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Growth response, psychosocial problems, and quality of life in children with growth hormone deficiency

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ABSTRACT

Aim: To establish an association between growth response to recombinant human growth hormone (rhGH) therapy and clinical and anthropometric parameters, d3-GHR polymorphism, psychosocial problems, and quality of life (QoL) in children with growth hormone deficiency (GHD).

Material and methods: The study included 46 prepubescent children with GHD and 80 healthy prepubescent children. To analyse growth re-sponse predictors for the rhGH therapy, a number of clinical and anthropometric parameters were selected. The poly-morphism of exon 3 of the *GHR* gene was determined using multiple PCR amplification. Psychosocial functioning was assessed by the Strengths and Difficulties Questionnaire. The self-esteem was studied by the Dembo-Rubinstein method. The QoL was determined using the Peds QL4.0 questionnaire. Assessment of differences between the mean values of 2 independent variation series by the value of *p* was performed. The relationship between predictors and growth response was assessed using the Spearmen coefficient of correlation.

Results: An association was found between height velocity (HV) (cm/yr; SDS) and chronological age, compliance, birth weight, height, height (SDS)-MPH (SDS), weight, peak GH response, rhGH dose, and d3-GHR/fl/l-GHR. The results suggest that the d3-GHR explains the better responsiveness to the rhGH therapy only for the first but not for the second year. The rhGH therapy leads to an improvement in the psychoemotional state, QoL, and self-esteem of children.

Conclusions: HV at the start of therapy, acceptable compliance, birth weight, growth at the start of therapy, height (SDS) – MPH (SDS), weight at the start of therapy, peak growth hormone response, and genotype d3-GHR are associated with the growth response to rhGH therapy. During the first and second years of therapy, a positive effect on the psychoemotional state, quality of life, and self-esteem of children with GHD was noted.

KEY WORDS:

quality of life, self-esteem, growth hormone deficiency, growth response, psychosocial problems.

INTRODUCTION

Current recommendations for recombinant human growth hormone (rhGH) therapy in children and adolescents with growth hormone deficiency (GHD) are well established and have a high level of evidence [1]. Controversies in the diagnosis and management of GHD in children include the principles of choosing and changing the dose of rhGH, as well as the identification of children who are not responsive to replacement therapy [2, 3]. In this regard, it is important to clarify the controversial and insufficiently studied role of exon d3/fl polymorphism of the growth hormone receptor in modulating the response to replacement therapy [4, 5]. Important criteria for evaluating the results of therapy with exogenous growth hormone can be not only the growth response, but also psychosocial and behavioural problems, which change significantly in children with GHD [6]. Researchers are trying to fill

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the gap in our knowledge about the association between the psychoemotional state, and self-esteem, quality of life (QoL) in children with GHD and height velocity as well as the correlation between clinical parameters, d3-GHR genotype, and growth response to rhGH.

MATERIAL AND METHODS

This prospective study with at least 2 years of observation of patients was conducted 2012–2020 at Odesa Regional Children's Clinical Hospital (Odesa, Ukraine). Informed consent was obtained from all children and parents in accordance with the provisions of the Helsinki Declaration and the principles of Good Clinical Practice. The inclusion criteria were the diagnosis of GHD in prepubescent children based on relevant clinical, auxological, paraclinical findings, and peak growth hormone levels in provocative testing (< 10 ng/ml). The non-inclusion criteria were other causes of short stature in children. There was no patient exclusion from the follow-up. The final size of the sample was 46 prepubescent children with GHD (12 girls and 34 boys) aged 8.0-12.1 years (M = 9.8; SD = 3.1), including 16 children with multiple pituitary hormone deficiencies and 30 with isolated GHD. Eighty prepubescent children (35 girls and 45 boys) with normal height at the age of 8.1-12.0 years (M = 9.6; SD = 2.7) were selected for the control group during the examination on the "healthy child's day" at the Outpatient Department. All the children received rhHG at an average dose of 0.033 mg/kg/day.

To analyse growth response predictors for the first year of rhGH therapy, a number of clinical and paraclinical parameters were selected. The indicator of optimal and suboptimal growth response was the height velocity. The exon 3-deleted/full-length GHR genotypes were determined using a gel-based triplex PCR technique [7]. Psychosocial problems were assessed using the Strengths and Difficulties Questionnaire (SDQ) [8] on scales "total difficulties", "emotional problems"; "behavioural problems"; "hyperactivity/inattention"; "peer problems", "internalizing problems", "externalizing problems". Higher scores corresponded to greater severity of problems. The level of assertion, self-esteem, and the difference between the level of claims and self-esteem were determined by the Dembo-Rubinstein method [9]. QoL was determined using the Pediatric Quality of Life Inventory 4.0 Generic Score Scales (Peds QL4.0 scales) questionnaire [10] on the scales "total score", "physical health", "psycho-social health", "emotional functioning", "social functioning", and "school functioning". Higher scores corresponded to better QoL.

The Mann-Whitney test was used to analyse binary predictors. Evaluation of quantitative variables was carried out using the *t*-test method and the Spearmen coefficient of correlation. Statistical processing of the results by estimating the differences between the mean values of 2 independent variation series by the value of p was performed. The p-value ≤ 0.05 was considered to be statistically significant. To check the statistical hypothesis on differences in relative frequencies, in 2 independent samples, the criteria of χ^2 was used [11].

Aim of the study was to establish an association of growth response to exogenous growth hormone with clinical and anthropometric parameters, d3-GHR polymorphism, psycho-social problems, and quality of life in children with GHD.

RESULTS

According to the results of the first year of rhGH therapy in children with GHD, the height velocity (HV) was 11.1 ±2.9 cm/yr; HV (SDS) 3.82 ±2.53; Δ height (SDS) 0.99 ±0.68. After the second year of replacement therapy, HV was 8.0 ±2.1 cm/yr; HV (SDS) 2.82 ±2.10; Δ height (SDS) 0.87 ±0.62. These parameters were not statistically different in children with multiple pituitary hormone deficiency compared with children with isolated GHD (p = 0.18; Mann-Whitney test) and had no gender differences (p = 0.17; Mann-Whitney test). According to the consensus conclusion, the replacement therapy was considered effective and growth response optimal when Δ height (SDS) > 0.5 after the first year of therapy. A suboptimal growth response was regarded as a consequence of low compliance or insensitivity to growth hormone [1].

Correlation analysis was used to assess potential predictors of the growth response of children with GHD to rhGH therapy. The clinical characteristics of the disease, auxological measurements, and biochemical and genetic parameters were taken into account. It was found that among the potential clinical predictors of growth response, compliance and chronological age at the start of rhGH therapy had a significant correlation with HV (Tables 1 and 2). Auxological indicators that had a correlation with

TABLE 1. Binary parameters as predictors for the first-year growth response to rhGH therapy. Height velocity (HV) in prepubertal children with GHD

Parameter	HV (cm/yr), correlation coefficient (r)	p-value	HV (SDS), correlation coefficient (r)	p-value
Gender (male/female)	0.122	0.48	0.132	0.52
GHD (IGHD/MDPH)	0.110	0.38	0.120	0.43
Compliance (acceptable/unacceptable)	0.280	< 0.03	0.244	< 0.03
Genotype d3-GHR/fl/fl-GHR	0.482	< 0.01	0.412	< 0.01

TABLE 2. Quantitative clinical/auxological parameters in prepubertal children with growth hormone deficiency for analysis of predictors for first-year growth response

Parameter	HV (cm/yr), correlation coefficient (*r*)	*p*-value	HV (SDS), correlation coefficient (*r*)	*p*-value
Chronological age (CA) (yr)	–0.364	< 0.04	–0.386	< 0.04
Bone age (BA) (yr)	–0.202	0.06	–0.218	0.08
BA/CA	–0.106	0.25	–0.186	0.17
Distance between BA and CA	0.164	0.34	0.176	0.44
Birth length [cm]	0.115	0.24	0.096	0.35
Birth length (SDS)	0.106	0.22	0.098	0.37
Birth weight [g]	0.240	0.10	0.260	0.10
Birth weight (SDS)	0.292	< 0.02	0.274	< 0.02
Father's height [cm]	0.128	0.16	0.188	0.13
Father's height (SDS)	0.215	0.11	0.198	0.21
Mother's height [cm]	0.194	0.34	0.255	0.49
Mother's height (SDS)	0.110	0.54	0.102	0.70
MPH (midparental height, cm)	0.222	0.21	0.298	0.21
MPH (midparental height, SDS)	0.344	0.23	0.355	0.28
Height (SDS) – MPH (SDS)	0.340	< 0.01	0.360	< 0.01
HV/previous year [cm/yr]	0.468	0.11	0.358	0.12
HV/previous year (SDS)	0.446	0.14	0.424	0.12
Height at the start of therapy [cm]	0.102	0.13	0.106	0.15
Height at the start of therapy (SDS)	0.384	< 0.01	0.406	< 0.01
Weight at the start of therapy [kg]	0.361	0.41	0.318	0.36
Weight at the start of therapy (SDS)	0.304	< 0.03	0.322	< 0.03
Body mass index (BMI) at start	0.317	0.22	0.298	0.34
BMI (SDS) at start	0.225	0.11	0.355	0.11
IGF-1 [ng/ml]	0.306	0.72	0.286	0.22
IGF-1 (SDS)	0.320	0.55	0.289	0.45
Peak GH response [ng/ml]	0.521	< 0.01	0.563	< 0.01
rhGH dose [ME/kg/week]	0.298	< 0.05	0.288	< 0.05

HV were birth weight (SDS), height (SDS) – MPH (SDS), height at start (SDS), and weight at start (SDS). Among the metabolic and genetic parameters, the peak GH level in provocative testing and the d3-GHR genotype had a predictive value regarding the growth response to rhGH therapy (Table 2).

The effect of d3GHR on baseline height (SDS) in children with GHD without previous rhGH treatment was assessed. The last was higher in patients with the d3-GHR genotype than in children with the fl/fl-GHR genotype (–3.3 ±0.1 vs. –3.6 ±0.1, $p = 0.04$). The "height (SDS) – MPH (SDS)" index was higher in the GHRd3 than in the fl/fl-GHR groups (–2.1 ±0.1 vs. –2.6 ±0.2, $p = 0.03$). A higher HV was detected in children with the d3-GHR genotype compared to children with the fl/fl-GHR genotype (12.7 ±0.8 vs. 10.5 ±0.7, $p = 0.04$) after the first year of r-hHG therapy. HV in children with the d3-GHR genotype (7.9 ±2.0 cm/year) did not have statistical differences compared with children with the fl/fl-GHR genotype (8.1 ±1.9 cm/year, $p = 0.25$) according to the results of the second year of therapy.

The effectiveness of rhGH therapy was assessed taking into account the dynamics of psychological problems, changes in the QoL, and decrease in self-esteem, which were previously identified in children with GHD [6]. The positive effect of rhGH in children with GHD was confirmed by a decrease in the severity of psycho-social problems according to the SDQ scale. The scores for total difficulties, emotional problems, peer problems, and internalizing problems did not differ from the indicators of children in the control group after the first year and the second year of replacement therapy (Table 3). A correlation between suboptimal growth response after first-year rhGH therapy and the total-difficulties score was found: OR 2.0

TABLE 3. Strengths and Difficulties Questionnaire (SDQ) scores for psychosocial problems in children with growth hormone deficiency

SDQ scores	Control group ($n = 80$) M ±SD	T 0 ($n = 46$) M ±SD	T 12 ($n = 46$) M ±SD	T 24 ($n = 46$) M ±SD
	1	2	3	4
Total difficulties score	10.2 ±5.6	13.0 ±9.1*	10.1 ±4.0	10.0 ±4.5
Hyperactivity/inattention score	3.7 ±1.9	4.3 ±3.2	3.5 ±2.7	3.5 ±2.8
Behavioural problems score	2.0 ±1.5	2.1 ±1.3	1.9 ±1.2	2.0 ±1.3
Emotional problems score	2.4 ±2.0	3.5 ±3.1*	2.5 ±1.5	2.5 ±1.9
Peer problems score	2.1 ±1.6	3.1 ±3.0*	2.1 ±1.3	2.0 ±1.4
Internalizing problems score	4.5 ±1.7	6.6 ±5.3*	4.6 ±3.8	4.5 ±2.7
Externalizing problems score	5.7 ±3.4	6.4 ±3.3	5.5 ±3.5	5.5 ±3.7

**P1–2 < 0.05; P1–3 < 0.05; P1–4 < 0.05*
Baseline (T 0), and after 12 (T 12) and 24 (T 24) months of rhGH therapy

TABLE 4. Peds QL4.0 scores for quality of life of children with growth hormone deficiency

Peds QL4.0 scores	Control group ($n = 80$) M ±SD	T 0 ($n = 46$) M ±SD	T 12 ($n = 46$) M ±SD	T 24 ($n = 46$) M ±SD
	1	2	3	4
Total score	87.4 ±10.6	82.9 ±9.6*	86.8 ±8.1	88.0 ±7.2
Physical health	89.7 ±8.0	86.2 ±10.8*	89.9 ±6.1	90.7 ±8.0
Psychosocial health	84.9 ±10.9	79.6 ±11.6*	83.7 ±7.4	85.4 ±7.8
Emotional functioning	81.7 ±12.1	76.8 ±14.1*	82.5 ±10.8	82.7 ±11.2
Social functioning	91.7 ±11.2	86.7 ±17.1*	92.3 ±8.8	92.9 ±12.0
School functioning	81.3 ±14.3	75.4 ±16.2*	76.3 ±11.0	80.6 ±11.9

**P1–2 < 0.05; P1–3 < 0.05; P1–4 < 0.05*
Baseline (T 0), and after 12 (T 12) and 24 (T 24) months of rhGH therapy

TABLE 5. Level of self-esteem and assertions in children with growth hormone deficiency

Indicator	Control group ($n = 80$) *n*; % (95% CI)	T 0 ($n = 46$) *n*; % (95% CI)	T 12 ($n = 46$) *n*; % (95% CI)	T 24 ($n = 46$) *n*; % (95% CI)
	1	2	3	4
Low level of assertions (< 60 points)	(1.7–13.3)	9; 19.6 (8.1–31.1)*	8; 17.4 (6.4–28.4)	2; 4.3 (–1.6–10.2)
Low level of self-esteem (< 45 points)	5; 6.2 (0.9–11.5)	8; 17.4 (6.4–28.4)*	2; 4.3 (–1.6–10.2)	2; 4.3 (–1.6–10.2)
Weak discrepancy between assertions and self-esteem (< 7 points)	7; 8.7 (2.5–14.9)	10; 21.7 (9.8–33.6)*	7; 15.2 (4.8–25.6)	3; 6.5 (–0.6–13.6)

n – absolute number of children; % – relative number of children
**P1–2< 0.05; P1–3 < 0.05; P1–4 < 0.05 baseline (T 0), and after 12 (T 12) and 24 (T 24) months of rhGH therapy*

(1.8–2.3), $p < 0.001$. The suboptimal growth response had an impact on internalizing problems: OR = 2.5 (1.3–3.2), $p < 0.05$. There was a normalization of QoL according to the Peds QL4.0 scales for the total score, physical health, psychosocial health, emotional functioning, social functioning, and school functioning as a result of first-year and second-year rhGH therapy (Table 4). A correlation was found between QoL and optimal growth response to the first-year replacement therapy (rs = 0.44, $p < 0.05$). A significant result of 12 and 24 months of rhGH therapy in children with GHD was a decrease in the frequency of low self-esteem, low level of aspirations, and slight discrepancy between the levels of aspirations and self-esteem (Table 5).

DISCUSSION

The high frequency of an unacceptably weak response to the rhGH therapy actualizes the problems of its prediction, identification, prevention, and correction within the framework of the developed standards for managing children with GHD. The prospects for improving mathematical models of the growth response of children with GHD to exogenous GH are to increase the proportion of explained variance and reduce the standard error of regression [3]. The study showed the role of compliance, including the accuracy of everyday injection of rhGH by patients, as a strong factor in the growth response to the rhGH therapy. The data obtained confirm the validity of predicting the growth response to the rhGH based on age at the beginning of therapy, birth weight, weight at the beginning of therapy, "height (SDS) – MPH (SDS)", and the peak of GH in provocative testing [12]. However, in our study, the dose of rhGH was not informative as a predictor of growth response, probably because the treatment was carried out according to the standard dose of 0.033 mg/kg/day. Another difference was the finding of a correlation between HV (SDS) and height at start of therapy (SDS) in children with GHD.

The controversy in the literature on the impact of the d3-GHR polymorphism on growth is likely to be because mathematical models did not fully consider confounding factors. Intending to clarify this controversy, we analysed the clinical and genetic data generated in a prospective observational cohort study. The study indicates that d3-GHR is associated with increased HV during the first year of rhGH treatment, which is consistent with the data of a number of studies [13, 14]. However, growth response to the second year of the rhGH treatment does not depend on the GHRd3 polymorphism [15]. Accounting on d3-GHR genetic polymorphism may increase the predictive value of growth response models in children with GHD.

Because height gain cannot be considered the only goal of the rhGH therapy, the influence of the optimal growth response on the psycho-emotional state, QoL, and self-esteem of children with GHD has been studied. The listed parameters were assessed in comparison with the control group in the dynamics of substitution therapy (T0; T12; T24) as indicators of psychosocial adaptation and a criterion of specific psychological functioning. The study confirms the evidence that psychosocial deprivation in children can be associated with GHD and short stature [16]. The improvement in psycho-social parameters, QoL, and self-esteem as a result of the first year of substitution therapy, judging by the results obtained after the second year of rhGH treatment, was sustainable. The study shows the importance of adherence and its impact on treatment outcomes and quality of life. These data can be used in the program of automated health monitoring for the management of growth disorders recom mended by Dunkel *et al.* [17].

Although the study deepens knowledge about the impact of the optimal growth response on psychoemotional indicators, QoL, and self-esteem of children with GHD and refines the possibilities of predicting growth based on the combined use of clinical, auxological, and genetic predictors, it nevertheless has limitations associated with the study of only short-term results of therapy for children with GHD and the absence of a comparison group in which rhGH treatment is carried out due to other causes of short stature. Although the SDQ and Peds QL4.0 scales are widely used in Ukraine, their validity is not yet proven for all contexts and target groups. The prospect of further research is to assess the long-term results of the rhGH in the context of QoL, self-esteem, and psychosocial problems in children with GHD, as well as to improve the prediction of growth response based on multiple regression analysis of potential predictors and genetic data. The pharmacogenetic effect associated with the d3GHR polymorphism might be considered to be included in future logistic regression models.

CONCLUSIONS

A number of indicators such as "HV at the start of therapy", "acceptable compliance", "birth weight", "growth at the start of therapy", "height (SDS) – MPH (SDS)", "the weight at the start of therapy", "peak GH response", and "genotype d3-GHR" showed significant correlation with the growth response to the rhGH therapy of children with GHD. The d3-GHR polymorphism explains the better growth response to rhGH therapy for the first but not for the second year.

During the first year and the second year of rhGH therapy, there was a normalization of the level of total difficulties score, emotional problems, peer problems, problems of internalization, level of self-esteem, level of assertions, and improvement in QoL, including physical health, psychosocial health, emotional functioning, social functioning, and school functioning in children with GHD.

The optimal growth response of children with GHD to the first year of the rhGH therapy is associated with a decrease in the level of general psychological problems according to the SDQ scale: OR = 2.0 (1.8–2.3), $p < 0.001$. Suboptimal growth response affects the conceptualization of internalizing problems: OR = 2.5 (1.3–3.2), $p < 0.05$ and is associated with a decrease in QoL according to the Peds QL4.0 scale (rs = 0.44, $p < 0.05$).

DISCLOSURE

The authors declare no conflict of interest.

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