A familial Sotos case caused

by a 1bp deletion of the *NSD1* gene has been recently reported [Högglund 2003]. Chromosome analysis of both parent needs to be performed when a deletion of *NSD1* is detected in the affected child. The recurrence risk for a family with an affected child is very low (<1%). Germline mosaicism has never been reported. The identification of *NSD1* has been a major step in Sotos history and has opened a new area in the elucidation of this syndrome. The evaluation of the tumour frequency in patients with *NSD1* anomalies will be extremely important to further define the tumoral risk of Sotos patients.

Management

In neonatal period, phototherapy is often required because of jaundice. Sucking and swallowing difficulties need adjustments of baby food. Alternate methods of feeding may need to be considered such as the use of a nasogastric tube. Another common problem is gastroesophageal reflux which causes heartburn, vomiting, oesophageal irritation and respiratory problems. Treatments may include adaptations such as eating upright and elevating the head of the bed, medications and in rare cases, surgery. Oral-motor treatment plan may be a part of the child's therapy program.

In infancy and the early years, general and specialized paediatrics follow-up is still important because of the possible clinical events (cf. below) such as constipation, respiratory infections, scoliosis, febrile seizures and the possible increased risk of tumours.

Early in childhood, programs such as infant stimulation, occupational therapy, speech therapy, and adaptative physical education play a significant role in the nurturing of a child with Sotos syndrome. Later, some children participate in regular classrooms with support and some others are enrolled in classes for appropriate education.

As mentioned previously, some Sotos patients develop behaviour problems during the school age years. As a result, parents and school staff may have to spend significant amounts of time and attention dealing with these problems because they can interfere with learning, social interaction and family functioning. A psychologist may work with parents and teachers to develop appropriate and effective methods.

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