Characteristics of Sotos syndrome

Boer, L. de

CHAPTER 6

Psychosocial, cognitive and motor functioning in patients suspected of Sotos syndrome. A comparison between patients with NSD1 gene alterations and patients without.

L. de Boer[1], I. Röder[2], J.M. Wit[1].

[1]Department of Paediatrics, Leiden University Medical Center, Leiden, the Netherlands
[2]Department of Psychology, Leiden University, Leiden, the Netherlands.

Submitted for publication

Abstract

The aim of this study was to investigate psychosocial, cognitive and motor functioning in patients clinically suspected of Sotos syndrome and to examine differences between patients with NSD1 deletions or mutations (NSD1+/-) (the major cause of the syndrome), and those without (NSD1+/+). Twenty-nine subjects clinically suspected of Sotos syndrome (mean age 11.8 years, range 1.8-48.4) were divided into a NSD1+/- group (n=12) and a NSD1 +/+ group (n=17). With an extensive test battery, intelligence, behaviour problems, ADHD symptoms, temperament, adaptive behaviour, health related quality of life and motor functioning were assessed. Scores were compared to control groups and scores of the two subgroups where compared with each other. Mean IQ in the whole group was 76 (range 47-105). High rates of behaviour problems were found and patients lagged 1.6 to 2.6 years behind in various aspects of adaptive behaviour. Health related quality of life reported by the parents was decreased on various scales, e.g. on the scales 'motor functioning' and 'communication'. Compared to a control group of mentally handicapped patients, motor functioning was better. NSD1+/- in comparison with NSD1+/+ patients showed easier temperament, and less NSD1+/- patients scored in the clinical range for 'total behaviour problems' (27% vs. 77%), 'internalising behaviour' (18% vs. 65%) and ADHD (0 vs. 27%).

Key words: Sotos syndrome, Cerebral Gigantism, NSD1, Behaviour problems, Social problems

Introduction

Sotos syndrome (cerebral gigantism,OMIM117550) was first described in 1964 (1). The syndrome is characterized by the following features: 1) facial characteristics, which include: frontal bossing, high hairline, dolichocephaly, prominent chin, high arched palate and antimongoloid slant of palpebral fissures; 2) overgrowth: large size at birth, rapid growth in the first four years and tall stature in childhood; 3) advanced bone age; 4) macrocephaly; 5) developmental delay. Recently, in a Japanese study heterozygous deletions were detected as the major cause of this syndrome, 77% of the cases showed NSD1 haploinsufficiency (2). In European studies inactivating mutations of the NSD1 gene were found in a majority of the cases (3-5).

Various studies have looked into psychological characteristics of children with Sotos syndrome. In these studies intelligence levels varied, ranging from 21 to 103 (6-9). Mental retardation, defined as an IQ lower than 70, was not found as common as initially thought (10). An early report, based on a study of six children found 83% mental retardation (11). However, following studies reported lower percentages, 10 %

in a study of 10 children (6) and 22% in a study of 27 children (9). Delayed speech, learning problems secondary to intellectual deficits (6) and impaired reading skills (7) have been reported. High rates of behaviour problems have been described, such as withdrawal, social problems, stereotypic behaviour and temper tantrums. However, the rates of behaviour problems of 27 patients were not higher than those observed in a comparison group of tall, dysmorphic children (9). Attention deficit hyperactivity disorder (ADHD) was reported in 38% of the patients in one study (9). Other problems mentioned by parents were eating and sleeping difficulties. Case reports have mentioned symptoms of autistic disorder (12) and tendency towards aggressiveness (13).

Up till now, no study has reported on psychological characteristics of the specific group of patients with NSD1 gene alterations. Moreover, only isolated aspects of behaviour in children with Sotos syndrome have been studied. Most studies included small samples (less than 16 patients). An exception is Finegan's study (9), in which language, behaviour problems and ADHD in twenty-seven children with Sotos syndrome were studied. However in that study no data were collected on other important aspects of a child's functioning, such as motor functioning, temperament, adaptive behaviour and health related quality of life (HRQoL).

The aim of our study was to describe a more complete spectrum of behavioural and personality variables in patients clinically suspected of Sotos syndrome, not only for children, but also for adolescents and adults. Furthermore, we wanted to investigate whether there are differences between the patients with detected mutations and deletions of the NSD1 gene (NSD1+/-) and those without gene alterations (NSD1+/+). The question was how the psychosocial, cognitive and motor functioning of these patients could be characterized. With questionnaires, behaviour problems, temperament, symptoms of ADHD, adaptive behaviour, parents' perception of the child's HRQoL and motor functioning were measured. In addition, intelligence levels were assessed.

Methods

Subjects

Individuals suspected of Sotos syndrome were recruited through the Parent support group in the Netherlands, clinical geneticists and paediatric endocrinologists. Clinical suspicion of Sotos syndrome was confirmed in 29 patients by clinical geneticists and a paediatric endocrinologist. Blood samples of these patients were screened for deletions and mutations in the NSD1 gene by Fluorescence In Situ Hybridisation (FISH) and sequencing analysis (de Boer, Kant et al, submitted). Patients were divided in a NSD1+/- group (n=12) and a NSD1+/+ group (n=17). In table 1 characteristics of both groups are shown.

Table 1. Characteristics, IQ scores and percentages of subjects in the clinical range for behaviour problems of patients clinically suspected of Sotos syndrome

	$NSD1^{+/-}$ n=12	$NSD1^{+/+}$ n=17	p-value
Male gender % (n)	67 (8)	77 (13)	0.57
Mean age (range)	11.4 (2.1-33)	12.0 (1.8-48)	0.90
Special education % (n)	50 (6)	82 (14)	0.18
Too young for school % (n)	8 (1)	6 (1)	
Living in institution % (n)	0	35 (6)	0.03
Level education parents % (n)*			0.23
Low	33 (8)	41 (14)	
Average	42 (10)	19 (10)	
High	13 (3)	6 (2)	
missing	13 (3)	24 (8)	
IQ score, mean (±SEM)			
Total	70 (±5.6)	79 (±4.5)	0.26
Verbal IQ score	74 (±5.6)	80 (±3.8)	0.36
Performal IQ score	72 (±5.1)	80 (±5.2)	0.31
Missing data % (n)	42 (5)	18 (3)	
IQ score < 70, % (n/total n)	43 (3/7)	21 (3/14)	0.32
CBCL Clinical range, % (n/total n)			
Total problems	27 (3/11)	77 (13/17)	0.01
Internalising behaviour	18 (2/11)	65 (11/17)	0.02
Externalising behaviour	27 (3/11)	53 (9/17)	0.19
ADHD Clinical range, % (n/total n)			
Total score	0 (0/9)	27 (4/15)	0.03
Attention deficit	11 (1/9)	31 (5/16)	0.18
Hyperactivity	0 (0/11)	33 (5/15)	0.02
Impulsiveness	0 (0/11)	31 (5/15)	0.03

*low= elementary school , average= high school , high= college education/university
$NSD1^{+/-}$ = NSD1 gene mutation or deletion
$NSD1^{+/+}$ = no NSD1 gene aberrations

Instruments

Intelligence

Dutch adaptations of the Wechsler Preschool and Primary Scale Intelligence-Revised (WPPSI-R) (14), Wechsler Intelligence Scale for Children-Revised (WISC-R) (15) and the Wechsler Adult Intelligence Scale (WAIS) (16) were used to assess Total, Verbal and Performance IQ scores. Twenty-one participants could be tested, eight were too young (n=2) or not cooperative (n=6). Two of these patients had been tested before, they lagged behind 7 months (at age 24 months) and 26 months (at age 4 years) in cognitive functioning according to the BOS 2-30 (Dutch version of the Bayley Scales of Infant Development). According to the medical records, the other patients 'lagged behind' in development, but this was not measured by a test instrument.

Behaviour problems

Rates of behaviour problems were established using a parent report checklist, the Child Behaviour Checklist (CBCL) and Young Adult Behaviour Checklist (YABCL) (17, 18). Dutch versions of the CBCL for children 2-3 years (99 items), CBCL for children 4-18 years (118 items) (19) and of the YABCL for adults 18-30 years (113 items) were used. Parents were asked to score each item on a three point Likert scale, with regard to the child's behaviour within the last 6 months and for the 2-3 years old within the last 2 months.

A Total Problem score in CBCL 4-18 is comprised of syndrome scales that cluster as an Internalising and an Externalising scale. The Internalising syndrome scales are named: 'Withdrawn', 'Somatic complaints' and 'Anxious/Depressed'. The Externalising scales are named 'Delinquent behaviour' and 'Aggressive behaviour'. The other syndrome scales are: 'Attention problems', 'Social problems', 'Thought problems', and 'Sex problems'. These last four scales are not assessed for children 2 to 3 years old, an extra scale at this age is 'Sleep problems'. Scores on the Total Problems scale, Internalising or Externalising scales are classified within the clinical range if the T score is > 63 (CBCL 2-3 and the YABCL > 64). For individual syndrome scales a T score > 70 is classified in the clinical range.

The Dutch norm group for the 4-18 year-olds was composed of 1300 children. For the other age groups the American normative data were used. The adjusted mean reference score is 50.

ADHD

Symptoms of ADHD were assessed with an 18 item Dutch list (20). A five point Likert scale is used to indicate how frequent the behaviour occurs. A Total score and scores for three subscales 'Attention-deficit', 'Hyperactivity' and 'Impulsiveness' can be calculated. A total score of > 48 is in the clinical range for ADHD. Normative data were available for a sample of 320 children with behaviour problems in treatment centres, aged 4-18 years.

Temperament

Temperament was assessed with a Dutch questionnaire (21) (22)derived from the American “Parent and Teacher Questionnaire for children 3-7 years of age" (23). It was adjusted for institutionalised mentally handicapped people aged 10-55 years of age. The 56-items (5 point scale) relate to ‘Approach’, ‘Adaptability’, ‘Intensity’, ‘Threshold of responsiveness’, ‘Mood’, ‘Persistence’, and ‘Soothability’. A combination score indicating ‘easy or difficult temperament’ can be calculated. A low score for ‘Intensity’ in combination with high scores for ‘Soothability’, ‘Mood’ and ‘Adaptability’ result in ‘easy temperament’. The opposite scores result in ‘difficult temperament’. Control data were available for 1020 mentally handicapped people of 33 institutions in The Netherlands. The majority of these people showed IQ scores below 50. Because the intelligence level was not corresponding with mean values in our study, no comparisons were made with the control data, the questionnaire was only used to compare the NSD1+/- with the NSD1+/+ group.

Adaptive behaviour

Adaptive behaviour was measured with the Vineland screener (24). One of the parents or caretakers was interviewed. The Dutch translated questionnaire consisted of 45 items indicating 3 domains of adaptive behaviour: 1) ‘Communication’ (verbal expression and comprehension), 2) ‘Daily Living Skills’ (self-care) and 3) ‘Social competence’. For each scale, an age score in years can be calculated. Normative data consisted of a sample of 536 children in the U.S. The calculated ages were compared to chronological ages.

Health related Quality of Life

Parents’ perception of the child’s HRQoL was measured with a 43-item questionnaire for children aged 1-5 years, named TAPQOL (TNO-AZL Preschool Children Quality of Life) (25). For children aged 6-15 years a 63-item list, named TACQOL, (TNO-AZL Child Quality of Life) (26, 27) was used. The TAPQOL consists of 12 scales: ‘Sleeping’, ‘Appetite’, ‘Lungs’, ‘Stomach’, ‘Skin’, ‘Motor functioning’, ‘Social functioning’, ‘Aggressive/Problem behaviour’, ‘Communication’, ‘Anxiety’, ‘Positive mood’ and ‘Liveliness’. Frequency of a specific symptom/problem or limitation during the last 3 months was reported. Moreover, whenever a problem was reported, the parent filled in how much the child was emotionally affected by it on a 4 point Likert scale. Scales were transformed in a 0 -100 scale, with higher scores indicating a better health-related quality of life. Normative data were derived of a general Dutch population sample of 362 children between aged 1-5 years. The TACQOL consists of 7 scales: ‘General physical functioning’, ‘Motor functioning’, ‘Autonomy’, ‘Cognitive functioning’, ‘Social functioning’, ‘positive moods’ and ‘negative moods’. Scale scores vary between 0 and 32 , except for Occurrence of Positive or Negative moods, which vary between 0 and 16. A high score indicates a higher HRQoL. Normative data were derived of a sample of 1318 healthy children aged between 6-15. Parents of children

visiting Centres for Preventive Youth Health Care were asked to fill out the questionnaire.

Motor skills

Gross motor skills, needed in daily life were assessed using a Dutch 22-item list (28) in a yes/no format, questioning about motor skills like sitting, walking, cycling and swimming. Control data were available from 4538 mentally handicapped people of 3 years and over. Data of children aged 3-7 years were collected at day care centres and for 7-18 years at schools for special education.

Procedure

The study was conducted with the prior consent of the Medical Ethical Committee of the Leiden University Medical Center. Clinical geneticists, paediatric endocrinologists and the parent support group in The Netherlands received a letter requesting them to send an invitation to all families with a member diagnosed as having Sotos syndrome. If they agreed to participate, the parents were asked to mail a reply-card to us. They were contacted by telephone to make an appointment. Questionnaires were sent to parents or caretakers and were filled in at home. Informed consent was obtained from all subjects and/or their parents included in the study. During a two-hour visit, IQs of the patients were tested and parents were interviewed about the child's adaptive behaviour, using the Vineland screener. For practical reasons two subjects were tested in the institution they lived and eight parents were interviewed by telephone. Students in clinical psychology, supervised by registered psychologists, performed the interviews and tests.

Data analysis

Data were analysed with SPSS for Windows version 10.0. Mean values of the study group were compared to those of the control groups as mentioned above for each questionnaire. Variables were compared between the two subgroups using the Student's t-test or the chi-square test, whatever was appropriate. Correlations were calculated to assess relationships between IQ scores and questionnaire outcomes. A p-value of < 0.05 was considered significant.

Results

In table 2 the numbers of subjects tested and the instruments used are listed. Whenever the 'whole group' is mentioned in the text below, NSD1+/- and NSD1+/+ groups together are meant.

Table 2. Instruments used and the numbers of patients tested.

Assessment	Instrument	Control population for instrument	n of individuals tested (n with $NSD1^{+/-}$)
Intelligence	WPPSI-R, WISC-R, WAIS (Wechsler)		21 (7)
Behaviour	CBCL (Koot), YABCL (Achenbach)	Normal controls (n=1300)	28 (11)
ADHD-symptoms	Scholte (AVL)	Children with behaviour problems in treatment centres (n=320)	27 (11)
Motor skills	Kraijer (SMZ)	Patients with mental handicap (n=4538)	26 (10)
Temperament	Blok (TVZ)	Patients with mental handicap in institutions (n=1020), data not used	26 (10)
Health related quality of life	TAPQOL, TACQOL (TNO-AZL)	Normal controls (n=362 and n=1318)	28 (11)
Adaptive behaviour	Vineland screener (Sparrow)	Normal controls (n=536)	21 (9)

$NSD1^{+/-}$ = NSD1 gene mutation or deletion

Intelligence

Levels of intelligence measured in the whole group, ranged from a total IQ score of 47 to 105 (n=21). Mean total IQ was 76 (SD=16), verbal IQ 79 (SD=14) and performance IQ 77 (SD=18). No significant difference was found between males and females and no correlation was found for IQ with age. No significant differences in IQ scores and percentages of mental retardation (IQ< 70) were detected between NSD1+/- and NSD1+/+ patients (see table 1).

Behaviour problems

For all ages (CBCL 2-3, 4-18 and YABCL 18-30) significantly more patients of the NSD1+/+ group than the NSD1+/- group scored in the clinical range for 'Total problems' and 'Internalising behaviour' (see table 1).

CBCL 2-3 years. The form was completed for four subjects (NSD1+/- n=3, NSD1 +/+ n=1). None scored in the clinical range for 'Total problems', ' Externalising behaviour problems' or for the syndrome scales. One subject scored in the clinical range for 'Internalising behaviour problems' (NSD1+/- patient).

CBCL 4-18 years. In the whole group (n=19) the mean score for 'Total problems' and Internalising and Externalising scales were significantly higher (total: M=69, t[18]=10.86, p< .001, Internalising: M = 64.47, t[18]=5.35, p< .001, Externalising: M =

62.74, t[18]=4.79, p< .001) than the mean score for normative data (M=50). Mean values of all syndrome scales, except 'Sexual problems' were also significantly elevated. Between the NSD1+/- and the NSD+/+ group no significant differences were detected. Mean T-scores for both groups are depicted in a bar chart (Figure 1). No difference was found for percentages of patients scoring in the clinical range for one of the syndrome scales.

YABCL 18-30 years. The form was completed for five subjects aged 18 years or more (NSD1+/- n=3, NSD1 +/+ n=2). Two subjects scored in the clinical range for 'Total problems' (both NSD1+/+). No subject scored in the clinical range for 'Internalising behaviour', 'Externalising behaviour' or for one of the syndrome scales.

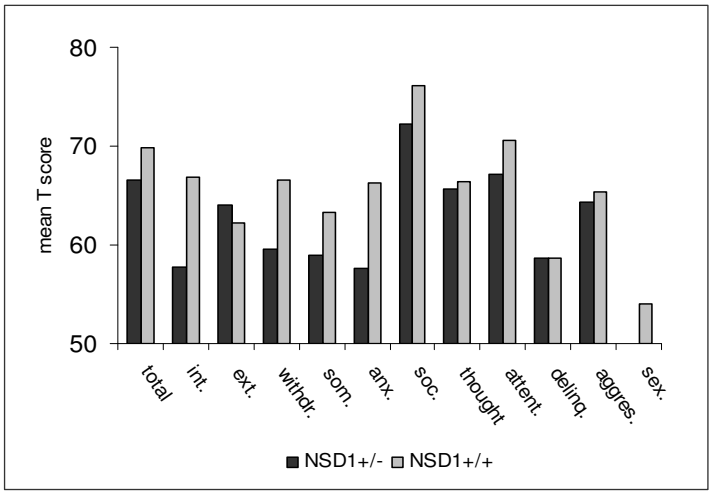

Figure 1. CBCL 4-18 years. Mean syndrome scale scores for $NSD1^{+/-}$ patients (n=5) and $NSD1^{+/+}$ patients (n=14). No significant differences were found between the two groups. Scales were (left to right): total problems, internalising behaviour, externalising behaviour, withdrawn, somatic complaints, anxiety/depressed, social problems, thought problems, attention problems, delinquent behaviour, aggressive behaviour, sexual problems. The groups together (n=19) compared to the reference score (T=50) showed significantly higher scores on all syndrome scales except sexual problems.

ADHD

Mean scores for ADHD in ages 4-18 years (n=20) of the whole group were not significantly different from the control group. When percentages of scoring in the clinical range were compared between the two subgroups, significantly less NSD1+/- patients scored in the clinical range for the 'Total score' and subscores 'Hyperactivity' and 'Impulsiveness' (see table 1). When mean scores were compared between the two groups 'Hyperactivity' in patients 4-12 years was significantly lower in the NSD1+/- group (t[14]=-2.2, p= .046).

Temperament

Mean values of all scales for NSD1+/- and NSD1+/+ patients were compared. Significant differences consisted of higher scores in the NSD1+/- group for 'Easy-difficult temperament' (easier temperament)($t[24]=2.5$, $p= .022$), 'Soothability' (easier to soothe, distract)($t[24] =2.3$, $p= .032$) and 'Mood' (better mood)($t[24]= 2.3$, $p= .028$).

Adaptive behaviour

Mean chronological age for participants (n=21) was 9.5 years. Mean age calculated with the Vineland screener for 'Communication' was 7.7 years, for 'Daily living skills' 7.1 years and for 'Social competence' 6.8 years. Mean age differences between chronological and developmental ages were 1.6 years, 1.6 years and 2.6 years respectively. All individual calculated ages are shown in scatter plots (Figure 2). No significant differences were found between the NSD1+/- group and the NSD1+/+ group. In the NSD1+/- group, a negative correlation was found between chronological age and developmental age for 'Communication' and 'Daily living skills' ($r = - .8$, $p = .01$ and $r = - .9$, $p = .008$), which means that the older subjects showed larger discrepancies between chronological and developmental age than the younger subjects.

Health related Quality of Life

TAPQOL. Compared with the normative data, lower scores of parents' perception of the child's HRQoL (NSD1+/- and NSD1+/+) were observed on the scales: 'Motor functioning' ($t[295]=10.8$, $p< .001$), 'Communication' ($t[292]=6.4$, $p< .001$), 'Liveliness' ($t[345]=3.4$, $p= .001$) and 'Social functioning' ($t[299]=2.1$, $p= .03$). No differences were found between the NSD1+/- group and the NSD1+/+ group.

TACQOL. Data were collected of questionnaires filled in for all ages above 6 years (n=18). In comparison with the normative data, lower scores on parents' perception of the HRQoL in children (NSD1+/- and NSD1+/+), were found for all scales except 'Physical complaints' (Table 3). Higher health related quality of life for 'Social functioning' was found in the NSD1+/- group in comparison with the NSD1+/+ group ($t[16]= 2.5$, $p= .025$).

Motor skills

Mean scores for gross motor function were significantly higher in the whole group (3-7 years) than in controls 3-7 years old ($t[6]=3.3$, $p= .016$). For subjects aged 7-18 years old only females showed higher mean scores meaning better gross motor skills ($t[4]=2.9$, $p= .046$). No differences were found between NSD1+/- and NSD1+/+.

Table 3 Mean (SD) scores for TACQOL scales for the control group, $NSD1^{+/-}$ and $NSD1^{+/+}$ together and separately.

TACQOL-scale	Control group (n=1318)	$NSD1^{+/-}$ and $NSD1^{+/+}$ (n=18)	$NSD1^{+/-}$ (n=5)	$NSD1^{+/+}$ (n=13)
score range 0-32				
Physical complaints	27.6 (3.7)	25.3 (4.8)	25.0 (4.5)	25.5 (5.1)
Motor functioning	31.0 (2.3)	26.6 (4.9)**	28.4 (3.9)	26.0 (5.2)**
Autonomy	31.4 (1.6)	28.0 (4.4)**	29.9 (4.1)	27.3 (4.4)**
Cognitive functioning	29.2 (3.7)	21.9 (4.3)**	22.3 (3.6)*	21.8 (4.7)**
Social functioning	30.0 (2.3)	25.5 (4.3)**	29.0 (2.0)	24.1 (4.2)**
score range 0-16				
Positive emotions	15.0 (1.8)	12.8 (2.3)**	13.8 (2.2)	12.5 (2.4)**
Negative emotions	11.7 (2.3)	9.7 (2.4)**	9.8 (2.4)	9.6 (2.5)**

* $p<0.05$, ** $p<0.01$ compared to control group.
$NSD1^{+/-}$ = NSD1 gene mutation or deletion
$NSD1^{+/+}$ = no NSD1 gene aberrations

Relationship between IQ and the studied parameters

Significant correlations were detected between IQ and scales in the CBCL and temperament questionnaire. IQ was positively related with the 'Total problems' scale (r= .5, p= .03) and Internalising behaviour' scale (r= .5, p= .04), suggesting parents of children with higher IQ reported more behaviour problems. In addition, correlations between the 'Total problems' scale and other parameters were studied. The 'Total problems' scale was inversely related with the delay in years concerning 'Social competence' (r=- .6, p= .003). The 'Total problems' scale was positively correlated with difficult temperament and ADHD total score. IQ was also positively correlated with 'Threshold of responsiveness' (r= .5, p= .048), a subscale of the temperament scale.

Discussion

Our question was how the psychosocial, cognitive and motor functioning of patients clinically suspected of Sotos syndrome could be characterized. And secondly, we wanted to investigate whether differences could be found between NSD1+/- and NSD1+/+ patients. In short, a number of problems on all fields, except on motor functioning (compared to mentally handicapped people), were found for the whole group. Differences were found between NSD1+/- and NSD1+/+ patients, all pointing into a direction of less severe problems in the NSD1+/- group.

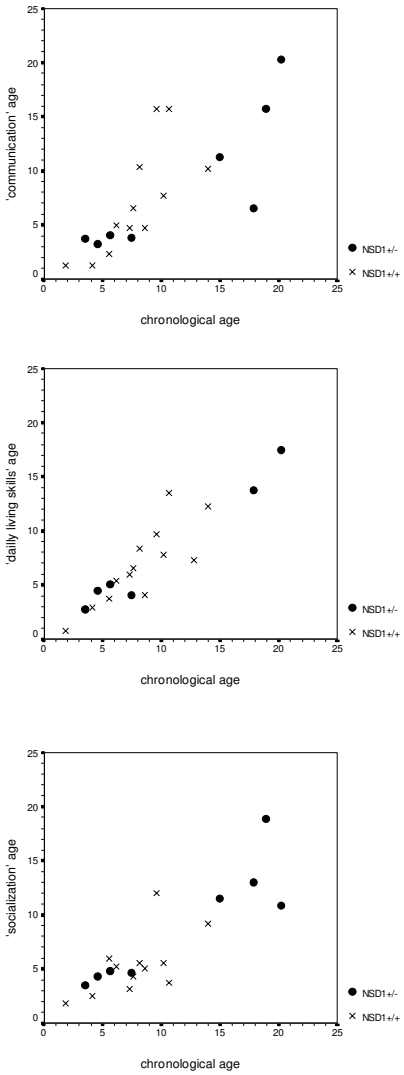

Figure 2 Scatter plots of chronological age as a function of 'communication age', 'daily living skills age' and 'social competence age' according to the Vineland screener. No significant differences were found in age differences between patients with and patients without NSD1 gene deletions or mutations.

The whole group can be described as a group with a mean IQ of 76 and high rates of behaviour problems, especially social and attention problems. Delay in adaptive behaviour concerned all three scales 'Communication', 'Daily living skills' and 'Social competence'. Parents' perception of the child's HRQoL at all ages was low with regard to motor and social functioning. Additionally, in their children aged 1-5 years, it was also low with regard to communication and liveliness and in their children aged 6-15 years it was also low with regard to cognitive and independent daily functioning. Regarding gross motor skills, they performed better than a control group of mentally handicapped children.

NSD1+/- patients differed from NSD1+/+ patients. Less of them scored in the clinical range for behaviour problems on the scales 'Total problems' and 'Internalising behaviour' according to the CBCL and less scored in the clinical range for ADHD. Concerning their temperament, they showed an easier temperament with better mood and higher soothability. Parents' perception of the child's Health related quality of life at age 6-15 regarding social functioning was higher.

Our study of the whole group of patients suspected of Sotos syndrome replicates other studies on certain aspects of behaviour and personality characteristics in Sotos syndrome. Data of IQ scores and behaviour problems will be discussed here. The IQ scores found in our study were comparable to those found in the study of Finegan et al. (9), in which a mean IQ score of 74 was described with 22% of the patients showing an IQ < 70. Mean IQ score in our study was 76, with 29% showing an IQ < 70. Only taking the NSD1+/- patients into account, a higher percentage of mental retardation was found of 43%. However, it has to be noted that 5 of the 12 NSD1+/- patients could not be tested with the intelligence tests because they were too young or not cooperative.

The CBCL4-18 was used in patients with Sotos syndrome in two other studies (8, 9), in which also high rates of problem behaviour were found. In one study (9), mean scores for 'Social problems' and 'Attention problems' were highest, similarly to the results in our study (see Figure 1). A same pattern was seen for both NSD1+/- and NSD1+/+, but NSD1+/- patients scored less in the clinical range for 'total problems' and 'internalising behaviour' on the Child Behaviour Checklist. In contrast with Finegan et al (9), we found a positive correlation between IQ and 'Total problems' score. For patients with a higher IQ, more behaviour problems were reported. An explanation for this could be that higher IQ in these patients was not combined with better adaptive skills in terms of social competence. Social competence was inversely correlated with behaviour problems. Another possibility is that these patients, especially with moderate developmental delay, could raise higher expectations from their environment because they are taller and therefore are taken to be older (10).

In agreement with comments in a recent study (29), we did not find that ADHD was a consistent problem in Sotos syndrome. Although the whole group scored high on CBCL subscale 'Attention problems', percentages of people scoring in the clinical range for ADHD were lower (17%) in our study than reported before (38%) (9). All patients scoring in the clinical range, did not have a NSD1 mutation or deletion.

Two aspects of adaptive behaviour, also investigated in our study, 'Daily living skills' and 'Social competence', have been studied in patients with Sotos syndrome (n=27) (29). In comparison with a control group of 29 children with intellectual disabilities, they scored slightly, but not significantly higher. We did not find differences between NSD1+/- and NSD1+/+. For the whole group the delay was highest for social competence. The delay in years ranging from 1.6 to 2.6 years for the various fields of adaptive behaviour could not be attributed to IQ alone, because no correlation was found between delay and IQ.

Two questionnaires used in this study were specifically designed for mentally handicapped children and adults. Thus, only control data of these groups were available. One of these is a temperament questionnaire. In previous studies, aspects of temperament as tantrums and impulse control impairment were reported as a problem of patients with Sotos syndrome (7), but this was based on single items of a questionnaire or parent interview. Assuming that temper tantrums are associated with high intensity, low soothability and a high sensitivity towards stimuli, we did not find this pattern for the NSD1+/- patients. Comparing NSD1+/- with NSD1+/+, results indicated easier temperament with higher soothability in the NSD1+/- group.
The other questionnaire measured motor skills. HRQoL related to motor functioning was a major concern of the parents in comparison with parents of healthy individuals. It is known that gross motor functioning is impaired in patients with Sotos syndrome (30), but gross motor functioning was scored better in comparison with mentally handicapped children and adults of the same age, with no difference between NSD1+/- and NSD1+/+.

Because not only the problems and limitations of the patients determine their psychological functioning, but also their emotional evaluation concerning these problems, we also studied HRQoL. The questionnaires used (TAPQOL and TACQOL) have the problem of being measured "by proxy". A child form of this list exists, but part of the group lacked the vocabulatory and reading skills for completing this list themselves. Parents were explicitly asked to assess their child's feelings with regard to functional problems and not their own feelings. Decreased HRQoL reported by the parents did not concern anxiety, problem behaviour/aggressiveness or physical functioning regarding, eating, sleeping, lung or skin problems. However at all ages HRQOL concerning motor functioning, communication/cognitive functioning, social functioning and autonomy were decreased.

When discussing these data, it has to be taken into account that the age range of our study group is wide, the number of patients in the subgroups small and multiple comparisons were made. This forces us to be cautious with conclusions. Because the various questionnaires use different control data, the results cannot be pulled together for the whole group. But strikingly, when comparing NSD1+/- with NSD1+/+ for various questionnaires, the differences point into the same direction of less severe problems in the NSD1+/- group.

In contrast to the NSD1+/- group, the NSD1+/+ group is a heterogeneous group. It possibly consists of patients with other growth disorders, caused by other gene alterations, or (less likely) having a NSD1 mutation not detected with our techniques. More problems were found in this group especially regarding behaviour problems and ADHD symptoms and more patients of this group were living in institutions.

In conclusion, patients clinically suspected of Sotos syndrome are at risk for a range of behaviour problems and limitations in social competence, communication, and daily living skills. NSD1+/- patients compared to NSD1+/+ patients showed less severe behaviour problems, easier temperament and ADHD was not a consistent finding in these patients.

Acknowledgements

We would like to thank the patients and their parents for participating in the study; Mrs. M van Leeuwen as a coordinator of the Parent Support Group, the paediatricians and clinical geneticists for contacting the patients; Saskia le Cessie for statistical advice, Saskia Lamers for the Vineland screener interviews, Lieselotte van der Meer for IQ testing and Joke Monne for help with ADHD and SMZ analysis. We gratefully acknowledge STINAFO (‘Dutch fund for disabled children’) and LUMC for their financial support.

References

1. 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; 271109-116.
2. Kurotaki N, Imaizumi K, Harada N, Masuno M, Kondoh T, Nagai T: Haploinsufficiency of NSD1 causes Sotos syndrome. Nature Genetics 2003; 30365-366.
3. 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.
4. 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.
5. 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.
6. 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.
7. Rutter SC, Cole TR: Psychological characteristics of Sotos syndrome. Dev Med Child Neurol 1991; 33(10):898-902.
8. Varley CK, Crnic K: Emotional, behavioral, and cognitive status of children with cerebral gigantism. J Dev Behav Pediatr 1984; 5(3):132-134.
9. 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.
10. Mouridsen SE, Hansen MB: Neuropsychiatric aspects of Sotos syndrome. A review and two case illustrations. European Child & Adolescent Psychiatry 2002; 11(1):43-48.
11. Sotos JF, Cutler EA, Dodre P: Cerebral gigantism. American Journal of Diseases in Childhood 1977; 131(6):625-627.
12. Morrow JD, Whitman BY, Accardo PJ: Autistic disorder in Sotos syndrome: a case report. Eur J Pediatr 1990; 149(8):567-569.
13. Mauceri L, Sorge G, Baieli S, Rizzo R, Pavone L, Coleman M: Aggressive behavior in patients with Sotos syndrome. Pediatric Neurology 2000; 2264-67.
14. Wechsler D: Dutch adaptation (1995) of the Wechsler Preschool and Primary Scale of Intelligence-Revised. 1989. New York, psychological corporation.
15. Wechsler D: Dutch adaptation (1986) of the Wechsler Intelligence Scale for Children-Revised. 1974. New York, psychological corporation.

16. Stinissen J, Willems PJ, Coetsier P, Hulsman WLL: Dutch adaptation of the Wechsler Adult Intelligence Scale, D. Wechsler (1955). 1970. Lisse, Swets & Zeitlinger.
17. Achenbach TM, Edelbrock C: Manual for the Child Behavior Checklist and Revised Child Behavior Profile. 1983. Burlington, Vermont, University of Vermont, Department of Psychiatry.
18. Achenbach TM, Edelbrock C, Howell CT: Empirically based assessment of the behavioral/emotional problems of 2- and 3- year-old children. J Abnorm Child Psychol 1987; 15(4):629-650.
19. Verhulst FC, Koot JM, Akkerhuis GW, Veerman JW: Praktische Handleiding voor de CBCL. 1990. Assen/Maastricht, van Gorcum.
20. Scholte EM, Ploeg JDvd: ADHD vragenlijst. AVL handleiding. 1998. Lisse, Swets & Zeitlinger.
21. Blok JB: Temperament bij zwakzinnigen; constructie van een meetinstrument. 1989. Lisse, Swets & Zeitlinger.
22. Blok JB, Berg van den P.T., Feij JA: Temperamentschaal voor Zwakzinnigen. 1990. Lisse, Swets & Zeitlinger.
23. Thomas A, Chess S: Temperament and development. 1977. New York, Brunner/Mazel.
24. Sparrow SS, Carter AS, Cicchetti DV: Vineland screener. 1994. Circle Pines, Minnesota, American Guidance Service.
25. Fekkes M, Theunissen NC, Brugman E, Veen S, Verrips EG, Koopman HM et al: Development and psychometric evaluation of the TAPQOL: a health-related quality of life instrument for 1-5-year-old children. Quality of Life Research 2000; 9(8):961-972.
26. Vogels T, Verrips GH, Verloove-Vanhorick SP, Fekkes M, Kamphuis RP, Koopman HM et al: Measuring health-related quality of life in children: the development of the TACQOL parent form. Quality of Life Research 1998; 7(5):457-465.
27. Vogels T, Verrips G.H.W., Koopman HM, Theunissen NCM, Fekkes M, Kamphuis RP: TACQOL Manual Parent Form and Child Form. 2000. Leiden, Leiden Center for Child Health and Pediatrics LUMC-TNO.
28. Kraijer DW, Kema GN: SMZ, Schaal voor Motoriek bij Zwakzinnigen. Handleiding. 1994. Lisse, Swets & Zeitlinger.
29. Sarimski K: Behavioural and emotional characteristics in children with Sotos syndrome and learning disabilities. Dev Med Child Neurol 2003; 45(3):172-178.
30. Cole TR, Hughes HE: Sotos syndrome: a study of the diagnostic criteria and natural history. J Med Genet 1994; 31(1):20-32.