GH dependence and GH withdrawal syndrome in GH treatment of short normal children: evidence from growth and cardiac output

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Abstract

The child's age is a significant determinant of the outcome of GH therapy; prepubertal children respond better on both short term and long term growth, whereas adolescents tend to accelerate their bone maturation more than growth. The present study was designed to evaluate the efficacy of an interrupted GH therapy protocol of young, short normal children. GH was given for a period of 3 years, or until they reached the 25th percentile, then discontinued at a young age (not more than 9 years), and then the children's growth followed until final height. Yet, after discontinuation of GH therapy, growth came close to a complete stand-still. The present report focuses on describing the period beyond GH withdrawal and its impact on growth and cardiac performance. Twenty-two children received daily s.c. injections of 0.9 mg/m² hGH and 12 children were the control, untreated group. Growth and echocardiography were followed during therapy and 2 years thereafter. During GH treatment growth velocity accelerated markedly over the first year; it slowed down over the second and third years, and decelerated after GH withdrawal to a velocity that was significantly lower than pretreatment values. Growth rate remained low for the next year, and recovered to pretreatment velocity by the fourth semiannual measurement. To evaluate the role of the GH–IGF-I axis during the growth deceleration, serum IGF-I, insulin-like growth factor-binding protein-3 (IGFBP-3), and an arginine stimulation test were performed at 1, 3 or 6 months after GH withdrawal, and compared with pretreatment response. GH response was 70% of pretreatment values by 1 month and recovered completely by 3 months post treatment. Serum IGF-I and IGFBP-3 levels were normal throughout. End-systolic and end-diastolic left ventricular dimensions as well as cardiac output did not change during the 2 year course of GH therapy, but fell significantly during the initial 6 months of GH withdrawal. Thus, daily injections of GH to prepubertal short normal children is associated with development of drug dependence, followed during the abstinence period by deceleration of growth and reduction of cardiac output to levels that are lower than pretreatment values. After GH therapy for 30–36 months the withdrawal syndrome persists for 18 months, and is not induced by alterations of serum levels of GH or IGF-I.

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Introduction

The controversy about growth hormone (GH) therapy of idiopathic short stature (ISS) consists of dilemmas on the definition of normal stature, the social approach, ethics and economical considerations (1). All these need to be based on factual grounds of the potential benefit and possible risks of such therapy. During 1–4 years of GH therapy, short children increase their growth rate and height standard deviation score (SDS) similar to the response seen in classical GH deficiency (GHD) (1–4). The long term results are variable, with reports of no increase in the final height (5, 6), a small increase (7), or a marked increase (8, 9). As the collaborative Israeli study of efficacy and safety of GH

therapy was analyzed (10), we realized that in 65 boys with GHD or neurosecretory dysfunction, aged 3–15 years, treated with 3 times weekly 0.1 mg/kg s.c. GH, the child's age was the most significant determinant of therapy outcome; boys of the prepubertal age group gained over the course of 3 years an average 8 cm of predicted adult height, pubertal boys over the age of 12 years showed a negative correlation of their predicted height gain against age, and boys over the age of 14 years showed a loss of predicted height during GH therapy.

The present study was, therefore, designed to evaluate the efficacy of GH therapy in an interrupted protocol of young ISS children, i.e. to treat them with GH for a period of 3 years or until they reached the 25th

percentile, to discontinue therapy at a young age (no more than 9 years), and to follow growth until final height.

As evidence is accumulating that GH is a physiological regulator of myocardial growth and performance (11), an echocardiography follow-up was added to the protocol.

The short term response to therapy was positive, as expected, and growth will be followed until final height. Yet, after interruption of GH therapy, growth came close to a complete stand-still.

The present report focuses on a description of the period after GH withdrawal and its impact on growth and cardiac performance.

Patients and methods

Thirty-four ISS children, aged 2–6 years were studied. Criteria for ISS were: height less than -2 SDS; growth rate more than -1 SDS; bone age less than 75% of chronological age; and serum GH concentration on an arginine stimulation test more than $10 \mu\text{g/l}$.

Twenty-two children received daily s.c. injections of hGH (BioTropin, BioTechnology General Ltd, Rehovot, Israel) at a dose of 0.9 mg/m^2 surface area. Twelve children were the control, untreated group. The control group were children who were referred by their parents to the growth clinic, but did not wish to receive GH therapy. The clinical characteristics of the treated group and the controls are summarized in Table 1. The protocol was approved by the Helsinki Committees of the Rambam Medical Center and the Israel Ministry of Health. Consent was obtained from the parents. Treatment was continued until the child reached the 25th percentile, but no longer than 3 years. The children were measured at 3-month intervals, bone age was assessed yearly (by the Greulich and Pyle method), as were serum insulin-like growth factor-I (IGF-I), insulin-like growth factor-binding protein-3 (IGFBP-3) and alkaline phosphatase. Twenty-one of the treated, and all 12 control children completed 5 years of follow-up.

Echo-Doppler evaluation was performed before GH therapy, and yearly for 2 years of GH therapy, as well as

at 6 and 12 months after interruption of therapy. Left ventricular long- and short-axis 2D-guided views were obtained. Apical four-chamber views were recorded (12). Heart rate, aortic and pulmonary valve area and flow integrals were determined to derive stroke volume and cardiac output. Results were normalized with respect to body surface area. Left ventricular dimensions were measured from left ventricular end-systolic and end-diastolic dimensions. Left ventricular wall width was measured in end-diastole, obtaining left ventricular (free) inferior wall and inter-ventricular septum dimensions. Aortic and pulmonary valve internal diameters served to calculate the respective valve areas. Valve area multiplied by its flow integral gave the stroke volume, which was multiplied by heart rate (per minute) to give cardiac output.

Serum GH was measured by a double antibody RIA kit (HGHK-2, Sorin Biomedica, Saluggia, Italy), with a sensitivity of $0.3 \mu\text{g/l}$ and intra- and interassay variability of 7.7 and 11% respectively. Serum IGF-I was measured by an RIA kit (Incstar Corp., Stillwater, MN, USA), with a sensitivity of 2 nmol/l , and intra- and interassay variability of 8.4 and 10.3% respectively. Serum IGFBP-3 was measured by an IRMA kit (Diagnostic System Lab., Webster, TX, USA), with an intra- and interassay variability of 3.9 and 8% respectively.

The body mass index (BMI, kg/m^2) is expressed as SDS for age. Results are expressed as mean $\pm$ s.d. Statistical significance was evaluated by a Student's *t*-test, and *P* values of less than 0.05 were considered statistically significant.

Results

Auxology

Nineteen of the children completed 3 years of GH therapy and three children discontinued treatment as they reached the 25th percentile after 30, 30 and 33 months. During the first year of GH treatment, growth velocity accelerated from -0.5 ± 1.1 SDS to 3.8 ± 1.3 SDS (Fig. 1, upper panel). It decelerated to 1.7 ± 1.0 SDS by the second year, and to 1.0 ± 0.9 SDS ($n=22$) by the third year ($n=19$). After GH withdrawal, growth decelerated in every child over the first 6 months to a velocity that was significantly lower than pretreatment values (-2.9 ± 1.9 SDS, $P<0.05$). It remained low at -2.8 ± 1.8 SDS for the next year, and recovered to pretreatment velocity by the fourth semiannual measurement. Growth velocity of the control group remained unchanged and fluctuated between -0.7 ± 0.6 SDS and -1 ± 1.4 SDS. Height SDS increased in the treatment group from -2.6 ± 0.4 SDS to -1.0 ± 0.3 SDS at therapy interruption, and declined to -1.6 ± 0.4 SDS in 2 years post treatment (Fig. 1, middle panel). Table 2 summarizes auxological data, including height predictions. Due to the young

Table 1 Clinical characteristics of the GH-treated group and the control patients before GH therapy (mean $\pm$ s.d.).

	GH treated (<i>n</i> = 22)	Control (<i>n</i> = 12)
Age (years)	5.4 ± 0.9	5.1 ± 1.0
Height (SDS)	-2.6 ± 0.4	-2.4 ± 0.4
BMI (SDS)	-0.77 ± 0.60	-0.70 ± 0.71
Growth velocity (SDS)	-0.5 ± 0.6	-0.7 ± 0.6
Peak serum GH ($\mu\text{g/l}$)	14.9 ± 3.7	12.5 ± 4.0
Serum IGF-I (nmol/l)	20.1 ± 8.9	14.5 ± 6.0
Serum IGFBP-3 (mg/l)	3.4 ± 0.7	3.0 ± 1.1

Figure 1 Auxological data in controls (hatched bars), during 3 years of GH therapy (dotted bars) in short normal children, and for 2 years after therapy discontinuation (open bars). Upper panel, growth velocity; middle panel, height; lower panel, BMI. Mean $\pm$ s.d. * $P < 0.05$, ** $P < 0.01$ vs pretreatment.

age, it was not possible to calculate height predictions before therapy. The difference in predictions between treated and control children averaged 8 cm by the end of treatment ($P < 0.001$) and 5 cm 2 years later ($P < 0.01$). The BMI on and off GH were not statistically different, but the trends were clear (Fig. 1, lower panel). On GH therapy BMI SDS decreased by the first year from a mean -0.77 to -0.91 . The effect waned by the second year (-0.87) and disappeared by the third (-0.76), thereby increasing by the second half year post therapy to levels that were higher than pretreatment (-0.59).

GH-IGF-I axis

To evaluate the role of the GH-IGF-I axis during the growth deceleration, an arginine stimulation test (0.5 g/kg) was performed in eight of the children 1 month after GH withdrawal, in five of the children 3 months and in ten of the children 6 months after GH withdrawal, and compared with pretreatment response by a paired t -test (Fig. 2). Peak GH was $14.9 \pm 3.7 \mu\text{g/l}$ before treatment, 9.7 ± 3.5 at 1 month, 12.3 ± 5.4 at 3 months, and 12.5 ± 5.2 at 6 months (not significant (NS) at all times). Serum IGF-I remained unchanged (Fig. 2), and was $20.1 \pm 8.9 \text{ nmol/l}$ pretreatment, 21 ± 7.9 at 1 month off treatment, 20.5 ± 7 at 3 months, and 18 ± 4.2 at 6 months (NS), and not different from control values. Serum IGFBP-3 remained unchanged (Fig. 2), and was $3.4 \pm 0.7 \text{ mg/l}$ pretreatment, 3.2 ± 0.4 at 1 month post treatment, 3.7 ± 0.5 at 3 months and 3.4 ± 1.3 at 6 months (NS), and not different from control values.

Bone maturation

The bone age advanced over chronological age by a mean of $3.3/3$ 'years'/year during treatment, and by a further $1.8/2$ 'years'/year after GH withdrawal (Fig. 3, upper panel). Serum alkaline phosphatase increased from a pretreatment value of $188 \pm 18 \text{ U/l}$ to 252 ± 40 at 2 years of GH treatment (NS), declined to $166 \pm 22 \text{ U/l}$ at 6 months off GH ($P < 0.05$), and normalized at 12 months post treatment at $215 \pm 56 \text{ U/l}$ (Fig. 3, lower panel).

Echocardiography

Incomplete compliance of the control group with yearly echocardiography did not allow for meaningful summary of that group. End-systolic and end-diastolic left ventricular dimensions of the GH-treated group are shown in Fig. 4A and B. The diastolic diameter did not change during the 2 year course of GH therapy, but it fell significantly during the initial 6 months of GH withdrawal from 4.9 ± 0.77 to $3.8 \pm 0.13 \text{ cm/m}^2$ ($P < 0.05$), and remained low at $3.7 \pm 0.6 \text{ cm/m}^2$ by 12 months post therapy. Likewise, the systolic diameter did not change during GH therapy, and fell significantly during the initial 6 months of GH withdrawal from 2.9 ± 0.17 to $2.0 \pm 0.04 \text{ cm/m}^2$ ($P < 0.01$), to normalize at $2.6 \pm 0.6 \text{ cm/m}^2$ by 12 months post therapy. Resting cardiac output was calculated from pulmonary and aortic stroke volumes and heart rates. Pulmonary output (Fig. 4C) did not change during the 2 years of GH therapy, but fell during the initial 6 months of GH withdrawal from 4.3 ± 2 to $3.1 \pm 0.9 \text{ l/min per m}^2$ ($P < 0.01$), and remained low at $3.2 \pm 1.1 \text{ l/min per m}^2$ by 12 months post therapy ($P < 0.01$). The aortic cardiac output (Fig. 4D) did not change during GH therapy, fell significantly during the initial 6 months of GH withdrawal from 5.3 ± 1.8 to $4.3 \pm 0.95 \text{ l/min per}$

Table 2 Summary of auxology before GH treatment, at the end of treatment and 2 years after GH therapy. Growth velocity data relate to the most recent 6 month period. Adult height predictions were done by the TW-2 method (13), and, due to the young age, were not possible before treatment. Mean $\pm$ s.d..

	GH treated	Control
Pretreatment		
Height (SDS)	-2.6 ± 0.4	-2.4 ± 0.4
Growth velocity (SDS)	-0.5 ± 0.6	-0.7 ± 0.6
Bone age – calendar age (years)	-1.1 ± 0.4	-1.0 ± 0.5
End of treatment		
Height (SDS)	$-1.0 \pm 0.3^{***}$	-2.2 ± 0.5
Growth velocity (SDS)	1.0 ± 0.9	-1.0 ± 0.4
Bone age – calendar age (years)	$-0.9 \pm 0.8^{**}$	-1.9 ± 0.6
Height prediction (cm)	$164 \pm 5^{***}$	156 ± 3
Two years after treatment		
Height (SDS)	$-1.6 \pm 0.4^*$	-2.0 ± 0.6
Growth velocity (SDS)	-0.6 ± 0.9	-1.0 ± 0.4
Bone age – calendar age (years)	$-1.3 \pm 0.9^*$	-2.0 ± 0.8
Height prediction (cm)	$166 \pm 4^{**}$	161 ± 3

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ vs control.

m^2 ($P < 0.01$), and remained low at 4.3 ± 0.89 l/min per m^2 by 12 months post therapy ($P < 0.01$). The patients and parents denied any symptoms that might be related to cardiac insufficiency.

Discussion

Based on our previous results showing a pivotal role of age in the outcome of GH therapy (10), the protocol of the present study included interruption of therapy at a prepubertal age. It was hoped that it would prevent pubertal initiation and shortening, and the accompany-

ing bone age acceleration reported by us and others (10). Under these conditions, every single child increased its growth rate. In fact, at the end of GH therapy, mean height prediction of the treated group was 8 cm higher than control. It is the deceleration of the patients' growth after GH withdrawal that constitutes the focus of the present report. Deceleration of growth was observed in every child in this group of patients. Its magnitude was striking, and it lasted for as long as 18 months. At that time, the children were 7 to 11.3 years old and still prepubertal (31/33, two girls just started Tanner breast stage 2). Despite

Figure 2 Endocrine data after GH discontinuation in short normal children. Left panel, GH peak value after 0.5 g/kg arginine; middle panel, plasma IGF-I; right panel, serum IGFBP-3. Mean $\pm$ s.d.

Figure 3 Bone maturation (upper panel) and serum alkaline phosphatase (lower panel) in the control group (diagonal bars) and in the GH-treated group during 3 years of GH therapy (dotted bars) and after GH withdrawal (open bars). Mean $\pm$ s.d. $\delta BA/\delta CA$ bone age advanced over calendar age advancement. * $P < 0.05$ vs 3 y GH.

deceleration, mean height prediction calculated 2 years after withdrawal was still 5 cm taller than control and statistically significant. This may be related to the simultaneous deceleration of bone maturation.

Little has been reported on the outcome of GH treatment in ISS after treatment withdrawal. Tanner *et al.* (14) reported on deceleration of growth after GH therapy for 6–12 months. Raiti *et al.* (4) identified a subgroup of patients with deceleration of growth after 6 months of GH therapy, and characterized them as short normal with greater pretreatment growth velocity than the others. Chalew *et al.* (15) observed deceleration of growth in 5 out of 11 patients. Ackland *et al.* (16) showed a fall in growth velocity to pretreatment values after 6 months of GH therapy and did not observe any deceleration of growth. The discrepancy of results with the present report, where all children showed deceleration of growth, seems to rest with the daily GH dose for a much longer treatment period. Apparently the withdrawal deceleration of growth is time dependent and more pronounced after prolonged GH treatment. The dose used in the present study was similar (14) or lower than the other reports (4, 15, 16). It was given by us as

Figure 4 Echocardiographic findings before, during 2 years of GH therapy (shaded bars) and off therapy (open bars). (A) Systolic left ventricular diameter. (B) Diastolic left ventricular diameter. (C) Cardiac output calculated for the pulmonary artery. (D) Cardiac output calculated for the aorta. Mean $\pm$ s.d. * $P < 0.05$, ** $P < 0.01$ vs pretreatment.

a daily subcutaneous injection and as 3 times weekly intramuscular (14) or subcutaneous (15, 16) injections in the previous reports. In the mechanism of deceleration of growth the dose is, therefore, of no importance, but the daily schedule of injections might be meaningful.

A similar tendency was observed for BMI, alkaline phosphatase and heart measurements, but the number of observations were too small to reach statistical significance in variables that vary so widely among children.

Cardiac effects of GH have been known from studies of GHD (17) and of acromegaly (18). It has been shown that GH administration normalizes cardiac performance in GH-deficient patients (19). After 2 years of GH therapy in ISS we observed no increase in resting

cardiac output that decreased post therapy to values that were lower than those observed before treatment or in the control group, but well within the normal range. The reduction in left ventricular size during the GH withdrawal period was accompanied by a corresponding reduction in cardiac output. From a consumption point of view the post-therapy decline seems advantageous, with a reduction of left ventricular dimensions and reduced cardiac output. These changes were observed at rest and did not manifest clinically. None of the patients had signs or symptoms of decompensation. The impact on exercise performance has not been evaluated, as it was felt that these patients were too young and of too small body size for a study of myocardial reserve under ergometric conditions.

Thus, GH treatment was associated in these children with development of a physical adaptation to continuous high serum levels of GH, and hence signs of tolerance followed by a withdrawal syndrome can indicate GH dependence. Waning of the growth promoting effect during treatment and subsequent recovery by increasing GH doses are well known further manifestations of drug dependence. The most obvious symptom is growth arrest for a period that apparently depends on the treatment duration and schedule. An increase in fat mass, a decrease in metabolic rate and a decline in resting cardiac output have been reported. Previously, Rudman *et al.* (20) showed in GH-deficient patients a rapid development of negative balances of nitrogen, phosphorus, sodium, and potassium immediately after GH withdrawal. By the end of a year of therapy, GH lost its anabolic effect, which was restored only after tripling the GH dose, and therapy ended in a catabolic state that was worse than pretreatment values. GH has been proposed to improve muscle performance, relative volume contraction, sleep, vitality, well-being and overall quality of life. All these actions may manifest themselves in the withdrawal syndrome and require further evaluation.

The mechanism by which chronic drug exposure elicits GH dependence and withdrawal effects is unclear. During the nadir of growth velocity, peak serum GH levels were normal, as were serum IGF-I and IGFBP-3 levels. Although spontaneous secretion of GH was not measured, normal levels of IGF-I and IGFBP-3 reflect an intact GH-IGF-I axis. Indeed, it was reported that exogenous GH therapy for as long as 12 months did not interfere with the endogenous pulsatile secretion of GH (16, 21), although these two protocols used 3 times weekly GH injections. Subcutaneous administration of daily GH results in an unphysiological serum GH profile, with peak levels at 4 h, and slow disappearance over the course of 12–24 h. This pattern can be regarded as continuous administration of GH, rather than the physiological pulses, with a frequency of eight per day. As previously observed in short term studies, alternate day therapy, which in a normal child would allow for normal GH pulsatility in the interval day, resulted

in zero or minimal deceleration of growth. Moreover, GH doses used in therapy stimulate IGF-I to reach supra-physiological serum levels. The mechanism seems, therefore, to rest with GH and IGF-I action at target tissues of the growing bone and the heart. By analogy with other models of long term memory and long term drug addiction and abstinence (22), such long lived adaptations involve relative stable changes in molecular switches, and transcription factors have been implicated in persistent drug-induced plasticity. These mechanisms may affect stem cells destined to differentiate into proliferating cells, such as cartilage cells, through signal mechanisms of GH and IGF-I receptors. It is concluded that the first 2 years of GH treatment contribute significantly to adult height prediction, and the third year does not, as previously reported for older children (10). Treatment of the young child is more economical and may have a better outcome, but the final height of these children is presently unknown. The withdrawal deceleration of growth seems to be related to daily GH injections for a long period, and resolves by the second post-treatment year. This is the first report of cardiac manifestations of GH withdrawal. The mechanism of GH withdrawal symptoms are presently unknown, but they are not induced by alterations of serum GH or IGF-I.

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