CLINICAL STUDY

GH secretory pattern in young adults who discontinued GH treatment for GH deficiency and decreased longitudinal growth in childhood

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Abstract

Objective: Some adolescents who discontinue GH treatment due to GH deficiency (GHD) and short stature in childhood do not have classical GHD at retesting in adult life. It is unknown whether there is a neuroendocrine disturbance in the spontaneous pattern of GH release in these patients.

Design/patients/methods: Thirty-seven adolescents, who had received treatment with GH due to impaired longitudinal growth, were included. The adolescents were divided into two groups; one (GHD; $n=19$) with classical GHD in adult life and another (GH sufficient (GHS); $n=18$) without classical adult GHD. One year after GH discontinuation, 24-h GH profiles were performed with blood sampling every 30 min. Sixteen matched healthy controls were also studied. All blood samples were analysed using an ultrasensitive GH assay and then, approximate entropy (ApEn) and deconvolution analysis were performed.

Results: The GHD group had higher mean ApEn level than the healthy controls ($P<0.05$). As measured by deconvolution analysis, they had lower basal GH secretion ($P<0.01$), increased number of GH peaks ($P<0.001$), but lower burst mass ($P<0.001$), lower percentage pulsatile GH secretion ($P<0.001$) and lower total GH secretion ($P<0.001$), compared with control subjects. Adolescents in the GHS group had a pattern of 24-h GH release similar to that in healthy controls.

Conclusion: Young adults with childhood-onset severe GHD have a high-frequency, low-amplitude GH secretion with decreased orderliness. The adolescents without classical GHD in adult life maintain a pattern of spontaneous GH release that is not statistically different from that in the healthy controls.

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Introduction

Hypopituitary adults with severe growth hormone (GH) deficiency (GHD) have increased abdominal/visceral obesity, decreased lean and bone mass, and metabolic abnormalities including insulin resistance and disturbed lipoprotein pattern (1–3). Premature atherosclerosis (4) and increased mortality from cardiovascular disease have also been observed (5–8). These clinical characteristics are observed in adults with both childhood- and adult-onset disease (9, 10). Serum insulin-like growth factor-I (IGF-I) level, and bone and muscle mass, may, however, be more reduced in childhood-onset disease, whereas the impairment of serum lipid levels may be more marked in patients with adult-onset disease (10, 11).

The multiple abnormalities observed in GHD adults could suggest that adolescents receiving GH therapy for decreased longitudinal growth and inadequate GH

secretion in childhood may need to continue the GH therapy also in adult life. Studies, in which young adults with GH therapy in childhood/adolescence have been retested, have shown that some, but not all, of these patients have persisting severe GHD according to the diagnostic criteria set in adult life (12, 13). Discontinuing GH therapy at final height in adolescents with severe GHD into adult life produces similar clinical characteristics as those observed in other groups of adult patients with GHD (14–22). Quality of life may, however, be less affected by GH discontinuation in this patient group (20). In addition, peak muscle and bone mass may never be obtained if the GH therapy is terminated too early as maximum muscle strength and bone density continuously improves several years after longitudinal growth has been completed (10, 23). Continued or reinstituted GH replacement can, however, maintain or reverse most of the abnormalities in

body composition and in bone and lipid metabolism in this group of patients (10, 22, 24).

Subjects with inadequate GH secretion and decreased longitudinal growth in childhood, but with normal GH reserve at retesting in adult life, have what appears to be a normal development in terms of body composition and metabolism during the first years after GH discontinuation (14–20). However, the transition studies with GH discontinuation have so far only had a duration of a few years (14–20), and the extent to which these patients may suffer from partial GHD later in life has, therefore, not been determined. The results of several studies suggest that also partial GHD can result in disturbed body composition and serum lipid pattern in hypopituitary adults (25, 26). Little is known whether the 24-h spontaneous GH secretory pattern differs between young adults with inadequate GH secretion and decreased longitudinal growth in childhood, but with normal GH reserve at retesting in adult life, and healthy young adult subjects.

In the present study, the young adults, previously treated in childhood/adolescence for decreased longitudinal growth and inadequate GH secretion, were included. The aim was to determine the spontaneous pattern of 24-h GH release in patients with persisting GHD (GHD group), or with a normal GH response at retesting in adult life (GH sufficient (GHS) group), vs healthy age- and body mass index (BMI)-matched controls. One year after GH discontinuation, 24-h plasma GH profiles (sampling every 30 min) were monitored in the GHD and GHS groups. Similar 24-h GH profiles were also performed in the healthy controls. Plasma GH concentrations were analysed using a highly sensitive chemiluminescence assay and GH secretory patterns were determined using deconvolution and approximate entropy (ApEn) analysis.

Subjects and methods

Patients and controls

Forty adolescent patients receiving GH treatment within clinical trials and 16 healthy control subjects were recruited for the study. Twenty-four-hour GH profiles were performed in 37 of the 40 patients and in all controls. Since the GH profiles were performed 1 year after GH discontinuation, three of the patients had withdrawn from the study during the first year. (One man with idiopathic, isolated GHD during childhood was not interested in further investigations after the baseline visit and two women with severe GHD withdrew from the study after 3 and 6 months, respectively, as a result of severe psychological symptoms, which were resolved after the reinstitution of GH replacement therapy). The present study, therefore, included 37 patients and 16 controls. The GH-treated subjects had been submitted for participation from 14 paediatric clinics. The criteria for inclusion were GHD, idiopathic

or organic, and isolated or multiple anterior pituitary hormone deficiencies. The patients had received GH treatment for the past three consecutive years and were otherwise being considered to end GH treatment. Patients who were not considered for inclusion were those who planned to finalise treatment for reasons other than reaching final height, those older than 25 years at the time of inclusion, pharmacological treatment for psychiatric disease, or mental retardation. The patients were partly selected for the study so as to have approximately half the patients with childhood-onset, idiopathic, isolated GHD and half with organic hypothalamic/pituitary disease with or without multiple pituitary hormone deficiencies.

Severe GHD in adult life was defined as: i) another anterior pituitary hormone deficiency associated with a spontaneous GH peak of less than 3 µg/l (14 subjects), or ii) an organic hypothalamic/pituitary disease associated with a GH peak of less than 3 µg/l during an insulin tolerance test (four subjects), or iii) in the absence of an organic hypothalamic/pituitary disease, a GH peak of less than 3 µg/l during two GH stimulation tests (one patient). Thus, using these criteria, 19 of the 37 patients were classified as having severe GHD in adult life, whereas 18 patients were classified as GHS.

Most patients in the GHS group had idiopathic and isolated pituitary deficiency, whereas most patients in the GHD group had organic hypothalamic/pituitary disease (Table 1). All patients with brain neoplasia and acute lymphoblastic leukaemia had received irradiation in the hypothalamic/pituitary area. Patients with other anterior pituitary hormone deficiencies received, when required, stable replacement therapy with glucocorticoids (cortisone acetate; mean, 20 mg; range, 15–30 mg/day), thyroid hormone (levothyroxine; mean, 0.1 mg; range, 0.05–0.15 mg/day) and gonadal steroids. The period of GH treatment was,

Table 1 Causes of the pituitary deficiency, degree of pituitary deficiency after reevaluation, and GH treatment years and onset of puberty in 19 GH deficient (GHD) and 18 GH sufficient (GHS) patients. All values are shown as number except for age at GH start and GH treatment years, which are given as means (S.E.M.)

	GHS	GHD
Causes of the pituitary deficiency		
Idiopathic	17	9
Acute lymphoblastic leukaemia	1	2
Brain tumour		5
Other		3
Degree of pituitary deficiency after reevaluation		
Isolated GHD	17	5
One additional deficiency	1	4
Two additional deficiencies		5
Three additional deficiencies		5
Age at GH start (years)	11.7 (0.9)	10.5 (0.7)
GH treatment years (years)	5.6 (0.7)	9.2 (0.7) ^a

^a*P* < 0.001 vs GHS group.

however, shorter in the GHS group (Table 1). Furthermore, a prospective evaluation showed that age at onset of puberty was somewhat higher in the GHS group than in the GHD group (14 vs 13 years, respectively).

Sixteen healthy control subjects were recruited. They were selected from subjects who responded to an advertisement and were closely matched with the GHS group in terms of age, gender, body height, body weight and BMI (Table 2).

Study protocol

During a stabilising period of 3 months, all patients received a standardised dose of GH, 0.03 mg/kg per day (0.1 IU/kg per day). After a baseline visit, the GH treatment was discontinued. One year after this, a GH profile was performed. During the year between the GH discontinuation and when the 24-h GH profile was performed, the patients were seen at the home paediatric clinic. The results of other measurements than the 24-h GH profiles have been published elsewhere (17–20).

Body composition

Body weight was measured in the morning to the nearest 0.1 kg with the subject wearing indoor clothing, and body height was measured barefoot to the nearest 0.01 m. The BMI was calculated as body weight in kilograms divided by height in metres squared. Dual energy x-ray absorptiometry (DEXA) was performed using a whole body scanner (Lunar DPX-L, Lunar Corp.; Madison, WI, USA). Total body fat (BF) and lean body mass (LBM) were analysed using the 1.31 software version. Precision errors for the scanner used (system number 7156), as determined from double examinations in 10 healthy subjects, were 1.7% for BF and 0.7% for LBM.

Ethical considerations

The study was approved by the Ethical Committee of the University of Göteborg and informed consent was obtained from each subject before the start of the study.

GH profiles

GH secretory status was assessed 1 year after GH discontinuation by 24-h GH measurements (beginning 1000 h) from repeated 30-min blood sampling using a withdrawal pump. Plasma GH concentrations and GH secretory patterns were analysed (blinded) by deconvolution analysis and analysis of ApEn.

The patients and the controls were allowed to maintain their ordinary consumption of caffeine and/or tobacco during the profiles. Ingestion of alcohol was not allowed the day before the profiles or during the profiles. The patients were allowed to move freely within the ward. Standardised meals were given at 0800, 1200, 1600 and 1900 h. The patients were instructed to go to bed at the same time as they used to do at home.

Deconvolution analysis

Two-compartment deconvolution analysis was applied. Fixed GH half-life was used (3.5 min fast component, 20.9 min slow component; fractional amplitude of slow component, 0.63) as previously determined directly in growth hormone-releasing hormone (GHRH)-stimulated and then somatostatin-suppressed adults (27). Daily pulsatile GH secretion is the product of secretory-burst frequency and the (mean) mass of GH released per pulse. Basal secretion represents the time-invariant interpulse component of the GH release profile (28). Analysis was carried out requiring 95% joint statistical confidence intervals for all GH secretory-burst amplitudes (29, 30). The analyst was blinded to the time series assignments.

Approximate entropy

ApEn quantifies the serial orderliness or pattern regularity of the (hormone) release process over 24 h (31). ApEn parameters of $m=1$ (series length) and $r=35\%$ (threshold) of the intraseries s.d. were used, as described previously (32). ApEn was normalised by calculating the ratio of observed to 1000 randomly shuffled versions of each GH time series. Thus, ApEn

Table 2 Characteristics in the study population of 19 GH deficient (GHD) patients, 18 GH sufficient (GHS) patients, and 16 healthy controls. Lean body mass and body fat was estimated using DEXA. All values are shown as the mean (s.e.m.). The controls and the GHS group were comparable in all variables given in this table.

	Controls	GHS	GHD	P-value*
Age (years)	19.3 (0.4)	19.8 (0.3)	19.7 (0.4)	0.96
Sex (men/women)	12/4	14/4	17/2	
Body height (cm)	173 (2)	171 (2)	174 (2)	0.48
Body weight (kg)	67.3 (3.5)	65.5 (3.2)	71.0 (3.1)	0.43
BMI (kg/m ²)	22.3 (0.8)	22.3 (0.8)	23.4 (0.8)	0.35
Lean body mass (kg)	51.1 (2.2)	49.1 (1.9)	46.4 (1.6)	0.13
Body fat (kg)	12.5 (2.6)	13.3 (2.2)	21.3 (2.1) ^{a,c}	<0.05
Serum IGF-I (µg/L)	374 (26)	409 (29)	190 (31) ^{b,d}	<0.001

^a $P<0.01$ vs controls; ^b $P<0.001$ vs controls; ^c $P<0.01$ vs GHS group; ^d $P<0.001$ vs GHS group. *P-values (between all three groups) are based on the Kruskal–Wallis ANOVA test by ranks. P-Values (between two groups) are based on a post hoc analysis using the Mann–Whitney U-test.

ratios approaching 1.0 denote mean expected random behaviour. Lower ApEn ratios (at equal series lengths and parameter values as used here) denote greater orderliness (regularity) of moment-to-moment hormone release. Conversely, high ratios are observed for GH in acromegaly (33) and in women compared to men (32).

Biochemical assays

Plasma GH concentrations were measured using an ultrasensitive chemiluminescence assay with a lower limit of detectability of 0.002 µg/l (at two standard deviations (s.d.) above assay blank) and 0.005 µg/l (at 3 s.d. above assay blank), as previously described (29). The median intra- and inter-assay coefficients of variation (CV) were 6.3 and 7.4%. All samples from an individual were assayed together.

The serum concentration of IGF-I was determined after hydrochloric acid–ethanol precipitation of binding proteins using RIA (Nichols Institute Diagnostics; San Juan Capistrano, CA, USA) with within-assay CV values of 2.5 and 4.2% at serum concentrations of 125 and 345 µg/l, respectively.

Statistical analysis

Descriptive statistical results are presented as the mean (s.e.m.). Differences among all the three study groups were accessed using the Kruskal–Wallis ANOVA test by ranks. In the variables, in which there was a significant difference between the three study groups, post hoc analyses were performed using the Mann–Whitney *U*-test. A one-way ANOVA was also performed, in which BF, as measured using DEXA, was used as a covariant. Correlations were sought using the Spearman rank-order correlation test. A two-tailed *P*-value ≤ 0.05 was considered significant.

Results

Age, body composition and serum IGF-I

The patients in the GHS group and the healthy controls were comparable in all variables given in Table 2. The GHD group was similar to the other two study groups in terms of age, gender distribution, body height, body weight, BMI and LBM as estimated using DEXA. BF, as estimated using DEXA, and serum IGF-I concentration were, however, higher and lower respectively in the GHD group as compared with the other two groups.

Nadir and peak GH concentrations

The mean nadir (minimum) GH concentration during the 24-h GH profiles was statistically similar in all the three study groups (control group 0.10 (0.03) µg/l, GHS group 0.06 (0.01) µg/l, GHD group 0.06 (0.01) µg/l).

The mean peak GH concentration during the 24-h GH profiles was lower in the GHD group (1.4 (0.3) µg/l) than that in the GHS (10.2 (1.5) µg/l, $P < 0.001$ vs GHD group) and the control group (9.5 (0.9) µg/l, $P < 0.001$ vs GHD group), but there was no statistical difference between the GHS and the control group.

Deconvolution analysis

The patients in the GHD group had lower basal GH secretion rate, increased half-duration of GH secretory bursts and number of GH peaks, but lower mean interburst interval and mean pulse area (burst mass) compared with the other two study groups. Basal, pulsatile and total GH secretion, and the percentage of total GH secretion that was pulsatile, were decreased in the GHD group as compared with both the GHS and the control group. In contrast, the young adults in the GHS group had a pattern of 24-h GH release that was statistically similar to that in the healthy controls. Number of GH peaks, basal GH secretion and total GH secretion are shown in Fig. 1A–C, whereas other results of the deconvolution analysis are shown in Table 3.

ApEn analysis

The patients in the GHD group had a higher mean ApEn ratio than both the patients in the GHS group and the healthy controls (Fig. 1D). In the GHS group, mean ApEn ratio was similar as in the healthy controls (Fig. 1D).

Correlations

In the total study population (patients and controls; $n = 53$), serum IGF-I concentration correlated positively with peak GH concentration ($r = 0.65$, $P < 0.001$), percentage pulsatile GH secretion ($r = 0.58$; $P < 0.001$), mean pulse area ($r = 0.52$; $P < 0.001$), pulsatile GH secretion ($r = 0.49$; $P < 0.001$), total GH secretion ($r = 0.46$; $P < 0.001$) and mean interburst interval ($r = 0.44$; $P < 0.01$) and negatively with half-duration of GH bursts ($r = -0.54$; $P < 0.001$) and number of GH peaks ($r = -0.49$; $P < 0.001$). In the total study population, serum IGF-I concentration was not correlated with nadir GH concentration or with basal GH secretion (data not shown). In the patient group (combined GHS and GHD groups; $n = 37$), serum IGF-I concentration correlated with all measures of 24-h GH secretion except for nadir GH concentration ($r = 0.20$).

Serum IGF-I concentration was not correlated with ApEn ratio in the total study population ($n = 53$), in the patient group ($n = 37$), or in the GHD group ($n = 19$) (data not shown).

In the total study population ($n = 53$), BF, as measured using DEXA, correlated positively with half-duration of GH secretory bursts ($r = 0.49$, $P < 0.001$), ApEn ratio

Figure 1 (A) Number of GH peaks, (B) basal GH secretion, (C) total GH secretion and (D) approximate entropy (ApEn) ratios obtained from 24-h plasma GH profiles in 19 GH deficient (GHD) patients, 18 GH sufficient (GHS) patients, and 16 healthy controls. All values are shown as the mean (S.E.M.). An ApEn ratio approaching 1.0 denotes approximately random GH profiles (indistinguishable from 1000 randomly shuffled versions of the same data series).

($r=0.36$, $P<0.01$) and number of GH peaks ($r=0.30$, $P<0.05$) and negatively with mean peak GH concentration ($r=-0.61$, $P<0.001$), pulse area ($r=-0.58$, $P<0.001$), total GH secretion ($r=-0.55$, $P<0.001$), pulsatile GH secretion ($r=-0.54$, $P<0.001$), percentage pulsatile GH secretion ($r=-0.46$, $P<0.001$) and basal GH secretion ($r=-0.42$, $P<0.01$).

In the patient group (combined GHS and GHD groups; $n=37$), BF, as measured using DEXA, was significantly correlated with GH secretion (data not shown). In the GHD group ($n=19$), BF correlated negatively with half-duration of GH secretory bursts ($r=-0.67$, $P<0.001$), and tended to correlate positively with mean interburst interval ($r=0.44$, $P=0.07$). There was no correlation

Table 3 Deconvolution analysis of 24-h plasma GH concentration profiles in 19 GH deficient (GHD) patients, 18 GH sufficient (GHS) patients, and 16 healthy controls. All values are shown as the mean (S.E.M.).

	Controls	GHS	GHD	P-value*
Basal GH secretion rate (µg/l per min)	0.010 (0.003)	0.005 (0.001)	0.003 (0.001) ^{a,c}	<0.01
Half-duration of GH secretory bursts (min)	17.5 (1.0)	18.1 (1.0)	24.9 (0.6) ^{b,d}	<0.001
Mean interburst interval (min)	184 (12)	193 (11)	131 (8) ^{a,d}	<0.001
Pulse area (pulse mass; µg/l per min)	17.4 (3.0)	13.5 (2.1)	1.48 (0.39) ^{b,d}	<0.001
Pulsatile GH secretion (µg/l per 24 h)	134.2 (21.3)	102.7 (16.8)	14.4 (3.4) ^{b,d}	<0.001
Percentage pulsatile GH secretion	78 (3)	92 (1)	67 (5) ^{b,d}	<0.001

^a $P<0.01$; ^b $P<0.001$ vs controls; ^c $P<0.05$; ^d $P<0.001$ vs GHS group. *P-values (between all three groups) are based on the Kruskal–Wallis ANOVA test by ranks. P-Values (between two groups) are based on a post hoc analysis using the Mann–Whitney U-test.

between BF and other measures of GH secretory patterns (all P -values > 0.13) in the GHD group.

Analysis of covariance

To evaluate the role of the increased BF in the GHD group, ANOVA was performed. These analyses, in which BF was used as a covariant, showed that all the observed between-group differences in measures of GH secretory patterns remained significant except for the difference in ApEn ratio between the GHD and the control group ($P=0.07$) (data not shown).

Discussion

This study distinguishes patterns of daily GH release in young adults after discontinuation of GH-treatment used for inadequate GH secretion and decreased longitudinal growth in childhood. The results of the 24-h GH profiles show that the patients with continued GHD in adult life had a high-frequency, low-amplitude 24-h pattern of GH release. The patients who were considered GHS in adult life maintained a 24-h pattern of spontaneous GH release similar to that in healthy controls.

In this study, blood sampling was performed every 30 min over 24 h. Previous validation of the deconvolution analysis have shown valid daily GH secretion rate estimates based on 30-min sampling, although the sensitivity for absolute peak number is lower than that using 10–20 min sampling schedules (34). Using a similar methodology, we previously identified clear differences in the 24-h GH secretory pattern in GHD adults with low and normal serum IGF-I concentrations compared with healthy subjects (35). In that analysis (35) and the present study comparing the GHD patients and the healthy controls, there was a between-group difference in mean number of peaks. It is therefore unlikely that any major between-group differences were not detected using the 30-min sampling. Analysis of normalised ApEn is less dependent on the sampling frequency, as indicated in a previous study using 60-min sampling protocol that yielded strong contrasts between patients with acromegaly and normal individuals in the regularity of GH secretory patterns (31, 36).

Fixed GH half-life was used in this study based on previous determinations in GHRH-stimulated and then somatostatin-suppressed adults (27). This is possible, as GH kinetics is very constant (37). Marked GH-receptor blockade via pegvisomant in adults does not alter *in vivo* GH kinetics after bolus infusion, an intervention that creates tissue hyposomatotropism (38). Systemic hyposomatotropism of critical illness or sarcopenia of aging, and IGF-I depletion in fasting, also do not alter GH kinetics (39–46). Lifetime developmental strata, whether in the neonatal, pubertal, adult or in the senescent individual (47–52) and excessive GH

secretion in acromegaly (53, 54), do not influence the GH half-life. End-stage hepatic and renal disease as well as i.v. bolus injections of GH to healthy men prolong the GH half-life (55, 56). Thus, GH kinetics is very stable, except in the state of severe organ failure and during pharmacological administration of recombinant GH.

The patients in the GHS group were comparable by way of age, gender distribution, body height, body weight, BMI, LBM and BF to healthy controls. These factors did, therefore probably, not influence the comparisons between these two groups. The correlation analyses showed that the measures of GH secretory patterns were highly related to BF in the total study population ($n=53$) as well as in the patient group ($n=37$), whereas in the GHD group ($n=19$), the only significant correlation was the negative one between half-duration of GH secretory bursts and BF. Therefore, although the number of patients was relatively small in the latter analysis, it appears that the relation between 24-h spontaneous GH release and BF was weak in the GHD group. To clarify if the observed differences in spontaneous 24-h GH release were dependent on the increased BF in the GHD group, we repeated the statistical analyses using ANOVA. In these analyses, using BF as a covariant, all the between-group differences in measures of GH secretory patterns remained significant except for the difference in ApEn ratio between the GHD and the control group ($P=0.07$) (data not shown). It is, therefore, unlikely that the observed alterations in 24-h spontaneous GH release among the study groups were due to the increased BF in the GHD group.

One hypothesis motivating this study was that not only absolute GH levels, but also the pattern of the 24-h GH release, may be important for the effects of GH administration. In rodents, pulsatile (intermittent) GH delivery is more effective in increasing longitudinal growth than continuous GH delivery (57). However, GHS and controls exhibited no difference in multiple measures of spontaneous 24-h GH release. Therefore, the pattern of GH release observed in young adult life cannot explain why patients in the GHS group had decreased longitudinal growth in childhood. An alternative speculative explanation could be that in normal subjects there is a very large increase in GH secretion during puberty (29), and this increase could have been inadequate or delayed in the GHS group, whereas GH levels were sufficiently high in adult life. In possible support of this, the patients in the GHS group had a mean onset of puberty at a relatively high age (14 years).

The patients in the GHD group exhibited the greatest detectable GH pulse frequency, along with the lowest pulse area. The anomalous GH secretory pattern mimics that previously observed in other groups of GHD adults and confirms that a low-amplitude, pulsatile GH secretion persists in adult GHD patients (35, 58, 59). Although pulsatile GH secretion persisted in patients with GHD, the relative amount of total GH secretion that

was pulsatile was decreased. Therefore, GH secretion was more nearly continuous in the GHD group than in the other study groups. This pattern of GH release may, based on that previously observed in rodents, be less effective in stimulating longitudinal growth (57). However, the results of some short-term human studies suggest that a constant GH level of a certain magnitude may be more important than GH pulsatility (60). We cannot, therefore, exclude the possibility that in the GHD group, the decreased longitudinal growth in childhood was mainly caused by their low absolute levels of GH.

Mean ApEn ratio was higher in the GHD group than in the other two groups. This outcome quantitates relatively greater disorderliness of GH secretion, which has not been associated with decreased longitudinal growth (61). In fact, ApEn is high in puberty (61), acromegaly (31, 36) and under exogenous GHRH and/or GHRP-2 drive (62, 63). The increase in ApEn ratio in the GHD group, therefore, suggests increased GHRH/GHRP drive and/or decreased IGF-I-dependent negative feedback. The former, if verified, could be hypothesised to be a compensatory phenomenon in order to restore GH action/secretion.

The present results give further evidence that a relatively high percentage of patients with short stature and inappropriate GH secretion in childhood do not have severe GHD into adult life (12, 13). In addition, this study shows that these young adult patients have a normal spontaneous pattern of 24-h GH release compared with healthy controls. We (17–19) and others (14–16) have also shown that these patients with normal GH secretion in adult life display normal longitudinal changes in body composition, muscle strength, bone metabolism and serum lipids during the first year after GH discontinuation (14–20). In the present study, there was, however, a weak non-significant tendency towards lower total GH secretion in the GHS patients than in the healthy controls. Furthermore, studies of GH discontinuation in young adults have extended for only a few years. Thus, whether GHS patients will maintain normal longitudinal body composition and metabolism throughout their entire lifespan remains unknown. Further studies are therefore needed to determine whether the metabolic syndrome in middle age, or frailty in late life, may be more frequent in the patients with idiopathic isolated GH deficiency in childhood.

In conclusion, this study distinguishes patterns of daily GH release in young adults after discontinuation of GH treatment initiated for inadequate GH secretion and decreased longitudinal growth in childhood. The results of the 24-h GH profiles show that patients considered to be GHD in adult life maintain a high-frequency, low-amplitude 24-h pattern of GH release. Patients considered to be GHS in adult life exhibit a normal pattern of 24-h GH release. Therefore, the pattern of GH secretion observed in young adult life cannot explain why GHS patients had inappropriate GH secretion and decreased longitudinal growth in childhood.

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