

# Final height and growth hormone secretion after completion of growth hormone therapy in patients with idiopathic growth hormone deficiency and with abnormalities of the hypothalamic-pituitary region

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## Abstract

**AIMS:** The aim of the study was an evaluation of final height and growth hormone (GH) secretion after completion of GH therapy (retesting) in patients with GH deficiency (GHD).

**PATIENTS AND METHODS:** The analysis comprised 53 patients (43 boys, 10 girls) with childhood-onset GHD, who completed GH therapy and reached final height. Magnetic resonance imaging (MRI), performed in all the patients, led to the following groups: pituitary stalk interruption syndrome (PSIS), pituitary hypoplasia (HP), *craniopharyngioma* (CP) – patients after tumour excision, patients with normal hypothalamic-pituitary region (NP).

**RESULTS:** In 51 patients, final height was normal. The height gain was significantly ( $p < 0.05$ ) greater in PSIS than in that other groups. In retesting, GH secretion was significantly ( $p < 0.005$ ) lower in PSIS and CP than in HP and in NP and also ( $p < 0.05$ ) in HP than in NP. Permanent severe GHD was confirmed in all the patients with PSIS and CP and in some patients with HP (37.5%), while it was excluded in all the patients with normal pituitary in MRI.

**CONCLUSIONS:** It seems that in patients with PSIS and CP, the confirmation of persistent character of GHD needs no retesting, while in patients with normal MRI results, GHD diagnosis should be established with special attention.

## Abbreviations

CA – chronological age  
CP – craniopharyngioma  
FH – final height  
GH – growth hormone  
GHD – growth hormone deficiency  
HA – height age  
HP – pituitary hypoplasia  
MPHD – multiple pituitary hormone deficiency  
MRI – magnetic resonance imaging  
NP – normal hypothalamic-pituitary region  
PHt – anterior pituitary height  
PSGHDA – permanent severe GHD in adults  
PSIS – pituitary stalk interruption syndrome  
SDS – standard deviation score

## Introduction

The diagnosis of growth hormone (GH) deficiency (GHD) is based on the combination of auxological data, i.e., short stature and low height velocity, in addition to low serum GH levels in response to stimulating agents [18, 19, 26]. The cut-off GH peaks in those tests were, in most countries, established arbitrarily. These tests still keep their position in the diagnostics of GHD for the lack of better alternatives for the evaluation of GH secretory capacity [8]. The physiological assessment of GH secretion by 24-hour profile is not more reliable, encompassing both sensitivity and specificity, than GH stimulation tests [7, 8].

In the past years, the use of magnetic resonance imaging (MRI) defined valuable diagnostic markers in a high percentage of children, previously labelled as idiopathic GHD, by showing abnormalities of the hypothalamic-pituitary region, such as anterior pituitary hypoplasia, agenesis or interruption of pituitary stalk and ectopy of posterior pituitary [1, 15]. Coutant et al. in 2001 [6] proved that children with GHD and abnormalities of the hypothalamic-pituitary region were shorter and younger at the time of diagnosing, while having better catch-up growth and reaching greater final height than those with normal results of MRI.

A number of studies, performed in recent years, have reassessed the GH secretory status of young adults after completion of GH replacement therapy in childhood [4, 13, 22, 25]. Those studies were performed to assess the number of patients with normal GH secretion, when re-evaluated, and to indicate the number of those with persisting severe GHD. All the patients were defined as GH-deficient in childhood, but GH secretion was regarded to be normal in a wide range (20–87%) at reassessment in different studies [9, 13, 22, 25]. It was shown by Maghnie et al. [11] that in children with childhood-onset GHD and congenital abnormalities of the hypothalamic-pituitary region, the diagnosis of permanent GHD was confirmed in retesting, while in children with isolated GHD and normal pituitary volume, GH secretion – in retesting – was within the normal range.

The aim of the study was an evaluation of final height and GH secretion after completion of GH therapy (retesting) in patients with GHD: either idiopathic or caused by abnormalities in the hypothalamic-pituitary region.

## Material and methods

The analysis comprised 53 short children (43 boys, 10 girls) with GHD, diagnosed at our Department, in age  $13.9 \pm 2.2$  years (mean  $\pm$  SD). The criterion of short stature was height SDS below  $-2.0$ , according to the actual national reference values for age and sex [14]. Growth hormone deficiency was diagnosed on the basis of decreased GH secretion in two stimulation tests (GH peak in both tests below  $10.0$  ng/mL), with clonidine,  $0.15$  mg/m<sup>2</sup> orally and with either insulin  $0.1$  U/kg *i.v.* (32 patients) or glucagon  $30$   $\mu$ g/kg *i.m.* (21 patients). Blood samples for GH estimation were collected every 30 min from 0 to 120 min in clonidine and insulin tests, and to 180 min in glucagon test. Concentrations of GH were measured, using the two-site chemiluminescent enzyme immunometric assay hGH (IMMULITE, DPC). In order to identify multiple pituitary hormone deficiency (MPHD), appropriate pituitary stimulation tests were considered necessary. Patients with chromosomal abnormalities, dysmorphic features, skeletal dysplasia, malabsorption syndrome, primary hypothyroidism and chronic diseases were excluded from the study.

In all the patients, MRI of the hypothalamic-pituitary region was performed. All the MRI scans were carried out on a 1.5-Tesla MRI unit, with slice thickness of 2–3 mm, before and after gadolinium injection. In 5 cases, MRI scanning revealed the presence of brain tumour in the hypothalamic-pituitary region. All those patients underwent neurosurgery (total excision of the tumour), followed by histopathological diagnosis of *craniopharyngioma*. After neurosurgery, in all the patients MPHD and *diabetes insipidus* (DI) developed, and appropriate substitutive therapy was applied. Control MRI examinations, performed – at least – after one year from neurosurgery, excluded tumour recurrence in all the patients. In the remaining 48 patients, the height of the anterior pituitary (PHt) was measured and the presence of pituitary stalk, as well as the localisation of the posterior pituitary lobe was assessed. Pituitary height, defined as the longest distance between the base and the top of the anterior lobe of the gland, was measured in the plane perpendicular to the base of the *sella turcica* (accuracy of measurement: 0.1 mm). The results of measurements were compared with published normal values for given age [1] and expressed as standard deviation score (SDS), with reference to chronological age (CA) and height age (HA). The pituitary gland was considered to be hypoplastic when PHt SDS was below  $-2.0$  for HA. In short children, HA is below CA, so, in some cases, the pituitary gland, classified as hypoplastic with reference to normative data for CA, turned out to be normal for HA. In 6 patients, the most complete form of abnormalities – pituitary stalk interruption syndrome (PSIS), including the absence of visible pituitary stalk (pituitary stalk interruption), ectopy of the posterior pituitary and hypoplasia of the anterior pituitary (HP), was observed. Isolated HP was diagnosed in other 14 patients, while in the remaining 28 patients, the picture of the hypothalamic-pituitary region in MRI examination was normal.

Thus, the obtained MRI results allowed dividing the patients into the following groups:

PSIS – pituitary stalk interruption syndrome;  
 HP – pituitary hypoplasia;  
 CP – craniopharyngioma;  
 NP – normal picture of hypothalamic-pituitary region in MRI.

The therapy with recombinant human GH, in the mean dose of 0.5IU/kg/week, was applied just after the diagnosis was confirmed, except from the patients with craniopharyngioma, who started the therapy, at least, after one year from neurosurgery, having tumour recurrence excluded. A complementary substitution of other hormones was also applied when necessary. The treatment with GH was stopped when either the patient's height velocity was below 2 cm/year or bone epiphyses were closed. The final height (FH) was assessed after completion of GH therapy, at Tanner's stage 5, with the bone age, at least, 17.5 years in boys and 16.0 years in girls.

The second evaluation of endogenous GH secretion (retesting) was performed after –at least – three months, but no more than after one year from the end of GH therapy. Permanent, severe GHD in adult patients (PSGHDA) was confirmed, when GH peak in insulin hypoglycaemia test (performed similarly as that in the first evaluation), was below 3 ng/mL.

Patients' height before and after the therapy was expressed as SDS, according to Tanner-Whitehouse's standards [21]. It should be noticed that the qualification of patients to the study was performed on the basis of actual normative data for Polish children [14], while the height SDS before GH therapy ( $H_0$ SDS) was calculated, according to the almost forty years old Tanner-Whitehouse's reference values [21]. Taking into consideration the acceleration phenomenon, one must expect that, in the examined group, there were some patients with height SDS below –2.0, according to the actual national reference values but above –2.0, according to that of Tanner-Whitehouse [21].

The work was approved by the local medical ethics committee, and the subjects gave their informed consent to participate in the study.

## Results

In the analysed group of 53 patients with GHD, the deficit of height before GH therapy (expressed as  $H_0$ SDS) was  $-2.56 \pm 0.88$ , maximal GH peak in stimulation tests was  $4.6 \pm 2.7$  ng/mL. The obtained final height (expressed as FHS) was  $-0.66 \pm 0.88$ . Height gain ( $\Delta$ HSDS) during the therapy was  $1.93 \pm 1.07$ .

Selected data of patients, classified according to MRI findings, obtained before the therapy onset are shown in Table I. Selected auxological parameters and the results

**Table I:** Selected auxological and hormonal data of particular groups of patients, classified according to MRI results, before GH therapy

	PSIS	CP	HP	NP
n	6	5	14	28
male/female	6/0	5/0	11/3	21/7
age at therapy onset [years]	$9.9 \pm 2.0^{a,b,c}$	$16.6 \pm 0.3^{a,d,e}$	$13.9 \pm 1.8^{b,d}$	$14.1 \pm 1.6^{c,e}$
$H_0$ SDS	$-3.50 \pm 0.96^f$	$-3.07 \pm 0.55^g$	$-2.49 \pm 0.97$	$-2.32 \pm 0.70^{f,g}$
GH peak before therapy [ng/mL]	$1.3 \pm 0.3^{h,j}$	$0.4 \pm 0.2^{h,k,l}$	$3.6 \pm 2.1^{k,m}$	$6.6 \pm 1.2^{j,l,m}$
<5 ng/mL (n)	6	5	11	4
5–10 ng/mL (n)	–	–	3	24
MPHD and/or DI (n)	6	5	1	–

PSIS – pituitary stalk interruption syndrome, CP – craniopharyngioma, HP – pituitary hypoplasia, NP – normal hypothalamic-pituitary region  
 $H_0$ SDS – height SDS before the therapy, GH – growth hormone, MPHDA – multiple pituitary hormone deficiency, DI – diabetes insipidus

Significant differences:

a, b, c, d, e, h, j, k, l, m –  $p < 0.005$

f, g –  $p < 0.05$

**Table II:** Selected auxological data of particular groups of patients, classified according to MRI results, after completion of the therapy

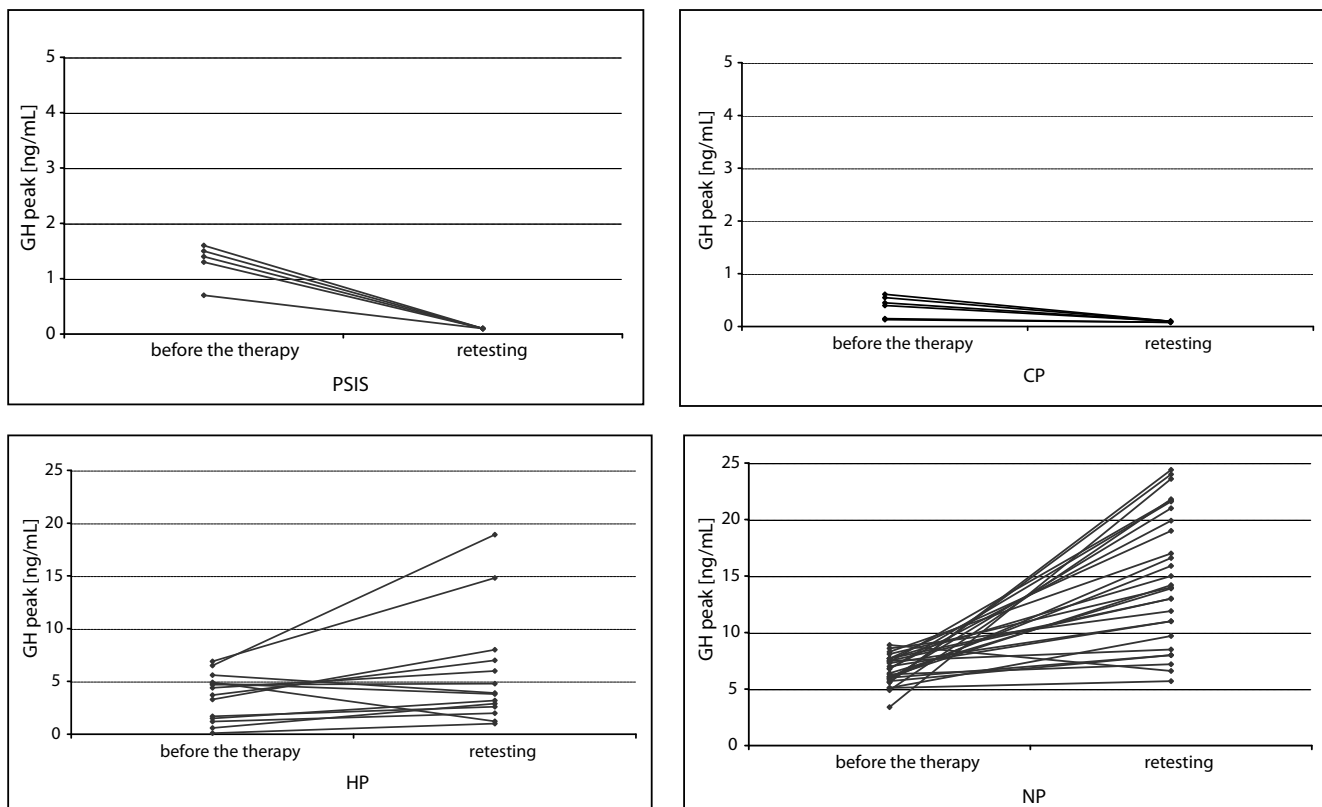
	PSIS	CP	HP	NP
therapy duration [years]	$9.1 \pm 1.8^{a,b,c}$	$2.1 \pm 0.3^{a,d,e}$	$4.5 \pm 1.9^{b,d}$	$3.5 \pm 0.9^{c,e}$
age at final height [years]	$19.0 \pm 1.0^f$	$18.7 \pm 0.3$	$18.2 \pm 1.7$	$17.6 \pm 1.3^f$
FH SDS	$0.17 \pm 0.33^g$	$-0.25 \pm 1.07$	$-0.60 \pm 0.89$	$-0.70 \pm 0.68^g$
GH peak in retesting [ng/mL]	$0.1 \pm 0.0^{h,j}$	$0.1 \pm 0.0^{k,l}$	$6.5 \pm 6.2^{h,k}$	$17.1 \pm 8.7^{j,l}$
PSGHDA (n)	6	5	5	–

PSIS – pituitary stalk interruption syndrome, CP – craniopharyngioma, HP – pituitary hypoplasia, NP – normal hypothalamic-pituitary region  
 FH SDS – final height SDS, GH – growth hormone, PSGHDA – permanent severe GH deficiency in adulthood

Significant differences:

a, b, c, h, j, k, l –  $p < 0.005$

d, e, f, g –  $p < 0.05$



**Figure 1:** GH secretion before the therapy and in retesting after completion of the therapy in particular groups of patients (see different scale of GH secretion for particular Groups)  
 GH – growth hormone, PSIS – pituitary stalk interruption syndrome, CP – craniopharyngioma, HP – pituitary hypoplasia, NP – normal hypothalamic-pituitary region

of GH retesting after completion of the therapy in the same groups of patients are shown in Table II.

The deficit of height before GH therapy was greater in PSIS than in all other groups. Growth hormone secretion was significantly ( $p < 0.005$ ) lower in CP than in all the other groups. Significant ( $p < 0.005$ ) differences between PSIS and NP and between HP and NP were also observed, while the difference between PSIS and HP was close to the border of significance ( $p = 0.07$ ).

Almost all of the examined patients (51 out of 53) reached their FH within the normal range. The obtained FH was the best in PSIS, slightly lower in CP, and the lowest in HP and NP; but the difference was significant ( $p < 0.05$ ) between PSIS and NP only. Height gain was the greatest in PSIS, being significantly ( $p < 0.01$ ) better than in other groups. With respect to therapy duration, the height gain/year of GH therapy was significantly ( $p < 0.05$ ) greater in CP than in other groups, in which it was similar.

After completion of the therapy, GH secretion was extremely low ( $0.1 \pm 0.0$  ng/mL) in PSIS and CP, being significantly ( $p < 0.005$ ) lower than that in HP and NP. Permanent, severe GHD was confirmed in all the patients with PSIS and with CP, in 5 out of 14 patients with HP (35.7%), and it was excluded in all the patients with NP. Moreover, only in 7 out of 24 patients with NP (29.2%), GH secretion in retesting was below 10.0 ng/mL (range: 5.7–9.7 ng/mL), while in the remaining 17 patients (70.8%), it ranged from 11.0 to 24.4 ng/mL. In HP, only in 2 out of 14 patients (14.3%), GH secretion

in retesting was above 10.0 ng/mL. The obtained results for all the groups are shown in Figure 1.

## Discussion

Several studies have attempted evaluation of GH therapy effectiveness in children with GHD. In the meta-analysis of 4529 patients with GHD, Guyda [8] found the mean height gain of 1.5 SDS during GH therapy, leading to the mean final height of  $-1.4$  SDS. Slightly worse were the results obtained by Carel et al. in the French population [5]. The height gain was  $1.1 \pm 0.9$  SDS, resulting in the adult height of  $-1.6 \pm 0.9$  SDS. In our study, both the mean height gain during GH therapy and the obtained FH were even better than the values reported by Guyda [8].

Along with an introduction of MRI scanning of the hypothalamic-pituitary region into routine practice in GH-deficient patients, a special attention was paid to MRI significance not only in excluding neoplastic processes but also in confirming permanent and severe GHD. In our study, the observed deficit of height was more severe in patients with PSIS and with CP than in patients with normal pituitary gland and isolated HP. Growth hormone deficiency was diagnosed in PSIS at a younger age than that in other groups of patients. The above results are consistent with the data, published by Coutant et al. in 2001 [6]. Children with abnormalities of the pituitary gland, visualised in MRI, had more profound GHD than children with normal MRI, and they

had higher incidence of MPHD, especially in PSIS and CP. Similar observations were obtained in previously published studies [7, 15].

The data concerning the relationships between GHD severity and the effectiveness of GH therapy are not consistent [17]. Some authors found GH therapy more effective in patients with severe GHD than in those with partial GHD while others found the effectiveness to be similar [2, 3, 20]. In our study, the best height gain was observed in patients with severe GHD, caused by PSIS, and even better height gain/year in patients with severe GHD after CP excision. Coutant et al. [6] showed, that patients with PSIS responded to GH therapy better than children with normal pituitary gland in MRI, while among patients with normal MRI no differences were observed in both height velocity improvement and FH between patients with severe and partial GHD. In the quoted study, the data of patients with PSIS and of those with isolated HP were not compared. Our results indicated significant differences in GH secretion, height deficit before the therapy and the effectiveness of GH therapy between those groups of patients.

In different studies [9, 13, 22, 25], permanent severe GHD after completion of the therapy was observed in 20–87% of patients. In the study performed by Thomas et al. [23] in retesting 100% patients with previous diagnosis of MPHD, 86% of patients with severe GHD and 47% of patients with partial GHD remained GH-deficient, according to paediatric criteria. Moreover, all MPHD patients but only 36% of the patients with severe GHD and none of the patients with partial GHD met the criteria of PSGHDA in adulthood. In our study 30.2% of patients remained GH-deficient as adults. Tillmann et al. [24] stated, that ectopy of the posterior pituitary and hypoplasia of anterior pituitary and/or pituitary stalk may be an additional confirmation for GHD diagnosis. In our study, permanent severe GHD was found in all the patients with PSIS and after CP excision and in 35.7% of patients with isolated HP, while it was excluded in all the patients with normal pituitary gland. The obtained results confirm the significance of both congenital and acquired abnormalities of the pituitary gland in the diagnosis of permanent GHD. Our results are consistent with the observations, published by Maghnie et al. [11], indicating that in all the patients with GHD and congenital hypothalamic-pituitary abnormalities, GH secretion remains decreased in adulthood. The authors suggest that these patients do not require retesting to confirm persistent GHD, while in patients with isolated GHD and either normal or hypoplastic anterior pituitary retesting is necessary. Disclosure of organic abnormalities in the hypothalamic-pituitary region, responsible for GHD, seems to be particularly important in the light of reports on the limitations of GH stimulation tests credibility in GHD diagnosing, as it was widely described by Rosenfeld et al. [19]. Pfeifer et al. [16] found the poor reproducibility of GH secretion in insulin tolerance test in adult men. In 2001 Loche et al. [10] showed that in patients with normal hypothalamic-pituitary region in MRI and decreased GH secretion in stimulation tests, the results of the same tests repeated after 1–6 months

were normal in 84.8% of patients. For this reason, the authors postulate repetition of GH stimulation tests in case of patients with normal pituitary gland, before the application of GH therapy. In the majority of our patients with normal pituitary gland in MRI (70.8%), GH secretion after completion the therapy was normal, even with respect to paediatric criteria (e.g. above 10.0 ng/mL). It seems difficult to fully assess the effectiveness of GH therapy, due to the lack of control group of untreated GH-deficient children with normal pituitary gland in MRI. In the presence of established indications to GH therapy in GHD, this kind of the study seems to be unethical. It is also impossible to assess, at which time point GH secretion became normal in such patients (if it was ever really decreased). The hypothesis of transient GHD for patients with the diagnosis of partial GHD, established in childhood, may be inappropriate. On the basis of the literature review, van den Broeck [26] stated that the phenomenon of normalisation of test results after GH therapy might be explained by the very low reproducibility of the tests and by the regression to the mean effect. In 1994, Marin et al. [12] obtained the maximal GH peak below 7 ng/mL in three stimulation tests, performed in each patient, in 61% normal prepubertal children. It seems possible that patients, diagnosed as those with partial GHD, with normal MRI and normal GH secretion in retesting (above 10 ng/mL) were, in fact, misdiagnosed short normal children.

The results of our study confirm the best effectiveness of GH therapy in patients with severe GHD and organic abnormalities of the hypothalamic-pituitary region. Permanent severe GHD after completion of growing was confirmed in all the patients with PSIS and in those after CP excision. It seems that in such patients, the confirmation of persistent character of GHD needs no retesting. Conversely, in patients with normal MRI results, GHD diagnosis should be established with special attention and the earlier retesting of GH secretion – before attainment of final height – should be considered.

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