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Efekt leczenia hormonem wzrostu pacjentów z niedoczynnością somatotropową w wieku dojrzewania

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Streszczenie

Wstęp
W warunkach polskich leczenie hormonem wzrostu pacjentów w wieku rozwojowym prowadzone jest od 1964 roku. Do 1993 roku terapia ta była prowadzona w sposób przerywany, co wynikało z okresowej dostępności leku. Dane na temat tak prowadzonego leczenia wskazywały, że wzrost ostateczny chorych jedynie w części przypadków osiągał wartości zbliżone do trzeciego centyla. Od 1995 roku hormon wzrostu stosowany jest w sposób ciągły, co umożliwia podsumowanie efektów terapii, zarówno co do osiąganego tempa wzrastania jak i uzyskiwanego wzrostu ostatecznego.

Materiał i metody
Badaniami objęto 117 dzieci i młodzieży obojga płci, w wieku od 4,6 do 18,1 lat z rozpoznaną somatotropinową lub wielohormonalną niedoczynnością przysadki, leczonych hormonem wzrostu. U wszystkich badanych analizowano szybkość wzrastania i osiągnięty wzrost ostateczny.

Wyniki
W ciągu pierwszych 6 miesięcy terapii hormonem wzrostu szybkość wzrastania osiągała 10,4 cm/rok u chłopców i 10,0 u dziewcząt i nie wykazywała zależności od statusu dojrzewaniowego. W drugim półroczu leczenia szybkość wzrastania nieznacznie obniżała się. W dalszych latach terapii, szybkość wzrastania wyraźnie zmniejszała się, co było widoczne zwłaszcza u dziewcząt. U 93% chorych, którzy zakończyli leczenie, osiągnięty wzrost ostateczny nie odbiega w sposób istotny od wzrostu prognozowanego.

Wnioski
1. Szybkość wzrastania w pierwszym półroczu terapii hormonem wzrostu była 3-krotnie wyższa niż przed leczeniem.
2. W drugim półroczu leczenia tempo nieznacznie obniżało się.
3. W dalszych latach następował wyraźny spadek szybkości wzrastania.
4. Osiągnięty u większości leczonych wzrost ostateczny nie odbiega w sposób znaczący od wzrostu prognozowanego.

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Słowa kluczowe: *hormon wzrostu, deficyt hormonu wzrostu, leczenie hormonem wzrostu, szybkość wzrastania, wzrost ostateczny*

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The effects of growth hormone treatment in patients with somatotropin deficiency during their developmental age

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Summary

Introduction
In Poland treatment with growth hormone of adolescent patients dates back to 1964. Till 1993 the therapy was conducted in an interrupted manner, depending on the periodic availability of the drug. The data form such forms of therapy suggested that the end height within 3rd centile was achieved only by a portion of treated patients. Since 1995 the growth hormone is used in continuous therapy, which allows to sum up the effects of the therapy, including the growth rate and end height.

Material and methods
A total of 117 children and adolescent of both sexes, aged 4.6 to 18.1 years, with diagnosed somatotropic or multihormonal pituitary insufficiency were included in the study. All of them were treated with growth hormone and had an analysis of growth rate and end height.

Results
In the first 6 months of growth hormone treatment the growth rate achieved 10.4 cm/year in boys and 10.0 in girls and showed no correlation with maturation status. In the second half of the year the growth rate declined slightly. During the remainder of the therapy the growth rate markedly declined, and this effect was most notable in girls. In 93% of patients after the end of therapy the final height was no different than the expected height.

Conclusions
1. The growth rate in first half a year of the treatment was 3 times higher than before the beginning of therapy.
2. In the second half of the first year the growth rate slightly declined.
3. In following years the growth rate declined notably.
4. The final achieved height in most of the patients does not differ from the prognosed height.

Key words: *growth hormone, growth hormone deficit, growth hormone therapy, growth rate, final height*

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Introduction

For many years, that is from the first time the treatment with growth hormone was introduced for therapy of patients with pituitary deficiency there is an ongoing debate about the effects of such treatment [1, 2]. The differences in achieved rates of growth, dosage and final stature are caused by both the changes in the treatment methods that have been seen for all these years (e.g. dosing, frequency of injections) but also the time during which the treatment was conducted. From 2, 3 injections per week we have switched to daily injections; a new, optimal dose of the drug was accepted [1, 2, 3, 4]. It seems then that there is no time like present to sum up the efficacy of this treatment and finding final answers for many troubling questions. In some European cities and in America there are some papers that deal with this subject. They are very valuable, because besides many years of experience they have an additional support of large databases encompassing many patients (e.g. KIGS Data-Base). In Poland Romer performed similar study, based on the effects of treatment of a large number of children hospitalized in Children Health's Center [1]. Presented data encompasses children and adolescents treated in previous years when, during therapy there were unexpected terminations of treatment of different durations, caused by administrative factors. It rendered the full evaluation of treatment effects impossible. The growth hormone treatment was introduced in 1995 and is still being continued till now. This should make the analysis of growth hormone therapy effects in different centers in the country possible. In this paper we aimed to share the results of our present treatment (from 1995), mainly because of continuity of both the therapy and observations.

Material and methods

The study comprised 117 children and adolescents aged 4.6 to 18.1 years, in whom either somatotropin alone or complete pituitary deficiency was diagnosed. There were 84 boys and 33 girls in study group. The diagnosis of growth hormone deficiency

was made based on two different stimulation tests (insulin challenge – 0.1-0.15 IU/kg body weight; Clonidine challenge – 100-150 µg/m^2 body surface) that allowed for evaluation of the pituitary reserve [2, 3, 5, 6, 7, 8]. In patients diagnosed with multihormonal pituitary deficiency, other hormonal deficiencies were taken care of, before the treatment with growth hormone was instituted. All patients received growth hormone: Genotropin 16 IU, 36 IU (Pharmacia-UpJohn), Norditropin Pen Set 12 and 24 (Novo Nordisk), Serono 10 IU (Serono). Each of those growth hormone preparations was used for the same duration of time. The 0.5 IU/kg body weight/ week dosage was used in daily evening injections. Constant change of the administration site was used. The drugs were given with semiautomatic dosers, as advised by manufacturers. The growth rate was measured with standiometer Holtain type (Holtain Limited, Crymych, Dyfed; 1 mm accuracy). The body weight was estimated always with the same scale. The dose of the growth hormone was corrected according to body weight every three months. With the same frequency the thyroid function was determined (TSH, FT_4 – radioassays). The development was ascertained based on Tanner scale. We assumed the drop in mean yearly growth rate below 1 cm/ year as the end of growth period. It was evaluated during two subsequent visits (six months apart), and complete epiphyseal ossification of long bones occurred, which was judged on the X-ray picture of the non-dominant upper extremity (hand and distal forearm section). For estimation of bone age the Greulich and Pyle method was used.

Results

The mean chronological age (CA) at the diagnosis of somatotropin deficiency and institution of growth hormone therapy was 13 years. In girls the diagnosis was made on an average a year earlier (12.6 years) than in boys (13.6 years). The bone age (BA) at the diagnosis was considerably lagging compared to chronological age. This lag was about 4 years, and was slightly higher in girls (-4.3 years). The bone age delay in boys was -3.9 years. This difference was statistically non significant. The above mentioned data are depicted in Table I.

The growth insufficiency before treatment was on an average -2.82 standard deviations (hSDS) and was slightly higher in boys than in girls. After correcting for paternal height (mpSDS) this growth lag declined to -1.47 standard deviations. This data is presented in Table II.

Table II. *The growth lag in children and adolescents with pituitary insufficiency corrected for parental height before the start of growth hormone treatment.*

Sex	hSDS	mpSDS	hSDS-mpSDS
Girls	-2.76	-1.49	-1.27
Boys	-2.84	-1.06	-1.53
Whole studied group	-2.82	-1.16	-1.47

Growth rate before treatment, measured in the last six months was 3.35 cm/year and was slightly higher for boys (3.5 cm/year) than in girls (3.2 cm/ year). Girls lacking the secondary sex characteristics grew noticeably slower than those in whom this development has already occurred. This difference was almost unnoticeable in boys – Table III.

Table III. *The growth rate in patients with pituitary insufficiency before growth hormone treatment (cm/year).*

Sex	Growth rate	Growth rate without secondary sex characteristics	Growth rate with secondary sex characteristics
Girls	3.20	2.40	3.40
Boys	3.50	3.40	3.40
Whole group	3.35	2.90	3.40

After the start of growth hormone therapy during first six months, the growth rate rose noticeably achieving 10.4 cm/year in boys and 10.0 cm/ year in girls. During this period the growth rate was independent of the presence of the secondary sex characteristics and was the same for both sexes – Table IV.

Table IV. *The growth rate during first six months of growth hormone therapy (cm/year)*

Sex	Growth rate	Growth rate before development of secondary sex characteristics	Growth rate during development of secondary sex characteristics
Girls	10.70	10.80	10.10
Boys	10.40	10.60	10.20
Whole group	10.55	10.70	10.15

Table I. *The characteristic of studied group, children and adolescent with somatotropin and multihormonal pituitary deficiency.*

Sex	Number of studied patients	Chronological age - beginning of treatment	Bone age - beginning of treatment	Bone age delay (CA-BA)
Girls	33	12.60	8.30	-4.30
Boys	84	13.60	9.70	-3.90
Whole group	117	13,00	9,00	-4,10

In the second half of the year the growth rate declined somewhat and was 10.0 cm/year for girls and 9.8 for boys. The difference in growth rate influenced by the presence or lack of the development of secondary sex characteristics, turned to be statistically insignificant – Table V.

Table V. *The growth rate in second half of the year during growth hormone therapy (cm/year)*

Sex	Growth rate	Growth rate before development of secondary sex characteristics	Growth rate during development of secondary sex characteristics
Girls	10.00	10.10	9.90
Boys	9.80	9.60	10.30
Whole group	9.90	9.70	10.10

During further years of the study the growth rate was markedly lower, especially in girls – Table VI.

Table VI. *The growth rate during growth hormone therapy after the first year of treatment (cm/year)*

Sex	Growth rate	Growth rate before development of secondary sex characteristics	Growth rate during development of secondary sex characteristics
Girls	6.60	7.20	6.20
Boys	8.20	7.80	8.60
Whole group	7.40	7.50	7.40

Some of the patients receiving growth hormone therapy have already finished their treatment. Their final achieved height in 93% of cases was in agreement with the estimated growth prognosis FH SDS-TH SDS= -0.5 (where FH SDS – standard deviation for final height, TH SDS – standard deviation for expected height). The mean growth deficiency at the termination of treatment was (-) 0.5 standard deviations compared to expected value based on paternal height. It proves that during growth hormone therapy the achieved height improved nearly one standard deviation. Compared to population mean, the final height deficiency was (-) 1.34 standard deviations. Mean chronological age at termination of treatment was 17.1 years (±1.3) for women and 18.6 years (±1.16) for men.

Discussion

In present days treatment of somatotropin deficiency doesn't confer a problem. Since 1958 when Raben extracted for the first time human growth hormone, the algorithm of injections evolved quite considerably [1]. Preparations of biosynthetic growth hormone – methionyl-hGH, appeared during the 80', acquired by plasmid exchange containing somatotropin gene substituted in Escherichia coli and also in culture of mammal tissues [1, 2]. Since then the growth hormone found its use in many diseases, however it is still the mainstay of somatotropin pituitary deficiency treatment [9, 10].

The lack of growth hormone can have different etiologies and can have various effects, ranging from complete lack of secretion to only partial pituitary deficiency. In both cases the growth hormone therapy will provide some benefits, but as diverse are the treated groups as different will be the results. We have tried to compile the treated group in such way that it should not have influenced the results. For study purposes we have only selected those patients in whom we have recognized somatotropin pituitary deficiency with idiopathic origin, or with perinatal insult in whom only partial secretion was preserved, and they have had the levels of GH within limits to warrant such a diagnosis [11]. From the study we have excluded all patients in whom the somatotropin deficiency occurred after pituitary removal, and there was a total lack of hormone secretion.

Second important element of treatment was establishing the schematic of growth hormone therapy regimen in which daily subcutaneous injections were performed, what is considered now a gold standard, contrary to what was used in previous years [1, 2, 3, 12]. Some doubts could arise as far as the optimal dosage of the growth hormone therapy. It is widely assumed that the therapeutic dose is comprised within 0.3-1.0 IU/kg body weight/week [1]. In studies conducted in Japan it was proven that somatotropin doses higher than 0.5 IU/kg body weight/week produce a better growth rate in the first year of treatment, however the growth rates for doses 0.5-1.0-1.5 IU/kg body weight/week after first year did not differ statistically [13]. In a second study conducted by the same team it was noticed that if the treatment was started with the dose of 0.5 IU/kg body weight/week in the first year of treatment and then subsequently increased during further therapy, the end growth rate was even better [13]. Comparing the results of these two studies it was noticed that the results achieved were much better than those of a control group receiving for the whole time 0.5 IU/kg body weight/week [13]. Since the therapy is still ongoing the researchers cannot say so far, if such design of the growth hormone doses will give a better final height. It might turn out that the achieved results do not justify the costs.

In our study the therapy was conducted with constant dose throughout the whole treatment period. We used a dose of 0.5 IU/kg body weight/week divided into daily injections. Despite the constant dose the end result in 93% of cases was not different from estimated final height (FH (Final Height) SDS – TH (Target Height) SDS= -0.53). Similar favorable results were achieved during growth hormone treatment in Belgium, where it

was found in over 87% of patients [14]. The results achieved by us are very good in view of the fact that, according to Swedish studies, only 75% of patients treated with growth hormone for IGHD (idiopathic growth hormone deficiency) achieved normal height, and the norms in that study were almost identical to our observations [15, 16]. However, there are some independent studies suggesting that the main determinant influencing the height achieved during growth hormone therapy is the parental height [17, 18, 19, 20, 21, 22]. From Polish observations one can only base the conclusion upon Romer studies and the achieved final results of treatment [1]. He concludes that, before 1993, the final height of patients receiving growth hormone therapy compared to patients receiving no therapy, improved by four standard deviations. At the same time only 50% of subjects reached lower threshold values. The rest remained within 3rd percentile. According to Romer the reason for such situation could be associated with the delay in beginning and disruption at conducted therapy [1]. Such conclusions could suggest that there is no reason for introducing higher doses of growth hormone in such patients in subsequent years. This phenomenon was seen both in girls and in boys. It is also worth noticing that, in Polish settings, important factor influencing the final height achieved during growth hormone therapy is the time of making the diagnosis and therefore instituting treatment. In our study the mean chronological age at administering the treatment was 12.6 years for girls and 13.6 years for boys. It seems that this is too late for beginning of the therapy (Table 1). At the same time the bone age development was delayed 4 years, and the mean bone age was 9 years, what is influenced by the disease itself, but also leaves more time for treatment and improves the final height achieved. It is known from the literature that at the start of the growth hormone therapy its effects correlate inversely with the age of the patients, their height, weight and the advancement of bone development [2, 3, 23]. During a study conducted on nearly 400 subjects with IGHD (idiopathic growth hormone deficiency) (KIGS-Pharmacia-UpJohn International Growth Database) it was proven that commonly dosed growth hormone therapy leads to achievement of normal height estimated from parental mean height. On the other hand it is believed, that introducing higher doses or individual doses might be necessary for those patients with IGHD, who are underprivileged because of late therapy initiation or low parental height [15]. So, those 7% of patients treated by us, in whom the final achieved height was not totally satisfactory, might require individualization of the doses at subsequent therapy. One has to remember that higher doses of growth hormone might speed up the maturation and its intensity, leading ultimately to shortening of the growth period [4]. Yet, according to Japanese studies, higher doses of growth hormone do not lead to expediting of the "closure" of the long bones' epiphyseal plate [13]. This problem will surely require further elucidation. It is however a fact, that better final growth is achieved by those patients who mature later [24].

The mean growth rate observed by us during first six months of treatment was 10.5 cm/year (Table IV). Compared to growth rate achieved by our patients before instituting the treatment we observed nearly 3 times improvement. Dash believes that during first year of therapy the mean growth rate is 6-8 cm/year [10]. This growth rate is in agreement with commonly described phenomenon observed at the beginning of therapy – the so-called "catch up" [1]. It is thought that achieved at that time acceleration of growth pattern correlates well with the initial growth lag, so the highest growth rate will be observed in those patients in whom the height lag was the greatest [20, 23, 25]. Also Sudfeld thinks that the main factor influencing the growth rate in the first year of treatment is the difference between expected height and the height deficiency at the beginning of therapy [25]. Similarly better effects of treatment will be achieved in patients with complete pituitary insufficiency than in those with only partial problem [26]. In conclusion, it seems that in our experiment choosing patients with only partial pituitary deficiency might have influenced the growth rate of our patients. Another point – at the beginning of therapy the mean growth lag was 2.8 standard deviations (hSDS), and after correction for parental height it was only -1.5 (Table II). The worse prognosis for the expected growth rate should be stressed here, caused by lack of growth potential [23]. In our study the growth rate at the second half year was only slightly lower and achieved 9.9 cm/year (Table V). It is difficult to strictly determine the duration of the "catch up" phenomenon. It is thought that it might last few or even 12 months after the beginning with growth hormone treatment. Most frequently it is estimated to last for half a year [1, 2]. In subsequent years of therapy, after the first year, the growth rate declined markedly and was 7.4 cm/year. This phenomenon is commonly observed. It is assumed that achieved growth speed during this time is equivalent to natural growth rate. However it is difficult to explain the similarity in growth rate of patients treated with growth hormone for at least a year, regardless of the development stage (Table VI). This could be only a coincidence, caused by increase in number of patients in whom the development process already lasted for same time, and the growth rate associated with this process already begun to show declining tendency associated with the approaching of the expected final height. The growth rate observed in patients without any signs of development seems similar to those observed in other studies.

The results of our study, especially the final height, are very optimistic effects of our therapeutic efforts. However it should be stressed that there is a potential for further improvement of our results. This could be achieved by lowering the age of initial diagnosis of somatotropin pituitary deficiency, so that the younger age could allow for lengthening of the growth hormone treatment duration [22, 27]. It also seems important to individualize, in some cases, the doses of the growth hormone.

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