Partial growth hormone deficiency (GHD) in children has more similarities to idiopathic short stature than to severe GHD

Częściowy niedobór hormonu wzrostu (GHD) u dzieci — więcej podobieństw do idiopatycznej niskorosłości niż do ciężkiego GHD

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Abstract

Introduction: Assessment of growth hormone (GH) secretion is based on stimulation tests. Low GH peaks in stimulation tests, together with decreased insulin-like growth factor-I (IGF-I) secretion, confirm a diagnosis of GH deficiency (GHD). However, limitations in interpreting the test results and discrepancies between GH and IGF-I secretion in particular patients have both been reported. GH therapy should improve the prognosis of adult height (PAH).

The aim of the study was to compare the deficit of height at diagnosis, IGF-I secretion and PAH in children with either decreased (in varying degrees of severity) or normal GH secretion in stimulation tests.

Material and methods: The analysis comprised 540 short children (373 boys, 167 girls), aged 11.7 ± 3.2 years. In all the patients two GH stimulation tests were performed, IGF-I serum concentration was measured, bone age was assessed and PAH was calculated. According to the GH peak in the two stimulation tests, the patients were classified into the following groups: severe GHD (sGHD) — GH peak < 5 ng/mL (n = 44), partial GHD (pGHD) — GH peak 5–10 ng/mL (n = 190), idiopathic short stature (ISS) — GH peak at least 10 ng/mL (n = 306).

Results: A significantly greater deficit of height, lower IGF-I secretion and worse PAH were observed in sGHD than in both remaining groups, while all the differences between pGHD and ISS in the parameters analysed were insignificant.

Conclusion: The results obtained indicate the necessity of applying another methods of qualifying short children for GH therapy other than GH stimulation tests with a cut-off value at a level of 10 ng/mL.

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Key words*: short stature, growth hormone deficiency, stimulation tests, insulin-like growth factor-I, predicted adult height*

Streszczenie

Wstęp: Podstawową metodą oceny wydzielania hormonu wzrostu (GH) są testy stymulacyjne. Stwierdzenie obniżonego maksymalnego wydzielania GH (maxGH) w testach stymulacyjnych oraz obniżonego stężenia insulinopodobnego czynnika wzrostowego-I (IGF-I) w surowicy stanowi podstawę rozpoznania niedoboru GH (GHD). Istnieje jednak szereg ograniczeń w interpretacji wyników testów stymulacyjnych, jak również rozbieżności pomiędzy wynikami testów a wydzielaniem IGF-I u poszczególnych pacjentów. Terapia preparatem GH powinna prowadzić do poprawy prognozy wzrostowej pacjentów.

Celem pracy było porównanie ciężkości niedoboru wzrostu, stężenia IGF-I i prognozy wzrostowej u pacjentów z prawidłowym i w różnym stopniu obniżonym wydzielaniem GH.

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Materiał i metody: Analizą objęto dane 540 dzieci (373 chłopców, 167 dziewcząt) z niedoborem wzrostu, w wieku 11,7 ± ± 3,2 lat, u których wykonano 2 testy stymulacyjne na wydzielanie GH i oznaczono stężenie IGF-I w surowicy oraz oceniono wiek kostny i obliczono prognozę wzrostową. W zależności od maksymalnego wydzielania GH w testach stymulacyjnych, pacjentów podzielono na grupy: ciężki GHD (sGHD) — maxGH < 5 ng/ml (n = 44), częściowy GHD — maxGH 5–10 ng/ml (n = 190), idiopatyczny niski wzrost (ISS) — maxGH ≥ 10 ng/ml (n = 306).
Wyniki: Stwierdzono znamiennie cięższy niedobór wzrostu, znamiennie niższe wydzielanie IGF-I oraz znamiennie gorszą prognozę wzrostową u pacjentów z sGHD niż w obu pozostałych grupach przy braku znamiennych różnic w zakresie wszystkich analizowanych parametrów pomiędzy pacjentami z pGHD i ISS.
Wniosek: Uzyskane wyniki wskazują na celowość stosowania w praktyce klinicznej innych metod diagnostycznych i kryteriów kwalifikacji dzieci z niedoborem wzrostu do terapii GH niż wartość progowa maxGH w testach stymulacyjnych na poziomie 10 ng/mL.

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Słowa kluczowe: niedobór wzrostu, niedobór hormonu wzrostu, testy stymulacyjne, insulinopodobny czynnik wzrostowy-I, prognoza wzrostowa

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Introduction

The most important hormonal causes of short stature in children include growth hormone deficiency (GHD) and other less frequent disorders of growth hormone (GH) secretion and action, such as synthesis of an inactive GH molecule, partial GH insensitivity and GH resistance (Laron syndrome). All the above-mentioned disorders result in decreased synthesis of insulin-like growth factor-I (IGF-I) and its binding proteins. In rare cases either reduced IGF-I bioavailability or IGF-I insensitivity (Bierich syndrome) may be diagnosed.

It is well known that both linear growth and GH secretion are variables with a continuous distribution in the population and an overlap exists between the results of both auxological and hormonal measurements in healthy and GH-deficient subjects [1]. Thus the borderline between normal and decreased GH secretion must be established arbitrarily [1–3]. Routine diagnosis of GHD is based on the assessment of GH peaks in stimulation tests and of spontaneous GH secretion. For many years diagnosis of the classic form of GHD has been formulated where there is decreased (i.e. lower than an arbitrarily established cut-off level) GH secretion in two stimulation tests with different pharmacological stimuli. The limitations in interpreting the results of stimulation tests [2, 4] as well as the poor reproducibility of the test results should be taken into account. For instance, in most children, previously diagnosed as GH-deficient, who have a normal image of the hypothalamic-pituitary region in magnetic resonance the results of the same stimulation tests repeated a few months later were normal [5, 6]. Moreover, the reverse situation, where there is decreased GH secretion in repeated stimulation tests in patients in whom it had previously been normal, has been observed. Another problem is the possibility of decreased spontaneous GH secretion, so-called neurosecretory dysfunction, despite a normal GH peak in stimulation tests [7].

The main peripheral mediator of GH action is IGF-I. Plasma concentration of IGF-I is considered a good marker of GH secretion; according to current studies it is no less reliable than the results of GH stimulation tests [6, 8]. It should be stressed that this is not a completely new approach to the problem of GHD. Ten years ago Rosenfeld [9–11] postulated that measurement of IGF-I plasma concentration should be the first step in diagnosing children with short stature. However GH stimulation tests still remain a standard in GHD diagnostics [7, 12].

Assessment of IGF-I secretion also has some limitations. Firstly, other disorders that may lead to decreased IGF-I secretion, such as malabsorption syndrome and liver diseases, should be excluded. Next, the physiological increase in IGF-I secretion related to both the patient's age and pubertal maturation must be taken into account [13, 14]. Thus the results should be interpreted with reference to appropriate normative data for a given population. Owing to the relative stability of the IGF-I molecule, it is sufficient to measure only basal IGF-I plasma concentration without performing more sophisticated diagnostic procedures. It is of great importance to remember that IGF-I secretion is decreased not only in patients with the classic form of GHD but also in children with neurosecretory dysfunction and in those with decreased GH sensitivity.

In some children with extremely severe height deficit, however, a very high GH secretion is observed instead of the expected decreased GH peak in stimulation tests, suggesting the presence of other disturbances of the growth signalling pathway [15], including decreased GH sensitivity [16].

The most important goal of GH therapy is an improvement in height velocity and, above all, in the final height of patients. It seems that patients who may

benefit during GH therapy should have decreased IGF-I secretion and a relatively poor prognosis for final height, especially with respect to their target height, determined by parental height.

The aim of the study was to compare the deficit of height at diagnosis, IGF-I secretion and prognosis of final height in children with either decreased (in varying degrees of severity) or normal GH secretion in stimulation tests.

Material and methods

The analysis comprised 540 children (373 boys and 167 girls) with short stature (i.e. body height below the 3rd centile according to the current centile charts for Warsaw children) [17]. At diagnosis patient age was 11.7 ± ± 3.2 years (mean ± SD), with a range of 3.0–17.5 years; for boys it was 12.3 ± 3.1 years (range: 3.0–17.5 years) and for girls 10.3 ± 2.9 years (range: 3.4–15.8 years). Additional criteria for eligibility for the diagnostics included delayed bone age (BA) and a height velocity (HV) below 4 cm/year, calculated on the basis of at least, 6 months' observation. In order to compare the deficit of height among male and female patients at different ages the value of the height standard deviation score (H SDS) was calculated for each patient according to the Tanner-Whitehouse normative data [18].

Patients with chromosomal abnormalities, dysmorphic features, skeletal dysplasia, malabsorption syndrome, primary hypothyroidism and chronic diseases, as well as all those with acquired GHD (due to either neoplastic processes or brain injury) were excluded from the study. Thus all the children whose growth had been disturbed by pathological processes unrelated to the GH/IGF-I hormonal axis as well as those with a growth curve change due to an acquired disease, were excluded from the analysis.

Two different standard stimulation tests were performed for all the patients, the first with clonidine (0.15 mg/m^2, *p.o.*) and the second with either insulin (0.1 IU/kg *i.v.*) or glucagon (30 μg/kg not exceeding 1 mg, *i.m.*). Concentrations of GH were measured, using the two-site chemiluminescent enzyme immunometric assay hGH IMMULITE, DPC) with a sensitivity of 0.01 ng/mL, with intra-assay coefficients of variation (CV) of 5.3–6.5% and inter-assay CV of 5.5-6.2%. Calibration of GH standards was performed according to the WHO reference standard 80/505.

GHD was diagnosed where there was a GH peak below 10 ng/mL in both tests. Next, all the patients with GHD were divided into two subgroups:
— those with severe GHD — GH peak in both tests was below 5 ng/mL (n = 44),
— those with partial GHD — GH peak in at least one test was between 5 and 10 ng/mL (n = 190).

For the purpose of the study all children with a GH peak over 10 ng/mL in at least one of the tests were qualified as having idiopathic short stature (ISS) (n = 306).

IGF-I secretion was assessed in a single blood sample collected at the beginning of first stimulation test before the application of the stimulating agent. Serum IGF-I concentration was measured by a solid-phase enzyme-labelled chemiluminescent immunometric assay (IMMULITE, DPC, calibrated to WHO NIBSC 1st IRR 87/518 and with an analytical sensitivity of 20 ng/ml, a calibration range up to 1600 ng/ml, intra-assay CV 3.1–4.3% and inter-assay CV 5.8–8.4%. For each patient IGF-I concentration was expressed as SDS for age and sex (IGF-I SDS).

The heights of all the patients' parents were measured and expressed as H SDS and the target height (TH) of the children was calculated and expressed as TH SDS.

In each patient radiography of the non-dominant hand and wrist was performed and BA was assessed according to Greulich and Pyle's standards [19]. Next, predicted adult height (PAH) was calculated according to the Bayley-Pinneau method [20] for 518 children and expressed as PAH SDS; for the remaining 22 patients it was not possible to calculate PAH by this method because BA was too young.

The concordance of the distribution of all the analysed variables with normal distribution was evaluated by means of the Shapiro-Wilk test. As the distribution of most of the variables was different from normal, the following non-parametric tests were applied in further analysis: the Mann-Whitney U test for two independent samples, the ANOVA rank Kruskall-Wallis test and the Newman-Keuls test for more than two independent samples.

The study protocol was approved by the local Ethics Committee for the Research Institute of the Hospital of the Polish Mother, Łódź, Poland.

Results

Patients' H SDS was significantly lower (p < 0.05) in the sGHD group than in the remaining groups and was almost the same in pGHD and ISS. Target height SDS was similar in all the groups and there was thus no need to calculate and compare either corrected H SDS (i.e. the difference between H SDS and TH SDS) or corrected PAH SDS (i.e. the difference between PAH SDS and TH SDS) in particular groups. PAH was significantly worse (p < 0.05) in sGHD than in both pGHD and ISS, and, somewhat surprisingly, significantly worse (p < 0.05) in ISS than in pGHD. Similarly, IGF-I SDS was significantly lower (p < 0.001) in sGHD than in both pGHD and ISS, although the difference between these latter groups was insignificant.

Table I
Height, IGF-I secretion, TH and PAH (expressed as SDS for age and sex) in particular groups of patients

Tabela I
Wzrost wydzielania IGF-I, TH i PAH (wyrażone wartościami SDS w poszczególnych grupach pacjentów)

	sGHD	pGHD	ISS
H SDS	−2.50 ± 0.89[a, b]	−2.10 ± 0.62[a]	−2.13 ± 0.61[b]
TH SDS	−0.70 ± 0.81	−0.62 ± 0.72	−0.76 ± 0.76
PAH SDS	−1.70 ± 0.91[c, d]	−1.00 ± 1.05[c, e]	−1.26 ± 0.96[d, e]
IGF-I SDS	−0.49 ± 1.27[f, g]	0.01 ± 1.11[f]	0.27 ± 1.39[g]

significant differences: a–e — $p < 0.05$, f–g — $p < 0.001$

Detailed data including H SDS at diagnosis, IGF-I secretion, TH and PAH in particular groups of patients with normal and subnormal results of GH stimulation tests are presented in Table I and illustrated on Figures 1–3.

The results obtained indicate a lack of significant differences in all the parameters analysed between the patients with pGHD and those with ISS, while in the patients with sGHD both the most severe deficit of height and the worst PAH were observed in association with the lowest IGF-I secretion.

Discussion

According to current standards [7, 12], the diagnosis of GHD is based on a decreased GH peak in two provocative tests with different stimuli. In routine practice the
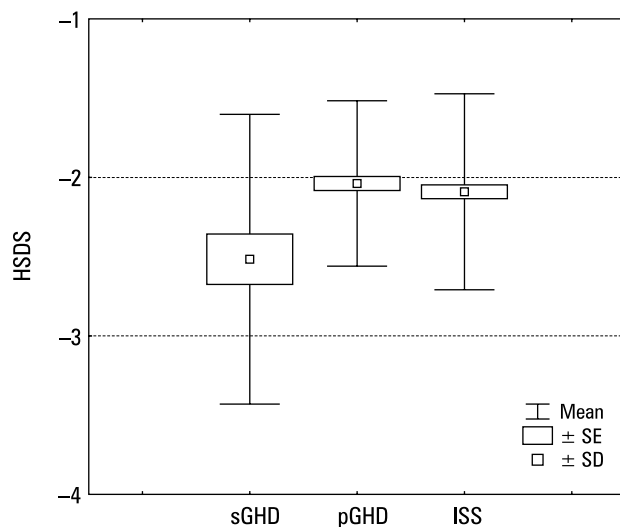

Figure 1. *Comparison of H SDS at diagnosis in particular groups of patients*
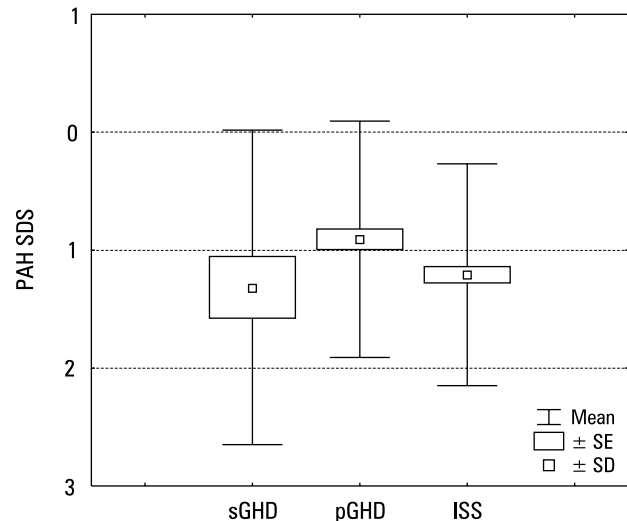**Rycina 1.** *Porównanie H SDS w momencie rozpoznania w poszczególnych grupach pacjentów*

Figure 2. *Comparison of PAH SDS in particular groups of patients*
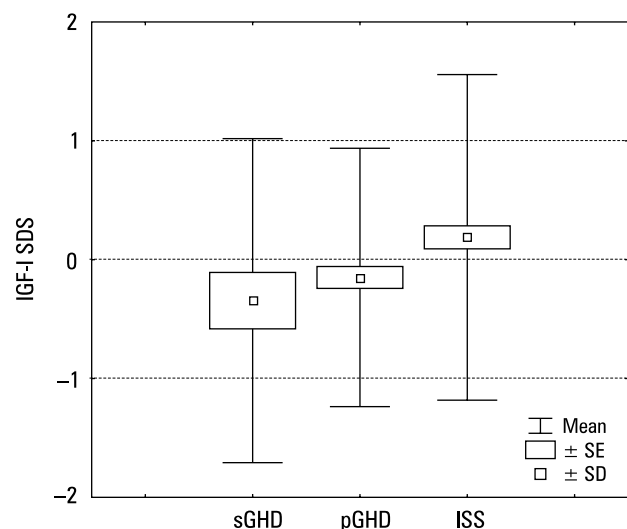**Rycina 2.** *Porównanie PAH SDS w poszczególnych grupach pacjentów*

Figure 3. *Comparison of IGF-I SDS in particular groups of patients*
Rycina 3. *Porównanie IGF-I SDS w poszczególnych grupach pacjentów*

same cut-off value for normal and subnormal GH secretion is approved at an arbitrarily established level [2] independently of the type of test and the diagnostic assay used, most frequently set at 10 ng/mL, as in Poland, or 7 ng/mL [21, 22]. This problem was discussed in depth by Rosenfeld et al. in 1995 [2], who stressed the lack of evidence for any arbitrarily established cut-off values for normal and subnormal results of GH stimulation tests. The findings of Shalet et al. [1] and Ranke et al. were similar [23]. Moreover, in studies on healthy

normally growing children maximal GH secretion fulfilled the criteria of GHD in many cases, being below 10 ng/mL [24] or even below 7 ng/mL in about 50% children of normal height and below 5 ng/mL in 30% of them [25].

Of particular interest is the study of Nwosu et al. [26], who assumed that the characteristics of patients with pGHD should be intermediate between those with sGHD and ISS. However, it turned out that the patients with pGHD constituted a group that was similar to those with ISS in all the features analysed, except in the results of GH stimulation tests, the basis on which the groups were separated. The results obtained in our study are very similar. Thus there is no evidence for the establishment of a border between normal and subnormal results of GH stimulation tests at the level of 10 ng/mL. In explanation of the above-mentioned findings, account should be taken of the poor reproducibility of GH stimulation tests [2, 5, 6] as well as of the possibility of obtaining a falsely decreased GH peak in both stimulation tests performed in a patient who is not GH-deficient [4, 27].

It is worth recalling that the most important problem in diagnosing children with short stature is not assessment of GH secretion but, first of all, identification of those patients who may benefit from GH therapy. In recent years the results of numerous studies have indicated that GH application may improve growth and increase the final height of children with ISS (defined as a normal GH response to pharmacological stimulation). For instance, in 2003 Frindik et al. [28] stated that there was no difference in near final height between children with idiopathic GHD and those with ISS treated with GH. In the same year a summary of Australian experience was published [29], strongly confirming the significance of auxology-based criteria in qualifying children for GH therapy. In 2004 a randomised double-blinded, placebo-controlled study was published, which confirmed the beneficial effect of GH therapy on near adult height in patients with ISS [30]. Next, Miller and Zimmerman [31] reported that GH treatment of children with ISS should not be withheld because of the inadequacy of current diagnostic tests. In the same year, Badaru and Wilson [8] stated that there was no longer evidence to use GH stimulation tests to diagnose childhood GHD and that alternative diagnostic tools should be applied, including auxological, biochemical, neuroradiological and genetic examinations. In 2005 Kemp et al. [32], in a relatively long-term cohort study, demonstrated the efficacy of GH therapy, resulting in a significant increase in H SDS in patients with ISS. In the same year Park and Cohen [33] reported that many patients with ISS had responded to GH therapy. The authors proposed measurements of IGF-I secretion in monitoring GH treatment in ISS patients to distinguish those in whom the therapy might be effective from others who suffered from partial or complete GH insensitivity. This year Ranke et al. [34] have published the results of the KIGS (Pfizer International Growth Database) study, confirming the effectiveness of GH therapy in children with ISS. In their analysis a good first-year response to GH therapy was demonstrated as a factor indicating the benefits of long-term treatment.

As many doubts concerning GH stimulation tests in the diagnosis of GHD still exist and as the effectiveness of GH therapy in patients with ISS seems to be well documented, the qualification of short children for GH therapy should not be based solely on the results of GH stimulation tests. It should be stressed that there is no evidence to disqualify a child from GH therapy on the ground of GH peak in stimulation tests that was previously established as normal. It seems that other tools, including more detailed auxological examinations and prediction of final height, assessment of spontaneous GH secretion, IGF-I measurements and monitoring of HV before and during GH administration, should be widely introduced into diagnostic protocols.

Finally, one more problem should be indicated, at least briefly. In diagnosing the causes of short stature other factors unrelated to decreased GH secretion, should also be taken into account, especially if GH secretion seems normal. In our study, the patients with ISS had, as a group, a worse PAH than those with pGHD, even despite a slightly better IGF-I secretion. The possibility of decreased GH sensitivity in some cases should be considered in order to identify those patients who should not be subjected to GH therapy.

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