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SOTOS SYNDROME (CEREBRAL GIGANTISM)

Analysis of 8 cases

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ABSTRACT - Sotos syndrome or cerebral gigantism is characterized by macrocephaly, overgrowth, mental retardation and central nervous system abnormalities. Congenital heart defects may be present. We report 8 patients with this syndrome and relate their clinical features, neuroimaging and echocardiographic findings.

KEY WORDS: Sotos syndrome, cerebral gigantism, macrocephaly, mental retardation.

Síndrome de Sotos (gigantismo cerebral): análise de 8 casos

RESUMO - A síndrome de Sotos ou gigantismo cerebral é caracterizada por macrocefalia, hipercrescimento, dismorfias faciais típicas, deficiência mental e alterações do sistema nervoso central. Malformações cardíacas podem estar presentes. Nós relatamos 8 pacientes com esta síndrome e descrevemos seus achados clínicos, de neuroimagem e ecocardiográficos.

PALAVRAS-CHAVE: síndrome de Sotos, gigantismo cerebral, macrocefalia, deficiência mental.

Sotos syndrome was first described by Sotos et al. (1964) in five children with overgrowth, acromegalic features, nonprogressive cerebral disorder with mental retardation and characteristic physiognomy[1]. Since then, over 250 cases have been reported[2] . Except for a concordant set of identical twins, most cases have been sporadic[3] .It occurs in all ethnic groups and has been detected throughout the world. The prevalence is not known, but is estimated to be between 1 in 10,000 and 1 in 50,000[4] .

The main clinical finding in Sotos syndrome is prenatal and postnatal overgrowth. Birth length is usually more significantly increased (above the 97th percentile) than weight (between the 75th and 97th percentile). Growth is excessive in the first years of life, after which time it proceeds at a relatively normal rate, but consistently falls in the high percentiles[4] . Bone age is also significantly advanced in most cases of Sotos syndrome, it is thought that all cases have advanced bone age at some time[4] . Head circumference is almost invariably large at birth, and generally proceeds above the 97th percentile throughout growth[5] . Distinctive craniofacial anomalies include dolichocephaly, prominent forehead, hypertelorism or telecanthus, epicanthic folds, flat nasal bridge, downslanting palpebral fissures, high arched palate, premature eruption of teeth and pointed chin[6]. Other features include cerebellar nystagmus, strabismus, pes planus, kyphoscoliosis, unequal lower limb length, syndactyly, large hands and feet, abnormal dermatoglyphics, functional megacolon and hemihypertrophy. Neonatal difficulties and/or feeding problems occur in 40 to 50%[4] .

Central nervous system manifestations are present. Delay in the attainment of milestones of development and, in particular, speech is almost always present, and clumsiness is frequent (60 to 80%), as are hypotonia and lax joints. Mental deficiency is present in 80 to 85% of the patients, with an average IQ of 72 and a range from 40 to borderline mildly retarded; 15 to 20% may be normal mentally and may have IQs up to 129. Some patients do not have global mental retardation but do have deficits in language and mathematics and visual motor coordination problems. Seizures may occur in 30% of the cases[4]. Magnetic resonance imaging (MRI) findings

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consistently seen in the syndrome include prominent extra-cerebral fluid filled spaces, modest thinning of the corpus callosum, enlarged ventricles, particularly in the trigone region, and a persistence cavum septi pellucidi and cavum vergae[7].

Congenital heart defects have been reported in Sotos syndrome patients with incidence approximately to 8%[2]. Koneko et al. found congenital heart defects in 5 to 10 Japanese patients with typical Sotos syndrome[8]. In another study from Canada 3 patients out of 14 had heart defects[2] .

In spite of a few chromosomal abnormalities have been reported in patients with Sotos syndrome, there is no biological marker for the disease, and chromosomes generally are normal[9]. The diagnosis is based on clinical grounds and neuroimaging findings[10]. The differential diagnosis is with Weaver syndrome, patients with mental retardation and overgrowth, patients with autosomal dominant macrocephaly, fragile X syndrome, Marfan syndrome, Bannayan-Riley-Ruvalcaba syndrome and XYY syndrome[4].

The most important problems of the patients with Sotos syndrome are mental retardation and excessive height. The management of the mental retardation is no different than for any other child with mental deficiency. The height is not a handicap for males, usually, but girls with a predicted ultimate height in excess of 178 cm (5 ft 10 in) may benefit from treatment with high doses of estrogen or octreotide, to curtail their linear growth, as indicated for tall normal girls[4]. The hypotonia and the problems with fine motor coordination may improve some what with age. Physical therapy or practice movement may be helpful to improve balance, motor skills, gait, and posture. Social and behavioral problems during childhood and immaturity in adults may benefit from psychological counsel. For speech development some recommend augmentative communication in addition to speech therapy [11] .

The other concern is the possibility of tumor development which is, apparently, increased[12] . There have been reports of malignant tumors; two Wilms tumors, two neuroblastomas, and one each of neuroectodermal tumor, mixed parotid tumor, small cell lung carcinoma, epdermoid carcinoma, vaginal carcinoma, hepatocarcinoma, non-Hodgkin's lymphoma and lymphocytic leukemia. There have also been some benign tumors, including cavernous hemangioma, hairy pigmented nevus and osteochondrome[12,13] .

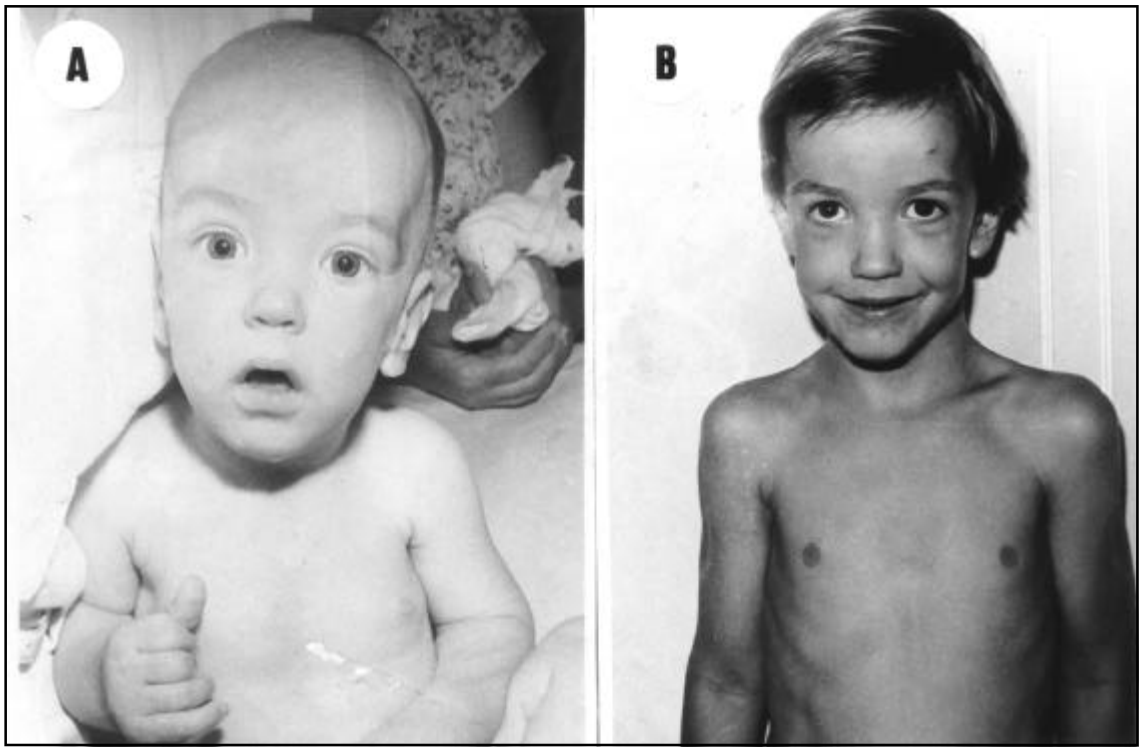

Fig 1. A) Patient 7 at age 6 months with appearance considered typical of Sotos syndrome. Note the prominent forehead, telecanthus, epicanthic folds, flat nasal bridge, downslanting palpebral fissures and pointed chin. B) Same patient at age 4 years and 6 months. Photos published with written authorization given by the patient´s parents.

Table 1. Clinical features in our patientes with Soutos syndrome.

Clinical features	Patients							
	1	2	3	4	5	6	7	8
sex	M	F	F	M	F	M	M	M
age	5 y	3 y 10 m	2 y	4 y 2 m	2 y	4 y 4 m	16 y	2 y 5 m
overgrowth	+	+	+	+	+	+	+	+
macrocephaly	+	+	+	+	+	+	+	+
advanced bone age	+	+	+	+	+	+	+	+
mental retardation	+	+	+	+	+	+	+	+
hypotonia	+	+	+	+	+	-	+	+
dolichocephaly	+	+	+	+	+	+	+	+
prominent forehead	+	+	+	+	+	+	+	+
hypertelorism	+	+	+	+	+	+	+	+
downslanting palpebral fissures	+	+	+	+	+	+	+	+
flat nasal bridge	+	+	+	+	+	+	-	+
high arched palate	+	+	+	+	+	+	+	-
premature eruption of teeth	+	-	-	-	-	+	+	-
pointed chin	+	-	+	+	+	+	+	+
Number	13	11	12	12	12	12	12	11

Affected individuals are fertile and there is no evidence that life span is shortened[6]. The other important consideration is the risk of transmission. Sotos syndrome usually has been reported as sporadic condition, but rarely genetic transmission as a dominant trait has been observed[14, 15] including male-to-male transmission[16]. Recessive inheritance has also been suggested [17] and this syndrome has been described in monosygotic twins[2], first cousins[18] and siblings[19]. Therefore, in spite of the natural history of Sotos syndrome has been elucidated over the years, its etiology and pathogenesis remains unknown[4] .

Here, we report 8 patients with Sotos syndrome and relate their clinical features, neuroimaging and echocardiografic findings.

METHOD

All 8 patients (5 males and 3 females, age range between 2 years and 16 years) had been seen in the Clinical genetics service of the University Hospital in Ribeirão Preto, University of São Paulo. The patients were seen by at least two clinical geneticists involved in this study (DGM, AXA, MAAS and JMPN). Only those patients with unambiguous classic Sotos syndrome [6] were included in this study. The neuroimaging of the eight patients was performed by magnetic resonance imaging (MRI) scans, which were visually inspected by two of the authors (ACS and JDVC), and the identified anomalies were tabulated. The neuroimaging findings were grouped into categories similar to those Schaefer et al.[7]. The criteria for ventriculomegaly was a lateral ventricular ratio larger than 0.36 and was obtained by the width of the body of the lateral ventricle divided by half the greatest internal transverse diameter of the calvaria. All patients were also studied by echocardiographic method, including doppler, and the anomalies were registered.

Chromosomal analysis revealed normal in the 8 patients.

RESULTS

Clinical manifestations, including craniofacial characteristics, in our patients with Sotos syndrome were reported in Table 1. The Figure 1 shows a patient with appearance considered typical of Sotos syndrome, and the Figure 2 shows linear growth in all patients reported in this study.

Table 2 shows the neuroimaging findings in patients, which were grouped into three categories: 1) ventricular abnormalities; 2) extracerebral CSF spaces; 3) midline variations.

The echocardiographic studies showed a small atrial septal defect (4.0 mm) without hemodynamic consequences in the sixth patient.

DISCUSSION

In a review, Cole and Hughes[3] clinically assessed 79 patients with a provisional diagnosis of Sotos syndrome and evaluated their photographs between

Table 2. Neuroimaging findings in patients with Sotos syndrome

Neuroimaging findings		Patients									
		1	2	3	4	5	6	7	8	N	%
Ventricles	large	-	+	-	-	+	-	+	+	4/8	50.0
	prominent trigone	+	-	+	+	-	+	-	-	4/8	50.0
Extracerebral	supratentorial	+	+	+	-	+	+	+	-	6/8	75.0
fluid increased	cavum septum pellucidum	-	-	-	-	-	-	+	-	1/8	12.5
	cavum vergae	-	-	-	-	-	-	+	-	1/8	12.5
	cavum velum interpositum	-	-	+	-	-	-	-	-	1/8	12.5
	hypoplasia of corpus callosum	+	+	+	-	-	-	-	-	3/8	37.5
	macrocisterna magna	-	+	-	-	-	-	-	-	1/8	12.5

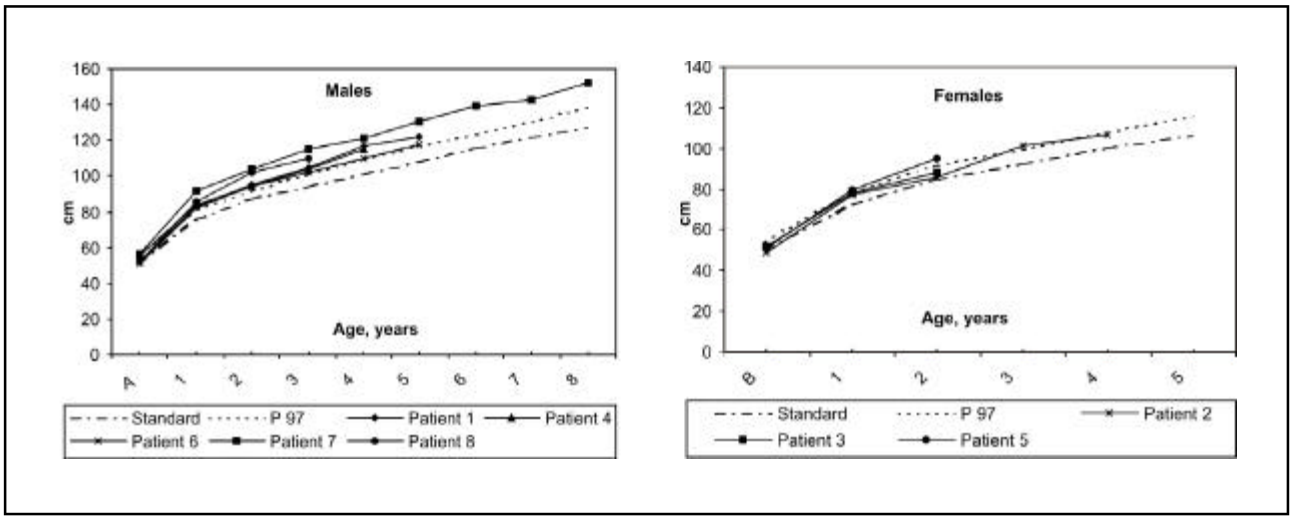

Fig 2. A) Sotos syndrome height, males, birth to 8 years . B) Sotos syndrome height, females, birth to 5 years.

ages 1 and 6 years. Theses photographs, together with photographs of first-degree relatives, also at age 1 to 6 years, were reviewed by four clinical geneticists and in 41 probands, but no first-degree relatives the facial gestalt was thought to be characteristic of Sotos syndrome. Comparison of anthropometric measurements, bone age and developmental delay in these 41 probands showed marker differences between them and the remaining 38 probands. Length was identified as the most significantly increased prenatal parameter. In childhood, occipitofrontal head circumference (OFC), height and weight were all increased OFC remained above the 97th percentile in all but one case throughout childhood and adulthood whereas height and weight had a tendency to return toward the mean. This normalization was more pronounced in females and was probably related to their early puberty. Early developmental delay and an advanced bone age were seen in 100% and 84% of cases, respectively. Like this, the authors suggested that facial gestalt (Fig 1), growth pattern (Fig 2), bone age and developmental delay are the major diagnostic criteria[7].

The neuroimaging abnormalities of Sotos syndrome provide support for the hypothesis of delayed or disturbed development of the brain and particularly of midline structures[20]. For example, it has been demonstrated that outside persistence of cavum septum and cavum velum interpositum are markers of disturb midline brain development and associated with increased risk of mental retardation[21,22] .

The neuroimaging changes of Sotos syndrome appear to be at least compatible with the proposition that the brain development, particularly in the midline, is delayed and/or disturbed and the enlarged CSF spaces and cerebral ventricles in these patients suggests that these children have normal size of brain inside a large head [7] .

Our patients did not have migrational abnormalities as described by Schaefer et al.[7] but we also observed that all the patients with Sotos syndrome had

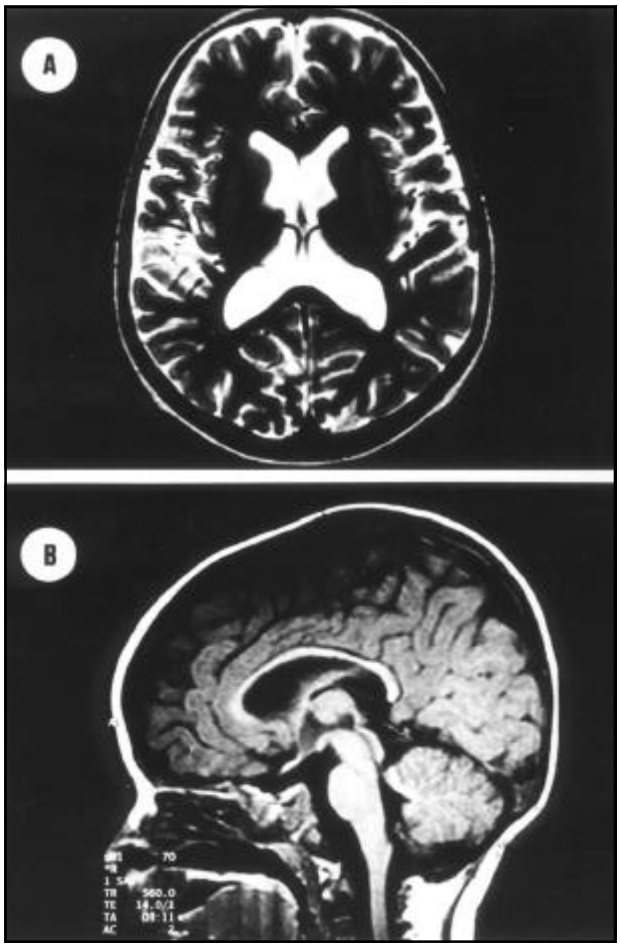

Fig 3. A) T1 weighted axial MRI image of patient 2 showing large global lateral ventricles. B) T1 weighted midsagital MRI image shows hypoplasia of the corpus callosum and persistence of the cavum velum interpositum.

abnormal MRI scans (Fig 3) and we concluded, in agreement with Schaefer et al.[7], that the neuroimaging findings in Sotos syndrome are very distinctive and that MRI studies can aid in the confirmation of diagnosis[7,23].

Noreau et al. reviewed all Sotos syndrome patients with congenital heart defects and related the incidence of it in approximately 8%, which is roughly a 10 fold increase over the population incidence of 0,6 to 1,0%[2] . Atrial septal defect, like in our patient, is the most common defect described in Sotos syndrome[23]. We concluded that is just to research CHD in Sotos syndrome patients.

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