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Original Article

The Effects of Growth Hormone Treatment in Patients with Isolated Growth Hormone Deficiency on Hematological Parameters

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ABSTRACT

Objective: A small number of studies were reported regarding the direct and indirect effects of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) especially on the erythrocyte series. The purpose of this study was to examine the effects of GH treatment (GHT) used in patients with isolated GH deficiency (IGHD) on hematological parameters.

Methods: The records of the patients who were diagnosed as having IGHD in our clinic and received GHT for at least two years between 2013 and 2019 were retrospectively examined. Height, height standard deviation scores (SDS), weight, weight SDS, IGF-1, annual growth rates, and changes in blood count parameters before and after the GHT were recorded. The statistical analyses were made using SPSS v.20 Package Program, and the significance level was accepted as $p<0.05$.

Results: A total of 37% (n=23) of the 62 patients that were included in the study were female, and 63% (n=39) were male. It was determined that the age of the patients was between 2-16 years at the time of diagnosis, and the median age at diagnosis was 10.8. After the GHT, a significant increase was detected in the distribution and volume of hemoglobin, hematocrit, and red sphere count ($p<0.05$). A statistically significant but clinically insignificant decrease was detected in the platelet count and there was an increase in the platelet volumes ($p<0.001$). A clinically significant decrease was detected in the number of white sphere, lymphocyte and neutrophil counts ($p<0.05$).

Conclusion: It was determined that GHT had a stimulating effect on erythropoiesis in IGHD. It was also shown that GHT caused a number of changes on the platelet count, white sphere count, and the lymphocyte and neutrophil parameters, which were not clinically important. We believe that studies at *in vitro* and molecular level are needed to explain the effects of GHD and GHT on the hematopoietic system.

Keywords: Growth hormone, isolated growth hormone deficiency, growth hormone therapy, hematological parameters, child

INTRODUCTION

Growth hormone deficiency (GHD) is a significant cause of short stature, seen in approximately 1/4,000 to 1/10,000 of the patients.[1,2] Isolated GHD (IGHD) can be defined as the deficiency of GH that is independent of other pituitary hormone deficiencies and the presence of an organic lesion.[3] GHD can be either congenital or acquired, while the height and weight of patients at birth are in the normal range. The children with GHD are expected to have regular growth during the first six months, while the growth slows down later in life. A proportionally short height ensues and the weight increases relative to the height, leading to delayed bone age.[2]

Treatment of GHD involves the use of biosynthetic human growth hormone produced by recombinant gene technologies (rhGH). The

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rhGH is safely used with very rare side effects. Growth hormone has been shown to have metabolic effects related to several systems besides its effects on height. Carbohydrate, fat, and protein metabolisms are adversely affected, body composition deteriorates, bone health is adversely affected, quality of life decreases, and cardiovascular morbidity increases in GHD.[4,5]

It is known that GH and insulin-like growth factor-1 (IGF-1) have effects on the hematopoietic system. GH and IGF-1 regulate hematopoiesis and cytokine production via bone marrow. GH plays a role in platelet production and differentiation. GH contributes to the regulation of erythropoiesis by increasing renal erythropoietin (EPO) production. It has been shown that erythropoiesis is slowed down due to GHD in hypophysectomized rats, recombinant GH treatment leads to an increase in EPO and stimulation of erythropoiesis, and GH increases IGF-1, which directly and indirectly stimulates erythropoiesis.[4,6]

There are few studies on the effect of long-term GH therapy on hematological parameters. This study aimed to investigate the changes in auxological and hematological parameters of patients who received GHT for IGHD.

MATERIALS and METHODS

Study Design

In this retrospective cross-sectional study, STROBE guideline was used for reporting purposes.[7] The study protocol was approved by the Local Ethics Committee at University of Health Sciences Turkey, Erzurum Regional Training and Research Hospital (IRB number: 2019/07-60, date: 15.04.2019).

Setting and Participants

The study was conducted in the Pediatric Endocrinology outpatient clinics between May 2013 and May 2019.

Out of the 187 patients, who presented with short stature to the center during the study period, 62 patients with IGHD, who received recombinant GH treatment for at least two years and attended regular follow-up visits, were included in the study. The exclusion criteria of the study were the presence of other endocrine or chronic diseases (n=1), receiving therapy with B12 or iron for anemia (n=2), and use of non-GH therapeutics with potential effects on hematological parameters (n=1) (Figure 1).

The IGHD is defined as a condition of GHD not associated with any organic lesion and also other pituitary hormone deficiencies.[8]

Variables

The demographic and clinical data were obtained from patient files such as age, sex, height and weight of the patients. The primary outcome of the study was set as the blood hemoglobin (Hb) level. Other variables investigated were the age, gender, height at the time of diagnosis, weight, standard deviation scores (SDS), annual growth rate after GH treatment, white blood cell count (WBC), total lymphocyte count (LYM), absolute neutrophil count (NEU),

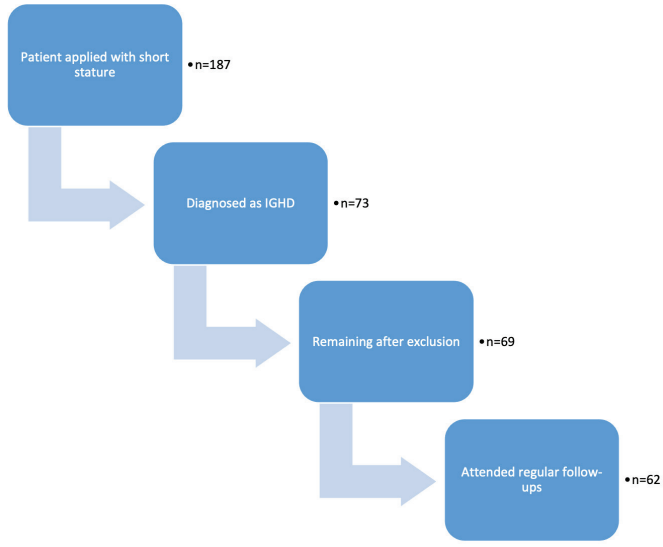

Figure 1. Participant flow diagram
IGHD: Isolated growth hormone deficiency

hematocrit (HCT), erythrocyte count (RBC), erythrocyte red cell distribution width (RDW), erythrocyte mean corpuscular volume (MCV), platelet count (PLT), mean platelet volume (MPV), and IGF-1 levels. The hematological parameters included in the complete blood count were measured via a Sysmex XN-1000 device (Sysmex Ltd, Turkey) using the WNR, WDF, RET, DCL, SLS, and PLT kits.

Anthropometric measurements were performed using a calibrated device (Seca, 216, Hamburg, Germany) that measured weight and height in ±100 gram and ±0.1 cm sensitivity SDs. Growth charts for Turkish children prepared by Neyzi et al.[9] were used to evaluate height, weight, and SDS.

The patients were subcutaneously administered with 0.025-0.035 mg/kg/day recombinant biosynthetic GHT in the evenings.[10] The values obtained at the onset of the therapy were compared with those in the 6th, 12th, 18th, and 24th months after the start of the GHT.

Study Size

The sample size was calculated based on the primary outcome, Hb level, using the GPower program.[11] Considering the effect size as 0.15 (small), α error as 0.05, power as 85%, the number of groups as 1, the number of repeated measurements as 5, correlations among repeated measures as 0.5, and non-sphericity correction as 1, a total of 61 participants were determined for inclusion in the study group.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) (SPSS for Windows, Version 20.0, Chicago, IC, USA). Results were presented as mean, SD, median, minimum, maximum, percentage, and numbers. The normal distribution of continuous variables was examined with the Shapiro-Wilk test. When the normal distribution could not be met for some

variables, the Friedman test was used to compare more than two dependent group variables. The threshold for statistical significance was accepted as p<0.05.

RESULTS

Of the 62 patients included in the study, 37% (n=23) were female and 63% (n=39) were male. The age at the time of diagnosis ranged between 2 and 16 years, with a median of 10.8 years (9.9 for girls, 11.3 for boys).

The auxological and hematological parameters of all patients before and after GHT and the results of different gender groups are shown in Table 1, Table 2, and Table 3.

DISCUSSION

Our study showed that there were significant changes in some of the hematological parameters of patients with idiopathic GHD after two years of GHT and follow-up compared to the baseline. It is known that the GH/IGF-1 axis has a role in the regulation of hematopoiesis. The facts that erythropoiesis is impaired in adults with GHD, and Hb and hematopoietic precursor cells increase after the GHT also support this relationship.[12,13]

It was found that the mean Hb values of the patients in our study increased significantly after the treatment compared to the baseline. Kawa et al.[14] compared the hematological parameters of patients receiving GHT at baseline and in the 3rd and 6th months

Table 1. Comparison of the repeated measurements in all patients (n=62)

	Baseline Mean ± SD	6th month Mean ± SD	12th month Mean ± SD	18th month Mean ± SD	24th month Mean ± SD	p
Height SDS	-2.96±1.03	-2.66±1.07	-2.43±1.05	-2.22±1.10	-2.14±1.05	<0.001
Weight SDS	-2.10±1.38	-2.07±1.33	-1.96±1.37	-1.85±1.34	-1.80±1.35	0.003
Hb (g/dL)	13.74±1.18	13.89±1.07	13.96±1.19	14.61±3.65	14.17±1.21	<0.001
HCT (%)	41.00±3.30	42.01±3.26	42.25±3.30	42.04±4.76	42.32±3.14	0.006
RBC (10^{12}/L)	5.03±0.98;	5.17±0.42.	5.20±0.44;	5.19±0.39;	5.31±0.69;	0.028
MCV (fL)	79.98±3.98	80.88±4.18	80.47±4.20	80.92±4.15	80.99±4.08	0.046
RDW (%)	12.54±1.54	12.18±1.03	12.20±1.12	12.50±1.14	12.70±1.10	0.005
PLT (10^9/L)	319.48±84.93	344.05±97.94	333.24±88.49	323.15±71.95	317.52±74.03	0.001
MPV (fL)	7.42±1.75	7.69±1.98	8.29±1.96	9.58±7.38	8.94±1.74	<0.001
WBC (10^9/L)	9.02±3.25	8.57±2.30	8.22±3.14	7.94±2.50	7.46±1.85	<0.001
LYM (10^9/L)	3.12±1.01	3.10±0.97	2.96±0.96	2.95±1.08	2.79±0.79	0.023
NEU (10^9/L)	5.12±3.29	4.80±2.46	4.26±2.72	4.11±2.35	4.28±2.06	0.035

SD: Standard deviation, SDS: SD scores, HCT: Hematocrit, RBC: Erythrocyte count, MCV: Mean corpuscular volume, RDW: Red cell distribution width, PLT: Platelet count, MPV: Mean platelet volume, WBC: White blood cell, LYM: Lymphocyte count, NEU: Neutrophil count

Table 2. Comparison of the repeated measurements in males (n=39)

	Baseline Mean ± SD	6th month Mean ± SD	12th month Mean ± SD	18th month Mean ± SD	24th month Mean ± SD	p
Height SDS	-2.93±1.1	-2.61±1.11	-2.37±1.05	-2.19±1.09	-2.13±1.03	<0.001
Weight SDS	-2.22±1.38	-2.14±1.36	-2.05±1.37	-1.94±1.35	-1.91±1.36	0.035
Hb (g/dL)	13.71±1.11	13.85±1.11	14±1.26	14.24±1.12	14.35±1.2	<0.001
HCT (%)	40.96±3.28	41.94±3.36	42.71±3.54	42.85±3.15	43.02±3.17	<0.001
RBC (10^{12}/L)	5.12±0.98	5.24±0.38	5.32±0.41	5.25±0.39	5.48±0.77	0.014
MCV (fL)	79.48±3.84	79.9±4.24	79.61±4.25	80.2±4.35	80.73±4.19	0.065
RDW (%)	12.63±1.61	12.32±1.13	12.33±1.1	12.66±1.23	12.69±1.11	0.171
PLT (10^9/L)	297.87±84.66	326.43±97.67	321.25±95.26	310.02±69.57	297.07±70.33	0.001
MPV (fL)	7.72±1.71	7.99±1.9	8.3±1.92	8.61±1.82	9.03±1.75	0.262
WBC (10^9/L)	9.08±3.43	8.74±2.47	8.27±3.36	8.04±2.55	7.2±1.45	<0.001
LYM (10^9/L)	3.05±0.97	3.13±0.99	2.93±0.92	3.08±1.02	2.88±0.65	0.359
NEU (10^9/L)	5.05±2.99; 4.4 (1.75-17.3)	4.74±2.41; 4.01 (1.8-12.1)	4.07±2.65; 3.4 (1.33-18)	3.64±1.39; 3.5 (1.37-8.8)	4.06±1.58; 3.8 (2-9.4)	0.044

SD: Standard deviation, SDS: SD scores, HCT: Hematocrit, RBC: Erythrocyte count, MCV: Mean corpuscular volume, RDW: Red cell distribution width, PLT: Platelet count, MPV: Mean platelet volume, WBC: White blood cell, LYM: Lymphocyte count, NEU: Neutrophil count

Table 3. Comparison of the repeated measurements in females (n=23)

	Baseline Mean ± SD	6th month Mean ± SD	12th month Mean ± SD	18th month Mean ± SD	24th month Mean ± SD	p
Height SDS	-3±0.92	-2.73±1	-2.5±1.06	-2.27±1.12	-2.15±1.08	<0.001
Weight SDS	-1.89±1.37	-1.95±1.29	-1.79±1.37	-1.67±1.34	-1.6±1.34	0.130
Hb (g/dL)	13.78±1.3	13.94±1.02	13.89±1.08	15.23±5.83	13.85±1.18	0.572
HCT (%)	41.07±3.38	42.13±3.15	41.46±2.74	40.66±6.52	41.12±2.76	0.254
RBC (10^{12}/L)	4.87±0.97	5.02±0.44	4.99±0.41	5.07±0.37	5.01±0.39	0.525
MCV (fL)	80.82±4.15	82.52±3.59	81.92±3.74	82.13±3.54	81.4±3.92	0.157
RDW (%)	12.38±1.42	11.92±0.76	11.96±1.12	12.22±0.92	12.7±1.08	0.028
PLT (10^9/L)	356.13±73.41	373.91±92.93	353.56±73.12	345.39±71.9	352.17±68.24	0.670
MPV (fL)	6.9±1.71	7.16±2.03	8.27±2.06	11.2±11.86	8.79±1.75	<0.001
WBC (10^9/L)	8.91±2.96	8.27±20	8.13±2.79	7.76±2.45	7.9±2.34	0.242
LYM (10^9/L)	3.22±1.07	3.05±0.93	2.99±1.03	2.7±1.15	2.62±0.98	0.020
NEU (10^9/L)	5.24±3.81	4.89±2.57	4.58±2.86	4.88±3.29	4.65±2.68	0.640

SD: Standard deviation, SDS: SD scores, HCT: Hematocrit, RBC: Erythrocyte count, MCV: Mean corpuscular volume, RDW: Red cell distribution width, PLT: Platelet count, MPV: Mean platelet volume, WBC: White blood cell, LYM: Lymphocyte count, NEU: Neutrophil count

of treatment and showed that GHT increased the erythroid cell line. Bergamaschi et al.[15] found that GHT improved normochromic normocytic anemia in prepubertal children and patients receiving GHT in adulthood. Miniero et al.[16] emphasized that among patients with idiopathic GHD, those with anemia before the GHT had a significant increase in Hb-SDS after 12 months of GHT, and normal Hb values were achieved in all of the children. It has also been mentioned that GH and IGF-1 directly modulate hematopoiesis through their proliferative and anti-apoptotic effects and indirectly through regulating cytokine production.[17] Considering these studies together, the effect of GH on hematopoiesis is obvious, but its role in hematopoiesis and the mechanisms that keep the balance are still not clear.

It was found that the mean HCT and RBC of the patients in our study increased significantly after the GHT compared to the baseline. In a study by Esposito et al.[18] 12 patients with GHD were diagnosed as having normocytic anemia, and Hb, HCT, and RBC of these patients were found to increase in the first two years of GHT. They also showed that the anemia improved in all of these patients in the 5th year of their treatment. In our study, 2 patients were found to have anemia before the GHT, and their anemia improved after 2 years of treatment, with a significant increase in RBC counts. Pankratova et al.[19] emphasized that the RBC counts were lower in children with GHD before treatment, which increased after 12 months of GHT.

The GHT indirectly increases Hb by increasing EPO production in the kidneys in the early period and by enhancing the effect of EPO at the receptor level. In addition, IGF-1 stimulates the maturation and proliferation of erythroid cell lines with an EPO-like effect by acting on its own receptors expressed on erythroid precursors. GH stimulates the production of IGF-1 by inducing the hematopoietic progenitor cells, and the increased IGF-1 stimulates erythropoiesis by inducing autocrine and paracrine effects in the hematopoietic system.[14,15,20,21] One of the limitations of our study was that it was done retrospectively; therefore, the EPO levels could not be measured, and no data could be obtained to evaluate this relationship. The fact that there was an increase in Hb, HCT, RBC, RDW, and MCV, which were among the parameters related to the erythroid cell line, after the GHT compared to the baseline supported the hypothesis that GHT stimulated erythropoiesis.

With regard to the platelet parameters, it was found that platelet values were not at levels that would be a risk factor for bleeding or thrombosis at the baseline or during the treatment, and the variations were not considered to be clinically significant. Xu et al.[22] showed that GH positively affected platelet production and differentiation *in vitro*. Similar to our study, Esposito et al.[18] did not detect a significant difference between the patient and control group in terms of PLTs before and after GHT. No effect of GHT has been shown on PLT in a small number of human studies.

In our study, it was found that the MPV increased significantly during the GHT compared to the baseline ($p<0.001$). There is no study in the literature examining the relationship between MPV and GHT. It was found that, in adults with acromegaly (with excess GH), MPV was higher before treatment compared to the control group, and MPV decreased with the decrease in GH levels after the treatment.[23,24] This finding is consistent with those of our study, which can be explained by the fact that GH increases platelet activation.

In our study, WBC, lymphocyte, and NEUs were significantly lower at baseline compared to those after the treatment. No previous study has been found about the effects of GHT on the WBC, lymphocyte, and neutrophil levels and their functions in children with GHD. In studies evaluating the hematological parameters, it was reported that GH had no effect on leukocyte count.[14,18,21] Positive effects of GHT have been demonstrated in children with GHD and phagocytic dysfunction.[25] It has been stated that treatments aimed at reducing GH in patients with acromegaly can reduce NEUs. However, a clear distinction could not be made regarding whether this is due to the decrease in GH levels or a drug-related side effect.[26]

In our study, WBC, lymphocyte, and NEUS were not below the limits in any of the patients at the baseline or during the 2-year treatment and follow-up, and the differences did not lead to any clinically significant change. The fact that our study did not evaluate the functions of erythrocytes, leukocytes, and thrombocytes, although the effect of GHT on the level of these cells was investigated, was a limitation of our study.

CONCLUSION

In conclusion, no significant hematological abnormality was detected before GHT in idiopathic GHD. GHT was found to have erythropoiesis stimulatory effects. In addition, it was shown that GHT was associated with some clinically insignificant changes on platelet, WBC, lymphocyte, NEUs and MPV. We think that *in vitro* and molecular studies to explain these effects of GHD and GHT may help clarify the subject matter.

Ethics

Ethics Committee Approval: The study protocol was approved by the Local Ethics Committee at University of Health Sciences Turkey, Erzurum Regional Training and Research Hospital (IRB number: 2019/07-60, date: 15.04.2019).

Informed Consent: Retrospective cross-sectional study.

Peer-reviewed: Externally and internally peer-reviewed.

Authorship Contributions

Concept: A.Ç., Design: A.Ç., Data Collection or Processing: D.Ş., Analysis or Interpretation: D.Ş., Literature Search: A.Ç., D.Ş., Writing: A.Ç., D.Ş.

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