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Behavioral evaluation of GH treatment in short statured children and adolescents: Findings from a pilot study

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ABSTRACT. A cohort of 93 short-statured children and adolescents undergoing GH treatment were evaluated with respect to behavior, emotions, and attitudes. The sample consisted of patients suffering from either idiopathic GH deficiency or neurosecretory dysfunction (no.=47), Turner syndrome (no.=20), organic GH deficiency due to brain tumors (no.=10), or other etiologies (no.=16). The Child Behavior Checklist (CBCL) together with a brief Evaluation of Treatment Questionnaire (ETQ) were filled out by the patient's parents. These evaluations were performed at onset and after 12 and 24 months of GH treatment, respectively. There was a highly significant but clinically small decline of behavioral abnormalities over time and parents saw major benefits of GH treatment in the total group of patients. The behavioral changes over time were independent of diagnostic category, gender, height velocity, puberty and age.
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INTRODUCTION

Various studies indicate that children with short stature are at increased risk for psychological maladjustment due to low self-esteem, stigmatization, and inadequate coping (1-3). These studies found distinct personality features, lower self-esteem, increased rates of behavior problems, and lower social competence in short-statured children (4-9).

In contrast, there is another small series of studies that found on average normal psychological functioning in their subjects (10-16). The obvious differences in results may be due to different patient selection, the variety of psychological instruments that were used, and the various informants, including parents, teachers, and the children themselves that were used in the various studies. In addition, referral bias may have contributed to the assumption that short stature implies a psychological handicap (14-15). In fact, a recent study has shown that non-referred short children in the population in contrast to short children referred for evaluation and treatment do not show behavioral abnormalities (17).

During the last 3 decades, short statured children have been treated with GH, but very limited psychological evaluation has been done on the effects of this kind of intervention. The first trials indicated that there are no behavioral effects of GH replacement *per se*. Clopper (18) concluded in his review that, as a group, children undergoing GH treatment, while not grossly maladjusted, are prone to experience problems with academic achievement and social adjustment. At that time, there was also conflicting evidence that GH treatment is associated with behavioral improvement.

During the last 10-12 yr, recombinant human GH treatment with daily sc injections has entirely replaced pituitary GH treatment. A few studies have been launched in order to evaluate the behavioral effects of this more recent treatment approach. However, beyond the study outlines, very limited findings have been reported so far (1, 10, 19-21). Currently, there is conflicting evidence concerning whether or not GH treatment has beneficial behavioral effects on short statured children (22, 23). Thus, the present study was undertaken in order to shed some light on the issue of a definite behavioral effect of GH treatment.

Key-words: Growth hormone treatment, behavior, evaluation, short statured children, adolescents.

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MATERIAL AND METHODS

Subjects

Short statured patients were recruited by pediatric endocrinologists from 68 children hospitals in Germany. Due to the inclusion criteria of the psychological study (chronological age of at least 4 yr; allowance for a time discrepancy of somatic and psychological assessment of ±3 months at T_2 and T_3), only 93 (39.2 %) of a total of 237 patients could be studied longitudinally. Based on clinical and laboratory assessments patients were grouped by the doctors into the following diagnostic categories: short stature due to: 1) idiopathic growth hormone deficiency or neurosecretory dysfunction (IGHD; no.=47), 2) Turner syndrome (TS; no.=20), 3) organic growth hormone deficiency (OGHD) due to brain tumors (no.=10), 4) other etiologies, including idiopathic short stature, chronic inflammatory disease, or chronic renal insufficiency (other etiologies (OE); no.=16). Thus, a total of 93 patients were evaluated for treatment with human GH (Somatropin; daily sc injections), and their auxological and laboratory data were documented within the Kabi Pharmacia International Growth Study (KIGS). A good response to GH treatment was defined by a constant height velocity of >+1 standard deviation score (SDS) at both 12 and 24 months. Start of puberty was defined by Tanner stage B2 for girls and testicular sizes ≥4 ml for boys.

Auxological and socio-demographic data of the subjects are shown in Table 1. The four groups did not differ significantly with regard to chronological age and social class distribution, whereas height SDS's [German references values (24)] were significantly lower (p<0,01) in patients with IGHD, TS, and OE than in patients with OGHD at the start of GH treatment. The mean GH dose was significantly higher (p<0.01) In groups 2 (TS) and 4 (OE) than in groups 1 (IGHD) and 3 (OGHD). Mean target height SDS of group 3 was significantly higher in comparison with the other groups. GH treatment induced a significant increase of height velocity and height velocity SDS in all groups after 1 and 2 yr.

Furthermore, a comparison of the auxological and GH treatment data (6 variables) of the 93 participants and the 144 non-participants did not reveal any statistically significant difference so that there was no selection bias of patients. A separate table may be requested from the Authors.

Procedure

GH stimulation tests and GH measurements were performed in the labs of the German children hospitals that are participating in the multicenter KIGS. Serum GH levels were measured locally by different methods. GH deficiency (GHD) was defined as a maximum GH level <10 ng/ml in 2 stimulation tests. Neurosecretory dysfunction (NSD) was defined as mean GH levels <3 ng/ml after an overnight spontaneous secretion profile (at least 30 samples). GH dose was not tailored by measuring IGF-I levels. The latter are not monitored in the KIGS. A good response to GH treatment was defined by a constant height velocity of >+1 SDS at both 12 and 24 months. Start of puberty was defined by Tanner stage B2 for girls and testicular sizes ≥4 ml for boys.

Behavioral assessment took place at baseline before treatment (t_1), and after 12 (9-15) months (t_2) and 24 (21-27) months (t_3) on GH therapy. At these times, German speaking parents filled out 2 questionnaires in terms of parallel forms. First, the German version of the Child Behavior Checklist (CBCL) was used (25). The items of the behavior problem section of the CBCL are grouped into 9 corresponding cross-informant syndromes labeled Withdrawn, Somatic Complaints, Anxious/Depressed, Social Problems, Thought Problems, Attention Problems, Delinquent Behavior, and Aggressive Behavior. From these syndromes 2 broad-band second-order scales are derived. These scales are called Internalizing Behavior and Externalizing Behavior and reflect the distinction between fearful, inhibited, and overly controlled behavior on the one hand and aggressive, antisocial, and under controlled behavior on the other hand. Furthermore, a total score is computed. Scores are expressed on a T-scale (mean=50, SD=10). In addition to the CBCL parents were asked to respond to a total of 10 questions in order to evaluate the attitude towards treatment. Because of the small number of items, there was no intention of forming a scale but rather the items were analyzed descriptively.

Table 1 - *Auxological (medium values) and sociodemographic data at start, first year and second year of GH-treatment.*

	IGHD (no.=47; 35 M, 12 F)			TS (no.=20; 20 F)			OGHD (no.=10; 7 M, 3 F)			OE (no.=16; 8 M, 8 F)		
	Start	1 yr	2 yr	Start	1 yr	2 yr	Start	1 yr	2 yr	Start	1 yr	2 yr
CA	9.3	10.3	11.3	9.2	10.2	11.2	11.6	12.4	13.4	8.8	9.8	10.8
Height SDS (CA)	-3.3	-2.4	-2.0	-3.6	-3,1	-2,9	-2.1	-1.6	-1.3	-4.0	-3.5	-3.0
Height velocity (cm/yr)	4.4	8.8	7.8	4.2	7.6	6.6	1.8	8.1	7.9	4.4	8.3	7.6
Height velocity standard deviation score (SDS) (CA)	-1.6	+2.4	+1.8	-2,3	+1,8	+1,2	-3.0	+2.4	+2.5	-1.5	+2.6	+1.2
GH dose (IU/kg/week)	0.50	0.54	0.57	0.87	0.91	0.85	0.44	0.47	0.53	0.66	0.77	0.72
Pubertal stages												
Tanner 1	40	34	28	20	17	14	9	8	8	15	15	14
Tanner G2/B2 or more	7	13	19	0	3	6	1	2	2	1	1	2
Target Height SDS		-1.31			-1.17			-0.57			-1.18	
SES (no)												
Lower class		21			11			6			8	
Middle class		18			9			3			8	
Missing data		8			-			1			-	

CA: chronological age; IGHD: idiopathic GH deficiency; OE: other etiologies; OGHD: organic GH deficiency; SDS: standard deviation score; SES: socioeconomics status; TS: Turner syndrome.

Statistical analyses

Data were analyzed by use of multivariate analyses of variance (MANOVA) and multiple regression analyses.

RESULTS

Firstly, the CBCL scale scores were analyzed controlling for the 3 times of assessment (repeated measurements), diagnostic category, and gender. The time factor indicating a significant decline of scores was significant for the following CBCL scales (Fig. 1): social withdrawal (WILKS LAMBDA=0.91, F=4.22, p=0.02), somatic complaints (WILKS LAMBDA=0.922, F=3.59, p=0.03), anxious/depressed (WILKS LAMBDA=0.869, F=6.38, p=0.003), and delinquent behavior (WILKS LAMBDA=0.928, F=3.32, p=0.04). As a consequence (Fig. 2) both secondary scales for measuring internalizing behaviors (WILKS LAMBDA=0.871, F=6.31, p=0.003) and externalizing behaviors (WILKS LAMBDA=0.927, F=3.34, p=0.04), and the total score (WILKS LAMBDA=0.905, F=4.46, p=0.01) showed a significant decline over time. There were no further significant effects on any scales scores, neither by diagnostic category nor by gender or any interaction of factors.

In order to better understand the potential determinants of behavioral change, 2 alternative hypotheses were tested. The first asked whether or not effective GH treatment itself resulted in behavioral changes, whereas the second hypothesis asked for

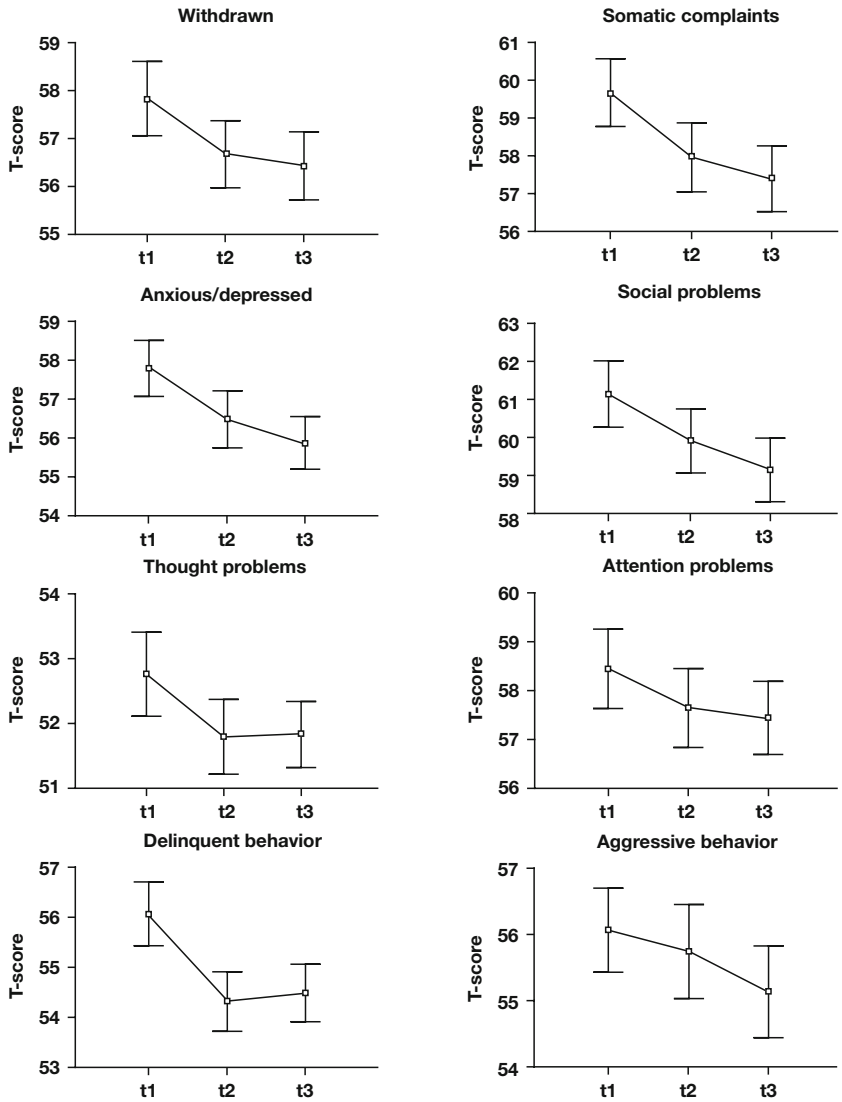

Fig. 1 - *Mean Child Behavior Checklist (CBCL) primary scale scores at baseline (t_1), after 12 months (t_2), and after 24 months (t_3) in the total group of patients (no.=93).*

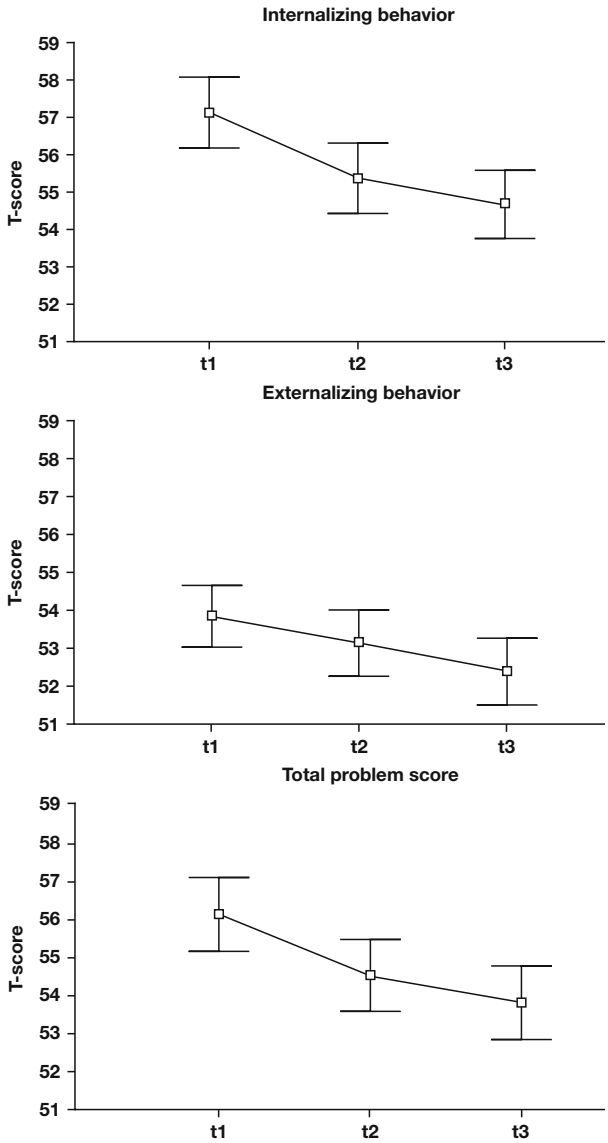

Fig. 2 - *Mean Child Behavior Checklist (CBCL) secondary scale scores at baseline (t_1), after 12 months (t_2), and after 24 months (t_3) in the total group of patients (no.=93).*

developmental changes as reflected by increasing age and pubertal development.

When testing the first hypothesis the total group of patients was split into those patients who had grown successfully during the entire treatment period and those in whom there was a good growth response only in one of the two observation periods (t_1 to t_2, or t_2 to t_3). For the behavioral scores of the CBCL, differences between t_1 and t_3 measurements were calculated. These difference scores were then compared between the groups with different height velocities during GH and either present or absent onset of puberty. Multivariate analyses across the 8 CBCL scales indicated that there was only a trend for a growth effect (WILKS LAMBDA=0.852, F=1.74, *p*=0.10) but no effect for onset of puberty (WILKS LAMBDA=0.890, F=1.30, *p*=NS). For the more aggregated scores of Internalizing and Externalizing Behaviors and the total scores, none of the various analyses for the CBCL scores resulted in any significant effect for either growth or onset of puberty. Subsample sizes were too small to analyze any differential effect for diagnostic category in these analyses.

The alternative hypothesis that the observed changes were due to developmental changes was tested by analyzing age effects. For the CBCL data, age at t_2 was categorized into 3 groups (<6, 6-13, >13 yr). There were no significant age effects (WILKS LAMBDA=0.818, F=1.10, *p*=NS) across the 8 primary scales. Furthermore, the parents' satisfaction with the treatment was evaluated both at t_2 and t_3. Findings are shown in Table 2. In general, the parents provided a favorable evaluation of treatment and showed little criticism. The responses at t_2 did not differ markedly from t_3 responses.

Finally, we tried to predict the change in behavior, *i.e.*, in the CBCL total score by the following variables: age, sex, socioeconomic status, and growth. The dependent variable was the difference between the two CBCL total scores that were measured at t_1 and t_3. Multiple regression analyses indicated that none of these variables was significantly related to the difference in CBCL total scores.

DISCUSSION

This pilot study clearly has some limitations, namely the relatively low participation rate of the original sample and the reliance on a single source of information, *i.e.*, the parent. However, the present study does not suffer from a selection bias of patients and is based on a sufficiently large sample of short statured children and adolescents who underwent GH treatment. Repeated behavioral evaluations showed that the overall effect on growth was associated with a decline of questionnaire scores for behavioral and emotional abnormalities according to the parents' evaluation. These changes are significant but small in magnitude because all mean profiles are within the normal range. However, the question as to the causal relation between behavioral changes and growth is not easy to answer. First, it has to be admitted that conclusions are jeopardized due to the lack of an untreated control group. Thus, the possibility cannot be entirely ruled out that the observed changes reflect the statistical phenomenon of regression toward the mean of

Table 2 - *Evaluation of treatment (percentages) by parents in the total group of patients (no.=93).*

	t_2 12 months	t_3 24 months
1. Treatment did not only help physically	84	76
2. Treatment is being experienced as distressing	19	22
3. Resistance towards the injections	4	19
4. Significant developmental progress since onset of treatment	84	70
5. Wish for discontinuation of treatment	2	10
6. Problems of coping with growth	4	11
7. Continuous encouragement needed in order to continue with treatment	14	17
8. Desire for remaining short	2	5
9. Acceptance of inconvenience of treatment because of desire to grow	97	81
10. Unproblematic treatment	82	65

the distribution over time. Whereas it would have been unethical to withhold treatment from a treatable control group, we were not in a position to repeatedly evaluate a control group of short statured children without an indication for GH treatment. Even a referred group of children with normal or idiopathic short stature would have been unsuitable because of a potential selection bias favoring psychosocial liability.

Alternatively, we performed various analyses as to the association of growth and behavioral changes. Clearly, there was no significant relation between these 2 parameters. Neither there was significant association between onset of puberty and behavioral changes. The alternative test for age as a significant predictor of behavioral changes also did not result in a viable explanation. Thus, there is little room for the assumption that our patients became less maladjusted with increasing age, reflecting a general pattern of psychosocial maturation. Although there are indications from this study that GH treatment is well tolerated and that parents perceive a strong association between the decline of distress and the decline of behavior abnormalities, the link between growth and behavior was not as evident as one might expect.

Hypothetically, some mediating psychological variable might create a causal relation between growth and decline of behavioral and emotional abnormalities. Variables of this kind might include improved coping skills or self-esteem that have been found to be relevant in many short statured children. Besides a relatively simple assessment in one study (20), these variables have so far not been studied in patients undergoing GH treatment and certainly deserve more attention in future studies. Furthermore, as Stabler *et al.* (21) have suggested, the effects may be related to the putative social value associated with increased height, the changing expectations of the parents, and perhaps even indirect effects of GH treatment on the brain due to neuroendocrine mechanisms. However, the latter would pertain mainly to the modulation of mood, affects, and attention via hypothalamic-pituitary mechanisms. Whereas this is a potential explanation for the decline of mainly internalizing behaviors, as found in the Stabler *et al.* study (21), this would be a less viable explanation for the decline of Externalizing Behaviors that were also seen in the present study. Furthermore, here was no significant effect on behavioral change by diagnostic category. These findings match our previous results in the larger sample of 311 children and adolescents with the same diagnostic categories (9). From these previous studies we concluded that probably short stature *per se*, rather than a specific diagnosis has an impact on behavioral adaptation. Thus, future studies with different diagnoses may wish to find out whether or not there is a specific effect of diagnosis on behavioral change in association with GH treatments.

So far, there is little room for comparison with other studies. Attempts to evaluate the behavioral effects of GH treatment have been scarce, and the sample compositions are different as regards the diagnostic entities that were included. Our findings of small, but statistically significant positive behavioral changes in association with GH treatment are somewhere between the observations of a recent collaborative study by Stabler *et al.* (21), who also used the CBCL for the evaluation of GH treatment over a 3-yr period, and the more reserved conclusion of a recent study by Downie *et al.* (10) that, to date, no psychological benefits of GH treatment have been shown. Long-term outcome studies must show whether any substantial behavioral effects are sustained and prevent the quality of life of short statured adults from being impaired.

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