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Incidence and predictors of persistent growth hormone deficiency (GHD) in patients with isolated, childhood-onset GHD

Częstość i czynniki prognostyczne trwałego niedoboru hormonu wzrostu u pacjentów z rozpoznaną w dzieciństwie izolowaną somatotropinową niedoczynnością przysadki

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Abstract

Introduction: In a considerable proportion of patients with childhood-onset growth hormone (GH) deficiency (GHD), a normalisation of GH secretion at the attainment of final height (FH) is observed. The aim of the present study was to assess the incidence of, and to find out the predictors of, persistent and transient GHD, available in the pre-treatment period, in patients with childhood-onset isolated, non-acquired GHD.

Material and methods: The analysis comprised 150 short children (117 boys), with childhood-onset isolated, non-acquired GHD who completed GH therapy and attained FH. Before treatment and at FH (in retesting), auxological parameters were measured, GH peak in stimulation tests and IGF-I concentration were assessed, and pituitary height (PHt) was measured before treatment.

Results: The incidence of persistent GHD was 12.0%. The patients with persistent GHD had before treatment significantly lower GH and IGF-I secretion, as well as significantly better increase of height SDS (ΔHSDS) during GH therapy than those with transient GHD. A negative correlation was observed between ΔHSDS and IGF-I concentration, but not between ΔHSDS and GH peak. There was no significant difference in the incidence of pituitary hypoplasia between the patients with persistent and transient GHD.

Conclusions: The incidence of persistent GHD in patients with childhood-onset, isolated, non-acquired GHD is relatively low. Despite the fact that the predictors of persistent and transient GHD may be identified in childhood, a diagnosis of GHD should be verified in retesting after the attainment of FH in each case. **(Endokrynol Pol 2014; 65 (5): 334–341)**

Key words: *short stature; growth hormone deficiency (GHD); growth hormone therapy; insulin-like growth factor-I; final height; persistent GHD; transient GHD*

Streszczenie

Wstęp: U znacznej części pacjentów z rozpoznaną w dzieciństwie somatotropinową niedoczynnością przysadki (SNP) stwierdza się normalizację wydzielania hormonu wzrostu (GH) po osiągnięciu wzrostu końcowego (FH). Celem pracy była ocena częstości i czynników prognostycznych trwałego i przemijającego niedoboru GH u dzieci z rozpoznaną w dzieciństwie izolowaną, nienabytą SNP.

Materiał i metody: Analizą objęto 150 dzieci (117 chłopców) z niedoborem wzrostu, z rozpoznaną w dzieciństwie izolowaną, nienabytą SNP, którzy zakończyli terapię GH i uzyskali FH. Przed leczeniem i po osiągnięciu FH oceniono wybrane wskaźniki auksologiczne oraz wydzielanie GH i IGF-I; przed leczeniem zmierzono ponadto wysokość przysadki (PHt).

Wyniki: Częstość trwałego niedoboru GH wynosiła 12,0%. Pacjenci z trwałym niedoborem GH mieli przed leczeniem znamiennie niższe wydzielanie GH i niższe stężenia IGF-I, a także uzyskali większy przyrost SDS wysokości ciała (ΔHSDS) podczas terapii GH niż pacjenci z przemijającym niedoborem GH. Stwierdzono ujemną korelację pomiędzy ΔHSDS i wydzielaniem IGF-I, przy braku korelacji między ΔHSDS a wydzielaniem GH. Częstość występowania hipoplazji przysadki u pacjentów z trwałym i przejściowym niedoborem GH nie różniła się znamiennie.

Wnioski: Częstość trwałego niedoboru GH u pacjentów z rozpoznaną w dzieciństwie izolowaną, nienabytą SNP jest względnie niska. Pomimo istnienia czynników warunkujących trwały niedobór GH w tej grupie pacjentów, możliwych do zidentyfikowania w momencie rozpoznania SNP w dzieciństwie, u wszystkich pacjentów z tej grupy rozpoznanie niedoboru GH wymaga weryfikacji podczas ponownej diagnostyki przeprowadzonej po uzyskaniu FH. **(Endokrynol Pol 2014; 65 (5): 334–341)**

Słowa kluczowe: *niedobór wzrostu; somatotropinowa niedoczynność przysadki; leczenie hormonem wzrostu; insulinopodobny czynnik wzrostowy-I (IGF-I); wzrost końcowy; trwały niedobór GH; przemijający niedobór GH*

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Introduction

It is well known that in a considerable proportion of patients with childhood-onset growth hormone (GH) deficiency (GHD), a normalisation of GH secretion is observed after the attainment of adult height and the withdrawal of growth-promoting therapy. Moreover, it has been clearly established that the cut-off value for GH peak in stimulation tests may be lower in adulthood than in childhood. Namely, for young adults, it is sufficient to achieve a GH peak in insulin tolerance test (ITT) at a level of 6.0 ng/mL [1–3].

In recent classifications, GHD has been defined as a secondary insulin-like growth factor (IGF-I) deficiency [4, 5]. Nevertheless, in current recommendations, the statement that — in adults — normal IGF-I concentration does not exclude GHD has been strongly emphasised [1, 3, 6–9], as an overlap in IGF-I levels between patients with GHD and normal controls has been reported [2]. On the other hand, it has been suggested in the same studies [2, 7, 9] that a very low IGF-I concentration might be diagnostic of GHD in the transition phase.

Numerous studies have shown that persistent GHD is highly probable in patients with multiple pituitary hormone deficiency, especially in cases of deficiency of at least three hormones, as well as in ones with isolated GHD caused by an identified mutation related to the functioning of the somatotropic axis [1, 3, 8]. Such patients do not require further diagnostics at the attainment of final height (FH), while — in the remaining subjects — a re-evaluation of GH secretion (so-called 'retesting') seems necessary [1]. However, among patients with isolated GHD diagnosed in childhood, the incidence of persistent GHD has been estimated as 40–75% [3], while in case of idiopathic GHD, a normalisation of GH secretion in the transition period has been reported in an even wider range of 20–88% [10].

Finally, very recently, Quigley et al. [8] have clearly stated that data on predictive factors of persistent GHD in patients with idiopathic GHD diagnosed in childhood is lacking.

With respect to such data, it would appear worthwhile to search for the predictors of persistent GHD in patients with childhood-onset isolated, non-acquired GHD, particularly if any such predictors could be identified not only after completion of growth-promoting therapy, but also before the therapy onset.

The aim of the present study was to assess the incidence of, and to find out the factors predictive of, persistent and transient GHD available in the pre-treatment period in patients with childhood-onset isolated, non-acquired GHD who completed GH therapy and attained FH.

Material and methods

This retrospective analysis comprised 150 short children (117 boys, 33 girls), with childhood-onset isolated, non-acquired GHD who completed GH therapy and attained FH. Patients' age at GH therapy onset was 12.5 ± 2.7 years (mean ± SD). The therapy with GH in a mean dose of 0.19 ± 0.06 mg (0.57 ± 0.06 IU)/kg/week was administered during 4.7 ± 2.2 years, up to the moment of fulfilling the criteria of its completion, i.e. when either bone epiphyses were closed or height velocity during treatment decreased below 2 cm/year.

Short stature was defined as patient's height below the 3rd centile for age and sex. Reference data for Polish children [11] was used, assuming an exact value of –1.88 for height SDS (HSDS) as an equivalent to 3rd centile.

Both the patients and their parents were measured using a Harpenden stadiometer according to the rules of height measurement. The measurement of parents was performed in order to calculate patients' target height (TH) and TH SDS.

Before treatment, 86 patients were prepubertal, and the remaining 64 were pubertal — in II or III stage of puberty according to Tanner's scale, and all the girls were premenstrual; before retesting, all the patients had completed puberty.

Bone age (BA) of the patients was evaluated on the basis of the radiogram of the non-writing (in most cases — left) hand and wrist, with respect to the Greulich-Pyle standards [12].

All the patients were diagnosed between 1997 and 2009 in the Polish Mothers' Memorial Hospital — Research Institute and treated in the same centre up to FH.

The diagnosis of GHD in childhood was based on GH peak below 10 ng/mL in two stimulation tests — with clonidine (0.15 mg/m^2, orally) and with either insulin (0.1 IU/kg, *i.v.*) or glucagon (30 μg/kg, *i.m.*). Severe GHD (sGHD) was diagnosed for GH peak below 5 ng/mL, and partial GHD (pGHD) for GH peak 5–10 ng/mL. In all patients, at least one month after completion of GH therapy, GH secretion was re-assessed in two stimulation tests — one with insulin and one with clonidine. Persistent GHD was diagnosed if GH peak in both tests was below 6 ng/mL, while transient GHD was diagnosed if GH peak at any time point of any test was greater than or equal to 6 ng/mL. Blood samples for GH estimation were collected every 30 min (from 0 to 120 min) in the tests with insulin and with clonidine, and at 0, 90, 120, 150, and 180 min in the test with glucagon. The concentrations of GH were measured by a two-site chemiluminescent enzyme immunometric assay (hGH IMMULITE, DPC).

Additionally, IGF-I serum concentrations were measured in all the patients at GH therapy onset and

— again — together with the retesting of GH secretion. IGF-I concentrations were assessed by a solid-phase, enzyme-labelled chemiluminescent immunometric assays (IMMULITE, DPC). Next, for each patient, the value of IGF-I SDS for chronological age and sex was calculated according to the reference data provided by the manufacturer. The logarithmic transformation of measured values before making further calculations was performed, as suggested by Blum and Schweitzer [13]. The calculation of IGF-I SDS was necessary to make possible the comparisons of IGF-I secretion among different patients, as well as in the same patient in different time points.

In all patients, the following auxological parameters were assessed:

— patient's height before treatment (H_0SDS) and at the attainment of FH (FH SDS);
— height SDS corrected by TH SDS at therapy onset (corrH_0SDS) and at FH (corrFH SDS);
— bone age (BA) delay with respect to chronological age (CA) at GH therapy onset, expressed as BA/CA ratio;
— an increase of height SDS during the therapy (ΔHSDS = FH SDS – H_0SDS).

In 139 out of 150 patients, magnetic resonance (MR) imaging (MRI) of the hypothalamic-pituitary region was performed before GH therapy, using a 1.5-Tesla MRI unit (Picker, model Edge), with sagittal and coronal slices, their thickness of 2–3 mm, depicted as midline images on T_1-weighted, before and after gadolinium injection. Pituitary height (PHt) was measured routinely as the greatest distance between the base and the top of the gland 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). Moderate-to severe pituitary hypoplasia was diagnosed for PHt below or equal 3 mm, as defined by Maghnie et al. [14]. Patients with decreased PHt, isolated or connected with pituitary stalk interruption syndrome (seven cases) and/or the ectopy of posterior pituitary (one case) and/or empty sella syndrome (four cases) were eligible for the study (all patients subjected to the study had isolated GHD and no other pituitary hormone deficiencies).

Next, the results of PHt measurements were compared to the normal values for the given age, published by Argyropoulu et al. [15] and expressed as PHt SDS, with reference to CA and to 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 some cases — the pituitary gland, classified as hypoplastic with reference to normative data for CA, turned out to be normal for HA. In the remaining 11 subjects (three with persistent and eight with transient GHD), MR examination was also performed, but either with another unit or with thicker slices, showing no abnormalities in the hypothalamic-pituitary region; nevertheless, these patients were excluded from the last part of the analysis.

The exclusion criteria encompassed patients with:

— any other detectable congenital abnormalities in the central nervous system;
— acquired brain damage (including neurosurgery, brain injuries, history of inflammatory processes, history of cranial irradiation);
— acquired GHD of any cause;
— other pituitary hormone deficiencies and endocrine diseases;
— any chronic diseases (diagnosed before or during GH therapy);
— congenital defects of internal organs;
— perinatal trauma;
— dysmorphic features and diagnosed, or even suspected, genetic syndromes (in girls, Turner syndrome was excluded by the karyotype assessment).

Non-acquired GHD was defined by the lack of an identifiable cause of decreased GH secretion, related to the perinatal and postnatal period (including the patient's history, concomitant diseases and the result of MR examination).

Statistical analysis included non-parametric Mann-Whitney's U test for independent samples for the assessment of differences among the groups in particular time points, and Wilcoxon's test for dependent samples for comparison of the same parameter in the same group in different time points (before treatment and at FH). The analysis of correlations was performed by calculating Pearson's correlation coefficients. The chi^2 Pearson's test was used for the analysis of the incidences of pituitary hypoplasia in particular groups of patients.

This study was approved by the local Ethics Committee of the Polish Mothers' Memorial Hospital — Research Institute.

Results

The relationships between hormonal (GH and IGF-I secretion), auxological (indices of somatic growth, BA delay) and radiological (PHt) findings before GH therapy onset and the incidence of persistent and transient GHD in retesting have been assessed.

GH and IGF-I secretion before treatment and during retesting

In the analysed group of 150 patients, there were 30 children with an initial diagnosis of sGHD and 120 with pGHD before the administration of GH therapy.

At the attainment of FH, persistent GHD, i.e. GH peak in two stimulation tests below 6 ng/mL, was observed in 18 patients, comprising nine with previously diagnosed sGHD and nine with pGHD. Thus the total incidence of persistent GHD was 12.0%. Persistent GHD was more frequently observed in the patients with an initial diagnosis of sGHD (30.0%) than in those with pGHD (7.5%). Taking into account only the result of ITT, we would have diagnosed persistent GHD in 35 cases (23.3%).

Significant differences between patients with final diagnoses of persistent GHD and transient GHD were observed in GH peak before treatment (4.9 ± 2.8 ng/mL *vs*. 7.3 ± 2.9 ng/mL, respectively, $p < 0.05$), as well as in IGF-I SDS (–2.13 ± 2.47 *vs*. –1.14 ± 1.58, respectively, $p < 0.05$), while the difference in IGF-I SDS after GH therapy withdrawal between the groups with persistent and transient GHD did not reach the level of significance (–1.81 ± 2.02 *vs*. -0.65 ± 1.24, respectively, $p = 0.07$) (Figs. 1 and 2).

There was absolutely no correlation between GH peak and IGF-I SDS before treatment ($r = 0.02$, NS), while a correlation was found between IGF-I SDS before treatment and after completion of GH therapy ($r = 0.27$, $p < 0.05$). Moreover, no correlation was observed between GH peak before treatment and in retesting ($r = 0.17$, $p < 0.05$), and only a poor correlation between GH peak in retesting and simultaneously assessed IGF-I SDS ($r = 0.22$, $p < 0.05$).

Auxological assessment before treatment and at the attainment of FH

There was no significant difference in any of the analysed auxological indices before treatment (patients' age, H_0SDS, corrH_0SDS, BA/CA ratio) between the patients with persistent GHD and transient GHD. However, both the attained FH SDS and ΔHSDS were significantly better in patients with persistent GHD than in those with transient GHD (Table I).

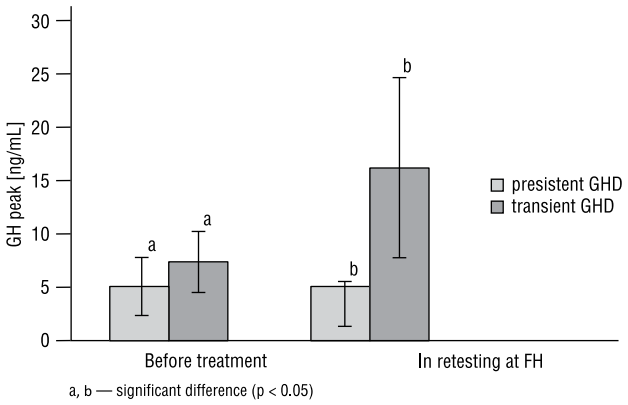

Figure 1. *GH peak in stimulation tests before GH therapy and in retesting in the patients with persistent and transient GHD, diagnosed at the attainment of FH*

Rycina 1. *Maksymalne wydzielanie GH w testach stymulacyjnych przed rozpoczęciem leczenia hormonem wzrostu i podczas ponownej oceny (retestingu) po uzyskaniu FH u pacjentów z trwałym i przemijającym GHD*

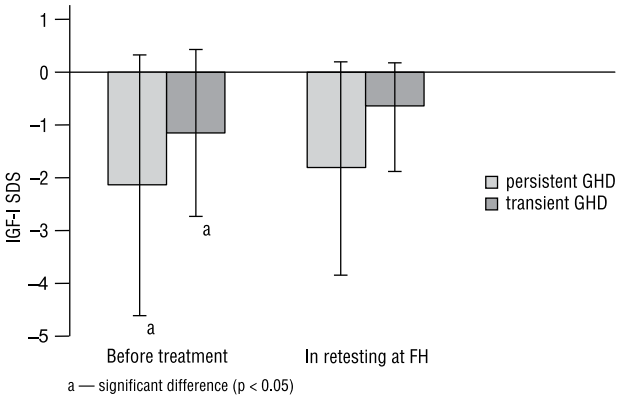

Figure 2. *IGF-I SDS before GH therapy and during retesting in the patients with persistent and transient GHD*

Rycina 2. *Wartości IGF-I SDS przed rozpoczęciem terapii GH i podczas retestingu u pacjentów z trwałym i przemijającym GHD*

Table I. ***Selected pre- and post-treatment auxological data of the patients with persistent and transient GHD***

Tabela I. ***Wybrane wskaźniki auksologiczne pacjentów z trwałym i przemijającym GHD ocenione przed leczeniem i po jego zakończeniu***

	Persistent GHD	Transient GHD	p
Age at therapy onset (years)	12.7 ± 3.4	12.5 ± 2.6	0.68
H_0SDS	–3.16 ± 0.85	–3.04 ± 0.73	0.51
TH SDS	–0.86 ± 0.90	–1.26 ± 0.80	0.07
corrH_0SDS	–2.01 ± 1.48	–1.78 ± 1.00	0.33
BA/CA	0.78 ± 0.15	0.83 ± 0.08	0.22
Age at FH (years)	17.0 ± 1.4	17.3 ± 1.1	0.61
FH SDS	–0.77 ± 0.88	–1.56 ± 0.86	0.001
corrFH SDS	–0.09 ± 1.10	–0.30 ± 0.88	0.28
ΔHSDS	2.39 ± 1.39	1.48 ± 0.87	0.003

a, b — significant differences ($p < 0.05$)

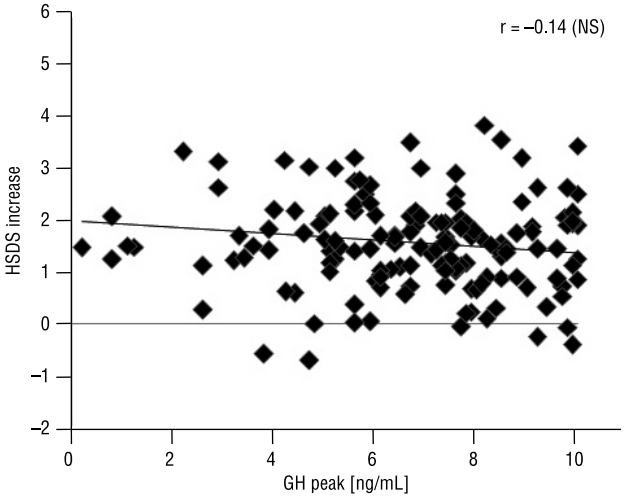

Figure 3. *Correlation between GH peak in stimulation tests before treatment and HSDS increase during GH therapy*

Rycina 3. *Korelacja pomiędzy maksymalnym wydzielaniem GH w testach stymulacyjnych przed rozpoczęciem leczenia i poprawą wartości HSDS podczas terapii GH*

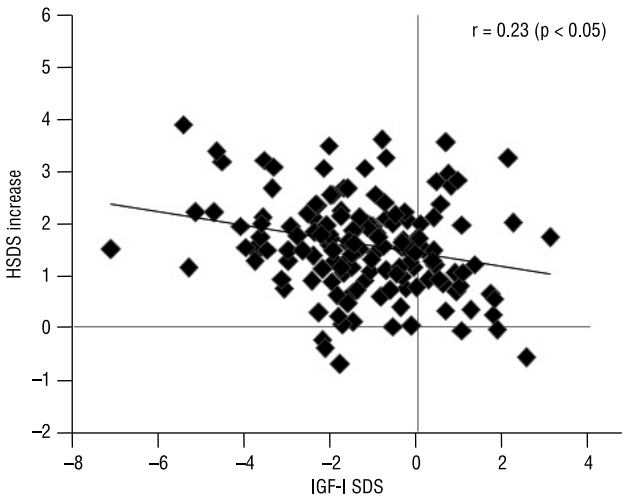

Figure 4. *Correlation between IGF-I concentration before treatment and HSDS increase during GH therapy*

Rycina 4. *Korelacja pomiędzy wartością IGF-I SDS przed rozpoczęciem leczenia i poprawą wartości HSDS podczas terapii GH*

Strong, negative correlations were observed between H_0SDS and ΔHSDS (r = –0.50, p < 0.05), as well as between corrH_0SDS and ΔHSDS (r = –0.55, p < 0.05).

There was no correlation between GH peak before treatment and ΔHSDS and (r = -0.14, NS), while a correlation was observed between ΔHSDS and IGF-I SDS before treatment (r = -0.23, p < 0.05) (Figs. 3 and 4). Similarly, no correlation was found between GH peak in retesting and ΔHSDS (r = –0.10, NS), while there was a correlation between IGF-I SDS during retesting and ΔHSDS (r = –0.32, p < 0.05).

MRI findings before treatment

Among the 139 patients in whom standardised MRI was performed, pituitary hypoplasia, defined as PHt equal to or below 3 mm, was found in 15 patients (10.8%), comprising eight children with sGHD and seven children with pGHD. Among the patients with PHt below or equal to 3 mm, persistent GHD was diagnosed at FH in four of them, and transient GHD in 11.

Thus, the incidence of such defined pituitary hypoplasia in the group of 15 patients with persistent GHD and assessed PHt was 26.7%, while in the group of 124 ones with transient GHD and assessed PHt it was 8.9% (the difference in the incidence of pituitary hypoplasia between the groups was insignificant).

On the other hand, according to the normative data of Argyropoulu et al. [15], 65 had decreased PHt SDS for CA, while in the remaining 63 ones, PHt SDS was normal. Moreover, there was no difference in the mean PHt SDS between the patients with persistent and transient GHD (–1.63 ± 3.28 *vs.* –1.78 ± 2.06, NS). However, in three of the patients, the pituitary gland was significantly enlarged with no visible pituitary adenoma: in one patient with persistent GHD (in whom PHt SDS was 8.13) and in two patients with transient GHD (with PHt SDS 6.58 and 3.38). Thus we decided to exclude them from further analysis. Taking into account the remaining 136 cases, PHt SDS for CA was slightly lower in the patients with persistent GHD than in ones with transient GHD (–2.38 ± 1.75 *vs.* –1.92 ± 1.80, NS). Pituitary hypoplasia with respect to the normative data for CA was observed before treatment in 10 out of 18 patients with persistent GHD (55.6%) and in 59 out of 120 patients with transient GHD (49.2%).

Next, a similar analysis was performed for PHt assessed with respect to patients' height (expressed as HA). Before treatment, PHt SDS for HA was lower in the patients with persistent GHD than in ones with transient GHD (–1.88 ± 1.91 *vs.* –1.21 ± 1.90), although still insignificantly. The incidence of pituitary hypoplasia for HA in patients with persistent GHD was 46.2%, while in those with transient GHD it was 30.2 % (the difference in the incidence of pituitary hypoplasia between these groups was insignificant). Moreover, there was no correlation between PHt SDS (both for CA and for HA) and GH peak at diagnosis in childhood (r = 0.18, NS and r = 0.20, p < 0.05, respectively), as well as no correlation between PHt SDS (both for CA and for HA) and GH peak in retesting (r = 0.11 and r = 0.13, respectively, NS),

Thus, in the studied group of children with isolated GHD and excluded organic abnormalities in the

hypothalamic-pituitary region, PHt was not a predictor of persistent and transient GHD.

Discussion

A high incidence of persistent GHD has been reported in patients with structural abnormalities in the hypothalamic-pituitary region [3, 8, 9], while GH secretion has been shown to normalise at the attainment of FH in patients with isolated GHD, even if the pituitary gland before treatment was small and/or ectopy of posterior pituitary lobe, and/or pituitary stalk interruption was found [9, 16]. The incidence of persistent GHD, observed in our study, was only 12%, relatively low with respect to other reports [3, 13]. This difference seems to be caused by a strict selection to the analysis only the patients with isolated GHD and the exclusion of all children with known causes of GHD except for those with anterior pituitary hypoplasia. Nevertheless, persistent GHD was confirmed more frequently in the patients with severe GHD than in those with partial GHD diagnosed in childhood. However, the incidence of persistent GHD in patients diagnosed in childhood as having sGHD, at 30%, is quite low.

According to the current recommendations [1, 3, 6, 17], in order to confirm GHD after the completion of growth-promoting therapy, it is sufficient to prove decreased GH peak in only one stimulation test. However, it has also been recently suggested that two stimulation tests should be used in order to diagnose isolated GHD in adults (due to a significant false-positive error rate in GH response in a single test) [7]. In our study, on the basis of the result of ITT, we would have diagnosed persistent GHD with almost double the incidence than taking into account the results of two stimulation tests. Another proposal for retesting is to lower the cut-off value of GH peak in ITT to 5 ng/mL [8, 18] or to 5.6 ng/mL [19]. In the whole studied group, only three patients (one with a previous diagnosis of sGHD and two with pGHD) had GH peak at FH between 5 ng/mL and 6 ng/mL. So, the incidence of persistent GHD, defined as GH peak in retesting in two stimulation tests below 5 ng/mL, was 10.0%.

Thus, our results may be explained by performing two stimulation tests in each patient. That approach significantly reduces the number of patients diagnosed at FH as GH-deficient. The results of the present study indicate a high incidence of false positive results of ITT, if this was used as the only GH stimulation test during retesting. Similar was the statement of Quigley et al. [8] who performed a single GH stimulation test to reassess the patients with multiple pituitary hormone deficiency, and two tests to confirm persistent isolated GHD. Moreover, our findings point at the possibility of using the test with clonidine in transition period, although that test has not been recommended in adults [6, 9, 17]. It seems worth mentioning that — in our study — almost half of the patients with decreased GH peak in ITT had a normal GH peak in the test with clonidine.

The last issue may be the criteria of how children are qualified for GH therapy in different countries, as well as the differences between populations. Very recently, Biczysko-Mokosa et al. [20] have reported the incidence of persistent GHD in Polish children from Western Pomerania as 18.3%, with the cut-off value for GH peak in ITT 6.0 ng/mL. In the quoted study, persistent GHD has been more frequently observed in the patients with sGHD than in those with pGHD. These results are quite similar to those obtained in our study.

Next, it should be noted that a significant difference was found in IGF-I secretion before treatment between the patients with persistent and transient GHD, despite the lack of correlation between GH and IGF-I secretion before treatment. Moreover, the correlation between IGF-I SDS before treatment and in retesting was better than the corresponding correlation between GH peaks in the same time points. This phenomenon may be partly related to the stability of IGF-I concentration and the variability of GH response to stimulation during the repeated assessments, as has been previously reported in patients who were re-assessed in childhood [21, 22]. In the light of previous reports questioning the reliability of GH stimulation tests [21, 22] and pointing to the significance of secondary IGF-I deficiency for the diagnosis of GHD [4, 5], it seems that severe IGF-I deficiency before treatment should be considered as a no less reliable predictor of persistent GHD than the results of GH stimulation tests performed in childhood. Interestingly, despite the fact that the difference in IGF-I SDS during retesting between the patients with persistent and transient GHD was insignificant, the mean value of IGF-I SDS before treatment was significantly lower in patients with persistent GHD than in those who normalised GH secretion. Our results remain in accordance with the data on the overlap between IGF-I secretion in the patients with persistent and transient GHD [2]. However, it has been proved that it is possible to establish a very low cut-off value of IGF-I SDS that reliably confirms persistent GHD, as well as another (higher) cut-off value that allows the exclusion of persistent GHD [8]. Thus, the 'grey zone' — in which GH stimulation tests are necessary — is very wide. Unfortunately, these threshold points may be appropriate only for the same method of IGF-I measurement and the same normative data.

In fact, we did not manage to find any auxological predictors of persistent and transient GHD, available at GH therapy onset. However, the effectiveness of

treatment was significantly better in the patients in whom GHD has proven to be persistent. Entirely consistent with our observations are the findings presented very recently by Krukowska-Andrzejczyk et al. [23] who have suggested relatively low effectiveness of GH therapy in patients with an initial diagnosis of partial GHD and normal GH secretion in retesting.

The results of numerous studies indicate that organic abnormalities in the hypothalamic-pituitary region lead to more severe and persistent GHD and to the deficits of other pituitary hormones. In our present study, anterior pituitary hypoplasia, defined as PHt below or equal to 3 mm, has been found in 10.8% of the patients. In a very recent study of Maghnie et al. [14] on a relatively large cohort of over 15,000 patients, pituitary hypoplasia has been reported in a fairly similar proportion of the patients with isolated GHD. However, taking into account the normative data of Argyropoulu et al. [15], we should diagnose pituitary hypoplasia in approximately 50% of our patients, which seems to be clearly overestimated in the patients with isolated, non-acquired GHD. Thus, the choice of appropriate reference data seems to be of crucial importance to draw any valuable conclusions.

It should be mentioned that somatotrophs comprise only about one third of anterior pituitary cells. Thus, pituitary volume depends on the amount of different cells. Even in a case of GHD caused by a decreased number of somatotrophs, it seems uncertain if this is related to a significant decrease of pituitary size. In 2007, Kalina et al. [24] reported that GH secretion was dependent on pituitary size only if there were coexisting structural defects in the hypothalamic-pituitary region, including ectopy of the posterior pituitary and empty sella syndrome. In our present study, only a slightly higher incidence of decreased PHt was found in children with severe and persistent GHD than in those with partial and/or transient GHD.

Another important issue is the relationship between PHt and pituitary volume. It has been suggested that there is a good correlation between these two parameters [25]. Unfortunately, other findings have not demonstrated such a correlation [26]. In fact, in our study, only PHt was assessed, assuming that this parameter should correspond to pituitary size. It is possible that the direct assessment of pituitary volume could lead to more significant results. On the other hand — as mentioned before — the poor reproducibility of the results of GH stimulation tests should be taken into account [21, 22]. Thus, there are several potential reasons why pituitary height may not correlate with its function, particularly with GH secretion, assessed on the ground of GH peak in stimulation tests.

Finally, studies on genetic defects leading to pituitary hormone deficiencies have shown that impaired pituitary function may be related not only to pituitary hypoplasia (or other structural abnormalities) but also to pituitary enlargement, for instance in the patients with *PROP1* mutations [27]. Unfortunately, in our study, a genetic assessment of the patients was not performed. However, we observed significant pituitary enlargement in three patients, while in others PHt was either normal or decreased.

In conclusion, the results of our present study confirm the relatively low incidence of persistent GHD at the attainment of FH in patients with childhood-onset, isolated, non-acquired GHD. Despite the fact that there are predictors of persistent and transient GHD that may be identified before treatment, a diagnosis of GHD should be verified in retesting after the attainment of FH in each case before a decision is made as to the continuation or discontinuation of GH therapy.

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