# Characteristics of Sotos syndrome

Boer, L. de

# CHAPTER 7

# GENERAL DISCUSSION

# Discussion

In this chapter, the following questions, formulated in the introduction, will be answered and the answers will be discussed.
What is the cause of Sotos syndrome? Is the IGF system involved? Furthermore what are the clinical and psychological characteristics and are these correlated with the genotype?

## 1. Aetiology of Sotos syndrome

The genetic cause of Sotos syndrome was elucidated in 2002 (14). A child with Sotos syndrome and the following translocation: 46, XX,t(5;8)(q35;q24.1) was reported (11). The gene disrupted by the 5q35 breakpoint was identified as NSD1. Subsequently, 42 Japanese individuals with Sotos syndrome were screened for deletions and mutations of this gene and 24 gene alterations were found (57% of the cases). The detected gene alterations consisted of 83% hemizygous deletions and 17% heterozygous mutations of the NSD1 gene. Haploinsufficiency of NSD1 was indicated as the major cause of Sotos syndrome. Since this report several European studies were published in which a percentage of 67-90% of NSD1 gene alterations was found among patients with typical Sotos syndrome (5, 20, 23). In the majority of these cases, mutations were detected instead of gene deletions.

In our own study only one patient with atypical Sotos showed a 46, XY,t(5,15)(q35;22) translocation (chapter 3). FISH analysis did not show a deletion of the NSD1 gene. Unfortunately he did not give consent for further research and mutation analysis was not performed.
After the publication of Kurotaki et al (14), we investigated NSD1 gene alteration in a group of 59 patients clinically suspected of Sotos syndrome (chapter 2). We found 19 different heterozygous mutations in 23 patients (including two families) in 1 copy of the NSD1 gene and 4 deletions of 1 copy. The highest percentage of gene alterations was detected in a selected group of patients with typical Sotos syndrome (81%). This was in agreement with other studies (5, 20), although categorisation of the patients was not exactly identical in the different studies. It is not yet clear what the cause is of the typical phenotype in cases without a detected NSD1 gene alteration ($NSD1^{+/+}$ 19% in our study), and what the aetiology is in the patients with less typical features without NSD1 gene alteration. With the techniques used, not all NSD1 gene mutations will be detected (i.e. splicing variants due to deletions or mutations in introns or mutations in the promoter region of NSD1). Future research should focus on other techniques (e.g. MLPA, multiple ligation dependent probe amplification) to detect NSD1 gene alterations. Probably, besides NSD1, many other genes are involved in overgrowth and clinical characteristics of Sotos syndrome. Other related genes will have to be discovered. It has recently been shown that 3

copies of an IGF1-R causes a Sotos-like phenotype (see below), which makes the IGF1-receptor gene a candidate gene for further analysis.
In Japanese patients gene deletions accounted for the majority of the phenotypes whereas in European patients intragenic mutations were the major cause. Several explanations for this have been proposed. First it was expected that with screening more patients, more deletions would be been found (5). As more reports indicated that intragenic mutations accounted for most of the cases in European countries, this view was not sustainable. A specific Japanese genomic structure or sample selection bias is a possibility (15). Up till now no specific hotspots for mutations have been identified. Nonsense, frame shift and splicing mutations are distrubuted over the whole gene, while missense mutations were preferentially located between exon 13 and 23.

The function of NSD1 is not yet fully understood. The protein has two nuclear receptor (NR) interaction domains and can act both as a NR corepressor or coactivator. It can interact in presence or absence of ligands with the retinoic acid receptor, thyroid hormone receptor and estrogen receptor (10). These nuclear receptors play an important role in growth regulation. The thyroid hormone receptor and retinoic acid receptor also seem important in intra-uterine growth regulation. It has been postulated that NSD1 acts as a corepressor of growth promoting genes leading to overgrowth in Sotos syndrome (14). From the results shown in this thesis it can be postulated that NSD1 either directly or indirectly influences the IGF system (chapter 4). Clinically it at least leads to overgrowth, increased arm span for height, increased hand length and typical facial characteristics (chapter 2 and 5).

## 2. Involvement of the IGF system in Sotos syndrome

Reports about IGF-I and IGF-IR gene alterations in animals and man have contributed to our hypothesis that overactivation of IGF plays a role in overgrowth in patients with Sotos syndrome. In transgenic mice overexpressing IGF-I, prenatal overgrowth was seen and small birth sizes were found in knockout mice for IGF-I, IGF-II and IGF-IR (12). In humans, a patient with total deficiency of IGF-I, caused by a homozygous partial deletion of the IGF-I gene, was described (24) with 'opposite' features of Sotos syndrome. This patient showed prenatal growth retardation, microcephaly, a low hairline and micrognathia. A recent report (18) described a patient with prenatal overgrowth and Sotos-like features with 3 copies of the IGF-IR gene and a patient with prenatal and postnatal growth retardation and 1 copy of the IGF-IR.

To study a possible relationship between the IGF system and Sotos syndrome we investigated plasma levels of IGFs, IGFBPs, ALS and IGFBP-3 protease activity (chapter 3, 4). In addition we used skin fibroblasts to study local IGF/IGFBP system activity (chapter 4). We found modest endocrine as well as paracrine differences in the IGF system between $NSD1^{+/-}$ patients and controls or $NSD1^{+/+}$ patients pointing to a

relationship between NSD1$^{+/-}$ and the IGF system. However the changes did not point to the hypothesized overactivation of IGF-I. In comparison with reference values NSD1$^{+/-}$ patients showed decreased levels of the IGFs in plasma, decreased levels of IGFBP-3 and IGFBP-4 and increased levels of IGFBP-2 and 6, two inhibitors of IGF action. In skin fibroblasts a lower basal proliferation activity was detected with a lower response to IGFs in comparison with controls.

With these IGF characteristics one would expect patients with short stature, rather than tall stature. It could be speculated that high IGFs and/or low inhibiting IGFBPs circulate only in the period of the highest growth velocity. The highest growth velocity in the patients with Sotos syndrome is prenatally and in the first year after birth, but plasma values in our study have only been measured in patients 2.1 years and older. Another explanation is that steady-state IGF plasma levels do not reflect the bioavailability at the target tissue level. In part, bioavailability of IGFs depends on IGFBPs and its proteases (12) and the actual tissue of interest concerning growth is the growth plate. By our studies (chapter 4) it is shown that NSD1 gene alteration is associated with changes in the IGF system. It is possible that these changes reflect local changes at the growth plate favouring overgrowth. On the other hand these changes could also be part of a negative feed back loop inhibiting the overgrowth induced by NSD1 gene alterations. As discussed in chapter 4 this is not sustained by the finding of a lower proliferation rate measured by [methyl-$^{3}$H] thymidine in the skin fibroblasts.

Mean IGFBP-6 plasma levels showed the highest difference compared to reference values (+1.5 SDS) in NSD1$^{+/-}$ patients. It is known that this IGFBP binds to IGF-II with a higher affinity than to IGF-I and acts as an IGF inhibitor (19). Together with IGFBP-2 it is the main IGFBP in cerebrospinal fluid, produced in the central nervous system. It could be speculated that these findings relate to cerebral overgrowth or developmental delay. However no difference was found in developmental delay between NSD1$^{+/+}$ and NSD1$^{+/-}$ and the difference in head circumference did not reach significance.
It is possible that NSD1 expression influences IGFBP-6 expression through interaction with retinoic acid and its receptor. The IGFBP-6 promoter contains retinoic acid response elements and an animal study showed that IGFBP-6 transcription in skeletal cells was stimulated by retinoic acid (4, 7).

## 3. Clinical characteristics in Sotos syndrome

Overgrowth, one of the main characteristics of Sotos syndrome, was more extreme in NSD1$^{+/-}$ patients compared to NSD1$^{+/+}$ patients as calculated by repeated measures analysis (chapter 2). No study has compared height data between NSD1$^{+/-}$ and

$NSD1^{+/+}$, but a French study (20) reported that overgrowth was not a consistent finding in $NSD1^{+/-}$ patients, whereas others did find overgrowth in the majority of the $NSD1^{+/-}$ patients (16, 23).

Firstly birth size parameters are discussed. For birth length of $NSD1^{+/-}$ patients, we found a mean value of 1.4 SDS in 13 patients (chapter 5) and in a larger group of 23 patients 1.9 SDS (chapter 2), which is significantly elevated compared to the reference, but not in comparison with $NSD1^{+/+}$ patients (0.8 SDS in 15 patients and 1.0 SDS in 25 patients). This was also found for head circumference, $NSD1^{+/-}$ 1.2 SDS in 13 patients and 1.5 SDS in 17 versus 1.0 SDS (n=15) and 1.2 SDS (n=24) in $NSD1^{+/+}$ patients. Mean birth weight in $NSD1^{+/-}$ patients was not significantly different from the reference population nor from the $NSD1^{+/+}$ patients. In one other study (16) birth size parameters were reported. In this study no significant difference was reported between patients with mutations and with deletions. No information was provided about the difference between $NSD1^{+/-}$ and $NSD1^{+/+}$.
Correction for target height, not described in other studies has been shown useful (chapter 5) to discriminate between $NSD1^{+/+}$ and $NSD1^{+/-}$. The difference between the two subgroups was larger with this correction ($NSD1^{+/-}$ 1.8 SDS vs. $NSD1^{+/+}$ 0.9 SDS, p=0.06), than without this correction (1.9 SDS vs. 1.4 SDS, p=0.40). This indicated that familial or genetic tall stature contributed to overgrowth in the $NSD1^{+/+}$ group.

One of the objectives of our study was to evaluate final height in patients with Sotos syndrome. In the literature final height of 11 patients with the clinical diagnosis of Sotos syndrome was reported in the normal range (1). In our study, final height was reached in nine patients with NSD1 gene alterations (chapter 2). The mean value was 0.9 SDS, which did not point to an extremely tall final height in agreement with the literature. There is no indication that many patients need treatment, because treatment is usually considered if height estimation is above 2 to 2.5 SDS.

No significant differences were found for mean sitting height/ height ratio between both subgroups. In both the ratio was decreased (chapter 5). Other auxology measures showed higher arm span after correction for height and hand length in the $NSD1^{+/-}$ group. Foot length showed a trend towards higher measures in $NSD1^{+/-}$ patients (2.1 SDS vs. 0.7 SDS. p=0.06).
Repeated measures analysis showed that head circumference SDS in $NSD1^{+/-}$ patients tended to be higher than in $NSD1^{+/+}$ patients, but this did not reach significance (p=0.06) (chapter 3). Mean head circumferences in adults were 2.8 ($NSD1^{+/-}$, n=7) and 2.6 ($NSD1^{+/+}$, n=7).

Bone age SDS as calculated by the Greulich & Pyle method was advanced in the NSD1$^{+/-}$ group (mean of all available X-rays: 2.7 SDS, chapter 2), but was not discriminating between the two subgroups.
Of six regularly described facial characteristics in Sotos syndrome, four showed a very high discriminating value: frontal bossing, high hairline, downslant palpebrals and pointed chin, whereas two others dolichocephaly and high arched palate were not significantly different between the two subgroups (chapter 2). Facial gestalt correlated well with the genotype, which was in agreement with other studies (5, 20).

In 1994 Cole et al suggested four major criteria for Sotos syndrome: facial gestalt, growth pattern, bone age and developmental delay (3), which have been used as a guidance in many studies. In order to objectivate the importance of the different criteria, a clinical score was introduced (chapter 3). This score reflected the decision making of a panel of clinical geneticists to categorise patients as typical, dubious or atypical Sotos syndrome. After discovery of the NSD1 gene we evaluated this score for its predictive value for NSD1 gene alterations. The total score had a high predictive value ($p< 0.001$). The subscores for developmental delay and advanced bone age were consistent findings in the preselected group, but not discriminating between patients with and without NSD1 gene alteration. The subscore for growth tended to be higher, but the difference did not reach significance ($p=0.07$). The subscores head circumference and facial characteristics discriminated between the two subgroups, with the highest predictability for the last one (chapter 2).

In order to describe the variables with the highest predictive value an adjusted score was calculated by logistic regression analysis. This resulted in the following score: total score= 2x (frontal bossing) + 1x (downslant palpebrals) + 1x (pointed chin) + 0.5x (growth score). Frontal bossing was found to be the most important characteristic. The marks in the growth score can be 0, 0.5 or 1. The total score ranges from 0 till 5. The calculated optimal cut-off limit was $\geq 3.5$, with this value the positive likelihood ratio was 3.16 (chapter 3). Although this score will need to be tested in new groups of patients, it can be used to assist selecting patients for mutation or deletion analysis.In this study the new score was used to describe the most important discriminating parameters between NSD1 mutations and deletions and a normal NSD1 gene in a preselected group of patients clinically suspected of Sotos syndrome.
From our familial cases we have learned that there is a milder phenotype without developmental delay or decreased cognitive function. These patients came under medical attention because their children showed Sotos syndrome. It also seems that with ageing the phenotype becomes milder. Consequences for these patients themselves may be small, but it could have consequences for their children, who could show a more pronounced phenotype.

In chapter 2 the incidence of clinical problems is reported. Incidence of feeding problems in the first year was higher in the $NSD1^{+/-}$ group (86%) compared to the $NSD1^{+/+}$ group (35%). Other studies have not compared the two subgroups, but in one study a lower incidence was reported of 6 out of 22 $NSD1^{+/-}$ patients having had feeding difficulties. The estimation of incidence of cardiac anomalies in Sotos syndrome has been high (8%), especially in Japanese reports (35%-50%), in comparison with the incidence in the general population (0.6-1%) (13, 17, 22). Comparison between patients with a deletion and a mutation in the NSD1 gene pointed in one study to a higher incidence in the group with deletions (16) and in one study (20) no difference was detected. A comparison between $NSD1^{+/-}$ and $NSD1^{+/+}$ was not yet made. Although a small number of patients were known with cardiac anomalies in our study (n=5), the incidence was higher in $NSD1^{+/-}$ than in $NSD1^{+/+}$ patients (21% vs. 0%).

Problems as neonatal jaundice, hypotonia, strabismus, febrile convulsions, scoliosis, pes planus and otitis occurred in the $NSD1^{+/-}$ patients, but the incidence did not differ from $NSD1^{+/+}$ patients. No cases of epilepsy were known in the $NSD1^{+/-}$ group. Brain anomalies on CT or MRI were found in both groups ($NSD1^{+/-}$ 63%, $NSD1^{+/+}$ 47%). We did not have complete clinical information of all patients.

Casuistic description of family members of Sotos patients showing a higher incidence of abortions have led some authors to conclude that infertility is associated with Sotos syndrome (2, 9, 21). In our study (chapter 2), a mother with characteristics of Sotos syndrome and a NSD1 mutation, gave birth to two children with Sotos syndrome, after IVF. This indeed points to a possible relationship between Sotos syndrome and infertility. The reason for this is unknown. Experimental data in NSD1 knock out mice suggest that homozygous deletion of NSD1 is embryonic lethal with time point of death early in gestation

Sotos syndrome has been associated with a higher incidence of malignancies (8). As discussed before in the introduction the numbers could be biased. Diverse tumours of various tissue origin have been described. In our study of 59 patients with Sotos syndrome, no patients were known to have a malignancy.

## 4. Psychological characteristics

The incidence of developmental delay in terms of delayed motor or speech milestones or mental retardation (IQ score < 70) (chapter 2 and 6) was not significantly different in both subgroups. This is in agreement with a French study (20). In that and another study (16) a tendency towards more severe mental retardation in patients with deletions was described. We did not find this in our study, but one has to realise that the number of patients with a deletion in our study was very small (n=4, chapter 2).

Cognitive functioning in 7 $NSD1^{+/-}$ patients was assessed by IQ tests in our study. A mean IQ was 70 (chapter 6). Results for 4 more patients were collected in a larger study (chapter 2) and for these 11 patients together mean IQ was 75 (range 47-107). In this thesis for the first time IQ data have been related to NSD1 gene alterations. No significant differences were found in comparison with $NSD1^{+/+}$ patients (mean IQ 78, range 48-105, n=17). Both groups showed a wide range of IQ scores.

As described in chapter 6 we found in $NSD1^{+/-}$ patients a wide range of behaviour problems, problems in adaptive behaviour and decreased health related quality of life as reported by the parents on several scales. The scales were related to motor functioning, communication, social functioning, cognitive functioning and autonomy. Most of these problems were also reported in $NSD1^{+/+}$ patients. Differences between the two subgroups pointed into the same direction of less severe problems in the $NSD1^{+/-}$ group. Less $NSD1^{+/-}$ patients scored in the clinical range for behaviour problems as assessed with the CBCL, less scored in the clinical range for ADHD and their temperament was classified as easier. Significantly more patients of the $NSD1^{+/+}$ group lived in an institution. No other studies have reported on psychological characteristics in relation to NSD1 gene alterations. Although we have to be careful with drawing conclusions from these small groups, the tendency towards less severe problems in $NSD1^{+/-}$ patients is noteworthy. It is of interest that ADHD has been related to clinical Sotos syndrome in earlier reports(6), but this could not be confirmed in our study for $NSD1^{+/-}$ patients.

## 5. Concluding remarks and future research

For the patients clinically suspected of Sotos syndrome it can be concluded from this thesis that $NSD1^{+/-}$ patients compared to $NSD1^{+/+}$ patients show more typical facial characteristics (frontal bossing, high hairline, downslant palpebrals, pointed chin), more extreme overgrowth, a higher arm span for height, a more increased hand length and a higher incidence of feeding problems and cardiac anomalies. In vitro they show lower circulating levels of IGFs, IGFBP-3 and –4, higher circulating levels of IGFBP-2 and –6, a decreased response to IGFs and higher IGFBP-3 mRNA expression in skin fibroblasts. Psychologically they tend to have less severe problems in behaviour, ADHD and temperament.

Future research could focus on the patients with clinical characteristics of Sotos syndrome, but without detected mutations or deletions. It is possible that the NSD1 gene is involved, but that with the techniques used, the aberrations were not detected. With other techniques (e.g. MLPA) this could be explored. Another possibility is that another gene alteration causes their phenotype. The fact that this group can be clinically and endocrine/paracrine discriminated from the $NSD1^{+/-}$ group favours this possibility. Duplication of the IGF-IR gene leading to three copies has been described in one patient with Sotos like clinical characteristics. We have recently discovered this in a $NSD1^{+/+}$ patient with clinical characteristics of Sotos syndrome.

Genes related to NSD1 could be of interest for further exploration of NSD1 function. In chapter 4 it is suggested that IGFBP-6, which is elevated in plasma of NSD1$^{+/-}$ patients, relates to NSD1. Studying IGFBP-6 expression in different tissues (e.g. growth plate) in humans could indicate if a relation to overgrowth is likely. With techniques as micro-array, differences in gene expression between the two subgroups could lead to other genes involved. Possibly genes could be identified explaining the mechanism by which NSD1 gene alteration induces overgrowth. Of special interest would be IGF and IGFBP gene expression.

One could question if there is reason for follow up or screening with regard to the clinical problems mentioned. Paediatric care will be needed in cases of neonatal jaundice, feeding problems and hypotonia. This could also include referral to physiotherapists, speech therapists or psychologists. Paediatric follow up is probably also useful for growth monitoring and overgrowth related problems as scoliosis and pes planus. A cardiac ultrasound after the detection of a NSD1 gene alteration should be considered. The reported malignancies in the literature are various in kind and methods to detect them vary. Therefore doctors should be aware of the possible elevated risk, but screening does not seem indicated.

In conclusion, with the identification of the NSD1 gene, an important cause of Sotos syn drome and overgrowth has become accessible to research. The results of the IGF and IGFBP characteristics in patients with Sotos syndrome show that more research will be needed to elucidate the chain of signals in which haploinsufficiency of NSD1 causes overgrowth.

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