Growth hormone (GH) secretion and pituitary size in children with short stature. Efficacy of GH therapy in GH-deficient children, depending on the pituitary size.

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O R I G I N A L   A R T I C L E

Abstract

INTRODUCTION: Certain relationships between pituitary size and growth hormone (GH) secretion have previously been observed, however they are still a matter of controversy. Organic abnormalities of the hypothalamic-hypophyseal region are important for predicting growth response to GH therapy.

AIM: Evaluation of relations between GH secretion and the pituitary size in short children and estimation of the efficacy of GH therapy in children with GH deficiency (GHD).

PATIENTS AND METHODS: The analysis comprised 216 short children (159 boys). Two GH stimulation tests, as well as magnetic resonance image (MRI) examination, were performed in each patient. All the patients with GHD were treated with GH for, at least, one year.

RESULTS: Significant correlations were found between pituitary height and GH secretion ($p < 0.05$). Patients were classified into three (3) groups: 1) pituitary hypoplasia (HP) for height age; 2) HP for the chronological age but not for the height age; 3) normal pituitary size. Significant differences in GH secretion were observed among the groups (6.1±5.3 vs. 8.1±4.4 vs. 12.3±9.1 ng/mL, respectively). There was a negative correlation between GH peak and height gain during GH therapy ($r = -0.34$). The highest growth improvement was noticed in patients with HP for the height age.

CONCLUSIONS: Pituitary hypoplasia for the height age is related to more severe GH deficiency and the best response to GH therapy.

Introduction

Growth hormone (GH) deficiency (GHD) may either be idiopathic or caused by congenital or inherited organic abnormalities of the hypothalamic-hypophyseal region. The deficit of GH may be isolated or associated with concomitant impairment of other pituitary hormoness. Magnetic resonance imaging (MRI) has become a selected technique in the neuroradiological evaluation of the anatomy of the hypothalamic-hypophyseal region and of its possible alterations, like hypoplasia of the anterior pituitary lobe (HP), interruption of the pituitary stalk (PS) and posterior pituitary ectopia [1, 2]. The most complete form out of the observed abnormalities is the pituitary stalk interruption syndrome (PSIS), including pituitary stalk invisibility (PS interruption), ectopic posterior pituitary (EPP), and the anterior pituitary hypoplasia (HP). In some cases, however, EPP may be associated with visible pituitary stalk [3, 4]. Pituitary hypoplasia may also occur without other features of PSIS.

Pituitary height (PHt) measurement allows assessing the pituitary size, since the age-dependent size progression of the gland appears to be mainly related to the changes in its height but not in its length or width. There is a strong correlation between PHt and the pituitary volume [5].

The relations between the morphological features of the pituitary and its size or function are still a matter of controversy. In the studies conducted by Abrahams et al. [6] and Cacciari et al. [7] no link could be found between PHt and GH secretion. The first investigation, confirming a correlation between PHt and GH secretion, was presented by Nagel et al. [8].

Recent reports have suggested a stronger growth response to GH therapy in patients with abnormalities of the hypothalamic-hypophyseal region, visualised in MRI than that in patients with normal MRI result [9]. Zenaty et al. [10] have stated that detection of congenital abnormalities of the hypothalamic-pituitary axis has a higher predictive value for the effectiveness of GH therapy than GH secretion assessment in stimulation tests.

The aim of the study was an evaluation of relations between GH secretion and the pituitary size in short children, as well as an estimation of the efficacy of GH therapy in children with GHD.

Patients and methods

The analysis comprised 216 children (159 boys, 57 girls) with short stature. The criterion for short stature was height SD score below –2.0, according to the actual national reference values for age and sex [11]. Next, patients' height was expressed as SD score, according to Tanner-Whitehouse's standards [12]. The standards were chosen, despite available national standards [11], since the more advanced auxological methods – like Bayley-Pinneau's method of calculation of predicted adult height (PAH) – are adjusted to them [13]. It should be noticed that the qualification of patients to the study was performed on the basis of the actual growth charts for Polish children [11], while the height SD score before GH therapy (H_0SDS) was calculated, according to the almost 40 years old Tanner-Whitehouse reference values [12]. Taking into consideration the acceleration phenomenon, one must expect that – in the examined group – there were some patients with height SD score below –2.0, according to the actual national reference values but above –2.0, according to that of Tanner-Whitehouse.

At the diagnosis, the patients' age was 12.5±2.9 years (mean±SD).

Two GH stimulation tests (with clonidine, 0.15 mg/m², orally and with insulin, 0.1 U/kg $i.v.$, or glucagon, 30 mg/kg, $i.m.$) were performed in each patient. Blood samples for human GH (hGH) estimation were collected every 30 min (from 0 to 120 min) in clonidine and insulin tests. In the glucagon test, blood samples were collected at 0, 90, 120, 150, 180 min of the test. The diagnosis of GHD was established on the basis of decreased GH secretion in two stimulation tests (GH peak in both tests below 10.0 ng/mL).

According to the highest GH peak in the stimulation tests, the patients were classified into the following groups:
1. severe, isolated GH deficiency (SIGHD, GH below 5 ng/mL; n = 37);
2. partial, isolated GH deficiency (PIGHD, GH 5–10 ng/mL; n = 110);
3. multiple pituitary hormone deficiency (MPHD; n = 24);
4. idiopathic short stature (ISS; GH at least 10 ng/mL; n = 45).

The concentration of GH was measured by the two-site chemiluminescent enzyme immunometric assay (hGH IMMULITE, DPC) with the sensitivity of 0.01 ng/mL, with intraassay coefficients of variation of 5.3–6.5% and interassay coefficients of variation of 5.5–6.2%. GH standards were calibrated, according to the WHO reference standard 80/505. In order to identify MPHD, further pituitary stimulation tests (GnRH, TRH, ACTH) were considered necessary.

In all the patients, MRI of the hypothalamic-hypophyseal region was performed before GH therapy, and the height of the pituitary gland was assessed. All the MRI scans were carried out on a 1.5-Tesla MRI unit (Picker, model Edge), with sagittal and coronal slices, their thickness being 2–3 mm, depicted as midline images on T_1-weighted, before and after gadolinium injection. The height of the pituitary gland (PHt), defined as the longest distance between the base and the top of the gland, was measured on the mid-sagittal T_1-weighted image, in a plane perpendicular to the base of the $sella$ $turcica$, after magnification through an overhead projector and using the scaling provided on the films (the accuracy of measurement: 0.1 mm). Pituitary height measurements were compared with the published normal values for given age [14] and expressed in SDS, with reference to the chronological
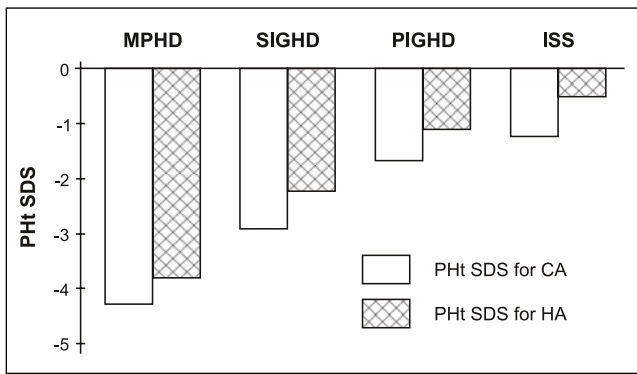
Figure 1: Pituitary height SDS in particular groups of patients, divided according to GH peak and the type of pituitary insufficiency
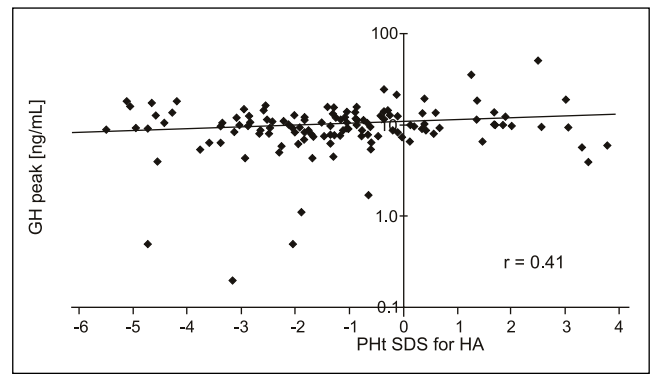

Figure 2: Correlation between PHt SDS for HA and GH peak in stimulation tests in children with short stature
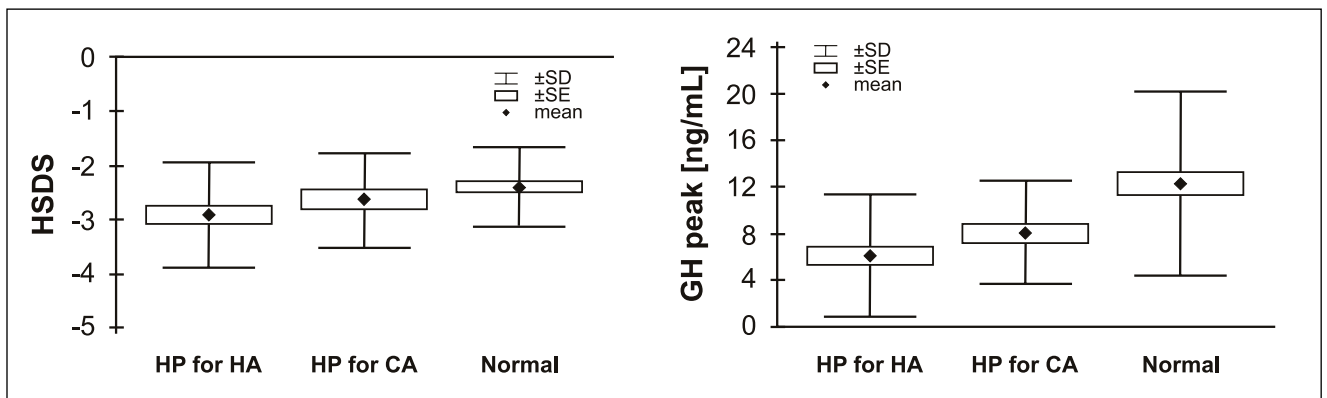

Figure 3: Height SDS and GH secretion in patients with short stature, divided according to pituitary height

age (CA) and to the height age (HA). The pituitary gland was considered hypoplastic when PHt SDS was below −2.0 for CA and for HA. In short children, HA is below CA, so, in certain cases, the pituitary gland, classified as hypoplastic with reference to normative data for CA, turned out to be normal for HA. In some cases, other abnormalities, included in PSIS, may be observed as well.

All the patients with GHD were treated with GH for, at least, one year, with the mean dose of 0.5 IU/kg/week. The efficacy of GH treatment was assessed as an improvement of height velocity and the height SD score (H SDS) gain during the therapy.

Results

Relations between GH secretion and pituitary size in children with short stature

In the analysed group of patients, HSDS was −2.49±0.83, according to Tanner-Whitehouse [10], and GH peak was 9.5±7.8 ng/mL in two stimulation tests. *Table 1* presents detailed data of the particular subgroups of patients, classified according to GH peak and to the type of pituitary insufficiency (isolated GHD or MPHD) (*Table 1*).

All the differences in height SDS among the analysed groups of patients were insignificant, while all the differences in PHt SDS for CA among all the presented groups were significant. In PHt SDS assessed

Table 1: Age, height SDS, GH peak and pituitary size of the particular subgroups of patients, classified according to GH peak and the type of pituitary insufficiency.

	n	CA [years]	HSDS	GH peak [ng/mL]	PHt SDS		Frequency of pituitary hypoplasia [%]	
					for CA	for HA	for CA	for HA
MPHD	24	9.1±3.9	−3.42±1.06	1.7±1,6	−4.29±1,22[abc]	−3.81±1.29[ghi]	100.0	91.7
SIGHD	37	12.8±2.2	−2.37±0.68	4.4±1.6	−2.90±2.36[ade]	−2.22±2.10[gk]	64.9	45.9
PIGHD	110	12.5±2.7	−2.29±0.67	7.5±1.2	−1.66±1.72[bdf]	−1.08±1.74[hl]	32.7	16.4
ISS	45	13.7±2.5	−2.63±0.86	19.9±9.2	−1.23±1.47[cef]	−0.51±1.49[ikl]	24.4	13.3

Significant differences: a, d, g – p<0.005; b, c – p<0.0001; e, k, l – p<0.05, f – p<0.01, h, i – p<0.001
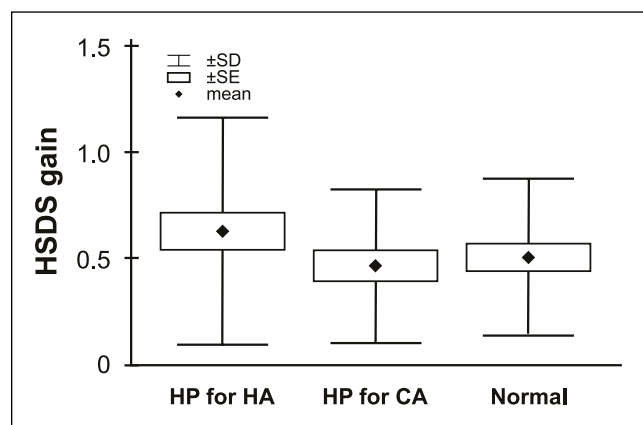
Figure 4: Height SDS gain after 1 year of GH therapy in particular groups of patients with GHD

Table 2: Age, height SDS and GH secretion of the patients with short stature, classified according to the pituitary size.

	Age[years]	HSDS	GH peak [ng/mL]
$HP_{FOR}HA$	11.4±3.3	−2.81±0.92	6.1±5.3 [ab]
$HP_{FOR}CA$	13.0±2.3	−2.62±0.88	8.1±4.4 [ac]
NORMAL	12.9±2.7	−2.31±0.70	12.3±9.1 [bc]

Significant differences: a, c – p<0.01; b – p<0.001

Table 3: Age, height SDS and GH secretion of the patients with GHD, classified according to the pituitary height.

	Age[years]	HSDS	GH peak [ng/mL]
$HP_{FOR}HA$	11.3±3.4	−2.63±0.99[a]	4.7±2.8[bc]
$HP_{FOR}CA$	12.8±2.3	−2.42±0.83	6.3±1.9[bd]
NORMAL	12.6±2.7	−2.17±0.35[a]	7.2±1.6[cd]

a – p<0,01; b, d – p<0,05; c – p<0,0001

Table 4: Selected data of particular groups of patients with GHD before GH therapy (H0SDS) and after 1 year of the therapy (H1SDS).

	H_0SDS	H_1SDS	Height SDS gain
$HP_{FOR}HA$	−2.68±0.98	−2.12±0.90	0.56±0.48
$HP_{FOR}CA$	−2.42±0.91	−1.95±0.83	0.47±0.36
NORMAL	−2.17±0.58	−1.75±0.58	0.42±0.32

for HA, significant differences were found among all the groups, except the difference between SIGHD and PIGHD (p = 0.09). The values of PHt SDS for CA and for HA were compared in the particular groups of the patients (*Figure 1*).

There was a very strong (r = 0.99) correlation between PHt SDS for CA and PHt SDS for HA. Significant (p < 0.05) correlations were also observed between PHt SDS for both CA and HA and GH peak,

expressed as the logarithm of the maximal GH peak in two stimulation tests (r = 0.39 and r = 0.41, respectively) (*Figure 2*).

Next, all the patients were classified according to the pituitary size (PHt SDS for CA and for HA). The following groups of patents were created:

1. $HP_{FOR}HA$ – patients with pituitary hypoplasia for HA (n = 69);
2. $HP_{FOR}CA$ – patients with pituitary hypoplasia for CA but not for HA (n = 39);
3. NORMAL– patients with normal pituitary height (n = 108).

Selected data of the patients with short stature, classified according to the pituitary size in MRI, are shown in *Table 2*.

All the differences in both patients' age and height SDS among the particular groups were insignificant, while – in contrast – all the differences in GH peak among all the groups were significant (*Figure 3*).

Efficacy of GH therapy in GH-deficient children with respect to pituitary size

The second part of the analysis comprised 169 short children (121 boys, 48 girls) with GHD; patients with ISS were excluded from further studies. All the patients with GHD were classified into the following groups, according to the pituitary size again:

1. $HP_{FOR}HA$ – patients with pituitary hypoplasia for HA (n = 63), including 10 patients with the complete form of PSIS;
2. $HP_{FOR}CA$ – patients with pituitary hypoplasia for CA but not for HA (n = 37);
3. NORMAL – patients with normal pituitary height (n = 59).

Table 3 presents selected data of the patients with short stature, classified according to the pituitary size in MRI.

Significant differences in GH peak were observed among all the groups, while all the differences, except the one between $HP_{FOR}HA$ and NORMAL (p < 0.05), in height SDS were insignificant among the groups in question.

At the onset of GH therapy, the patients' HSDS was −2.51±0.85. Before the treatment, height velocity (HV) was below 4 cm/year in all the patients. Selected data of particular groups of patients before GH therapy and after 1 year of the therapy are shown in *Table 4*. The first-year effectiveness of GH therapy was assessed as the height SDS gain after one year of the therapy (*Figure 4*).

After 1 year of GH therapy, all the differences in H SDS became insignificant (NS). The obtained growth improvement (expressed as H SDS gain) was insignificantly higher in the HP for HA group than that in other groups. There was a negative correlation (r = −0.34) between GH peak and H SDS gain.

Discussion

A high incidence of morphological abnormalities in the hypothalamic-hypophyseal region, as revealed in MRI, has been reported in patients with GHD [2, 7, 8]. The pituitary stalk interruption and the ectopy of the posterior lobe of the pituitary gland may be considered as diagnostic markers of permanent GHD, since they have been more frequently reported in patients with MPHD than in those with isolated GHD [2, 7, 8]. Pellini et al. [15] described an invisible stalk in all of their subjects with MPHD and in 44.4% of subjects with isolated GHD; similarly, further investigation, performed in the same groups, revealed the above abnormalities in 95% of subjects with MPHD and in 39% subjects with isolated GHD [16]. Recently, Kemp et al. [17] have observed a higher incidence of abnormal findings in MRI in patients with severe GHD than in patients with partial GHD and normal GH secretion. On the other hand, MRI-diagnosed abnormalities, e.g., ectopy of the neurohypophysis, are not invariably associated with MPHD, as they are also observed in healthy children [18]. Since normal subjects display a fairly broad spectrum of hypophysis shapes, a markedly concave hypophysis with normal volume can wrongly be mistaken as too short, while the values for a convex shape would – analogously – imply the gland as too high. Pituitary height measurement is a reliable tool for the assessment of pituitary size, although the limits of this method must be kept in mind. It is very important to maintain careful attention while measuring PHt [8, 16].

Some data exist that isolated anterior HP in the absence of additional anatomical defects of the hypothalamic-hypophyseal region does not significantly contribute to the diagnosis of GHD, due to the lack of any correlation between the pituitary size and GH response to pharmacological stimuli [2]. In our study, anterior HP for the height age was related to the lowest GH secretion, while most of patients with HP only for the chronological age (but not for the height age) demonstrated either partial GHD or normal GH secretion. Pituitary height in the patients with MPHD and SIGHD was significantly lower from respective values in all the other groups. Our findings are consistent with the previous observations of Argyropoulu et al. [14].

In the recent years, the relationships between the pituitary size and/or structure and the effectiveness of GH therapy have become a subject of particular interest. Coutant et al. [9] reported higher effectiveness of GH therapy (assessed as the catch-up growth and the final height) in patients with abnormalities of the hypothalamic-hypophyseal region than that in patients with normal hypothalamic-hypophyseal MRI, with both severe and partial GHD. Zenaty et al. [10] found a strongergrowth response to GH therapy in the first 3 years in patients with congenital abnormalities of the hypothalamic-hypophyseal area than that in children with normal pituitary in MRI scanning. The highersignificance of detection of developmental hypothalamic-pituitary abnormalities

was reported as even a more important parameter in prediction of growth response to GH therapy than the maximal GH secretion in stimulation tests. Our study showed a higher effectiveness of GH therapy in the first year of its application in children with severe HP (HP for HA) than in patients with normal or mild form of anterior HP (HP for CA). An assessment seems necessary of the long-term response to GH therapy and – particularly – of the obtained final height.

In conclusion, anterior HP with respect to patient's height age is connected with more severe GHD and a higher– at least, short-term – responsiveness to GH therapy. Further observation seems necessary for a more accurate assessment of the long-term effectiveness of GH therapy in particular groups of patients.

Acknowledgements

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