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Childhood malignant disease and consequences for growth hormone secretion, intellectual function and cardiovascular risk

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2005

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Citation for published version (APA):

Link, K. (2005). *Childhood malignant disease and consequences for growth hormone secretion, intellectual function and cardiovascular risk*. [Doctoral Thesis (compilation), Medicine, Lund]. Lund University, Faculty of Medicine Doctoral Dissertation Series.

Total number of authors:

1

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Low individualized growth hormone (GH) dose increased renal and cardiac growth in young adults with childhood onset GH deficiency

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(Received 18 April 2001; returned for revision 12 June 2001; finally revised 13 July 2001; accepted 20 July 2001)

Summary

OBJECTIVE In childhood onset GH deficiency (GHD) a reduction in left ventricular mass (LV-mass) and impairment of systolic function as well an impairment in glomerular filtration rate (GFR) has been shown. The aim of the present study was to assess if a low GH dose resulted in an improvement in morphological and functional parameters of these organs.

DESIGN AND PATIENTS Eleven patients with childhood onset GHD were investigated before and after 10 months of GH treatment at a dose of 1.5 IU/day (range 1–2), corresponding to 0.02 IU/kg/day or 7 µg/kg/day. The GH dose resulted in a serum IGF-I level in the normal range in all but one patient.

MEASUREMENTS Doppler echocardiography of the heart and ultrasound examination of the kidneys was performed. Glomerular filtration rate (GFR) was estimated with iohexol clearance and urinary proteinuria was measured with 24-h urinary samples collected for analyses of albumin, alpha-1-microglobulin, IgG and albumin/creatinine clearance ratio. Body composition was measured by bioelectric impedance analysis.

RESULTS LV-mass index increased significantly after GH treatment ($P = 0.04$), and there was a clear trend for a positive correlation between the increase in serum IGF-I and the increase in LV-mass index, although it did not reach significance ($r = 0.57$, $P = 0.07$). GH treatment did not increase cardiac fractional shortening. Kidney length increased

significantly ($P = 0.02$) with an average increase of 1 cm (range –0.5–1.5 cm). No significant changes in median GFR or serum creatinine were recorded. Three patients with subnormal GFR before GH treatment normalized after 10 months of treatment. Urine analysis showed no abnormalities before or after GH treatment. A significant decrease in percentage fat mass was recorded ($P = 0.03$).

CONCLUSION A low individualized GH dose to adults with childhood onset GHD resulted in an increase in LV-mass index and kidney length. Re-establishing GH treatment with a low dose in this patient group can lead to a further somatic maturation of these organs, probably not accomplished previously.

Introduction

The biochemical and clinical presentation of GH deficiency (GHD) in adults seems to be dependent on whether GHD started in childhood or adulthood (Attanasio *et al.*, 1997). Appropriate therapy with GH has previously been discontinued at the end of linear growth, although somatic growth is unlikely to be completed at this time. Thus, it seems obvious that GHD onset in a period of somatic maturation has more profound effects on organ development than GHD starting later in life. In fact, in childhood onset GHD a reduction in left ventricular mass (LV-mass) and an impairment of systolic function have been observed (Amato *et al.*, 1993; Merola *et al.*, 1993; Cittadini *et al.*, 1994), whereas such cardiac abnormalities have not been found in patients with adult onset disease (Dunne *et al.*, 1995; Valcavi *et al.*, 1995; Johannsson *et al.*, 1996; Bülow *et al.*, 2000). Moreover, age at onset of GHD is found to be of significant importance for the response of GH therapy with respect to changes in body composition, lipids and quality of life (Attanasio *et al.*, 1997). It seems reasonable to believe that cardiac effects of GH treatment are also dependent on the initial status and function of the heart, and it is therefore essential that the two clinical entities childhood and adult onset GHD are investigated separately.

It is well known that glomerular filtration rate (GFR) is increased in acromegaly and decreased in hypopituitarism (Falkheden & Sjögren, 1964) and the nephromegaly found in acromegalic patients was reduced after hypophysectomy (Falkheden & Wickbom, 1965). GH treatment of GHD patients has resulted in an increase in GFR (Jørgensen *et al.*, 1989;

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Caidahl *et al.*, 1994), but whether kidney size increases in parallel is not known.

The optimal GH replacement dose has not yet been established. Recently, the importance of an individualized GH dose has been emphasized in order to avoid negative metabolic effects (Johannsson *et al.*, 1997; Drake *et al.*, 1998; Bülow & Erfurth, 1999). Serum IGF-I is generally subnormal in untreated childhood onset GHD (Attanasio *et al.*, 1997) so this marker has been suggested to be useful in monitoring GH treatment (De Boer *et al.*, 1996). Acromegalic patients, with excess GH, have an increased risk for cardiac hypertrophy (Fazio *et al.*, 2000). High GH doses in GHD patients have resulted in LV-mass index even above those of normal subjects (Johannsson *et al.*, 1996). Therefore, it seems essential to avoid dose-dependent negative cardiac effects of GH treatment especially in young patients, who will have to look forward to lifelong treatment with GH. There is still limited knowledge of cardiac as well as renal effects of a low GH dose in GHD patients. Thus, we aimed to assess if a low individualized GH dose resulted in an improvement of these organs in a group of young adults with childhood onset GHD.

Patients and methods

Study group

Eleven patients, nine males, with childhood onset GHD were included in the study. Characteristics of patients are shown in Table 1. All but one patient had been treated with GH during

childhood. The median time of GH therapy discontinuation before the study was 7 years (range 5–10). The median age of onset of GHD was 11 years (range 2–18). Before the start of the study, GHD was diagnosed with an insulin tolerance test in 10 patients with a serum GH response (1.6 mIU/l). One patient (no. 11) had a history of craniopharyngioma and post-apoplectic seizures, which disqualified him for an ITT, and the diagnosis of GHD was based on a low IGF-I together with three deficient hormone axes (Toogood *et al.*, 1994). Before the start of GH treatment all patients but two had subnormal serum IGF-I levels for age (Table 1). When required, the patients received stable replacement therapy for at least 6 months prior to the study, with cortisone acetate (10–30 mg), levothyroxine (0.1–0.2 mg), desmopressin (0.2–1.6 mg) and gonadal steroids. In males intramuscular injection of testosterone enanthate (250 mg every 3–4 weeks) was given. One of the female patients received treatment with conjugated oestrogens and medroxy-progesterone acetate and the other had no gonadal insufficiency but used contraceptives. One patient received treatment with bromocriptine (patient no. 6). Replacement therapies were kept constant during the study in all patients but two, in whom the dose of cortisone acetate was increased by 5 mg (patient no. 9) and the dose of levothyroxine was increased from 0.1 mg to 0.2 mg per day (patient no. 5).

Study design

The study was of open design and cardiac and renal examinations were performed before and after 10 months of

Table 1 Clinical and endocrine characteristics of 11 patients with childhood onset growth hormone deficiency at inclusion in the study

Patient no.	Sex	Age (years)	Diagnosis	Pituitary deficiency	Treatment	Height/weight (cm/kg)	BMI (kg/m ²)
1	m	27	Suprasellar cyst	A/T/G/GH	S	167/101	36.2
2	m	25	Craniopharyngioma	A/T/G/ADH/GH	S + RT	189/124	34.7
3	f	22	Idiopathic GHD	GH		160/79	30.9
4	f	27	Idiopathic hypopituitarism	T/G/GH		158/54	21.6
5	m	26	Idiopathic hypopituitarism	A/T/G/GH		172/70	23.7
6	m	25	Prolactinoma	T/G/GH	M	176/71	23.4
7	m	22	Idiopathic GHD	GH		160/87	34.0
8	m	22	Optic glioma	GH	S + RT	162/70	26.7
9	m	28	Craniopharyngioma	A/T/G/ADH/GH	S	177/78	24.9
10	m	27	Craniopharyngioma	A/T/G/ADH/GH	S	178/81	25.6
11	m	19	Craniopharyngioma	A/T/G/ADH/GH	S + RT	190/107	29.6
						172/79	26.7
						158–190/54–124	21.6–36.2

A, ACTH deficiency; T, TSH deficiency; G, gonadotrophin deficiency; ADH, deficiency of antidiuretic hormone; GH, growth hormone deficiency according to an insulin tolerance test; S, surgery; RT, radiotherapy; M, medical treatment (dopamine agonist). The median age was 25. The age range was 19–28.

GH treatment. Body composition and serum IGF-I were measured before and after 1.5, 3, 6 and 10 months of GH treatment. Thyroid hormones were measured before and after 10 months of treatment.

Treatment with biosynthetic human GH (Genotropin, Pharmacia & Upjohn, Stockholm, Sweden) was administered in the evening by sc. injection with a commencing dose of 0.5 IU/d. The dose was increased over 2 weeks to 1.5 IU/d and thereafter, according to the response in serum IGF-I levels, aiming at the middle of the normal range. At the end of the study the median GH dose was 1.5 IU/day (range 1–2), corresponding to 0.02 IU/kg/day or 7 µg/kg/day.

Due to side-effects, dose reductions were necessary in patients no. 2 (oedema) and 3 (arthralgia and oedema). After 10 months of GH treatment, serum IGF-I levels were normalized in 10 patients and above the normal range in one patient, who started with a normal serum IGF-I level (patient no. 8) (Table 2).

The patients gave written informed consent and the Ethics Committee of the University of Lund approved the study.

Body composition

Body composition was measured in the supine position by bioelectric impedance analysis (BIA) using the BIA 101-S technique (RJL Systems, Detroit, MI) with a 50-KHz, 800-µA.

Doppler echocardiography and blood pressure

Doppler echocardiography was performed using a Hewlett-Packard Co. Sonos 500 (Palo Alto, CA, USA). The same investigator performed all echocardiograph examinations. Left

ventricular end-diastolic (LVIDd) and end-systolic (LVIDs) cavity dimension, as well as interventricular septal wall thickness (IVSd), left ventricular posterior wall thickness (LVPWd) and left atrial dimension (LA) were measured. Left ventricular fractional shortening (FS) was used as an index of left ventricular systolic function and was calculated as: $[(LVIDd - LVIDs)/LVIDd] \times 100$. The left ventricular mass (LV-mass) was calculated as: $1.04 [(LVIDd + IVSd + LVPWd)^3 - LVIDd^3] - 13.6$ (Devreux & Reichek, 1977). LV-mass index was determined by dividing the LV-mass with the body surface area of the patient. The upper normal limit for men is 134 g/m² and for women 110 g/m².

Blood pressure was measured in the right arm to the nearest 5 mmHg with the patient in the supine position after resting for 10 minutes.

Ultrasound of the kidneys, glomerular filtration rate (GFR) and urinary samples

The ultrasound examination of the kidneys was performed with a Toshiba SSA-270-A and a convex array 3.75 MHz transducer, or a Domier A1 3200 and a 5-MHz curved linear transducer. The same investigator performed all examinations. Only the right kidney was evaluated because of the technical difficulties in imaging the left kidney. At least three measurements were performed to image the longest projection of each kidney and the received value was abbreviated to the closest 0.5 cm. The intrainvestigator variation was estimated as 5%.

GFR was estimated with iothexol clearance in a standardized manner. The plasma concentration of iothexol was analysed by high performance liquid chromatography with reference

Table 2 Final GH doses, changes in serum IGF-I, left ventricular mass index (LV-mass index), body resistance and fat mass in 11 patients with childhood onset GH deficiency treated with GH for 10 months

Patient no.	Final GH dose (IU/kg/week)	S-IGF-I before/after GH (µg/l)	LV-mass-index before/after GH (g/m ²)	Change in body resistance (%)	Change in percentage fat mass (%)
1	0.1	30/148	94/90	-10.7	-4.9
2	0.09	38/331	92/110	+1.2	-2.5
3	0.14	63/236	58/68	-22.6	-5.5
4	0.19	< 20/313	60/67	-8.9	-2.6
5	0.14	82/231	111/118	-8.6	-2.3
6	0.09	140/372	81/90	-7.4	-3.2
7	0.16	83/229	107/95	+0.2	-1.6
8	0.14	172/506	67/79	-10.4	-4.2
9	0.18	35/231	60/61	-11.6	-1.0
10	0.17	< 20/375	78/95	-9.7	-6.6
11	0.09	< 20/177	74/102	+1.7	-3.7
Median	0.14	38/236	78/90	-8.9	-3.2
Range	0.09–0.19	20–172/148–506	58–111/61–118	+1.7(-22.6)	-1.1(-6.6)

interval 80–125 ml/minutes \times 1.73 m². Urinary proteinuria was measured with 24-h urinary samples collected for analyses of albumin, alpha-1-microglobulin, IgG and albumin/creatinine clearance ratio. The same nephrologist throughout the study examined urinary specimens.

Biochemical assays

Serum GH was analysed by an immunofluorometric method (Wallac Oy, Turku, Finland). At 4 mIU/l, the interassay and intra-assay coefficients of variation (CVs) were 4.3 and 5.0%, respectively. Serum IGF-I was measured by radioimmunoassay after formic acid-ethanol extraction (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). The intra- and interassay CVs were 3.6% or less and 9.1% or less, respectively. The detection level was 20 μ g/l, and the reference range for adults aged 21–28 years was 129–385 μ g/l. Serum free T4 was analysed with an immunofluorometric technique (Auto Delfia, Wallac Oy) and serum free T3 by a radioimmunoassay. The reference ranges for serum free T4 and T3 were 9–22 and 3.4–7.2 pmol/l. Serum creatinine was analysed by a routine enzymatic methods, with a reference range of 60–115 μ mol/l.

Statistical analysis

Data are presented as median and range. Intra-individual comparisons of data before and after GH treatment were made

with the Wilcoxon matched-pair signed-rank test. Univariate correlations were assessed using Spearman's rank order correlation test. The level of significance was set at $P \leq 0.05$.

Results

Doppler echocardiography, blood pressure and heart rate

LV-mass index increased significantly after GH treatment ($P = 0.04$) (Table 3) and there was a trend for a positive correlation between the increase in serum IGF-I and the increase in LV-mass index, although it did not reach statistical significance ($r = 0.57$, $P = 0.07$) (Fig. 1). Further, there was a tendency of an increase in LVIDd and LVPWd after GH treatment, but no changes in LA, LVIDs or IVSd were observed (Table 3). GH treatment did not influence systolic function (FS), determined from fractional shortening.

No statistically significant change in systolic or diastolic blood pressure was recorded after treatment with GH, but heart rate at rest increased significantly ($P = 0.05$).

Ultrasound of the kidneys, glomerular filtration rate (GFR) and urinary samples

Kidney length increased significantly ($P = 0.02$) with an average increase of 1 cm (range –0.5–1.5 cm). There was no significant correlation between the increase in serum IGF-I and the increase in kidney length. No significant changes in median

Table 3 Echocardiograph findings, heart rate and blood pressure in 11 patients with childhood onset GHD before and after GH treatment for 10 months

	Before GH treatment		After GH treatment		<i>P</i>
	Median	Range	Median	Range	
Left heart dimensions and function					
LVIDd (mm)	48	(42–63)	51	(43–66)	0.07
LVIDs (mm)	29	(25–48)	30	(25–49)	0.5
LVPWd (mm)	7	(6–10)	8	(6–10)	0.08
IVSd (mm)	8	(6–12)	10	(7–12)	0.3
LA (mm/m ²)	36	(30–44)	37	(32–43)	0.1
LV-mass index (g/m ²)	78	(58–111)	90	(61–118)	0.04
FS (%)	40	(24–42)	38	(26–45)	> 0.5
Heart rate and blood pressure at rest					
Heart rate (beats/minutes)	68	(54–87)	72	(57–98)	0.05
Systolic blood pressure (mmHg)	120	(105–135)	120	(105–150)	0.2
Diastolic blood pressure (mmHg)	80	(60–110)	80	(65–95)	> 0.5

LVIDd, left ventricular end-diastolic cavity dimension; LVIDs, left ventricular end-systolic cavity dimension; IVSd, interventricular septal wall thickness; LVPWd, left ventricular posterior wall in diastole; LA, left atrium; LV-mass index, left ventricular mass index; FS, fractional shortening.

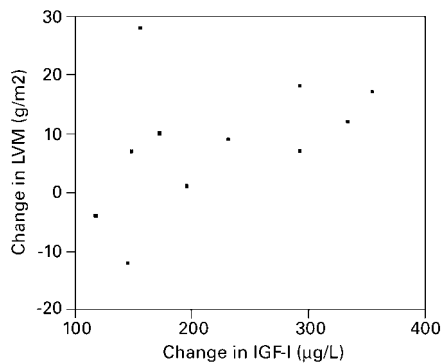


Fig. 1 Correlation between the increase in left ventricular mass index and the increase in serum IGF-I in 11 patients with childhood onset growth hormone deficiency, treated with a low dose GH (median 1.5 IU/day) for 10 months ($r = 0.57$, $P = 0.07$).

GFR (92 vs. 97 ml/min; $P = 0.2$) or serum creatinine were recorded (68 vs. 71 $\mu\text{mol/L}$; $P > 0.5$). Three patients had a subnormal GFR before GH treatment and GFR levels were normalized in these patients after GH treatment. All patients had normal serum creatinine levels before as well as after GH therapy. Urine analysis showed no abnormalities before or after GH treatment. Further, no tubular or glomerular proteinuria, in the form of urinary α -1 microglobulin (HC), Ig-G or albumin was detected before or after GH treatment.

BMI, body composition and thyroid hormones

No significant change was recorded in BMI with GH treatment

(26.7 kg/m² vs. 27.8 kg/m², $P = 0.1$). GH treatment resulted in a decrease in whole body resistance ($P = 0.02$) and a decrease in percentage fat mass ($P = 0.03$) (Table 2). Serum free T4 decreased after treatment (15.0 vs. 13.0 pmol/l; $P = 0.04$) but no significant change in free T3 (5.5 vs. 5.1 pmol/l; $P = 0.09$) was detected.

Discussion

The present study revealed that 10 months of a low individualized GH dose (median dose 7 $\mu\text{g/kg/day}$) to young adults with childhood onset GHD increased LV-mass index and kidney length. In contrast to most previous studies, the GH dose was not based on weight or body surface area, but adjusted according to the response in serum IGF-I. GH treatment normalized serum IGF-I in all patients but one, who started with a normal IGF-I level and at the end of the study had a level above the normal range.

To our knowledge the GH dose used in the present study is the lowest dose reported so far (Table 4), showing significant effects on LV-mass index in adults with childhood or adult onset GHD. With the dose of GH used here there were still positive effects with a significant decrease in body fat mass. Moreover, in a previous investigation including a majority of the patients in the present study, the same GH dose had no significant negative effect on glucose tolerance (Bilow & Erfurth, 1999). An association between the increase in serum IGF-I levels and the increase in LV-mass index was recorded, which strongly indicates the importance of IGF-I on cardiac growth. This is in agreement with Merola *et al.* (1993), showing a close relation between serum IGF-I levels and LV-mass index in childhood onset GHD.

There is accumulating evidence that GH has an important role in the maintenance of normal cardiac growth and function

Table 4. Effect of GH treatment on left ventricular mass index and systolic function in studies of patients with childhood onset GH deficiency

	No. of treated patients	GH dose $\mu\text{g/kg/day}$	Duration of GH treatment (months)	Diagnostic method	Left ventricular mass index	Systolic function
Amato <i>et al.</i> , 1993	7	10	6	Echo	↑	FS↓
Cittadini <i>et al.</i> , 1994	5	17	6	RA	NP	LVEF↓
Cuocolo <i>et al.</i> , 1996	14	17	6	RA	NP	LVEF↓
Sartorio <i>et al.</i> , 1997	8	24	6	Echo	↑	NP
Ter Maaten <i>et al.</i> , 1999	37	15	12	Echo	↑	LVEF→
	37	13	24		→	LVEF→
	37	13	36		→	LVEF→
	30	11	60		→	LVEF→
Present study	11	7	10	Echo	↑	FS→

Echo, echocardiography; RA, radionuclide angiography; NP, not performed; LVEF, left ventricular ejection fraction; FS, fractional shortening.

(Isgaard *et al.*, 1999). Both GH and IGF-I receptors are expressed in the myocardium (Mathews *et al.*, 1989; Guse *et al.*, 1992), and in the rat it has been demonstrated that IGF-I stimulates myofibril development (Donath *et al.*, 1994) and increases isometric force (Freestone *et al.*, 1996). Compared to normal subjects, patients with childhood onset GHD have a reduction in LV-mass and an impairment of systolic function (Amato *et al.*, 1993; Merola *et al.*, 1993; Cittadini *et al.*, 1994). The median age at GHD onset was lower in the study by Merola *et al.* (1993) (5.4 years *vs.* 11 years), compared to the present study. Interestingly, there was also an obvious disparity in the average LV mass index (54 g/m² *vs.* 78 g/m²) before re-starting GH treatment, indicating that the age at onset of GHD is of great importance for the degree of somatic underdevelopment, within the group of childhood onset GHD patients. GH treatment for 6 months to childhood onset GHD patients has resulted in an increase in LV-mass index (Amato *et al.*, 1993; Sartorio *et al.*, 1997) and improvement in systolic function measured by echocardiography (Amato *et al.*, 1993; Sartorio *et al.*, 1997) or radionuclide angiography (Cittadini *et al.*, 1994; Cuocolo *et al.*, 1996) (Table 4). In the present study there was no increase in FS; however, the increase in LV mass index might render an improvement in physical capacity, especially after starting regular physical exercise. None of the patients in the present study developed cardiac hypertrophy, as the LV mass index was well within the normal range after GH treatment. Compared to our patients, those in the studies by Amato *et al.* (1993) and Sartorio *et al.* (1997) had lower initial LV mass index before restarting GH treatment, which might be one explanation for the more pronounced effects on systolic function shown in those previous investigations after GH treatment.

In a recent study by Ter Maaten *et al.* (1999), male patients with childhood onset GHD were examined with echocardiography for a longer period of GH treatment (median 55 months). During the study the GH dose was reduced gradually to a mean dose of 11 µg/kg/day, which was still higher than in the present study (7 µg/kg/day). LV-mass increased after 1 year of treatment, but decreased thereafter. An increase in cardiac output and maximal workload was observed with the longer period of treatment, stressing the importance of a long follow-up for a proper evaluation of cardiac effects of GH replacement.

In agreement with previous observations there was an increase in heart rate at rest after GH treatment (Caidahl *et al.*, 1994; Johannsson *et al.*, 1996; Ter Maaten *et al.*, 1999). One explanation could be an increase in serum free T₃, due to the increased conversion from T₄ to T₃ seen after GH treatment. In the present study there was a significant decrease in serum free T₄, but no change in serum free T₃. Another possible explanation could be an effect of GH on the release or tissue sensitivity of catecholamines (Sacca *et al.*, 1994). However,

this is in contrast to recent findings of an increased muscle sympathetic activity in patients with GHD (Sverrisdottir *et al.*, 1998) as with a normal sympathetic outflow to skeletal muscles, measured with noradrenalin turnover in acromegalic patients (Capaldo *et al.*, 2000). In accordance with previous studies (Amato *et al.*, 1993; Cittadini *et al.*, 1994; Ter Maaten *et al.*, 1999) no change in blood pressure, which could account for the increase in LV-mass index, was recorded after GH treatment.

A reduction in GFR has been recorded in patients with childhood onset GHD (Jørgensen *et al.*, 1989) and GH treatment to these patients showed an increase in GFR levels to that of controls. This accords with a previous finding in a case report of a childhood onset GHD patient, in whom a high GH dose (4 IU/day) increased kidney size and GFR from subnormal to normal levels (Westman *et al.*, 1997). In the present study we confirmed our previous finding (Westman *et al.*, 1997) with an increase in kidney size, but now with a much lower GH dose. However, no change in GFR was recorded in the present study probably due to the fact that only three subjects had subnormal GFR before reassessment of GH. With a higher GH dose (2 IU/m²; present study 0.84 IU/m²) a significant increase in GFR has been recorded in childhood onset GHD (Jørgensen *et al.*, 1989).

Ultrasound examination of the kidney has been shown to be a reliable method for measuring kidney size (Hederström & Forsberg, 1985) and the measurement of kidney length seems to be the most adequate method to estimate kidney size. The intraobserver variation with ultrasound examination of the kidney has been described to be 4–6 mm (Sargent & Wilson, 1992), thus well below an enhancement in length of 10 mm that was recorded in the present study. In accordance with others, neither glomerular nor tubular proteinuria was detected during GH treatment (Levine *et al.*, 1993).

In conclusion, an individualized treatment with a low GH dose for 10 months to adults with childhood onset GHD resulted in an increase in LV-mass index, without any case of cardiac hypertrophy. Moreover, GH therapy caused a significant increase in kidney length. The exact mechanisms behind the morphological improvement cannot be ascertained by the present study design, but it seems reasonable to believe that reassessment of GH treatment in this patient group can lead to a further, not previously accomplished somatic growth of these organs. We believe that it is of importance that these patients will be followed for a longer time period to be able to establish whether this low GH dose will lead to any positive functional effects of the heart and kidney.

Acknowledgements

This work was supported by The Swedish Medical Research

Council (grant no. K 1999-27X013074-01A) and the Medical Faculty, Lund University, Sweden. We are grateful to Pharmacia & Upjohn, Stockholm, Sweden, for their support.

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