Growing pains?

Psychological evaluation of children with short stature after intrauterine growth retardation, before and after two years of growth hormone treatment

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Psychologische evaluatie van kinderen met een kleine gestalte
na intra-uteriene groeiretardatie, voorafgaand aan en
na twee jaar groeihormoonbehandeling

Proefschrift

ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
op gezag van de Rector Magnificus
Prof.Dr P.W.C. Akkermans M.A.
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
woensdag 28 februari 1996 om 15.30 uur

door

Elisabeth Adrienne van der Reijden-Lakeman

geboren te Purmerend

Promotiecommissie

Promotor:	Prof. Dr F.C. Verhulst
Co-promotor:	Mw Dr F.M.E. Slijper
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"It is hard to be brave", said Piglet, sniffing slightly,
"when you're only a Very Small Animal".

A.A. Milne; Winnie-the-Pooh

CIP-GEGEVENS KONINKLIJKE BIBLIOTHEEK, DEN HAAG
Reijden-Lakeman, Elisabeth Adrienne van der

Growing pains? : psychological evaluation of children with short stature after intrauterine growth retardation, before and after two years of growth hormone treatment / Elisabeth Adrienne van der Reijden-Lakeman. - Rotterdam : Afdeling Kinder- en Jeugdspychiatrie, Sophia Kinderziekenhuis/Academisch Ziekenhuis/Erasmus Universiteit Rotterdam
Proefschrift Erasmus Universiteit Rotterdam. - Met lit. opg. - Met samenvatting in het Nederlands.
ISBN 90-75584-04-0
NUGI 712
Trefw.: groeistoornissen ; kinderen ; psychologische aspecten.

The study in this thesis was performed at the Department of Child and Adolescent Psychiatry, Sophia Children's Hospital/University Hospital Rotterdam, Erasmus University Rotterdam. This research was financially supported by the Sophia Foundation for Medical Research, by Novo Nordisk A/S in Denmark and by Novo Nordisk Farma B.V. in the Netherlands.
The printing of this thesis was financially supported by Novo Nordisk Farma B.V., the Netherlands.

Cover: Jaap Lakeman, Matthias van der Reijden, Ilse van der Reijden-Lakeman

Printed by Haveka BV, Alblasserdam, The Netherlands

Contents

Chapter 1

General introduction

1.1. Introduction

Since the availability of biosynthetic human growth hormone (hGH) in 1985, many studies on the effects of hGH administration on various groups of children with short stature have been performed. The present study reports on the psychological evaluation of children with short stature after intrauterine growth retardation (IUGR), before and after two years of hGH treatment. Prior to the description of the study, the terms 'short stature' and 'intrauterine growth retardation' will be defined and possible etiological factors will be discussed.

1.1.1. Short stature

Short stature is the generic term for children who are small for their chronological age (usually indicating a height below the 3rd, 5th or 10th percentile), and comprises a heterogeneous group of children. Short stature may be etiologically related to several factors, including: growth hormone deficiency (partial or total absence of the release of growth hormone); cartilage or bone disturbances (e.g. achondroplasia); chronic diseases (e.g. renal insufficiency or heart disease); chromosomal abnormalities (e.g. Turner syndrome or Down syndrome); severe emotional deprivation; constitutional/familial factors (e.g. small parents), or IUGR. The present study pertains to short stature associated with IUGR.

1.1.2. Intrauterine growth retardation

IUGR is, just like short stature, a descriptive category, comprising a heterogeneous group of children[1]. Several possible etiological factors are described, although the etiology of IUGR in individual children is often not clear. In the literature, fetal, placental, maternal and environmental etiological factors were described[2]. According to Heinrich, fetal

anomalies comprise chromosomal disturbances, primary growth failure syndromes (e.g. the Silver-Russell syndrome), congenital infections like rubella or toxoplasmosis, and congenital anomalies (e.g. defects of the neural axis). Placental factors include abnormal implantations, vascular diseases or tumors of the placenta. Maternal disorders are for example cardiovascular disorders, chronic diseases, anaemias and substance abuse (alcohol, tobacco, narcotics). Environmental factors include maternal malnutrition, occupational hazards and irradiation. When no underlying condition of IUGR can be elucidated, this is called 'idiopathic IUGR'[2].

Besides the fact that IUGR comprises different etiological factors, a diversity of terminologies and criteria are used to refer to IUGR in the literature. Examples of terminologies are 'small for gestational age', 'dysmature' and 'small for date', and examples of different criteria that are used are birth length, birth weight, preterm or term birth, or ponderal index (PI)[3,4]. Furthermore, sometimes a distinction is made between children who are proportionately small (birth weight and birth length below a certain percentile), and children who are disproportionately small (birth weight or birth length below a certain percentile)[2,5]. In most studies, the criterion for IUGR is 'low birth weight' (LBW, birth weight either below P3, P5 or P10). The use of birth weight and/or birth length as criteria result in very different groups of children with IUGR, although growth retardation in utero may result in both limited birth weight and limited birth length[6,7].

Since the focus in the present study concerned limited height during childhood, we used the definition of IUGR as 'birth length <P3 for gestational age'[8]. Details concerning inclusion criteria, partly regarding etiology as well, are described in paragraph 1.5.1. In the majority of the children in the present study, however, the etiology of IUGR was unknown.

1.2. History

From earlier studies, we know that the beneficial effect of hGH treatment on height and height velocity is related to the etiology of growth failure. Growth hormone deficient children, as well as children with chronic renal failure, show significant increase in height velocity during treatment[9,10]. However, height and height velocity of children with short

stature, without further specification, seem to benefit less clearly from GH treatment [11,12]. This is possibly related to the heterogeneity of the group.

In the pediatric endocrinological departments of several hospitals in the Netherlands (e.g. Sophia Children's Hospital in Rotterdam, Free University Hospital in Amsterdam, Wilhelmina Children's Hospital in Utrecht and Juliana Children's Hospital in the Hague), several children with short stature and growth failure met the criteria for IUGR. It appeared that about 15% of all children, born after IUGR, fail to catch up growth resulting in a height above the third percentile for chronological age[13]. This specific subgroup of children with short stature met problems related with their limited height and the parents and/or children themselves requested treatment. Psychological evaluation of these children, before and during treatment, was considered relevant, since physical appearance might affect psychological functioning considerably[14-19].

We know from the literature that the psychological consequences of short stature for intellectual functioning, attentional capacity, self-concept and emotional and behavioral functioning, varied considerably[14-17,20]. To our knowledge, there are only few studies on the psychological effects of growth hormone treatment in children with short stature, and none on the effect of hGH treatment in IUGR children.

1.3. Aims of the present study

The primary aim of this study was to evaluate psychological functioning in children with short stature and born after IUGR, before and after two years of human growth hormone (hGH) treatment. The main questions were: a) do the psychological variables 'intelligence', 'attention', 'behavior problems' and 'self-concept' of IUGR children with short stature differ significantly from children of normal height?; b) does the outcome on these variables change significantly during hGH treatment?

To answer these questions, a study containing a medical and a psychological part was conducted.

1.4. Procedure

The present study was part of the IUGR study of the Dutch Working Group on Growth

Hormone, containing a medical and a psychological part. It was a double-blind, randomized, parallel group, multicenter study, comparing two dose levels of hGH: hGH, 3IU/m2 body surface 7 days/week, and hGH 6IU/m2 body surface 7 days/week. The hGH used was Norditropin^{R} of Novo Nordisk A/S. The study will continue until final height of all children has been reached, unless medical or psychological evaluation after two years of treatment would show serious adverse effects. The dose regimens of the children remain unknown until the end of the study. Both the medical and the psychological protocols were approved by the Ethics Committees of the participating centers. Informed consent was obtained from the parents.

1.5. Patient sample

1.5.1. Patient sample of the medical study

The medical study contained 79 children, selected from four Dutch medical centers, including three university clinics (Sophia Children's Hospital in Rotterdam, the hospital of the Free University in Amsterdam, the Wilhelmina Children's Hospital in Utrecht and the Juliana Children's Hospital in the Hague). All patients were selected after thorough review of the clinical data (record of the patient plus anthropometric examination) by the medical investigator, or the local clinical trial assistant. The inclusion period was two years. The inclusion criteria of the present study were:

a) birth length $<$P3 for gestational age[8];
b) uncomplicated neonatal period, i.e. no severe signs of asphyxia (defined as Apgar score $<$3 after 5 minutes), no sepsis, no respiratory ventilation;
c) no catch up growth above the P3 for chronological age[21] within the first two years of life or at a later stage;
d) height velocity (cm/year) for chronological age $\leq$P50[22];
e) chronological age at start of treatment 3.00-8.99 years for girls and 3.00-10.99 years for boys;
f) prepubertal signs defined as Tanner stage 1 or testicular volume $<$4 ml[22];
g) well-documented growth data from birth up to two years and at least one year before start of hGH treatment.

Exclusion criteria were:

a) any endocrine or metabolic disorder, such as diabetes mellitus, diabetes insipidus, hypothyroidism or inborn errors of metabolism;
b) disorders of the genito-urinary tract, cardio-pulmonary or gastro-intestinal tract, nervous system, nutritional and/or vitamin deficiencies;
c) chromosomal abnormalities or signs of a syndrome, except of Silver-Russell syndrome;
d) chondrodysplasia;
e) hydrocephalus;
f) patients with active malignant diseases or with increased risk of leukaemia;
g) serious suspicion of psychosocial dwarfism (emotional deprivation);
h) previous anabolic sex steroid or hGH therapy.

While waiting for the study to begin, 11 children passed the age to be included in the medical study. Because it was thought unethical to exclude these children from hGH treatment, they were also offered the opportunity to receive hGH treatment. Because of their age, these children all received the high dose of hGH. However, these children were no longer part of the medical study and were not included in the statistical analyses.

1.5.2. Patient sample of the psychological study

The psychological part of the study consisted of the behavioral and cognitive assessment of the children, described in paragraph 1.4.1. Since the 11 children, who were too old to be included in the medical study, met all inclusion criteria except the age criterion with some months, they were included in the psychological study. Thus, the total number of children in the psychological study was 90. Demographical, auxological and perinatal data of the psychological study sample are presented in table 1.1.

Since the study is to be followed up until final height, and the effects of hGH treatment was unknown, it was thought unethical to assign the children randomly to either a hGH treatment or a non-treatment/placebo condition, in order to obtain a control group. Therefore, this study does not contain a control group, and psychological test results were compared with normative data.

Table 1.1. Demographical, auxological and perinatal data of study group (N=90), before start of hGH treatment

		IUGR group
Sex	*boys/girls*	55/35
Age in years	*mean ± sd*	7.71 ± 2.52
	range	3.00 - 13.17
SES	*I and II*	40%
	III and IV	38%
	V and VI	22%
Birth length (SDS)*		-3.71
Birth weight (SDS)*		-2.65
Current height (SDS)*		-2.98
Gestation (weeks;days)*		36;6
Gestation (range)		28;2 - 42;0
Artificial delivery		31%
Height father (cm)*		174.3
Height mother (cm)*		160.3
Target height (SDS)*		-0.78

* table entries are mean scores; SDS = Standard Deviation Score
note: SES is defined as the level of parental occupation: I and II = skilled and unskilled manual; III and IV = skilled non-manual and self-employed; V and VI = intermediate and professional[23].

1.6. Methods

1.6.1. Methods of the medical study

All patients underwent medical assessments, including physical and anthropometric examination, bone age assessments and laboratory tests. These evaluations were performed at baseline (within three months before start of the hGH treatment), and at three or six months intervals during the treatment. Every three months during the study, control visits took place in order to check for side effects and to map growth results regularly. For further details on the procedure of the medical study, see de Waal[24].

1.6.2. Methods of the psychological study

Psychological assessment took place before start of hGH treatment (within one month

Table 1.2. Design of the psychological study

	Before start of treatment	After 6 months of treatment	After 12 months of treatment	After 24 months of treatment
Instruments	TES	TES	TES	TES
	WISC-RN			WISC-RN
	SVAT			SVAT
	SPPC			SPPC
	CBCL			CBCL
	TRF			TRF

note: WISC-RN = revised, Dutch version of the Wechsler Intelligence Scale for Children; SVAT = Sonneville Visual Attention Tasks; SPPC = Self Perception Profile for Children; CBCL = Child Behavior Checklist; TRF = Teacher Report Form; TES = Therapy Evaluation Scale

before start of hGH treatment), and after two years of treatment. Psychological variables that were measured, were intelligence, attention, self-concept, behavioral/emotional problems and therapy evaluation. Children were assessed at the outpatient departments of the participating hospitals. Children, parents and teachers were assessed to obtain a picture of the child's functioning. Table 1.2. presents an overview of the instruments used in the present study.

1.7. Structure of the thesis

In the chapters 2 to 7, the different assessment procedures will be described in detail and results will be presented. Chapter 8 contains a general discussion as well as some critical remarks and recommendations for the future, and chapter 9 presents a summary of the findings.

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Chapter 2

The association between intrauterine growth retardation without catch up growth and intelligence

Ilse (E.A.) van der Reijden-Lakeman, Froukje M.E. Slijper, Wouter J. de Waal, Lya (C.) Euser and Frank C. Verhulst

Abstract

The objective of this study was to determine the intelligence in children with intrauterine growth retardation (IUGR, birth length <P3) and limited current height (<P3). WISC-R scores of 63 IUGR children without catch up growth were significantly lower than those for normative Dutch children. This was true for the TIQ as well as for the VIQ and the PIQ. Scores for the Bannatyne and Kaufman factors were significantly lower than normative scores. With regard to growth parameters and perinatal data, current head circumference and current height were significantly associated with intelligence in this study. The results suggest that IUGR without catch up growth is related to lower intelligence.

2.1. Introduction

Intrauterine growth retardation (IUGR) can be defined as birth length below the 3rd percentile for gestational age. The majority of children born after IUGR show catch up growth. However, 15% fail to do so, resulting in a height for chronological age below the third percentile (P3)[1]. Since cognitive development partly depends on the physical development of the child, and particularly that of the brain, it is of interest to assess intellectual functioning in this specific group of small children.

Reports on the intelligence of IUGR children who failed to catch up growth, are rare. Studies on the cognitive functioning of short children, other than IUGR children, showed somewhat divergent results. Several studies reported that IQs of short people do not differ significantly from those of the general population[2,3], although learning problems, under-achievement and a high degree of grade retention may be present[4-7]. One study reported 37% of children with idiopathic short stature and 32% of girls with Turner syndrome attending schools for special education, even in children of normal intelligence[8]. However, the variation in etiologies for short stature in these studies hampers comparability.

In the literature, different terminologies and different criteria are used for IUGR. Furthermore, children may be proportionately small (weight **and** length below a certain percentile) or disproportionately small (weight **or** length below a certain percentile)[9,10]. The use of birth weight and/or birth length as a selection criterion, results in very different groups of children with IUGR[11,12]. In the present study, IUGR was defined as a birth length <P3 for gestational age[13]. Since the majority of the target group in the present study had low birth weight (LBW; birth weight <P3), in addition to their limited birth length (<P3), results of LBW-studies are relevant too. Some LBW-studies showed significant relations between LBW and low intelligence scores[14-21]. Other studies reported intelligence scores within the normal range[22-24]. Furthermore, academic problems and poor concentration[25,26], as well as developmental delay[27] are described in LBW children.

The aims of the present study were to compare intellectual functioning in a group of 63 IUGR children who failed to catch up growth (birth weight <P3 for gestational age and current height <P3 for chronological age), with Dutch normative data for the WISC-R.

We compared the contribution of current height to intellectual functioning with the contribution of current head circumference and perinatal factors, including mean gestation, birth length and birth weight, ponderal index and the proportion of artificial deliveries. The contribution of socio-economic status (SES) was investigated because of the known relation between SES and intelligence, as described in the literature[7,21,25,28-31]. We determined the relative contribution of these various factors to later intellectual

functioning by a stepwise multiple regression analysis.

2.2. Subjects and methods

2.2.1. Patient sample

We assessed the intelligence of 65 children with IUGR (all children, meeting the age criteria for the intelligence test: from 6 years onwards), who did not show catch up growth. Children were selected from four medical centers in the Netherlands, including three university clinics, if they had a birth length below the third percentile (-1.88 Standard Deviation Score, SDS) for gestational age[13] and had not shown catch up growth above this percentile for chronological age[32]. In 78% of the subjects, birth weight was below the third percentile. Nine infants (15%) had a ponderal index (PI; the proportion of weight to height) below the 10th percentile at birth[33,34], indicating an asymmetrical IUGR, while the majority had a symmetrical IUGR which reflects early gestational growth retardation[10].

At birth, none of the children from the IUGR group had signs of severe asphyxia (defined as an Apgar score below 3 after 5 minutes). There were no indications of complicated sepsis neonatorum, and no long-term complications of respiratory ventilation. Children with chromosomal abnormalities or other possible organic causes for growth retardation were excluded, except for Silver-Russell syndrome (5 children, 8%)[35]. The IUGR group consists of 39 boys and 24 girls.

Two of the 65 children were not native speakers of the Dutch language. Therefore, these children were excluded from the analyses. The mean age (± sd) of the IUGR group was 8.92 (± 1.73) years (range 6.17-13.17 years). The distribution of the socio-economic status (SES), defined as the level of parental occupation, was: I and II (skilled and unskilled manual) 22%; III and IV (skilled non-manual and self-employed) 43%; V and VI (intermediate and professional) 22%[36]. If both parents worked, the highest level of parental occupation was used. In 13%, both parents were unemployed. In analyses, SES was recategorized in three groups (1 to 3) and parental unemployment was classified in the lowest SES level.

2.2.2. Instruments

Intelligence was assessed with the Wechsler Intelligence Scale for Children - revised, Dutch version (WISC-RN)[37]. From the raw scores on the intelligence test a Total IQ (TIQ), a Verbal IQ (VIQ) and a Performance IQ (PIQ) as well as standardized subtest scores were calculated according to the instructions in the manual. All children were assessed in the outpatient department of the participating hospitals*. All protocols were approved by the Ethics Committees of the participating centres. Informed consent was obtained from the parents.

2.3. Statistical analyses

Data were analyzed by means of t-tests and a multiple regression procedure. To correct for multiple testing, Holm corrections[38] were applied whenever necessary. In advance, a significance level of $\alpha=0.05$ was chosen.

2.4. Results

2.4.1. WISC-RN: comparison with normative data

The mean TIQ, VIQ and PIQ of the IUGR group were significantly lower than the normative scores (see table 2.1.). Four children obtained a TIQ<70 (<2 sd). After exclusion of these children, the IUGR group still had significantly lower mean scores than normative scores (a TIQ and VIQ of 93 versus a normative mean of 100 ($p<0.001$) and a PIQ of 94 versus 100 ($p<0.01$)). No significant difference between VIQ and PIQ was found in the IUGR group. Eight mean subtest scores were significantly lower than normative subtest scores. Seventy-one per cent of the children obtained a TIQ below 100, while the median corresponded with a TIQ of 91.

No sex differences were found with regard to the TIQ, VIQ or PIQ, nor on any of the mean subtest scores.

* Sophia Children's Hospital (Rotterdam), the hospital of the Free University (Amsterdam), the Wilhelmina Children's Hospital (Utrecht) or the Juliana Children's Hospital (The Hague)

Table 2.1. WISC-RN: mean IQ scores of the IUGR group (N=63), and results of t-tests between IQ for the IUGR group and normative data

Subtest	Mean	sd	range	t-value
TIQ	91	16	54-126	4.85**
VIQ	92	16	47-121	4.26**
PIQ	91	16	55-132	4.51**
Information	9.46	3.64		ns
Similarities	9.17	3.57		ns
Arithmetic	8.52	3.22		3.85**
Vocabulary	8.92	2.96		2.81**
Comprehension	7.98	2.74		5.27**
Digits	8.46	3.10		4.01**
Picture Completion	8.97	2.80		2.69*
Picture Arrangement	9.86	2.99		ns
Block design	7.73	2.53		5.94**
Object assembly	8.19	3.53		4.69**
Coding	8.87	3.54		2.93*
Mazes	9.35	3.30		ns

* $p<0.01$; ** $p<0.001$; sd = standard deviation; ns = not significant
note: levels of significance are corrected for chance findings (Holm)

2.4.2. Bannatyne and Kaufman factors

In order to obtain information about specific areas of cognitive functioning, WISC-RN scores were recategorized into Bannatyne factors and Kaufman factors[39,40]. Bannatyne distinguished the factors: "spatial-analytic"; "verbal conceptualizing"; "acquired knowledge" and "sequential". Kaufman describes the factors "verbal comprehension", "perceptual organization" and "freedom from distractibility". All Bannatyne factors, as well as all Kaufman factors were significantly lower than the same factors, calculated on normative data (see table 2.2.).

2.4.3. The contribution of growth parameters and perinatal factors to IQ

In table 2.3., information on growth parameters, perinatal factors and SES is presented. Multiple regression analysis was performed to investigate the contribution of these factors to intelligence. In the analysis, the way of delivery was dichotomized (artificial delivery

or not). The results of the stepwise procedure showed that current head circumference SDS[41] and current height SDS were the only variables that contributed significantly to TIQ (ß=0.42, $p<0.001$ and ß=0.27, $p<0.05$ respectively).

Table 2.2. WISC-RN: mean Bannatyne and Kaufman factors and results of t-tests between those factors for the IUGR group and normative data

	IUGR group		
	Mean	sd	t-value
Bannatyne factors			
spatial-analytic	8.30	2.49	-5.42**
verbal conceptualizing	8.69	2.63	-3.95**
acquired knowledge	8.97	2.91	-2.81*
sequential	8.62	2.56	-4.28**
Kaufman factors			
verbal comprehension	8.88	2.72	-3.27*
perceptual comprehension	8.82	2.21	-4.24**
freedom from distractibility	8.62	2.56	-4.28**

* $p<0.01$; ** $p<0.001$; sd = standard deviation
note: levels of significance are corrected for chance findings (Holm)

2.5. Discussion

WISC-R intelligence scores of a group of IUGR children with limited current height were compared with WISC-R normative data for Dutch children. The IUGR group obtained significantly lower intelligence scores. The lower intelligence scores might be explained by biological environmental influences during the prenatal and perinatal period as well as by psychosocial factors during postnatal development.

The gestational stage in which growth retardation occurs might be related to decreased intellectual functioning[9,25]. Children with early growth retardation had lower developmental quotients, and achieved less well at school, than children whose growth

Table 2.3. Growth parameters, perinatal data and SES of the IUGR group (N=63)

variables	IUGR group
Mean gestation	37;3*
Gestation range	28;3-42;0**
Artificial delivery	22%
Birth length (SDS)	-3.64
Birth weight (SDS)	-2.62
Ponderal Index	0.54
Current height (SDS)	-2.92
Head circumference (SDS)	-1.67
SES	1.87

* weeks;days; ** 37% of the children was born prematurely (<37 weeks); SDS = standard deviation score
note: data are expressed as mean, except for artificial delivery (percentile) and Ponderal Index (mean percentile score)

retardation started later in pregnancy[25]. Early growth retardation may be associated with decreased head size[42], and decreased later cognitive functioning[43-45]. The earlier in pregnancy the growth retardation occurs, the more harmful the effect on the developing foetus will be. This theory was supported by the present study, since the majority of IUGR children had early IUGR, which can be inferred from their normal Ponderal Index (>P10).

Environmental factors that adversely influence the developing child in utero include abnormalities of the placenta (e.g. abnormal implantation, or a tumor), maternal disorders (e.g. anaemia and hypertension) or maternal environmental factors (e.g. maternal malnutrition or irradiation)[10]. These influences may be harmful even if they occur later during pregnancy.

Psychosocial factors during postnatal development, like overprotection by parents, juvenilization (treating the child as if it was younger) and low self-esteem of the child, may also influence cognitive functioning[6]. Parents and teachers may respond to the child's limited height by decreasing their demands and expectations for age appropriate functioning[28]. The child may respond to this attitude by showing behavior in a way that reflects the child's size rather than the child's age[6]. It is our impression that adults in the

environment of the child erroneously suppose that the child's intellectual functioning will improve across time without additional educational support. In the present study, 10% of the children attended schools for special education, which is twice the rate of special school attenders in the general population. However, based on our findings we expected 38% of the children in our sample (all children with a TIQ of <85) to attend special education. Another Dutch study involving children with Turner syndrome and children with idiopathic short stature, reported 37% of the children receiving special education[8]. To draw conclusions on this topic, further research on coping mechanisms and behavior is essential.

In the present study, SES did not contribute significantly to IQ. Positive correlations between SES and intelligence, as described in literature[7,21,25,28-31] were not found in our study. We did not assess the influence of the parental intelligence level on the intellectual functioning of the child. However, since intelligence is related to the level of education and profession, and thus to the SES as defined in our study, we do not expect the intelligence level of the parents to have a great influence on the child's intelligence.

The possible mechanisms by which congenital endocrine and growth factors exert their influence on intellectual functioning in IUGR children is yet unclear. Since current head circumference and current height contributed significantly to intelligence, and birth length or other variables did not, the level of intelligence might be related to postnatal growth rate[28,46]. In the literature, it was stated that the degree of growth retardation in utero was related to later growth (at the age of 24 months) in term IUGR children[34]. In the present study, this effect could not be confirmed as we observed no significant relationship between birth length and current head circumference or current height. Furthermore, there appeared to be no clear relation between growth hormone secretion and current height in the present IUGR group[47]. It is possible that there is an underlying factor which is responsible for both decreased intellectual functioning and short stature.

Causes of lower intelligence in IUGR children are still speculative and further (neuro)-psychological and endocrinological research is necessary to increase knowledge about this subject. Given the results of the present study, early stimulation of cognitive

functions in the at-risk group of IUGR children plus thorough counselling and follow-up by medical and psychological specialists, are recommended.

Acknowledgements

This research has been generously supported by Novo Nordisk Ltd. Denmark and the Sophia Foundation of Scientific Research.

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Chapter 3

Evaluation of intelligence after two years of growth hormone treatment in intrauterine growth retarded children without catch up growth

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Abstract

The objective of this study was to compare intelligence in 59 children with short stature and intrauterine growth retardation (IUGR) after two years of growth hormone (hGH) treatment (T2), with pretreatment intelligence. All children had a birth length below the third percentile (P3), and a current height <P3 before start of treatment (T1). The mean total IQ and the mean performance IQ increased significantly after two years of treatment. So did the mean subtest score 'Block Design', and mean scores on Bannatyne's "spatial-analytic factor" and Kaufmans "perceptual organization factor". The total IQ as well as the verbal IQ score were still significantly lower than normative scores. The increase in total IQ was not significantly correlated with length gain or current height at T2.

From the present study we can hypothesize that intelligence was influenced by the secondary effects of hGH treatment.

3.1. Introduction

Fifteen per cent of intrauterine growth retarded (IUGR) children (height below the third percentile (P3) for gestational age) do not show spontaneous catch up growth to a height

above this percentile for chronological age[1]. Since the availability of biosynthetic human growth hormone (hGH), the effects of hGH therapy on height and psychological functioning can be evaluated. Previously, we reported lower intelligence scores in this specific group of small children. As cognitive development partly depends on the physical development of the child, and particularly on that of the brain, it is of interest to assess intellectual functioning during hGH treatment.

Intellectual functioning of IUGR children with short stature during hGH treatment has never been described in the literature, to our knowledge. Since 78 per cent of the IUGR children in our study had LBW in addition to limited birth length, studies on the intellectual functioning of children with IUGR, defined as low birth weight (LBW; birth weight <P3), were also relevant for understanding the relation between early physical growth and intelligence. These studies reported significant relations between LBW and low intelligence scores[2-9], but intelligence scores within the normal range were described as well[10-12]. For more details see van der Reijden-Lakeman and colleagues[13].

The aims of the present study were: a) to assess intelligence of IUGR children (birth length <P3 for gestational age) after two years of hGH treatment; b) to compare these results with intelligence scores of the same group of children before start of treatment; and c) to assess the correlation between intelligence and current height, length gain or head circumference after two years of treatment.

3.2. Subjects and methods

3.2.1. Procedure

This study was part of the IUGR study of the Dutch Working Group on Growth Hormone. All children were selected from four medical centers in the Netherlands*, including three university clinics. The first 90 children, who entered the study and met the inclusion criteria, were accepted in the treatment group. The patients were assigned in a randomized and double-blind fashion to one of two dose regimens: hGH, 3 IU/m2 body

* Sophia Children's Hospital (Rotterdam), the hospital of the Free University (Amsterdam), the Wilhelmina Children's Hospital (Utrecht) and the Juliana Children's Hospital (The Hague)

surface 7 days/week and hGH, 6 IU/m2 body surface 7 days/week. Growth hormone was administered with one subcutaneous injection daily, in the evening. All protocols were approved by the Ethics Committees of the participating centres. From the parents, informed consent was obtained.

When this study was started, it was thought unethical to assign IUGR children without catch up growth randomly to either a hGH treatment group or a non-treatment/placebo condition. Therefore, our study does not contain a control group and results of the treatment group are compared with Dutch normative data.

3.2.2. Patient sample

Children were selected if they had a birth length below the third percentile (-1.88 SDS; standard deviation score) for gestational age[14] and had not shown catch up growth above this percentile for chronological age at T1[15]. In 78 per cent of the subjects, birth weight was below the P3 as well. Table 3.1. presents demographic information about the group. The socioeconomic status (SES) was defined as the level of parental occupation[16]. If both parents worked, the highest level of parental occupation was used. In analyses concerning

Table 3.1. Demographic information of the treatment group before (T1) and after two years of hGH treatment (T2)

		IUGR group (N=59)	
		T1	T2
sex	*boys*	37	37
	girls	22	22
age (in yrs)	*mean (sd)*	8.85 (1.67)	10.86 (1.67)
	range	6.17-13.17	8.17-15.08
SES*	*I or II*	22%	22%
	III or IV	44%	49%
	V or VI	22%	22%
	unemployed	12%	7%

* levels of socioeconomic status: I and II = skilled and unskilled manual; III and IV = skilled non-manual and self-employed; V and VI = intermediate and professional

SES, this variable was recategorized into three groups (1 to 3), and unemployment of both parents was classified in the lowest SES level.

At birth, none of the children had shown signs of severe asphyxia (defined as an Apgar score below 3 after 5 minutes). There were no indications of complicated sepsis neonatorum, and no long-term complications of respiratory ventilation. Children with chromosomal abnormalities or other possible organic causes for growth retardation were excluded, except for Silver-Russell syndrome (four children, 7 per cent)[17].

We assessed the intelligence of 59 IUGR children without catch up growth (current height <P3) before start of hGH treatment (T1) and after two years (T2) of hGH treatment, with the Dutch version of the revised Wechsler Intelligence Scale for Children (WISC-R). The remaining part of the children of the treatment group did not meet age criteria for the WISC-R (from six years onwards), and were therefore not assessed with this instrument. Two children were not native speakers of the Dutch language and were excluded from the analyses.

3.2.3. Instrument

Intelligence was assessed with the Wechsler Intelligence Scale for Children - revised, Dutch version (WISC-RN)[18]. From the raw scores on the intelligence test a Total Intelligence Quotient (TIQ), a Verbal IQ (VIQ) and a Performance IQ (PIQ) as well as standardized subtest scores were calculated according to the instructions in the manual. All children were assessed in the outpatient department of the participating hospitals.

3.3. Statistical analyses

Data were analyzed by means of paired t-tests. To correct for chance findings as a result of multiple testing, Holm correction was applied whenever necessary[19]. In advance, the significance level was set at $p<0.05$.

3.4. Results

3.4.1. Intelligence scores

Before start of treatment, intelligence scores were significantly lower than normative

scores[13]. After two years of hGH treatment, the TIQ as well as the PIQ improved significantly. The TIQ and VIQ were still significantly lower than normative scores, while the PIQ did not differ significantly from the normative PIQ anymore. One subtest score improved significantly as well (see table 3.2.). At T1, 71 per cent of the children obtained a TIQ below 100, while this percentage was 66 per cent at T2. The median corresponded with a TIQ of 92 at T1, and with a TIQ of 94 at T2. There were no significant differences between boys and girls at T1 or at T2. Differences in TIQ scores between T1 and T2 ranged from -16 to +16 points. On average, the group of children gained three points on the TIQ, while the median was two points. The correlation

Table 3.2. WISC-RN: mean IQ scores of IUGR group (N=59) before (T1) and after two years of hGH treatment (T2), and results of paired t-tests between IQ at T1 and T2

Subtest	T1 Mean	T1 sd	T2 Mean	T2 sd	t-value	correlation T1-T2 (r)
TIQ	91	16	93	17	-3.24*	0.92**
range	54-126		55-128			
VIQ	92	16	93	18	ns	0.86**
range	47-121		47-140			
PIQ	92	17	96	17	-3.75**	0.87**
range	55-132		54-139			
Information	9.4	3.7	9.3	3.6	ns	0.74**
Similarities	9.2	3.6	9.5	3.4	ns	0.68**
Arithmetic	8.4	3.2	9.2	3.4	ns	0.76**
Vocabulary	8.9	2.9	8.7	2.9	ns	0.78**
Comprehension	8.0	2.8	8.3	2.7	ns	0.62**
Digits	8.5	3.2	8.4	2.9	ns	0.67**
Picture Completion	9.0	2.9	9.2	2.9	ns	0.43**
Picture Arrangement	10.0	3.0	10.6	3.3	ns	0.76**
Block design	7.6	2.5	8.6	2.8	-4.48**	0.79**
Object assembly	8.2	3.6	8.8	3.4	ns	0.75**
Coding	8.8	3.6	9.0	3.2	ns	0.67**
Mazes	9.5	3.3	10.2	2.9	ns	0.63**

* $p<0.01$; ** $p<0.001$; sd = standard deviation; ns = not significant
note: levels of significance are corrected for chance findings (Holm)

between the TIQ at T1 and T2 was $\underline{r}$=0.92 ($p<0.001$). Correlation coefficients of mean subtest scores ranged from $\underline{r}$=0.43 (Picture Completion) to $\underline{r}$=0.79 (Block Design).

3.4.2. Bannatyne and Kaufman factors

To obtain information about specific areas of cognitive functioning, WISC-RN scores were recategorized into Bannatyne factors and Kaufman factors[20,21]. Bannatyne distinguished the factors: "spatial-analytic"; "verbal conceptualizing"; "acquired knowledge" and "sequential". Kaufman describes the factors "verbal comprehension", "perceptual organization" and "freedom from distractibility". At T1, all Bannatyne factor scores, as well as all Kaufman factor scores were significantly lower than the same factor scores, calculated on normative data (for detailed information see: van der Reijden-Lakeman et al[13]). At T2, scores on Bannatyne's "spatial-analytic factor" and Kaufmans "perceptual organization factor" increased significantly (see table 3.3.). Except for the latter factor, however, all factor scores were still significantly lower than normative factor scores.

3.4.3. Intelligence and growth

The mean current height of the children in our study group at T1 was -2.94 SDS, and after two years of treatment -1.50 SDS. The average length gain of the group was 18.1 cm in two years, which means a length gain of 1.44 SDS. The mean head circumference before start of treatment was -1.67 SDS, and -0.98 SDS at T2 (SDS scores according to Gerver[22]).

The delta TIQ-score (difference between TIQ at T2 and T1) was not significantly correlated with length gain in cm ($\underline{r}$=0.25, ns) nor with length gain in SDS ($\underline{r}$=0.21, ns), nor with the mean amount of growth hormone secretion pretreatment ($\underline{r}$=-0.22, ns), nor with the increase in head circumference (SDS) ($\underline{r}$=0.13, ns). Of the two growth parameters that contributed significantly to TIQ at T1[13], current height (SDS) was not significantly correlated with TIQ at T2 ($\underline{r}$=0.23, ns), while head circumference showed a significant correlation with this variable after two years of treatment ($\underline{r}$=0.49, $p<0.001$).

Table 3.3. WISC-RN: mean (sd) Bannatyne and Kaufman factor scores and results of paired t-tests between those scores before (T1) and after two years of hGH treatment (T2)

	IUGR group		t-value
	T1	T2	
Bannatyne factors			
spatial-analytic	8.25 (2.54)	8.85 (2.45)	-2.76*
verbal conceptualizing	8.69 (2.66)	8.81 (2.68)	ns
acquired knowledge	8.93 (2.88)	9.06 (2.97)	ns
sequential	8.57 (2.56)	8.85 (2.57)	ns
Kaufman factors			
verbal comprehension	8.88 (2.76)	8.94 (2.78)	ns
perceptual organization	8.85 (2.25)	9.49 (2.34)	-3.79**
freedom from distractibility	8.57 (2.56)	8.85 (2.57)	ns

* $p<0.01$; ** $p<0.001$; sd = standard deviation; ns = not significant
note: levels of significance are corrected for chance findings (Holm)

3.5. Discussion

In the present study, intelligence was assessed in 59 children with short stature (<P3) after intrauterine growth retardation (IUGR), who were treated with human growth hormone (hGH) for two years. Paired t-tests showed a significantly higher mean TIQ and PIQ after two years of hGH treatment (T2), compared with pretreatment scores (T1). The mean score of the subtest Block Design, as well as the mean scores of Bannatynes "spatial analytic factor" and Kaufmans "perceptual organization" factor, were also significantly higher at T2 versus T1. However, the TIQ as well as the VIQ after two years of treatment were still significantly lower than normative scores.

The high correlation coefficients between intelligence scores at T1 and at T2 indicate that the individual children in our sample tended to preserve their rank orders within the group across the treatment interval, despite the significant increase in scores. This means that the developmental increase in intelligence was quite equally distributed

across the sample. If the increase in intelligence was the result of hGH treatment, this indicates that the effect of hGH was quite similar across the individuals in the study group. Correlation coefficients between the delta TIQ-score (difference between TIQ at T2 and T1) and length gain in cm, length gain in standard deviation score (SDS), current height (SDS) at T2, or increase in head circumference (SDS) were not significant.

Significantly higher scores after two years of hGH treatment suggest that there might be a relation between the treatment and intelligence. We hypothesize that the higher scores after two years of hGH treatment might be related to biological or psychological factors. Since the correlation coefficients between intelligence and length gain were not significant, the increase in intelligence scores does not seem to be directly related to the degree of length gain.

Several studies reported significant correlations between head size and intelligence at different ages[23-26]. Results of our study confirmed this finding, since head circumference and intelligence were significantly correlated before start of the hGH treatment and after two years of treatment. However, the correlation between the increase in head circumference and the delta-intelligence score during those two years was not significant. Data on brain size, probably a more proper variable to correlate intelligence with than external head circumference[27,28], were not available in this study. The underlying mechanisms that might affect intelligence during hGH treatment are not clear yet. Furthermore, the influence of the gestational age at which growth retardation occurred on intelligence[29,30], or that of environmental factors in utero[31], can only be hypothesized in this study.

A psychological, secondary, effect of hGH treatment on intellectual functioning might be caused by a changed attitude towards the child. It is likely that reactions on the child's short stature, like overprotection and juvenilization, diminished during the treatment since the children's height increased considerably. Since it is known that these psychosocial factors may influence cognitive functioning[32], and that parents and teachers may adapt their demands and expectations to the child's height[33], decrease of these reactions may have caused more age-appropriate demands and thus improved intellectual functioning of the child.

Furthermore, the child's idea that his or her length problem was taken seriously and that hGH treatment could actually be started, could have had a stimulating effect on his or her activities, including school matters.

The increase in mean intelligence scores might also be a statistical regression effect. However, this effect is most likely to be found if subjects were selected on extreme scores of the dependent variable. This was not the case in our study.

Causes of the significantly increased intelligence scores in the present study are still speculative. Despite the significant higher TIQ and PIQ scores after hGH treatment, the IUGR children in our study are still vulnerable with regard to intelligence. To learn about the intellectual development of these children during longterm hGH treatment, and to increase knowledge about the association between hGH treatment and intelligence, further endocrinological and psychological follow-up is needed.

Acknowledgements

This research has been generously supported by Novo Nordisk Ltd. Denmark and the Sophia Foundation of Scientific Research. We thank Wouter de Waal for providing the growth data.

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Chapter 4

Evaluation of attention before and after two years of growth hormone treatment in intrauterine growth retarded children

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Abstract

The objective of this study was to assess attention in children with short stature after intrauterine growth retardation (IUGR), before and after two years of growth hormone (hGH) treatment. All children had a birth length below the 3rd percentile, and had not shown catch up growth at T1 (current height <P3). The attention measures (Sonneville Visual Attention Tasks; SVAT) of the IUGR group were compared with similar measures of a comparison sample. In the pretreatment analyses (T1), 48 IUGR children and 119 children of the comparison sample were included. After two years of hGH treatment in the IUGR group (T2), 41 children of the IUGR group and 68 children of the comparison sample were included in the analyses.

At T1, children of the IUGR group showed deficits in divided, focused and sustained attention. They were less accurate, showed more variability in reaction time (RT), performed slower and more impulsive than the comparison sample. After two years of hGH treatment, the IUGR group showed deficits in divided and sustained attention but not in focused attention. They were still less accurate, showed more variability in RT and more impulsiveness, but the tempo did not differ significantly from that of the comparison sample. Current head circumference, the way of delivery and intelligence were significantly correlated with attention measures in the IUGR group.

From the present study we can hypothesize that short stature after IUGR and attention deficits are related. Growth hormone treatment seems to have some beneficial effect on attentional capacity, but further research is needed to draw firm conclusions about this subject.

4.1. Introduction

Intrauterine growth retardation (IUGR) is one of the causes of short stature. Up to 15% of the children, born after IUGR, fail to catch up growth[1] and therefore tend to remain small without medical intervention. Since the availability of biosynthetic human growth hormone (hGH) in 1985, it is possible to treat children with short stature with hGH. We reported earlier that the intelligence of children born after IUGR (defined as birth length <P3 for gestational age) and with short stature (current height <P3 for chronological age) was significantly lower compared with normative data[2], but increased significantly after two years of hGH treatment[3]. However, very little is known about the association between neuropsychological functions and short stature in general, and of short stature after IUGR in particular. Furthermore, the consequences of hGH treatment on these functions have never been described, as far as we know.

In the literature, no study concerning neuropsychological functioning and IUGR, defined as limited birth length for gestational age, was found by us. However, studies on neuropsychological functioning in children with low birth weight (LBW) were relevant too, since 73% of the present study sample had LBW in addition to limited birth length. In some of these studies, LBW was significantly associated with attention deficits and hyperactivity[4-6]. Ens-Dokkum and co-workers reported that 12% of very preterm and very low birth weight children attended special schools, with attention problems as a possible underlying cause[7]. Besides, several studies described the relation between LBW and minor neurological dysfunction (MND), although percentages of MND varied (26%-50%) and definitions of IUGR were not entirely comparable as well (subjects had either a LBW (<P3, <P5 or <P10) or a LBW plus a low Ponderal Index (<P5 or <P10), and were either preterm or full-term born)[5-10].

To learn about the attentional capacity of children with IUGR, defined as low birth length, comparing their test results with reported results of LBW children is not properly possible, for the use of birth length and/or birth weight as a criterion for IUGR result in different groups of children[11,12]. Therefore, we studied the association between short stature after IUGR, defined as low birth length, and attention, in a group of IUGR children who failed to show catch up growth (birth length <P3 for gestational age, current height <P3 for chronological age).

Our aims were: a) to assess divided, focused and sustained attention before start of hGH treatment and after two years of treatment; b) to assess the contribution of growth parameters and perinatal data to attention. Since it was stated in the literature that functions like attention and concentration were associated with academic achievement[8,13], we assessed the correlation between intelligence and attention as well.

4.2. Subjects and methods

4.2.1. Procedure

This study was part of the IUGR study of the Dutch Working Group on Growth Hormone. All children were selected from four medical centers, including three university clinics, in the Netherlands*, and assessed in the outpatient department of the participating hospitals. The first 90 children, who entered the study and met the inclusion criteria, were accepted in the treatment group. The patients were assigned in a randomized and double-blind fashion to one of two dose regimens: hGH, 3 IU/m2 body surface 7 days/week and hGH, 6 IU/m2 body surface 7 days/week. The dose regimens of the children remain unknown until the end of the study, that is until all children have reached final height. Growth hormone was administered with one subcutaneous injection daily, in the evening. All protocols were approved by the Ethics Committees of the participating centers. From the parents, informed consent was obtained.

When this study was started, it was thought unethical to assign IUGR children

* Sophia Children's Hospital (Rotterdam), the hospital of the Free University (Amsterdam), the Wilhelmina Children's Hospital (Utrecht) or the Juliana Children's Hospital (The Hague)

without catch up growth randomly to either a hGH treatment group or a non-treatment/placebo condition. Therefore, this study does not contain a control group. Since we wanted to assess attention measures of IUGR children during hGH treatment, we considered it important to compare these attention measures with those of non-treated children. Therefore, our study contains a comparison group of Dutch school children.

4.2.2. Patient sample

We assessed selective and sustained attention in 48 IUGR children without catch up growth (current height <P3) before start of treatment (T1) and after two years of hGH treatment (T2), with a computerized battery[13]. The remaining part of the treatment group did not meet the age criteria for the test (from 7 years onwards), and were therefore not assessed with this instrument. Only children who met the age criteria at T1 and at T2, were included in the analyses for this study.

All children were born after intrauterine growth retardation (IUGR), defined as a birth length below the third percentile (-1.88 SDS; standard deviation score) for gestational age[15] and had not shown catch up growth above this percentile for chronological age[16]. In 73% of all children who were assessed with the test battery, birth weight was below the third percentile. Six infants (13%) had a ponderal index (PI, the proportion of weight to height) below the 10th percentile at birth[17], indicating an asymmetrical IUGR, while the remaining part had a symmetrical IUGR which reflects early gestational growth retardation[19]. At birth, none of the children from the target group had shown signs of severe asphyxia (defined as an Apgar score below 3 after 5 minutes). There were no indications of complicated sepsis neonatorum, and no long-term complications of respiratory ventilation. Children with chromosomal abnormalities or other possible organic causes for growth retardation were excluded, except for Silver-Russell syndrome (7 children, 8%)[20]. Table 4.1. presents demographic information about the group. The socioeconomic status (SES) was defined as the level of parental occupation[21]. If both parents worked, the highest level of parental occupation was used. In analyses concerning SES, this variable was recategorized into three groups (1 to 3), and unemployment of both parents was classified in the lowest SES level.

4.2.3. Comparison sample

The comparison sample contains children aged 7-12 years old from three regular schools situated in the centre of the Netherlands (province of Utrecht). One school was situated in the middle of a big city and thought to represent the lower socioeconomic level. The second school, lying in the countryside, was expected to represent the middle socioeconomic level and the third school, situated in the wealthy part of a medium-sized city, was thought to represent the higher socioeconomic level. More detailed information

Table 4.1. Demographic variables of the IUGR group and the comparison sample

		IUGR group		comparison sample	
		T1 (N=48)	T2 (N=41)	T1 (N=120)	T2 (N=69)
sex	*boys*	29	26	55	31
	girls	19	15	65	38
age (in yrs)	*mean (sd)*	9.48 (1.52)	11.02 (1.21)	9.66 (1.49)	10.73 (0.90)
	range	7.00-13.36	8.79-12.95	7.00-12.50	9.25-12.50
SES*	*I/II*	23%	27%	---	---
	III/IV	46%	54%	---	---
	V/VI	19%	19%	---	---
	unemployed	12%	0%	---	---

* distribution of the socioeconomic status (SES): I and II = skilled and unskilled manual; III and IV = skilled non-manual and self-employed; V and VI = intermediate and professional
--- = data are not available

on the SES of this group was not available. Children who did not have thorough command of the Dutch language were excluded form the analyses. The comparison sample did not contain children with apparent physical or genetical abnormalities. Demographic information of the comparison sample is presented in table 4.1. as well.

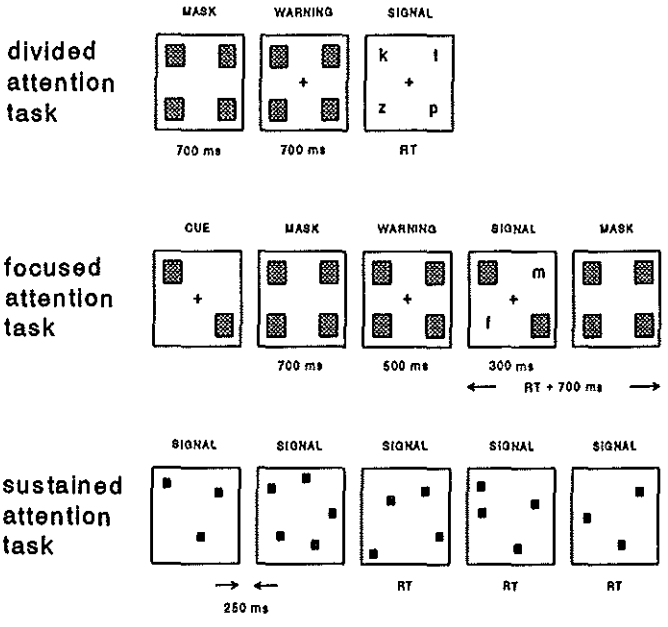
Contrary to the age of the IUGR group, the mean age of the comparison sample had not increased at T2, since no longitudinal data of this sample were present. In order to obtain mean ages that are comparable in both groups at T2, the youngest children of the comparison sample and the oldest children of the IUGR group were excluded from the

analyses (see table 4.1.).

4.2.4. Instrument

All children were assessed with a computerized battery of reaction time tasks for divided, focused and sustained attention in which children had to respond by a keypress to stimuli displayed on a PC monitor. Prior to actual testing, the children received practice trials to ensure that the task instruction was understood properly. The order of the tasks was the same in all children. The following tasks were selected (timing of stimulus presentation for all tasks are portrayed in figure 4.1.):

Figure 4.1. Timing between signals. Timing sequence in divided attention task (top panel), focused attention task (middle panel), and sustained attention task (lower panel)



note: RT = reaction time

Divided attention tasks. Divided attention is the ability to divide attention across the necessary cognitive operations. A deficit is reflected by a decline in response speed.

The divided attention task employs a display load of four letters and consists of three blocks in which target set size, or memory load, is increased from one to three target letters. A 'yes'-response is required to signals containing the complete target set. Signals that contained none of the target letters, and signals that contain incomplete target sets should be rejected ('no'-response). The latter types serve as distracter signals. Reaction time to these distracter signals is expected to increase with the number of distracters, because their presence complicates decision processes. The reaction time of a 'yes'-response is expected to increase linearly with target set size, the slope of reaction time denoting the rate of memory search. The reaction time to distracter signals is expected to increase with the number of distracters.

Focused attention task. Focused attention refers to the ability to attend to relevant information while ignoring irrelevant stimuli. A deficit manifests itself in the processing time of irrelevant information.

In this task, the display load consists of two diagonally presented letters. Subjects have to attend to one of the diagonals only (the relevant diagonal), and press the 'yes'-key when a target letter is present. Nontarget letters on the relevant diagonal, or letters (irrespective of type) on the irrelevant diagonal require a 'no'-response. Target search is, therefore, only necessary when letters are presented on the relevant diagonal. As a consequence, the processing of nontarget signals should take longer than target signals. Irrelevant targets (foils) may break through the focused attending of the relevant diagonal. This attention shift takes time, resulting in longer reaction times to foils than to relevant targets. Lack of inhibitory control is reflected by the error rate to foils.

Sustained attention task. Sustained attention is defined as the ability to maintain a stable performance level over time. A deficit is apparent through a progressive decline and/or fluctuation in processing rate or accuracy over time.

In this task, 50 series of 12 patterns (600 signals) are presented in continuous succession. Each series contains an equal number of patterns consisting of three, four or five dots. Four dots (target) require a 'yes'-response, and three and five dots (nontargets)

a 'no'-response. Main parameters are the fluctuation in speed of performance over time, and the change (deterioration) of speed and accuracy during task performance. Because two-thirds of the signals require a 'no'-response, a response bias will develop: that is, rejecting signals while being alert (vigilance) for the occurrence of the less frequent targets. This strategy should result in more errors on targets (misses) than nontargets (false alarms). During performance on this task, the subjects are informed about error responses by a beep signal.

Where the validity and reliability of the task battery is regarded, reference can be made to several studies in which the battery was shown to be a sensitive detector of attention deficits, such as in children with a history of nonoptimal neonatal neurological condition[22], in children with minor neurological dysfunction[23], in children and adults with treated phenylketonuria[24-26], and in hyperactive children[27].

4.3. Statistical analyses

Data of the test battery were analyzed by means of ANCOVAs and multiple regression analyses. ANCOVAs on test results were performed in a two groups (IUGR group versus comparison sample) x two sex (boys and girls) factorial design with age as a covariate.

In order to limit the risk of chance findings (type I errors) with multiple tests, we set the p-value at 0.01. P-values, resulting from the ANCOVAs and falling between 0.01 and 0.05, will be discussed in light of the significance of other outcomes.

4.4. Results

4.4.1. Task main effects

The task manipulations produced highly significant effects on processing time in the expected direction (see table 4.2.). Reaction time increased as a function of memory load, distraction, and as a result of stimulus-response incompatibility. In the focused attention task, the processing of nontarget signals took longer than that of target signals, but this effect was observed only for the relevant diagonal. This finding underscores the operation of a focused attention strategy. In the sustained attention task, reaction time to patterns

Table 4.2. Test of the model: main effects of task manipulation in the comparison sample

	F	df	p-value	1st grade polynome* t-value	p-value	remarks
DIVIDED ATTENTION						
Memory search task						
memory load (yes)	321.1	2,236	$p<0.0001$	19.4	$p<0.001$	RT increased with load
memory load (no)	84.0	2,236	$p<0.0001$	10.1	$p<0.001$	RT increased with load
distraction (block 3)	279.9	2,236	$p<0.0001$	20.9	$p<0.001$	RT increased with distraction (number of targets)
response type (yes vs. no, block 1)	128.0	1,119	$p<0.0001$	11.3	$p<0.0001$	incompatible response slower than compatible response
FOCUSED ATTENTION						
stimulus type (target vs. nontarget)	89.9	1,113	$p<0.0001$	9.5	$p<0.0001$	see interaction
signal relevance x stimulus type	109.3	1,113	$p<0.0001$	-10.5	$p<0.0001$	RT nontarget signal slower than RT target signal, but this holds only for relevant diagonal
SUSTAINED ATTENTION						
pattern type	60.3	2,226	$p<0.0001$	10.0	$p<0.0001$	RT increased with number of dots in patterns
feedback (beep)	118.1	1,113	$p<0.0001$	10.9	$p<0.0001$	response delay after error
pattern type (error %)	129.3	2,234	$p<0.0001$	7.9	$p<0.0001$	% misses larger than % false alarms

* linearity was tested by means of a first grade polynomial contrast; RT = reaction time

increased with the number of dots in the signal. The miss rate was, as predicted, higher than the false alarm rate (10% misses on four dots versus 7% false alarms on three and five dots). The subjects also showed a delayed response after committing an error.

Having confirmed the task main effects in the comparison sample, the next step was to focus on possible differences in attentional control between the IUGR group, before start of hGH treatment, and the comparison sample: does task manipulation differentially affect groups?

4.4.2. Before start of growth hormone treatment (T1)

Divided attention task. All 48 children of the IUGR group and 119 children of the comparison sample were able to perform this task. No significant differences in reaction time (RT), variability in RT or error rate were detected between the IUGR group and the comparison sample. The effect of memory load on RT and error rate was not significantly different between the groups, either. The effect of distraction on RT was significant and more pronounced in the IUGR group [$F(2,326)=5.76$, $p<0.01$], with a linear contrast showing that RT increased with the number of distracters ($p<0.01$) (see figure 4.2.). Distraction did not significantly affect the error rate.

The effect of the covariate age was significant [$9.05<F(1,162)<88.37$, $p<0.01$], except for the percentage of false alarms. Older children performed faster and more accurate than younger children. Boys showed a significantly higher percentage of misses [$F(1,162)=7.56$, $p<0.01$] and more variability in RT than girls [$F(1,162)=6.86$, $p<0.001$]. No other significant sex effects or group by sex interaction effects were present.

Focused attention task. At T1, nine children of the IUGR group and four children of the comparison sample obtained an error rate of more than 50% (chance level), and were therefore excluded from the analyses. Furthermore, two children of the IUGR group were not able to perform this task because of insufficient comprehension of the instructions, and task results of five children of the comparison sample were incomplete. In the end, task results of 37 children of the IUGR group and of 110 children of the comparison sample were included in the analyses.

The RT of the IUGR group and the comparison sample did not differ significantly, but the error rate of the IUGR group was higher [$F(1,142)=4.64$, $p<0.05$]. This higher error rate was mainly caused by false-positive reactions on nontargets on the relevant diagonal: 19% in the IUGR group versus 13% in the comparison sample. Furthermore, stimulus type interacted significantly different with the error rates of both groups ([$F(1,142)=6.28$, $p<0.05$], indicating that the rate of false-positive reactions on nontargets in the IUGR group was higher than that of the comparison sample (see figure 4.3.).

Figure 4.2. Divided attention at T1. The panel portrays response latency as a function of distraction

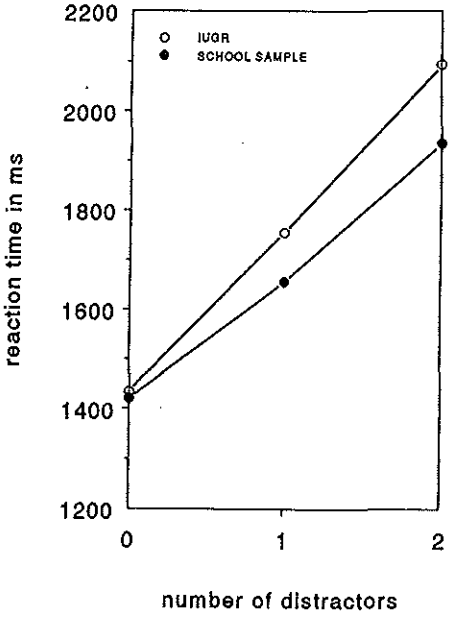
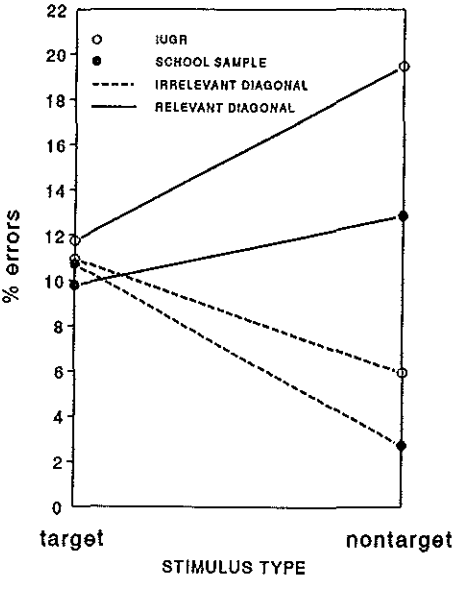


Figure 4.3. Focused attention at T1. The panel portrays error rate as a function of signal type (relevance and stimulus)



note: ms = milliseconds

The covariate age was significant with regard to RT [$F(1,142)=83.95$, $p<0.001$] and error rate [$F(1,142)=13.77$, $p<0.001$]; older subjects were faster and more accurate than younger subjects. No significant sex differences were present.

Sustained attention task. One child of the IUGR group was unable to complete a sufficient number of series (at least one-fifth = 10 series), and task results of two children of the comparison sample were incorrect. Data of 47 children of the IUGR group and 116 children of the comparison sample were included in the analyses.

The mean tempo in the IUGR group was significantly lower [$F(1,158)=4.88$, $p<0.05$], and the overall error rate was significantly higher in the IUGR group, compared with the comparison sample [$F(1,158)=9.16$, $p<0.01$]. The fluctuation in RT did not differ between the two groups.

To evaluate slow changes in vigilance (miss rate) during time-on-task, the total of 50 series was divided in five periods of 10 series each. Although the time per period did not differ between the groups, the effect of time-on-task was significantly different between the two groups [$F(4,596)=10.70$, $p<0.0001$]. A linear contrast showed that the time per period, needed by the IUGR group, decreased significantly more during the task than the time per period, needed by the comparison sample ($p<0.001$) (see figure 4.4.). The miss rate was significantly higher in the IUGR group [$F(1,148)=4.00$, $p<0.05$], and increased with time-on-task. Neither the effect of the 'beep' signal after an error, nor the effect of the number of dots, nor interaction effects on RT were significantly different between the groups.

The effect of the covariate age was significant [$6.82<F(1,158)<89.13$, $p<0.01$]; older subjects performed faster and more accurate than younger children. No significant sex differences were present, except for the overall percentage of errors, which was higher in boys [$F(1,158)=12.39$, $p<0.001$].

4.4.3. After two years of treatment (T2)

Divided attention task. At T2, all 41 children of the IUGR group and all 68 children of the comparison sample were able to perform this task. After two years of

Figure 4.4. Sustained attention at T1. The panel shows the tempo and percentage of misses over time during sustained attention

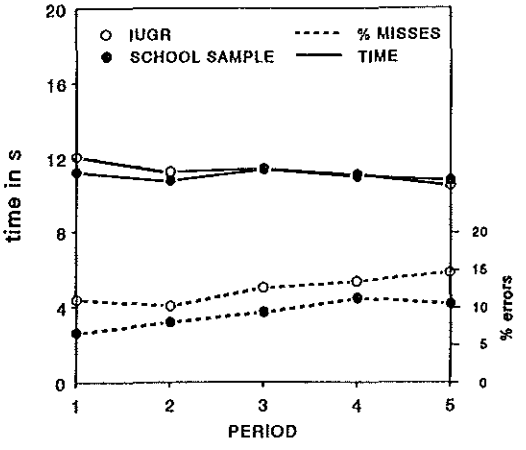
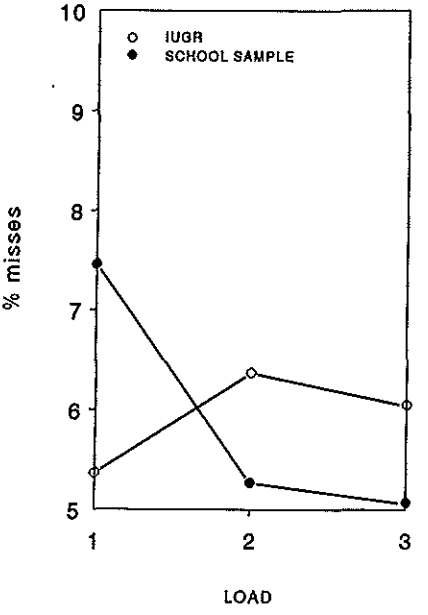


Figure 4.5. Divided attention at T2. The panel portrays the effect of memory load on the percentage of misses



note: s = seconds

hGH treatment in the IUGR group, overall differences in RT, variability in RT or error rate were not significant between the groups. However, memory load affected the percentage of misses of both groups in significantly different way ([F(2,212)=3.79, $p<0.05$]. Linear contrasts showed that the percentage of misses increased with memory load in the IUGR group, while it decreased in the comparison sample ($p<0.05$) (see figure 4.5.). The effect of distraction on RT was not significantly different between the groups, but the IUGR group showed more variability in RT [F(1,105)=4.63, $p<0.05$], and a higher percentage of false alarms than the comparison sample [F(1,105)=4.10, $p<0.05$]. In addition, distraction differentially affected the percentage of false alarms [F(2,212)=4.51, $p<0.05$]: the increase in error rate with distraction was higher in the

IUGR group than in the comparison sample (see figure 4.6.).

The effect of the covariate age was significant for all variables [$9.00 < F(1,105) < 18.50$, $p < 0.001$], except for the error rate: older children performed faster than younger children. Significant sex effects, all in favor of the girls, were found with respect to the percentage of misses [$F(1,105) = < 11.02$, $p < 0.01$] and the variability in RT [$F(1,105) = 6.25$, $p < 0.05$]. No other effects were significant.

Focused attention task. Nine children of the IUGR group and one child of the comparison sample were not able to perform this task and were therefore excluded from the analyses. Thirty-two children of the IUGR group and 67 children of the comparison sample were included in the analyses.

No significant differences in overall RT or error rate were present between the groups. Signal relevance did not interact significantly with the groups.

The effect of age was significant on RT as well as on error rate ([$F(1,94) = 14.07$, $p < 0.001$] and [$F(1,94) = 10.42$, $p < 0.01$] respectively), again indicating that older children performed faster and more accurate than the younger ones. The effect of diagonal relevance on the error rate was significantly different between boys and girls [$F(1,95) = 7.18$, $p < 0.01$]: boys showed more false-positive reactions on nontargets on the relevant diagonal than girls.

Sustained attention task. At T2, 39 children of the IUGR group and all 68 children of the comparison sample were included in the analyses. Two children of the IUGR group were excluded because they were unable to complete a sufficient number of series (at least 10 series).

No significant difference in mean tempo or in variability in RT was detected between the IUGR group and the comparison sample. However, the percentage of misses was higher in the IUGR group than in the comparison sample [$F(1,100) = 5.41$, $p < 0.05$]. The percentage of false alarms did not differ significantly between the groups.

As at T1, the effect of time-on-task on tempo was significantly different between the two groups [$F(4,404) = 2.41$, $p < 0.05$] (see figure 4.7.). Neither the effect of the 'beep' signal after an error, nor the number of dots, nor any other interaction effects were significantly different between the groups.

No significant age or sex effects were present.

4.4.4. Attention task results and growth parameters or perinatal data

Stepwise multiple regression analyses were performed to investigate the contribution of the growth parameters (birth length, birth weight, current height and current head circumference), perinatal data (mean gestational age, way of delivery and Ponderal Index), and SES to the attentional capacity of the IUGR group at T1. The way of delivery was dichotomized (artificial delivery or not) and the Ponderal Index was described in

Figure 4.6. Divided attention at T2. The panel shows the effect of distraction on the percentage of false alarms

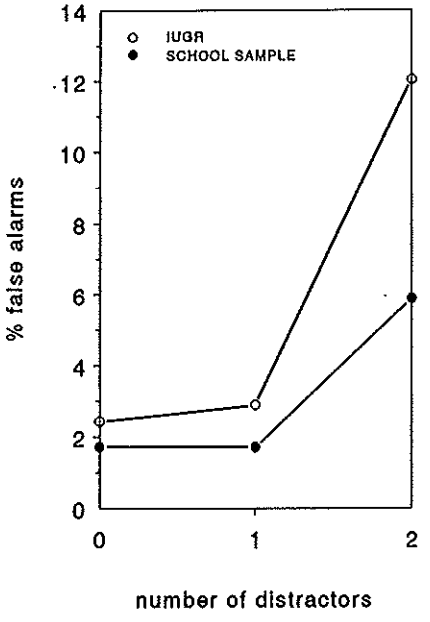
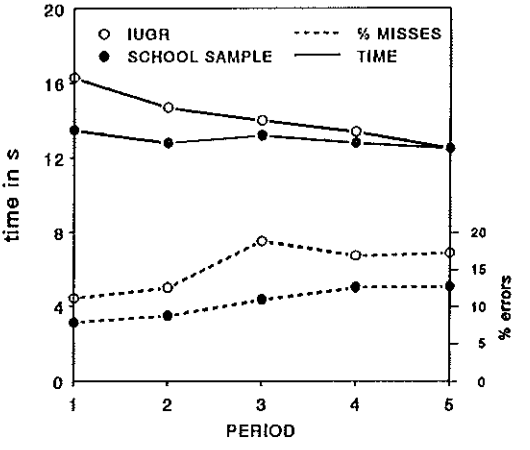


Figure 4.7. Sustained attention at T2. The panel portrays the tempo and percentage of misses per period during sustained attention



note: s = seconds

percentile scores.

At T1, results of the stepwise procedure showed that current head circumference (in standard deviation score, SDS) and the way of delivery were the only variables that contributed significantly to the task results. In the divided attention task, the way of delivery contributed significantly to the memory search speed (β=-0.48, T=-3.71, $p<0.001$). In the sustained attention task, current head circumference (SDS) contributed significantly to the delay in RT after an error response (β=0.38, T=2.69, $p<0.01$) (see discussion).

At T2, no variables contributed significantly to the attentional capacity of the IUGR group.

4.4.5. Attention task results and intelligence

In the present IUGR group, intelligence was assessed with the Dutch version of the revised Wechsler Intelligence Scale for Children (WISC-RN)[28]. The total intelligence quotient (TIQ) as well as the verbal IQ (VIQ) and the performance IQ (PIQ), were significantly lower than that of the general population before start of treatment[2]. After two years of hGH treatment, the TIQ and the PIQ increased significantly but the TIQ as well as the VIQ were still significantly lower than normative data[3]. Since intelligence might influence the performance of the present attentional task battery, we assessed the correlation between intelligence and results of the task battery. The mean of nine standardized WISC-RN subtest scores was used as a measure for intelligence. The subtests Arithmetic, Digit Span and Coding, belonging to Kaufmans 'Freedom from distractibility factor', were excluded from the analyses for this factor pretends to give an indication for attentional capacity[29].

At T1, baseline speed and "distraction RT" (RT while distracters are present) of the divided attention task were significantly correlated with intelligence (r=-0.45, $p<0.01$ and r=-0.39, $p<0.01$ respectively). None of the variables of the focused attention task showed significant correlations with intelligence. The sustained attention task showed significant correlations between the mean tempo and intelligence (r=-0.58, $p<0.0001$), between the fluctuation in tempo and intelligence (r=-0.59, $p<0.0001$), and

between the increase in tempo during the task and intelligence ($r=-0.47$, $p<0.01$).

At T2, baseline speed of the divided attention task was significantly correlated with intelligence ($r=-0.45$, $p<0.001$). Variables of the focused attention task were not significantly correlated with intelligence. With regard to the sustained attention task, significant correlations between the mean tempo and intelligence ($r=-0.55$, $p<0.0001$), and between the fluctuation in tempo and intelligence were present ($r=-0.43$, $p<0.001$).

4.5. Discussion

In the present study, divided, focused and sustained attention was assessed in 48 children with short stature (<P3) after intrauterine growth retardation (IUGR), before treatment (T1) and after treatment with human growth hormone (hGH) for two years (T2). Task results were compared with results of a comparison sample.

At T1, a pattern emerges of clear differences in information processing and attentional capacity between the IUGR group and the comparison sample. The additive effects of task manipulation in the IUGR group, as compared to the comparison sample, is indicative of deficits in divided attention as well as in focused and sustained attention. On the whole, the IUGR group was less accurate, showed more variability in reaction time (RT) and was sometimes slower. In addition, memory search strategies were inefficient and decision strategies were inadequate. The RT of the IUGR group increased with increasing task demands (see figure 4.2.), tempo increased while vigilance decreased during the sustained attention task (see figure 4.4.), and the IUGR group suffered from impulsiveness (see figure 4.3.). The focused attention task as well as the sustained attention task both contain a response bias, which the IUGR group could not resist sufficiently. In the focused attention task, 60 out of 80 signals on the relevant diagonal require a 'yes'-response (targets), while only 20 signals require a 'no'-response (nontargets). The IUGR group was not able to control this response bias and to adapt its task behavior. In the sustained attention task, the frequency of 'no'-responses is twice as high as the frequency of 'yes'-responses. The IUGR group is not able to sufficiently resist this response bias: children reacted faster and less accurate. Both task behaviors imply a lack of inhibition, instead of a focused or sustained attention deficit. These findings are to

some extent comparable with reported -unspecified- attention problems in children with low birth weight (LBW)[4-6,30].

Weisglas-Kuperus and co-workers[30] stated that attention problems in very LBW children might be related to brain abnormalities. Whether part of the IUGR children in the present study had brain abnormalities or not, remains unclear since no extensive neurological examination had taken place at birth. However, according to the relation between LBW and minor neurological dysfunctions, as described in the literature, this might be a possible explanation[5-10].

The stepwise multiple regression analyses in the IUGR group at T1, performed to investigate the contribution of growth parameters and perinatal data to divided, focused and sustained attention, indicated also that a 'normal' delivery contributed significantly to a faster memory search, and that the delay in RT after an error is lower in children with a smaller head circumference. We hypothesize that the latter finding suggests some suboptimal neurological functioning in IUGR children with small head circumference, which was also indicated by the significant contribution of head circumference to intelligence[2].

Our finding that attentional capacity and intelligence were significantly correlated, is in agreement with the results of Weisglas-Kuperus and co-workers[30]. The finding that all significant correlations concerned tempo, might be either explained by the important role of tempo in the calculation of performance subtest scores of the WISC-RN, or by the capacity of brighter children to resist the response bias and to perform the task with a calm and stable tempo.

At T2, deficits in divided and sustained attention were still present in the IUGR group, although the IUGR group was not significantly slower than the comparison sample anymore. The effect of increased task demands on the error rate was more pronounced in the IUGR group than in the comparison sample (see figure 4.5.). Moreover, the variability in RT and the inhibition problem of the IUGR group increased significantly more than that of the comparison sample, in the presence of distracting stimuli (see figure 4.6.). Furthermore, the sustained attention task showed that tempo as well as error rate increased with task duration, indicating impulsiveness.

No growth parameters or perinatal data contributed significantly to attentional capacity of the IUGR group at T2. Since significant contributions at T1 concerned speed factors, this finding might be related to the change of tempo in the IUGR group at T2. The correlations between intelligence and attentional capacity at T2 concerned the same, although not all, task variables as at baseline. Again, all correlations involved tempo. The fact that these correlations remained significant, despite the relative increase in tempo of the IUGR group, might be explained by the increased intelligence in this group[3]. In the literature, reports about the possible relation between attention and intelligence are conflicting. Some studies described a significant correlation between sustained attention and intelligence in children[31] and undergraduates[32]. Rutter and co-workers, however, reported no correlation between the hyperkinetic syndrome and intelligence: they diagnosed two out of 2199 10- and 11-year old children in their epidemiological study as being hyperkinetic, while 2½% of these children were intellectually retarded (IQ $\leq$ 2 SD below the mean)[33]. De Sonneville and Njiokiktjien[22] described significantly slower, but equally accurate, performance on the divided attention task, also used in the present study, in children with significantly lower IQ scores than their controls. To draw conclusions on this subject, further research is needed.

Whether the relative effect of tempo in the IUGR group is related to the primary or secondary effects of the hGH treatment, remains unclear. We hypothesize that the influence of the hGH treatment might be related to biological or to psychological factors. From a biological point of view, the hGH treatment in our study might have influenced the neurological system, and thus the attentional capacity, in a positive way. From the literature we know of two studies in which cognitive performance was investigated in growth hormone deficient (GHD) subjects receiving four and eight weeks of GH suppletion respectively[34,35]. The latter study, on five adult patients, suggested some beneficial effect of GH on memory function, while the first study stated that the degree of attentional improvement after GH suppletion in eight GHD children correlated with the blood levels of replacement GH. To our opinion, conclusions on these studies should be drawn very carefully since both studies contained very few subjects and GH was supplied for only four and eight weeks, respectively.

On the other hand, psychological effects of growth might be present as well. The child's idea that his or her length problem is taken seriously and that hGH treatment can actually be started could have had a stimulating effect on the child's activities, including cognitive functioning. This way, the children were probably able to pay more energy to their activities, while less attention had to be paid to worries about their short stature and reactions of the environment[36]. Secondly, attentional capacity might have improved because of a changed attitude towards the child. We know from the literature that possible reactions on the child's short stature, like juvenilization and overprotection, may affect cognitive functioning[37] and that parents and teachers adapt their expectations and demands to the child's height[38]. An increase in height might have caused more age-appropriate demands and thus improved attentional capacity. This hypothesis was underlined by the earlier finding that the intellectual level of the present IUGR group increased significantly after two years of hGH treatment[3]. Thirdly, we hypothesize that an improvement in attentional capacity might be related to an increase in self-confidence, since the mean scores on a self-concept scale improved significantly after two years of hGH treatment in the present IUGR group[39].

The reported significant effects of the covariate age confirmed the earlier reported finding that attentional capacity improves with age[22]. The described sex-effects in favor of the girls correspond with the higher incidence of attention deficit hyperactivity disorders in boys[40].

Besides the relative increase in tempo during the hGH treatment in the IUGR group, the results of the present study indicate also that part of the attentional deficits were still present at T2. Given the results of the present study and of earlier reported studies on this IUGR group, IUGR might affect attentional capacity as well as intellectual functioning. However, to learn more about neuropsychological functioning of IUGR children during hGH treatment, further research is needed to increase knowledge about this subject.

Acknowledgements

This research has been generously supported by Novo Nordisk Ltd. Denmark and the Sophia Foundation of

Scientific Research. We thank Lya Euser for help in examining the children.

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Chapter 5

Self-concept before and after two years of growth hormone treatment in intrauterine growth retarded children

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Abstract

The objective of this study was to assess self-concept in children with short stature after intrauterine growth retardation (IUGR), before and after two years of growth hormone (hGH) treatment. We assessed 25 children before treatment, and 40 children after a 2-year treatment period. Seventeen of the 25 children of whom we had pretreatment data, were reassessed after two years of hGH treatment. All children had a birth length below the 3rd percentile, and did not show catch up growth (current height <P3). We compared the self-concept measures (Self-Perception Profile for Children; SPPC) of the IUGR group with similar measures of a Dutch school sample.

Four of the six SPPC mean scale scores of the IUGR group prior to treatment were significantly lower than mean scores of the school sample. Mean scale scores of the group of children, assessed after two years of hGH treatment, did not differ significantly from those of the school sample. In the group of 17 children, who were assessed before as well as after two years of treatment, the mean scale scores of 'social acceptance' and 'general self-worth' were significantly higher at the second assessment ($t=-5.93$, $p<0.001$ and $t=-4.36$, $p<0.001$ respectively).

From the present study we can hypothesize that short stature after IUGR and a low

self-concept are related.

5.1. Introduction

Fourteen per cent of intrauterine growth retarded (IUGR) children (height <P3 for gestational age) do not show spontaneous catch up growth to a height above the 3rd percentile (P3) for chronological age within the first two years of life[1]. IUGR children who remain small might experience psychosocial disadvantages because of their short stature[2-6]. Since the availability of biosynthetic human growth hormone (hGH), the effects of hGH therapy on height and psychosocial well-being can be evaluated.

Self-concept refers to the way someone perceives and appreciates him or herself. Self-concept includes perceived competence in cognitive and athletic skills, the perception of the degree to which one is accepted by peers or feels popular, and the perception of one's behavior and physical appearance. Since short stature may influence social interactions, emotional adjustment and school achievement[2-6], it is therefore likely to influence the child's self-concept.

To our knowledge, no study on the self-concept in IUGR children with short stature is available in the literature. A number of studies reported on self-concept in children with short stature other than IUGR[7-14]. These studies revealed contradictory results, with some indicating less favorable and others indicating more favorable self-concept than comparison groups. Comparisons were either made with normative data, with children with short stature but other etiologies, or with children with normal height.

Studies on hGH treated children with short stature other than IUGR children are hard to compare with studies on IUGR children, because of differences in etiology of short stature, and in height and age of the subjects studied. Furthermore, the use of different self-concept measures hampers comparability[12,15,16].

The aims of the present study were: a) to assess self-concept of IUGR children who failed to catch up growth (birth length <P3 for gestational age, current height <P3 for chronological age) before start of hGH treatment and after two years of treatment; and b) to assess the correlation between self-concept scores and current height or length gain

after two years of hGH treatment.

5.2. Subjects and methods

5.2.1. Procedure

This psychological study was part of the IUGR study of the Dutch Working Group on Growth Hormone. The patients were assigned in a randomized and double-blind fashion to one of two dose regimens: hGH, 3 IU/m2 body surface 7 days/week and hGH, 6 IU/m2 body surface 7 days/week. The dose regimen of each individual child will remain unknown until all children have reached their final height and children will continue to be treated at the dose-level to which they were originally assigned. Growth hormone was administered with one subcutaneous injection daily, in the evening. All children were gathered from four medical centers in the Netherlands*. The first 90 children, who entered the study and met the inclusion criteria, were accepted in the treatment group. All protocols were approved by the Ethics Committees of the participating centres. From the parents, informed consent was obtained.

We did not have a control group, since it was thought unethical to assign IUGR children without catch up growth randomly to either a hGH treatment group or a non-treatment/placebo condition. Therefore, we compared the results of the treatment group with scores of a Dutch school sample.

5.2.2. Patient sample

We assessed 25 IUGR children before hGH treatment was started, and 40 IUGR children after a 2-year treatment period, with the Self-Perception Profile for Children (SPPC). The remaining part of the 90 subjects did not meet school grade criteria of the SPPC (3rd to 6th grade of regular schools), and were therefore not assessed with this instrument. All children on whom we had pretreatment data (17 of the 25 children), were reassessed after two years of hGH treatment. Table 5.1. presents demographic information as well as

* Sophia Children's Hospital (Rotterdam), the hospital of the Free University (Amsterdam), the Wilhelmina Children's Hospital (Utrecht) and the Juliana Children's Hospital (The Hague)

auxological data about the groups. Socioeconomic status (SES) was measured on a six-step scale of parental occupation, with 'I' as the lowest level[17]. If both parents were employed, the highest level of parental occupation was used. In the analyses, SES was recategorized into three groups (1 to 3), and unemployment of both parents was classified in the lowest SES level.

All children were born after IUGR, defined as a birth length below the P3 for gestational age[18], and had not shown catch up growth above this percentile for chronological age[19]. At birth, none of the children had shown signs of severe asphyxia (defined as an Apgar score below 3 after 5 minutes). There were no indications of complicated sepsis neonatorum, and no long-term complications of respiratory ventilation. Children with chromosomal abnormalities or other possible organic causes for growth retardation were excluded, except for Silver-Russell syndrome (four children in the pretreatment group and three in the treated group)[20].

We will present results for three different samples: a) a group of 25 IUGR children prior to treatment; b) a group of 40 IUGR children who were treated with hGH during a 2-year period, and c) a group of 17 children on whom we obtained both pretreatment (Time 1) data and data after two years of treatment (Time 2). All children of the latter group were among the 25 untreated children as well as among the 40 children at Time 2. Since the untreated group of children (N=25) and the treated group children at Time 2 (N=40) contained only partly the same children (that is, all children of the longitudinal group), we considered it not possible to compare these groups statistically. Therefore, comparing analyses between those two groups were not executed.

5.2.3. Instrument

The Self-Perception Profile for Children is a 36-item questionnaire measuring self-concept in children from 8 to 12 years old[15]. The questionnaire contains six subscales: 'scholastic competence', 'social acceptance', athletic competence', physical appearance', behavioral conduct' and 'general self-worth'. The Dutch version of the SPPC was administered in order to assess the child's perception of his or her own physical appearance, its attributions of competence in cognitive, social, athletic and behavioral skills, and to

Table 5.1. Demographic characteristics and auxological data of the pretreatment IUGR group (N=25), the posttreatment IUGR group (N=40), and the longitudinal treatment group (N=17). Mean scores between Time 1 and Time 2 in the longitudinal treatment group were compared by paired t-tests.

		pretreatment IUGR group	posttreatment IUGR group	longitudinal treatment group Time 1	longitudinal treatment group Time 2	p-value
sex	*boys/girls*	15/10	26/14	12/5	12/5	
age (in yrs)	*mean (sd)*	10.23 (0.91)	10.88 (1.31)	10.05 (0.89)	12.07 (0.87)	$p<0.001$
	range	8.58-11.33	8.58-13.17	8.58-11.25	10.75-13.17	
SES*	*I/II*	12%	23%	12%	12%	
	III/IV	60%	47%	59%	65%	
	V/VI	16%	25%	17%	23%	
	unemployed	12%	5%	12%	0%	
TIQ	*mean (sd)*	98.8 (16.6)	94.6 (15.4)	97.2 (18.7)	100.3 (18.9)	ns
VIQ	*mean (sd)*	99.5 (16.2)	94.0 (15.6)	98.4 (17.4)	98.2 (17.5)	ns
PIQ	*mean (sd)*	98.1 (16.7)	96.9 (17.3)	96.2 (18.4)	102.6 (20.3)	$p<0.05$
birth length**	*mean (sd)*	-3.75 (1.30)	-3.32 (1.11)	-3.23 (0.97)	-3.23 (0.97)	
birth weight**	*mean (sd)*	-2.65 (1.04)	-2.45 (0.95)	-2.30 (1.08)	-2.30 (1.08)	
current height**	*mean (sd)*	-2.58 (0.67)	-1.52 (0.66)	-2.74 (0.61)	-1.44 (0.64)	$p<0.001$
head circumference**	*mean (sd)*	-1.43 (1.13)	-0.97 (1.09)	-1.52 (1.22)	-1.01 (1.13)	ns
bone age (in yrs)	*mean (sd)*	10.18 (1.96)	12.35 (1.85)	9.83 (1.92)	13.61 (1.42)	$p<0.001$
Tanner stage	*mean (sd)*	1.20 (0.50)	1.43 (0.84)	1.06 (0.24)	1.65 (1.06)	$p<0.05$

* socioeconomic status

** in standard deviation scores

obtain an independent measure of self-worth. Dutch data are available from a school sample of 300 children, aged 8-12 years in grades 3 to 6 of regular schools[21]. Statements are presented in a forced choice format and the child is asked to compare himself or herself to his or her peers. Mean subscale scores range from 1 to 4 and a higher score is associated with higher perceived self-concept. Test-retest reliability correlations of the Dutch SPPC subscales ranged from 0.66 to 0.83[21].

5.3. Statistical analysis

Data were analyzed by means of (paired) t-tests, chi-squares and ANCOVAs. ANCOVAs on mean SPPC scale scores were performed in a two groups (IUGR group versus school sample) x two sex (boys and girls) factorial design with age as a covariate. In this way the effects of age on self-concept were partialled out. To correct for multiple testing, Holm correction was applied whenever necessary[22]. The significance level was set at $p<0.05$.

5.4. Results

5.4.1. IUGR group prior to treatment (N=25)

ANCOVAs showed that mean scale scores of IUGR children were significantly lower than those of the school sample in the areas of social acceptance, athletic competence, physical appearance and general self-worth (see table 5.2.). Significant effects for the covariate age were found for the scales 'scholastic competence' [$F(1,320)=8.91$, $p<0.01$; $ß=-0.16$], 'athletic competence' [$F(1,320)=6.39$, $p<0.05$; $ß=-0.13$], 'physical appearance' [$F(1,320)=3.96$, $p<0.05$; $ß=-0.11$] and 'behavioral conduct' [$F(1,320)=20.74$, $p<0.001$; $ß=-0.25$], with lower scores for older children. There were no significant sex effects or group by sex interactions on any of the scales.

5.4.2 IUGR group after two years of hGH treatment (N=40)

ANCOVAs showed that mean scale scores of IUGR children after two years of hGH treatment did not differ significantly from those of the school sample. Significant age effects were found on the scales 'scholastic competence' [$F(1,335)=10.11$, $p<0.01$;

Table 5.2. Mean (sd, standard deviation) SPPC scale scores and results of comparisons of the pretreatment IUGR group (N=25) versus the school sample (N=300)

	pretreatment IUGR group mean (sd)	school sample mean (sd)	F-value
scholastic competence	2.54 (0.35)	2.81 (0.69)	ns
social acceptance	2.32 (0.40)	3.08 (0.68)	F=27.43**
athletic competence	2.59 (0.48)	3.07 (0.62)	F=11.50*
physical appearance	2.63 (0.40)	3.16 (0.75)	F=9.89*
behavioral conduct	2.67 (0.54)	2.89 (0.58)	ns
general self-worth	2.39 (0.46)	3.28 (0.59)	F=48.40**

* $p<0.01$ ** $p<0.001$

ß=0.17], 'athletic competence' [F(1,335)=6.80, p=0.01; ß=-0.14], 'physical appearance' [F(1,335)=5.14, $p<0.05$; ß=-0.13] and 'behavioral conduct' [F(1,335)= 22.89, $p<0.001$; ß=-0.26], with lower scores for older children. There were no significant sex effects or group by sex interactions on any of the scales.

5.4.3. Longitudinal treatment group (N=17)

For the longitudinal treatment group, paired t-tests showed significantly higher mean scale scores at Time 2 on the scales 'social acceptance' and 'general self-worth' than at Time 1 (see table 5.3.).

When compared with the school sample, ANCOVAs showed that mean scores of the longitudinal treatment group on the scales 'social acceptance' and 'general self worth' were significantly lower at T1 ([F(1,312)=13.50, $p<0.001$] and [F(1,312)=32.64, $p<0.001$] respectively). Significant effects for the covariate age were found on the scales 'scholastic competence' [F(1,312)=9.44, $p<0.01$; ß=-0.17], 'athletic competence' [F(1,312)=5.97, $p<0.05$; ß=-0.13] and 'behavioral conduct' [F(1,312)=20.75, $p<0.001$; ß=-0.25], again with lower scores for older children. No significant sex effects or group by sex interactions were found on any of the scales.

Table 5.3. Mean (sd, standard deviation) SPPC scale scores of the longitudinal treatment group (N=17) at Time 1 and Time 2 (paired t-tests)

	longitudinal treatment group		
	Time 1 mean (sd)	Time 2 mean (sd)	t-value
scholastic competence	2.50 (0.35)	2.96 (0.82)	ns
social acceptance	2.35 (0.43)	3.18 (0.50)	t=-5.93*
athletic competence	2.63 (0.54)	2.98 (0.57)	ns
physical appearance	2.64 (0.44)	2.88 (0.80)	ns
behavioral conduct	2.59 (0.52)	2.81 (0.70)	ns
general self-worth	2.34 (0.42)	3.34 (0.66)	t=-4.36*

* $p<0.001$

ANCOVAs at T2 showed no significant group effects, sex effects or group by sex interactions. Significant age effects were found on the scales 'scholastic competence' [$F(1,312)=10.47$, $p=0.001$; ß=-0.19], 'athletic competence' [$F(1,312)=5.54$, $p<0.05$; ß=-0.14] and 'behavioral conduct' [$F(1,312)=23.25$, $p<0.001$; ß=-0.29].

5.4.4. Demographic and auxological data

Age, growth parameters (like current height, bone age and pubertal stage), as well as PIQ of the longitudinal treatment group changed significantly during growth hormone treatment. Other variables, including SES, did not differ significantly at Time 1 and Time 2. Of the families in the longitudinal treatment group, 15 families had the same SES level at Time 1 and at Time 2, while two families in which both parents were unemployed at Time 1, had SES level 2 and 3 respectively after two years of treatment.

Current height and length gain. Information on current height of the IUGR groups is presented in table 5.1. The average length gain of the longitudinal treatment group (N=17) was 17.1 cm in two years, which means a length gain of 1.3 SDS.

Correlations SPPC and height. For the pretreatment group (N=25) and for the group after two years treatment (N=40), correlation coefficients were computed between

current height (SDS) and mean scale scores of the SPPC. However, no correlations were significant after Holm correction. No significant correlations between the SPPC scales after two years of treatment, and length gain (in cm) were found in the longitudinal group of 17 children.

Correlations SPPC and intelligence. Intelligence in the present group of IUGR children, as measured with the Dutch version of the Wechsler Intelligence Scale for Children[23], was significantly lower than that of the general population (van der Reijden-Lakeman et al, unpublished data). Since intelligence might influence the way a child evaluates his or her competencies, and perceived cognitive skills are part of the self-concept, we assessed the correlation between intelligence and self-concept (see table 5.4.).

Mean SPPC scale scores of the pretreatment group (N=25) and of the IUGR group at Time 1 were not significantly correlated with intelligence (TIQ, VIQ and PIQ) after Holm correction. However, scholastic competence scores for children after two years of treatment (N=40) were significantly correlated with TIQ, VIQ and PIQ, and scholastic competence scores of the longitudinal treatment group (N=17) at Time 2 were significantly correlated with TIQ and VIQ.

5.5. Discussion

In the present study, ANCOVAs showed significantly lower mean scores on four scales (social acceptance, athletic competence, physical appearance and general self-worth) of the SPPC in 25 non-treated children with short stature (<P3) after intrauterine growth retardation (IUGR), compared with a Dutch school sample from the general population. After two years of treatment with human growth hormone (hGH), ANCOVAs showed that mean SPPC scale scores for the treatment group of 40 children did not differ significantly from scores of the school sample. In a group of 17 children who were longitudinally assessed, mean scale scores on 'social acceptance' and 'general self-worth' had increased significantly after two years of hGH treatment.

Correlation coefficients between self-concept and intelligence scores in IUGR children prior to treatment were not significant, while significant positive correlations between intelligence and the mean scale score of 'scholastic competence' were found in

Table 5.4. Correlation coefficients between mean self-concept scale scores and intelligence of the pretreatment IUGR group (N=25), the posttreatment IUGR group (N=40), and the longitudinal treatment group (N=17)

	pretreatment			posttreatment			longitudinal treatment group					
							Time 1			Time 2		
	TIQ	VIQ	PIQ	TIQ	VIQ	PIQ	TIQ	VIQ	PIQ	TIQ	VIQ	PIQ
scholastic competence	.10	-.04	.24	.59*	.55*	.46*	.10	.03	.16	.74*	.75*	.63
social acceptance	.31	.21	.37	.04	-.07	.15	.37	.26	.47	.05	-.12	.20
athletic competence	.50	.41	.54	.17	.19	.12	.61	.59	.60	.38	.35	.39
physical appearance	.20	.02	.37	.04	.12	-.06	.26	.15	.35	.14	.18	.04
behavioral conduct	.33	.16	.46	.20	.16	.18	.32	.20	.43	.29	.24	.28
general self-worth	.22	.13	.29	.20	.29	.06	.26	.21	.28	.35	.44	.19

* $p<0.001$

note: only correlations that remained significant after Holm correction were marked

children who were treated with hGH for two years.

Significantly lower mean scale scores in the pretreatment group, compared with the school sample, suggests that there might be a relation between short stature and self-concept. Of the two other studies in the literature that also examined the relation between short stature and SPPC-scores, one study was hardly comparable with the present study because the authors used a different version of the SPPC[7], while the other study reported significantly higher mean scores on three scales in the study group, compared with age norms[13]. The conflicting results of the latter study with ours may be related to a higher than average socioeconomic status, higher than average Iqs in the study group, or to different ages than the age restrictions of the Dutch version of the SPPC allow (8-15 years versus 8-13 in our study).

The finding that ANCOVAs showed significantly lower scores on four scales in the pretreatment group versus the school sample, and no significant differences in the treated group after two years of hGH treatment, suggests that the hGH treatment had a beneficial effect on children's sense of self-worth. This finding was supported by the increase in mean scores on the 'social acceptance' and 'general self-worth' scales after two years of hGH treatment in the longitudinal treatment group. The increase in self-concept scores might be related to growth as well as to psychological factors. The longitudinal treatment group gained an average of 17.1 cm during the two years of treatment, and height of the children became more like that of friends and classmates. Some children were even no longer among the shortest in the classroom. Table 5.1. shows that current height, bone age and pubertal stage increased significantly during two years of treatment. Although correlation coefficients between SPPC scales and length gain were not significant after Holm correction, the experience of growth was probably more important to the self-concept of these children than the number of centimeters length gain.

Besides, since height is known to be an important factor in the interaction with peers[4-6], catch up growth in children with short stature may change these interactions. We know that most of the children in the treatment group received positive reactions concerning their growth, from peers as well as from adults. This way, the objective growth, in combination with these positive reactions, probably made social contact with

others easier. This might explain the significant increase of the mean scale score of 'social acceptance', comprising the number of friends the child has, and the child's evaluation of his or her popularity. Positive reactions of peers and adults may also result in an increase in the way a child likes him- or herself and is happy with the way he or she is. Besides, many of the children and their parents told us that they were treated more often according to age instead of height, and were overprotected and teased less often. Hence, the significant increase of the scores on the 'general self-worth' scale may be related to the great impact of height and catch up growth on many aspects of psychosocial functioning[2]. Another possible explanation of the significant increase of two mean scale scores in the longitudinal treatment group, is the fact that the children obtained special medical attention. The knowledge that the doctor and psychologist were taking the height problem seriously and tried to do something about it by prescribing hGH treatment, might have had a positive influence on the self-concept.

Four studies investigated the influence of hGH treatment on the self-concept in children with short stature. Rovet et al reported more favorable self-concept in girls with Turner syndrome after 18 months of hGH treatment, compared with non-treated controls[24]. However, a study of Huisman and his colleagues on girls with Turner syndrome did not reveal improved self-concept after two years of hGH treatment[25]. A study of children with short stature failed to show any differences in self-concept after two years of hGH treatment, when compared with normative scores[26], and a fourth study, involving children with growth retardation following renal transplantation, reported no significant changes in self-concept after two years of hGH treatment either (Sinnema et al, unpublished data). Contradictory results of these studies may be caused by different mean ages[25,26] and by studying groups of patients with short stature with different etiologies[24-26].

In the school sample, SPPC subscale intercorrelations range from 0.29 to 0.64, with the highest correlations between subscales and the general self-worth scale ($0.48 < r < 0.64$). Of the correlations between each specific domain and 'general self-worth', physical appearance and 'global self-worth' showed the highest correlation ($r=0.64$)[21]. The finding that the mean scale score of 'physical appearance' did not increase significantly in the present study, probably indicates that physical appearance is a rather

stable aspect of children's self-concept, especially when it is negatively judged. Furthermore, children might be not entirely happy with their body in particular, yet. This is not unlikely, since the majority of the children were still smaller than their peers. The intercorrelation between the subscales 'social acceptance' and 'general self-worth', of which the mean scores increased significantly in the present study, was 0.51[21]. We hypothesize that social acceptance is a part of self-concept that is more easily adapted to changes, probably while it is also influenced by the reaction and attitude of others, while a change in perceived physical appearance depends mainly on ones own opinion.

Negative coefficients ß in the ANCOVAs with significant cross-sectional age effects indicate that age is inversely related to the mean scores in this study: the older the child, the lower the scores. The finding that the longitudinal treatment group showed significantly higher scores on two scales after two years of treatment, runs counter to the cross-sectional age effect indicating lower scores for older children, and underscores the assumption that the higher scores were related to the hGH treatment instead of getting older.

Although the results of this study are suggestive of the beneficial effects of hGH treatment on the psychological well-being of IUGR children, no definitive conclusions with respect to a causal relation can be drawn. Only a placebo-controlled study design can give more conclusive evidence of the effects of hGH on IUGR children's self-concept. However, it is clear that it is not possible to give children daily injections with placebo. Similarly we did not think it ethical to withhold IUGR children and their parents a possible treatment that may be a relief for their worries over their child's physical characteristics.

The lack of statistically significant correlation coefficients between SPPC scales and length gain (in cm) in the longitudinal treatment group is probably due to the relatively small range in growth between the children (range 12.1-19.8 cm or 0.4-1.7 SDS).

In conclusion, the present study reported on the self-concept of IUGR children with short stature prior to, and after two years of hGH treatment. The improved perception of 'social acceptance' and 'general self-worth', and the lack of difference in

self-concept between treated IUGR children and normal age mates, might be due to the positive effects of two years of hGH treatment. Short stature may have great psychosocial impact on children's well-being, and clinicians should be sensitive to social and emotional needs of these children.

Acknowledgements

This research has been generously supported by Novo Nordisk Ltd. Denmark and the Sophia Foundation of Scientific Research. We thank Lya Euser (psychologist) for her help in examining the children, and the 'Dutch Working Group: Psychologists and Growth Hormone' for their cooperation.

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Chapter 6

Behavioral and emotional problems before and after two years of growth hormone treatment in intrauterine growth retarded children

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Abstract

We assessed the emotional/behavior problems, as reported by parents and teachers, in children born after intrauterine growth retardation (IUGR) and without catch up growth, before (T1) and after two years (T2) of human growth hormone (hGH) treatment. Results were compared with Dutch normative data. The possible influence of growth parameters, perinatal data, socioeconomic status and intelligence on behavior problems were examined as well. The patient sample showed significantly more behavior problems than the reference group at T1 and T2, although the number of syndromes with significantly higher scores decreased after two years of treatment. Boys obtained significantly higher scores than girls on various syndromes. Intelligence contributed significantly to the behavior problems as reported by parents (at T1) and by teachers (at T2). Results of the present study suggest a beneficial effect of hGH on emotional/behavior problems in children with short stature after IUGR, although conclusions should be drawn carefully.

6.1. Introduction

Fourteen per cent of children, born after intrauterine growth retardation (IUGR; birth length below the third percentile (P3) for gestational age) do not show catch up growth to

a height above this percentile for chronological age[1]. Since the availability of biosynthetic human growth hormone (hGH), the effects of hGH treatment on height and psychological functioning can be evaluated.

In the literature, no studies on children with IUGR, defined as limited birth length, and short stature were present to our knowledge. However, results of studies concerning children with low birth weight (LBW, <P10) are of importance as well, since 77% of the children in the present study sample had a birth weight <P3, beside a limited birth length. In these studies, as well as in studies on children with idiopathic short stature (ISS, current height <P5), behavior problems were described. However, results are contradictory and the composition of patient samples differed considerably, hampering the comparison between studies.

Parents of children with LBW reported more hyperactivity, clumsiness and poor concentration[2], more behavior problems[3-5], concentration difficulties and aggression[6] than comparison children.

Studies on children with ISS showed a higher Total Problem score on the Child Behavior Checklist (CBCL)[7], contrasted with normative data or a comparison group[8-13]. More specifically, children were significantly less socially competent and showed significantly more attention problems, social problems, thought problems and somatic complaints[8,9,11,12]. Furthermore, parents of girls with short stature and Turner syndrome reported more cruel and hyperactive behavior, and less social competence[14,15], and parents of children with growth hormone deficiency reported less social competent behavior as well[13]. Studies describing behavior at school, as reported by teachers of children with ISS, showed significantly more attention problems and social problems[12] and more hyperactivity[16], compared with children with normal height (>P3 and >P10 respectively). However, there are also studies that described no significant differences in behavior problems between children with ISS and a normative sample, as reported by parents[17,18], or between children with ISS and children with normal height (>P5), as reported by teachers[9].

In the literature, a significant relation between behavior problems and intelligence was described in children with LBW[5,19] and in children with ISS[12]. We reported earlier

that the mean intelligence quotient of the present study sample before start of growth hormone treatment was significantly lower than that of a Dutch normative sample[20]. After two years of treatment, the intelligence quotient of this sample increased significantly, but was still significantly lower when compared with the Dutch normative data[21].

Studies on the effect of hGH treatment on the behavior of children with IUGR and short stature have never been described before. The only studies that described effects of hGH treatment on behavior in children with short stature concerned girls with Turner syndrome and children with ISS. Parents of girls with Turner syndrome reported a decrease of immature/hyperactive behavior[22-24] and less internalizing behavior after two years of hGH treatment, compared with pretreatment behavior[23,24]. Teachers of this study sample reported no significant behavioral differences after two years of treatment. Two years of hGH treatment in children with ISS did not result in significant changes in behavior, as reported by their parents[23].

Results of studies on children with LBW or with short stature later during childhood are hard to compare with children with IUGR that do not show catch up growth, because of the use of different definitions and differences in etiology. Furthermore, different instruments were used. In the present study, we wanted to: (1) assess the behavior of children born after IUGR and without catch up growth (birth length <P3 for gestational age, current height <P3 for chronological age) before start of hGH treatment and after two years of treatment; (2) assess the relation between behavior and growth parameters, perinatal data and socioeconomic status. Because of the reported relation between behavior and intelligence in other studies, and the significantly lower intelligence quotients in the present sample, we investigated the relation between behavior and intelligence as well.

6.2. Subjects and methods

6.2.1. Patient sample

This study was part of the IUGR study of the Dutch Working Group on Growth Hormone. All children in the present study had a birth length below the third percentile (-1.88 SDS; standard deviation score) for gestational age[25] and had not shown catch up

growth above this percentile for chronological age at T1[26]. In 77% of the subjects, birth weight was below the P3 as well. At birth, none of the children had shown signs of severe asphyxia (defined as an Apgar score below 3 after 5 minutes). There were no indications of complicated sepsis neonatorum, and no long-term complications of respiratory ventilation. Children with chromosomal abnormalities or other possible organic causes for growth retardation were excluded, except for Silver-Russell syndrome (7 children, 8%)[27].

All children were selected from four medical centers in the Netherlands*, including three university clinics. The first 90 children, who entered the study and met the inclusion criteria, were accepted in the treatment group. The patients were assigned in a randomized and double-blind fashion to one of two dose regimens: hGH, 3 IU/m2 body surface 7 days/week and hGH, 6 IU/m2 body surface 7 days/week. The dose regimen of each child remains unknown until the end of the study, that is until all children have reached final height. Growth hormone was administered with one subcutaneous injection daily, in the evening. All protocols were approved by the Ethics Committees of the participating centres. From the parents, informed consent was obtained.

CBCL patient sample. At T1, parents of 83 children provided usable CBCLs, which means a response rate of 92%. Seven CBCLs were not completed because the child was too young (N=4), or because the parents showed insufficient understanding of the Dutch language (N=3).

At T2, 85 usable CBCLs were obtained. The response rate after two years, corrected for patients who voluntarily stopped the hGH treatment within two years (N=2) was 97%. One CBCL was not completed because of insufficient understanding of the Dutch language and two CBCLs were never returned.

TRF patient sample. A total of 79 teachers provided usable TRFs at T1. Of the remaining 11 children, no TRFs were available because children did not go to school yet (N=8), because parents did not allow the child's teacher to complete the TRF (N=1), or

* Sophia Children's Hospital (Rotterdam), the hospital of the Free University (Amsterdam), the Wilhelmina Children's Hospital (Utrecht) and the Juliana Children's Hospital (The Hague)

because of refusal of the teacher to fill in the TRF (N=1). One TRF was never returned. The response rate was 88%.

At T2, 81 teachers completed the TRF (response rate of 92%). Four TRFs were not completed because the child attended a new school for only a few weeks yet, three TRFs were never returned and TRFs of two children were not available since they voluntarily stopped the hGH treatment within two years.

Table 6.1. presents demographic information and growth parameters about the CBCL and TRF samples. Socioeconomic status (SES) was measured on a six-step scale of parental occupation, with 'I' as the lowest level[28]. If both parents were employed, the highest level of parental occupation was used. In the analyses, SES was recategorized into three groups (1 to 3), and unemployment of both parents was classified in the lowest SES level.

Reference groups. When this study was started, it was thought unethical to assign children with IUGR without catch up growth randomly to either a hGH treatment group or a non-treatment/placebo condition. Therefore, our study does not contain a control group. To compare CBCL and TRF scores of children with IUGR, we used data derived from the Dutch normative samples assessed with the same instruments[29]. The CBCL reference group at T1 consisted of 623 boys and 618 girls, aged 3-11 years. Since only two children of the CBCL patient sample were 12 and 13 years old, the age range of the reference group was selected until 11 years of age, instead of until 13 years. The two 12- and 13-year olds were included in the analyses. The CBCL reference group at T2 consisted of 712 boys and 713 girls, all 5 to 13 years old. Again, two children of the CBCL patient sample, who were 14 and 15 years old at T2, were included in the analyses.

The TRF reference group at T1 contained 518 boys and 497 girls, aged 4-11 years. One child of 12 years old and two children of 13 years old, belonging to the TRF patient sample, were included in the analyses. At T2, the TRF reference group contained 595 boys and 566 girls aged 5-13 years. One 14-year-old child of the TRF patient sample was included in the analyses.

Table 6.1. Demographic information and growth parameters of the patient sample before (T1) and after two years of hGH treatment (T2)

	CBCL		TRF	
	T1 (N=83)	T2 (N=85)	T1 (N=79)	T2 (N=81)
Age in years				
Mean (sd)	7.31 (2.31)	9.16 (2.48)	7.67 (2.28)	9.09 (2.47)
Range	3 - 13	5 - 15	4 - 13	5 - 14
Sex (%)				
Boys	64	63	60	61
Girls	36	37	40	39
SES (%)*				
I and II	39	34	43	33
III and IV	39	41	34	43
V and VI	22	25	23	24
Birth length (SDS)				
Mean (sd)	-3.65 (1.47)	-3.67 (1.44)	-3.79 (1.48)	-3.63 (1.39)
Birth weight (SDS)				
Mean (sd)	-2.63 (1.09)	-2.63 (1.07)	-2.69 (1.06)	-2.63 (1.08)
Current height (SDS)				
Mean (sd)	-2.98 (0.73)	-1.51 (0.86)	-2.95 (0.72)	-1.54 (0.87)

sd = standard deviation; SDS = standard deviation score; * I and II: skilled and unskilled manual; III and IV: skilled non-manual and self-employed; V and VI: intermediate and professional

6.2.2. *Instruments*

Parental and teacher's behavior report. The Child Behavior Checklist (CBCL)[30], and the Teacher's Report Form (TRF)[31] were used to obtain standardized parents' and teacher's reports on children's competence and emotional/behavioral problems. Both questionnaires consist of competence items (20 and 4 respectively) and 120 problem items. The competence items of the CBCL include the number of sports, hobbies, organizations, jobs and friendships, as well as ratings for the amount and quality of participation in these activities. Parents were also asked to rate how well the child gets along with siblings, with other children and with the parents. Furthermore, they were asked to rate how well the child plays and works alone. CBCL competence ratings can be

scored on the Total Competence score and on the three competence scales: Activities, Social and School. The TRF contains a scale for the teacher's mean ratings of the child's performance in academic subjects, plus a competence scale of four adaptive characteristics (how hard the child is working, how appropriately he or she is behaving, how much he or she is learning and how happy the child is) besides the problem items. In the present study, the School scale of the CBCL and the TRF scale for the academic performances were not used since intelligence data of the patient sample were present. As a result, no CBCL Total Competence score could be obtained.

The CBCL and TRF consist of eight empirically derived cross-informant syndromes (Withdrawn, Somatic Complaints, Anxious/Depressed, Social Problems, Thought Problems, Attention Problems, Delinquent Behavior and Aggressive Behavior), two broad-band syndromes (Internalizing and Externalizing), and a Total Problem score[7]. The Internalizing scale, consists of the Anxious/Depressed, Somatic Complaints, and Withdrawn syndromes, and reflects internal distress. The Externalizing scale consists of the Aggressive and Delinquent Behavior syndromes and reflects conflicts with other people and with their expectations of the child. The syndromes Social Problems, Thought Problems and Attention Problems belong neither to the Internalizing nor to the Externalizing scale. The problem items of both instruments were scored on a 3-point scale based on the preceding six months and two months respectively: *0* if the problem item was not true for their child, a *1* if the item was somewhat or sometimes true, and a *2* if it was very true or often true. Total Problem scores on both CBCL and TRF were obtained by summing the responses of each problem item. Verhulst and his co-workers translated the CBCL and TRF into Dutch and derived norms for the Dutch population[32,33].

6.3. Statistical analyses

The mean CBCL and TRF syndrome scores of the patient sample and the reference groups were compared by performing analyses of covariance (ANCOVAs) with group and sex as between-subject factors and age and SES as covariates. In order to limit chance findings (type I errors) with multiple tests, we applied a Holm correction for 11 comparisons (Total Problem Score and 10 scale scores)[34]. The contributions of growth

parameters, perinatal data, SES and intelligence to mean CBCL and TRF Total Problem scores were analyzed by means of multiple regression analyses.

6.4. Results

6.4.1. CBCL and TRF results at T1

Proportions of problem children. We compared the proportions of children in the CBCL patient sample and reference group who scored in the deviant range of the CBCL and TRF. The 90th percentile of the cumulative frequency distribution of the CBCL and TRF Total Problem scores, obtained for the reference groups used in this study, were chosen as the cut-off to distinguish children with problem behavior from children without problem behavior. Table 6.2. presents the proportions of children with problem behavior on the CBCL and the TRF in both samples and the significance of differences between the independent proportions. Due to gaps between rank ordered scores, the percentages of children from the reference group scoring above the 90th percentile were not exactly 10%. The percentage of boys and girls with behavior problems on the CBCL was significantly greater in the patient sample than in the reference group. The percentage of TRF Total Problem scores exceeding the cut-off did not differ significantly between the patient sample and the reference group.

Mean problem scores. Table 6.2. shows the mean Total Problem scores for the patient samples and for the reference groups. The Total Problem score of the CBCL was significantly higher in the total patient sample than in the reference group [$F(1,1318)=9.93$, $p<0.01$]. The TRF Total Problem score of the two total samples did not differ significantly. Table 6.3. shows the mean scores of the syndrome scales for the patient groups and for reference groups at T1. Sex effects that remained significant after Holm correction were not listed in the table. CBCL analyses showed significant sex effect on Attention Problems [$F(1,1318)=9.95$, $p<0.01$], Delinquent Behavior [$F(1,1318)=7.91$, $p<0.01$], Aggressive Behavior [$F(1,1318)=11.92$, $p<0.001$] and the Externalizing group [$F(1,1318)=12.76$, $p<0.001$]. The mean scores of boys were higher than those of the girls. TRF analyses showed significant sex effects on the same syndrome scales: Attention Problems [$F(1,1008) = 14.65$, $p<0.001$], Delinquent Behavior [$F(1,1008) =$

Table 6.2. Percentages of the patient samples (IUGR) and the reference groups exceeding cut-off scores, and mean CBCL and TRF Total Problem scores at T1

	> Cut-off (%)			Total Problem score	
	IUGR	reference	p-value	IUGR	reference
CBCL					
Boys	22.6	10.1	$p<0.01$	29.8	22.7
Girls	26.7	10.7	$p<0.01$	24.7	20.1
TRF					
Boys	14.9	10.2	ns	26.3	23.5
Girls	6.2	10.1	ns	17.5	15.9

note: mean scores are presented as adjusted means; ns = not significant

8.80, $p<0.01$], Aggressive Behavior [$F(1,1008)=19.23$, $p<0.001$], and the Externalizing scale [$F(1,1008)=19.01$, $p<0.001$], plus on the Total Problem score [$F(1,1088)=11.87$, $p<0.001$]. In all cases, scores of boys were higher as well. Neither the CBCL analyses nor the TRF analyses showed significant group by sex interaction effects. The percentage of variance of the syndrome scales that differed significantly between the patient sample and the reference group accounted for <1.0% (Aggressive Behavior) to 1.9% (Social Problems). According to Cohen's criteria for analyses of covariance[35], effects accounting for 1-5.9% of variance are considered small; 5.9%-13.8% are judged medium and >13.8% are considered large. According to these criteria, all obtained effects were small.

Competence scores. Mean scores on the CBCL competence scales Activities and Social did not differ significantly between the patient sample and the reference group. In these analyses, no sex effect or group by sex interaction effects were significant.

The mean score on the TRF competence scale of adaptive functioning was significantly lower in the patient sample [$F(1,1040)=4.45$, $p<0.05$], and girls obtained significantly higher scores than boys [$F(1,1040)=11.82$, $p<0.001$]. The group by sex interaction effect was not significant.

Table 6.3. Mean problem scores for CBCL and TRF syndrome scales of the patient samples (IUGR) and reference groups at T1

	CBCL				TRF			
	IUGR	reference	F-value*	p-value	IUGR	reference	F-value*	p-value
Withdrawn	2.23	1.80	3.50	ns	2.03	2.09	0.03	ns
Somatic Complaints	1.00	0.90	0.32	ns	0.60	0.43	1.74	ns
Anxious/Depressed	2.64	2.52	0.11	ns	2.95	3.37	0.71	ns
Social Problems	2.48	1.37	24.96	<0.001	2.51	2.17	0.80	ns
Thought Problems	0.26	0.49	3.76	ns	0.39	0.44	0.16	ns
Attention Problems	4.67	3.05	22.42	<0.001	7.96	6.49	3.25	ns
Delinquent Behavior	1.77	1.16	11.38	<0.001	0.81	0.76	0.09	ns
Aggressive Behavior	8.26	6.34	9.47	<0.01	5.38	4.57	1.01	ns
Internalizing	5.81	5.12	1.34	ns	5.50	5.76	0.11	ns
Externalizing	10.03	7.50	11.53	<0.001	6.19	5.33	0.86	ns

* degrees of freedom are (1,1318) in CBCL analyses and (1,1088) in TRF analyses; ns = not significant

6.4.2. CBCL and TRF results at T2

Proportions of problem children. The proportions of children in the patient sample and the reference group who scored in the deviant range of the CBCL and TRF after two years were compared. Results are presented in table 6.4. The percentage of boys with a Total Problem scores exceeding the cut-off was significantly higher in the patient samples than in the reference groups on both the CBCL and TRF. The percentage of girls with a Total Problem scores exceeding the cut-off did not differ significantly between the two groups.

Table 6.4. Percentages of the patient samples (IUGR) and the reference groups exceeding cut-off scores, and mean CBCL and TRF Total Problem scores at T2

	> Cut-off (%)			Total Problem score	
	IUGR	reference	p-value	IUGR	reference
CBCL					
Boys	22.2	10.3	$p<0.01$	27.1	21.9
Girls	12.9	10.4	ns	21.2	19.7
TRF					
Boys	22.4	10.3	$p<0.01$	30.9	24.4
Girls	12.5	10.4	ns	19.1	15.8

note: scores are presented as adjusted means; ns = not significant

Mean problem scores. The mean Total Problem scores of the CBCL and the TRF for the patient samples and the reference groups are presented in table 6.4. The mean scores of both total samples did not differ significantly. Table 6.5. shows the mean syndrome scale scores for the patient samples and the reference groups. After Holm correction, CBCL analyses showed significant sex effects on Attention Problems [$F(1,1504)= 11.02, p<0.001$], Aggressive Behavior [$F(1,1504)=14.90, <0.001$] and the Externalizing group [$F(1,1504)=14.40, p<0.001$]. In all cases, boys scored higher than girls. Significant sex effects on TRF problem scores were found for Social Problems

[F(1,1236)=8.01, p<0.01], Attention Problems [F(1,1236)=16.55, p<0.001], Delinquent Behavior [F(1,1236)=10.56, p<0.001], Aggressive Behavior [F(1,1236)= 40.68, p<0.001], the Externalizing scale [F(1,1236)=37.50, p<0.001] and Total Problem score [F(1,1236)=18.26, p<0.001]. All sex effects indicated higher problem scores for boys than for girls. Group by sex interaction effects were not significant. The percentage of variance accounted for on the syndrome scales, that showed significant differences between the patient sample and the reference group, was 1.1% (Attention Problems on both the CBCL and TRF).

Competence scores. At T2, mean scores on the CBCL competence scales Activities and Social did not differ significantly between the patient sample and the reference group. Girls obtained a significantly higher score on the Social competence scale than boys [F(1,1486)=3.99, p<0.05], but no group by sex interaction effects were significant. The mean score on the TRF competence scale of Adaptive functioning was again significantly lower in the patient sample [F(1,1194)=15.99, p<0.001]. The mean score of girls was significantly higher than that of the boys [F(1,1194)=10.91, p<0.001]. The group by sex interaction effect was not significant.

Mean problem score and growth parameters, perinatal data or SES. At T1, stepwise multiple regression analyses were performed in the patient sample to investigate the contribution of growth parameters (birth length, birth weight, current height and current head circumference), perinatal data (mean gestational age, way of delivery and Ponderal Index) and SES. Current height and head circumference were described as standard deviation scores (SDS), the way of delivery was dichotomized (artificial delivery or not) and the Ponderal Index was described in percentile scores. None of these variables contributed significantly to the mean Total Problem scores of either the CBCL or the TRF. After two years of hGH treatment, current height or current head circumference did not contribute significantly to the mean Total Problem scores, either.

Mean problem score and intelligence. In the present patient sample, the total intelligence quotient (TIQ) as well as the verbal IQ (VIQ) and the performance IQ (PIQ), as assessed with the Dutch version of the revised Wechsler Intelligence Scale for Children (WISC-RN)[36], were significantly lower than that of the general population before start of

Table 6.5. Mean problem scores for CBCL and TRF syndrome scales of the patient samples (IUGR) and reference groups at T2

	CBCL				TRF			
	IUGR	reference	F-value*	p-value	IUGR	reference	F-value*	p-value
Withdrawn	1.92	1.84	0.10	ns	2.38	2.10	0.87	ns
Somatic Complaints	0.92	0.95	0.03	ns	0.38	0.45	0.34	ns
Anxious/Depressed	2.69	2.71	0.00	ns	3.84	3.57	0.28	ns
Social Problems	1.84	1.38	4.49	<0.05**	2.80	2.21	2.36	ns
Thought Problems	0.34	0.48	1.46	ns	0.36	0.45	0.49	ns
Attention Problems	4.52	3.12	17.29	<0.001	9.51	6.60	13.13	<0.001
Delinquent Behavior	1.53	1.15	4.08	<0.05**	0.94	0.76	1.02	ns
Aggressive Behavior	7.50	5.88	7.32	<0.01**	6.03	4.66	2.73	ns
Internalizing	5.46	5.39	0.01	ns	6.47	5.99	0.38	ns
Externalizing	9.02	7.03	7.58	<0.01**	6.79	5.42	2.61	ns

* degrees of freedom are (1,1504) in CBCL analyses and (1,1236) in TRF analyses; ** not significant after Holm correction; ns = not significant

treatment[20]. After two years of hGH treatment, the TIQ and the PIQ increased significantly but the TIQ as well as the VIQ were still significantly lower than normative data[21]. Since intelligence might influence behavior, we assessed the contribution of intelligence to Total Problem scores of the CBCL and TRF as well. Stepwise multiple regression analyses at T1 showed that intelligence contributed significantly to the mean Total Problem score of the CBCL (β=-0.30, T=-2.42, $p<0.02$), indicating that children with a higher intelligence quotient obtained lower CBCL scores. Intelligence did not contribute significantly to the mean Total Problem score of the TRF. After two years of treatment, intelligence contributed significantly to the Total Problem score of the TRF (β=-0.28, T=-2.02, $p<0.05$), but not to that of the CBCL.

6.5. Discussion

In the present study, we assessed the behavior of a patient sample of children, all born after intrauterine growth retardation (IUGR, birth length <P3) and without catch up growth (current height <P3), before (T1) and after (T2) two years of human growth hormone (hGH) treatment. Results were compared with those of a Dutch normative sample.

At T1, the patient sample obtained significantly higher problem scores on the Child Behavior Checklist (CBCL) than the reference group: 22.6% of the boys and 26.7% of the girls of the patient sample obtained a Total Problem score within the deviant range (>P90). These results corresponded with significantly higher CBCL Total Problem scores in studies regarding children with idiopathic short stature (ISS)[8-13]; and children with low birth weight (LBW)[3-5]. Verhaar, Bosch and Maidman however, did not describe significant differences in Total Problem scores[18]. This might be explained by the way samples were selected. The latter study sample contained children with short stature (<P3), derived from the general population during a routine health check who did not seek pediatric help for their short stature. The studies on children with ISS, as well as the patient sample in the present study, contained children with short stature who sought help for their height problem in pediatric endocrine clinics. This distinction between samples might be related to the presence of more (psychosocial) problems, beside the height

problem, in the referred samples.

The patient sample obtained significantly higher scores on Social Problems, Attention Problems, Delinquent Behavior and the Aggressive Behavior syndromes, and, consequently, on the Externalizing scale at T1. In the literature, higher CBCL scores on Attention Problems and Social Problems were also described[2,6,8,9,11,12]. The higher score on Attention Problems in our patient sample was also confirmed by significantly worse performance of this patient sample on computerized attention tasks, when compared to a reference group[37]. Problems in social functioning might be related to a decrease in self-esteem. Significantly lower scores on self-esteem indices, beside significantly higher behavior problem scores, were reported in children with ISS[8,9], and in girls with Turner syndrome[14]. The present study sample obtained significantly lower scores on a self-concept scale than a comparison group before hGH treatment[38]. Problems in social functioning might also be related to the tendency in adults to treat short children as if they were younger than they are (juvenilization), the inclination to overprotect these children and the tendency to evade demands of age-appropriate behaving[39,40]. This attitude towards short children hampers social behavior like that of peers with a normal height. Furthermore, part of the parents and children told us that the child was not accepted, or did not feel accepted within peer groups because of his or her short stature. The significantly higher scores on Aggressive Behavior and Delinquent Behavior that we found in our study were not reported earlier. We hypothesize that this behavior might be a reaction on the aforementioned psychosocial attitude, or that it might be related to the child's feelings of dissatisfaction concerning his or her limited height and social functioning. More generally, we hypothesize that behavior problems in the present patient sample might also be affected by a combination of factors. The reported lower mean intelligence scores[20,21] might influence social coping mechanisms negatively, which as a result might affect self-concept in a negative way. The decrease in self-concept scores[38], again, might be related to emotional/behavior problems.

The fact that mean scores on CBCL competence scales, including the Social scale, did not differ significantly between the patient sample and the reference group, while the mean score on Social Problems was significantly higher, might be explained by the

contents of the Social Problems syndrome: this syndrome contains items that seem particularly applicable to children with short stature, like 'acts too young', 'too dependent', 'not liked by peers' and 'prefers younger kids'.

Our finding that syndrome scores, as reported by teachers on the Teacher's Report Form (TRF), did not differ significantly between the patient sample and the reference group, was also reported in a group of children with ISS[9]. Skuse and colleagues, nevertheless, found significantly more Attention Problems, Social Problems and a higher Total Problem score in children with ISS[12]. In both studies, study samples were comparable and the same instrument was used, but neither sex nor age nor the socioeconomic status (SES) were included in the statistical analyses as factors. Hence, results of these studies should be carefully interpreted.

Although TRF Total Problem scores of the present patient sample did not differ from normative data, teachers in our study reported significantly lower mean scores on the Adaptive competence scale. This finding suggests that children in the patient sample differ in their behavior at school and at home, or that teachers are less sensitive in detecting emotional/behavioral problems of the children. A relatively large percentage of children from the patient sample attended schools for special education (10% before treatment and 14% after two years treatment, versus 5% in the general population). Behavior problems, probably more frequent in children who attend schools for special education than in those attending regular schools, might be detected by parents. Parents' tendency to report problem behavior will not be influenced by the type of school the child attends, whereas teachers tend to relate the child's behavior to the average level of problems in the classroom. Special education teachers, therefore, might report slightly less problems in the child in their classroom than parents do.

Significant sex effects, with higher scores for boys than for girls, were found on both the CBCL and TRF. This result was a confirmation of an earlier study in a pediatric endocrine patient sample[11]. Since no significant group by sex interaction effects were detected in the present study, these sex effects reflect differences in scores between sexes in the Dutch general population[32]. A possible explanation for the fact that Verhaar and colleagues[18] did not detect sex effects in a study sample of short children in the general

population, is the difference in sample selection. Short statured children from the general population who did not seek pediatric help for their length might be using other coping mechanisms than referred children, and therefore behave otherwise.

Current height did not contribute significantly to the mean Total Problem scores of the CBCL or the TRF. This might be explained by the small range in height within the patient sample. Other growth parameters, perinatal data or the socioeconomic status did not influence the Total Problem scores significantly either. Intelligence, however, contributed significantly to the Total Problem score of the CBCL. This relation between behavior and intelligence was described earlier in children with LBW[5,19], and in children with ISS[12].

At T2, the mean CBCL Total Problem score of the patient sample was significantly higher than that of the reference group in boys (22.2% >P90), but not in girls. This relative decrease of behavior problems in girls was not reported in the other hGH studies concerning girls with Turner syndrome and children with ISS[23,24]. However, results of these studies are hard to compare with the present study, because of the presence of only one sex in the first study, different etiologies of short stature, and a much broader age range in both studies. Furthermore, the possible influence of sex, age and socioeconomic status were not partialled out in the statistical analyses of those studies.

The decrease in the percentage of CBCL Total Problem scores above the P90, plus the relative decrease in number of CBCL syndromes with a significantly higher mean score in the patient sample than in the reference group, might be related to growth and the hGH treatment. The children had to be less preoccupied with their short stature because their height problem was taken seriously and treatment could actually be started. This way, they were able to concentrate on other things, like social interactions with peers[39]. Juvenilization and overprotection might have been diminished as a result of their growth and children told us that they got more easily accepted in peer groups. Furthermore, a relative increase in self-concept[38] might have influenced the behavior of these children in a positive way.

The one mean syndrome score on both the CBCL and the TRF that remained

significantly higher in the patient sample after two years of treatment concerned Attention Problems. Our earlier finding that attention deficits in the present patient sample are rather stable[37], correspond with this result. The fact that the mean score on TRF Attention problems of the patient sample was significantly higher than that of the reference group at T2, but not at T1, might be related to the increased age during treatment: a larger part of the patient sample took part in scholastic tasks at T2, so that attention problems could have become more obvious to the teachers.

Sex differences in mean CBCL and TRF syndrome scores and the percentage of CBCL Total Problem score above the cut-off were also present at T2: boys obtained higher scores than girls. This again confirms the sex effects as described in the Dutch general population[29].

Scores on the CBCL competence scales did not differ significantly between the two groups, while the mean score of the TRF Adaptive competence scale was again significantly lower in the patient sample than in the reference group.

As at T1, growth parameters, perinatal data and socioeconomic status did not contribute significantly to the mean Total Problem scores of the CBCL or the TRF after two years treatment. Intelligence contributed significantly to the Total Problem score of the TRF now, but not to that of the CBCL.

The present study's results suggested a beneficial effect of hGH treatment on the emotional and behavioral functioning of children who were born after IUGR and with short stature. However, results should be carefully interpreted since no control group was available. Future studies might focus on the possible effects of (psychological) attention during medical treatment per se on emotional and behavioral problems.

Acknowledgements

This study has been generously supported by Novo Nordisk Ltd. Denmark and the Sophia Foundation of Scientific Research. We thank Wouter de Waal for providing the growth data, and the 'Dutch Working Group: Psychologists and Growth Hormone' for their cooperation.

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Chapter 7

Evaluation of growth hormone treatment by intrauterine growth retarded children with short stature and their parents

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7.1. Introduction

Since the availability of biosynthetic human growth hormone (hGH) in the mid 1980's, several growth hormone studies have been executed on various groups of children with short stature, but very little is known about how hGH treatment is experienced by children and their parents. We know of only two studies: one in children with idiopathic short stature, and one in girls with Turner syndrome[1]. Since height affects psychological functioning[2-6], and hGH treatment might influence height, the evaluation of treatment and its effects by children and parents is important.

7.2. Subjects and methods

7.2.1. Procedure

All parents and all children of at least six years old, were asked to complete the Therapy Evaluation Scale (TES) before the start of treatment and after 6, 12 and 24 months of treatment. Before the start of treatment and after 24 months, completion of the TES was part of the psychological assessment. After 6 and 12 months of treatment, the TES was completed during the regular medical control visits by 50 and 65 children, respectively. For 15 and nine children respectively, the TES was mailed to the child and its parents at

home. When the TES was completed during the medical examination, children who were not able to read thoroughly were helped by the investigator by reading questions out loud and writing the answers down. If completed at home, parents were asked to help explaining questions for their child whenever necessary, but they were explicitly requested not to influence the answer of their child in any way. Then, the TES questionnaires were either returned by mail to the psychological investigator, or returned via the medical investigator of this study.

7.2.2. Patient sample

Table 7.1. presents the numbers of children and parents who completed the TES before and during hGH treatment. Before the start of treatment, 65 from the 90 children were at least six years old. Six children had not been informed yet about the hGH treatment by their parents at the time of the first psychological assessment, because the parents preferred to tell the child about the treatment just prior to the actual start of treatment. Therefore, the number of children who were confronted with the TES before the start of treatment was 59. At the first follow-up assessment (after 6 months of treatment), 67 children reached the age criterion for the TES. However, information of two children was excluded because we expected that the parents had influenced the child during completion of the TES at home. At the follow-up assessment after 12 months of treatment, the questionnaire of one child was excluded, because this child did not understand the questions well enough to provide reliable information. At the third follow-up assessment,

Table 7.1. Number of children and parents who filled in the Therapy Evaluation Scale (TES)

	child	father	mother
Before the start of treatment	59	82	90
After 6 months of treatment	65	78	87
After 12 months of treatment	74	81	87
After two years of treatment	81	75	86

after two years of treatment, two children had voluntarily stopped the hGH treatment, and seven children, still younger than six years, did not complete the TES.

Of the parents, all mothers and 82 fathers completed the TES before the start of treatment (in eight of the 90 families, no father was present). Parents who had problems with the Dutch language, were helped by the investigator. At the follow-up assessment after 6 months of treatment, two of the mothers did not have thorough understanding of the Dutch language to complete the TES at home, and one mother never returned her questionnaire. Furthermore, information of 10 fathers lacked because no father was present, and two fathers did not return the TES forms. At the follow-up assessment after 12 months of treatment, in nine families no father was present. Furthermore, two mothers did not complete a TES because of language problems and one mother did not return her TES for unknown reasons. At the follow-up assessment after two years of hGH treatment, parents of two children did not complete the TES because their child had voluntarily stopped the treatment. Besides, in 12 parents no father was present, one mother again did not fill in the TES because of language problems, and one father and one mother did not return their questionnaire for unknown reasons.

7.2.3. Instrument

The TES was constructed by the Dutch Working Group 'Psychologists and Growth Hormone', and was used in two earlier Dutch growth hormone studies. The TES has a child and a parent version, and versions that are slightly adapted for assessment before, versus during treatment (see Appendix A for a description of the TES). The TES provides qualitative information on the expectations and experiences of the hGH treatment by the child and parents. In this chapter, a selection of TES items was described. There is no information available on the validity and reliability of this instrument.

The TES items are of an ordinal or a categorical level. The response format of ordinal items are: *1* = very easy/not painful, to *4* = very difficult/very painful, or *1* = no, to *4* = a lot. The perceived effect of hGH treatment was scored on a 6-point scale, where *1* = no growth at all, and *6* = very much growth. The categorical item, concerning the person who is giving the daily injection, was described in table 7.2. and

not further recategorized. The response possibilities of the items regarding disadvantages of treatment and changes as a result of treatment, are binomial (yes or no, present or not present). The answering category 'don't know/not answered' in various items was excluded from statistical analyses.

7.3. Statistical analyses

Frequency distributions of the TES answering categories were obtained, and mean scores of ordinal questions were analyzed. Furthermore, changes in evaluations during treatment were analyzed by repeated measurement ANOVAs with 'time' as within-factor, and sex as between-factor.

7.4. Results

7.4.1. Expectations and experiences

Table 7.2. provides information on the person who administered the daily injection. Before the start of treatment, the majority of the children reported that they expected to administer the injection themselves, while this turned out to be a minority after two years of hGH treatment. However, parents appeared to underestimate the number of children that actually injected themselves: before the start of treatment, 17% of the mothers and 22% of the fathers expected their child to inject him- or herself, while the actual percentage after two years treatment, was 35% according to the mothers, and 36% as reported by fathers.

In figure 7.1., expectations regarding the treatment prior to the start, as well as experiences after 6, 12 and 24 months of treatment by children, mothers and fathers are reported. Table 7.3. shows significant differences in treatment evaluation over time, according to figure 7.1.

The vast majority of both children and parents evaluated the administration of the injection as 'easy' or 'very easy'. Parents expected it to be significantly more difficult before the start of treatment, than it actually appeared to be.

Prior to treatment, the expected pain, caused by the daily injection, was significantly overestimated by parents. After two years of treatment, very few children

Table 7.2. Person who will administer/administers the daily injection

	before	6 months	12 months	24 months
Reported by child:				
parent(s)	15%	41%	47%	52%
child	63	40	35	37
parents and child	22	14	12	6
parents, child and others	0	2	0	3
parents and others	0	0	6	2
others	0	3	0	0
Reported by mother:				
parent(s)	35	60	64	56
child	17	26	27	35
parents and child	39	9	7	5
parents, child and others	7	0	1	1
parents and others	0	5	1	3
others	2	0	0	0
Reported by father:				
parent(s)	34	63	63	56
child	22	29	31	36
parents and child	33	8	4	5
parents, child and others	10	0	1	0
parents and others	0	0	1	3
others	1	0	0	0

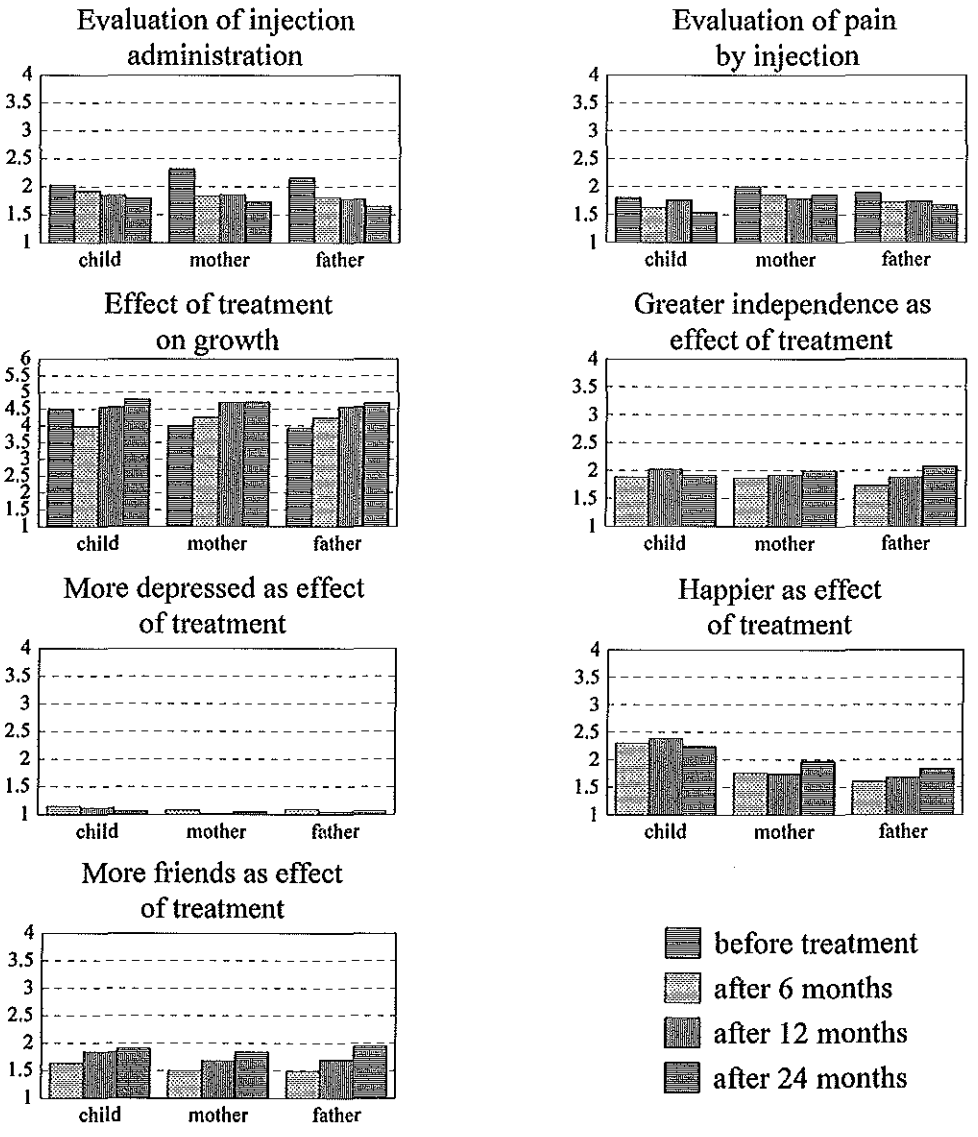
and parents evaluated the injections as 'painful' (5% of the children, 2% of the mothers and 3% of the fathers). None of the subjects evaluated the injections as 'very painful' after two years of treatment.

Concerning the effect of the hGH treatment on the child's growth, parents and children were very optimistic before the start of treatment ($\geq$80% expected that the effect on growth would at least be 'reasonable'). However, the reported effects during treatment even exceeded pretreatment expectations.

During treatment, an increasing percentage of children and parents reported that the child had become more independent as a result of hGH treatment. This increase reached the level of significance in fathers' evaluation.

The vast majority of both children and parents reported that the child had not

Figure 7.1. Expectations and evaluation of the treatment by children and their parents



note: Y-axis reflects the number of answering categories; presented data are mean scores

Table 7.3. Significant differences between mean scores at different times of assessment

item	informant	F-value	df	p-value	contrast
evaluation of injection administration	mother	16.87	3,246	<0.0001	T1>T2,3,4*
	father	13.70	3,210	<0.0001	T1>T2,3,4 and T2>T4 and T3>T4
evaluation of pain by injection	mother	2.84	3,246	<0.05	T1>T3,4
	father	4.65	3,210	<0.01	T1>T2,3,4
effect of treatment on growth	child	7.50	3,168	<0.0001	T1>T2 and T2<T3,4
	mother	30.28	3,243	<0.0001	T1<T2,3,4 and T2<T3,4
	father	25.78	3,207	<0.0001	T1<T2,3,4 and T2<T3,4
more independent as effect of treatment	father	6.40	2,140	<0.01	T2<T3,4
happier as effect of treatment	mother	3.32	2,162	<0.05	T2,3<T4
more friends as effect of treatment	mother	4.23	2,162	<0.05	T2<T3,4
	father	7.13	2,138	<0.01	T2<T3,4 and T3<T4

* 'T1' to 'T4' respectively represent evaluations before the start of treatment, and after 6, 12, and 24 months of treatment

note: since 21 repeated measurement ANOVAs were performed, significant findings on 'Evaluation of pain by injection', 'Happier as effect of treatment' and 'More friends as effect of treatment' as reported by mothers, might be chance findings

become more depressed/unhappier during treatment. On the contrary, according to their mothers, children were judged to be significantly happier as a result of treatment. Furthermore, making friends was evaluated as becoming easier during hGH treatment by children and parents.

After two years of treatment, 17% of the children reported positive changes as a result of treatment; 56% of the mothers and 41% of the fathers judged that their child had changed in a positive way as a result of treatment. These changes regarded aspects like being more self-confident, being and/or feeling more accepted by peers, and not being the shortest child in the classroom anymore.

Prior to treatment, 48% of the children, 69% of the mothers and 61% of the fathers expected disadvantages of the treatment. After two years of treatment, actual disadvantages were reported by 54% of the children, 35% of the mothers and 32% of the fathers. As disadvantages of the treatment, children often mentioned the painful vena punctures during medical control visits, and the fact that the hGH injections had to be given daily. Parents reported practical problems, such as the need for a refrigerator during holidays to store the hGH, or finding someone to inject the child while he or she was away from home (like staying a night over at a friends place, or going on a school camp).

7.4.2. Sex effects

Significant sex effects were not found. Sex by time interactions were only present with regard to the evaluation of pain by the daily injection, as reported by mothers [$F(3,246)=2.84$, $p<0.05$] and fathers [$F(3,210)=3.91$, $p<0.05$]. Mothers of sons reported more pain in their child than mothers of daughters, but pain in daughters temporarily exceeded that in sons after 6 months of treatment. Fathers of sons reported more pain in their child than fathers of daughters, although the pain in sons steadily decreased during treatment, while the pain in daughters did not show a linear change.

7.5. Discussion

Growth hormone treatment in IUGR children with short stature was evaluated before the

start of treatment as well as after 6, 12 and 24 months of treatment respectively. Evaluation was based on reports by the children themselves, and by their parents.

Before the start of treatment, 63% percent of the children expected to administer the daily hGH injection themselves, while the actual percentage after two years of treatment turned out to be 37%. This overestimation before the start of treatment might be related to several factors. First, the administration of the injection might have seemed easier than it was in reality. Furthermore, most of the children in the study sample had suffered from short stature and had to wait for the treatment to start. Once it was decided to start the treatment, the children might have denied possible difficulties as a consequence of their eagerness to become taller. Thirdly, parents might have told the child that the administration of hGH would be very easy, in order to reduce fear or to let the child accept the treatment (more) easily. Fourthly, differences before and after two years of treatment might be due to a difference in the sample compositions before and after two years treatment.

Parents' underestimation of the percentage of children, who administered the injections themselves, might be related to their own expectations concerning the injection, as well as to expectations regarding the child. Parents themselves might either have judged the administration to be difficult, and therefore not expect their child to inject him- or herself, or they might have expected their child to evaluate the administration as being difficult. Expectations concerning administration, as well as actual administration during treatment, seemed not to be clearly influenced by the child's age: some 6- or 7-year-olds injected themselves daily, while some 13- or 14-year old children still did not dare to do this. Expectations of the parents seemed to be related to personal characteristics (like parental overprotection[5] or a high level of anxiety in the child).

Two hGH studies, concerning children with idiopathic short stature (ISS) and girls with Turner syndrome, showed some reverse development in administration of the daily injection: before the start of treatment, only 14% of the children in both studies expected that they would administer daily injections themselves, while 74% of the ISS children and 50% of the girls with Turner syndrome appeared to do so after two years of treatment[1]. The same trend was reported by parents of these children. Differences between findings

of these two studies and the present study, might be related to differences in ages of the study samples (prior to treatment, mean ages in the ISS and Turner studies were 10.3 years/range 5.8-15.1 years, and 12.2 years/range 6.4-18.8 years respectively, versus 9.2 years/range 6.3-13.2 years in the IUGR sample). This might indicate that older children do not deny possible difficulties of hGH treatment prior to its start, but overestimate them.

Administration of the injection in the present study was evaluated as 'easy' or 'very easy' by the majority of parents (up to 96%) and children (88%) after two years of treatment. Surprisingly, not even half of these children administered the injection themselves. Thus, injecting oneself may remain hard or scary, even though the administration per se is easy. In the studies concerning ISS children and girls with Turner syndrome, more children evaluated the administration of the injection as 'difficult' after two years of treatment (13% and 27% respectively, versus 7% of the IUGR children in the present study)[1]. This difference is possibly related to the difference in subjects administering the injection: injecting yourself, as most of the ISS children and half of the girls with Turner syndrome did, might be evaluated as more difficult than being injected by your parents (as was the case in most of the IUGR children).

In the present study, the reported pain as caused by the injection, decreased during the treatment. After two years of treatment, the majority of the parents reported that their child perceived a little pain, as caused by the injection, while 51% of the children judged the injection as 'not painful'. Some parents and children added orally that the injection did not hurt every day, but occasionally. Complete denial of pain seems unrealistic, while some pain might be perceived: the injection still contains a needle that, although very small, might hurt sometimes. The ISS children and Turner girls, again, were more pessimistic prior to treatment and expected much more pain. Findings after two years treatment were comparable to our study: the vast majority of children and parents reported no pain at all, or a little pain after two years treatment[1]. However, 11% of the ISS children evaluated the injection as '(very) painful', against 5% of the IUGR children. An explanation for this difference remains unclear.

Pretreatment expectations of the IUGR sample regarding the effect of hGH

treatment on growth were high (80% of the children, and 82% and 83% of mothers and fathers respectively, expected that the effect would at least be 'reasonable'). Surprisingly, reported effects after two years of treatment even exceeded pretreatment expectations. These results resemble those of the ISS and Turner studies.

An increase in independence, as reported by IUGR children and their parents, was also found in the ISS and the Turner studies[1]. This finding might be related to actual growth (the child was more and more able to participate in age-related activities), as well as to an increase in self-confidence as a result of growth.

Almost all parents of IUGR children reported that their child had not become depressed/unhappier, as a result of the hGH treatment (95% of the fathers and 97% of the mothers after two years of treatment). This percentage was somewhat lower for IUGR children's self-reports (78%). However, 17% of the IUGR children did not answer this question. The ISS and Turner studies reported a higher percentage of children who had become 'a little depressed/unhappy' as a result of treatment (15% and 19% respectively)[1]. Since all ISS and Turner children answered this question, the reported higher percentages indicate a more negative effect of hGH treatment in these studies than in the IUGR study. This finding might be related to the higher mean ages in the ISS and Turner study samples, and thus be influenced by depressive feelings during puberty.

During treatment, 61% of the mothers and 54% of the fathers evaluated their child as becoming more happy as a result of the hGH treatment. Children themselves were somewhat less positive than parents after two years of treatment. This finding may be related to the fact that they got used to the (positive) effects of treatment on growth. A similar increase in happiness was reported in both the ISS and the Turner study[1].

Children as well as parents reported that making friends became easier for the child during treatment. This finding might be related to actual growth: both children and parents told that the child was more easily accepted by peers when it showed catch up growth. Besides, an more positive self-concept of the child might also have facilitated social contacts with other children[7].

Positive changes in the child, as a result of two years of treatment, were mentioned more often by parents than by the children themselves (56% of mothers and

41% of fathers, versus 17% of the children). This difference might be largely due to the fact that children's answers often concerned 'growth' ("I have grown", or "My feet have become taller and I need new shoes again"). However, according to test instructions, changes primarily regarding 'growth' were recategorized as 'no change'. The studies on ISS children and girls with Turner syndrome, did not report on this matter.

Questions concerning independence, feeling depressed/unhappy, feeling happier and the evaluation of making friends, often seemed hard to answer. The children and their parents often hesitated whether changes were due to the hGH treatment, or instead would have occurred anyhow, regardless of the treatment (and were related to other factors, like the child's age). Therefore, children and parents probably only reported changes of which they were rather certain, and results may thus be seen as fairly positive.

Examples of disadvantages of the hGH treatment were also mentioned in this chapter. Both children and parents seemed to experience some inconvenience of the treatment, despite the positive effects on growth and psychosocial well-being. This indicates that daily injections still is some load, although a bearable one.

Differences between boys and girls were hardly present, except for the pain, caused by the injection, as reported by parents. Children themselves did not report this difference. This findings indicate that hGH treatment was evaluated similarly by boys and girls.

In conclusion, the perceived advantages of hGH treatment in IUGR children with short stature seemed to exceed the disadvantages. This is also indicated by the fact that 88 of the 90 children were voluntarily treated after two years and wished to continue. Children appeared to feel and function better in daily life, and parents enjoyed the observed changes in their child. However, since no control group was available in the present study, since the secondary effects of hGH treatment (e.g. attention paid to the child by the medical doctor and psychologist, and reactions by the environment) are still unknown, and since information on the validity and reliability of the TES is not available, results should be interpreted with care.

7.6. References

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Chapter 8

General discussion

8.1. Introduction

The present study concerned the psychological effects of biosynthetic human growth hormone (hGH) treatment in intrauterine growth retarded (IUGR) children with short stature, prior to and after two years of treatment. In this chapter, clinical implications of the results as well as methodological considerations will be discussed. Finally, recommendations for future research will be presented.

8.2. Clinical consequences

This study showed that untreated intrauterine growth retarded children with short stature obtained significantly lower intelligence scores, and had significantly more attention problems, than normative Dutch children. These results suggest that these children may have been subjected to intrauterine factors causing neuropsychological dysfunction[1-3]. This dysfunction is probably related to limited head size[4-7]. However, it is also possible that neuropsychological dysfunction is a secondary effect of short stature, as a result of lack of energy for school functioning in these children, because they have to put more energy in making friends and coping with prejudices regarding height, than children with average height.

The present study also suggested a relation between short stature after IUGR and low self-esteem. These results confirm findings, described in the literature[8-13]. Lower scores in the present study sample on a self-concept questionnaire concerned the scales Social Acceptance, Athletic Competence, Physical Appearance and General Self-Worth. Regarding Social Acceptance, the impression is that IUGR children with short stature are often excluded from peer groups, because they are too small to participate in games, or because they are judged as too young as a result of their short stature. Besides, the reported low intelligence and attention problems might influence social interactions in a

negative way. As far as Athletic Competence is concerned, participation in sports is often much more difficult for small children than for children with average height. Children in the present study reported that they were often regarded as less popular in case a sports team during school gym needed to be formed. Children who are confronted with these difficulties, may develop a lower self-concept. Significantly lower scores on the Physical Appearance scale are probably related to social ideas of what is generally regarded as normal. Very short people are rare and are regarded as striking in Dutch society. Furthermore, feelings of disability, as mentioned with regard to Athletic Competence, probably interfere in a negative way with the child's evaluation of his or her own physical appearance.

Behavioral/emotional problems were found in the present study in IUGR children. Several other studies described similar results[8-16]. Significantly higher scores on the CBCL syndrome Social Problems, correspond with the above mentioned problems with social contacts and the low self-concept regarding social acceptance. Significantly higher CBCL Attention Problem scores for the IUGR group versus the comparison group corresponds with the attention deficits found with the SVAT. Significantly higher CBCL scores on the Delinquent Behavior syndrome might be related to decreased feelings of self-worth and being less accepted by peers. Children may be inclined to do things that are not allowed in order to obtain some respect or admiration.

All these findings indicate that the present study sample is at-risk for maladaptive behavior, and that these children require help. Fortunately, this group can be detected in an early stage: IUGR can be noticed at birth, and, if so, catch up growth usually will take place before the age of two[17]. Furthermore, since small head circumference appeared to be significantly related to problems with cognitive functioning, cognitive development and school functioning should be assessed at regular intervals in order to detect problems. Developmental risks can thus be determined for each individual child, and extra stimulation in cognitive functions may be advised whenever necessary.

Besides, parents should be informed about possible developmental risks of their child and should be offered educational support. In the present study, parents often told the investigators about persistent eating problems of their child, starting when he or she

was very young. Eating becomes even more important for parents of short children, since parents worry about the child's height and relate eating directly to growing. Thus, serious conflicts between parents and the child can occur during early development of the child, and these conflicts may be harmful for the parent-child relationship. Providing information at an early stage and offering help whenever necessary, may be beneficial.

Results of the present study showed that intelligence scores increased and attention problems decreased somewhat during the period of hGH treatment. Increase of intelligence might be a primary or a secondary effect of the hGH treatment. It is largely unknown if cerebral mechanisms are involved in hGH suppletion. The finding that the increase in intelligence regarded the performance IQ, but not the verbal IQ, might suggest some relation between hGH suppletion and cerebral mechanisms, since performance tasks are believed to be more directly related to cerebral functions than verbal functions (which depend more on social interactions). A possible secondary effect of hGH treatment is that children, treated with hGH, can pay better attention to school tasks as a result of their increased psychological well-being. These children may show an increase in social functioning (e.g. increase in self-concept, more social contacts, being teased less often), and this in turn may influence cognitive functions in a positive way.

The decrease in attention problems may be related to similar mechanisms. In addition, the relative increase in tempo on the attention task might be an effect of increased muscle power, one of the believed (side-)effects of hGH suppletion. However, the presence of the majority of attention problems after two years of hGH treatment might indicate at least some neuro(psycho)logical dysfunction.

Furthermore, the present study reported an increase in self-concept after two years of hGH treatment: scale scores of Social Acceptance and General Self-Worth increased significantly in longitudinal analyses. Parents reported that children were more often able to perform age-appropriate (like participating in sports or cycling on a 'large' bike). As a result, these children were accepted by peers more easily and their self-confidence increased. The present results suggest that self-concept in short IUGR children can be influenced. Therefore, we recommend stimulation of positive self-concept as early as possible, maybe as soon as children with short stature go to school and are confronted

with criticism by other children and adults. This can for example be effectuated by praising the child's qualities and positive characteristics, instead of emphasizing limitations as a result of short stature. Parents should talk with their child about negative reactions on their short stature, and explain that these prejudices are linked to social standards but therefore are not automatically true. Alternatively, ideas like 'small is beautiful' or 'a short stature is just perfect' might be promoted.

The decrease in behavioral/emotional problems after two years of hGH treatment concerned a decrease in scores on the CBCL scales Social Problems and Delinquent Behavior. The decrease in social problems probably reflects the aforementioned amelioration in social functioning. We hypothesize again that a decrease in delinquent behavior might be closely related to this phenomenon as well: there is less need for these children to attract (negative) attention because they obtain more positive attention. The finding that attention problems persist, largely underlines the SVAT results after two years of treatment.

Growth hormone treatment probably gives children the feeling that their growth problem is taken seriously by parents and doctors, and children may experience some control over their situation as a result of active treatment. Besides, hGH treatment seemed to have some very positive primary and/or secondary effects on psychological functioning of IUGR children with short stature, during an important developmental phase. These positive effects may influence the further development of the child, irrespective of the effect of treatment on final height. Even if the final outcome on growth turns out to be disappointing in the future, the increase in e.g. self-concept and social contacts might have had a tremendous positive effect on the development of the child's personality.

Prenatal checks in pregnant at-risk women (e.g. women with infections like rubella or toxoplasmosis, women with placental dysfunctions in earlier pregnancies, women with (a history of) substance abuse, or women with other IUGR children)[18] are recommended in order to detect IUGR at an earlier stage. That way, it might be considered to shorten the duration of such pregnancies deliberately, in order to restrict prenatal developmental risks in the child.

Moreover, thorough follow-up by medical and psychological specialists in this at-

risk group is advised as well, especially when these children and their parents were not counselled and supported early during development. Pediatricians should pay attention to the psychosocial well-being of the child. Furthermore, they should inquire about school functioning and concentration problems, since several studies described higher percentages of children with short stature, enrolled in special education, than children of average height[19-23]. Close collaboration between pediatricians and psychologists is important, in order to detect any developmental problems of the child and, if necessary, to refer the child to other specialists.

8.3. Methodological considerations

This study did not employ a control group of untreated IUGR children with short stature because of ethical considerations. Although the results of the present study are very suggestive for a positive outcome of hGH treatment on psychological functioning, a randomized pretest-posttest design is required to draw definitive conclusions about this subject[24]. Possible secondary effects, such as the preoccupation with height and growth, the effects of getting daily injections, or the obtained extra attention by (medical) specialists, parents and the social environment, remain unknown in a study design without a control group. Furthermore, the possible influence of normal development can only be studied when an untreated, randomized control group of IUGR children with short stature is part of the study design.

Secondly, the present study sample is rather heterogeneous with respect to duration of gestation of the children, their birth weight, chronological age and parental height. Thus, the effect of hGH treatment on growth and, secondarily, on psychological functioning, might be affected by these factors.

Another methodological problem concerns the number of children in the present study. Psychological assessment procedures often have age restrictions and, as a result, only a subgroup of the entire present study sample could be assessed with a particular assessment procedure. This problem became even clearer in the longitudinal analyses. Therefore, test results often concerned a much smaller number of children than the maximum of 90 and conclusions became less clear because of a decrease in statistical

power.

8.4. Recommendations for future research

The only way to draw firm conclusions about psychological effects of a medical treatment, is to study a treated group and an untreated control group in a randomized way. Therefore, in future studies regarding IUGR children with short stature, an untreated control group is required. In order to avoid ethical problems, a study design should contain treatment periods for both study groups, being 'treatment group' and 'control group' alternately. For example, the first group might be treated with hGH for a two- or three-year period, while the second (control) group remains untreated. Then, the group who received hGH treatment becomes control group during the same period of two or three years, while the former control group receives hGH treatment.

Secondly, study samples in future studies should be more homogeneous than the present study sample with respect to duration of gestation (either preterm or term born children), birth weight (below P3 or not), age (because of the relation between age and growth) and parental height (e.g. both parents with a height above P3). Thus, the effects of differences in these factors on outcome measures will be minimized.

Furthermore, as many psychological instruments have age restrictions, age ranges of future study samples should be narrow in order to study enough children longitudinally.

In addition, information about the etiology of IUGR is desirable, since it may help in understanding the possible relation between IUGR and the failure to catch up growth. In the future, advancement in prenatal assessments might provide information about this subject.

The present study has generated ideas about the psychological development of IUGR children with short stature. It has given rise to some hypotheses about relations between hGH treatment and psychological functioning, and it has provided suggestions for future research. Hopefully, future studies will give us information about the long-term psychological effects of hGH treatment in IUGR children with short stature.

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Therapy Evaluation Scale; child version for use before start of treatment

Subject no.: .....
Date: .....
Medical centre: .....

The following questions concern the growth hormone treatment.
Please mark the circle that reflects your expectation.

1. **Who will give the daily injections?**
   o parent(s) o child o parent(s) and child
   o parent(s), child and others o parent(s) and others o others
2. **What is your opinion about how the administration of the injections will be?**
   o very easy o easy o difficult o very difficult
3. **I expect the injections to be:**
   o not painful o a little painful o painful o very painful
4. **What effect do you expect of the growth hormone treatment? (How much do you expect to grow?)**
   o no growth at all o very little growth o a little growth
   o reasonable growth o much growth o very much growth
5. **What is your height at this moment? .....**
   How many cm have you grown in the last year? .....
   How many cm do you expect to grow in the next year? .....
6. **The decision to start growth hormone treatment was probably not an easy decision. Can you tell me why you want to start with the growth hormone treatment? Please describe .....**
7. **Do you expect any disadvantages of the treatment?**
   o yes, present o no, not present o don't know

Therapy Evaluation Scale; parental version for use during treatment

Subject no.: .....
Date: .....
Medical centre: .....

The following questions concern the six months of growth hormone treatment in your child.
Please mark the circle that reflects your opinion.

1. **Who administers the daily injections?**
   o parent(s) o child o parent(s) and child
   o parent(s), child and others o parent(s) and others o others
2. **What is your opinion about the administration of the injections?**
   o very easy o easy o difficult o very difficult
3. **I think the injections are:**
   o not painful o a little painful o painful o very painful
4. **What is the opinion of <u>your child</u> about the administration of the injections?**
   o very easy o easy o difficult o very difficult
5. **<u>My child</u> thinks the injections are:**
   o not painful o a little painful o painful o very painful
6. **How much length did your child gain?**
   o no length at all o very little o a little
   o reasonable o much o very much
7. **How long is your child at this moment? .....**
   How many cm has your child grown during the past six months of growth hormone treatment? .....
   How many cm do you expect that your child will grow in the next year? .....
8. **Will you continue the growth hormone treatment? If yes, for what reasons? If no, why not?**
9. **Disadvantages of the treatment are**
   o present o not present o don't know
10. **Has your child become more independent as an effect of treatment?**
    o no o a little o rather o a lot o don't know/not answered

Therapy Evaluation Scale; parental version for use during treatment (continued)

11. **Has your child become depressed/unhappier as an effect of treatment?**
    o no o a little o rather o a lot o don't know/not answered
12. **Has your child become happier as an effect of treatment?**
    o no o a little o rather o a lot o don't know/not answered
13. **Is it easier for your child to engage in social contacts/with friends as an effect of treatment?**
    o no o a little o rather o a lot o don't know/not answered
14. **Do you think your child has changed in a positive way as an effect of treatment (besides growth)?**
    o no o yes o don't know
    If yes, please describe the change(s)
    .....

Summary

In the present study, we investigated the psychological effect of short stature in children with intrauterine growth retardation, before and after two years of biosynthetic human growth hormone (hGH) treatment.

In **chapter 1**, the criteria for 'short stature' and 'intrauterine growth retardation' (IUGR) were outlined: 'short stature' was defined as current height <P3 for chronological age, and 'IUGR' as birth length <P3 for gestational age. The main aim of the present study was to compare intelligence, attentional capacity, behavior problems and self-concept of IUGR children before start of hGH treatment, with that of children of normative samples, and to assess possible changes of these variables across the two year treatment period. To answer these questions, 90 children, born after IUGR and with short stature, were studied. All children received hGH treatment, and were assessed twice: the first assessment took place within one month before the start of treatment, and the second assessment was two years later. At the start of the current study, there were objections against an untreated control group of IUGR children with short stature.

In **chapter 2**, the intelligence of 63 IUGR children with short stature was described (Dutch version of the revised Wechsler Intelligence Scale for Children; WISC-RN). Total IQ, and both verbal and performance IQ, were significantly lower than those of normative Dutch children. Current head circumference and current height were significantly associated with total IQ: the larger the head circumference and the taller the children, the higher the intelligence scores. These results suggest a relation between IUGR without catch up growth and lowered intelligence.

Chapter 3 concerned the intelligence of children during hGH treatment. In 59 IUGR children with short stature, pretreatment intelligence scores were compared with results after two years of treatment. The mean total IQ and the mean performance IQ increased significantly across the two year period. This was also the case for the mean score on the subtest 'Block Design', as well as for the Bannatyne spatial-analytic factor and the Kaufman perceptual organization factor. Both the total IQ and the verbal IQ after

two years of hGH treatment were lower than those for Dutch normative children. Neither length gain nor current height were significantly correlated with the increase in total IQ after two years treatment. In this chapter, effects of hGH treatment on intelligence were suggested.

In **chapter 4**, we reported on the assessment of attention (Sonneville Visual Attention Tasks; SVAT) before and after two years of hGH treatment in a sample of 48 IUGR children (pretreatment) with short stature, and 41 IUGR children (after two years treatment). Results were compared with a sample of Dutch school children. Before start of treatment, IUGR children showed significantly more deficits in divided, focused and sustained attention than the comparison sample. IUGR children performed less accurate, more impulsive and slower, and they showed more variability in reaction time than the school children. After two years of hGH treatment, deficits in divided and sustained attention were significantly greater in the IUGR group than in the comparison sample. However, deficits in focused attention were not present anymore. At the second assessment, IUGR children were less accurate, more impulsive and showed more variability in reaction time, but their tempo in performing the task was not lower anymore than the comparison children. The influence of various growth parameters and perinatal data was assessed. Current head circumference and the way the child was delivered were significantly correlated with attention measures: delay in reaction time after an error was lower in children with smaller head circumference, and a 'normal' delivery contributed significantly to a faster memory search. Besides, intelligence appeared to affect attention significantly as well: the higher the intelligence scores, the better the performance on these attention tasks. We hypothesized that IUGR and attention deficits are related.

In **chapter 5**, we described the comparison of the self-concept (Self-Perception Profile for Children; SPPC) of IUGR children with short stature, with that of Dutch school children. Prior to treatment, IUGR children obtained significantly lower mean scores on the scales 'social acceptance' and 'general self-worth', compared with the Dutch school sample. After two years of treatment, the mean scale scores of the 17 IUGR children, who were assessed at the two time points, did not differ significantly from those of children in the school sample. After two years of treatment, intelligence was

significantly correlated with the SPPC scale 'scholastic competence': the higher the intelligence, the higher the scores on this scale. The results in this chapter suggest that shorter children have a lower self-concept than children with average height.

In **chapter 6**, we reported on behavioral and emotional problems in IUGR children with short stature (measured with the Child Behavior Checklist; CBCL). IUGR children showed significantly more behavioral and emotional problems than children in a Dutch normative sample before and after two years of hGH treatment. However, the number of syndromes with significantly higher scores for IUGR children versus norm children, was lower for the second assessment after two years. Growth parameters, perinatal data nor SES contributed to the mean total behavior problem score, but there was a significant relation between intelligence and behavioral/emotional problems: the higher the intelligence level, the lower the level of behavioral/emotional problems. The results of this chapter suggest some beneficial effect of hGH treatment on behavioral and emotional problems.

In **chapter 7**, we described the treatment evaluation by both children and parents. After two years of hGH treatment, the injection was administered by parents in the majority of the families. During treatment, the administration of the injection appeared to be easier than was expected by parents, and they overestimated the pain, caused by the injection. Prior to treatment, the majority of both the children and their parents had high expectations regarding the hGH treatment. Reported effects after two years treatment even exceeded these expectations. Neither children nor their parents reported that children became depressed or unhappy as a result of treatment. On the contrary, fathers and mothers, respectively, evaluated the children as significantly more independent and happier. Furthermore, parents reported that making friends became significantly easier during treatment. Reported disadvantages of the hGH treatment by parents often concerned practical problems like needing a refrigerator during holidays to store hGH, while children often mentioned the painful vena puncture during medical control visits. When asked for positive changes as a result of treatment, children and parents frequently mentioned the child's enhanced psychosocial well-being.

In **chapter 8**, some consequences and recommendations for the clinical practice

were reported, as well as critical remarks and recommendations for future research. Concerning clinical practice, the present study group was indicated as an at-risk group, requiring help at an early stage of development. Assessment of the cognitive development and school functioning at regular intervals was recommended, in order to detect problems. Thus, extra stimulation in cognitive or school functioning can be advised whenever necessary. Furthermore, parents should be informed about developmental risks, and educational support should be offered. Thorough follow-up of these at-risk children by medical and psychological specialists was recommended, in addition to early stimulation of a positive self-concept. Finally, prenatal checks in at-risk women were advised.

Critical remarks regarded methodological aspects of the study. For future research, a pretest-posttest control group was strongly recommended, in order to draw firm conclusions about the effects of hGH treatment. Moreover, the study group should be homogenous with respect to duration of gestation, birth weight and chronological age of the child, and parental height (height $>$P3). Information about the etiology of IUGR is desirable in future studies.

Samenvatting

In deze studie onderzochten we het psychologische effect van kleine gestalte na intra-uteriene groeiretardatie (IUGR) vóór de start van groeihormoonbehandeling (GH-behandeling), en na respectievelijk 6, 12 en 24 maanden behandeling.

In **hoofdstuk 1** werden de criteria voor 'kleine gestalte' en 'IUGR' gedefinieerd. Met 'kleine gestalte' werd een lengte beneden de 3e percentiel (P3) voor chronologische leeftijd bedoeld, en met 'IUGR' een geboortelengte beneden de P3, gecorrigeerd voor de duur van de zwangerschap. De belangrijkste doelstelling van deze studie was om: a) intelligentie, aandachtsvermogen, zelfbeeld, en gedragsproblemen en emotionele problemen van kinderen met IUGR vóór aanvang van de GH-behandeling te vergelijken met gegevens van kinderen uit normpopulaties, en b) eventuele veranderingen van deze variabelen na twee jaar GH-behandeling te onderzoeken. Om deze doelstelling te bereiken, werden 90 IUGR-kinderen met een kleine gestalte onderzocht. Alle kinderen werden met GH behandeld en tweemaal psychologisch getest: de eerste keer binnen een maand voor aanvang van de GH-behandeling en de tweede keer twee jaar later. Er waren bij de aanvang van dit onderzoek overwegende ethische bezwaren tegen het betrekken van een onbehandelde controlegroep van IUGR-kinderen met een kleine gestalte in de studie.

In **hoofdstuk 2** werd het intelligentieniveau van 63 IUGR-kinderen met een kleine gestalte beschreven (gemeten met de Nederlandse, herziene versie van de Wechsler Intelligence Scale for Children). Zowel het totale IQ, als het verbale en performale IQ van deze groep kinderen lag significant lager dan dat van kinderen uit de Nederlandse normpopulatie. Hoofdomtrek en huidige lengte bleken significant van invloed te zijn op het totale IQ: hoe groter de hoofdomtrek en hoe langer de kinderen, hoe hoger het IQ was. De resultaten suggereerden een verband tussen een kleine gestalte na IUGR en een verlaagd intelligentieniveau.

In **hoofdstuk 3** werd het intelligentieniveau van IUGR-kinderen tijdens GH-behandeling beschreven. Het IQ van 59 IUGR-kinderen met kleine gestalte werd vergeleken met het IQ van diezelfde groep kinderen na twee jaar GH-behandeling. Het

gemiddelde totale IQ en het performale IQ stegen significant tijdens deze periode. Ditzelfde gold voor de gemiddelde score van de subtest 'Blokpatronen' en voor Bannatyne's ruimtelijk-analytische factor en de perceptuele organisatiefactor van Kaufman. Zowel het totale IQ als het verbale IQ van de IUGR-kinderen bleef echter significant lager dan dat van kinderen uit de Nederlandse normgroep. Huidige lengte noch lengtegroei tijdens twee jaar behandeling waren significant gerelateerd aan de toename in de totale IQ-score na twee jaar behandeling. In dit hoofdstuk werd een effect van GH-behandeling op intelligentie verondersteld.

In **hoofdstuk 4** werd een onderzoek naar het aandachtsvermogen beschreven (gemeten met Sonneville Visual Attention Tasks). Voorafgaand aan de GH-behandeling werden 48 IUGR-kinderen met kleine gestalte getest, na twee jaar behandeling waren dit 41 kinderen. De testresultaten zijn vergeleken met die van een steekproef van Nederlandse schoolkinderen. Voorafgaand aan de behandeling hadden de IUGR-kinderen significant meer problemen met verdeelde, gefocusseerde en volgehouden aandacht dan de groep schoolkinderen. Ze waren minder accuraat, reageerden impulsiever en trager, en hun reactietijd varieerde meer. Na twee jaar GH-behandeling had de IUGR-groep meer problemen met verdeelde en volgehouden aandacht in vergelijking met de groep schoolkinderen, maar de problemen met gefocusseerde aandacht waren verdwenen. Hoewel het tempo van de IUGR-kinderen tijdens de test niet verschilde van dat van de groep schoolkinderen, varieerde hun reactietijd wel meer. Verder presteerden de IUGR-kinderen minder accuraat en reageerden ze impulsiever. De invloed van diverse groeiparameters en perinatale gegevens op aandachtsvermogen werd ook onderzocht. Zowel hoofdomtrek als de wijze waarop de bevalling van het kind plaatsvond (al dan niet d.m.v. een kunstverlossing), bleken significant te zijn gecorreleerd met het aandachtsvermogen. Kinderen met een geringere hoofdomtrek lieten, nadat ze een fout hadden gemaakt tijdens de test, minder vertraging in reactietijd zien dan kinderen met een grotere hoofdomtrek. Kinderen, die zonder kunstverlossing waren geboren, hadden een snellere geheugenzoektijd dan kinderen die door middel van een kunstverlossing waren geboren. Daarnaast bleek intelligentie een significante invloed op het aandachtsvermogen te hebben: hoe intelligenter het kind, hoe beter zijn of haar aandachtsvermogen was. In

dit hoofdstuk werd gesteld dat IUGR en aandachtsproblemen gerelateerd zijn.

In **hoofdstuk 5** werd het zelfbeeld van IUGR-kinderen met een kleine gestalte vergeleken met dat van een groep Nederlandse schoolkinderen (onderzocht met het Self-Perception Profile for Children). Voorafgaand aan de GH-behandeling behaalden IUGR-kinderen significant lagere gemiddelde scores op de schalen 'sociale acceptatie' en 'algemene zelfwaardering', dan de groep Nederlandse schoolkinderen. Na twee jaar GH-behandeling waren er geen significante verschillen tussen de schaalgemiddelden van de 17 longitudinaal onderzochte IUGR-kinderen en de vergelijkingsgroep. Intelligentie in de IUGR-groep na twee jaar GH-behandeling bleek significant gecorreleerd te zijn met de schaal 'schoolse bekwaamheid': hoe hoger de intelligentie, hoe hoger de scores op deze schaal waren. Resultaten van dit hoofdstuk suggereerden dat kinderen met een kleine gestalte een lager zelfbeeld hebben dan langere kinderen.

In **hoofdstuk 6** werden de gedragsproblemen en emotionele problemen van IUGR-kinderen met een kleine gestalte beschreven (gemeten met de Child Behavior Checklist; CBCL). Zowel voor de start van de GH-behandeling, als na twee jaar behandeling vertoonden IUGR-kinderen significant meer gedragsproblemen en emotionele problemen dan kinderen uit een Nederlandse normatieve steekproef. Na twee jaar GH-behandeling bleek het aantal CBCL-syndromen, met een significant hogere score dan de vergelijkingsgroep, echter kleiner te zijn. Groeiparameters, perinatale gegevens noch sociaal-economische status droegen significant bij aan de gemiddelde probleemscore van de CBCL. Er bleek echter wel een significant verband te bestaan tussen intelligentie enerzijds, en gedragsproblemen en emotionele problemen anderzijds: hoe hoger het intelligentieniveau, des te geringer de gedragsproblemen en emotionele problemen. De bevindingen van dit hoofdstuk suggereerden enig positief effect van GH-behandeling op gedragsproblemen en emotionele problemen.

In **hoofdstuk 7** werd de subjectieve evaluatie van de GH-behandeling door IUGR-kinderen en hun ouders beschreven. Na twee jaar behandeling bleek de dagelijkse prik meestal door de ouders te worden gegeven. Ouders vonden het toedienen van de GH-prik makkelijker, en gaven aan dat hun kind deze als minder pijnlijk beoordeelden, dan ouders vooraf hadden verwacht. Het merendeel van de IUGR-kinderen en hun ouders hadden

vooraf hoge verwachtingen van de GH-behandeling ten aanzien van de groei, maar het effect van de behandeling bleek de verwachtingen nog te overtreffen. Kinderen noch ouders gaven aan dat de kinderen somberder of ongelukkiger waren geworden door de GH-behandeling. Daarentegen rapporteerden vaders een toename in het percentage kinderen, dat zelfstandiger was geworden, en moeders een toename in het percentage kinderen dat gelukkiger was geworden ten gevolge van de behandeling. Ouders gaven ook aan dat het voor hun kind makkelijker was geworden om sociale contacten te leggen en vrienden te maken, als gevolg van de GH-behandeling. Als nadelen van de behandeling noemden ouders vaak praktische problemen, zoals de noodzakelijke aanwezigheid van een koelkast tijdens vakanties om GH in te bewaren, terwijl kinderen de pijnlijke bloedafname tijdens de medische controle vaak als nadeel noemden. Gevraagd naar positieve veranderingen in het kind ten gevolge van de GH-behandeling, werden vaak verbeteringen in het psychosociale functioneren en het welzijn genoemd.

Hoofdstuk 8 bevat zowel aanbevelingen voor de klinische praktijk, als kritische opmerkingen en aanbevelingen voor toekomstig onderzoek. De huidige onderzoeksgroep werd aangeduid als een risicogroep, waaraan in een vroeg stadium van de ontwikkeling hulp en aandacht zou moeten worden geboden. Er werd aangeraden om de cognitieve ontwikkeling van deze kinderen regelmatig te onderzoeken en hun schoolfunctioneren te evalueren. Op die manier kunnen eventuele problemen tijdig worden onderkend en kan extra hulp worden geboden. Daarnaast werd geadviseerd om informatie aan de ouders te verschaffen betreffende de mogelijke risico's in de ontwikkeling van hun kind, en om hen hulp te bieden bij het opvoeden. Medische en psychologische controle in de loop van de ontwikkeling van deze kinderen werd eveneens aanbevolen, naast het vroegtijdig stimuleren van een positief zelfbeeld. Tenslotte werd prenataal onderzoek geadviseerd bij vrouwen met een verhoogd risico op het krijgen van een kind met IUGR.

Kritische kanttekeningen met betrekking tot de huidige studie betroffen methodologische aspecten. In toekomstig onderzoek is de aanwezigheid van een onbehandelde controlegroep onontbeerlijk om de effecten van GH-behandeling goed te kunnen onderzoeken. Daarnaast dienen de IUGR-kinderen in een toekomstig onderzoek zo min mogelijk variatie in zwangerschapsduur, geboortegewicht en chronologische leeftijd te

tonen, is het wenselijk dat verschillen in de lengte van de ouders kleiner zijn (bv. lengte boven de P3) en is meer informatie omtrent de etiologie van IUGR gewenst.

Dankwoord

Bij de uitvoering van het hier beschreven onderzoek en de totstandkoming van dit proefschrift zijn veel mensen betrokken geweest. Velen hebben hun medewerking verleend en actief bijgedragen, even zovelen hebben op de achtergrond een belangrijke rol gespeeld. Al deze mensen wil ik graag bedanken.

Alle kinderen en ouders uit het onderzoek wil ik hartelijk danken voor hun medewerking aan het psychologisch onderzoek en voor de prettige contacten. Ik vond het, mede dankzij jullie, heel leuk om dit onderzoek uit te voeren en heb veel van jullie geleerd.

Prof. dr F.C. Verhulst; beste Frank, ik wil je graag bedanken voor je stimulerende begeleiding en voor je bereidheid om te allen tijde mee te denken over het onderzoek. Daarnaast wil ik je bedanken voor je begrip en steun tijdens moeilijke fasen van het onderzoek en voor de kansen die je me hebt geboden.

Mw dr F.M.E. Slijper; lieve Froukje, ik heb veel aan jou te danken. Jij hebt vanaf het begin van het onderzoek onvoorwaardelijk vertrouwen in mij en mijn functioneren gehad en dat ook regelmatig laten merken. Jij hebt me altijd gesteund en me veel geleerd, en doet dat nog steeds. Ik ervaar de vele momenten van persoonlijk contact, evenals onze samenwerking, als heel bijzonder.

Prof. dr S.L.S. Drop, prof. dr J. Passchier en prof. dr J.D. van der Ploeg wil ik hartelijk danken voor hun bereidheid om deel uit te maken van de kleine commissie en het manuscript voor mijn proefschrift kritisch te lezen. Prof. dr J.M. Wit en prof. dr F. Verheij dank ik voor het feit dat zij zitting willen nemen in de grote commissie.

Prof. dr S.L.S. Drop, mw dr A.C.S. Hokken-Koelega en mw dr S.M.P.F. de Muinck Keizer-Schrama; beste Sten, Anita en Sabine, jullie wil ik hartelijk bedanken voor jullie inzet als kinderarts-endocrinologen om aan de studie ook een psychologisch protocol te verbinden. Jullie overtuiging dat het psychologisch functioneren van de "IUGR-kinderen" tijdens groeihormoonbehandeling van groot belang is, is een waardevolle stimulans voor mij geweest.

Verder wil ik Novo Nordisk A/S Denmark en Novo Nordisk Farma B.V. Nederland bedanken voor de bereidheid om de psychologische studie financiëel en praktisch te steunen. Novo Nordisk Farma B.V. Nederland wil ik verder graag danken voor de financiële steun bij het uitgeven van het proefschrift.

Mw dr A.A.J.M. Hazebroek-Kampschreur wil ik hartelijk danken voor haar hulp en inzet bij het samenstellen van een vergelijkingsgroep vanuit de GG en GD. Dat deze vergelijkingsgroep in de praktijk, tot mijn grote teleurstelling, te heterogeen bleek om onderzoeksvragen te helpen beantwoorden, doet niets af aan de fijne samenwerking.

Dr J. Huisman, dr G. Sinnema, drs R. Drost; beste Jaap, Gerben en Rob, graag wil ik jullie en de medewerkers van het VU-ziekenhuis, Wilhelmina Kinderziekenhuis en Juliana Kinderziekenhuis bedanken voor de prettige samenwerking, de gastvrijheid en de mogelijkheid tot patiëntenoverleg wanneer dit nodig was.

Sandra van Mourik-Huigens, Lya Euser en Ienke Buik wil ik danken voor hun hulp bij het onderzoeken van de kinderen en het voeren van de gesprekken met de ouders. Lya, jou wil ik in het bijzonder bedanken voor de nauwgezette en betrokken manier waarop je gedurende drie jaar aan het onderzoek hebt meegewerkt.

Janneke van Nieuwkasteele, ik vond het leuk om met jou samen te werken. Nog steeds loop ik graag even je kamer binnen om te horen hoe het met de studie-kinderen gaat, of om gezellig bij te praten.

Verder wil ik alle collega's van de afdeling Kinder- en Jeugdspychiatrie bedanken voor alles wat ik van hen heb geleerd en voor de plezierige jaren. Er zijn een aantal collega's en oud-collega's die ik met name wil bedanken. Jan van der Ende, jou wil ik natuurlijk bedanken voor je hulp en geduld bij statistische problemen en voor het feit dat je altijd tijd had of tijd wilde maken, maar vooral voor het prettige persoonlijke contact. Inge Gravesteijn, ik wil je bedanken voor de fijne samenwerking als collega en voor alle momenten die onze omgang voor mij meer dan 'collegiaal' maakten. Ik vind het ontzettend leuk dat je mijn paranimf wilt zijn! Marianne Kasius, dank je wel voor je gezelligheid, je steun en de gedeelde ervaringen als "eerste AIO's". Ik hoop dat we in de toekomst weer collega's worden. Hans Koot, ik wil je bedanken voor je adviezen en het meedenken wanneer ik met een (onderzoeks-)vraag bij je kwam. Q Andriessen, ik vind

dat jij altijd met veel respect omgaat met patiënten en ouders. Dank je wel voor de manier waarop je "mijn" patiënten vlekkeloos wist in te voegen in de gebruikelijke patiëntenstroom. Robert Ferdinand, ook al ben je even geen directe collega meer, het was een leuke tijd samen op de afdeling en hopelijk wordt het dat in de toekomst ook weer. Edwin van den Oord, wij begonnen tegelijkertijd op de afdeling te werken, samen op één kamer. Ik wil je bedanken voor de flexibiliteit die het vereist om met iemand die patiënten ziet, een kamer te delen. Het was misschien niet altijd praktisch, maar wel leuk. Francine Leenders, dank je wel voor je bereidheid om in te springen en een oudergesprek te voeren wanneer ik 'omhoog zat'.

Ik wil mijn vriendinnen en vrienden bedanken voor hun medeleven en interesse in mijn doen en laten. Deze klus zit erop, maar ik hoop dat de wederzijdse betrokkenheid blijft.

Een wel heel speciale plaats in dit onderzoek heeft Wouter de Waal ingenomen. Lieve Wout, via jou ben ik bij het onderzoek betrokken geraakt. Sommige mensen waren aanvankelijk wat terughoudend toen zij hoorden dat wij samen, als neef en nicht, het onderzoek zouden uitvoeren, maar ik heb geen ogenblik getwijfeld. Ik vond het fantastisch om samen met jou ruim vier jaar "onze" kinderen te volgen. Zo vertrouwd, gezellig en eigen als met jou had de samenwerking met niemand anders kunnen zijn.

Dan mijn ouders; lieve mam en pap, ik wil jullie danken voor de mogelijkheden die jullie me altijd hebben geboden, en vooral voor de ruimte die jullie me gaven om mijn eigen weg te gaan. Pap, ik los met veel plezier de belofte in om jou als paranimf te vragen!

Mijn zussen, Astrid en Carola, jullie wil ik bedanken voor de gezelligheid en het plezier dat we hebben. Ik hoop dat dat zo blijft!

Tot slot, Matt. Ik moet er niet aan denken dat ik dit onderzoek niet was gaan doen.... Het leven met jou is heerlijk.

Curriculum vitae

Ilse van der Reijden-Lakeman werd geboren op 12 november 1967 te Purmerend. Vanaf 1979 bezocht zij het Titus Brandsma Lyceum in Oss en behaalde in 1985 haar V.W.O.-diploma. Van 1985 tot 1991 studeerde zij Psychologie aan de Rijks Universiteit Utrecht, met als afstudeerrichting Cognitieve Functiestoornissen. In het kader van deze studie onderzocht zij de effectiviteit van een taalbehandelingsprogramma bij kinderen met taal- en/of spraakproblemen (september 1988 tot januari 1989), en liep zij stage op de afdeling Neuropsychologie van het Academisch Ziekenhuis in Leiden (september 1989 tot juli 1990). In maart 1991 begon zij haar promotieonderzoek op de afdeling Kinder- en Jeugdpsychiatrie van het Sophia Kinderziekenhuis te Rotterdam (hoofd: Prof. Dr F.C. Verhulst), resulterend in dit proefschrift. Vanaf september 1994 is zij, gedurende één dag per week, verbonden aan de afdeling Plastische Chirurgie en belast met de psychodiagnostiek en begeleiding van kinderen met een schedel- en/of aangezichtsafwijking. Sinds september 1995 is zij voor drie dagen per week werkzaam op de afdeling Kinder- en Jeugdpsychiatrie van het Sophia Kinderziekenhuis als psychodiagnosticus.

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