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Effect of nutritional status on growth velocity in the first year of growth hormone treatment of children with Growth Hormone Deficiency

Wpływ odżywienia dzieci z somatotropinową niedoczynnością przysadki na szybkość wzrastania w pierwszym roku leczenia hormonem wzrostu

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growth hormone, nutritional status, children

Słowa kluczowe
hormon wzrostu, stan odżywienia, dzieci

S u m m a r y

Introduction. The main aim of growth hormone (GH) treatment is improvement in growth velocity in children.

Aim. To assess the effect of nutritional status of children with Growth Hormone Deficiency (GHD) on growth velocity in the first 12 months of treatment with growth hormone (GH).

Material and methods. Cohort of 200 patients with GHD: 139 boys and 61 girls, mean age: 11.84 ± 3.1 years. Body height and body mass measurements were taken before of GH treatment and after 12 months. Cole index and BMI (Body Mass Index) were determined. Body fat percentage was calculated from Slaughter equation. The analysis of growth velocity in relation to Cole Index before treatment and after 12 months of GH therapy was performed.

Results. Before the start of GH treatment malnutrition were determined in 17% of study patients. Overweight patients constituted 27%. Growth velocity before treatment was estimated at 4.86 ± 1.30 cm and increased to 9.11 ± 1.72 cm after one year of treatment. After 12 months of GH treatment overweight was reported in 23.5% of the study cohort, malnutrition were still observed in 17%. Normal nutritional status of GHD children recognized at the start of GH treatment correlated with growth velocity in the first year of treatment. Better growth velocity was observed for children with Cole index 90-110% and for overweight children (Cole index > 110%).

Conclusions. 1. Malnutrition in children decreases the effect of growth hormone treatment. 2. Nutritional disorders in children with Growth Hormone Deficiency (GHD) require intervention of specialists.

S t r e s z c z e n i e

Wstęp. Poprawa szybkości wzrastania u dzieci jest podstawowym celem leczenia hormonem wzrostu.

Cel pracy. Ocena wpływu stanu odżywienia dzieci z SNP na szybkość wzrastania w pierwszym roku leczenia GH.

Materiał i metody. 200 pacjentów z somatotropinową niedoczynnością przysadki (SNP): 139 chłopców i 61 dziewcząt, średni wiek: 11,84 ± 3,1 roku. Przed leczeniem hormonem wzrostu (GH) i po roku wykonano pomiary wysokości i masy ciała. Wyliczono wskaźnik Cole'a i BMI (ang. *Body Mass Index*). Określono zawartość procentową tłuszczu (%FAT) ze wzoru Slaughtera. Analizowano szybkość wzrastania przed leczeniem i po 12 miesiącach leczenia GH w zależności od wskaźnika Cole'a.

Wyniki. Przed włączeniem leczenia GH upośledzenie stanu odżywienia stwierdzono u 17% badanych. Pacjenci z nadwagą stanowili 27%. Szybkość wzrastania przed leczeniem wynosiła 4,86 ± 1,30 cm, po roku leczenia GH – 9,11 ± 1,72 cm. Po roku leczenia nadwagę stwierdzono u 23,5% badanych, zły stan odżywienia nadal u 17%. Prawidłowy stan odżywienia dzieci z SNP na początku terapii GH korelował z szybkością wzrastania w pierwszym roku leczenia. Lepszą szybkość wzrastania obserwowano u dzieci ze wskaźnikiem Cole'a – 90-110%, oraz u dzieci z nadwagą (wskaźnik Cole'a > 110%).

Wnioski. 1. Niedożywienie u dzieci zmniejsza efekt terapii hormonem wzrostu. 2. Zaburzenia stanu odżywienia u dzieci z SNP wymagają interwencji specjalisty w zakresie żywienia.

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INTRODUCTION

The process of development is inseparably related to growth and depends on numerous factors including cell expansion, maturation and increase in cell size. The process of growth is determined by regulatory factors which are active in fetal life and later in postnatal life. In intrauterine life a significant role is attributed to insulin, insulin-like growth factors (IGF-1, IGF-2), IGF binding receptors and proteins, specific protein carriers (IGFBP 1-6), mainly IGFBP 3. Shortly after birth the fetal mechanisms are still active and it is only in the neonatal period that the growth hormone (GH) is activated. Other growth-affecting hormones include thyroid hormones, cortisol, and growth hormone-releasing peptides. In puberty growth is also affected by sex hormones (1-5).

AIM

The aim of the study was to assess the effect of the nutritional status on growth velocity in the first year of growth hormone (GH) treatment in a cohort of children with growth hormone deficiency (GHD).

MATERIAL AND METHODS

The study cohort included short stature children diagnosed at the Department of Pediatric Endocrinology in the period 2000-2011.The analysis involved 200 GHD patients: 139 boys and 61 girls (GH concentration < 10 ng/ml after provocation), with no other chronic diseases; mean age 11.84 ± 3.1 years.

Body height and body weight measurements were taken from each child at the start of GH treatment and 12 months later. Body weight was measured in underwear on medical scales (accuracy up to 0.1 kg). Body height was a mean of three measurements taken with Holtain stadiometer (accuracy up to 0.1 cm), in an anthropometric position, erect, at rest, facing directly ahead (the Frankfurt plane). Skinfold measurements were taken with Harpenden caliper at two sites (triceps and subscapular folds). Individual age of height was calculated (age for which height was on the 50th centile) at the beginning of treatment and after 12 months.

Cole index and BMI (Body Mass Index) were calculated from body height and body weight measurements.

The Cole Index was calculated from the following equation (6): current body weight/standard body weight x 100 and interpreted according to McLaren's classification:

110% – overweight,
90-100% – normal,
85-90% – mild malnutrition,
75-85% – moderate malnutrition,
75% – severe malnutrition.

Body mass index (BMI) was calculated from the following equation:

$$BMI = \frac{\text{current body weight (kg)}}{\text{current body height (m}^2\text{)}}$$

Body weight and BMI values were then standardized according to average (x) and standard deviation (SD) for the population of Warsaw children (7):

$$\text{SDS b.w./BMI} = \frac{\text{current body weight/BMI}}{\text{standard body weight/BMI : SD}}$$

The calculated values were interpreted as body weight/BMI expressed as SDS (Standard Deviation Score), with 0 ± 1 SDS accepted as normal. Body height was standardized and interpreted as short stature < -1.2 SDS.

Data on the nutritional status of the study children was supplemented with body fat percentage data (calculated from Slaughter equation from triceps and subscapular skinfold measurements) taking into account the stage of sexual development (puberty) (8).

Eligible data set the normal body fat value at 19% for girls and 15% for boys (9). The stage of sexual development (puberty) was evaluated by endocrinologists during hospitalization. Microsoft Excel 2003 calculation sheet was used for analysis of growth velocity data (cm) before GH treatment and 12 months later. Detailed statistical calculation/analysis was performed using Statistica 9.0 with: Student's t-test and Pearson's correlation coefficient (linear regression analysis). The significance level of $p < 0.05$ was accepted.

RESULTS

A cohort of 200 patients with GH deficiency were enrolled in the study: 139 boys (70%) and 61 girls (30%); mean chronological age: 11.84 ± 3.1 years. 29% (n = 58) were below 9 years of age, 54.5% were between 10 and 14 (n = 109) and 16.5% were over 14 (n = 33).

Before the start of GH treatment growth velocity for boys and girls was similar and ave aged 4.88 ± 1.26 cm/year and 4.83 ± 1.33 cm/year respectively. The mean height was 129.8 ± 14.12 cm for girls and 136.1 ± 16.85 cm for boys. Body height expressed as standard deviation scores (SDS) was -2 to -4. Differences in height shortage between study boys and girls (in SDS) were not significant but the difference in relation to the mean of the general population was statistically significant.

At the start of GH treatment the difference between age of height and chronological age of study children was estimated at approximately 3 years at average (8.88 ± 2.72 years for girls and boys). Mean body weight was 32.44 ± 11.63 kg (for the age of height -0.02 ± 0.85 SDS at the average). Mean body weight values expressed as SDS were normal for body height. Mean BMI value was 17.38 ± 3.34 kg/m^2.

Cole index showed no severe malnutrition in the cohort of 200 GHD patients before the start of GH treatment. Moderate and mild malnutrition was recognized in 34 (17%) children, normal nutritional status in 56%. Overweight patients constituted a relatively large group of 54 children (27%). Observation showed that malnutrition (mild or moderate) affected girls (21%) rather than boys (15%) and just the opposite for overweight where the number of overweight boys was larger than that of girls (30 vs 20%).

The mean body fat percentage before GH treatment was estimated at 19.83 ± 6.76% (22.5 ± 5.15% for girls, 18.73 ± 7.07% for boys).

After the first 12 months of GH treatment the body height of patients improved markedly. Growth velocity was estimated at +9.11 ± 1.72 cm at the average; 8.2 ± 1.25 cm/year for girls and 9.43 ± 1.80 cm/year for boys.

Mean body height expressed as SDS was estimated at -2.05 ± 0.79. Age of height increased by 1.5 for both sexes. Body height shortage reduction was comparable for both sexes: 0.59 SDS for boys and 0.56 SDS for girls. The mean body weight increment was estimated at 5.64 ± 3.15 kg and the values ranged from -0.6 kg to +20.8 kg; 40.45 ± 13.92 kg mean body weight for boys and 32.6 ± 10.45 kg for girls. Mean BMI value was 17.85 ± 3.25 kg/m^2 and for age of height -0.06 ± 0.97 expressed in SDS. Mild and moderate malnutrition (Cole index) still prevailed in 16.5% (33) of children. One case of severe malnutrition was reported. Slight improvement of nutritional status was observed in children with overweight. The number of excessive nutrition cases decreased to 47 (23.5%). After 12 months of GH treatment the overweight rate decreased by 3.5% for both boys and girls (tab. 1).

Before GH treatment the highest percentage of subjects (38%) were in the -2.1 and -2.5 body height range as expressed in SDS. In 178 children (89%) the SDS values were below 3 on the centile chart (-2 SDS). After 12 months of treatment with GH the body height improved markedly. Only 87 patients (43.5%) were placed below 3 on the centile chart (-2 SDS). Patients with body height above of -2.0 as expressed in SDS were the most numerous group.

After 12 months of GH treatment the mean body fat percentage was estimated at 16.39 ± 6.39% (no statistically significant differences in body fat reduction were found between sexes). It was 20.0 ± 5.1% for girls and 14.82 ± 6.27% for boys.

The cohort of GHD children was divided into subgroups according to the above criteria for underweight, normal weight and overweight. In each subgroup growth velocity was determined in relation to nutritional status (tab. 2).

The data demonstrate that nutritional status (Cole index) affects growth velocity during GH treatment in both boys and girls. Higher body height increment was observed for children with normal body weight (Cole index 90-110%) and overweight children (Cole index > 110%) than for children with nutritional disorders (Cole index < 90%). In the first year of treatment the correlation between growth velocity and the Cole index was statistically significant (fig. 1).

DISCUSSION

Our study presents a cohort of 200 pre-pubertal children (61 girls and 139 boys) with GHD and no other diseases who were subjected to a 12 months treatment with GH. The study analysis was focused on the first 12 months as the crucial period for GH therapy (10-15). The mean age of children was 11.84 ± 3.1 and mean body weight and BMI were normal for their body height. Weight/height was normal for 56% of patients. Underweight was determined in 17% (Cole index < 85%), overweight and obesity in 27% (Cole index > 110%). Nutritional status was assessed from body fat percentage taken from skinfold measurements (2 sites: triceps and subscapular).

Table 1. Mean and standard deviation values for body mass, BMI and Cole index for age of height in children with GHD before the start of GH treatment and 12 months later (n = 200).

Parameter	Start of therapy boys n = 139	Start of therapy girls n = 61	After 12 months of therapy boys n = 139	After 12 months of therapy girls n = 61
Age of height (years)	9.19 ± 2.83	8.18 ± 2.31	10.75 ± 2.94	9.60 ± 2.37
Body weight (kg)	34.38 ± 12.19	28.03 ± 8.88	40.45 ± 13.92	32.60 ± 10.45
Body weight (SDS)	0.06 ± 0.86	-0.2 ± 0.83	0.03 ± 0.80	-0.3 ± 0.73
BMI (kg/m^2)	17.91 ± 3.43	16.19 ± 2.79	18.42 ± 3.25	16.6 ± 2.91
BMI (SDS)	0.13 ± 1.18	-0.24 ± 1.1	0.06 ± 0.96	-0.3 ± 0.96
Cole index < 75%	–	–	–	1
Cole index 75-85%	7	8	11	6
Cole index 85-90%	14	5	8	8
Cole index 90-110%	76	36	83	36
Cole index > 110%	42	12	37	10

Table 2. Nutritional status of GH-treated children with GHD and mean growth velocity (cm).

Cole index	n boys	Growth velocity at the start of GH therapy boys	Growth velocity at the start of GH therapy girls	n girls	Growth velocity after 12 months of GH therapy girls	Growth velocity after 12 months of GH therapy boys
< 90%	21	4.72	8.9	13	5.11	7.92
90-110%	76	5.6	9.99	36	4.6	8.72
≥ 110%	42	4.72	10.18	12	4.69	8.45

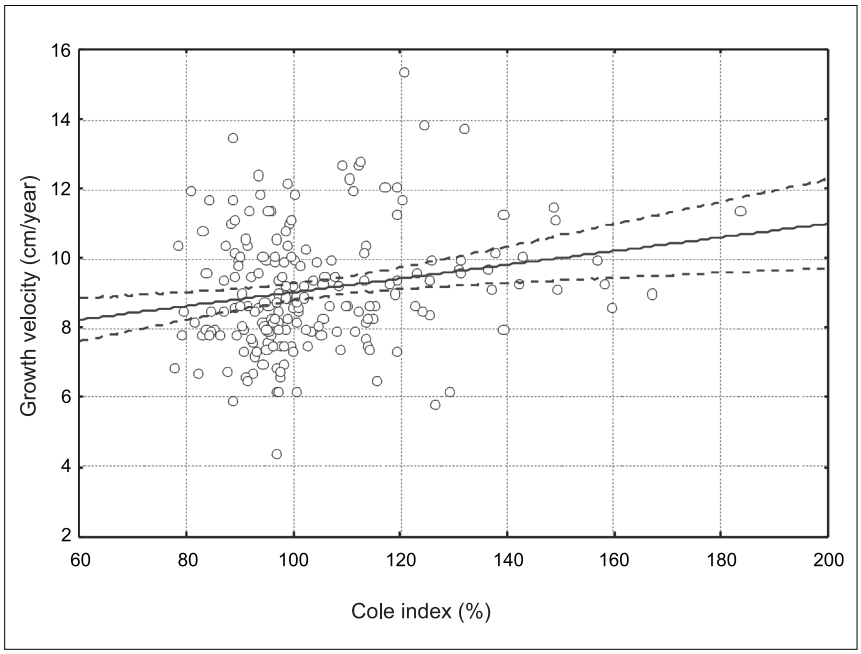

Fig. 1. Correlation between Cole index and growth velocity during 12 months of GH therapy in children with GHD.

Sexual dimorphism was apparent. After a year of treatment we observed reduction in fat percentage for both sexes; the difference between sexes was not statistically significant. One of the additional benefits of GH therapy is the lipolytic effect (12, 13, 16-18). It is important in patients with GHD who are at risk of "secondary hyperlipoproteinemia" (13, 16, 19-21). Pac-Kożuchowska et al. (19, 20) reported higher mean levels of triglycerides, total cholesterol, VLDL fractions and serum apo-B in GHD children as compared to control and also lower levels of apo-AI and HDL cholesterol. The differences were not statistically significant (n = 27) but the authors suggest that lipid disorders in GH treated children need to be monitored and early atherosclerosis symptoms should not be underestimated.

The aim of our study was to assess the effect of nutritional status before the start of GH treatment on growth velocity observed during therapy. Statistical analysis revealed significant correlation between nutritional status of children before therapy and growth velocity after the first 12 months of treatment. For children with normal body weight or overweight before the start of GH treatment the response was statistically more significant. Weight increment was only slight for some overweight or obese children therefore weight-height parameters became normalized. The greatest recorded increment was approximately 20.8 kg at growth velocity of +12.8 cm/year. The *status quo* of children with poor nutritional status at the beginning of study did not change after a year of treatment with GH. Their weight increment was below the average for the whole group. It seems therefore warrented that physicians pay more attention to nutrition of both underweight and overweight children on GH therapy and rely on the expertise of dieticians. Parents must be instructed accordingly. Zadik et al. (22) reported decrease in serum iron levels after 12 month observations of 115 GH treated children and analysis of their diet and biochemical parameters. Multivariable analysis demonstrated caloric intake to be one of the crucial growth-promoting factors. In a study of Han et al. (23) 20 boys with constitutional growth delay were randomized to either observation or aggressive nutritional supplementation for 6 months. After 6 months, GH therapy was initiated in all subjects in both arms of the study and continued for a total of 12 months. Subjects who had been randomized to the nutrition group, continued nutritional supplementation for the full 18 months. No statistically significant differences in growth response between the two study groups were found. The study group was relatively small (n = 20) and the boys enrolled in the study had no GH deficiency. The authors provide no information on nutritional status before the start of GH treatment.

GH therapy is used for a variety of purposes in medical centers worldwide (5, 10, 11, 13-16, 22). Positive effects of GH therapy depend on numerous factors among which genetic, environmental and puberty factors also play an important role (24-28). Optimal diagnostic testing and mathematical models are being sought to determine the appropriate growth response to GH treatment. Another important motivation for GH therapy is to avoid metabolic complications related to growth hormone deficiency (28-30).

Observations from the first 12 months of GH treatment of our cohort of 200 children with GHD confirm the therapy to be effective. A significant improvement was reported as compared to growth velocity before GH treatment (9.11 ± 1.72 vs 4.85 ± 1.31 cm/year). Body height shortage was reduced and age of height

advancement by ca 1.5 year was reported. There is still however the need for a more detailed analysis of nutritional status of children before the start of the GH therapy and for control of body weight increments in order to achieve the best effects and to evade metabolic disorders (16-18, 20-22, 30, 31).

CONCLUSIONS

1. Malnutrition in children decreases the effect of growth hormone treatment.
2. Nutritional disturbances in children with Growth Hormone Deficiency (GHD) require intervention of a specialist.

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