Characteristics of Sotos syndrome

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CHAPTER 1

INTRODUCTION

1. Preface

Sotos syndrome, or cerebral gigantism, is an overgrowth syndrome and its major cause was elucidated in 2002. NSD1 (nuclear receptor SET domain containing protein) gene alterations were found responsible (1). In this general introduction, firstly some general aspects of growth and its regulators will be described, followed by a classification of overgrowth disorders. Different aspects of Sotos syndrome will be discussed with a separate paragraph on genetics and the NSD1 findings. Finally the outline of this thesis will be given.

2. Growth

2.1. Human growth

Human growth is a complex process that is influenced by many factors. Genetic, hormonal and also environmental (e.g. nutrition) factors play a role. Longitudinal growth in the human can be divided into four phases, the prenatal phase, birth to three years of age, three years till puberty and the pubertal phase (2). Skeletal growth is responsible for longitudinal growth and is determined by endochondral ossification in the epiphyseal growth plate. Endochondral ossification is the process of chondrocyte proliferation, differentiation, maturation and apoptosis and its subsequent replacement by bone.

The highest growth velocity in humans is present in utero. Important prenatal growth regulators are insulin and insulin-like growth factors (IGFs) (3). Growth Hormone (GH) is not an important regulator of foetal growth, but plays an important role in postnatal growth. Besides GH, insulin and IGFs, postnatal growth is hormonally also influenced by thyroid hormone, glucocorticoids and sex steroids (4). In the infancy phase (0-3 years) growth velocity decreases and the child "seeks its own curve" according to its genetic potential. In the childhood phase, approximately from 18 months of age until the onset of puberty (according to the ICP model (5)), growth velocity further decreases. After this, sex steroids contribute to the pubertal growth spurt (the pubertal phase) and play a role in bone maturation and finally in epiphyseal fusion (6). After the peak of the pubertal growth spurt, growth will go on for another three years at a progressively decreasing rate until complete fusion of the epiphyseal plates occurs.

In growth analysis target height is used as a parameter of genetic potential. Target height can be calculated from parental heights. Using the Dutch standards of 1997 (7), the target height in cm can be calculated by the following formula:

$$\frac{(\text{height father} + \text{height mother} \pm 13)}{2} + 4.5 \text{ cm}$$

The difference between mean height of boys and girls is 13 cm, so +13 applies for boys and –13 applies for girls. A mean secular trend of 4.5 cm is expected per generation (30 years). One should be careful using this formula in cases where one of the parents (or both) have an unusual tall or short stature, because of the possibility of a dominant hereditary disorder. Most children reach final height within the target height + 10 cm.

For the individual child final height can be predicted by different methods using height and bone age (2). For the Bayley-Pinnaeu method input of height, chronological age and bone age is needed, and final height can be extracted from tables. The models are based on children showing a normal growth pattern, which should be realised if these are used in children with overgrowth syndromes.

In cases of extreme short or tall stature, depending on its cause, treatment can be considered. There are a number of indications for GH treatment in cases of short stature (e.g. GH deficiency), which will not be discussed further. In some cases of extreme tall stature, for instance if final height prediction is above 200-205 cm for boys and 180-185 cm for girls, treatment with sex steroids in order to try to diminish final height can be considered. Sex steroids induce secondary sexual characteristics and cause an acceleration of bone maturation with premature closure of the epiphyseal growth plate. The effect is dependent of the age at the start of treatment. More effect is obtained when treatment is started early, but most clinicians are hesitant to prescribe sex steroids before the onset of puberty (8).

2.2. Growth hormone and the insulin-like growth factor family

2.2.1. GH

GH, mainly important for postnatal growth, is produced in the anterior lobe of the pituitary gland. Secretion is pulsatile and among other factors regulated by hypothalamic growth hormone releasing hormone (GHRH) and somatostatin. In the circulation it is partly bound to GH binding protein and cells in many tissues have GH receptors. GH has anabolic and metabolic effects. Part of the anabolic effects of GH is mediated through liver-derived IGFs. In mice models, GH receptor/binding protein knockouts showed severe postnatal growth retardation (9). Transgenic mice overexpressing GH demonstrated increased postnatal growth (body weight 200% of normal) (10). In humans GH deficiency or insensitivity leads to dwarfism/short stature and GH excess leads to gigantism or acromegaly (6).

2.2.2. IGFs

In 1957 Salmon and Daughaday demonstrated the existence of a GH dependent sulfation factor, which was able to stimulate cartilage sulfation in rats (10). In 1972 sulfation factor was renamed somatomedin (mediator of the effects of somatotropin, which is another term for GH). Two separate factors were identified to be responsible for somatomedin activity. They were called insulin-like growth factor I and II because their structure showed similarity with proinsulin.

These small polypeptides play a role in cell proliferation and differentiation, but also have metabolic effects. They are synthesized in the liver and many other tissues and besides endocrine effects they also show paracrine and autocrine effects on cell proliferation, differentiation and apoptosis (11).

The "somatomedin hypothesis" as proposed in 1957 has been adapted several times as illustrated in figure 1. Besides the indirect effect of GH on growth, mediated through the endocrine action of circulating IGFs, in 1985 direct effects of GH and IGFs on the growth plate were demonstrated (12, 13). In 2000 liver specific IGF-I knock out mice with reduced (25% of normal) IGF-I serum levels, showed normal growth, pointing to a major role of autocrine/paracrine effects of IGF (14). However a minimal level of circulating IGF is needed as shown by growth retardation in mice with further reduction of serum levels. These were double knock out mice of liver specific IGF-I and acid labile subunit (ALS) (15, 16).

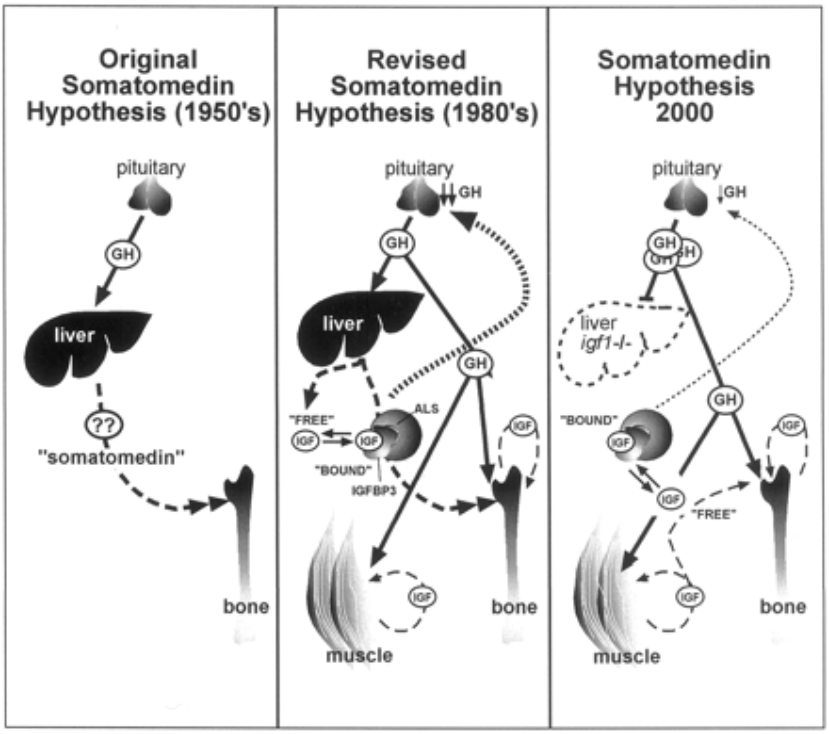

Figure 1. Evolving concepts in the somatomedin hypothesis. Left, the original hypothesis proposed that GH controls somatic growth by stimulating the liver production of a circulating substance (somatomedin or IGF-I). Middle, the hypothesis was later modified after the discovery that IGF-I is expressed by almost all tissues of the body, and this led to the additional possibility of an autocrine/paracrine role for IGF-I. Right, the results of gene deletion experiments have questioned the role of liver IGF-I and the bound form of circulating IGF-I in controlling postnatal growth and development. Adapted from Le Roith et al, 2001.

Most of the IGF effects are mediated by binding to the IGF-I receptor (IGF-IR). The IGF-II receptor (IGF-IIR) or mannose 6-phosphate receptor binds IGF-II and lysosomal enzymes but has no known role in IGF signalling. Whereas IGF-I is thought to play an important role in both prenatal and postnatal life, IGF-II is thought to be more important prenatally. IGF-II is also secreted by several tumours, together with pro-IGF-II (17). IGF-I knockout mice are small (60% of normal birth weight) at birth and postnatal growth is reduced. Most die before adulthood. IGF-II knockouts are also small at birth (60%) but show normal postnatal growth. IGF-IR knockouts show birth weights 45% of normal and die early postnatally. IGF-IIR knockout mice die in utero, but in combination with IGF-II knockout they show birth weights 60% of normal and are born alive. IGF-I overexpression in mouse models leads to birth weights of 130% of normal (10).

In human severe pre- and postnatal growth retardation with a small head circumference was reported in a patient with a homozygous partial deletion of the IGF-I gene (18). A similar phenotype was observed in a patient with a homozygous missense mutation in the IGF-I gene (Walenkamp et al, abstract ESPE 2003). Recently a study was published about a growth-retarded patient lacking one copy of the IGF-IR. Another patient showed overgrowth with three copies of the IGF-IR (19). Two patients have been described with heterozygous IGF-IR mutations and pre-and postnatal growth retardation (20).

2.2.3. IGFBPs

In the circulation IGFs are bound to IGF binding proteins (IGFBPs). Six IGFBPs, sharing the ability to bind to IGFs, have been identified, named IGFBP-1 to -6. They are produced in many tissues and are present in the circulation. They are assumed to have four major functions in regulating the activities of IGFs: 1) transporting IGFs in the circulation, 2) prolong the half-lives of the IGFs, 3) providing tissue and cell type-specific localisation and 4) modulate interaction of IGFs with their receptors (10). Besides IGF-mediated functions, also IGF independent functions have been proposed (11).

Almost all IGFs in serum are bound to IGFBPs. The dominant IGFBP in serum is IGFBP-3, which forms a 150 KDa complex with one of the IGFs and ALS. The other IGFBPs form 50 KDa complexes with the IGFs. Only a small amount of IGFs circulates as ‘free-IGF’. Both IGFBP-3 and IGFBP-1 can either inhibit or potentiate IGF action. IGFBP-2, -4 and -6 are inhibitors of IGF action. IGFBP-2, -5 and –6 have a higher affinity for IGF-II than for IGF-I (21), the others show equal affinity. Affinity can be reduced by specific proteases for IGFBPs, which may cleave these proteins. It is assumed that IGF bioavailability is affected by local variations in amount of IGFBPs and these proteases (10).

Transgenic mouse models for IGFBP-1 show abnormal brain development, reduced pre- and postnatal growth and impaired fertility. IGFBP-2 transgenic mice show reduced body weight. In IGFBP-3 transgenic mice organomegaly of spleen, liver and heart is shown. IGFBP-4 transgenic mice exhibit hypoplasia of smooth muscle (22). Reproduction abnormalities were found in IGFBP-6 transgenic mice (23).

3. Overgrowth

Overgrowth, characterized by tall stature is often defined by a height of more than two standard deviations (SD). Numerous overgrowth disorders are known and genetic and hormonal causes have been identified, but not all pathogenic mechanisms have been elucidated (24). In many cases overgrowth can be explained by familial (genetic) tall stature (2). Fragile-X is an important cause of overgrowth in combination with mental impairment, and it is the most common form of inherited mental retardation. A classification of overgrowth disorders is shown in table 1. Sotos syndrome is classified as an overgrowth disorder with a genetic cause. The syndrome, characterised by a typical facial gestalt, macrocephaly, advanced bone age and developmental delay, recently discovered to be caused by NSD1 gene alteration, will be discussed in paragraph 4. Two syndromes, Fragile-X and Weaver, showing both overgrowth and mental retardation and resembling Sotos syndrome to some extent are briefly discussed below.

Patients with fragile-X are characterised by postnatal overgrowth, mental retardation, large ears, a prominent forehead and jaw, long face and macroorchidism in men. Often autism and hyperactivity is also seen in these patients. Bone age is advanced, which means that final height is usually not extremely tall (2, 25). The syndrome is caused by increased copy repeats in the FMR-I gene (Fragile-X Mental Retardation), located on the long arm of the X chromosome (q27.3). The prevalence is higher in men than in women.

Patients with Weaver syndrome are characterised by pre- and postnatal overgrowth, developmental delay, hypertonia, macrocephaly with a flat occiput, hypertelorism, broad face with micrognathia and camptodactyly. Although bone age is strongly advanced in these patients, final height is often very tall (2, 26). The cause is unknown, although recently a few patients with NSD1 gene mutations have been described (27, 28). Many features resemble Sotos syndrome. In table 2 a number of similarities and differences are listed.

Table 1. Classification of tall stature/overgrowth disorders, adapted from JF Sotos, 1996

Postnatal Overgrowth

A **Normal variants**
Familial (genetic) tall stature
Familial (genetic) rapid maturation

B **Nutritional**
Overnutrition (obesity)

C **Hormonal**

1 *Growth hormone excess*
Pituitary gigantism
Pituitary adenoma
McCune-Albright syndrome
Multiple Endocrine Adenomatosis (MEN-1)
Ectopic adenomas (sphenoid-nasal cavity)
Growth hormone releasing hormone excess
Intracranial gangliocytomas
Extracranial tumors (carcinoid, pancreatic islets, bronchial adenomasd, etc)

2 *Growth factor excess?*
Acromegaloidism

3 *Hyperthyroidism*

4 *Hyperinsulinism*
Lipodystrophy

5 *Prepubertal sex hormone excess*
Isosexual precocious puberty
Adrenal androgens or estrogens
Gonadal androgens or estrogens

6 *Sex hormone deficiency or insensitivity*
Eunichoidism
Male: Hypogonadotrophic
Testicular deficiency
Female: Hypogonadotrophic
Anovarian
Estrogen resistance and aromatase deficiency
Androgen resistance
XY gonadal dysgenesis (Swayer syndrome)
XY 17-hydroxylase deficiency

D **Genetic**

1 *Chromosomal abnormalities*
Klinefelter XXY, XXYY
XYY syndrome
Trisomy X (47, XXX females)
Fragile X syndrome
Trisomy 8, mosaicism
Trisomy 8p

2 *Syndromes and others*
Marfan syndrome
Beals syndrome (CCA)
Homocystinuria
Sotos syndrome
Weaver syndrome
Neurofibromatosis
Beckwith-Wiedemann syndrome
Bannayan-Zonana syndrome
Rubvalcaba-Myhre syndrome
Riley-Smith syndrome
Nevo syndrome
Simpson-Golabi-Behmel syndrome
Elejalde syndrome
Teebi syndrome

Prenatal Overgrowth

Infant of diabetic mother
Infant giant
Beckwith-Wiedemann syndrome
Lipodystrophy
Sotos syndrome
Nevo syndrome
Weaver syndrome
Marshall-Smith syndrome
Perlman syndrome
Simpson-Golabi-Behmel syndrome
Elejalde syndrome

Table 2. A number of similarities and differences between Sotos and Weaver syndrome

SOTOS SYNDROME	WEAVER SYNDROME
SIMILARITIES	
prenatal /postnatal overgrowth	
macrocephaly	
developmental retardation	
advanced bone age	
DIFFERENCES	
dolichocephaly	flat occiput
prominent chin	micrognathia
hypotonia	hypertonia
	limited joint extension
	camptodactyly
	large ears
	hypertelorism

4. Sotos syndrome

4.1. History

Sotos syndrome (cerebral gigantism) is named after Professor Juan Sotos, who described five children with excessively rapid growth with acromegalic features and a nonprogressive neurologic disorder in 1964 (29). Possibly the first reported patient was described in 1931 (30).

The five patients described by Sotos et al. showed accelerated growth without evidence of a tumour of the pituitary gland or another recognized disorder associated with overgrowth. The children also showed a large head circumference, advanced bone age and similarity in facial appearance with a long face, downward slant of the eyes laterally and a prominent forehead and jaw. Since then many case reports have been published, but diagnosis was difficult because the incidence of the characteristics were variable among the patients. In 1994 Cole et al (31) suggested the following diagnostic criteria: 1) facial gestalt 2) height above the 97th percentile 3) head circumference above the 97th percentile 4) bone age above the 90th percentile 5) developmental delay. Less than four criteria should raise doubt about the diagnosis. In 2002 Kurotaki et al (1) discovered that haploinsufficiency of the NSD1 gene was the major cause of Sotos syndrome. In following reports heterozygous deletions or inactivating mutations in the NSD1 gene were detected in 60-75% of the patients clinically suspected of Sotos syndrome (27, 28, 32, 33).

4.2. Growth

Prenatal overgrowth is a well-recognised characteristic in Sotos syndrome. In the majority of cases increased birth length, weight and head circumference without an abnormal weight for length were found (31, 34, 35). Growth is mostly accelerated in the first year of life. After the first four years the growth velocity stabilises and patients follow their curve usually above the 97th percentile, (31, 34, 36) (see figure 2). Information on onset of puberty and final height is limited. Age at menarche in girls is normal or slightly advanced (31, 37). Final height based on 11 men and 11 women was in the upper normal range (37). However, two patients receiving hormonal treatment to limit their adult height, were excluded. Head circumference often shows a rapid increase in the neonatal period and at two years a mean SDS of +3.5 SDS (n=33) has been reported (31). Overgrowth in these patients is almost always accompanied by advanced bone age (31, 35). Arm span is usually increased (38, 39) and hand and feet are large (31).

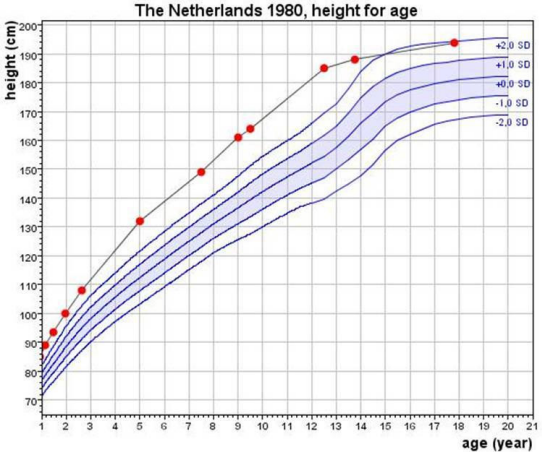

Figure 2. Characteristic growth chart of a patient with Sotos syndrome

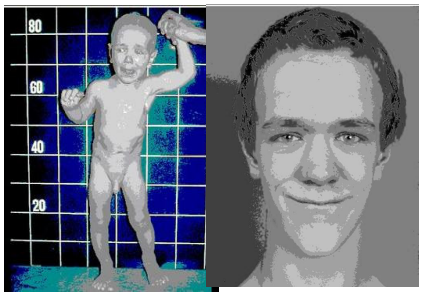

Figure 3. patient with Sotos syndrome at age 1.2 and 13 years

4.3. Facial characteristics

The following characteristics have been considered typical for Sotos syndrome: frontal bossing, high hairline, antimongoloid slant of palpebral fissures, prominent jaw, dolichocephaly, high palate and facial flushing (31, 40) (see figure 3). The frequency of these features range from 70 to 100%. Also a clinical impression of hypertelorism is often present (31). With aging the jaw becomes more prominent and the facial shape resembles the outline of an inverted pear (40).

4.4. Development

Developmental delay is an important feature of Sotos syndrome. In the neonatal period hypotonia often leads to feeding problems (31). In infancy and childhood motor and speech milestones are delayed and clumsiness, impaired gross movement and poor coordination are often present, but tend to improve with age (31, 35, 41). Cognitive abilities vary and in different studies IQ scores range from 21 to 129, with mean IQ scores around 75 (31, 41-44). Many, but not all children need special education (45).

4.5. Additional features

In table 3, adapted from Visser & Matsumoto (33) an overview is given of clinical features found in patients with Sotos syndrome.

4.5.1. neurological findings

Seizures, partly febrile convulsions, have been reported (31). CT and MRI images of the head have shown that macrocephaly in Sotos syndrome is both related to enlargement of cerebral parenchyma as well as retention of cerebrospinal fluid in the ventricles and the subarachnoid spaces (46). Review of 40 neuroimaging studies have shown many cerebral ventricle abnormalities, prominence of the trigone in 90%, the occipital horns in 75% and ventriculomegaly in 63%. Abnormalities of the corpus callosum, especially thinning, were almost universal (47).

4.5.2. cardiac anomalies

The incidence of cardiac anomalies is estimated at 8% in Sotos syndrome, whereas the incidence in the population is 0.6 to 1 % (48). In Japanese studies higher frequencies were reported, 50% (5/10), 41% (7/17) and 35% (17/49) (49, 50). The most reported congenital heart defects were patent ductus arteriosus and atrial septum defect. Two cases of dysrhythmias were reported: one patient with Wolff-Parkinson-White syndrome (51) and one patient with supraventricular tachycardia (31).

4.5.3. skeletal features

Patients with Sotos syndrome usually have large feet and pes planus is a common problem. Also scoliosis has been reported in these patients (31, 33). Possibly the incidence of fractures is higher than usual, but this was not objectivated (31). With metacarpophalangeal pattern profile (MCPP) analysis, three different hand profiles have been described in Sotos syndrome (52). With this analysis hand bone lengths of 19 tubular bones are measured and compared to reference values. MCPP analysis has been used in a number of syndromes as a diagnostic tool (53).

4.5.4.ectodermal features

Early eruption of the first teeth has been reported (31, 54). Several authors have described thin, brittle nails, sunken into the surrounding skin (31, 34). Three patients have been described with cutis laxa characteristics, showing redundant skin folds (55).

Table 3 Clinical features (number of cases) in Sotos syndrome, adapted from Visser & Matsumoto, 2003

Musculoskeletal

Spine and thorax:	*Hands/Feet:*	*Miscellaneous:*
Kyphosis and/or scoliosis (39)	Pes planus (32)	Laxity joints/skin (20)
Pectus carinatum (4)	Pes cavus (1)	Genu valgus (11)
Pectus excavatum (2)	Valgoid feet (5)	Genu varus (6)
	Syndactyly (toes/hands) (9)	Congenital dislocation of hip (2)
	Large hand/feet and nail anomalies	Abduction limitation both hips (1)

Cardiac

Ductus arteriosus:	*Septum defects:*	*Arythmia:*
Patent Ductus Arteriosus (PDA) (16)	ASD (12)	Supraventricular tachycardia (1)
In combination with:	VSD (4)	Wolff-Parkinson-White syndrome(1)
Atrial Septal Defect (ASD) (8)	ASD + hypertrophic cardiomyopathy (1)	Incomplete right bundle branch block + right ventricular hypertrophy (1)
Ventricular Septal Defect (VSD) (1)	Epstein anomaly (2)	
Mitral valve regurgitation (1)	Unspecified (1)	
Pulmonary stenosis (1)		*Miscellaneous:*
	Valve malformation:	Ejectic systolic murmur (3)
	Pulmonary atresia (+/-tricuspid atresia) (2)	Murmur + right ventricular hypertrophy (1)
	Pulmonary stenosis (5)	Aorto-pulmonary window (1)
	Aortic valve + mitral valve malformation(1)	Abnormal aorta (2)
	Mitral valve prolaps (1)	Tetralogy of Fallot (1)

Urogenital

Renal:		*Testis:*
Hydronephrosis (10)	Chronic renal failure (1)	Cryptorchidism (8) (16%)
Dilation renal pelvis (4)	Unspecified renal malformations (1)	Testis redux (5)
Atrophic/hypoplastic kidneys (6)	*Bladder/Ureter/Uretra:*	
Renal agenesis (2)	Vesico-ureteric reflux (VUR) (-/+ hydro-nephrosis) (29)	*Miscellaneous:*
Autosomal dominant polycystic kidney disease (1)	Bladder diverticulae/nodule (3)	Inguinal herniae in males (32%)
	Hypospadia (1)	

Ophthalmic		**Endocrinological**
Strabismus (41%)	Retinal anomalies (5)	Primary hypothyroidism (3)
Refractive anomalies	Optic nerve anomalies (5)	Thyrotoxicosis (2)
Hyperopia >+2.00 Diopters (50%)	Iris anomalies (2)	Hashimoto's disease (1)
Myopia (15%)	Lens/cataract (2)	
Nystagmus (4) (33%)	Megalocornea (2)	

Neurological/Psychiatric		**Behavioral**
Hypotonia and affected coordination	Autism (1)	Temper tantrums (40-81%)
Increased tendon reflexes		Hyperactivity disorder (27-56%)
Seizures (non febrile) (28)		Anxious and aggressive behavior
West syndrome (2)		Social contact and sleep problems

Neoplastic

	Fibroma:	*Leukolymphoproliferative:*
Wilms tumor (2)	Cardiac fibroma (1)	Acite lymphoblastic leukaemia (4)
Hepatocellular carcinoma (1)	Ovarian fibroma (1)	Non-Hodgkin lymphoma (3)
Epidermoid carcinoma vagina (1)		
Gastric carcinoma (1)		
Neuroblastoma (3)	*Germ cell tumor:*	
Pilmonary blastoma (1)	Sacrococcygeal teratoma (4)	
Giant cell granuloma of mandible (1)	Testicular yolk sac tumor (1)	
Osteochondroma (1)		

4.5.5.urogenital anomalies

Vesico-ureteric reflux has been reported in 6 out of 40 cases (15%) (31) and 3 out of 7 cases (49). In case reports also hydronephrosis, renal failure and bladder diverticula have been described (56-58).

4.5.6. fertility

Data on fertility are limited. In family members of patients with Sotos syndrome, a high rate of spontaneous abortions was reported in one study (59). Delayed menarche was mentioned in a study of a mother and a child with Sotos syndrome (60). In parents of two children with characteristics of Sotos syndrome subfertility was reported (61). Whether one of the parents has characteristics of the syndrome is not clear.

4.5.7.ophthalmic anomalies

Apart from strabismus, which was estimated to be present in 41% of the cases (35), no increased frequencies of ocular problems have been reported. Case reports have been published about cataract (62, 63), macular degeneration (64) and glaucoma (65).

4.5.8.neoplasms

Sotos syndrome, as other overgrowth syndromes, is often associated with an increased risk of malignancies, but different tumour risk percentages have been reported (34, 66-69). A questionnaire study including 224 patients with Sotos syndrome, revealed a tumor risk of 2.2% (66). The risk of 1:41 is much higher than in the general population (1:7100 in the U.S.), but the authors suggest that this risk could well be overestimated, biased by failure to report cases of Sotos syndrome without tumors. There is not one specific malignancy/tumor associated with Sotos syndrome.

4.5.9. behavior and psychological characteristics

High rates of behavior problems occur in Sotos syndrome (42, 44, 70). Problems in social contacts, anxious behavior (45), symptoms of ADHD (44), aggression (71), temper tantrums and eating or sleeping difficulties (42) have been reported frequently. Due to their overgrowth these children might be treated as older than they are, which could lead to problem behavior and low self-esteem (72). Single cases have been reported showing autism (73), Asperger syndrome (74) and pervasive developmental disorder (75).

4.5.10 endocrine and biochemical findings

In the neonatal period hyperbilirubinemia has been reported (31). Three cases were reported of hypothyroidism (76, 77). In search for the aetiology of overgrowth, GH and IGF bioactivity levels have been measured in several patients. Many authors reported normal plasma GH levels (78-81). Plasma IGF bioactivity levels have been reported normal (82-84), decreased (79, 85, 86), increased (80, 87-89) or showed different values at different ages (34).

4.6. Genetics

4.6.1. chromosomal abnormalities

Cytogenic aberrations have been reported in several cases and are shown in table 3. The patient described by Imaizumi (90) carried a de novo balanced translocation. Kurotaki et al (1) discovered that the 5q35 translocation breakpoint disrupted the NSD1 gene, which was subsequently indentified as the cause of Sotos syndrome (see below). In the patient with a balanced translocation described by Schrander-Stumpel (91), recently a NSD1 mutation was detected . The relation of this translocation and its contribution to the clinical presentation of this patient is presently unclear. Of the other patients with cytogenic aberrations listed in table 4, it is as yet unknown whether NSD1 gene alterations are present.

Table 4 Cytogenic aberrations in patients with Sotos syndrome reported in the literature

author	year	Chromosomal aberration
Nakada et al	1982	Inversion chromosome 8
Koyama et al	1985	46 XX t(5;15)(q35;q22)
Schrander-Stumpel et al	1990	46 XY t(3;6)(p21;p21)
Koiffmann et al	1991	46 XY del 15 (q12 or q13)
Haeusler et al	1993	Pericentric inversion chromosome Y Pericentric inversion chromosome 9
Cole et al	1994	46 XY t(2;4)(2qter? 2p15:4p14-4pter;4qter? 4p14:2p16.2? 2pter)
Faivre et al	2000	46 XY dup(20)(p11.2-p12.1) [12]/46 XY [66]
Imaizumi et al	2002	46 XX t(5;8)(q35;q24.1)

4.6.2. The NSD1 gene

The NSD1 gene is located on chromosome 5q35. NSD1 consists of 23 exons, has an 8088 bp open reading frame and encodes 2696 amino acids (92). NSD1 contains the following functional domains: SET (SU[VAR]3-9,E[Z], trithorax), SAC (SET-associated Cys-rich), PWWP-I and II (proline-tryptophan-tryptophan-proline) and PHD-I, II and III (plant homeodomain). These domains have been associated with chromatin structure (27, 92). The NSD1 gene also contains two Nuclear receptor-Interaction Domains, NID-L and NID+L, which interact with the ligand binding domains of nuclear receptors (NR), either in the absence or presence of ligand. The gene can act both as a corepressor or coactivator of the NR. Interaction of NID-L, but not NID+L, with the unliganded ligand binding domains (LBD) of retinoic acid receptors (RAR) and thyroid hormone receptors (TR) results in repression. In contrast, NID+L, but not NID-L, interacts with the liganded LBDs of RAR, TR,

retinoid X receptor (RXR), and estrogen receptor (ER) and this interaction results in coactivation of gene transcription (388). These NR all play a role in growth and development. NSD1 is expressed in fetal and adult brain, kidney, skeletal muscle, spleen, thymus and faintly in the lung (92). NSD1, fused to the nucleoporin 89 gene (UP89) is associated with childhood acute myeloid leukaemia (93).
In studies with NSD1 knockout mice, heterozygous mice were viable and displayed a normal growth rate, showing no characteristics resembling Sotos syndrome. Homozygous mice displayed a high incidence of apoptosis after initiation of mesoderm formation and died early in gestation. This indicates that the protein has a function in early post-implantation development (94). Although detailed characterisation is absent, it appears that mice are not a good model for Sotos syndrome.

4.6.3. NSD1 gene alteration in Sotos syndrome

Hemizygous deletions and heterozygous mutations of the NSD1 gene were discovered as the major cause of Sotos syndrome. Kurotaki et al (1) identified 20 submicroscopic deletions, 1 nonsense and 3 frameshift mutations in the NSD1 gene among 42 patients with Sotos syndrome. Subsequent reports showed NSD1 gene alteration in 67% - 90% of the patients clinically suspected of Sotos syndrome (27, 28, 32). It has to be noted that the study group with 90% mutations was the smallest and that patients in the various studies were selected in different ways. In European studies mostly intragenic mutations were identified, whereas in Japan mostly deletions were detected. The reason for this difference is unclear, but it has been suggested that a patient selection bias is more likely than a Japanese–specific genomic structure predisposing to a microdeletion at 5q35 (95). The distribution of the protein truncating mutations (frame shift, nonsense) is throughout the gene between exon 2 and 23 (1, 27, 28, 32, 95). Missense mutations were reported between exon 13 and 23. Splice site mutations have also been reported. No clear hot spots have been identified for the intragenic mutations in Sotos syndrome (96). Locations of the detected mutations reported until 1st March 2004 are shown in figure 4.

Reconsidering the clinical characteristics, Rio et al (28) suggested that the facial gestalt and macrocephaly were more important diagnostic criteria for Sotos syndrome (with NSD1 gene alterations) than overgrowth and advanced bone age. Other studies have focussed on clinical differences between patients with deletions and patients with mutations. Cardiovascular (12/21) and urogenital anomalies (7/13) were exclusively found in patients with deletions in one study (97), but it has to be noted that only 5 patients with a mutation were included in this study. In the French study (28) congenital heart defects were present in both patients with mutations and patients with deletions, but a higher percentage was seen in patients with deletions (2/16 vs 3/6). Again the number of patients was small. Mental retardation seemed

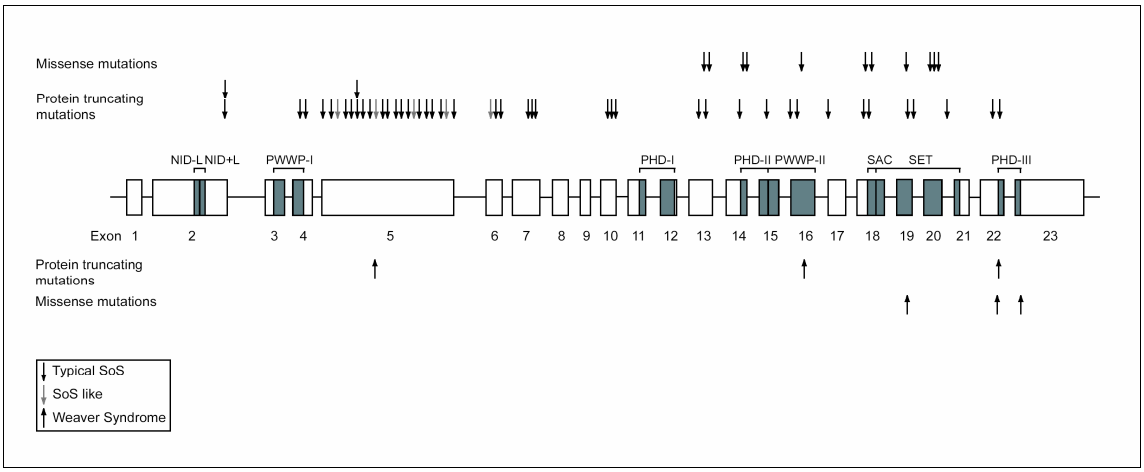

Figure 4 The NSD1 gene, adapted from Visser & Matsumoto, 2003. Shaded boxes represent the functional domains. Arrows above the gene show mutations reported until March 2004 in Sotos syndrome, arrows below the gene indicate mutations found in Weaver syndrome.

more extreme and overgrowth less in patients with deletions in two studies (27, 28). A more severe phenotype in patients with a NSD1 deletion is also suggested by the higher reported incidence of cardiac anomalies in Japanese Sotos patients with a NSD1 deletion (12/21) compared to those with a NSD1 mutation (0/5). This issue, however, needs further study.
In three studies the NSD1 gene was also analysed for patients with Weaver syndrome (n=7, n=6, n=5) (27, 28, 32). In two studies mutations of NSD1 were detected (both n=3) (27, 28). According to the authors, it is still possible that a separate Weaver gene exists, as mutations were not detected in all of them, whereas phenotypes were typical (27, 28).

4.6.4. familial Sotos syndrome

Although Sotos syndrome is mostly described in isolated cases, 15 families with evident characteristics of Sotos syndrome, have been reported in the literature (35, 49, 60, 61, 63, 83, 84, 98-103). In some studies (39, 104) the diagnosis of Sotos syndrome has been questioned by others (35, 105) and in one study the patients have been assigned to a new syndrome, Nevo syndrome (106). Almost always an autosomal dominant inheritance was seen. An exception is the study by Boman describing two brothers suggesting autosomal recessive inheritance. Monozygotic twins with Sotos syndrome have been described, of which one was discordant (38, 82, 102). Since the discovery of the NSD1 gene, one family has been described in which a father and son carried a frame shift mutation due to 1 base pair deletion in the NSD1 gene, resulting in a premature stop codon (103).

5. Outline of the thesis

The purpose of this thesis was to search for the aetiology of Sotos syndrome and describe the clinical and psychological characteristics of patients with Sotos syndrome. The clinical characteristics, including prenatal overgrowth in Sotos syndrome and the knowledge about the essential role of IGF-I in foetal and postnatal growth regulation, combined with the findings of growth retardation and a small head circumference in a patient with a homozygous deletion of the IGF-I gene opposite to the phenotype of Sotos patients (18), suggest that an elevated sensitivity to IGF-I could be part of the syndrome. This was supported by a recent report on a patient with three copies of the IGF-I receptor, resulting in increased responsiveness to IGF-I, who displayed overgrowth and a Sotos-like phenotype (19). Thus alterations in the IGF-I system either caused by increased production of IGFs (in utero), decreased secretion of IGFBPs or increased sensitivity to IGFs by a (post) IGF-I-receptor defect, could provide an explanation for the overgrowth in Sotos syndrome.

With a study group of patients suspected of having Sotos syndrome, we wished to answer the following three questions:

1) What is the cause of Sotos syndrome?
We approached this question by studying the following issues:

A) Can we detect translocations with cytogenetic studies, which could lead us to a candidate gene?
B) Are there endocrine alterations in IGFs or their regulating IGFBPs?
C) What is the responsiveness to IGFs in vitro using skin fibroblasts?

2) **What are the clinical characteristics, including data on height/final height, and are these correlated with genotype?**
3) **What are the psychological characteristics and are they correlated with genotype?**

These questions are addressed in the following chapters:

Chapter 2 After the discovery of the responsible gene for Sotos syndrome by a Japanese group, the NSD1 gene, we studied NSD1 gene alterations in 59 patients suspected of Sotos syndrome. The genotype-phenotype correlation and data on growth were studied. Furthermore the predictive value of the clinical scoring system described in chapter 3 for NSD1 gene alterations was evaluated.

Chapter 3 A clinical scoring system was designed for categorising the patients clinically suspected of Sotos syndrome. Circulating levels of members of the IGF family are described (IGFs, IGFBPs, ALS, IGFBP-3 protease activity).

Chapter 4 Endocrine and paracrine aspects of the IGF family were studied in patients clinically suspected of Sotos syndrome. A comparison was made between patients with NSD1 gene alterations and those without. We studied circulating levels of IGFs and IGFBPs. Furthermore we studied the mitogenic response to IGFs in skin fibroblasts and IGFBP-3 secretion, as well as IGFBP-3 mRNA expression.

Chapter 5 In this chapter auxological parameters were compared between patients with and without NSD1 gene alteration.

Chapter 6 Aspects of psychosocial, cognitive and motor functioning in patients clinically suspected of Sotos syndrome were studied. A comparison was made between patients with NSD1 gene alteration and those without.

Chapter 7 This chapter contains a general discussion of the experimental and clinical data collected in the preceding chapters.

References

1. Kurotaki N, Imaizumi K, Harada N, Masuno M, Kondoh T, Nagai T: Haploinsufficiency of NSD1 causes Sotos syndrome. Nature Genetics 2003; 30365-366.
2. Wit JM, Muinck Keizer-Schrama SM, Delamarre-van de Waal HA: Groeistoornissen. 1999.
3. Hill DJ, Petrik J, Arany E: Growth factors and the regulation of fetal growth. Diabetes Care 1998; 21 Suppl 2B60-B69.
4. Van den Brande JL, Monnens LAH: Kindergeneeskunde. 1993.
5. Karlberg J: A biologically-oriented mathematical model (ICP) for human growth. Acta Paediatr Scand Suppl 1989; 35070-94.
6. Sperling MA: Pediatric Endocrinology. 1996.
7. Fredriks AM, van Buuren S, Burgmeijer RJ, Meulmeester JF, Beuker RJ, Brugman E et al: Continuing positive secular growth change in The Netherlands 1955-1997. Pediatr Res 2000; 47(3):316-323.
8. Drop SL, De Waal WJ, De Muinck Keizer-Schrama SM: Sex steroid treatment of constitutionally tall stature. Endocr Rev 1998; 19(5):540-558.
9. Zhou Y, Xu BC, Maheshwari HG, He L, Reed M, Lozykowski M et al: A mammalian model for Laron syndrome produced by targeted disruption of the mouse growth hormone receptor/binding protein gene (the Laron mouse). Proc Natl Acad Sci U S A 25-11-1997; 94(24):13215-13220.
10. Jones JI, Clemmons DR: Insulin-like growth factors and their binding proteins: biological actions. Endocr Rev 1995; 16(1):3-34.
11. Hwa V, Oh Y, Rosenfeld RG: The insulin-like growth factor-binding protein (IGFBP) superfamily. Endocr Rev 1999; 20(6):761-787.
12. Green H, Morikawa M, Nixon T: A dual effector theory of growth-hormone action. Differentiation 1985; 29(3):195-198.
13. Isaksson OG, Jansson JO, Gause IA: Growth hormone stimulates longitudinal bone growth directly. Science 11-6-1982; 216(4551):1237-1239.
14. Sjogren K, Liu JL, Blad K, Skrtic S, Vidal O, Wallenius V et al: Liver-derived insulin-like growth factor I (IGF-I) is the principal source of IGF-I in blood but is not required for postnatal body growth in mice. Proc Natl Acad Sci U S A 8-6-1999; 96(12):7088-7092.
15. Le Roith D, Scavo L, Butler A: What is the role of circulating IGF-I? Trends Endocrinol Metab 2001; 12(2):48-52.
16. Yakar S, Rosen CJ, Beamer WG, Ackert-Bicknell CL, Wu Y, Liu JL et al: Circulating levels of IGF-1 directly regulate bone growth and density. Journal of Clinical Investigations 2002; 110(6):771-781.
17. Kiess W, Yang Y, Kessler U, Hoeflich A: Insulin-like growth factor II (IGF-II) and the IGF-II/mannose-6-phosphate receptor: the myth continues. Horm Res 1994; 41 Suppl 266-73.

18. Woods KA, Camacho-Hubner C, Savage MO, Clark AJ: Intrauterine growth retardation and postnatal growth failure associated with deletion of the insulin-like growth factor I gene. The New England Journal of Medicine 31-10-1996; 335(18):1363-1367.
19. Okubo Y, Siddle K, Firth H, O'Rahilly S, Wilson LC, Willatt L et al: Cell proliferation activities on skin fibroblasts from a short child with absence of one copy of the type 1 insulin-like growth factor receptor (IGF1R) gene and a tall child with three copies of the IGF1R gene. Journal of Clinical Endocrinology and Metabolism 2003; 88(12):5981-5988.
20. Abuzzahab MJ, Schneider A, Goddard A, Grigorescu F, Lautier C, Keller E et al: IGF-I receptor mutations resulting in intrauterine and postnatal growth retardation. N Engl J Med 4-12-2003; 349(23):2211-2222.
21. Rajaram S, Baylink DJ, Mohan S: Insulin-like growth factor-binding proteins in serum and other biological fluids: regulation and functions. Endocr Rev 1997; 18(6):801-831.
22. Schneider MR, Lahm H, Wu M, Hoeflich A, Wolf E: Transgenic mouse models for studying the functions of insulin-like growth factor-binding proteins. The FASEB Journal 2000; 14(5):629-640.
23. Bienvenu G, Seurin D, Grellier P, Froment P, Baudrimont M, Monget P et al: IGFBP-6 transgenic mice: post-natal growth, brain development and reproduction abnormalities. Endocrinology 28-1-2004.
24. Sotos JF: Overgrowth disorders. Clin Pediatr Phila 1996; 35(10):517-529.
25. Sotos JF: Genetic disorders associated with overgrowth. Clin Pediatr Phila 1997; 36(1):39-49.
26. Sotos JF: Overgrowth. Section VI. Genetic syndromes and other disorders associated with overgrowth. Clin Pediatr (Phila) 1997; 36(3):157-170.
27. Douglas J, Hanks S, Temple IK, Davies S, Murray A, Upadhyaya M et al: NSD1 mutations are the major cause of Sotos syndrome and occur in some cases of Weaver syndrome but are rare in other overgrowth phenotypes. American Journal of Human Genetics 2003; 72(1):132-143.
28. Rio M, Clech L, Amiel J, Faivre L, Lyonnet S, Le Merrer M et al: Spectrum of NSD1 mutations in Sotos and Weaver syndromes. J Med Genet 2003; 40(6):436-440.
29. Sotos JF, Dodge PR, Muirhead D, Crawford JD, Talbot NB: Cerebral gigantism in childhood. A syndrome of excessively rapid growth with acromegalic features and a nonprogressive neurologic disorder. The New England Journal of Medicine 1964; 2 71109-116.
30. Schlesinger B: Gigantism (acromegalic in type). Proc R Soc Med 1931; 241352-1353.
31. Cole TR, Hughes HE: Sotos syndrome: a study of the diagnostic criteria and natural history. J Med Genet 1994; 31(1):20-32.
32. Turkmen S, Gillessen-Kaesbach G, Meinecke P, Albrecht B, Neumann LM, Hesse V et al: Mutations in NSD1 are responsible for Sotos syndrome, but are not a frequent finding in other overgrowth phenotypes. European Journal of Human Genetics 2003; 11(11):858-865.

33. Visser R, Matsumoto N: Genetics of Sotos syndrome. Curr Opin Pediatr 2003; 15(6):598-606.
34. Wit JM, Beemer FA, Barth PG, Oorthuys JW, Dijkstra PF, Van den Brande JL et al: Cerebral gigantism (Sotos syndrome). Compiled data of 22 cases. Analysis of clinical features, growth and plasma somatomedin. Eur J Pediatr 1985; 144(2):131-140.
35. Cole TR, Hughes HE: Sotos syndrome. J Med Genet 1990; 27(9):571-576.
36. Karlberg J, Wit JM: Linear growth in Sotos syndrome. Acta Paediatr Scand 1991; 80(10):956-957.
37. Agwu JC, Shaw NJ, Kirk J, Chapman S, Ravine D, Cole TR: Growth in Sotos syndrome. Arch Dis Child 1999; 80(4):339-342.
38. Hook EB, Reynolds JW: Cerebral gigantism: endocrinological and clinical observations of six patients including a congenital giant, concordant monozygotic twins, and a child who acheived adult gigantic size. J Pediatr 1967; 70(6):900-914.
39. Halal F: Male to male transmission of cerebral gigantism. Am J Med Genet 1982; 12(4):411-419.
40. Allanson JE, Cole TR: Sotos syndrome: evolution of facial phenotype subjective and objective assessment. Am J Med Genet 2-10-1996; 65(1):13-20.
41. Bloom AS, Reese A, Hersh JH, Podruch PE, Weisskopf B, Dinno N: Cognition in cerebral gigantism: are the estimates of mental retardation too high? J Dev Behav Pediatr 1983; 4(4):250-252.
42. Rutter SC, Cole TR: Psychological characteristics of Sotos syndrome. Dev Med Child Neurol 1991; 33(10):898-902.
43. Cohen MM, Jr.: Mental deficiency, alterations in performance, and CNS abnormalities in overgrowth syndromes. Am J Med Genet 15-2-2003; 117C(1):49-56.
44. Finegan JK, Cole TR, Kingwell E, Smith ML, Smith M, Sitarenios G: Language and behavior in children with Sotos syndrome. J Am Acad Child Adolesc Psychiatry 1994; 33(9):1307-1315.
45. Sarimski K: Behavioural and emotional characteristics in children with Sotos syndrome and learning disabilities. Dev Med Child Neurol 2003; 45(3):172-178.
46. Aoki N, Oikawa A, Sakai T: Serial neuroimaging studies in Sotos syndrome (cerebral gigantism syndrome). Neurol Res 1998; 20(2):149-152.
47. Schaefer GB, Bodensteiner JB, Buehler BA, Lin A, Cole TR: The neuroimaging findings in Sotos syndrome. Am J Med Genet 11-2-1997; 68(4):462-465.
48. Noreau DR, Al Ata J, Jutras L, Teebi AS: Congenital heart defects in Sotos syndrome. Am J Med Genet 2-10-1998; 79(4):327-328.
49. Kaneko H, Tsukahara M, Tachibana H, Kurashige H, Kuwano A, Kajii T: Congenital heart defects in Sotos sequence. Am J Med Genet 1987; 26(3):569-576.

50. Tsukahara M, Murakami K, Iino H, Tateishi H, Fujita K, Uchida M: Congenital heart defects in Sotos syndrome. Am J Med Genet 21-5-1999; 84(2):172.
51. Sharma PP, Vidaillet H, Dietz J: Patient with Sotos syndrome, Wolff-Parkinson-White pattern on electrocardiogram, and two right-sided accessory bypass tracts. Am J Med Genet 1-2-2003; 116A(4):372-375.
52. Butler MG, Dijkstra PF, Meaney FJ, Gale DD: Metacarpophalangeal pattern profile analysis in Sotos syndrome: a follow-up report on 34 subjects. Am J Med Genet 1988; 29(1):143-147.
53. Butler MG, Meaney FJ, Kaler SG: Metacarpophalangeal pattern profile analysis in clinical genetics: an applied anthropometric method. Am J Phys Anthropol 1986; 70(2):195-201.
54. Crosher R: Advanced dental development in cerebral gigantism. Br Dent J 22-11-1986; 161(10):374.
55. Robertson SP, Bankier A: Sotos syndrome and cutis laxa. J Med Genet 1999; 36(1):51-56.
56. Adam KA, Salih Al Frayh AR, Sharma A, Ali TS: Cerebral gigantism with hydronephrosis: a case report. Clin Genet 1986; 29(2):178-180.
57. Eijgenraam FJ, Donckerwolcke RA, Wit JM: Normal growth, despite renal failure, in a child with Sotos syndrome [letter]. Eur J Pediatr 1995; 154(2):167-168.
58. Hammadeh MY, Dutta SN, Cornaby AJ, Morgan RJ: Congenital urological anomalies in Sotos syndrome. Br J Urol 1995; 76(1):133-135.
59. Hooft C, Schotte H, Van Hooren G: [Familial cerebral gigantism]. Acta Paediatr Belg 1968; 22(3):173-186.
60. Smith A, Farrar JR, Silink M, Judzewitsch R: Investigations in dominant Sotos syndrome. Ann Genet 1981; 24(4):226-228.
61. Boman H, Nilsson D: Sotos syndrome in two brothers. Clin Genet 1980; 18(6):421-427.
62. Yeh H, Price RL, Lonsdale D: Cerebral gigantism (Sotos' syndrome) and cataracts. J Pediatr Ophthalmol Strabismus 1978; 15(4):231-232.
63. Koenekoop RK, Rosenbaum KN, Traboulsi EI: Ocular findings in a family with Sotos syndrome (cerebral gigantism). Am J Ophthalmol 1995; 119(5):657-658.
64. Ferrier PE, de Meuron G, Korol S, Hauser H: Cerebral gigantism (Sotos syndrome) with juvenile macular degeneration. Helv Paediatr Acta 1980; 35(1):97-102.
65. Yen MT, Gedde SJ, Flynn JT: Unilateral glaucoma in sotos syndrome (cerebral gigantism). Am J Ophthalmol 2000; 130(6):851-853.
66. Hersh JH, Cole TR, Bloom AS, Bertolone SJ, Hughes HE: Risk of malignancy in Sotos syndrome. J Pediatr 1992; 120(4 Pt 1):572-574.
67. Corsello G, Giuffre M, Carcione A, Cuzto ML, Piccione M, Ziino O: Lymphoproliferative disorders in Sotos syndrome: observation of two cases. Am J Med Genet 6-9-1996; 64(4):588-593.

68. Cole T, Allanson J: Reply to "lymphoproliferative disorders in Sotos syndrome: observation in two cases". Am J Med Genet 13-1-1998; 75(2):226-227.
69. Cohen MM, Jr.: Tumors and nontumors in Sotos syndrome. Am J Med Genet 21-5-1999; 84(2):173-175.
70. Varley CK, Crnic K: Emotional, behavioral, and cognitive status of children with cerebral gigantism. J Dev Behav Pediatr 1984; 5(3):132-134.
71. Mauceri L, Sorge G, Baieli S, Rizzo R, Pavone L, Coleman M: Aggressive behavior in patients with Sotos syndrome. Pediatric Neurology 2000; 2264-67.
72. Livingood AB, Borengasser MA: Cerebral gigantism in infancy: implications for psychological and social development. Child Psychiatry Hum Dev 1981; 12(1):46-53.
73. Morrow JD, Whitman BY, Accardo PJ: Autistic disorder in Sotos syndrome: a case report. Eur J Pediatr 1990; 149(8):567-569.
74. Tantam D, Evered C, Hersov L: Asperger's syndrome and ligamentous laxity. J Am Acad Child Adolesc Psychiatry 1990; 29(6):892-896.
75. Trad PV, Schlefer E, Hertzig M, Kernberg PF: Treatment strategies for a case of concurrent pervasive developmental disorder and cerebral gigantism. J Am Acad Child Adolesc Psychiatry 1991; 30(3):499-506.
76. Sotos JF, Romshe CA, Cutler EA: Cerebral gigantism and primary hypothyroidism: pleiotropy or incidental concurrence. Am J Med Genet 1978; 2(2):201-205.
77. Hulse JA: Two children with cerebral gigantism and congenital primary hypothyroidism. Dev Med Child Neurol 1981; 23(2):242-246.
78. Bejar RL, Smith GF, Park S, Spellacy WN, Wolfson SL, Nyhan WL: Cerebral gigantism: concentrations of amino acids in plasma and muscle. J Pediatr 1970; 76(1):105-111.
79. Saenger P, Levine LS, Wiedemann E, Schwartz E, New MI: Letter: Somatomedin in cerebral gigantism. J Pediatr 1976; 88(1):155-156.
80. Sakano T, Yoshimitsu T, Tanabe A, Tanaka T, Kobayashi Y, Usui T et al: Cerebral gigantism: a report of two cases with elevated serum somatomedin A levels and a review of the Japanese literature. Hiroshima J Med Sci 1977; 26(4):311-319.
81. Mace JW, Gotlin RW: Cerebral gigantism. Triad of findings helpful in diagnosis. Clin Pediatr 1970; 9(11):662-667.
82. Lecornu M, Fonlupt J, Jezequel C, Coutel Y: [Cerebral gigantism in twins]. Arch Fr Pediatr 1976; 33(3):277-285.
83. Goumy P, Malpuech G, Gannat M, Menut G: [Familial cerebral gigantism. A new case with autosomal dominant transmission?]. Pediatrie 1979; 34(3):249-256.
84. Hansen FJ, Friis B: Familial occurrence of cerebral gigantism, Sotos' syndrome. Acta Paediatr Scand 1976; 65(3):387-389.
85. DuCaju MVL, Van den Brande JL: Plasma somatomedin levels in growth disturbance. Acta Paediatr Scand 1973; 6296.

86. Lecornu M: [The serum level of sulfatation factor (somatomedine) in growth retardations, cerebral gigantism and acromegaly]. Arch Fr Pediatr 1973; 30(6):595-608.
87. Ambler GR, Cowell CT, Quigley CA, Silink M: Growth hormone hypersecretion in Sotos' syndrome? Acta Paediatr 1993; 82(2):214-216.
88. Ranke MB, Bierich JR: Cerebral gigantism of hypothalamic origin. Eur J Pediatr 1983; 140(2):109-111.
89. Kjellman B: Cerebral gigantism. Acta Paediatr Scand 1965; 54(6):603-609.
90. Imaizumi K, Kimura J, Matsuo M, Kurosawa K, Masuno M, Niikawa N et al: Sotos syndrome associated with a de novo balanced reciprocal translocation t(5;8)(q35;q24.1). Am J Med Genet 1-1-2002; 107(1):58-60.
91. Schrander-Stumpel CT, Fryns JP, Hamers GG: Sotos syndrome and de novo balanced autosomal translocation (t(3;6)(p21;p21)) [see comments]. Clin Genet 1990; 37(3):226-229.
92. Kurotaki N, Harada N, Yoshiura K, Sugano S, Niikawa N, Matsumoto N: Molecular characterization of NSD1, a human homologue of the mouse Nsd1 gene. Gene 28-11-2001; 279(2):197-204.
93. Jaju RJ, Fidler C, Haas OA, Strickson AJ, Watkins F, Clark K et al: A novel gene, NSD1, is fused to NUP98 in the t(5;11)(q35;p15.5) in de novo childhood acute myeloid leukemia. Blood 15-8-2001; 98(4):1264-1267.
94. Rayasam GV, Wendling O, Angrand PO, Mark M, Niederreither K, Song L et al: NSD1 is essential for early post-implantation development and has a catalytically active SET domain. The EMBO Journal 16-6-2003; 22(12):3153-3163.
95. Kurotaki N, Harada N, Shimokawa O, Miyake N, Kawame H, Uetake K et al: Fifty microdeletions among 112 cases of Sotos syndrome: Low copy repeats possibly mediate the common deletion. Hum Mutat 2003; 22(5):378-387.
96. Kamimura J, Endo Y, Kurotaki N, Kinoshita A, Miyake N, Shimokawa O et al: Identification of eight novel NSD1 mutations in Sotos syndrome. J Med Genet 2003; 40(11):e126.
97. Nagai T, Matsumoto N, Kurotaki N, Harada N, Niikawa N, Ogata T et al: Sotos syndrome and haploinsufficiency of NSD1: clinical features of intragenic mutations and submicroscopic deletions. J Med Genet 2003; 40(4):285-289.
98. Zonana J, Sotos JF, Romshe CA, Fisher DA, Elders MJ, Rimoin DL: Dominant inheritance of cerebral gigantism. J Pediatr 1977; 91(2):251-256.
99. Winship IM: Sotos syndrome--autosomal dominant inheritance substantiated. Clin Genet 1985; 28(3):243-246.
100. Bale AE, Drum MA, Parry DM, Mulvihill JJ: Familial Sotos syndrome (cerebral gigantism): craniofacial and psychological characteristics. Am J Med Genet 1985; 20(4):613-624.
101. Lippert MM: Malignancy in Sotos syndrome [letter; comment]. J Pediatr 1993; 122(2):328.

102. Brown WT, Wisniewski KE, Sudhalter V, Keogh M, Tsiouris J, Miezejeski C et al: Identical twins discordant for Sotos syndrome. Am J Med Genet 2-10-1998; 79(4):329-333.
103. Hoglund P, Kurotaki N, Kytola S, Miyake N, Somer M, Matsumoto N: Familial Sotos syndrome is caused by a novel 1 bp deletion of the NSD1 gene. J Med Genet 2003; 40(1):51-54.
104. Townes PL, Scheiner AP: Cerebral Gigantism (Sotos' syndrome): Evidence for recessive inheritance. Pediatr Res 1973; 7349.
105. Opitz JM, Weaver DW, Reynolds JF, Jr.: The syndromes of Sotos and Weaver: reports and review. Am J Med Genet 2-10-1998; 79(4):294-304.
106. Nevo S, Zeltzer M, Benderly A, Levy J: Evidence for autosomal recessive inheritance in cerebral gigantism. J Med Genet 1974; 11(2):158-165.