A case of Sotos syndrome with 5q35 microdeletion and novel clinical findings

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Sotos syndrome is a multiple anomaly syndrome characterized by pre- and postnatal overgrowth with advanced bone age, macrocephaly, developmental delay, and distinctive facial phenotype. Autosomal dominant mutations and deletions of the nuclear receptor set domain gene (NSD1), which is located at chromosome 5q35, are responsible for most of the cases. We describe a six-year-old boy who had tall stature, macrocephaly, typical facial appearance, learning disability, megaloencephaly, corpus callosum dysgenesis, and colpocephaly. Although he had normal bone age, the diagnosis of Sotos syndrome was suspected with these clinical findings, and fluorescence in situ hybridization analysis of the patient showed a heterozygous deletion covering the NSD1 region in the 5q35 locus. A brief overview of the syndrome is presented.

Key words: Sotos syndrome, fluorescence in situ hybridization analysis, 5q35.3 deletion, megaloencephaly, colpocephaly.

Sotos syndrome is a childhood overgrowth condition first described in 1964[1]. The four major diagnostic criteria are: overgrowth with advanced bone age, macrocephaly, characteristic facial appearance, and development delay[2]. The exact prevalence remains unknown.

Other clinical findings are scoliosis, cardiac and genitourinary abnormalities, neonatal hypotonia, feeding difficulties, seizures, and high risk of benign/malignant tumors. Ventricular and extracerebral fluid abnormalities, midline abnormalities and migration abnormalities are the most common brain malformations in Sotos syndrome[3]. The prominence of occipital horns was defined in 75% of Sotos patients[4]. Despite the well-defined phenotype, Sotos syndrome will be difficult to diagnose for inexperienced clinicians. We describe a six- year-old boy with Sotos syndrome who had tall stature, macrocephaly, typical facial appearance, learning disability, megaloencephaly, corpus callosum dysgenesis, and colpocephaly.

Case Report

The patient, a six-year-old boy, was the second child of healthy non-consanguineous parents. There was no family history of any genetic disease. His sister was healthy. He was born at 40 weeks gestation by cesarean section. Polyhydramnios and macrocephaly were recorded as prenatal ultrasonographic findings. Birth weight was 4550 g (>97th centile) and length was 53 cm; occipitofrontal circumference was not recorded. Because of cyanosis, neonatal hypoglycemia, feeding difficulties, vomiting, and jaundice, he was observed in the neonatal intensive care unit for two weeks. At the age of two months, he was consulted to our department with macrocephaly. On physical examination, his weight was 5,170 g (10th-25th centiles), length was 61 cm (25th-50th centiles) and head circumference was 43.5 cm (>95th centile). He had prominence of forehead, macro-dolichocephaly, hypertelorism, high arched palate, small chin, and large ears. The routine laboratory tests, thyroid function tests and initial metabolic workout were normal. Karyotype was normal, 46,XY. Computerized tomography of the brain was normal. The abdominal ultrasonography, hearing test and eye examination were normal. Echocardiography revealed bicuspid aortic valve and mild aortic regurgitation. Brain magnetic resonance (MR) imaging showed megaloencephaly, corpus callosum dysgenesis and colpocephalic

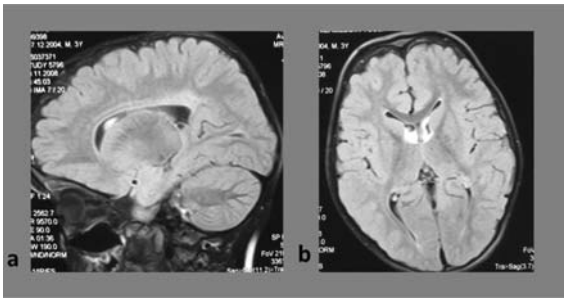

Fig. 1. At age 4, brain MR imaging showed megaloencephaly, a. corpus callosum dysgenesis and b. ventricular dilatation.

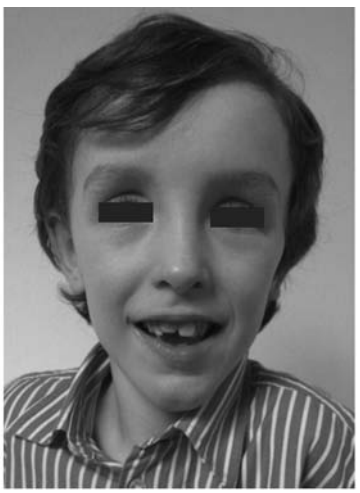

Fig. 2. Dysmorphic facial features, large bossed forehead, hypertelorism, malar hypoplasia, prominent jaw, and macro-dolichocephaly were marked on the physical examination.

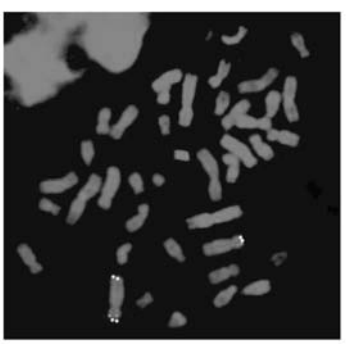

Fig. 3. FISH analysis from his peripheral blood showing a heterozygous deletion covering NSD1 and spanning in the 5q35.3 locus (chromosome 5-specific probe on each p arm of chromosome 5, and a second probe specific for 5q35 NSD1 locus that hybridizes only to the undeleted chromosome 5; this signal is absent on the deleted chromosome 5).

dilatation on ventricles (Fig. 1). He was not able to sit without support before one year of age. At two years, he walked unaided, and at five years, he had two-word sentences. Wrist radiographs were taken at age 4, and bone age was consistent with his chronological age. At age 6, his weight was 27 kg (90th-97th centiles), length was 133 cm (>97th centile) and head circumference was 58 cm (>95th centile). Large and prominent forehead, hypertelorism, malar hypoplasia, prominent jaw, and macro-dolichocephaly were marked on the physical examination (Fig. 2). Although bone age was normal, clinical findings with characteristic facial appearance suggested a fluorescence in situ hybridization (FISH) analysis for Sotos syndrome. FISH analysis from his peripheral blood lymphocytes with commercial probes (Cytocell LPU 013) showed a heterozygous deletion covering nuclear receptor set domain gene (NSD1) and spanning in the 5q35.3 locus (Fig. 3).

Discussion

Sotos syndrome, or cerebral gigantism (MIM 117550), is an autosomal dominant overgrowth syndrome characterized by prenatal and childhood overgrowth with advanced bone age, macrocephaly with characteristic facial appearance, and learning difficulties, with a wide spectrum of associated features including hypotonia, seizures, high risk of benign/malignant tumors, scoliosis, feeding difficulties, cardiac and genitourinary anomalies, and social isolation.

The diagnosis of the disease was based on clinical criteria until NSD1 gene mutations and deletions were identified in 2002[5]. De novo mutations and deletions of NSD1, which is located at chromosome 5q35, are responsible for more than 75% of cases[5,6]. NSD1 plays a role in growth and brain development in humans. The deletions/mutations of the NSD1 gene can be documented by FISH analysis, multiplex ligation probe amplification or sequencing[7,8]. Most cases are sporadic, and several families with autosomal dominant inheritance are described[8]. The recurrence risk for a family with an affected child is very low (<1%), and germline mosaicism has not been reported.

The presented case was typical with his large birth weight, childhood overgrowth,

developmental delay, macrocephaly, and characteristic facial appearance. The diagnosis was confirmed with FISH analysis showing 5q35 microdeletion. Ten percent of clinically diagnosed Sotos syndrome patients had 5q35 microdeletions identified by FISH analysis. The patients with microdeletions have less prominent overgrowth and more severe mental retardation than patients with mutations[7]. One of the interesting features of the presented patient is his marked overgrowth despite confirmed microdeletion. Another interesting feature is the normal bone age of this patient, despite the incidence of advanced bone age in Sotos cases being reported as 74-100%.

Patients with Sotos syndrome may have cerebral findings, ventriculomegaly and thin corpus callosum. The presented patient had ventriculomegaly and colpocephalic dilatation on occipital horns. Colpocephaly is defined as an abnormal enlargement of occipital horns of lateral ventricles and is associated with other brain abnormalities. Dilatation of the cerebral ventricles is a common finding in Sotos syndrome, while prominence of occipital horns was reported in 75% and ventriculomegaly in 63% of cases[3]. However, to our knowledge, the term colpocephaly has not been mentioned previously. Sotos syndrome patients have non-progressive neurological dysfunction; 97% of patients have learning disabilities, 50% have seizures, and 30% have behavioral problems, social isolation and psychiatric disorders (depression, anxiety, psychosis)[7]. Our patient had no seizures but had a moderate learning disability and social difficulties.

Sotos syndrome belongs to a group of overgrowth syndromes that have pre- and postnatal overgrowth and advanced bone age. The main differential diagnoses are Weaver syndrome, Beckwith-Wiedemann syndrome, Fragile X syndrome, Simpson-Golabi-Behmel syndrome, and 22q terminal deletion syndrome[6]. Many of these syndromes can be excluded on the basis of major clinical features.

Sotos syndrome is a rare disease, and recently, the birth prevalence was reported as 7/100,000[9]. Despite the well-defined phenotype, it may be difficult to diagnose for inexperienced clinicians. A multidisciplinary management with general pediatric follow-up, a psychological and educational program, speech therapy, and motor stimulation plays an important role in the global development of patients.

Sotos syndrome should be considered in infants with prenatal and postnatal overgrowth, developmental delay, macro-dolichocephaly with typical facial appearance, megaloencephaly, and ventriculomegaly, even in the absence of advanced bone age. This well-known syndrome should be kept in mind when encountering overgrowth and behavioral problems in routine pediatric practice.

REFERENCES

1. Sotos JF, Dodge PR, Muirhead D, Crawford JD, Talbot NB. Cerebral gigantism in childhood. A syndrome of excessively rapid growth and acromegalic features and a nonprogressive neurologic disorder. N Engl J Med 1964; 271: 109-116.
2. Cole TR, Hughes HE. Sotos syndrome: a study of the diagnostic criteria and natural history. J Med Genet 1994; 31: 20-32.
3. Schaefer GB, Bodensteiner JB, Buehler BA, Lin A, Cole TR. The neuroimaging findings in Sotos syndrome. Am J Med Genet 1997; 68: 462-465.
4. Niikawa N. Molecular basis of Sotos syndrome. Horm Res 2004; 62: 60-65.
5. Kurotaki N, Imaizumi K, Harada N, et al. Haploinsufficiency of NSD1 causes Sotos syndrome. Nat Genet 2002; 30: 365-366.
6. Baujat G, Cormier-Daire V. Sotos syndrome. Orphanet J Rare Dis 2007; 2: 36.
7. Tatton-Brown K, Douglas J, Coleman K, et al. Childhood overgrowth collaboration. Genotype-phenotype associations in Sotos syndrome: an analysis of 266 individuals with NSD1 aberrations. Am J Hum Genet 2005; 77: 193-204.
8. Donnelly DE, Turnpenny P, McConnell VP. Phenotypic variability in a three-generation northern Irish family with Sotos syndrome. Clin Dysmorphol 2011; 20: 175-181.
9. Orphanet report series - Prevalence of rare diseases: Bibliographic data - May 2012-Number 1- page: 26.