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Do the intervals in growth hormone therapy positively affect the growth velocity?

Czy przerwy w leczeniu hormonem wzrostu mogą pozytywnie wpływać na tempo wzrastania?

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Abstract

Introduction: A significant increase in growth velocity is observed during recombinant human growth hormone (rhGH) therapy in patients with growth hormone deficiency (GHD), especially just after the beginning of treatment. This phenomenon is referred to as "catch-up growth". After some time, the growth velocity decreases to the physiological value, i.e. the value that is observed in healthy children. The treatment is continued until the time of the growth process is completed. The continuity of the therapy makes it impossible to assess whether the catch-up phenomenon occurs only at the beginning of the treatment or may be observed after treatment cessation and its re-introduction.

Material and methods: Growth velocity was evaluated in a group of 35 patients with GHD after repeated therapy application, in which, due to non-medical reasons, the rhGH treatment was abandoned for a short time.

Results: Patients with GHD after treatment re-introduction presented the catch-up growth phenomenon and obtained growth velocity results that were significantly higher than those observed during primary treatment.

Conclusions: Re-introduction of rhGH treatment after short-term therapy cessation leads to the re-occurrence of catch-up growth in patients with GHD.

Key words:

growth hormone deficiency, growth hormone, children, catch-up growth, growth velocity.

Streszczenie

Wstęp: Podczas terapii rekombinowanym ludzkim hormonem wzrostu (rhGH) u pacjentów z niedoborem hormonu wzrostu (GHD) obserwuje się znaczne przyspieszenie tempa wzrastania, szczególnie tuż po rozpoczęciu leczenia. Zjawisko to nazywane jest *catch-up growth* – nadrabianiem zaległości. Po pewnym czasie tempo wzrastania spada do wartości fizjologicznej, obserwowanej u zdrowych dzieci, a leczenie kontynuuje się do czasu zakończenia procesu wzrastania. Ciągłość terapii uniemożliwia ocenę, czy zjawisko *catch-up growth* występuje tylko na początku leczenia, czy też może być obserwowane po przerwaniu leczenia i jego ponownym rozpoczęciu.

Materiał i metody: Tempo wzrastania oceniano w grupie 35 pacjentów z GHD po powtórnym rozpoczęciu leczenia rhGH, które z przyczyn pozamedycznych zostało na krótko przerwane.

Wyniki: Pacjenci z GHD po ponownym wprowadzeniu leczenia wykazywali przyspieszone tempo wzrastania, a uzyskane wyniki były wyższe niż obserwowane podczas leczenia pierwotnego.

Wnioski: Powtórne rozpoczęcie leczenia rhGH po krótkotrwałym zaprzestaniu terapii prowadzi do ponownego wystąpienia zjawiska *catch-up growth* u pacjentów z GHD.

Słowa kluczowe:

somatotropinowa niedoczynność przysadki, hormon wzrostu, dzieci, *catch-up growth*, tempo wzrastania.

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Introduction

Growth hormone therapy in patients with short stature resulting from growth hormone deficiency (GHD) has been conducted since 1958. Recombinant human growth hormone (rhGH) has been used since the year 1985. The experiences concerning this treatment effectiveness, possible side effects, and optimal doses have been collected for decades [1–3].

Attention has been paid, inter alia, to the "catch-up growth" effect occurring just after the beginning of growth hormone therapy. It is referred to as supra-physiological height velocity, resulting from efforts to make up for the growth delays caused by the disease, in response to the treatment applied. The time of this phenomenon is variously determined in the literature, generally between a few months and a year. It was observed that the growth velocity achieved during this time depends on the degree of bone age (BA) delay, height deficiency, and adherence to growth hormone therapy. The higher the growth deficiencies, BA delay, and adherence to the treatment, the higher the growth velocity in an initial therapy period and the longer lasting the catch-up growth [4–7].

In this study we decided to analyse patients with GHD, treated long-term with growth hormone, who had a gap in drug administration and then re-application of the treatment. The idea of the study was to verify whether the catch-up effect is a single phenomenon, occurring only at the initiation of growth hormone therapy, or if it is repeated in the case of treatment interruption and re-introduction.

Material and methods

The study involved 35 patients in developmental age (6.4–16.9 years) with a diagnosis of GHD, who were treated with rhGH (Omnitrope, Sandoz) in a mean dose of 0.171 mg/kg body weight/week (dose range: 0.170–0.174 mg/kg/week). The examined group included 22 boys and 13 girls. They were selected from among 62 patients in a retrospective analysis of their medical history after the exclusion of other accompanying diseases, including hypothyroidism, multiple pituitary hormone deficiencies, malabsorption, allergies, and other additional chronic diseases. All the patients were previously treated with rhGH for a period longer than one year (1.24–12.9 years). The intervals were caused by non-medical reasons, mainly due to interruptions in drug availability. Due to natural, time-dependent changes in puberty status among children in the studied group, the same group could not be used to compare primary growth velocities. Instead, another, larger group of children was used, further divided depending on puberty status. This control group consisted of 79 patients with GHD (56 boys and 23 girls) of similar age, in whom the growth velocity was evaluated after three and six months since the beginning of rhGH treatment. Height measurements were always performed by the same person with an accuracy of 1 mm, using a stadiometer from Holtain Ltd. Bone age was determined according to the Greulich and Pyle method.

For the purpose of statistical analysis, the Kolmogorov-Smirnov test was used to evaluate the compatibility of the variables with the normal distribution. *T*-test and paired *t*-test were used for normally distributed variables. Mann-Whitney Rank Sum Test and Wilcoxon Signed Rank Test were used for the variables not compatible with the normal distribution.

The study was based on retrospective analysis of patients' data collected in the years 2014–2018, in accordance to the World Medical Association Declaration of Helsinki regarding ethical conduct of research.

Results

Table I presents the growth velocity in boys and girls with GHD from the control group after three and six months of rhGH

Table I. Growth velocity (V0) in boys and girls with GHD from the control group measured during the first time of rhGH therapy implementation, and after 3 and 6 months

Boys (n = 56)	Metrical age (years)	Bone age (years)	V0 (cm/year)	
			after 3rd month	after 6th month
Mean value ±SD	11.40 ±3.49	9.35 ±3.96	9.47 ±2.82	8.95 ±2.47
Value range	4.6–16.8	1.5–16	3.9–15.5	4.2–14.0
Girls (n = 23)	Metrical age (years)	Bone age (years)	V0 (cm/year)	
			after 3rd month	after 6th month
Mean value ±SD	10.51 ±3.20	8.29 ±3.23	9.45 ±2.72	7.95 ±1.67
Value range	5.1–17.3	3.0–13.0	5.7–14.2	4.7–12.1

Table II. Growth velocity in boys and girls with GHD during continuous rhGH therapy (V1), and after an interval in treatment and its re-introduction (V2)

Boys (n = 22)	Metrical age (years)	Bone age (years)	V1 (cm/year)	V2 (cm/year)	Therapy break (days)
Mean value ±SD	12.77 ±2.97	10,61 ±3.64	6.98 ±2.48	12.50 ±5.66	37.59 ±20.44
Value range	6.4–16.9	4.0–15.0	3.2–10.9	5.2–21.9	13–82
Girls (n = 13)	Metrical age (years)	Bone age (years)	Bone age (years)	Bone age (years)	Bone age (years)
Mean value ±SD	11.15 ±3.04	8.89 ±3.24	8.38 ±2.92	13.56 ±7.11	50.54 ±24.86
Value range	6.9–15.4	4.0–13.0	3.1–12.4	3.2–23.1	9–96

treatment (V0). Table II, in turn, presents the results of growth velocity for the last three months of continuous rhGH treatment (V1) and the results achieved after therapy re-introduction after an interval (V2). The treatment interval time ranged from 9 to 82 days (38 days on average). The growth velocity in boys after treatment re-introduction was 1.8-fold higher compared to previous continuous treatment (p = 0.003). The growth rate was also higher after treatment re-introduction compared to the beginning of primary treatment (1.3- and 1.4-fold higher, for the first three and six months, respectively [p = 0.003; p = 0.01]).

In case of the girls with GHD, the break in treatment was 51 days on average (9–96 days). After rhGH therapy re-introduction, the growth rate in girls was 1.6-fold higher compared to the previous value, during the continuous therapy. Compared to the control group, the growth velocity achieved by the girls after therapy re-introduction was 1.4- and 1.7-fold higher compared to the values observed in the case of the beginning of primary therapy, after three and six months of rhGH administration (p = 0.027). Figure 1 presents a graphic comparison of growth velocity for boys and girls at the start of primary treatment, in the case of long-term continuous treatment, and after therapy re-introduction.

The growth velocity in girls in the prepubertal period was 1.46-fold greater after therapy re-introduction compared to previous continuous treatment, and 1.3-fold greater compared to the control group. For the girls in pubertal period that value was 1.87, and with respect to the control group it was 1.36 after three months, and 1.74 after six months. In the case of boys, these values were 1.42 for the prepubertal period and 2.08 in the pubertal period after treatment re-introduction, respectively. Compared to the control group, that rate was 1.1-fold higher in prepubertal boys with treatment re-introduction after three and six months. In the pubertal period, the growth rate in boys in whom rhGH treatment was re-introduced was 1.4- and 1.6-fold higher after three and six months, respectively (p = 0.0043; Tables III and IV).

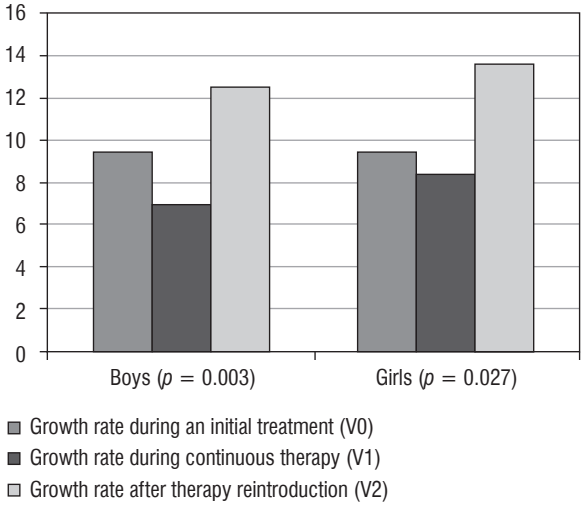

Figure 1. Growth velocity (cm/year) in boys and girls with GHD treated with rhGH after the start of primary treatment, during longer continuous therapy, and after treatment re-introduction

Discussion

As was demonstrated based on the literature data, the catch-up effect occurs after the start of growth hormone treatment and lasts from a few months up to a year. The growth velocity achieved during this time is higher than the respective physiological growth rate for age and sex [4, 5]. To the authors' knowledge, no studies on re-occurrence of that phenomenon in patients who stopped rhGH therapy for a short time have been conducted so far. Such situations are met only sporadically in each large group of patients. However, there are some studies describing the influence of planned intermittent therapies on growth in children. A study involving children born small

Table III. Growth velocity (V0) in boys and girls with GHD after the start of primary rhGH treatment depending on maturation status

Boys (n = 56)	Metrical age (years)	Bone age (years)	V0 (cm/year)	
			after 3rd month	after 6th month
Mean value ±SD (value range) Prepubertal (n = 27)	7.67 ±2.74 (4.6–11.8)	5.79 ±2.81 (1.5–11.0)	8.26 ±2.94 (3.9–12.3)	8.46 ±2.25 (4.3–12.7)
Mean value ± SD (value range) Pubertal (n = 29)	14.25 ±2.32 (10.5–16.8)	12.61 ±1.56 (11.0–16.0)	10.67 ±2.56 (5.3–15.5)	9.39 ±2.68 (4.2–14.0)
Girls (n = 23)	Metrical age (years)	Bone age (years)	V0 (cm/year)	
			after 3rd month	after 6th month
Mean value ±SD (value range) Prepuberal (n = 14)	8.71 ±2.65 (5.1–12.3)	6.61 ±2.41 (3.0–11.0)	9.53 ±2.48 (5.7–13.0)	8.24 ±1.88 (6.5–12.1)
Mean value ±SD (value range) Pubertal (n = 9)	13.31 ±1.81 (10.9–17.3)	11.64 ±1.08 (10.0–13.0)	9.29 ±2.95 (4.6–14.2)	7.50 ±1.33 (4.7–9.7)

Table IV. Growth velocity in boys and girls with GHD during continuous rhGH therapy (V1) and after an interval in the therapy and treatment re-introduction (V2), depending on pubertal status

Boys (n = 22)	Metrical age (years)	Bone age (years)	V1 (cm/year)	V2 (cm/year)	Therapy break (days)
Mean value ±SD (value range) Prepubertal (n = 10)	10.12 ±2.33 (6.4–13.6)	7.15 ±2.14 (4.0–10.0)	6.77 ±2.11 (3.4–9.4)	9.64 ±4.84 (6.4–18.3)	35.1 ±16.7 (16–66)
Mean value ±SD (value range) Pubertal (n = 12)	14.98 ±1.34 (12.0–16.9)	13.46 ±1.28 (11–15.0)	7.16 ±2.90 (3.5–10.9)	14.88 ±5.46 (5.2–21.9)	39.67 ±23.5 (10–82)
Girls (n = 13)	Metrical age (years)	Bone age (years)	V1 (cm/year)	V2 (cm/year)	Therapy break (days)
Mean value ±SD (value range) Prepubertal (n = 6)	8.28 ±1.42 (6.9–10.9)	6.54 ±2.32 (4.0–10.0)	8.68 ±2.43 (6.4–12.4)	12.66 ±7.29 (7.2–23.1)	45.17 ±22.1 (19–73)
Mean value ±SD (value range) Pubertal (n = 7)	13.61 ±1.22 (11.9–15.4)	11.7 ±1.15 (10–12.5)	7.65 ±3.28 (3.1–10.8)	14.32 ±7.55 (3.2–21.3)	55.14 ±27.9 (9–96)

for gestational age suggested no negative effect of intervals in rhGH administration on the achieved height [8]. Another study with GHD patients showed no negative growth results of less frequent growth hormone administration – three times a week gave similar effects as six times a week in children who were previously treated continuously for two years [9]. Other intermittent therapies involving various therapeutic substances may be used in different health conditions, but their effectiveness is not always clear – for example large intermittent doses of calcitriol lowered elevated parathyroid hormone (PTH) levels in children with chronic renal failure, but they could also diminish the linear body growth [10, 11].

Our study was based on patients who had been treated with growth hormone for more than one year, after completion of primary catch-up growth, and their therapy intervals were not planned but also not caused by complications or diseases. A very good growth response was observed after treatment re-introduction. It was demonstrated, based on the data collected, that the height velocity after repeated growth hormone administration was nearly 1.5- to 2-fold higher compared to the previous value achieved during continuous rhGH application. Thus, it was proven that the catch-up phenomenon is not a single effect. Moreover, the growth velocity obtained after treatment re-introduction seems to be even higher compared to the observed value when starting the treatment for the first time. Concurrently, the treatment interval was not long enough to cause an acceleration in bone age delay, or to intensify the degree growth deficiency. Analysing the factors affecting the catch-up growth, bone age delay at primary treatment implementation was greater in all the cases than at the moment of treatment re-introduction. Also, regarding the degree of growth deficiency, it was considerably more pronounced at the moment of introduction of the first therapy compared to the time of the therapy interval. Thus, the effect of bone age and growth deficiency does not seem to be a significant issue in the case of growth velocity obtained after a short break in rhGH therapy. Hence, this process may also be dependent on other mechanisms. The rapid growth response stimulated with rhGH administration cannot only be dependent on the concentration of GH and IGF-I, which, after the start of primary treatment, causes growth acceleration. The observed catch-up effect is less pronounced in comparison to that noted after treatment re-introduction after a short break. Presumably, rhGH administration for a certain time "prepares" target tissues for proliferation processes, transforming their metabolism. A possible mechanism would include increased tissue sensitivity and, consequently, increased intensity of response to a given growth hormone. This issue requires further research.

Conclusions

It can be concluded, based on the conducted study, that short-term cessation in rhGH treatment in patients with GHD and therapy re-introduction leads to the re-occurrence of catch-up effect. The growth velocity obtained after treatment re-introduction seems to be considerably higher than in the case of continuous treatment, and also higher than that observed during primary therapy commencement. If these preliminary observations are confirmed in further research, the usefulness of such short-term intervals in rhGH therapy for obtained final growth could be considered.

References

1. Ranke MB, Wit JM. Growth hormone – past, present and future. Nat Rev Endocrinol 2018; 14: 285–300. doi: 10.1038/nrendo.2018.22
2. Polak M, Konrad D, Tonnes Pedersen B, et al. Still too little, too late? Ten years of growth hormone therapy baseline data from the NordiNet® International Outcome Study. J Pediatr Endocrinol Metab 2018; 31: 521–532. doi: 10.1515/jpem-2017-0489.
3. Adamczuk D, Leszczyńska B, Skrzypczyk P, et al. Twenty years of growth hormone treatment in dialyzed children in Poland-Results of national multicenter study. Adv Med Sci 2019; 64: 90–99. doi: 10.1016/j.advms.2018.12.001
4. Wit JM, Boersma B. Catch-up growth: definition, mechanisms, and models. J Pediatr Endocrinol Metab 2002; 15 Suppl 5:1229–1241.
5. Gafni RI, Baron J. Catch-up growth: possible mechanisms. Pediatr Nephrol 2000;14: 616–619. doi: 10.1007/s004670000338
6. van Dommelen P, Koledova E, Wit JM: Effect of adherence to growth hormone treatment on 0-2 year catch-up growth in children with growth hormone deficiency. PLoS One 2018; 13: e0206009. doi: 10.1371/journal.pone.0206009
7. Mohseni S, Heydari Z, Qorbani M, et al. Adherence to growth hormone therapy in children and its potential barriers. J Pediatr Endocrinol Metab 2018; 31: 13–20. doi: 10.1515/jpem-2017-0157.
8. Phillip M, Lebenthal Y, Lebl J, et al. European Norditropin SGA Study Group. European multicentre study in children born small for gestational age with persistent short stature: comparison of continuous and discontinuous growth hormone treatment regimens. Horm Res 2009; 71: 52–59. doi: 10.1159/000173742
9. Cavallo L, De Luca F, Bernasconi S, et al. The effect of different growth hormone administration frequencies on growth in growth hormone-deficient patients. Horm Res 1998; 49 Suppl 2: 73–77. doi: 10.1159/000053091
10. Kuizon BD, Goodman WG, Jüppner H, et al. Diminished linear growth during intermittent calcitriol therapy in children undergoing CCPD. Kidney Int 1998; 53: 205–211. doi: 10.1046/j.1523-1755.1998.00724.x
11. Salusky IB, Goodman WG, Kuizon BD. Implications of intermittent calcitriol therapy on growth and secondary hyperparathyroidism. Pediatr Nephrol 2000; 14: 641–645. doi: 10.1007/s004670000352