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Growth response and metabolic effects of growth hormone therapy in appropriate-for-gestational-age growth hormone-deficient children in relation to birth size and gestational age: A preliminary study

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The aim of the study was to investigate the influence of birth weight (BW), birth length (BL) and gestational age (GA) on growth pattern and metabolic profile in appropriate-for-gestational-age (AGA) growth hormone-deficient children before and during recombinant human growth hormone (rhGH) therapy. Forty children with isolated idiopathic growth hormone deficiency underwent auxological and biochemical assessment at baseline and after 6 and 12 months of rhGH therapy. Biochemical analysis included: insulin-like growth factor I (IGF-I), adiponectin, resistin, fasting glucose, fasting insulin, total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG) and glycated haemoglobin (HbA1c). There was a tendency for positive association between BW and baseline height standard deviation score (SDS). GA correlated with baseline weight SDS (p=0.019) and BMI SDS (p=0.039). GA was associated with baseline fasting glucose (p=0.031), fasting insulin (p=0.027), HOMA-IR (p=0.010) and QUICKI (p=0.016). BW correlated with baseline HbA1c (p=0.032). After the initiation of rhGH therapy we did not find any significant relationships between birth size parameters or GA and metabolic profile of the studied children. In conclusion, our results suggest that AGA GH-deficient children born with higher birth size parameters and higher GA had better first-year growth response to rhGH therapy and better baseline metabolic profile, especially parameters of carbohydrate metabolism. In order to optimize the effects of rhGH therapy, higher rhGH doses should be considered in those GH-deficient children who were born with lower birth size and GA.

Key words: growth hormone deficiency, appropriate for gestational age, birth size, gestational age, recombinant human growth hormone therapy

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Abbreviations: AGA, appropriate for gestational age; BA, bone age; BL, birth length; BMI, body mass index; BW, birth weight; CA, chronological age; GA, gestational age; GHD, growth hormone deficiency; HA, height age; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; HV, height velocity; IGF-I, insulin-like growth factor-I; LDL-C, low-density lipoprotein cholesterol; QUICKI, quantitative insulin sensitivity check index; rhGH, recombinant human growth hormone; SDS, standard deviation score; SGA, small for gestational age, TG, triglycerides; total-C, total cholesterol.

INTRODUCTION

Growth hormone deficiency (GHD) and short stature in children born small for gestational age (SGA) are the most frequent indications for recombinant human growth hormone (rhGH) therapy in children and adolescents in Europe (Straetemans *et al.*, 2018). Good response to rhGH therapy depends on a variety of factors, which vary between different groups of treated children (Savage & Bang, 2012; Grimberg *et al.*, 2016; Deodati & Cianfarani, 2017; Korpysz & Szalecki, 2019). The main factors influencing the growth response to rhGH therapy in GH-deficient children are: severity of GH deficiency, chronological age, pubertal status and bone age delay at the beginning of therapy and rhGH doses (Ranke *et al.*, 1999; Ranke *et al.*, 2005; Kriström *et al.*, 2009; Wit *et al.*, 2013). The impact of birth weight (BW), birth length (BL) and gestational age (GA) on growth and metabolic status are well documented in children without GH deficit such as short SGA children or girls with Turner syndrome (Ranke *et al.*, 2000; Cianfarani *et al.*, 2006; Hernández & Mericq, 2011; Hong & Chung, 2018; Rapaport *et al.*, 2018; Hvidt *et al.*, 2019; Renes *et al.*, 2019), while in children with GHD born appropriate for gestational age (AGA) these associations are not so clear. Taking into account the fact that longitudinal growth depends not only on GH secretion, but also on a cluster of factors which influence individual sensitivity to its action (Kriström *et al.*, 2009; Witkowska-Sędek *et al.*, 2016; Deodati & Cianfarani, 2017; Witkowska-Sędek *et al.*, 2018; Pozzobon *et al.*, 2019), we hypothesized that birth size parameters and GA might influence growth and metabolic response to rhGH therapy also in GH-deficient children, even those born AGA due to a relatively wide reference range of those parameters. Confirmation of such relationships might be an additional argument in favour of the need for an individual approach to rhGH dosing in GH-deficient children.

The aim of our study was to investigate the influence of birth weight, birth length and gestational age on growth pattern and metabolic profile in AGA GH-deficient children before and in the first year of rhGH therapy.

MATERIALS AND METHODS

The protocol of the study was approved by the Bioethics Committee of the Medical University of Warsaw.

The study was prospective and was performed in the Department of Paediatrics and Endocrinology of the Medical University of Warsaw, Warsaw, Poland in accordance with the Declaration of Helsinki without any external financial support or funding. The study group included 40 children (mean baseline age 10.6±3.38 years, 24 boys and 16 girls) with isolated idiopathic GHD diagnosed based on the following criteria: maximal GH release – 10 ng/ml in a nocturnal test of spontaneous GH secretion and in two pharmacological tests with different stimuli (clonidine, insulin, arginine or glucagon). Median maximal GH release in pre-treatment diagnostic tests was 7.8 ng/ml (6.2–8.8). Turner syndrome was excluded in all the girls recruited by an analysis of karyotype. Chronic comorbidities or genetic syndromes that could lead to growth impairment were excluded in the course of GHD diagnosing. None of the patients recruited to the study had birth size parameters that fulfilled SGA criteria defined as BW and/or BL – 2 standard deviation score (SDS) for GA. None of the patients was born prematurely, median GA was 39 weeks (38–40 weeks). Mean BW was 3313±364 g, mean BL was 53.7±2.6 cm. Both of the birth size parameters (BW, BL) were expressed as SDS for sex and GA (Pawlus *et al.*, 2017). In all the patients recruited, anthropometric measurements were taken three times: at baseline (at the start of rhGH therapy) and after the first 6 and 12 months of therapy. Baseline height velocity (HV) was calculated based on two height measurements: the first taken 6 to 12 months before the initiation of rhGH therapy and the second taken at the start of therapy. Taking into account the fact that there are no reliable reference values for HV SDS for Polish children, first-year growth response to rhGH therapy was expressed as a reduction in height deficit (Δheight SDS) in that period. Body mass index (BMI) was calculated according to the following formula: weight (kg) divided by height in square meters (m^2). Height was expressed as SDS for chronological age (CA), weight and BMI were expressed as SDS for height age (HA) (Palczewska & Niedźwiecka, 2001). Bone age (BA) was evaluated using the Greulich and Pyle method at baseline and after 12 months of rhGH therapy (Greulich & Pyle, 1969). Recombinant human GH was given subcutaneously once daily at bedtime. Mean rhGH dose administered in the first 6 months of rhGH therapy was 0.187±0.01 mg/kg/week, mean rhGH dose in the whole first year of therapy was 0.188±0.01 mg/kg/week.

Biochemical measurements. lood samples were taken after an overnight fast. Biochemical analysis included the following parameters: pre-treatment GH serum concentrations in diagnostic tests and baseline and treatment serum levels of insulin-like growth factor I (IGF-I), adiponectin, resistin, fasting glucose, fasting insulin, total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG) and the value of glycated haemoglobin (HbA1c). Insulin resistance indices such as the Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) and the Quantitative Insulin Sensitivity Check Index (QUICKI) were calculated at baseline and after 12 months of rhGH therapy based on fasting glucose (mg/dl) and fasting insulin (μU/ml) concentrations (Singh & Saxena, 2010). Serum IGF-I levels were normalized for sex and BA and were expressed as SDS based on the normative data provided by the manufacturer (Siemens Healthcare Diagnostics Inc.). Serum concentrations of GH, IGF-I and fasting insulin were measured by immunoassay using IMMULITE 2000 Xpi Analyzer (Siemens, Erlangen, Germany). The concentrations of fasting glucose (glucose oxidase colorimetric method) and lipid profile parameters (total-C, LDL-C, HDL-C, TG) were determined in blood serum using Vitros 5600 analyzer (Ortho Clinical Diagnostics, Raritan, New Jersey, USA). The levels of HbA1c were measured in whole blood by ion-exchange high-performance liquid chromatography (HPLC) using D-10 Hemoglobin Analyzer (BIO-RAD, California, USA). Serum concentrations of adiponectin and resistin were measured by enzyme immunoassay ELISA test (Mediagnost, Gesellschaft für Forschung und Herstellung von Diagnostica GmbH, Reutlingen, Germany).

Statistical analyses. Data were analysed using Statistica 13.3. All data were tested for normality by the Shapiro-Wilk test and were reported as means ± standard deviation (S.D.), median, and interquartile ranges, as appropriate. Comparisons between baseline and treatment values of the same parameter were conducted using the repeated measures ANOVA with Bonferroni post hoc test for normally distributed data and the Friedman test with post hoc comparisons for non-normally distributed data. Correlation analyses were performed using the Pearson correlation test for normally distributed data and the Spearman correlation analysis for non-normally distributed data. A p value <0.05 was considered significant.

RESULTS

Characteristics of birth parameters of the study group are presented in Table 1. Characteristics of baseline and treatment values of all evaluated anthropometric and biochemical parameters with statistically significant changes occurring after the initiation of rhGH therapy are presented in Table 2.

Associations between BW, BL and GA and anthropometric parameters

After the initiation of rhGH therapy significant increases in height SDS were accompanied by significant decreases in weight SDS and BMI SDS (Table 2). All associations between BW, BL, GA and anthropometric parameters, which were evaluated at baseline and after the first 6 and 12 months of rhGH therapy are characterized in Table 3. Our analysis indicated that first-year growth response to rhGH therapy, expressed as a reduction in height deficit (Δheight SDS), was related to BL and GA. Nutritional status, both at baseline and during rhGH therapy, was better in children born with higher GA. BW did not significantly affect either the growth response to rhGH therapy or the nutritional status of the studied children.

Associations between BW, BL and GA and biochemical parameters

After the initiation of rhGH therapy, IGF-I values increased significantly, as expected. Serum levels of adi-

Table 1. Characteristics of birth parameters of the study group

Variable	Value at birth
Weight (g)	3313±364
Weight (SDS)	–0.45 (–0.95–0.00)
Length (cm)	53.7±2.6
Length (SDS)	–0.4 (–1.2–0.4)
Gestational age (weeks)	39.0 (38.0–40.0)

Data are presented as mean ± standard deviation (S.D.) or median with interquartile range, as appropriate; SDS, standard deviation score.

Table 2. Characteristics of baseline and treatment values of all evaluated anthropometric and biochemical parameters

Variable	Baseline	6 months	12 months
Chronological age (years)	10.6±3.38	11.1±3.38	11.6±3.38
Bone age (years)	8.5±3.5	–	9.9±3.5**
Anthropometric:			
Height SDS for CA	-2.5±0.5	-2.1±0.5**	-1.9±0.6**
Weight SDS for HA	0.0±0.7	-0.1±0.7*	-0.2±0.7*
BMI SDS for HA	0.0±1.0	-0.1±0.9	-0.2±0.9**
HV (cm/year)	5.4±1.3	9.6±1.9**	9.1±1.6**
Biochemical:			
IGF-I SDS	-0.6 (-1.3–0.1)	0.9 (0.4–2.2)**	1.0 (0.1–1.5)**
Adiponectin (ng/ml)	18473.5 (10036.6–30204.4)	21168.3 (13658.6–31189.5)	18398.0 (9306.2–19963.7)
Resistin (ng/ml)	3.8±1.3	3.8±1.2	3.7±0.9
Fasting glucose (mg/dl)	82.6±9.1	85.2±10.4	84.4±7.6
Fasting insulin (μlU/ml)	2.6 (2.0–4.4)	5.8 (3.2–8.7)*	8.3 (2.9–11.4)**
HbA1c (%)	5.2±0.3	5.3±0.3	5.2±0.3
HOMA-IR	0.56 (0.39–0.90)	1.30 (0.73–1.97)*	1.88 (0.84–2.40)*
QUICKI	0.43 (0.39–0.46)	0.37 (0.35–0.41)*	0.35 (0.33–0.39)*
Total-C (mg/dl)	171.5±24.7	168.1±25.6	164.1±24.2
LDL-C (mg/dl)	93.8±23.4	90.0±23.5	86.7±21.6
HDL-C (mg/dl)	63.5±19.1	61.9±18.2	59.9±17.7
TG (mg/dl)	65.5 (50.5–90.5)	67.0 (50.0–113.5)	85.0 (57.0–115.0)

Data are presented as mean±standard deviation (S.D.) or median with interquartile range (IR), as appropriate; SDS, standard deviation score; CA, chronological age; HA, height age; BMI, body mass index; HV, height velocity; IGF-I, insulin-like growth factor-I; HbA1c, glycated haemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; QUICKI, quantitative insulin sensitivity check index; Total-C, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; * $p<0.05$ *vs*. baseline value; ** $p<0.01$ *vs*. baseline value

ponectin, resistin, fasting glucose, total-C, LDL-C, HDL-C and TG, as well as HbA1c values did not change significantly during rhGH therapy. However, we noticed a significant increase in fasting insulin levels, which led to significant changes in both of the insulin resistance indices evaluated (Table 2). Correlation analysis mainly revealed significant associations between GA and baseline parameters of carbohydrate metabolism. Taking into account the fact that the power of the test for those associations varied from 0.6 to 0.74, those findings should be confirmed in a larger group of children. All the studied associations between BW, BL, GA and baseline values of biochemical parameters are presented in Table 4. After the initiation of rhGH therapy we did not find any significant relationships between GA or birth size parameters and metabolic profile of the studied group. Nevertheless, we noticed a tendency for a positive relationship between GA and adiponectin levels ($p=0.063$) and a negative one between GA and resistin levels ($p=0.089$) after 6 months of therapy. After 12 months of rhGH therapy we only found a tendency for lower LDL-C levels in children born with higher BW ($p=0.092$).

It is worth noting that GH deficit (maximum GH levels in pre-treatment diagnostic tests), baseline and treatment IGF-I levels and BA delay were not related to birth size parameters or GA.

DISCUSSION

Our findings suggest that AGA GH-deficient children born with higher birth size parameters and higher GA had better first-year growth response to rhGH therapy and better baseline metabolic profile, especially parameters of carbohydrate metabolism. Longitudinal growth, affected in postnatal life mainly by the GH/IGF-I axis, is a complex multifactorial process. The GH/IGF-I axis is regulated by a number of external and internal stimuli, including chronological age, gender, pubertal status, nutrition, sleep, body composition and exercise (Hartman *et al.*, 1993). Disturbances in GH and/or IGF-I secre-

Table 3. Characteristics of associations between birth weight, birth length, gestational age and anthropometric parameters at baseline and during rhGH therapy

	BW	BL	GA
Height SDS for CA			
At baseline	$p=0.09$*	ns	ns
6 months	ns	ns	ns
12 months	ns	ns	ns
Delta height SDS			
after 6 months	ns	R=0.45, $p=0.017$	ns
after 12 months	ns	R=0.52, $p=0.041$	R=0.52, $p=0.034$
Weight SDS for HA			
At baseline	ns	ns	R=0.37, $p=0.019$
6 months	ns	ns	R=0.33, $p=0.041$
12 months	ns	ns	$p=0.061$*
BMI SDS for HA			R=0.33, $p=0.039$
At baseline	ns	ns	ns
6 months	ns	ns	$p=0.051$*
12 months	ns	ns	

BW, birth weight; BL, birth length; GA, gestational age; SDS, standard deviation score; CA, chronological age; HA, height age; BMI, body mass index; *almost significant; ns, not significant

Table 4. Characteristics of associations between birth weight, birth length, gestational age and baseline biochemical parameters

	BW	BL	GA
IGF-I SDS	ns	ns	ns
Fasting glucose (mg/dl)	ns	ns	R=-0.34, p=0.031
Fasting insulin (μIU/ml)	ns	ns	R=0.35, p=0.027
HOMA-IR	ns	ns	R=-0.40, p=0.010
QUICKI	ns	ns	R=0.38, p=0.016
HbA1c (%)	R=0.34, p=0.032	ns	ns
Adiponectin (ng/ml)	ns	ns	p=0.055*
Resistin (ng/ml)	ns	ns	ns
Total-C (mg/dl)	ns	ns	ns
LDL-C (mg/dl)	ns	ns	ns
HDL-C (mg/dl)	ns	ns	ns
TG (mg/dl)	ns	ns	ns

BW, birth weight; BL, birth length; GA, gestational age; HOMA-IR, homeostasis model assessment of insulin resistance; QUICKI, quantitative insulin sensitivity check index; HbA1c, glycated haemoglobin; Total-C, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; *almost significant; ns, not significant

tion or action lead to growth impairment and could be an indication for rhGH therapy. Gaining a better understanding of the pathophysiology of GH/IGF-I action is crucial for increasing the effectiveness of rhGH therapy. Several previous studies indicate that responsiveness to this therapy depends on a variety of factors which are not identical in different groups of children treated with rhGH. Severity of GH deficit seems to be the most powerful factor influencing the growth response in children with isolated GHD, while in conditions with short stature but without GH deficit, such as Turner syndrome or short stature in children born SGA, other factors gain importance (Ranke *et al.*, 1999; Ranke *et al.*, 2000; Ranke *et al.*, 2005; Wit *et al.*, 2013; Straetemans *et al.*, 2018). It has been confirmed that birth parameters have a significant influence on growth pattern and metabolic profile in patients without GH deficit (Hong & Chung, 2018; Wang *et al.*, 2018; Renes *et al.*, 2019; Ranke *et al.*, 2000). Nevertheless, the influence of those factors on the response to rhGH therapy has also been evaluated in GH-deficient children. Mathematical models identify BW as one of the main factors determining growth response to rhGH therapy in prepubertal GHD children (Ranke *et al.*, 1999; Ranke *et al.*, 2005).

In our study we evaluated whether GA and birth size parameters influence the growth response and metabolic status in appropriate-for-gestational-age GH-deficient children born at term before the initiation of rhGH therapy and in the first year of rhGH therapy. Confirming those relationships could support the need for individual approach to rhGH dosing in this group of children and may emphasize the importance of birth parameters in conducting such therapy. Our study indicated that higher BW was associated with lower baseline height deficit, while GA was related positively to baseline weight SDS and BMI SDS for HA. On the other hand, after the initiation of rhGH therapy, BL and GA influenced positively the growth response to rhGH therapy. Ranke *et al.* (2005), who compared two groups of children with idiopathic GHD: very young children with rhGH therapy started at less than 3 years of age and older prepubertal children with rhGH therapy started at 7–8 years of age, confirmed that BW SDS, as well as current weight SDS, is one of the most important predictors positively related to the first-year growth response in both age groups. Simultaneously, in the model derived from the younger children, the numerical influence of BW SDS and weight SDS was lower than in the older group. Ranke and others (Ranke *et al.,* 1999) indicate that while the strong predictive value of height deficit, baseline chronological age, severity of GH deficit, and rhGH dose as important factors predicting the first-year growth response to rhGH therapy is compatible with our understanding, there is no simple explanation for why BW and current weight are also independent predictors in mathematical models. They hypothesized that BW reflects the overall organism responsiveness to growth-promoting factors, whereas current weight may reflect the eating habits and metabolic handling of nutrition by the organism (Ranke *et al.*, 1999). In our study we did not notice any relationship between current weight and Δheight SDS in the first year of rhGH therapy. It is worth noting that we did not find any relationships between birth size parameters or GA and severity of GH deficit, BA delay and baseline or treatment IGF-I serum levels, IGF-I SDS and changes in IGF-I or IGF-I SDS after the initiation of rhGH therapy.

A number of studies describe the effect of being born SGA on growth response during rhGH therapy in GH-deficient children, while only some papers evaluate those associations in GH-deficient children born AGA (Balsamo *et al.*, 1995; Achermann *et al.*, 1998; Di Cesare Merlone *et al.*, 2005; Meazza *et al.*, 2013). Meazza and others (Meazza *et al.,* 2013), who compared long-term response to rhGH therapy (including the first 5 years of treatment) in GH-deficient children born SGA or AGA, concluded that birth size is an important factor affecting the effectiveness of such treatment. Their results indicate that BW affects both growth during childhood and response to rhGH therapy. They also noticed that their study confirmed results from previous researchers showing a better response to rhGH therapy both during the first year and after the first 3 years of treatment in those GH-deficient children who were born AGA than in those born SGA (Balsamo *et al.*, 1995; Achermann *et al.*, 1998). Poorer response to rhGH therapy in GH-deficient children born SGA seems to be related mainly to reduced GH sensitivity (de Waal *et al.*, 1994; Chatelain

et al., 1996; Maiorana & Cianfarani, 2009). On the other hand, the results of studies evaluating the impact of BW on final height in children with GHD are contradictory; some of them showed that GH-deficient children born SGA reach lower final height than GH-deficient children born AGA (Cacciari *et al.*, 1999; Zucchini *et al.*, 2001), while others authors reported that BW has no significant impact on final height in children with GHD (Di Cesare Merlone *et al.*, 2005).

Apart from the evaluation of the influence of birth size parameters and GA on growth response to rhGH therapy, we focused on the impact of those parameters on baseline and treatment metabolic profile in AGA GH-deficient children. We found that children born with higher, but within normal range, GA had lower fasting glucose and insulin levels, lower HOMA-IR and higher adiponectin levels and QUICKI at baseline. The impact of BW was not so significant; at baseline BW was related only to HbA1c values. After the initiation of rhGH therapy we found a tendency for a positive relationship between GA and serum adiponectin levels and a negative one between GA and serum resistin levels after the first 6 months of therapy. Nevertheless, taking into account the fact that our study consisted of 40 GH-deficient children, our results should be confirmed in a larger group of patients and should be considered as a pilot study. In the literature most studies focused on the impact of birth size parameters and GA on metabolic pattern in short children born SGA without GHD, while the number of papers evaluating carbohydrate and lipid metabolism in GH-deficient children according to their birth parameters is scanty. Epidemiological studies have confirmed close relationships between reduced birth size parameters and long-term risk for overweight and obesity, insulin resistance, type 2 diabetes, hypertension and cardiovascular disease in adulthood (Forsén *et al.*, 2000; Ong *et al.*, 2000; Eriksson *et al.*, 2002). Although the exact mechanisms regulating the relationships between birth size and growth in childhood are not well described, the influence of adipokines and hormones, as well as a number of growth factors, are also postulated (Bozzola *et al.*, 2010; Oświęcimska *et al.*, 2017; Ciresi *et al.*, 2018; Renes *et al.*, 2019). Several changes in carbohydrate and lipid metabolism occurring after the initiation of rhGH therapy in GH-deficient children are related mainly to the action of the GH/IGF-I axis itself and, especially in adolescents, to the influence of sex steroids (Møller & Jørgensen, 2009; Rothermel & Reinehr, 2016; Stawerska *et al.*, 2017; Ciresi & Giordano, 2018; Witkowska-Sędek *et al.*, 2018). On the other hand, our data indicate that, similar to results reported in short children born SGA without GHD, birth size parameters and GA seem to influence growth pattern and metabolic profile in children with GHD born AGA. In order to optimize effects of rhGH therapy, higher rhGH doses should be considered in those AGA GH-deficient children who were born with lower birth size and GA.

Conflict of Interest Statement

The authors declare no conflict of interest in relation to this article.

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