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Original article

Evaluation of Growth Hormone Results in Different Diagnosis and Trend Over 10 Year of Follow up: A Single Center Experience

Aycan Z et al. Growth Hormone in Rare Diseases

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What is already known on this topic?
Growth hormone (GH) treatment has long been used in rare diseases such as isolated growth hormone deficiency (IGHD), multiple pituitary hormone deficiency (MPHD), small for gestational age (SGA), and Turner syndrome (TS). Early diagnosis and early initiation of GHT are important to optimize the effects of treatment.

What this study adds?
Although there are larger series in the literature, our study is one of the largest single-center patient series performed after the KIGS database was terminated. GH treatment onset age was late in our cohort and no differences have been observed in the last 10 years. The improvement in the height standard deviation score was seen most in the IGHD and MPHD groups, the least in the TS and SGA groups, the patients' treatment compliance was high (92%) and the incidence of side effects was low (2,7%).

Abstract
Objective:We aimed to evaluate the results of diagnosis, follow-up and treatment of the patients who recieved growth hormone (GH) treatment for the last 10 years and to determine the differences in the process and results over the years.
Methods:Anthropometric, clinical, laboratory data, treatment adherence and side effects were evaluated retrospectively in 767 patients who recieved GH treatment between 2009-2018. Patients were grouped as isolated growth hormone deficiency (IGHD), multiple pituitary hormone deficiency (MPHD), small for gestational age (SGA), Turner syndrome (TS) according to their diagnosis.
Results:GH treatment was started in 689 cases(89.8%) with IGHD, 24(3.1%) with MPHD, 26(3.4%) with SGA and 28(3.7%) with TS. Median age of GH treatment onset was the earliest on SGA (8.4years) while and the latest on IGHD group (12.0years). At the time of treatment offset, height standard deviation score (SDS) in IGHD and MPHD were significantly higher than treatment onset time, whereas there was no significant difference in TS and SGA. One hundred eighty-nine cases reached the final height. Final heights for girls/boys were respectively in IGHD:154/164.9cm, MPHD:156.2/163.5cm; TS:146.7cm, SGA:145.7/-cm. Target height SDS-Final Height SDS median values were IGHD:0.2, MPHD:0.6, SGA:0.5, TS:2.4 respectively in groups.
Conclusions:In our cohort, GH treatment onset age was late and no differences have been observed in the last 10 years. The improvement in the height SDS was seen most in the IGHD and MPHD groups, the least in the TS and SGA groups, the patients' treatment compliance was high (92%) and the incidence of side effects was low (2.7%).
Keywords: Rare disease, growth hormone treatment, follow up,

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Introduction
The introduction of recombinant human growth hormone (GH) in 1985 ended the phase of pituitary-derived human growth hormone and its associated limitations and risks, opening the possibility of widespread clinical use (1). Growth hormone (GH) treatment has long been used in rare diseases such as isolated growth hormone deficiency (IGHD), multiple pitutiary hormone deficiency, (MPHD), small for gestational age (SGA), and Turner syndrome (TS). Today, it is also used in different indications such as chronic renal failure, SHOX deficiency, Prader-Willi syndrome and idiopathic short stature besides GHD (2).
The foremost aims of GH treatment in children are the normalization of height during childhood, attainment of a timely and normal pubertal growth and the achievement of an adult height that is normal for the population and genetic target, in conjunction with normalization of other aspects (body composition, metabolism and quality of life) (1). In all pediatric indications, early diagnosis and early initiation of GH treatment are important to optimize the effects of treatment.
The Pfizer International Growth Study (KIGS) (3), the National Cooperative Growth Study (NCGS) (4) and the NordiNet International Outcome Study (5), are multicenter, international databases created to monitor the efficacy and safety of GH

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treatment. The advantage of these databases is to create a standardized common platform for uniform documentation of data on GH treatment in centers participating in the database, potentially reveal differences between clinics, and offer the possibility of reliable observation of potentially rare results due to the large number of participants (6). The KIGS database, in which data entries were made from many centers in our country and where we evaluate the treatment results of patients with GH treatment was terminated approximately 10 years ago. However, there are no new outputs regarding the diagnosis and treatment processes of these diseases in our country in recent years. In this study, we aimed to determine the follow-up, and treatment results and final heights of patients with rare diseases who had been treated with GH treatment in the last 10 years, and to determine the differences in the process and results over the years.

Methods

In present study, we recruited 767 patients who had received GH treatment in Dr. Sami Ulus Obstetrics and Gynecology, Children's Health and Disease Training and Research Hospital between 2009 and 2018. The study was conducted in accordance with the principles of the Declaration of Helsinki and approved by a Local Ethics Committee (no:1686). Anthropometric, clinical, laboratory findings, treatment adherence and side effects of patients during, admission, GH treatment onset time, follow-up, GH treatment offset time were evaluated retrospectively. Patients were grouped as IGHD, MPHD, TS, SGA, according to their diagnosis.

After systemic disease screening, at least two different growth hormone stimulation tests were performed in patients with pathological short stature whose growth rate <25 percentile and height standart deviation score (SDS) <-2,5. Apart from these, height SDS> -2.5, but the growth rate was below -2 SDS in the last year or below -1.5 SDS in the last two years, cases with thought to have GHD, and patients with a regression in growth rate for more than six months clinically and genetically confirmed TS were also evaluated (7,8). Before the last change in the social security institution regulation regarding TS and SGA patients, two different GH tests were required from all patients in order to pay for GH treatment in our country. Since TS and SGA patients included in the study were diagnosed before these changes related to these patients, all patient groups, including TS and SGA cases, were administered a growth hormone stimulation test.

GHD was defined as <10 ng/mL serum peak GH concentration. (7). It was required that the bone age should be at least 2 years retarded than the chronologic age in the prepubertal period, and the epiphyseal plates were open in puberty. In addition, male and female subjects were primed with sex steroids prior to provocative GH testing, particularly in the patients with delayed puberty. For both boys and girls, 2 mgβ-oestradiol (1 mg for body weight <20 kg) (not ethinyl oestradiol) was administered orally on each of the two evenings preceding the test, while boys were also given intramuscular testosterone (50–100 mg of a depot formulation administered 1 week before the test). Puberty was defined as breast development ≥ 2 Tanner stage in girls and testicular volume ≥ 4 ml in boys (9).

Isolated GH deficiency (IGHD) was defined as a condition of GHD not associated with other pituitary hormone deficiencies. MPHD was defined as a deficiency of at least two pitutier hormones, with one being growth hormone. SGA was defined as birth weight less than −2 SDS for gestational age. Turner syndrome was defined females who have partial or complete absence of the second sex chromosome with a variety of phenotypic features.

All measurements were calculated with the reference developed for Turkish children and expressed as SDS (10,11). Target (mid-parental) height was calculated by adding 6.5 cm to the mean of the parents' heights for boys or by subtracting 6.5 cm from the mean of the parents' heights for girls (12). If those who reached the final height were within range of ± 5 cm of the target height, they were considered as having reached target height.

After the growth hormone tests were evaluated, organic pathology that may accompany in cases with growth hormone deficiency was evaluated by performing pituitary magnetic resonance imaging (MRI). GH was administered subcutaneously at a dose range of 0,2-0,4 mg/kg/week, 6 days per week. According to the rules of social security institution in our country the GH treatment is discontinued when the height reaches 155 cm in girls and 165 cm in boys. In addition, GH treatment was discontinued if the annual growth rate was < 2 cm and/or bone age was ≥16 in boys and ≥14 in girls (7).

GH product, type of injection device, dosage, GH storage conditions, number of missed injections, reasons of missed injections, person administering daily GH injections and problems in follow-up were recorded at each visit and patients' compliance process was evaluated. Adherence categories were established following the criteria of Smith et al (13), and patients were categorized into one of 4 segments based on the percent of doses omitted at each evaluation period: excellent if 0%, good if 5%, fair if 5 to 10%, and poor if >10%. Patients in the poor category were considered to be incompatible with treatment.

Statistical Analysis

The Predictive Analytics Software 18 (PASW) 2009 program was used for statistical analysis. The conditions where the type-1 error level was below 5% were interpreted statistically. Kolmogorov-Smirnov and Shapiro-Wilk tests were used for normality distribution of the data. In descriptive statistics, categorical variables are expressed as number and percentage, and numerical variables are presented as median, minimum and maximum values. Student's t and Mann-Whitney U tests were used for variables that did not show normal and normal distribution, respectively, to compare the two groups. The Friedman test was used to examine the change in the age, bone age, height SDS, body mass index (BMI) SDS, puberty, and follow-up time during the admission, GH treatment onset, and GH treatment off set time separately in all patients and groups. The Wilcoxon signed-ranks test was used in post-hoc analysis. Bonferroni correction was used in post-hoc analysis whenever appropriate. In all patients and in the IGHD group, the Kruskal-Wallis test was used for comparison analysis of numerical values between date groups.To evaluate the relationship between final height-SDS with target height SDS, first year growth velocity, treatment duration, GH treatment onset time age, bone age, height SDS, puberty, gender, and IGF1, IGFBP3, values multiple lineer regression analysis was performed with backward method. A p value <0.05 was considered statistically significant.

Results

The median age of our patients (63% male) who were admitted to the clinic due to short stature was 10.4 years. GH treatment was started in 689 cases (89.8%) with IGHD, 24 (3.1%) with MPHD, 26 (3.4%) with SGA, and 28 (3.7%) with TS. The median age of GH treatment onset was 12.0 years, the earliest was in SGA (8.4 years) and the latest was in IGHD (12.0

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years) When the age of first admission to the hospital and the GH treatment onset age were compared by years, it was found that there was no difference between them in the last 10 years (p>0.05) (Table 1).
The height SDS at the GH treatment onset time, was below <-2.5 in entire group and subgroups. The lowest height SDS was in the MPHD group, and the height SDS values of TS, and SGA groups were lower than the IGHD group. The lowest peak response to GH tests was in the MPHD, GHD, and TS groups, respectively. The lowest serum insulin-like growth factor 1(IGF1) and insulin-like growth factor-binding protein 3 (IGFBP3) values were in the MPHD group. The serum IGF1 level was < -2 SDS in 330 (43.9%) patients, between -2 SDS and -1 SDS in 380 (50.5%) patients, and >1 SDS in 42 (5.6%) patients (Table 2).
The pituitary MRI was pathological in 27.1% of the patients, and the most common accompanying pathology was pituitary hypoplasia (60%). Various pathologies (pitutiary hypoplasia, ectopic neurohypophysis, microadenoma/suspected microadenoma, empty sella, partial empty sella, rathke cleft cyst, arachnoid cyst) were detected in 25.9% of patients with GHD and 78.3% of patients with MPHD. Patients with suspected microadenoma and microadenoma were consulted with neurosurgery before GH treatment. In none of the cases, organic pathology that could interfere with GH treatment was found on MRI.
The median follow-up time without treatment was 11 months and the median follow-up time with treatment was 2.1 years. The longest duration of treatment was in the MPHD group at 3.8 (range, 0.3-9) years, and the shortest duration of treatment was in the IGHD group at 2 (range, 0.3-10.8) years. The median treatment dose was 0.2 (range, 0.2-0.4) mg/kg/week in entire group and subgroups, while it was 0.3 mg/kg/week in the TS group. During the treatment, the changes in patients' GH dose were minimal (7.0%) and the doses of GH were adjusted in relation to weight, elevation of IGF1 concentrations or changes in glucose metabolism.
Growth velocity were highest in the first year of treatment in entire group and subgroups, and gradually decreased in the following years. The median value of the first-year growth velocity was 8.2 cm/year in entire group, while it was MPHD 9.8 cm/year, IGHD 8.3 cm/year, TS 7.8 cm/year and SGA 7.1 cm/year in the subgroups respectively.
Considering GH treatment offset time, height SDSs in IGHD and MPHD groups were significantly higher than treatment onset time (p<0.001), whereas there was no significant difference in TS (p=0.225) and SGA groups (p=0.191). In the same period, no statistically significant difference was found in terms of the BMI SDS in the subgroups, except for the IGHD group (Table-3).
A number of 189 patients reached the final height (IGHD: 166, TS: 11, MPHD: 8, SGA: 4). Except for the TS and SGA groups, the percentage of patients reaching final height was higher in boys. In groups outside TS and SGA, final height SDSs were above -2 SDS. Final height for girls/boys were as follows: IGHD:154/164.9 cm, MPHD:156.2/163.5 cm, TS:146.7 (range, 133-156.4) cm, and SGA:145.7 (range, 136.7-150.3) cm. Of the 166 IGHD patients who reached their final height, 104(67.5%) were found to reach their target height. Target height SDS-Final height SDS was the highest in the TS group and the percentage of final height was the lowest in the TS group (Table 4). The change in the height SDS of our patients from the beginning of treatment to the final height is given in Figure 1.
Of our IGHD patients who reached their final height, 93 (56.0%) were prepubertal and 73 (44%) were pubertal at the beginning of GH treatment. At the time of onset of GH treatment, the age and bone age of pubertal IGHD patients were significantly higher than in prepubertal IGHD patients (p <0.001). The duration of treatment was longer in prepubertal IGHD patients than in pubertal patients. (p <0.001) (Table 5). There was no statistically significant difference between prepubertal and pubertal IGHD patients in terms of height SDS, BMI-SDS, Final height SDS, Target height-SDS, first year growth velocity and treatment dose.
In multiple lineer regression analysis, GH treatment onset time height SDS, target height SDS, first year growth velocity and puberty status were predictive factors for final height SDS. (Table-6)
Patients' compliance with treatment was high (92%), and treatment was interrupted in 16% of patients due to problems in compliance with treatment during treatment, low growth rate, and high IGF-1. Treatment incompatibility was lowest in the IGHD group and highest in the SGA group. Adverse effects were seen in 2.7% (n=21) of our patients. These side effects were; significant CK elevation (n: 8), scoliosis (n: 5), cardiac causes (n: 2 subaortic segmental hypertrophy- left ventricular hypertrophy), orthopedic causes (slipped capital femoral epiphysis (n:1) Osgood Schlatter's Disease (n:1), non-injection site rash (n: 2), disorders of glucose metabolism (n: 1 impaired fasting glucose) and malignancy (n: 1 Osteochondroma). Both patients with cardiac side effects were in the IGHD group, they did not have syndromic features. Scoliosis, slipped capital femoral epiphysis and impaired fasting glucose were thought to be related to GH treatment. Scoliosis was newly developed in four cases and an increase in existing scoliosis in one case. Our patient with malignancy was followed up because of TS, the total treatment duration was 2.92 years, and the treatment dose was 0.3 mg / kg / week. It was found that the patient, whose treatment was discontinued after malignancy was detected, did not continue with her subsequent follow-ups.

Discussion

Our study which has the highest number of patients, following a study named Turkey KIGS Database analysis which was published in 2004 with 1008 patients', who were receiving GH treatment etiology and treatment results were evaluated (13). In our study, similar to the literature, the highest proportion of patients were in the IGHD group and patients were mostly male (14, 15).
It has been shown that the age at onset of GH treatment is correlated negatively with the response to treatment, which emphasizes the need for early diagnosis and treatment (7). In a recently study by Sävendahl et al.data from the The American Norditropin Studies: Web-Enabled Research Program (ANSWER-USA) and the NordiNet International Outcome Study (NordiNet IOS-Europe) were compared. Growth hormone onset age in GHD, TS, and SGA patients were 11.09.8.92 and 9.0 in the ANSWER trial, respectively, while a was 9.12.8.72 and 7.92 in the NORDINET-IOS trial, respectively. and the authors concluded that onset age of GHT was higher in all indications in the USA (16). Pfäffle et al. reported that the age of initiation of treatment was similar between the USA and Germany, but higher in the indications in France (17). Data from these different analyses show that the average age at the start of GH treatment is higher than desired worldwide.

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In the study in which patients were registered in the KIGS database in Turkey and were treated with GH, the age at onset of GH treatment was 11.3 years (13), and 11.2 ± 2.67 years in the study performed by Soyöz et al. (18). In our study, the median age at onset of treatment was found as 12.0 years; the age at onset of treatment was latest in the IGHD group and earliest in the SGA group, and there was no difference in the ages at admission and at initiation of treatment in the last 10 years. Our findings show that despite the increase in health awareness and easier access to health services in recent years age at onset of GH treatment is still late in our cohort.

In our study, the highest growth velocity in the first year of treatment was in the MPHD and IGHD groups, besides height SDS was -3,0 and -3.84 in patients in the IGHD and MPHD groups at the GH treatment onset time while the final height SDS was -1.5 in both of these groups. Previous studies in our country final height SDSs in IGHD and MPHD were found to be -1.8 and -1.6 by Kurnaz et al. and -1.4 and -1.1 by Darendeliler et al. (19, 20). The final height SDSs in the IGHD and MPHD groups in our study, with a similar dose range but shorter median treatment time, were similar to other studies in our country. It was thought that the better response in our patients in the MPHD group was associated with lower IGF1 and peak GH values in the growth hormone stimulation tests, as well as lower chronologic age and bone age at the beginning of treatment compared with patients with IGHD.

The effect of GH treatment on final height in TS is variable and many factors such as polymorphisms associated with the GH receptor and/or IGFBP3 gene, age at the beginning of treatment, dose of GH, duration of treatment, bone age retardation, maternal X chromosome origin, first year response to target height, and oxandrolone treatment affect the treatment response (21, 22, 23). The IGFBP3 gene's promoter region contains several single nucleotide polymorphisms (SNPs). The202 A/C SNP which located 202 bp upstream of the transcription start site consists of an A to C nucleotide change and correlated with serum IGFBP-3 concentrations in healthy adults. Serum IGFBP-3 levels are highest in patients with the AA genotype, followed by the AC and CC genotypes (24). An association of the A allele in the IGFBP-3 promoter region with increased IGFBP-3 concentration and growth velocity after GH therapy has been observed in prepubertal children with GHD and Turner syndrome (25,26).

Recently Ahn et al., in a study with 73 patients with TS, reported that the height SDS at the beginning was correlated with final height SDS, and that early treatment was very important (27). Evaluation of the data of 70 TS patients registered from 11 centers in Turkey in the KIGS database who received GH in a dose of 33 µg/kg/d subcutaneously, 6-7 times per week, with onset of therapy at age 12.5 (7.1-15.6) years revealed a non-significant increase in growth velocity 6.3 cm/year in the first year and 5.9 cm/year in the second year (28). In another study in which 842 patients with TS were evaluated with the participation of 35 centers from our country, it was stated that the average age to start treatment in patients with TS was 10.5 ± 4.8 years and that treatment was initiated at the age of 10.7 ± 3.5 year (29). In our study, the age at onset of treatment, the dose of treatment, and the first year response to treatment in patients with TS were consistent with the literature previously published in our country, and although there was no significant difference in terms of height SDS between GH treatment onset and offset times, the rate of reaching the target height was the lowest in the TS group. We thought that this result was due to the age at onset of treatment being late in our patients and that the height SDS at the beginning of treatment were significantly lower.

Growth hormone treatment in infants with SGA is effective in the correction of body composition and improvement of metabolic complications, in addition to its contribution to stature in adulthood (30). The dose recommended by the Pediatric Endocrinology and Growth Hormone Research Society in children with SGA is 35-70 mg/kg/day, and higher doses are recommended for patients with severe growth retardation. Treatment dose, age of onset, height at onset of treatment, and mid- parental height are among the factors affecting the response of GH in children with SGA (31). The multidisciplinary follow-up of many of SGA cases by other departments in our hospital has caused these patients to be referred to our clinic earlier and to start treatment earlier by diagnosing growth disorders. However, there was no significant difference between GH treatment onset and offset in terms of height SDSs in the SGA group and the final height SDS was the lowest in the SGA group. These findings were thought to be due to the fact that the doses used in the SGA group were at the lower limit of the recommended dose and were associated with a treatment mismatch in this group.

In this study, although the chronological age and bone age were higher in the pubertal IGHD patients and the duration of GH treatment was longer in the prepubertal IGHD patients, there was no statistically significant difference between two groups terms of final height SDS. Similarly, Kurnaz et al.'s study did not show a difference in final height SDS of prepubertal and pubertal patients, but it was reported that delta height SDS was higher in pubertal patients (20). These results support that even if the GH treatment is initiated at pubertal age, it may be beneficial in achieving the final height compatible with the genetic potential together with the pubertal growth spurt.

Finally, our results justifies the incorporation of height SDS at the beginning of treatment, target height SDS, first-year response to treatment as a major parameters in all predictive models of final height in all GH-treated children (21, 32, 33).

Study Limitations

The main limitations of this study are that it was designed retrospectively and the number of patients who could be evaluated in the final heights was low.

Conclusion

As a result, in this study it was found that GH treatment was started late in entire group and there was no difference in the last 10 years. It was observed that patients who were admitted with short stature received GH treatment approximately 1.5 years later and this negatively affected the treatment responses. Pediatric endocrinologists should be more careful and shorten follow-up periods without treatment. As a result of late start of GH treatment, improvement in the height SDSs of SGA and TS groups was minimal. In the IGHD group, it was seen that approximately 68% of those who reached the final height achieved the target height. Treatment compliance of patients receiving GH treatment was very fairly high.

Although our results cannot be generalized for the whole country, we think that GH treatment does not show regional differences, the data obtained from large patient series are important, and in this context, our study may reflect the current situation in GH treatment in our country. Therefore, with the findings obtained from this study, it was concluded that it is

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necessary to conduct awareness studies for short stature, to make rapid diagnosis in patients with pathological short stature, to shorten the follow-up periods without treatment, and to start treatment earlier.

Ethics

Ethics Committee Approval: The ethics committee approval of this study was received on 23.05.2018 from Keçiören Training and Research Hospital Clinical Research Ethics Committee (No: 1686).

Informed Consent: The study was retrospective and no interventions were used. Therefore we did not obtain informed consent from the patients or their parents.

Peer-review: Internally peer-reviewed.

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Authorship Contributions

Medical Practices: Aslıhan Araslı Yılmaz, Servet Yel, Zehra Aycan, Concept: Zehra Aycan, Şenay Savaş Erdeve, Semra Çetinkaya, Design: Zehra Aycan, Şenay Savaş Erdeve, Semra Çetinkaya, Data Collection or Processing: Aslıhan Araslı Yılmaz, Servet Yel, Zehra Aycan, Analysis or Interpretation: Aslıhan Araslı Yılmaz, Servet Yel, Zehra Aycan, Şenay Savaş Erdeve, Semra Çetinkaya, Literature Search: Aslıhan Araslı Yılmaz, Zehra Aycan, Writing: Aslıhan Araslı Yılmaz, Zehra Aycan.

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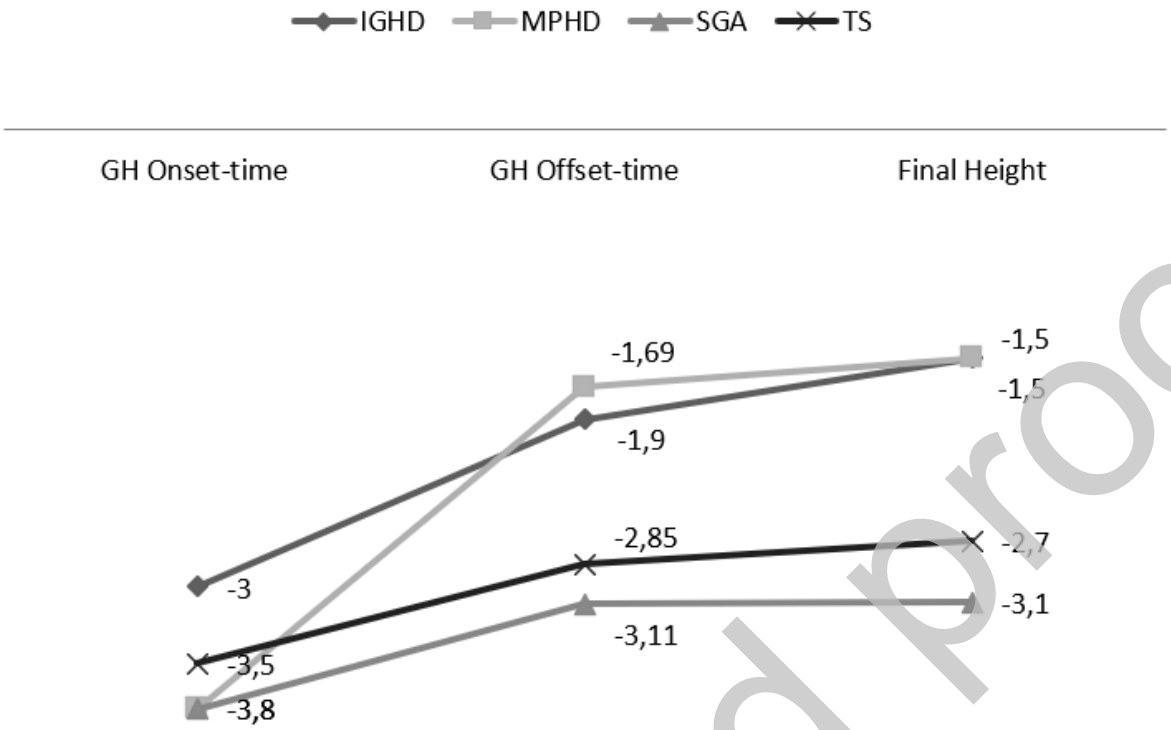

Table 1 Age at admission and GHT onset age by years

(Year)		Age at admission- Entire group		Age at onset of treatment Entire group		Age at admission **IGHD group**		Age at onset of treatment **IGHD group**
	n	Median (Min.-Max.)	n	Median (Min.-Max.)	n	Median (Min.-Max.)	n	Median (Min.-Max.)
2009	23	9.9 (3.6-17)	23	11.5 (4-17.3)	18	10.1 (4-17)	18	11.5 (4.2-17.3)
2010	84	9.7 (0.1-15.4)	84	11.7 (4.6-16.3)	68	10.2 (2,9-15.4)	68	12 (4.6-16.3)
2011	98	10.9 (1.8-16.6)	98	12 (5.1-17)	92	10.8 (1.8-16.6)	92	12 (5.1-17)
2012	86	10.7 (0.2-15.6)	86	1.8 (0.8-16.4)	77	10,8 (0,6-15,6)	77	11,8 (0,8-16,4)
2013	104	11 (0-16.8)	104	12 (1.4-16.9)	95	11,1 (1-16,8)	95	12,1 (1,4-16,9)
2014	93	11.1 (0-15.6)	93	12.2 (2.1-17)	88	11,2 (0,5-15,6)	88	12,2 (2,1-16)
2015	83	10.5 (0-15.8)	83	12 (3.1-16.5)	78	10,7 (2-15,8)	78	12,2 (3,1-16,5)
2016	70	9.1 (0.3-15.1)	70	11.8 (2-16.4)	60	9,2 (0,8-15,1)	60	12 (2,5-16,4)
2017	87	9.3 (0-16)	87	11.7 (3.1-16.6)	80	9,8 (0-16)	80	11,7 (3,1-16,6)
2018	39	11.3 (2.7-15.7)	39	12.8 (3.7-16)	33	11,6 (3,3-15,7)	33	12,8 (5,1-16)
P		0.091		0.232		0.294		0.472

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IGHD: Isolated Growth Hormone Deficiency

Table 2 Anthropometric and laboratory features of patients at the GHT onset period

	Entire group (N=767)	**IGHD (n=689)**	MPHD (n=24)	**SGA** (n=26)	TS (n=28)
Chronologic Age	12	12.0	9.3	8.4	10.6
(years)	(0.83-17.3)	(0.83-17.3)	(1.8-17)	(3.0-14.4)	(2.4-15.4)
Bone Age (years)	9	10	5	5.3	8.1
	(0.5-15)	(0.5-15)	(0.5-13.5)	(1.1-13.5)	(2-13)
Sex n/% (female)	289(37.7)	240(34.8)	6(25)	15(57.7)	28(100)
(male)	478 (62.3)	449 (65.2)	18 (75)	11 (42.3)	0(0)
Birth weights	0.09	0.11	0.09	-2.45	-0.47
SDS	(-3.30-3.19)	(-1.97-3.19)	(-1.96-1.42)	(-3.30- -2.02)	(-1.72-1.17)
Height SDS	-3	-2.9	-3.8	-3.4	-3.4
	(-8.5 - -1.0)	(-8.5 - -1.7)	(-7.8 - -1)	(-5.9 - -2.5)	(-6.9 - -1.82)
BMI SDS	-0.8	-0.9	0.2	-1.21	0.7
	(-6.3-3.6)	(-6.3-3.6)	(-4-3.2)	(-2.8-1.7)	(-2.8-1.9)
Puberty	1 (1-5)	1 (1-5)	1 (1-2)	1 (1-5)	1 (1-2)
L-dopa-peak	3.86	3.86	0.48	9.5	3.66
GH (ng/mL)	(0.01-18.9)	(0.01-9.88)	(0.07-9.6)	(0.46-18.9)	(0.55-11.4)
Clonidine peak	5.05	5.05	0.52	11.36	5.19
GH (ng/mL)	(0-25.1)	(0.02-9.74)	(0.13-9.11)	(0-25.1)	(0.73-10.1)
ITT peak GH	1.8	1.8	0.3	6.39	2.46
(ng/mL)	(0-10.4)	(0.04-9.67)	(0-1.7)	(1.1-10.4)	(0.28-7.66)
Serum IGF1	146.3	148	50.1	117	147
(ng/mL)	(11.5-555)	(11.5-555)	(16.9-231)	(37.3-222)	(43.3-375)
IGF1 SD < -2	330 (43.9%)	303 (44.6%)	16 (80%)	7(26.9%)	4 (15.4)
(n/%)					
IGF1SD	380 (50.5%)	340 (50%)	4 (20%)	17 (65.4%)	19 (73.1)
-1 to -2(%)					
(n/%)					
IGF1SD > -1 (%)	42(5.6)	37 (5.4%)	0 (0%)	2 (7.7%)	3 (11.5)
(n/%)					
Serum IGFBP3	3840	3890	1470	3245.5	3759
(ng/mL)	(49.4-8800)	(49.4-8800)	(500-5570)	(1800-6120)	(1340-6780)
IGFBP3 SD < -2	83 (11.1%)	72 (10.5%)	11 (55%)	0 (0%)	1 (3.9)
(n/%)					
IGFBP3SD					
-1 to -2	489 (65.5%)	454 (67.3%)	7 (35%)	14 (53.8%)	14 (53.8)
(n/%)					
IGFBP3SD	175 (23.4%)	150 (22.2%)	2 (10%)	12 (46.2%)	11 (42.3)
> -1					

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(n/%)

IGHD: Isolated Growth Hormone Deficiency, MPHD: Multiple Pituitary Hormone Deficiency, **SGA: Small for gestational age**, TS: Turner syndrome, SD (S): Standard deviation score, BMI: Body mass index, ITT: Insulin tolerance test, IGF1: Insulin-like growth factor 1, IGFBP3: Insulin-like growth factor-binding protein 3, Median (Minimum-Maximum)

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Table 3 Anthropometric and Clinical Findings of Patients at the Time of Admission, GHT Onset Time, and GHT off set time

		n	Admission Median (Min.Max.)	GH treatment OnsetTime Median (Min.Max.)	GH treatment Offset Time Median (Min.Max)	p
Entire Group	Age (years)	499	11.2 (0-17)^{bc}	12.2 (0.8-17.3)^{ac}	15.1 (2.9-21)^{ab}	<0.001*
	Bone age (years)	449	8.1 (0-15)^{bc}	10 (0.8-15)^{ac}	14 (1-17)^{ab}	<0.001*
	Height SDS	499	-2.9 (-8.5-1.8)^{bc}	-3 (-8.5--1.7)^{ac}	-2 (-7.2-1)^{ab}	<0.001*
	BMI SDS	498	-0.9 (-5.5-4)^{c}	-1 (-6.3-3.6)	-0.8 (-10.2-4.2)^{b}	0.005*
	Puberty	495	1 (1-5)^{c}	1(1-5)^{c}	4 (1-5)^{ab}	<0.001*
	Follow-up (year)	767	-	0.9 (0-12.5)	2.1 (0.3-10.8)	<0.001*
IGHD	Age (years)	453	11.4 (0.6-17)^{bc}	12.3 (0.8-17.3)^{ac}	15.1 (2.9-19)^{ab}	<0.001*
	Bone age (years)	407	8.1 (0-15)^{bc}	10 (0.8-15)^{ac}	14 (1-17)^{ab}	<0.001*
	Height SDS	453	-2.8 (-8.5--0.2)^{bc}	-3 (-8.5--1.7)^{ac}	-1.9 (-7.1-1)^{ab}	<0.001*
	BMI SDS	452	-0.9 (-4.3-3.5)	-1 (-6.3-3.6)^{c}	-0.8 (-10.2-4.2)^{b}	0.011*
	Puberty	449	1 (1-5)^{c}	1(1-5)^{c}	4 (1-5)^{ab}	<0.001*
	Follow-up (year)	689	-	0.9 (0-12.5)	2.1 (0.3-10.8)	<0.001*

MPHD	Age (years)	15	7.2 (0-14.9)[bc]	9.9 (1.8-17) [ac]	16.3 (3.8-21)[ab]	<0.001*
	Bone age (years)	13	5 (1-11)[c]	6 (2.9-13.5)[c]	14 (7-17)[ab]	<0.001*
	Height SDS	15	-3.5 (-5.98- -0.97) [bc]	-3.84 (-6.08- -2.18) [ac]	-1.69 (-6.3- -0.24) [ab]	<0.001*
	BMI SDS	15	-0.2 (-2.4-1.9)	-0.52 (-2.39-1.91)	-0.16 (-3.38-1.54)	0.207
	Puberty	15	1 (1-2)[c]	1(1-2)[c]	3 (1-5)[ab]	0.007*
	Follow-up (year)	24	-	1.5 (0-6.8)	3.8 (0.3-9)	0.023*
SGA	Age (years)	14	9.01 (0.19-14.01)[bc]	10.35 (3.01-14.4) [ac]	13.91 (5.1-17.3)[ab]	<0.001*
	Bone age (years)	13	8.1 (1.6-13.6)[c]	9 (1.06-13.5)[c]	14 (3-16)[ab]	<0.001*
	Height SDS	14	-3.87 (-5.81- -2.6)	-3.84 (-5.87- -2.49)	-3.11 (-7.2- -1.9)	0.191
	BMI SDS	14	-1.2 (-3.7-4)	-1.67 (-2.64-0.97)	-1.21 (-3.08-1.82)	0.257
	Puberty	17	1 (1-3)[c]	1(1-3)[c]	2 (1-5)[ab]	0.040*
	Follow-up (year)	26	-	1.5 (0.1-5.3)	2.4 (0.5-8.3)	0.038*
TS	Age (years)	17	9.4 (0-13.6)[bc]	11.11 (7-13.8)[ac]	14.6 (7.3-17)[ab]	<0.001*
	Bone age (years)	16	7.6 (0.5-13)[c]	8.1 (5-13)[c]	13.5 (10-15)[ab]	<0.001*
	Height SDS	17	-3.42 (-4.33-1.79)	-3.5 (-4.33 - -1.95)	-2.85 (-5.2- -1.1)	0.225
	BMI SDS	17	0.7 (-5.5-1.7)	0.75 (-1.22-1.9)	0.4 (-1.16-2.41)	0.814
	Puberty	17	1 (1-2)[c]	1(1-2)[c]	4 (1-5)[ab]	0.001*
	Follow-up (year)	28	-	0.5 (0-11)	2.8 (0.3-6.3)	0.008*

SD(S): Standard deviation score, BMI: Body Mass Index, **IGHD: Isolated Growth Hormone Deficiency**, MPHD: Multiple Pituitary Hormone Deficiency, **SGA: Small for gestational age**, TS: Turner syndrome, a: Different from admission time, b: Different from GH treatment onset-time, c: Different from GH treatment offset-time, *: p< 0.05

Table 4 Descriptive analysis of patients reaching final height

	Entire group (n=189)	**IGHD** (n=166)	MPHD (n=8)	**SGA** (n=4)	TS (n=11)
Age (years)	17 (12.7-23)	17 (12.7-23)	17.8 (14.6-19.6)	16.3 (14.9-18)	16.4 (15-18)
Bone age (years)	16 (12.5-17.4)	16 (13.6-17.4)	16 (12.5-16)	16	-
Sex (female)	95 (50.3)	77 (46.4)	3 (37.5)	4 (100)	11 (100)
(male)	94 (49.7)	89 (53.6)	5 (62.5)	0 (0)	0 (0)
Final Height (Girl)	153.3 (133-170.8)	154 (137.5-170.8)	156.2 (150-160.6)	145.7 (136.7-150.3)	146.7 (133-156.4)
Final Height (Boy)	164.9 (146.7-173.2)	164.9 (152-173.2)	163.5 (146.7-171.8)	-	-

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Final Height (FH) SDS	-1.6 (-4.6 -0.7)	-1.5 (-3.5-0.7)	-1.5 (-2.5 - -0.4)	-3.1 (-4.5 - -2.1)	-2.7 (-4.6 - -1.2)
Target Height (TH) SDS	-1.5 (-3.4-0.5)	-1.5 (-3.4-0.5)	-1.1 (-1.8 - -0.3)	-2 (-3.4 --1.06)	-1.2 (-1.7-0.1)
TH-FH SDS	0.2 (-2.3-3.4)	0.1 (-2.3-3)	0.6 (-1.2-1.8)	0.5 (-0.1-2.8)	2.4 (0.4-3.4)
BMI	20.4 (15-37.6)	20.1 (15-33)	23.4 (16.7-26.6)	19.3 (18.9-20.7)	24.2 (19.2-37.6)
BMI -SDS	-0.6 (-4.2-4.3)	-0.7 (-4.2-3.8)	0.5 (-3.1-1.6)	-0.6 (-1.5-1.5)	0.7 (-1.1-4.3)
Puberty	5 (2-5)	5 (3-5)	4 (2-5)	5 (4-5)	5 (3-5)
Age at onset of treatment	12.4 (4-17.3)	12.5 (5.4-17.3)	9 (4-17)	12.3 (12.1-13.9)	11.1 (8.4-13.2)
Duration of treatment (year)	2.9 (0.2-12)	2.8 (0.2-12)	6 (1.5-9)	1.9 (1-4)	4.5 (1.3-6.3)
Treatment dose (mg/kg/wk)	0.2 (0.2-0.4)	0.2 (0.2-0.3)	0.2 (0.2-0.2)	0.2 (0.2-0.3)	0.3 (0.2-0.4)
Not reaching target height	62 (35.8)	50 (32.5)	3 (42.9)	2 (50)	7 (87.5)
Reaching target height	111 (64.2)	104 (67.5)	4 (57.1)	2 (50)	1 (12.5)

SD(S): Standard deviation score, BMI: Body Mass Index, **IGHD: Growth Hormone Deficiency**, MPHD: Multiple Pituitary Hormone Deficiency, **SGA: Small for gestational age**, TS: Turner syndrome, **TH:Target Height, FH:Final Height**

Table 5 Comparison of IGHD patients reaching final height according to their puberty status at the beginning of treatment

	Prepubertal (n=93) Median (Min.Max.)	Pubertal (n=73) Median (Min.Max	p
Age (years)	12 (5.4-14.4)	14 (11.11-17.3)	<0.001
Bone age (years)	8.1 (3-10)	12 (10.50-15.00)	<0.001
Height SDS	-3.00 (-5.54 - -2.39)	-2.81 (-5.10 - -1.70)	0.140
BMI SDS	-1.16 (-3.91-1.98)	-1.14 (-5.03-1.70)	0.912
Target Height SDS	-1.63 (-3.38-0.13)	-1.23 (-3.03-0.49)	0.052
Final Height SDS	-1.59 (-3.10 - -0.13)	-1.42 (-3.5-0.70)	0.444
First year growth velocity (cm)	8.5 (3.9-11.8)	8.7 (2.0-11.6)	0.867
Duration of treatment (year)	3.5 (1.4-9)	2.00 (0.3-4.8)	<0.001
Treatment dose (mg/kg/wk)	0.2 (0.2-0.3)	0.2 (0.2-0.3)	0.335

SD(S): Standard deviation score, BMI: Body Mass Index

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Table 6: Multiple lineer regression analysis on final height standart deviation score (SDS)

R^2=0,377

P<0,001

Variable	B	SE	Beta	t	p
Target Height SDS	0.161	0.080	0.139	2.019	0.045
Bone age (year)	-0.078	0.042	-0.195	-1.847	0.067
GH treatment -onset-time Height SDS	0.482	0.093	0.358	5.199	<0.001
Puberty	-0.168	0.076	-0.161	-2.209	0.029
First year growth velocity(cm/year)	0.144	0.035	0.278	4.105	<0.001

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