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What should be the diagnosis and management of short children with normal growth hormone secretion and non-primary IGF-I deficiency?

Jakie powinno być rozpoznanie i sposób postępowania u dzieci z prawidłowym wydzielaniem hormonu wzrostu i niepierwotnym niedoborem IGF-I?

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Słowa kluczowe: hormon wzrostu (GH); insulinopodobny czynnik wzrostowy I (IGF-I); testy stymualcyjne, niedobór IGF-I, terapia GH, wzrost końcowy

ABSTRACT/*STRESZCZENIE*

Growth hormone (GH) deficiency (GHD) is currently defined as secondary IGF-I deficiency. In the patients with normal GH secretion, significant increase of IGF-I during generation test excludes primary IGF-I deficiency, however is not an approved indication for GH therapy. **The aim** of the study was to assess GH therapy effectiveness in children with IGF-I deficiency which turned to be out non-primary, despite normal GH secretion. **Patients and methods.** Analysis comprised 42 patients with spontaneous (after falling asleep) and stimulated GH peak >10.0 ng/ml, and IGF-I SDS for age and sex <-1.0, in whom IGF-I concentrations increased significantly during generation test, suggesting that IGF-I deficiency is non-primary (npIGFD Group). All patients were subjected to GH therapy. First-year response to treatment: height velocity (HV) increase and IGF-I SDS increase were assessed in all of them, final height (FH) – in 28 patients. The therapy efficacy was compared with 110 children with isolated, partial GHD (pGHD Group), including 42 treated up to FH. **Results.** In npIGFD Group, height SDS before treatment (H_0SDS) was -2.87±0.72, in 1st year of treatment HV increased from 3.8±0.9 to 9.4±1.9 cm/year, IGF-I SDS increased from -2.19±0.78 to 0.34±1.07, FH SDS was -1.14±0.82. In pGHD Group, H_0SDS was -2,79±0.59, HV increased from 3.8±1.4 to 9.8±2.1 cm/year, IGF-I SDS increased from -1.76±0.88 to 0.52±0.87, FH SDS was -1.20±0.80. The differences in all the analysed indices of GH therapy effectiveness between the Groups were insignificant. **Conclusions.** Children with short stature, normal spontaneous and stimulated GH secretion and non-primary IGF-I deficiency may benefit during GH therapy similarly to children with partial GHD. It seems worth considering not diagnose idiopathic short stature in such patients. Pediatr. Endocrinol. 13/2014;4(49):9-18.

Somatotropinowa niedoczynność przysadki (SNP) definiowana jest obecnie jako wtórny niedobór IGF-I. U pacjentów z prawidłowym wydzielaniem hormonu wzrostu (GH) znamienny wzrost sekrecji IGF-I podczas testu generacji wyklucza pierwotny niedobór IGF-I, natomiast nie jest uważany za wskazanie do terapii preparatem GH. **Celem pracy** była ocena skuteczności terapii GH u dzieci z niedoborem IGF-I, który okazał się niepierwotny pomimo prawidłowego wydzielania GH w testach dynamicznych. **Pacjenci i metody.** Analizą objęto 42 pacjentów z prawidłowym wydzielaniem GH po zaśnięciu i w testach stymulacyjnych (>10.0 ng/ml) oraz obniżonym stężeniem IGF-I (IGF-I SDS dla wieku i płci <-1.0) wzrastającym znamiennie w teście generacji, tj. z niepierwotnym niedoborem IGF-I (npIGFD). Pacjenci byli leczeni preparatem GH. Skuteczność leczenia oceniono na podstawie poprawy tempa wzrastania i poprawy wartości IGF-I SDS w pierwszym roku terapii u wszystkich pacjentów oraz uzyskanego wzrostu końcowego u 28 pacjentów. Grupę porównawczą stanowiło 110 dzieci z izolowanym, częściowym niedoborem GH (pGHD), w tym 42 pacjentów którzy uzyskali FH. **Wyniki.** W grupie npIGFD wartość SDS wysokości ciała przed leczeniem (H_0SDS) wynosiła -2,87±0,72, w pierwszym roku terapii nastąpił wzrost HV z 3,8±0,9 to 9,4±1,9 cm/rok, wartość IGF-I SDS wzrosła z -2,19±0,78 do 0.34±1,07, wartość FH SDS wynosiła -1.14±0.82. W grupie pGHD wartość H_0SDS wynosiła -2,79±0,59, w pierwszym roku leczenia nastąpił przyrost HV z 3,8±1,4 do 9,8±2,1 cm/rok i wzrost, IGF-I SDS z -1,76±0,88 do 0,52±0,87 wartość FH SDS wynosiła -1,20±0,80. Wszystkie analizowane wskaźniki nie różniły się znamiennie pomiędzy grupami. **Wnioski.** U dzieci z niepierwotnym niedoborem IGF-I, pomimo prawidłowego wydzielania GH po zaśnięciu i w testach stymulacyjnych, leczenie preparatem GH może być równie skuteczne, jak u dzieci z pGHD. Wydaje się, że w takich przypadkach nie należy rozpoznawać idiopatycznego niedoboru wzrostu.Endokrynol. Ped. 13/2014;4(49):9-18.

Growth hormone (GH) deficiency (GHD) is the main indication to recombinant human GH (rhGH) therapy in children with short stature. The diagnosis of GHD is routinely based on decreased GH secretion in stimulation tests. Nevertheless, other disorders of GH secretion and action – potentially treatable with rhGH – decreased spontaneous GH secretion, *i.e*. neurosecretory dysfunction (NSD) and decreased GH bioactivity, may be diagnosed in the patients with normal results of GH stimulation tests, however GH insensitivity should be excluded in any case before rhGH therapy administration. Moreover, the effectiveness of rhGH therapy has been documented in children with idiopathic short stature (ISS) but the variability in growth response as well as the relatively high proportion of poor responders has also been reported [1–4].

In Europe the diagnostic criteria of GHD in children with short stature, as well as indications to rhGH therapy in them, were established by GH Research Society in 2000 [5]. Nonetheless, the limitations of credibility and reliability of GH stimulation tests in clinical practice have been raised in subsequent years [4]; the poor reproducibility of these tests has also been reported in our previous study [6]. Otherwise, in Poland, the assessment of GH secretion after falling asleep has been introduced as an obligatory screening procedure in diagnosing GHD in children, in accordance with the national recommendations [7]. Decreased GH secretion in this test is required for qualifying the child to the Program of rhGH therapy, reimbursted by the National Health Fund [8]. On the other hand, in 2008, the leading international societies in paediatric endocrinology, have published the consensus on the diagnosis and treatment of ISS, including the indications for rhGH therapy in children with ISS [9].

Insulin-like growth factor-I (IGF-I) is the main peripheral mediator of GH action. The importance of documenting IGF-I deficiency for the diagnosis of GHD has recently been underlined [8,9]. In current classifications, GHD has even been defined as secondary IGF-I deficiency, while GH insensitivity has been defined as primary IGF-I deficiency [10,11].

The patients with excluded both classic form of GHD and NSD, should be diagnosed for GH insensitivity. Thus, the diagnostic algorithm requires IGF-I generation test, *i.e*. the assessment of IGF-I increase during short-term rhGH administration. The lack of IGF-I response to rhGH confirms GH insensitivity, while the patients with significant increase of IGF-I secretion during this test are suspected for secretion of bioinactive GH [12]. This diagnosis is still a matter of discussion and GH bioinactivity is not listed among the approved indications for rhGH therapy in Europe and in United States [4]. Recently, Petkovic et al. [13] have been reported that the patients with endogenous GH bioinactivity may attain normal catch-up growth on rhGH therapy. Similarly, Pagani et al. [14] have documented that children with GH bioinactivity, confirmed by the increase of serum IGF-I levels

during generation test, attained similar adult height during rhGH therapy as children with GHD. The authors have stated that the cost of rhGH therapy in the patients with bioinactive GH was justified by the effectiveness of treatment.

In our centre, IGF-I generation test has routinely been performed in children with normal results of GH stimulation tests, normal GH peak after falling asleep and decreased IGF-I secretion for several years. We have observed significant increase of IGF-I serum concentrations, leading to the normalisation of IGF-I level in the majority of the patients subjected to IGF-I generation test. These results have indicated that IGF-I deficiency in these patients is non-primary, suggesting the potential efficacy of rhGH therapy in such patients. Unfortunately, children with confirmed GH insensitivity can be treated with recombinant human IGF-I (rhIGF-I), while the patients with excluded GH insensitivity are not qualified to the program of rhGH therapy. There are no clear recommendations, concerning the management of such patients. We decided to observe them in the outpatient clinic. As in the majority of these children, during follow-up, their height velocity (HV) remained slow, we decided to repeat assessment of GH secretion in them. This time, in many cases, IGF-I secretion was still decreased but the results of GH stimulation tests were different from the previous ones, allowing to diagnose GHD at this time point and to start rhGH therapy (most of patients were diagnosed before the introduction of obligatory screening assessment of GH secretion after falling asleep). In our opinion these patients could not be GH-sufficient during 1st assessment, while GH-deficient during 2nd assessment, as they were evaluated for the 1st time just due to short stature, slow HV and IGF-I deficiency, and the only difference between 1st and 2nd assessment was GH peak in stimulation tests. Up to now, a relatively large group of these patients has completed rhGH therapy and attained final height (FH).

The aim of the study was to assess the efficacy of rhGH therapy in children with normal results of GH stimulation test during 1st assessment and normal GH peak after falling asleep, compared to the patients with isolated partial GHD (pGHD), treated in the same time, with similar rhGH doses.

Patients and methods

The retrospective analysis comprised 42 children (34 boys, 8 girls), age 12.0±2.3 years (mean±SD) with short stature, normal GH secretion (both spontaneous and stimulated) and non-primary IGF-I deficiency (npIGFD Group), treated with rhGH for – at least – 1 year, including 28 patients who completed the growth-promoting therapy and attained FH.

Short stature was defined as patients' height below 3rd centile for age and sex (*i.e*. height SDS below an exact value -1.88), according to reference data for Polish children [15]. Additionally, in all the patients both before 1st assessment and during at least 6 months between 1st and 2nd assessment of GH secretion and until rhGH therapy onset their height velocity (HV) was permanently below -1.0 SD with respect to reference data [7]; their bone age (BA), assessed according to Greulich- Pyle's standards [16] was delayed with respect to chronological age (CA). All the patients were serially measured on the Harpenden stadiometer and at least 6-months intervals between measurements were required for calculation of HV.

Spontaneous GH secretion was assessed during first 3 hours after falling asleep, the samples for measurement of GH serum concentration were collected in 60, 90, 120, 150 and 180 minute of physiological, nocturnal sleep. Stimulated GH secretion was assessed in 2 tests with pharmacological agents: clonidine (0.15 mg/m^2, orally, GH concentrations measured every 30 minutes during 120 minutes) and glucagon (30 µg/kg *i.m*., not exceeding 1000 µg, GH concentrations measured in 0, 90, 120, 150 and 180 minute). The cut-off value for normal and decreased GH peak in any test was 10.0 ng/ml. The patients were subjected to further diagnostics if GH peak after falling asleep and in at least in one of the stimulation tests exceeded 10.0 ng/ml, thus excluding GHD and NSD.

In all the patients IGF-I serum concentrations were measured and expressed as IGF-I SDS for age and sex. The diagnosis of IGFD was established if IGF-I SDS was low, *i.e*. below -1.0, as recommended by Cianfarani et al. [17] and only the patients with IGF-I deficiency were subjected to further diagnostic procedures. In all of them, IGF-I generation test was performed with daily rhGH dose of 0.033 mg/kg (0.1 IU/kg) administered during 7 days. For the purpose of the study, the own criteria of sufficient IGF-I responsiveness to short-term rhGH administration were established and we decided to qualify to the study only those patients in whom IGF-I concentration at least doubled and reached reference range during generation test. Thus in each of our patients, IGF-I deficiency could be considered non-primary.

In the majority of the patients, GH stimulation tests were repeated after about 6 months of observation and – this time – their results allowed the diagnosis of GHD and the qualification of the patients to rhGH therapy. Additionally, in all the patients persistent IGF-I deficiency was confirmed by decreased basal IGF-I concentration in the another measurement, performed just before rhGH therapy administration.

Next, all the patients were subjected to rhGH therapy in the dose of 0.18±0.03 mg/kg/week (0.54±0.1 IU/kg/week), divided into 7 daily doses, according to the rules of therapy.

The efficacy of rhGH therapy was assessed on the ground of first-year response to treatment in all the patiets and the attained FH – in 28 ones, in whom linear growth was almost completed (an increase of growth during the last 6 months of treatment was below 1.0 cm confirming the decrease of HV below 2.0 cm/year) and BA was advanced over 16 years in boys and over 14 years in girls.

The therapy effectiveness was compared with the group 110 short children (75 boys, 35 girls), age 11.2±3.3 years with (pGHD, treated with the very similar GH dose, including 42 who attained of FH and completed the therapy. The diagnosis of pGHD was established if GH peak in 2 stimulation tests was between 5 and 10 ng/ml. In each patient IGF-I serum concentration was assessed before treatment, however the patients were qualified to the therapy independently from the result of this measurement, in concordance with the rules of the therapeutic program for children with GHD [7]. All the patients from the pGHD Group fulfilled the criteria for inclusion in the therapeutic program. The appropriate diagnostic procedures (measurements of height, BA assessment, GH stimulation tests and assessment of IGF-I serum concentration) were performed in the same manner as in npIGFD Group.

Summing up, the following data obtained before and at rhGH therapy onset were assessed and compared in both groups:

- height SDS before treatment (H_0SDS),
- height velocity in last 6 months before rhGH therapy administration (HV_0),
- IGF-I SDS for age and sex before treatment (IGF-I_0SDS).

Next, the following indices of rhGH therapy effectiveness were compared in both groups:

- first-year response to treatment:
  - height velocity in 1st year of treatment (HV_1) and an increase of HV ($\Delta HV = HV_1 - HV_0$)
  - IGF-I SDS in 1st year of treatment (IGF-I_1SDS) and IGF-I SDS increase (ΔIGF-I SDS = IGF-I_1SDS - IGF-I_0SDS)
- final height (FH), expressed as FH SDS for the normative data for the age of 18 years and sex.

Chronic diseases that might disturb IGF-I synthesis, including malabsorption syndromes, malnutrition, liver diseases, were excluded in each case. The patients who were small for gestational age (SGA) were excluded from the studied group. All the girls in both groups had normal female karyotype (46,XX). In all the patients thyroid function was normal during the study period, none of them required other hormonal substitution. All the patients in both groups had no abnormalities in hypothalamic-pituitary region (except for isolated anterior pituitary hypoplasia in some patients with pGHD), visualised in magnetic resonance examination. Acquired GHD (including brain trauma, tumours, cranial irradiation and other diseases) was excluded in any case.

Concentrations of GH were measured by the two-site chemiluminescent enzyme immunometric assay (hGH IMMULITE, DPC) for the quantitative measurement of human GH, calibrated to WHO IRP 98/574 standard, with the analytical sensitivity up to 0.01 µg/l, the calibration range up to 40.0 µg/l, the sensitivity of 0.01 µg/l, the intraassay coefficient of variation (CV) of 5.3-6.5% and the interassay CV of 5.5-6.2%.

Serum IGF-I concentrations were assessed by a solid-phase, enzyme-labelled chemiluminescent immunometric assay, (IMMULITE, DPC), calibrated to WHO NIBSC 1st IRR 87/518, with analytical sensitivity 20.0 µg/l, the calibration range up to 1600.0 µg/l, the intra-assay CV 3.1-4.3% and the inter-assay CV 5.8-8.4%.

Statistical analysis was performed with non-parametric tests: Wilcoxon's test for dependent samples and Mann-Whitney's U test for independent samples.

The study was approved by the Committee of Ethics of Scientific Research in the Polish Mother's Memorial Hospital – Research Institute.

Results

Despite significantly higher GH secretion after falling asleep and in 2 stimulation tests in npIGFD Group than in pGHD Group, the deficit of height at rhGH therapy onset (expressed as H_0SDS) was slightly more severe in npIGFD Group than in

pGHD Group, while the mean HV_0 was exactly equal in both Groups. The patients in npIGFD Group had significantly lower IGF-I_0SDS than the patients in pGHD Group, which can be explained by the fact that only in the former Group decreased IGF-I secretion was a criterion for inclusion (for the detailed data see Table I).

In 1st year of rhGH therapy, HV and IGF-I SDS increased significantly in both Groups (see Figure 1 and 2). The difference between the Groups in ΔHV and HV_1 was insignificant. Despite the higher ΔIGF-I SDS in npIGFD than in pGHD, the patients in npIGFD Group had still significantly lower IGF-I_1SDS than children with pGHD, however in both Groups IGF-I_1SDS was within the reference range (see Table I).

The negative correlation was observed between HV_0 and ΔHV ($r = -0.36$, $p<0.05$), with no correlation between HV_0 and HV_1 ($r = 0.05$, NS), while the correlation between H_0SDS and ΔHV was positive ($r = 0.35$, $p<0.05$). There was no correlation between the assessed parameters of hormonal function of somatotrophic axis (GH peak, IGF-I_0SDS) and any of the auxological indices assessed before treatment (H_0SDS, HV_0) , as well as after 1 year of rhGH therapy (HV_1, ΔHV). There was also no correlation between GH peak before treatment (both in stimulation tests and after falling asleep) and IGF-I_0SDS. However, the correlations were found between IGF-I_1SDS and GH peak in stimulation tests ($r = -0.33$, $p<0,05$), as well as between IGF-I_0SDS and IGF-I_1SDS ($r = 0.36$, $p<0.05$), but there was no correlation between IGF-I_1SDS and GH peak after falling asleep. Moreover, ΔIGF-I SDS correlated only with IGF-I_0SDS ($r = -0.63$, $p<0.05$) and with IGF-I_1SDS ($r = 0.49$, $p<0.05$), while there was no correlation between ΔIGF-I SDS and GH peak, as well as between ΔIGF-I SDS and any of the auxological indices assessed before treatment and after 1 year of rhGH therapy.

In the patients from both Groups, who completed rhGH therapy, FH SDS increased significantly with respect to H_0SDS (see Fig. 3) and both FH SDS and ΔHSDS were even better – however insignificantly – in npIGFD Group than in pGHD Group (see Table II).

Significant correlations were observed between FH SDS and patient's age at rhGH therapy onset ($r = 0.27$, $p<0.05$) and at the therapy withdrawal ($r = 0.63$, $p<0.05$). The correlation between FH SDS and H_0SDS was positive ($r = 0.30$, $p<0.05$). The attained FH SDS correlated also with both HV_0

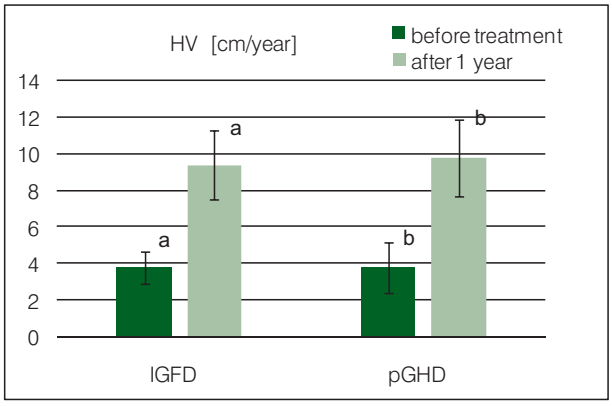
Table I. Auxological and hormonal data of the patients with npIGFD and with pGHD before treatment (for the patients with npIGFD, the hormonal results from 1st assessment are presented) and after 1 year of rhGH therapy

Tabela I. *Wskaźniki auksologiczne i wyniki badań hormonalnych pacjentów z npIGFD i pacjentów z pGHD przed leczeniem (w przypadku pacjentów z npIGFD podano wyniki badań uzyskane podczas pierwszej diagnostyki) oraz po roku terapii preparatem GH*

	npIGFD	pGHD	p
Before treatment			
Age [years]	12.0±2.3	11.2±3.3	0.36
H_0SDS	-2.87±0.72	-2.79±0.59	0.67
HV_0 [cm/year]	3.8±0.9	3.8±1.4	0.92
GH peak after falling asleep [ng/ml]	17.23±6.78	7.30±3.65	<0.001
GH peak in 2 stimulation tests [ng/ml]	17.43±7.62	7.54±1.43	<0.001
IGF-I_0SDS	-2.19±0.78	-1.76±0.88	0.01
After 1 year of rhGH therapy			
HV_1 [cm/year]	9.4±1.9	9.8±2.1	0.17
ΔHV	5.7±2.1	6.2±2.4	0.14
IGF-I_1SDS	0.34±1.07	0.52±0.87	0.01
ΔIGF-I SDS	2.54±1.15	2.28±0.90	0.11

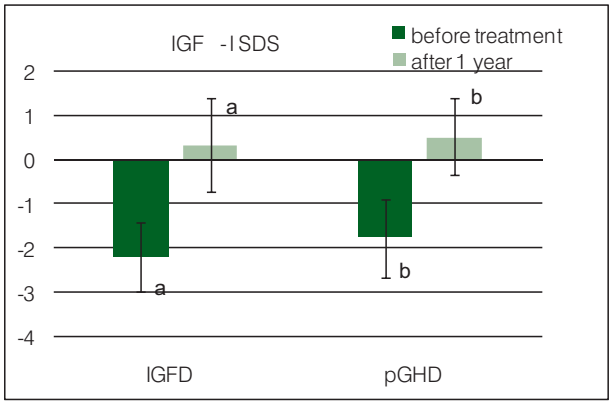
Table II. Auxological indices of rhGH therapy effectiveness of 28 patients with npIGFD and 42 patients with pGHD who completed treatment and attained FH
Tabela II. *Wskaźniki auksologiczne skuteczności terapii rhGH w grupie 28 pacjentów z npIGFD i 42 pacjentów z pGHD, którzy zakończyli leczenie i osiągnęli FH*

	npIGFD	pGHD	p
Before treatment			
Age [years]	12.5±2.0	13.0±1.6	0.43
H_0SDS	-2.75±0.67	-2.68±0.52	0.93
GH dose [mg/kg/week]	0.18±0.02	0.19±0.02	0.78
After completion of rhGH therapy			
Age [years]	17.4±1.2	16.8±1.5	0.14
FH SDS	-1.14±0.82	-1.20±0.80	0.78
ΔHSDS	1.61±1.08	1.48±0.83	0.92



Significant differences: a, b – p<0.001

Fig. 1. Height velocity of the patients with npIGFD and with pGHD before treatment and after 1 year of rhGH therapy
Ryc. 1. *Tempo wzrastania pacjentów z npIGFD i pacjentów z pGHD przed leczeniem i w 1 roku terapii rhGH*



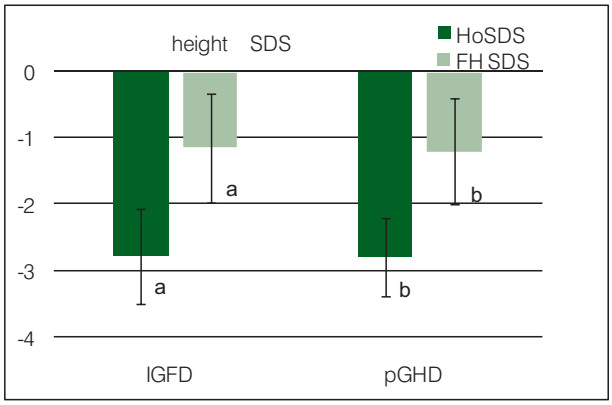
Significant differences: a, b – p<0.001

Fig. 2. The values of IGF-I SDS in the patients with npIGFD and with pGHD before treatment and after 1 year of rhGH therapy
Ryc. 2. *Wartości IGF-I SDS u pacjentów z npIGFD i u pacjentów z pGHD przed leczeniem i w 1 roku terapii rhGH*

– negatively (r = -0.27, p<0.05) and with HV_1 and ΔHV – positively (r = 0.38, p<0.05 and r = 0.47, p<0.05, respectively). There was also the negative correlation between FH SDS and $IGF\text{-}I_0$SDS (r = -0.30, p<0.05) but there was no correlation between FH SDS and GH peak, both in stimulation tests (r = 0.03, NS) and after falling asleep (r = 0.12, NS).

Discussion

In the patients with normal spontaneous and stimulated GH secretion and IGF-I deficiency, after exclusion of undernutrition and its other possible causes, unrelated to the function of somatotrophic axis, the most important issue is to perform the diagnostics towards GH insensitivity (*i.e.* primary IGF-I deficiency). The main diagnostic procedure for this purpose is IGF-I generation test. The lack of IGF-I increase during short-term rhGH administration confirms primary IGF-I deficiency and is an approved indication to the therapy with rhIGF-I. Unfortunately, the significance of IGF-I increase during generation test as a predictor of growth response to rhGH therapy has been questioned for many years [18, 19]. On the other hand, it has been reported in more recent studies that IGF-I generation test may be predictive on growth response to rhGH therapy in children with



Significant differences: a, b – $p<0.001$

Fig. 3. The attained FH SDS with respect to H_0SDS in the patients with npIGFD and with pGHD who completed rhGH therapy

Ryc. 3. *Wartość uzyskanego FH SDS w porównaniu do H_0SDS u pacjentów z npIGFD i u pacjentów z pGHD, którzy zakończyli terapię rhGH*

GHD or ISS [14, 20, 21]. Our previous data have also confirmed the relationships between the increase of IGF-I (and of IGF-I/IGFBP3 molar ratio) and the response to rhGH therapy in children with normal results of GH stimulation tests, during 3 years of treatment [22].

The most important result of present study is to demonstrate similar effectiveness of rhGH therapy in children with pGHD and in those with normal GH peak in stimulation tests and after falling asleep, who respond to short-term rhGH administration by IGF-I increase. It seems that in such patients the most appropriate diagnosis may be the bioinactivity of endogenous GH. It has been previously reported by Radetti et al. [23] that GH immunoreactivity did not reflect bioactivity. In the study of Pagani et al. [14], normalisation of previously decreased IGF-I concentration in generation test was considered sufficient to diagnose GH bioinactivity in children with normal GH response to stimulation and IGF-I deficiency, while doubling a pre-treatment HV in 1st year of therapy was a marker of positive response to treatment. Such criteria are quite consistent with those used by Pagani et al. [14] but different from those proposed in the most recent Polish manual of clinical endocrinology [12]. According to the latter recommendations, IGF-I increase by at least 160 ng/ml during 4 days of rhGH administration confirms normal GH sensitivity and excludes primary IGF-I deficiency. In our study, the own criteria of IGF-I responsiveness in generation test have been proposed, including normalisation of IGF-I concentration and at least doubling its initial level. Taking into account the age-dependent differences of reference ranges for IGF-I concentration in childhood, we decided to link the interpretation of IGF-I generation test with the normative data for given age and sex. In fact, IGF-I increase in most of our patients, except for few youngest children, exceeded the cut-off value of 160 ng/ml.

Most of our patients could be treated with rhGH due to the results of repeated assessment of GH secretion, allowing to establish the diagnosis of GHD in them. It should be recalled that – in our opinion – these patients could not be GH-sufficient during 1st assessment and develop GHD just before 2nd assessment. It seems that the two situations may be takin into account in our patients. First is the secretion of bioinactive GH and obtaining falsely decreased GH peak in stimulation tests during 2nd assessment. The possibility of falsely decreased GH peak in response to pharmacological stimulation is the main purpose for performing 2 tests in each patient, however the relatively high incidence of falsely decreased GH peak in both tests, performed in the same GH-sufficient patient should be taken into account [24]. Second option, however very difficult to confirm, is the very variable GH secretion in our patients, leading to obtaining divergent results of GH stimulation tests in different time points. Anyway, the total GH secretion in them would be permanently too low to ensure proper IGF-I secretion. In both situations, rhGH therapy should be effective and in our patients it was effective.

It was also demonstrated in present study that the analysed indices of response to rhGH therapy correlated both with the auxological parameters assessed before treatment and with IGF-I secretion before and during the therapy but not with GH peak in any test, despite the fact that the analysed group consisted of children with normal and subnormal GH secretion.

In the very interesting papers, Rosenthal et al. [25] and of Cohen [26] have suggested that focusing on the diagnosis of IGF-I deficiency and searching out the patients, who may benefit during rhGH therapy among all IGF-I deficient ones may more appropriate than distinguishing between GHD and idiopathic short stature, based on the results of GH stimulation tests.

In Poland, according to the inclusion criteria of the therapeutic programs [8, 27], children with severe deficit of height, normal GH peak and

IGF-I deficiency are qualified to the therapy with rhIGF-I if they do not respond to short-term rhGH administration, while remain untreated if they respond to short-term rhGH administration by the increase and normalisation of IGF-I secretion. Taking into account the results of other studies [14] and our own experience, it is very difficult to explain patients and their parents in all conscience, why the child is not eligible to rhGH therapy, if he or she normalised previously very low IGF-I secretion after only few injections of rhGH.

Conclusions

In children with short stature, normal spontaneous and stimulated GH secretion and decreased IGF-I concentration which increases significantly in generation test, IGF-I deficiency is – in fact – secondary. Such patients may benefit during rhGH therapy similarly to children with pGHD. It seems worth considering not diagnose ISS in them.

Both NSD and endogenous GH bionactivity are the causes of secondary IGF-I deficiency. As these diseases do not fulfil the definition of secondary IGFI deficiency – which is considered to be a synonym of GHD – we propose to introduce for any other form of IGF-I deficiency that responds to rhGH administration the term: non-primary IGF-I deficiency.

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