Universiteit
Leiden
The Netherlands

Characteristics of Sotos syndrome

Boer, L. de

Citation
Boer, L. de. (2005, April 28). *Characteristics of Sotos syndrome*. Retrieved from https://hdl.handle.net/1887/4565

Version:	Corrected Publisher's Version
License:	Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden
Downloaded from:	https://hdl.handle.net/1887/4565

Note: To cite this publication please use the final published version (if applicable).

Summary

Summary

Sotos syndrome or cerebral gigantism was first described in 1964 by Professor Sotos. He described five children with overgrowth, mental retardation, delayed motor milestones and the following facial characteristics: frontal bossing, pointed chin and downslant palpebral fissures. Many case reports with similar patients have been published since then. In 2002 it was discovered that heterozygous mutations or deletions in the NSD1 gene were the major cause of Sotos syndrome. The NSD1 gene is located on chromosome 5.

Chapter 1 is the general introduction in which an overview is given of different aspects of growth and overgrowth followed by a review of the literature about clinical characteristics and the etiology of Sotos syndrome. The aims and outline of this thesis are described. It was hypothesized that elevated sensitivity to IGF plays a role in Sotos syndrome, since IGFs are important intra-uterine growth factors and intra-uterine overgrowth is one of the characteristics of Sotos syndrome. The aim was to study patients with clinical characteristics of Sotos syndrome, search for the aetiology, and describe the clinical and psychological characteristics in relation to the genotype. The following questions were formulated:

- Can chromosomal translocations be detected with cytogenetic studies, which could lead us to a candidate gene?
- Are there endocrine changes in the IGF-IGFBP system?
- What is the responsiveness to IGFs at the paracrine level, using skin fibroblasts?
- What are the clinical characteristics, including data on height/final height, and are these correlated with the genotype?
- What are the psychological characteristics and are they correlated with the genotype?

In chapter 2 genotype-phenotype correlation was described in 59 patients. For these patients deletion and/or mutation screening of the NSD1 gene was performed. In the subgroup of patients with typical Sotos syndrome 81% were carriers of a deletion or mutation in the NSD1 gene. In the dubious and atypical groups these percentages were 38% and 0%, respectively. The best predictive parameters for a NSD1 alteration were frontal bossing, down-slanted palpebral fissures, pointed chin and overgrowth. Higher incidences of feeding problems and cardiac anomalies were found. Delayed development and advanced bone age did not differ between the patients with or without a NSD1 gene alteration.

Chapter 3 describes plasma IGF and IGFBP values in patients with clinical characteristics of Sotos syndrome. ALS and IGFBP-3 proteolysis were also measured. The aim was to investigate whether altered levels in the IGF-IGFBP system are related

to Sotos syndrome. Thirty-two patients were categorised into three groups (typical, dubious and atypical Sotos syndrome) with a clinical scoring system. The patients in the typical Sotos syndrome group showed significantly lower levels of IGF-II, instead of higher as might be expected. IGFBP-3 and IGFBP-4 levels were lower than control values for age and sex. IGFBP-3 proteolysis was higher than in controls. The possible explanation of these differences and whether these plasma values reflect tissue activity is discussed.

Chapter 4 describes IGF-IGFBP system characteristics at endocrine and paracrine level related to mutations in the NSD1 gene. Twenty-nine patients with clinical characteristics of Sotos syndrome were divided into a group of patients with heterozygous deletions or mutations in the NSD1 gene (n=11) and patients without (n=18). Plasma IGF and IGFBP values were measured and in skin fibroblasts the mitogenic response to IGFs was determined, as well as IGFBP-3 secretion and expression. The patients with NSD1 gene alterations showed significantly lower values of IGF-I, IGF-II and IGFBP-4 and significantly higher values of IGFBP-2 and IGFBP-6 compared with the reference population and the patients without NSD1 gene alterations. Both patient groups showed low IGFBP-3 levels. The mitogenic response to IGFs was diminished in skin fibroblasts of patients with a NSD1 gene alteration compared to controls and patients without NSD1 gene mutations. IGFBP-3 mRNA expression was elevated. It was concluded that endocrine and paracrine alterations in the IGF-IGFBP system were found in patients with NSD1 gene aberrations. How these findings, a diminished instead of higher sensitivity towards IGFs, could be related to overgrowth are discussed. The relation between the NSD1 gene and the IGF system is not yet clear, and possible explanations for the unexpected findings are discussed.

In chapter 5 auxology parameters are compared between patients clinically suspected of Sotos syndrome with NSD1 gene alterations (n=13) and patients without (n=19). The statistical performance of these parameters to predict NSD1 gene mutation was assessed. Arm span for height and hand length were significantly higher in the patients with NSD1 gene mutations or deletions.

In chapter 6 psychosocial, cognitive and motor functioning in patients clinically suspected of Sotos syndrome were studied and compared between patient with (n=12) and without a NSD1 gene alteration (n=17). Intelligence, behaviour problems, ADHD symptoms, temperament, adaptive behaviour, health-related quality of life and motor functioning were assessed. Mean IQ in the whole group was 76, and there was no difference between the two subgroups. High rates of behaviour problems were found and patients lagged 1.6-2.6 years behind in adaptive behaviour. Health related quality of life reported by parents was decreased on various scales, e.g. motor functioning and communication. Compared to a control group of mentally handicapped children motor functioning was better. The patients with NSD1 gene mutations showed an easier temperament and less severe behaviour problems compared with the patients without

NSD1 gene alteration. Less patients with NSD1 gene alterations scored in the clinical range for ADHD and behaviour problems.

Chapter 7 contains the conclusions and general discussion of the thesis. Patients clinically suspected of Sotos syndrome with NSD1 gene alterations show more typical facial characteristics, more extreme overgrowth, a higher arm span for height, a more increased hand length and a higher incidence of feeding problems and cardiac anomalies compared to patients without NSD1 alterations. In vitro they show different endocrine and paracrine characteristics of the IGF-IGFBP-system. Psychosocially they tend to have less severe behaviour problems. Suggestions for future research are also provided in this chapter.