Growth hormone (GH) peak in stimulation tests and the severity of IGF-I deficiency before treatment as the predictors of GH therapy effectiveness in children with short stature

Wydzielanie hormonu wzrostu (GH) w testach stymulacyjnych i stopień ciężkości niedoboru IGF-I jako czynniki prognostyczne skuteczności terapii GH u dzieci niskorosłych

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Key words

short stature, growth hormone (GH), insulin-like growth factor-I (IGF-I), GH deficiency, IGF-I deficiency, GH therapy, final height

Słowa kluczowe

niedobór wzrostu, hormon wzrostu, insulinopodobny czynnik wzrostowy-I (IGF-I), somatotropinowa niedoczynność przysadki, niedobór IGF-I, wzrost końcowy

Abstract

Introduction. The diagnosis of growth hormone (GH) deficiency is based on the results of GH stimulation tests. Growth hormone therapy in children with normal GH secretion is a matter of discussion. Recently, GH deficiency has been defined as a secondary insulin-like growth factor-I (IGF-I) deficiency. **Objective.** The aim of the study was to assess GH therapy efficacy in short children with respect to GH peak in stimulation tests and IGF-I secretion before treatment. **Material and methods.** The retrospective analysis comprised 182 children with partial GH deficiency (GH peak in stimulation tests 5–10 ng/ml), qualified to pGHD Group, and 75 children with normal GH peak in stimulation tests (>10 ng/ml), qualified to normGH Group. According to IGF-I secretion, expressed as IGF-I SDS for age and sex, the patients were qualified to the following subgroups: pGHD-1 and normGH-1 – IGF-I SDS < -2.0; pGHD-2 and normGH-2 – IGF-I SDS between -2.0 and -1.0; pGHD-3 and normGH-3 – IGF-I SDS ≥ -1.0. The increase of the final height SDS with respect to the height SDS before treatment (Δ HSDS) was calculated as the main index of the GH therapy effectiveness. **Results.** The best Δ HSDS was in pGHD-1 (1.65 ± 0.89)

Streszczenie

Wstęp. Podstawę rozpoznania somatotropinowej niedoczynności przysadki (SNP) stanowią wyniki testów stymulacyjnych oceniających wydzielanie hormonu wzrostu (GH). Leczenie GH dzieci z prawidłowym wydzielaniem GH jest przedmiotem dyskusji. Ostatnio zdefiniowano SNP jako wtórny niedobór insulinopodobnego czynnika wzrostowego-I (IGF-I). **Cel pracy.** Celem pracy była ocena skuteczności leczenia GH dzieci z niedoborem wzrostu w zależności od maksymalnego wyrzutu GH w testach stymulacyjnych oraz wydzielania IGF-I przed leczeniem. **Materiał i metody.** Analizę retrospektywną objęto 182 dzieci z częściowym niedoborem GH (wyrzut GH w testach stymulacyjnych 5–10 ng/ml), zakwalifikowanych do grupy pGHD, oraz 75 dzieci z prawidłowym wydzielaniem GH w testach stymulacyjnych (>10 ng/ml), zakwalifikowanych do grupy normGH. W zależności od wydzielania IGF-I, wyrażonego wartością IGF-I SDS dla wieku i płci, pacjentów zakwalifikowano do następujących podgrup: pGHD-1 i normGH-1 – IGF-I SDS < -2.0; pGHD-2 i normGH-2 – IGF-I SDS od -2.0 do -1.0; pGHD-3 i normGH-3 – IGF-I SDS ≥ -1.0. Obliczono przyrost wartości SDS wzrostu końcowego (FH SDS) w stosunku do wartości SDS wysokości ciała

and normGH-1 (1.86 ± 0.93), the worse in normGH-3 (0.99 ± 0.71), with insignificant differences between pGHD-1 and normGH-1, pGHD-2 and normGH-2, as well as pGHD-3 and normGH-3. **Conclusions.** The effectiveness of the GH therapy was the best in the patients with the most severe IGF-I deficiency but almost independent from either decreased or normal GH secretion in stimulation tests before treatment.

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przed leczeniem (Δ HSDS) jako podstawowy wskaźnik skuteczności terapii preparatem GH. **Wyniki.** Najwyższe wartości Δ HSDS uzyskano w grupach pGHD-1 (1.65 ± 0.89) i normGH-1 (1.86 ± 0.93), najniższą w grupie normGH-3 (0.99 ± 0.71), przy czym różnice pomiędzy grupami pGHD-1 i normGH-1, pGHD-2 i normGH-2 oraz pGHD-3 i normGH-3 były nieznamiennie. **Wnioski.** Skuteczność terapii preparatami GH była największa u pacjentów z najcięższym niedoborem IGF-I oraz prawie niezależna od wydzielania GH w testach stymulacyjnych wykonanych przed rozpoczęciem leczenia.

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Introduction

The most important goal of the growth hormone (GH) therapy in children with short stature is to obtain normal final height (FH). The therapy with recombinant human GH (rhGH) is widely approved in children with GH deficiency (GHD), diagnosed on the grounds of decreased GH peak in stimulation tests. In the patients with normal GH secretion and excluded GH insensitivity, in whom the diagnosis of idiopathic short stature (ISS) seems most appropriate [1], the rhGH therapy is still a matter of controversy [2–4]. Lower efficacy of the rhGH therapy in children with ISS than in those with GHD has been reported, however with a high variability of growth response among treated patients [2, 5–7]. A few years ago, GHD has been defined as secondary insulin-like growth factor-I (IGF-I) deficiency (IGFD) [8–9]. The Assessment of growth rate and IGF-I concentration has been proposed as a screening procedure in diagnosing GHD [10–11]. Interestingly, for the first time such approach was presented more than 30 years ago [12]. Nevertheless, GH stimulation tests still remain the main procedure in diagnosing GHD, despite the limitations of their diagnostic accuracy [13–17].

At present, the patients with IGF-I deficiency (IGFD) may be treated either with rhGH (in case of secondary IGFD) or with recombinant human IGF-I (in case of primary IGFD). The main diagnostic tool to confirm primary IGFD (*i.e.* GH insensitivity) is IGF-I generation test. Although IGF-I (and IGFBP-3) generation test was originally used in the diagnosis of GH insensitivity [18–19] and has not been recommended for predicting growth response to the rhGH therapy [9], its usefulness in identi-

fying children who may benefit during treatment has also been presented in several reports [20–22]. Unfortunately, there is no clear recommendation what should be IGF-I increase in generation test to support rhGH therapy administration in short children with IGFD and normal results of GH stimulation tests. These patients may still be classified as ones with ISS and the management of such cases depends on the approach to the diagnosis of ISS.

The aim of the present study was to compare GH therapy effectiveness in the patients with isolated, non-acquired partial GHD and with normal results of GH stimulation tests, with respect to IGF-I secretion before treatment.

Patients and methods

The analysis comprised 257 children (198 boys, 59 girls), age 12.2 ± 2.8 years (mean $\pm$ SD) with short stature, defined as patients' height below 3rd centile for age and sex, according to standards for Polish children [23]. All patients were serially measured by Harpenden stadiometer and had decreased height velocity (HV) below -1.0 SD for age and sex, according to national reference data [24] and delayed bone age (BA), according to the Greulich-Pyle's standards [25].

In each patient, GH secretion was assessed in 2 stimulation tests: with clonidine (0.15 mg/ m^2 , orally, GH concentrations measured every 30 minutes during 120 minutes) and either glucagon (30 mg/kg, *i.m.*, not exceeding 1000 mg, GH concentrations measured in 0, 90, 120, 150 and 180 minute) or insulin (0.1 IU/kg, *i.v.*, GH and glucose concentrations measured every 30 minutes during

120 minutes, hypoglycaemia confirmed in each case). The diagnosis of GHD was established on the grounds of GH peak below 10 mg/l, while GH peak equal to or over 10 mg/l was recognized as normal GH secretion (normGH). The patients with severe GHD (sGHD, GH peak in both tests below 5 mg/l) were not subjected to the study.

In all the patients IGF-I, concentration was measured before treatment and IGF-I SDS for age and sex was calculated. The concentration of IGF-I was considered low if IGF-I SDS was below -1.0. Severe IGFD was diagnosed for IGF-I SDS below -2.0, partial IGFD – for IGF-I SDS between -1.0 and -2.0, while IGF-I SDS over -1.0 excluded IGFD. In all the patients with IGFD and normal GH peak in stimulation test, GH insensitivity was excluded by significant IGF-I increase in generation test, leading to at least doubling of IGF-I concentration and reaching its normal range (we applied the own criteria of sufficient IGF-I responsiveness in the generation test).

With respect to GH peak in stimulation tests and IGF-I concentration before treatment, the patients were divided into 6 groups:

pGHD-1 – GH peak 5-10 mg/l, IGF-I SDS below -2.0,
pGHD-2 – GH peak 5-10 mg/l, IGF-I SDS between -2.0 and -1.0,

pGHD-3 – GH peak 5-10 mg/l, IGF-I SDS over -1.0,
normGH-1 – GH peak over 10 mg/l, IGF-I SDS below -2.0,

normGH-2 – GH peak over 10 mg/l, IGF-I SDS between -2.0 and -1.0,

normGH-3 – GH peak over 10 mg/l, IGF-I SDS over -1.0.

Concentrations of GH were measured by hGH IMMULITE, DPC, calibrated to WHO IRP 98/574 standard, with analytical sensitivity up to 0.01 mg/l, calibration range up to 40.0 mg/l, sensitivity of 0.01 mg/l, intraassay coefficient of variation (CV) of 5.3-6.5% and interassay CV of 5.5-6.2%. Serum IGF-I concentrations were assessed by IMMULITE, DPC, calibrated to WHO NIBSC 1st IRR 87/518, with analytical sensitivity of 20.0 mg/l, calibration range up to 1600.0 mg/l, intra-assay CV 3.1–4.3% and inter-assay CV 5.8–8.4%.

The exclusion criteria were: congenital defects in the hypothalamic-pituitary region (except for isolated anterior pituitary hypoplasia), acquired lesions (neurosurgery, brain injuries, the history of inflammatory processes, *etc.*), cranial irradiation, multiple pituitary hormone deficiency, other endocrine diseases, history of malignancy, malnutrition, malabsorption syndromes, other chronic dis-

eases, congenital defects, diagnosed or suspected genetic syndromes (all female subjects included to the study had normal female karyotype), intrauterine growth retardation.

The therapy with rhGH in the mean dose of 0.19 ± 0.06 mg/kg/week was administered for at least 2 years, until the criteria of its completion were met, *i.e.*, when either bone epiphyses were closed or height velocity was below 2 cm/year. The therapy duration was 5.2 ± 2.8 years and patients' age at its withdrawal was 17.2 ± 1.3 years.

At rhGH therapy onset, patients' height SDS (H_0 SDS) and BA delay with respect to chronological age (CA), expressed as BA/CA ratio, were assessed. Additionally, target height SDS (TH SDS) was calculated on the grounds of the height of parents.

For the evaluation of the GH therapy efficacy, the following auxological indices were calculated:

- FHSDS – final height SDS
- DHSDS – improvement of FHSDS vs. H_0 SDS, calculated according to the formula: $DHSDS = FH\ SDS - H_0\ SDS$
- corrected H_0 SDS ($corrH_0\ SDS$) = $H_0\ SDS - TH\ SDS$
- corrected FH SDS ($corrFH\ SDS$) = $FH\ SDS - TH\ SDS$.

Statistical analysis started from Levene's test, which confirmed the homogeneity of variances for all variables analysed. Next, one-way analysis of variance (ANOVA) by groups was performed, followed by post-hoc analysis (least significant differences test).

The study was approved by the Ethics Committee in the Polish Mother's Memorial Hospital – Research Institute, Lodz, Poland.

Results

The detailed data on the assessed auxological indices in particular groups are presented in Table I (p value in the last column is related to the result of one-way ANOVA analysis).

The absolute deficit of height (H_0 SDS) was similar in all Groups, while the relative deficit of height ($corrH_0$ SDS) was insignificantly more severe in pGHD-1 Group and normGH-1 Group (*i.e.* in the patients with most severe IGFD) than in other Groups. There was no significant difference in BA delay before treatment among the Groups. Significant differences in patients' age at rhGH therapy onset were found between pGHD-1 and pGHD-3 ($p = 0.01$), pGHD-1 and normGH-3 ($p = 0.005$), pGHD-2 and normGH-3 ($p = 0.02$), as well as between normGH-1 and normGH-3 ($p = 0.04$). The

Table I. Auxological indices of the patients from particular groups at the beginning of the rhGH therapy and at the attainment of FH

Tabela I. Wskaźniki auksologiczne poszczególnych grup pacjentów w momencie rozpoczęcia terapii rhGH i po uzyskaniu FH

	normGH-1	normGH-2	normGH-3	pGHD-1	pGHD-2	pGHD-3	p
N	34	28	13	49	35	98	
boys/girls	28/6	18/10	10/3	41/8	30/5	70/28	
At the beginning of the rhGH therapy							
Age [years]	12.6±3.2	12.2±2.0	10.7±3.5	13.2±1.9	12.9±2.5	11.9±3.1	0.03
H ₀ SDS	-3.22±0.75	-2.94±0.61	-3.02±0.75	-3.00±0.71	-3.03±0.90	-3.11±0.76	0.67
TH SDS	-1.16±0.77	-1.17±0.77	-1.34±0.86	-0.97±0.73	-1.32±0.97	-1.33±0.78	0.19
corrH ₀ SDS	-2.07±1.03	-1.76±0.93	-1.68±0.73	-2.03±0.93	-1.70±1.16	-1.78±0.98	0.37
BA/CA	0.82±0.08	0.84±0.07	0.82±0.17	0.80±0.15	0.81±0.08	0.83±0.15	0.59
At the attainment of FH							
Age [years]	17.6±1.4	17.1±1.2	17.4±1.1	17.3±1.5	17.2±1.4	17.3±1.4	0.78
FH SDS	-1.37±0.72	-1.50±1.02	-2.03±0.88	-1.35±0.66	-1.74±0.87	-1.67±0.80	0.02
corrFH SDS	-0.21±0.84	-0.33±0.92	-0.69±0.68	-0.40±0.85	-0.42±0.98	-0.34±1.02	0.73
DHSDS	1.86±0.93	1.44±0.77	0.99±0.71	1.65±0.89	1.29±0.77	1.44±0.92	0.01

patients in pGHD-1 were the oldest while those in normGH-3 – the youngest at rhGH therapy onset.

There was no significant difference in patients' age at rhGH therapy withdrawal.

The best and similar FH SDS was obtained in normGH-1 and pGHD-1. The post-hoc analysis showed that FH SDS was significantly better in pGHD-1 than in pGHD-2 ($p = 0.03$) and pGHD-3 ($p = 0.02$), as well as in normGH-1 compared to normGH-3 ($p = 0.01$). The worse FH SDS, with the mean value below -2.0 was achieved in normGH-3 Group. The increase of FH SDS with respect to H₀SDS is illustrated in Figure 1. The attained corrFH SDS was also the worse in normGH-3, despite the lowest TH SDS in this Group, however all differences among the Groups were insignificant.

The best DHSDS was observed in normGH-1 and pGHD-1. There was no significant difference in DHSDS between normGH-1 and pGHD-1 ($p=0.42$), between normGH-2 and pGHD-2 ($p=0.49$), and between normGH-3 and pGHD-3 ($p=0.10$), *i.e.* between the Groups with similar IGF-I secretion, despite different GH peak in stimulating tests. The worse DHSDS was observed normGH-3 Group (*i.e.* in patients with normal GH and IGF-I secretion).

In a post-hoc analysis, DHSDS was significantly better in normGH-1 than in pGHD-2 ($p = 0.01$), pGHD-3 ($p = 0.02$) and normGH-3 ($p = 0.03$), as well as in pGHD-1 than in normGH-3 ($p = 0.02$). The data are illustrated in Figure 2.

Discussion

In the Consensus statement on the diagnosis and treatment of children with ISS, published in 2008 [1], the definition of ISS included height below -2 SD and no disease found by pediatric endocrinologist during the evaluation, including stimulated GH levels. Savage et al. [9] have not regarded IGFD as a hormonal disorder that excludes the diagnosis of ISS and have even reported the 25-50% incidence of IGFD among the patients with ISS. In turn, Navarro et al. [26] have defined the criteria of ISS as patients' height below -2.25 SD and the absence of systemic, endocrine, nutritional, or chromosomal abnormalities. The authors have also stated that measuring serum IGF-I and IGFBP-3 levels is a better method of diagnosing GHD than direct measurement of GH levels [26]. According

Significant differences: a – p = 0.01; b – p = 0.03; c – p = 0.02

Fig. 1. The attained FH SDS with respect to H_0 SDS in particular groups of patients

Ryc. 1. Uzyskany FH SDS w odniesieniu do H_0 SDS w poszczególnych grupach pacjentów

Significant differences: a, b – p = 0.01; c, d – p = 0.02

Fig. 2. The increase of FH SDS with respect to H_0 SDS (DHSDS) in particular groups of patients

Ryc. 2. Przyrost FH SDS w odniesieniu do H_0 SDS (DHSDS) w poszczególnych grupach pacjentów

to Wit et al. [27], ISS may be diagnosed in children with short stature after excluding known conditions. Our observations, pointing at rhGH therapy effectiveness in children with isolated, non-primary IGFD – independently of GH peak in stimulation test – seem to correspond with this line of reasoning. In our opinion, ISS should not be diagnosed in any patient with IGFD.

The data from the randomized controlled studies indicate that FH of untreated subjects with ISS remains below -2.0 SD [2, 28–29]. In the present study, we have not compared the treated patients with untreated controls because of the drop-out of untreated patients, as well as due to qualifying to rhGH therapy some of the previously untreated, poorly growing children. According to the review of Deodati & Cianfarani [6], the mean height gain in rhGH treated subjects with ISS was 1.2 SD. In our study, the height gain of the patients with normal GH secretion in stimulation tests and IGFD has been better than that reported in the quoted review, especially in the patients with severe IGFD (normGH-1 Group). The worse height gain was observed only in the patients with no GHD and no IGFD (normGH-3 Group). On the other hand, the effectiveness of rhGH therapy in all the subgroups of our patients was significantly worse than that reported by Korpál-Szczyrska et al. [30] in the patients with more severe and persistent GHD, in whom DHS during rhGH therapy exceeded 3.3 SD. In turn, Mysiek-Prucnal et al. [31] reported the difference between the groups of children with sGHD and pGHD in parental height but not in 2-year rhGH therapy effectiveness. The report of Krukowska-Andrzejczyk et al. [32] pointed at the existence of many similarities between children with pGHD and ISS, especially relating to auxological indices. Similar were previous observations of our research group [33], indicating more similarities between pGHD and ISS than between pGHD and sGHD.

According to the very recent paper of Loche et al. [5], the mean increase of adult height in patients with ISS during the rhGH therapy is modest and the individual response to treatment is unpredictable. In our study, growth response to treatment was significantly better in patients with severe IGFD than in those with normal IGF-I levels and almost independent of GH peak in stimulation tests. It seems that in children with normal GH peak in stimulation tests, non-primary IGFD (confirmed by a significant IGF-I increase during generation test) may be a predictor of better efficacy of

the rhGH therapy. On the contrary, relatively poor growth response for rhGH administration (increase of FH SDS with respect to H_0 SDS less than 1.0 SD, the mean FH SDS below -2.0) in the patients with normal GH and IGF-I secretion (normGH-3 Group) speaks against rhGH administration in these patients. It seems that only in such patients ISS may be considered, while in children with IGFD the diagnosis of ISS is not appropriate. We are convinced that if the rhGH therapy is justified in any child with sGHD (after exclusion of contraindications), it should no longer be administered in any child with partial GHD and waived in any child with normal GH peak in stimulation tests.

In 2009, Pedicelli et al. [4] pointed at a significantly lower IGF-I SDS in children with non-familial short stature (non-FSS), than in those fulfilling the criteria of FSS. The authors have suggested the measurement of IGF-I and IGFBP-3 concentrations should be first-line screening in diagnosing GHD, however – in their further analysis – IGFD was not a criterion for the exclusion of ISS [4]. In our study, children with severe IGFD (pGHD-1 Group and normGH-1 Group) had also the most severe relative deficit of height with respect to TH (the lowest $\text{corr}H_0\text{SDS}$). Our observations speak for possible relationships between non-FSS and IGFD.

In the light of our findings, the paper of Pagani et al. [22] is of significant interest, in which they have reported similar efficacy of rhGH therapy in children with reduced GH bioactivity and with GHD, justifying the cost of the rhGH therapy in the former group [22]. The diagnosis of GH bioinactivity in children with normal GH levels, low IGF-I concentration and normal catch-up growth on the rhGH therapy was suggested by Kowarski et al. in 1978 [34]. However, this diagnosis is still a matter of discussion and GH bioinactivity is not listed among the approved indications for the rhGH therapy in USA and Europe [7].

Interestingly, in 1981 Hayek and Peake [35] suggested that IGFD (at the time referred to as somatomedin-C deficiency) and growth response to short-term exogenous GH therapy may be a more precise method of identifying children who will benefit from long-term treatment than GH peak in stimulation tests. Our results seem to correspond with that statement quite well.

Finally, we should come back to the definition of GHD as secondary IGFD. It is well known that the diagnosis of secondary hypothyroidism or secondary adrenal insufficiency may be established in the patients with thyrotropin (TSH) or corti-

cotropin (ACTH) levels within normal range but too low to ensure proper secretion of thyroid hormones or corticoids, respectively. Of course, each of the pituitary hormones (TSH, ACTH and GH) has other secretion profile and the diagnostic tests for their deficiencies have to be different. However, it seems possible that GH peak in stimulation tests above the arbitrarily established cut-off level is not enough to confirm GH sufficiency.

We would like to suggest that rhGH therapy should be considered in children with short stature and non-primary IGFD, independently of the results of GH stimulation tests, while the diagnosis of ISS should be limited to the patients with excluded IGFD.

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