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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

THE ROLE OF HORMONAL STATUS IN GROWTH RETARDATION IN PRESCHOOL-AGED CHILDREN BORN PRETERM

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Field of science:	Medical Sciences
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GENERAL DESCRIPTION OF THE WORK

Relevance of the research. Physical development is one of the principal criteria of a child's health status. Physical developmental delay not only reflects unsatisfactory development of the child's organism, but also predisposes to a number of diseases and leads to impaired psychological and social adaptation[1].

The severity of the condition of preterm infants is determined, on the one hand, by morphofunctional immaturity and, on the other, by the consequences of intensive care[2]. In children who have experienced hypoxia, damage occurs not only to the central nervous system (CNS) but also to other organs and systems. In most cases, however, these lesions remain unrecognized. In this regard, hypoxia-related damage to the endocrine system may underlie various developmental disorders in this group of children later in life. Therefore, identifying the causes of this problem in children with physical developmental delay is of great importance[3].

Inadequate monitoring of growth in preschool children with physical developmental delay, as well as difficulties in organizing the proper diagnostic work-up of children with growth retardation, frequently lead to the development of various somatic and metabolic disorders[4].

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[2] Iutinsky E.M., Zheleznov L.M., Dvoryansky S.A. Sex differences of the fetus and maternal anthropometry: analysis of their influence on newborn weight // Siberian Scientific Medical Journal. 2025;45(3):61–68. doi: 10.18699/SSMJ20250306 [in Russian]

[3] Khmilevskaya S.A., Zryachkin N.I., Shcherbatyuk E.S., et al. Current state of the problem of nursing extremely preterm infants // Pediatrician (St. Petersburg). 2017;8(2):81–88. doi: 10.17816/PED8281-88 [in Russian]

[4] Fleig, L. Growth outcomes of small for gestational age preterm infants before and after implementation of an exclusive human milk-based diet / L.Fleig, J.Hagan, M.L.Lee // Journal of perinatology: official journal of the California Perinatal Association, - 2021. vol. 41 (8), - p. 1859-1864.https://doi.org/10.1038/s41372-021-01082

According to the latest protocols of the European and American Endocrine Societies, initiation of growth hormone (GH) therapy after the age of 2–4 years in children born preterm and small for gestational age (SGA) with physical developmental delay not only helps them attain their target final height, but also helps prevent metabolic disturbances that may develop in these children in the future. Indeed, published studies indicate that GH therapy is particularly important in these children for the prevention of impaired carbohydrate metabolism and insulin resistance[5]. Furthermore, thyroid disorders are among the endocrine pathologies most frequently encountered in children with short stature and growth retardation. Another relevant aspect of the topic is the investigation of gluten enteropathy, a chronic intestinal disease that may cause growth retardation, and the prescription of an appropriate diet in affected children to promote full recovery of somatic development[6].

For the first time, the present study investigated mutant GH1 gene polymorphisms using a next-generation sequencing (NGS) panel as a cause of growth retardation due to growth hormone deficiency (GHD)[7].

Numerous studies have examined the diagnosis of GHD and the beneficial effects of its treatment in growth retardation among children born SGA. However, no such comprehensive study has been conducted in preterm-born children in whom physical developmental delay is detected at 3–5 years of age.

The purpose of the study. The aim of the study was to investigate the hormonal status of preterm-born preschool children

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[6] Arjunan A, Sah DK, Woo M, Song J.Cell Biosci /Identification of the molecular mechanism of insulin-like growth factor-1 (IGF-1): a promising therapeutic target for neurodegenerative diseases associated with metabolic syndrome.//2023Jan 23;13(1):16. doi: 10.1186/s13578-023-00966-z.PMID: 3669108

[7] Vasques, G.A. IHH Gene mutations causing short stature with nonspecific skeletal abnormalities and response to growth hormone therapy / J Clin Endocrinol Metab. 2018 Feb 1;103(2):604-614. PMID: 29155992 doi: 10.1210/jc.2017-02026

with physical developmental delay and to predict the optimal treatment.

Research Objectives.

1. To determine the somatic status of preterm-born preschool children with physical developmental delay.
2. To substantiate the diagnosis of short stature on the basis of anthropometric assessment in preterm-born preschool children with physical developmental delay.
3. To evaluate the hormonal system (IGF-1, IGFBP-3, cortisol, prolactin, fT4, TSH) in preterm-born preschool children with physical developmental delay.
4. To evaluate mutant polymorphisms of the GH1 gene using a genetic panel in preterm-born preschool children with physical developmental delay.
5. To diagnose GHD by means of GH stimulation tests and to predict the outcome of GH therapy in preterm-born preschool children with physical developmental delay.

Research methods.

The research was conducted during 2020–2024. The study was performed retrospectively and prospectively at the Republican Endocrinology Center and the K.Y. Farajova Scientific Research Institute of Pediatrics (SRIP). The required laboratory investigations were carried out at the "Referans" clinic and the Endocrinology Center.

Main propositions of the Dissertation for Defense:

- Comprehensive anamnestic, anthropometric, clinical-laboratory and instrumental examinations established the severity of developmental delay and the final height prognosis in preschool children;
- Hormonal evaluation of preschool children with developmental delay identified the causes of short stature and enabled appropriate targeting of treatment;
- Investigation of genes responsible for short stature in preterm-born preschool children with developmental delay demonstrated that GH1 is not the principal mutant gene in isolated growth hormone deficiency;

- The studies conducted in preschool children with developmental delay established that timely initiation of somatotropin therapy at an optimal dose is required to attain genetic target height.

Scientific novelty of the study:

- Persistence of anthropometric parameters below −2 SDS up to the age of 1 year allows prediction of continued physical developmental delay at preschool age;

- A more pronounced height SDS deficit was observed in children born with very low birth weight (1A1) and in term-born children appropriate for gestational age (2A); thus, being born SGA was identified as a lower risk factor for physical developmental delay than preterm birth (1B SDS < 2B SDS);

- The outcome of GH therapy was predicted in preterm-born SGA preschool children with short stature, and a more effective level of the initial maximal therapeutic dose was determined;

- Investigation of GH1 variants in children with isolated short stature revealed statistically significant group differences in the single-nucleotide variants rs6171, rs695, rs2005172 and rs11568827, the rs11568827 variant having been detected only in the present study.

Theoretical and practical significance of the study:

- Assessment of anthropometric, laboratory and instrumental parameters in preschool children with developmental delay established the time of onset and the severity of the delay;

- The doses and duration of action of GH therapy in children with short stature were refined according to gestational age;

- The GH1 gene was investigated in children with isolated growth hormone deficiency, and the detection of changes in several alleles proved to be of diagnostic value.

Implementation of the results. The results of the study have been implemented at the Endocrinology Center of the Republic of Azerbaijan and in the endocrinology departments of hospitals.

Approbation and application of the study: The results of the study were presented at various conferences and congresses: “Growth hormone deficiency in children: diagnosis and treatment”, K.Y. Farajova Scientific Research Institute of Pediatrics (2021, oral presentation); “Neonatal hypoglycemia and its treatment”, First Pediatric Endocrinology

Conference in Azerbaijan (2022, oral presentation); conference trainer on "Diabetes mellitus in children" under the Temporary Rules on Continuing Professional Development of Physicians of the Ministry of Health of the Republic of Azerbaijan (Ganja, 2022); International Pediatric Endocrinology Congress (Antalya, 2024).

Published works. Based on the findings of the study, a total of 13 scientific publications, including 8 research articles and 5 conference abstracts, were published.

Volume and structure of the Dissertation. The dissertation is written in Azerbaijani and comprises 160 pages (200445 characters). It consists of an introduction (8894 characters), Chapter I – literature review (65317 characters), Chapter II – materials and methods (23854 characters), Chapters III (24484 characters), IV (30043 characters) and V (13895 characters) presenting the author's own research, a discussion (29974 characters), conclusions (2962 characters), practical recommendations (1022 characters), a reference list and appendices.

The dissertation draws on 170 literature sources, including works by 8 Azerbaijani, 42 Russian and 120 foreign authors. The dissertation is illustrated with 20 tables and 12 figures.

MATERIALS AND METHODS OF THE RESEARCH

The study was conducted at the Republican Endocrinology Center and the K.Y. Farajova Scientific Research Institute of Pediatrics (SRIP). For each of the 108 children enrolled, birth length, birth weight, gravidity, parity, mode of delivery and course of pregnancy were established from anamnestic data obtained from the parents and from review of medical records. The somatic status of the children was assessed concurrently. In addition, parental height was measured, and physical development of children with developmental delay was comprehensively evaluated by anthropometry. Bone age and its delay relative to chronological age were determined by left hand–wrist radiography using a radiological atlas (W.W. Greulich, S.I. Pyle). Height and weight were assessed using percentile charts. Deviations from the mean were calculated on the basis of centile tables. The normal value is

0, with lower and upper limits of −2 and +2. Persistent growth below −1 SDS for age and sex is considered pathological. Height below −2 SDS may be indicative of growth hormone deficiency.

The children were grouped according to gestational age at birth and divided into 3 groups. The main group comprised 57 children born preterm at 29–36 weeks of gestation with growth retardation detected at preschool age; the comparison group comprised 31 children born at 38–40 weeks of gestation with growth retardation detected at preschool age.

The children of main group I were divided into 2 subgroups: subgroup 1A included 45 children born appropriate for gestational age (AGA), and subgroup 1B included 12 children born small for gestational age (SGA). Group IA was further divided into 2 groups: group IA1 included 8 children born at 29–31 weeks of gestation and group IA2 included 37 children born at 32–36 weeks. Of the SGA children, 2 (group IB1) were born at 29–31 weeks and 10 (group IB2) at 32–36 weeks of gestation. The comparison group (group II) included 31 children born at 38–40 weeks of gestation. The children of the comparison group were also divided into 2 subgroups: subgroup 2A included 26 children born AGA and subgroup 2B included 5 children born SGA.

The control group comprised 20 children born preterm at 29–36 weeks of gestation who had a relatively uncomplicated antenatal and intrapartum course and no physical developmental delay.

The following investigations were performed: complete blood count; TSH and fT4 (CMIA, chemiluminescent microparticle immunoassay); insulin-like growth factor 1 (IGF-1); insulin-like growth factor-binding protein 3 (IGFBP-3); somatotropin and GH stimulation testing (CMIA); and, in selected cases, cortisol (CMIA), prolactin (ECLIA) and creatinine (spectrophotometric method).

Statistical analysis was performed using the STATISTICA 12 for Windows software package. Student's t-test (including the paired Student's t-test) was used to compare quantitative parameters and proportions, and the χ^2 test (Pearson's goodness-of-fit) was used for qualitative analysis. In groups with small numbers of patients, Fisher's exact test and the non-parametric Mann–Whitney U test were applied; the Wilcoxon test was used to compare a single group before and during/after treatment. Associations between variables were assessed using standard

correlation analysis. ROC analysis was used to determine the sensitivity and specificity of these tests.

RESULTS AND DISCUSSION

The structure of somatic diseases and developmental anomalies in children with physical developmental delay was determined retrospectively.

Respiratory diseases predominated among the examined children. Respiratory diseases were detected in 36 (64.4%) children of group I and in 17 (54.8%) children of group II ($p > 0.05$). In the control group this figure was 3 (15%), which differed significantly from the main and comparison groups ($p < 0.05$).

Nervous system disorders were observed in 31 (54.4%) children of group I and in 9 (27%) children of group II, the difference between the groups being significant ($p < 0.05$). Various neurological signs were observed in 1 (0.5%) child of the control group, which differed significantly from the main group ($p < 0.05$).

Thus, among preterm-born preschool children with developmental delay, the most frequent conditions were respiratory pathologies (36; 64.4%), nervous system pathologies (31; 54.4%) and endocrine pathologies (100%), all differing significantly from the control group ($p < 0.05$).

Assessment of height using centile tables at enrollment showed a height SDS of -3.5 ± 0.15 in the main group and -3.3 ± 0.21 in the comparison group ($p = 0.3743$, $t = 0.89$). Assessment with centile tables revealed marked growth retardation in children of both the main and comparison groups. Body weight was 12.7 ± 0.51 kg in preschool children of the main group and 18.5 ± 1.46 kg in term-born children of the comparison group, a statistically significant difference ($p = 0.0006$). Body weight was also evaluated using standard scales: weight SDS was -3.0 ± 0.23 in the main group and -2.8 ± 0.25 in the comparison group; although a difference was observed, it was not statistically significant ($p = 0.4922$, $t = 0.69$).

Parental height, target height and predicted adult height (PAH) of the examined children were analyzed. In the main group, maternal height was 157.8 ± 0.88 cm and paternal height 171.2 ± 1.02 cm. Target height

in this group was 164.9 ± 0.97 cm, and predicted adult height (PAH) was 156.9 ± 3.74 cm. No difference in target height was observed between the control and main groups ($p = 0.2152$, $t = 1.25$).

Height at enrollment was 85.0 ± 5.15 cm in group IA1 and 94.2 ± 1.98 cm in group IA2. Height SDS was −4.5 ± 0.36 in group 1A1 and −3.1 ± 0.17 in group 1A2, a statistically significant difference ($p = 0.0070$, $t = 1.54$). Height percentiles were 0.2 ± 0.19 and 1.5 ± 0.34, respectively ($p = 0.0031$, $t = 3.09$). Body weight at enrollment was 10.7 ± 1.28 kg in group IA1 and 13.5 ± 0.63 kg in group IA2. Weight SDS was −4.2 ± 0.58 in group IA1 and −2.6 ± 0.25 in group IA2, the difference being statistically significant ($p = 0.0248$, $t = 2.31$).

Height was 105.2 ± 3.69 cm in group IIA and 112.8 ± 7.88 cm in group IIB; height SDS was −3.4 ± 0.24 in group IIA and −2.8 ± 0.33 in group IIB. Thus, no difference in height standard deviation scores was observed among the children of group 2 ($p = 0.1915$, $t = 0.83$). At enrollment, body weight in group IIA was 18 ± 1.61 kg (weight SDS −2.9 ± 0.29), and in group IIB 20.8 ± 3.74 kg (SDS −2.3 ± 0.38). Six-month height gain was found to correlate inversely with birth length, age at onset of developmental delay, and height and weight at enrollment. In addition, a direct correlation was found between height SDS and weight SDS at enrollment ($p < 0.05$).

In the main group, bone age was 2.8 ± 0.47 years in AGA children born at 29–31 weeks of gestation (group IA1) and 2.3 ± 0.25 years in SGA children born at 29–31 weeks (group IB1), with no statistically significant difference. Bone age was 3.6 ± 0.29 years in AGA children born at 32–36 weeks (group IA2) and 3.0 ± 0.45 years in SGA children born at the same gestational age (group IB2), again without a statistically significant difference. In the comparison group, bone age was 5.2 ± 0.62 years in group IIA and 6.0 ± 1.59 years in group IIB, indicating that bone age in the comparison group corresponded to chronological age. Although bone age in these children was consistent with chronological age, more serious hormonal and genetic factors appear to have caused their physical developmental delay. Overall, bone age was 3.4 ± 0.22 years in group 1 and 5.3 ± 0.57 years in group 2, a statistically significant difference. Moreover, among both SGA and AGA preterm-born children, bone age at preschool age was more delayed in those born at 29–31 weeks than in

those born at 32–36 weeks of gestation, which further confirms that very low birth weight has a substantial impact on developmental milestones at later ages. An inverse correlation was found between chronological age and bone age, as well as with target height, in the examined children.

The state of the hormonal system that actively influences growth was investigated in children with physical developmental delay. The thyroid-stimulating hormone (TSH) level was 6.7 ± 3.87 μIU/mL in group IA and 3.4 ± 0.67 μIU/mL in group IB. Thus, TSH was elevated in both groups, with no statistically significant difference between them.

In view of elevated TSH in 29 children of the main group, fT4 levels were measured in these children. The fT4 level was 5.3 ± 1.32 pmol/L in group IA and 14.0 ± 2.51 pmol/L in group IB. fT4 was higher in SGA children of group IB, the difference being significant ($p = 0.0125$, $t = 2.58$).

In groups IIA and IIB, TSH was 2.7 ± 0.30 μIU/mL and 3.9 ± 1.08 μIU/mL, respectively. No significant difference was observed between these values; however, they differed from the control group ($p = 0.0040$, $t = 2.96$).

In the control group, the TSH level was 1.8 ± 0.18 μIU/mL. In the main group, TSH was 6.7 ± 3.87 μIU/mL in group IA and 3.4 ± 0.67 μIU/mL in group IB, differing significantly from the control group ($p = 0.0040$, $t = 1.35$).

The examined children were euthyroid. The high-normal fT4 levels in group IB and the low-normal levels in group IA were attributed to a compensatory state.

The lower TSH and near upper-normal fT4 levels in group IB indicated a greater influence of perinatal factors on the intrauterine development of these children and a stronger capacity for adaptation to the environment.

Given its important role, the level of insulin-like growth factor 1 (IGF-1) was investigated in children with developmental delay. IGF-1 was 53.7 ± 5.99 ng/mL in group IA and 57.2 ± 17.47 ng/mL in group IB, with no difference between the groups. In the control group, IGF-1 was 216.9 ± 17.82 ng/mL, which differed significantly from groups IA and IB ($p = 0.0001$).

IGFBP-3 was not measured in all children enrolled. It was measured in a subset of children, and its relationship with IGF-1 was determined. IGFBP-3 was measured in 7 children of group IA, in whom it was 1.6 ± 0.41 ng/mL, whereas in group IIA it was 13.9 ± 12.77 ng/mL. Thus, IGFBP-3 levels in comparison subgroup IIA were several times higher than in group IA. The high level of the binding protein in term-born children of the comparison group suggests that it does not play a particular role in their short stature. The low IGF-1 level in group IA is probably related to morphofunctional immaturity.

Somatotropic hormone (STH) levels were 1.8 ± 0.32 ng/mL in group IA and 0.6 ± 0.16 ng/mL in group IIA. In group IB, the STH level was 3.0 ± 1.17 ng/mL, and in group IIB 0.8 ± 0.09 ng/mL. In the main group, the STH level was three times higher than in the comparison group. Despite the elevated STH levels in these preterm-born children whose birth weight was inappropriate for gestational age, tissue sensitivity to the hormone was apparently reduced.

Congenital isolated growth hormone deficiency (IGHD) is most commonly associated with mutations in the GH1 gene, which encodes growth hormone, or in the gene encoding the growth hormone receptor (GHR).

To identify gene mutations, 20 patients with IGHD (10 from each of the main and comparison groups) were enrolled, and the GH1 gene was analyzed.

No pathogenic GH1 mutation was detected in any of the 10 children of main group I. In group II, a completely normal GH1 sequence was found in 5 of the 10 children. In group I, variants were classified as likely benign in 9 children, as probably benign in 1 child, and as a variant of uncertain significance in 1 child (to be investigated as a potential novel mutation). In group II, gene polymorphisms were classified as probably benign in 3 children, benign in 1 child, and as a variant of uncertain significance in 1 child (to be investigated as a newly identified mutation).

The rs6171 polymorphism was detected in 8 children of the main group (4 homozygous and 4 heterozygous; 30% of patients) and as a heterozygous genotype in 1 patient (7%) of comparison group II. This variant was significantly more prevalent among preterm-born children.

In group I, it was observed in 6 of the 8 preterm-born patients carrying rs6171, and in group II in 1 SGA child. The rs695 variant was found in the heterozygous state in 3 patients (10%) of group I and in 1 patient (7%) of group II. The rs2005172 variant was detected in 9 patients (30%) of group I (3 heterozygous and 6 homozygous) and in 4 patients (30%) of group II (2 homozygous and 2 heterozygous). The rs11568827 polymorphism was found in 3 patients (10%) of group I (2 heterozygous and 1 homozygous) but in none of the patients in group II. The children carrying this polymorphism were SGA and extremely low birth weight infants who required very high GH doses and showed very low annual growth velocity.

The rs6171 polymorphism was significantly predominant among preterm-born children. This variant was observed in 8 patients of group I, and in group II the same variant was found in an SGA patient. It can therefore be concluded that this variant is of particular importance for the genetic prognosis of children with low birth weight for gestational age.

To diagnose growth hormone deficiency in the examined children, GH stimulation tests were performed with GlucaGen 1 mg at a dose of 0.03 mg/kg. Serum somatotropin responses were measured at 30, 60, 90 and 120 minutes.

At 30 minutes after GlucaGen administration, at the time of the rise in blood glucose, no notable difference was found between subgroups 1A and 1B of the main group. In the comparison group, the somatotropin response was 7.2 ng/mL in SGA children of group 2B and 2.6 ng/mL in AGA children of group 2A, i.e., three times lower than in group 2B. At 60 minutes, the time of the principal hypoglycemic phase of the test, the somatotropin response was 5.2 ng/mL in the AGA subgroup 1A and 1 ng/mL in the SGA subgroup 1B of the main group, a statistically significant difference ($p = 0.005$).

No difference between subgroups of the comparison group was found at 60 minutes. At 90 minutes, there was no statistically significant difference in somatotropin responses between the subgroups of either the main or the comparison group. At 120 minutes, there was no difference between the AGA subgroup 1A and the SGA subgroup 1B of the main group, nor between the somatotropin

responses of subgroups IA1 and IA2, whereas a significant difference was found between subgroups IB1 and IB2. Thus, among SGA children, the somatotropin response at 120 minutes was 7.6 ng/mL in those born at a lower gestational age (group IB1) versus 2.6 ng/mL in those born at a higher gestational age (group IB2).

In subgroups 1A and 1B of main group I, basal GH was higher in SGA children; however, after stimulation, during hypoglycemia, a lower GH response was obtained in SGA children (group 1B).

Total growth hormone deficiency was identified in AGA children born at a lower gestational age (group IA1) and in SGA children born at a higher gestational age (group IB2). In the comparison group, partial growth hormone deficiency was found among both SGA and AGA children. Hence, children born preterm at a lower gestational age, as well as those born SGA, are also at higher risk of total growth hormone deficiency.

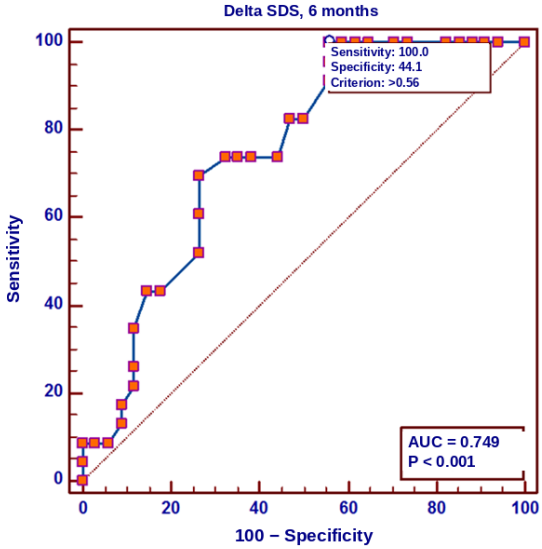


Figure 1. ROC analysis in Group 1

Children of group I were analyzed according to 6-month delta SDS. As shown in the figure, a delta SDS greater than 0.75 over 6

months is a good indicator for predicting treatment response, with a specificity of 44% and a sensitivity of 100%. Compared with group II, group I shows moderate discriminatory power. This is of particular importance for predicting the course of treatment (Figure 1).

Among the children of the main AGA subgroup IA (n = 45), those born at 32–36 weeks (n = 37; group 1A2) started GH therapy at 0.031 mg/kg/day, currently continued at 0.034 mg/kg/day. In these children, height gain was 5.3 cm at 6 months (based on data from 22 children) and 10.7 cm at one year. Children of subgroup 1A born at 29–31 weeks (group IA1) started GH therapy at 0.033 mg/kg/day, continued at 0.035 mg/kg/day. In these children, height gain was 5.8 cm at 6 months and 13.7 cm at one year.

Children of group II were analyzed according to 6-month delta SDS. As shown in the figure, a delta SDS greater than 0.86 over 6 months is a good indicator for predicting a strong treatment response, with a specificity of 100% and a sensitivity of 81.2%. By providing both high sensitivity and complete specificity, this cut-off point yields a more balanced and clinically more reliable model. This is of particular importance for predicting the course of treatment (Figure 2).

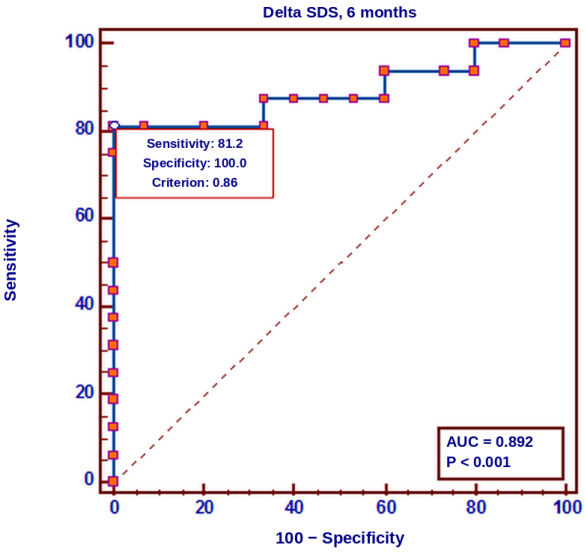


Figure 2. ROC analysis in Group 2

Thus, among AGA children, the initial and current GH doses did not differ significantly between those born at 29–31 weeks and those born at 32–36 weeks of gestation.

In SGA children, i.e., group 1B (n = 12; 2 born at 29–31 weeks and 10 at 32–36 weeks), the starting GH doses were 0.035 mg/kg/day and 0.031 mg/kg/day, respectively. That is, children born at 29–31 weeks received GH at 0.035 mg/kg/day and those born at 32–36 weeks at 0.031 mg/kg/day. Currently, children born at 29–31 weeks receive 0.045 mg/kg/day and those born at 32–36 weeks 0.034 mg/kg/day. Six-month height gain was 6.1 cm in children born at a higher gestational age and 2.5 cm in those born at a lower gestational age, while one-year gain was 9.5 cm and 7 cm, respectively.

Annual height gain was 13.7 cm in group 1A and 7 cm in group 1B ($p < 0.05$). In group II, i.e., the comparison group, the 31 children were divided into groups 2A and 2B (AGA and SGA, respectively): IIA (n = 26) and IIB (n = 5). In group 2A, the initial GH dose was 0.029 mg/kg/day and the current dose 0.032 mg/kg/day; height gain was 5.6 cm at 6 months and 13 cm at 1 year. In group IIB, the initial GH dose was 0.028 mg/kg/day and the current dose 0.029 mg/kg/day; six-month height gain was 6.7 cm. No statistically significant within-group differences in the starting or maintenance GH doses were found in these children. Between the main and comparison groups, the starting GH dose was higher in group I.

Thus, AGA children born at 29–31 weeks of gestation demonstrated a higher annual growth velocity than those born at 32–36 weeks, despite receiving the same GH dose. In contrast, SGA children required higher starting and maintenance GH doses, and among them those born at 29–31 weeks showed lower annual growth.

In our study, a prognostic formula was derived from the obtained criteria to predict height gain (as height SDS) after 6 months of treatment. The variables included in the model were baseline height SDS, bone age (left hand–wrist), GH at 60 min of the stimulation test (GH-60), IGF-1 and current dose. The results are presented in the table below (Table 1).

Baseline height SDS was identified as the factor with the strongest positive effect on treatment outcome ($p < 0.0001$). Bone age

(left hand–wrist; $p < 0.0001$), GH-60 ($p < 0.0001$), IGF-1 ($p < 0.0001$) and current dose ($p = 0.0004$) had a negative effect on the outcome. On the basis of these parameters, a prognostic formula was developed to determine height 6 months after the start of treatment:

Table 1

Results of multiple regression analysis

Independent variables	Regression coefficient	Standard error	t	p	$r_{partial}$	$r_{semipartial}$	VIF
(Constant)	1.9326536						
Baseline height SDS	1.0063092	0.01931257	52.1	<0.0001	0.990	0.854	1.663
Bone age (L hand–wrist)	−0.1107570	0.01693345	−6.5	<0.0001	−0.675	0.107	1.493
GH-60	−0.01910504	0.004519793	−4.2	0.0001	−0.509	0.069	1.244
IGF-1	−0.00311303	0.0004808892	−6.5	<0.0001	−0.671	0.106	1.088
Current dose	−12.8818212	3.3876303	−3.8	0.0004	−0.470	0.062	1.030

[6-month SDS = 1.9326536 + Baseline height SDS × 1.0063092 + Bone age (left hand–wrist) × (−0.1107570) + GH-60 × (−0.01910504) + IGF-1 × (−0.00311303) + Current dose × (−12.8818212)]

The variation of the observed height SDS values after 6 months and the values obtained from the regression function (recorded as MREGR_Pred) is shown in the diagram. As can be seen, the values calculated by the model closely track the actual values (Figure 3).

Conversely, bone age (left hand–wrist; $p < 0.0001$), GH-60 ($p < 0.0001$) and IGF-1 ($p < 0.0001$) showed negative associations. These results indicate that advanced bone age and elevation of certain biochemical parameters lead to a weaker treatment response. This suggests that, in clinical practice, more rapid skeletal maturation may limit the treatment effect.

The regression coefficient for current dose was $\beta = 12.88$ ($p = 0.0004$). This finding suggests that higher doses yield better results when applied in poor responders, i.e., increasing the starting dose improves the height prognosis.

Results of multiple regression analysis

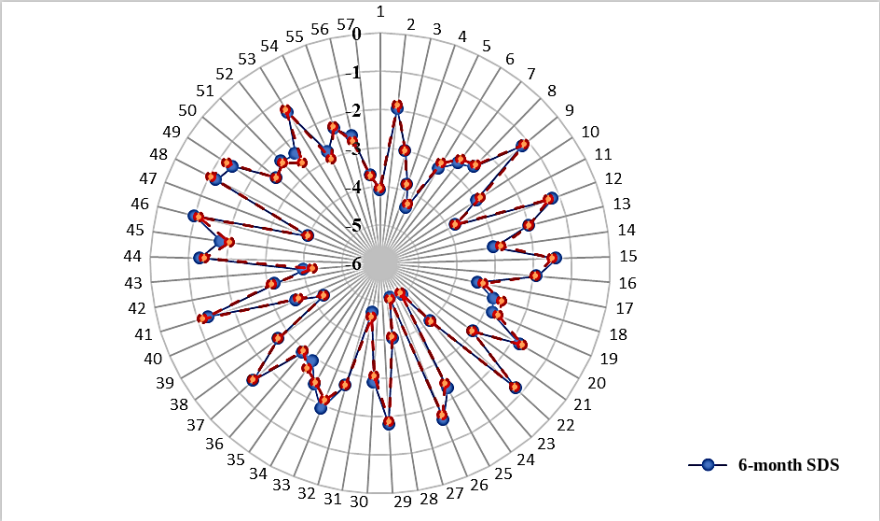


Figure 3

Thus, the results of multiple regression analysis show that baseline height SDS was the most important positive factor in predicting the 6-month treatment response, whereas bone age, IGF-1 level and current dose confirmed that the treatment effect depends not only on the dose of therapy but also on the anthropometric and biochemical characteristics of the patients. These findings are of considerable importance in clinical practice for predicting height gain at the initiation of GH therapy using the above criteria, particularly the dose prescribed by the physician.

RESULTS

1. Among preschool children with physical developmental delay, nervous system diseases were found in 31 (54.4%) preterm-born children (group I), 9 (27%) term-born children (group II) and 1 (0.5%) child in the control group (group III), with a significant difference between the groups ($p < 0.05$). Respiratory diseases were

found in 36 (64.4%) children of the main group, 17 (54.8%) of the comparison group and 3 (15%) of the control group, the main and comparison groups differing significantly from the control group ($p < 0.05$). Endocrine pathologies were present in 100% of the main and comparison groups, differing significantly from the control group ($p < 0.01$). Thus, in this group of patients, endocrine disorders were followed in frequency by nervous system and respiratory diseases (3, 4).

2. At preschool age, height was −4.5 ± 0.36 SDS in AGA children born at 29–31 weeks (1A1) and −3.7 ± 0.15 SDS in SGA children (1B1). At enrollment, height was −3.1 ± 0.17 SDS in AGA children born at 32–36 weeks (1A2) and −4.0 ± 0.41 SDS in SGA children (1B2). At initial examination, height SDS was −3.4 ± 0.24 in term-born children (IIA) and −2.8 ± 0.33 in term-born SGA children (IIB) ($p > 0.05$). It follows that more severe physical developmental delay is observed in preterm-born children with very low birth weight (5, 8, 10, 11).

3. At 60 minutes, the most informative time point of the GH stimulation test, STH levels in children with physical developmental delay were 5.2 ± 0.81 ng/mL in preterm AGA children, 1.0 ± 0.26 ng/mL in preterm SGA children, 3.1 ± 0.63 ng/mL in term AGA children and 4.7 ± 0.97 ng/mL in term SGA children, without statistically significant differences ($p > 0.05$). Total growth hormone deficiency was identified in preterm SGA children, which provides grounds to predict a future need for higher GH doses in these children (1, 6, 7).

4. Analysis of the GH1 gene, based on rs number (Reference SNP) statistics for gene variants, revealed statistically significant group differences in the single-nucleotide variants rs6171, rs695, rs2005172 and rs11568827. The rs11568827 variant was identified, in the present study only, as a polymorphism with a statistically significant difference in our population. The mutant rs6171 polymorphism was significantly predominant among preterm-born children (12, 13).

5. During treatment, 6-month height gain was 5.8 ± 0.46 cm in AGA children born at 29–31 weeks (group IA1) and 5.3 ± 0.24 cm in

those born at 32–36 weeks (group IA2) ($p = 0.30$, $t = 1.03$). In SGA children, 6-month gain was 2.5 ± 0.00 cm in those born at 29–31 weeks (IB1) and 6.1 ± 0.38 cm in those born at 32–36 weeks (IB2) ($p = 0.0002$, $t = 5.04$). Despite receiving a high therapeutic GH dose (0.045 mg/kg/day), children of group IB1 gained only 2.5 cm over 6 months, which has informed the future treatment protocol for this group of children (2, 9).

PRACTICAL RECOMMENDATIONS

1. In children with pathological short stature due to growth hormone deficiency, irrespective of whether they were born at term or preterm, initiation of GH therapy at preschool age is recommended in order to achieve a favorable final height prognosis.

2. In severe growth retardation (SDS < −3), high initial GH doses are not always appropriate: in children born with very low birth weight and SGA, treatment may be started at doses higher than 0.045 mg/kg/day. In term-born SGA children, normal growth velocity is achieved with the standard therapeutic dose (0.035 mg/kg/day), and initiation of high-dose GH therapy is not recommended in these children.

3. To achieve a more optimal outcome, it is advisable to calculate the 6-month height prognosis using the formula derived in this study from the factors that strongly influence treatment outcome: [6-month SDS = 1.9326536 + Height SDS at enrollment × 1.0063092 + Bone age (left hand–wrist) × (−0.1107570) + Somatotropic hormone at 60 min × (−0.01910504) + IGF-1 × (−0.00311303) + Current dose × (−12.8818212)].

THE LIST OF PUBLISHED SCIENTIFIC WORKS ON THE DISSERTATION TOPIC

1. Hajiyeva A.S., Nasibova S.N. The role of hormonal status in the physical development of preschool children // Saglamlig Journal, 2021, No. 2, pp. 200–204

2. Aliyeva A.M., Nasibova S.N. Multiple deficiency of adenohypophyseal hormones // Azerbaijan Journal of Perinatology and Pediatrics, 2021, No. 2, pp. 79–83

3. Hajiyeva A.S., Nasibova S.N. Somatic status and incidence of developmental anomalies in preterm-born preschool children // Azerbaijan Journal of Perinatology and Pediatrics, 2022, No. 2, pp. 8–16

4. Nasibova S.N., Hajiyeva A.S. The role of neonatal risk factors in physical developmental delay of preterm-born preschool children // Proceedings of the International Scientific-Practical Conference "Current Problems of Medicine – 2022" dedicated to the "Year of Shusha" in the Republic of Azerbaijan, 24–25 May 2022, pp. 143–144

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7. Nasibova S.N., Gadzhieva A.S. State of the hormonal system in preterm-born preschool children with delayed physical development // IX Congress of Pediatricians of Uzbekistan with International Participation "Current Issues of Pediatrics at the Present Stage", October 2024, p. 51 [in Russian]

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The list of Abbreviations

CNS – Central nervous system
fT4 – Free thyroxine
GH – Growth hormone
GHD – Growth hormone deficiency
GH1 gene – Growth hormone 1 gene
GHR – Growth hormone receptor
IUGR- Intrauterine growth restriction
IGF-1 – Insulin-like growth factor 1
IGFBP-3 – Insulin-like growth factor-binding protein 3
IGHD – Isolated growth hormone deficiency
NGS – Next-generation sequencing
PAH – Predicted adult height
ROC – Receiver operating characteristic
rs number – Reference SNP cluster identifier
SDS – Standard deviation score
SGA – Small for gestational age
STH – Somatotropic hormone (somatotropin)
TSH – Thyroid-stimulating hormone



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