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Research Article

Adherence to Growth Hormone-Determined by a Consensual, Center-Based Supply-Associates with Height Outcomes in Youth

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Abstract

Objective: The efficacy of recombinant human growth hormone (rhGH) therapy in children and adolescents depends on underlying cause, younger age and height at therapy onset, expected height related to mid-parental height (MPH), duration of treatment and optimal adherence. Here, we investigated the association between adherences to rhGH-therapy with gain in height standard deviation (ΔHSD) in reference to mid-parental height (MPH), from treatment start to the most recent visit.

Methods: Single-center, retrospective data analysis in patients on rhGH between 2006-2020. Anthropometric data were normalized using national representative growth charts. Adherence was calculated as the ratio (%) of rhGH distributed / rhGH needed (reported by specialized nursing staff and treating endocrinologist). Linear interpolation was used to calculate annualized follow-up data. Multiple linear regression modelling was applied.

Results: A total of 125 patients received rhGH, of whom 102 had longitudinal data (>12 months) over a mean of 5.4 years (SD 2.9). In the first year after treatment start, the mean (SD) growth velocity (GV) was 9.4cm/y (2.5), followed by measures in the upper normal range in subsequent years. Adjusted for duration of treatment, sex and MPH, adherence (per 10% increment) was associated with ΔHSD (β-coefficient 0.36, 95% confidence interval 0.04-0.67, p-value 0.026).

Conclusion: In the setting of a centre-based distribution of rhGH, the assessment of adherence as the ratio of rhGH distributed/ needed can help to identify those who respond poorly and may benefit from further support to optimize treatment efficacy.

Keywords: Adherence; Growth hormone; Short stature; Children

Introduction

Children with short stature due to various underlying causes including growth hormone deficiency, Turner syndrome and chronic renal failure are treated with recombinant human growth hormone (rhGH), aiming to achieve their genetically determined adult height and body composition. The largest published longitudinal study undertaken by the Safety and Appropriateness of Growth hormone treatments in Europe (SAGhE) consortium, including more than 400,000 patient-years of follow-up, has provided evidence that treatment with rhGH is safe and effective [1]. Efficacy of rhGH treatment for short stature depends on the underlying cause. In addition, younger age and lower height at therapy-onset, higher mid-parental height [2], appropriate rhGH dosing and better therapy adherence [3-6] have all been identified as factors contributing to efficacy. Adherence has previously been defined as "the extent to which a person's behaviour, with regard to taking medication, following a diet and/or executing lifestyle changes, corresponds with agreed recommendations from a health-care provider" [7]. Challenges for optimal adherence to rhGH treatment include a requirement for daily, long-term subcutaneous injections, lower socio-economic status [8], adolescent age [9], and an inadequate understanding of the treatment goals [9]. Observational evidence has shown non-adherence to rhGH treatment in up to 82% of individuals [10]. Poor adherence to rhGH therapy is associated with reduced height velocity and ultimately with unsatisfactory final adult height [4,6]. From a public health perspective, poor adherence to rhGH treatment causes unnecessary costs [11]. Despite key for efficacy, methods to assess adherence are sparse. Here, we investigate adherence and efficacy of rhGH therapy in all children and adolescents treated with rhGH since 2006 in a Swiss tertiary centre. Our study aims were to i) assess efficacy of growth hormone treatment in our centre and ii) to investigate any association between adherence and height achievement, assessed by the increase in height SD from treatment start to the most recent visit (ΔHSD).

Methods

Design and Patients

This study is a single-centre, retrospective, observational analysis of all patients who received rhGH treatment between January 2006 and October 2020 at the department of paediatric endocrinology at the Inselspital Berne, Switzerland. The study did not require approval by the ethics committee as it was subject to an internal audit. The study fully conforms to the World Medical Association Declaration of Helsinki. Patients were reviewed at the timepoint of diagnosis (baseline), 3 months after initiation of rhGH treatment and every 6 months thereafter.

Data collection

Participant`s data included sex, age (y), height (m), weight (in kg), BMI (determined by weight in kg divided by height in m^2), sex-related mid-parental height expectation (MPH, calculated as half the combined parental heights minus 6.5 cm for females, plus 6.5 cm for males) and pubertal status according to Tanner [12,13]. Height was measured using a wall mounted Harpenden stadiometer (Ulmer Stadiometer 751.000, Busse Design+Engineering®, Elchingen, Germany). Growth velocity (GV) was calculated in centimetres per year with a minimum of 6 months interval between assessments. Height, weight, BMI, MPH and GV were given in absolute measures and in standard deviations (SD) based on national normative reference data [14]. Baseline and annualized data for height and GV since treatment start were estimated using linear interpolation of measures obtained at visits before and after each anniversary, as previously described [15]. Annualized growth rate and annualized height SD in relation to individual mid-parental height SD were determined for every patient for the number of treatment-years completed and used to assess efficacy. Annual bone age results were obtained by comparison of a left wrist X-ray compared with the Greulich and Pyle radiographic atlas [16] by trained paediatric endocrinologists. Growth hormone stimulation testing was performed according to site-specific protocols, using either Arginine or Insulin tolerance tests. Serum growth biomarkers IGF-1 and IGF-BP3 were measured using Chemiluminescent Immunoassay technology (Siemens, Immulite® 2000).

Categorization of patients on rhGH treatment

Variability of indications for rhGH treatment affects anticipated efficacy. For descriptive purposes we therefore categorized patients according to a modified Sävendahl et al. risk group classification (1) (indications and baseline characteristics are described in Table 2).

Characteristic	n (%)	Mean (SD)	Range (min - max)
Sex, males (%)	76 (61)		
Age (y)	125	6.04 ± 3.12	0.50 - 16.09
Weight (kg)	125	17.0 ± 7.6	5.3 - 46.0
Weight SD	125	-1.83 ± 1.38	-7.07 to 3.34
Height (m)	125	1.03 ± 0.19	0.54 - 1.50
Height SD	125	-2.40 ± 1.33	-8.78 to 1.16
BMI (kg/m2)	125	15.4 ± 2.0	11.6 - 25.7
BMI SD	125	-0.39 ± 1.26	-3.72 to 4.73
Tanner stage	125 (100)		
n pre-pubertal	120 (96)		
n peri-pubertal	5 (4)		
n post-pubertal	0		
Difference in BA to CA (y)	118 (91)	-1.34 ± 1.26	-5.72 to 4.77
Category	125 (100)		
1a	60 (48)		
1b	22 (18)		
2a	18 (14)		
2b	13 (10)		
3	12 (10)		
Abbreviations: n, number of individuals; BA, Bone age; CA, chronologic age: y, years; BMI, body mass index.			

Table 1: Patient characteristics.

	1a (60)			1b (22)			2a (18)			2b (13)			3 (12)		
Characteristic	n (%)	Mean (SD)	Range (min-max)	n (%)	Mean (SD)	Range (min-max)	n (%)	Mean (SD)	Range (min-max)	n (%)	Mean (SD)	Range (min-max)	n (%)	Mean (SD)	Range (min-max)
Sex, males (%)	41 (68)			16 (72)			10 (56)			5 (38)			4 (33)		
Age(y)	60	6.67 ± 3.12	1.29 - 16.09	22	5.91 ± 1.81	4.13 - 10.19	18	3.50 ± 2.36	0.50 - 7.93	13	4.68 ± 2.74	2.16 - 11.51	12	8.41 ± 3.30	3.14 - 13.30
Weight (kg)	60	17.5 ± 7.2	5.6 - 44.5	22	15.6 ± 4.2	9.8 - 26.2	18	12.7 ± 6.3	5.3 - 27.4	13	15.2 ± 5.7	8.0 - 27.0	12	25.3 ± 10.7	11.1 - 46.0
Weight SD	60	-2.04 ± 0.92	-5.65 to 0.18	22	-2.10 ± 1.01	-4.23 to 0.51	18	-1.89 ± 2.26	-7.07 to 1.90	13	-1.32 ± 2.10	-4.75 to 3.34	12	-0.88 ± 1.36	-2.55 to 2.10
Height (m)	60	1.05 ± 0.18	0.61 - 1.50	22	1.02 ± 0.12	0.84 - 1.27	18	0.86 ± 0.20	0.54 - 1.30	13	0.96 ± 0.14	0.78 - 1.30	12	1.20 ± 0.20	0.85 - 1.50
Height SD	60	-2.53 ± 0.98	-7.36 to -1.12	22	-2.56 ± 0.78	-4.44 to -0.71	18	-2.75 ± 2.46	-8.78 to 1.16	13	-2.00 ± 1.69	-4.08 to 1.12	12	-1.55 ± 1.10	-3.13 to 0.08
BMI (kg/m2)	60	15.1 ± 1.6	12.6 - 20.1	22	14.8 ± 1.5	11.6 - 17.9	18	16.1 ± 1.7	13.1 - 19.3	13	16.0 ± 2.4	13.1 - 23.4	12	16.8 ± 3.3	13.9 - 25.7
BMI SD	60	-0.64 ± 1.03	-3.07 to 1.54	22	-0.57 ± 1.22	-3.72 to 1.31	18	0.08 ± 1.25	-2.24 to 2.51	13	0.11 ± 1.60	-1.93 to 4.73	12	0.03 ± 1.59	-1.60 to 4.10
Tanner stage	60			22			18			13			12		
n pre-pubertal (%)	58 (97)			22 (100)			17 (94)			13 (100)			10 (83)		
n peri-pubertal (%)	2 (3)			0			1 (6)			0			2 (17)		
n post-pubertal	0			0			0			0			0		
Difference in BA to CA (y)	58	-1.62 ± 1.09	-5.72 to 0.76	22	-1.49 ± 1.07	-3.46 to 0.90	13	-0.74 ± 1.97	-3.59 to 4.77	11	-1.42 ± 0.99	-3.59 to 0.03	12	-0.84 ± 1.55	-4.63 to 1.40

Category 1a: children with isolated growth hormone deficiency; 1b: children born small for gestational age; 2a: children with multiple pituitary hormone deficiencies and rare genetic syndromes; 2b: children with Turner syndrome and SHOX-gene deficiency; 3: children with short stature related to cancer treatment and chronic renal failure. Abbreviations: n, number of individuals; BA, Bone age; CA, chronologic age: y, years; BMI, body mass index.

Table 2: Patient characteristics by category.

Adherence analyses

The specialized endocrine nursing staff exclusively distribute rhGH to all patients, according to their reported remaining household stock from the previous visit, and the clinician`s prescribed daily dose for the period until the next visit. Hence, adherence was calculated in retrospect at each visit, based on the ratio of rhGH distributed to the rhGH dose needed for the relevant interval. During follow-up visits, the rhGH dose was adjusted based on the patient's weight, growth velocity and IGF-1 result as per published recommendations for the underlying diagnosis [17-20]. For the analysis, the cumulative adherence over the whole duration of treatment was used until the most recent consultation. Adherence values above 100% for patients who received a higher amount of rhGH than needed at the start of the rhGH treatment to secure sufficient stock (in the magnitude of ~10-20% in case of postponed clinical follow-up visits) were set to 100% for the inferential analysis. Patients with less than 12 months of longitudinal data (i.e, two follow-up visits) were excluded from the adherence analyses.

Statistics

Descriptive statistics for patient characteristics were mean, SD and range (min-max) for continuous variables and proportions for categorical variables. Linear regression modelling was performed to examine any association between adherence to rhGH treatment (independent variable) and efficacy of GH treatment (dependent variable). Efficacy was calculated as the difference in baseline height SD to the most recent height SD (ΔHSD) in reference to individual MPH. The final model was adjusted for duration of treatment and sex.

Results

A total of 125 patients with an exposure of 578 patient-years to rhGH were included (see Table 1 and Table 2). Mean pre-treatment height SD varied from -2.56 SD in category 1b to -1.55 in category 3. A sex ratio of 3:1 in favour of the male sex was seen. Two patients presented a height SD >1 at the start of GH therapy: one diagnosed with late onset congenital adrenal hyperplasia had a bone age 4.8 years advanced above chronological age, the second patient was started on rhGH in the first year of life due to persistent hypoglycaemia in the context of septo-optic dysplasia and multiple pituitary hormone deficiencies.

Adherence

Data for adherence was available for a total of 102 patients covering 553 patient years. Cumulative adherence results were 100% in 51 patients (50%), between ≥90-100% in 32 patients (31%), ≥80-90% in 16 patients (16%) and <80% in 3 patients (3%). The results of the regression model to investigate any association between adherence to and efficacy of rhGH treatment, adjusted for sex, MPH and the duration of treatment are shown in Table 4. The β-coefficient (95% confidence interval, p-value) for a 10% increase in adherence was 0.37 SD (0.06-0.7, p=0.026) in ΔHSD.

Efficacy

A total of 107 patients had longitudinal data with a mean (SD) duration of treatment of 5.4 years (2.8). The largest increases in mean (SD) height and absolute measures of growth velocity (GV) were seen during the first year of treatment with 0.77 (0.55) and 9.4 cm/y (2.5), respectively. After the first year of treatment, mean GV remained within the upper normal range adjusted for age and sex. Figure 1 illustrates catch-up growth per year of treatment with rhGH for participants with longitudinal data. Figure 2 illustrates efficacy-trajectories of rhGH treatment per category. Relevant GVs and increases in height SD in relation to baseline height SD are summarized in Table 3.

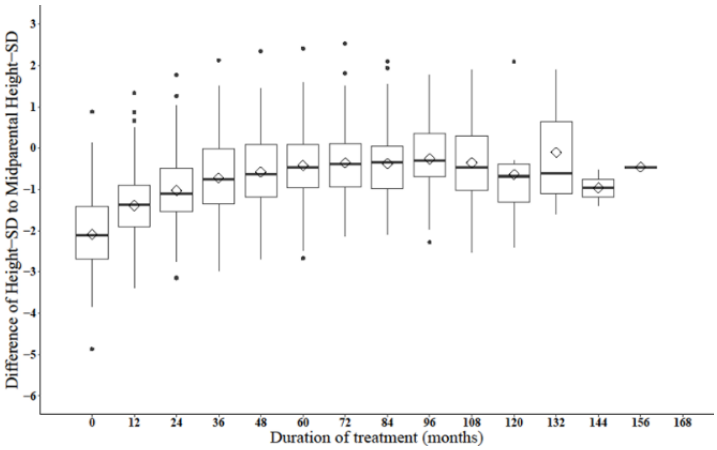

Figure 1: Box and whisker plot to indicate the difference between height SD at commencement of rhGH to individual MPH-SD over time. Bold line indicates median, rectangle indicates upper and lower quartile, diamond indicates mean value.

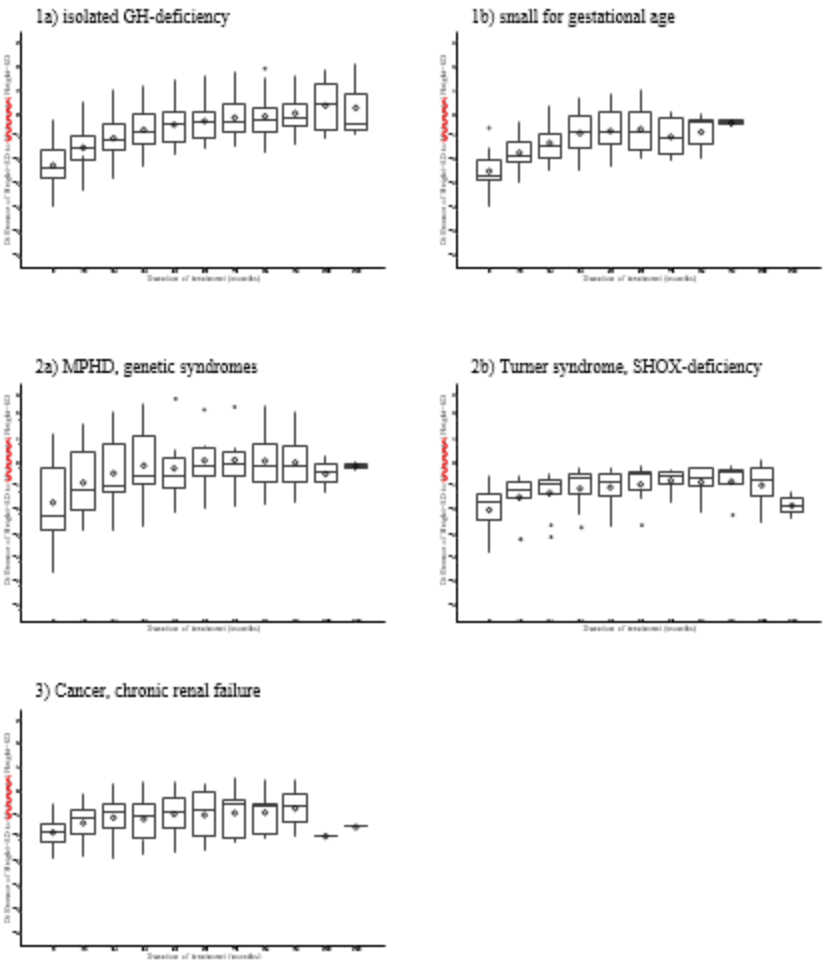

Figure 2: Box and whisker plot to indicate the difference between heights SD at rhGH-treatment start to individual MPH-SD over 10 years. Bold line indicates median, rectangle indicates upper and lower quartile, diamond indicates mean value. Number of participants for each category: 1a) 53; 1b) 20; 2a) 14; 2b) 11; 3) 9.

		1a (53)			1b (20)			2a (14)			2b (11)			3 (9)			Total (107)		
Year	Characteristic	n Mean (SD)		Range (min - max)	n	Mean (SD)	Range (min - max)	n	Mean (SD)	Range (min - max)	n	Mean (SD)	Range (min - max)	n	Mean (SD)	Range	n	Mean (SD)	Range
1	GV (cm/y)	53	9.4 ± 2.5	5.7 - 16.3	20	9.0 ± 2.1	4.7 - 13.3	14	10.9 ± 3.2	6.3 - 18.8	11	9.1 ± 1.7	5.9 - 11.7	9	8.4 ± 2.2	5.9 - 12.	107	9.4±2.5	4.7 - 18.8
	Δ Height SD*	53	0.84 ± 0.62	-0.05 to 3.30	18**	0.77 ± 0.41	-0.07 to 1.67	11**	0.82 ± 0.55	-0.01 to 2.18	11	0.53 ± 0.37	-0.25 to 1.00	9	0.39 ± 0.62	-0.84 to 1.29	102**	0.75±0.57	-0.84 to 3.30
2	GV (cm/y)	48	7.5 ± 1.4	4.6 - 11.0	18	7.3 ± 1.6	3.5 - 10.1	11	8.1 ± 1.3	6.7 - 11.4	10	7.4 ± 0.8	6.2 - 8.7	9	6.2 ± 2.1	3.4 - 9.2	96	7.4±1.5	3.4 - 11.4
	Δ Height SD*	48	1.25 ± 0.87	-0.30 to 4.54	18	1.13 ± 0.56	0.09 - 2.18	11	1.26 ± 0.80	0.14 - 3.32	10	0.75 ± 0.47	-0.20 to 1.40	9	0.62 ± 0.65	-0.29 to 1.72	96	1.12±0.78	-0.30 to 4.54
3	GV (cm/y)	42	6.9 ± 1.2	5.3 - 10.7	13	7.0 ± 1.5	4.9 - 10.7	11	7.6 ± 1.1	6.2 - 9.1	9	6.5 ± 0.8	5.0 - 8.2	8	5.6 ± 2.3	0.9 - 7.7	83	6.8±1.4	0.9 - 10.7
	Δ Height SD*	42	1.46 ± 0.81	0.28 - 4.28	13	1.50 ± 0.58	0.59 - 2.46	11	1.55 ± 0.92	0.54 - 3.94	9	1.09 ± 0.44	0.26 - 1.59	8	0.55 ± 0.81	-0.53 to 1.80	83	1.35±0.80	-0.53 to 4.28

4	GV (cm/y)	41	6.4 ± 1.4	3.1 - 10.1	10	6.3 ± 1.0	5.3 - 83	7	7.0 ± 1.5	4.8 - 8.6	8	5.9 ± 0.5	5.2 - 6.8	7	5.2 ± 2.1	2.0 - 7.6	73	6.3±1.4	2.0 - 10.1
	Δ Height SD*	41	1.64 ± 0.88	0.15 - 4.84	10	1.67 ± 0.66	0.63 - 2.66	7	2.06 ± 1.12	1.15 - 4.44	8	1.21 ± 0.56	0.32 - 2.21	7	0.64 ± 0.95	-0.82 to 1.77	73	1.54±0.91	-0.82 to 4.84
5	GV (cm/y)	38	6.5 ± 3.5	3.1 - 26.3	7	6.2 ± 0.7	5.4 - 7.4	7	7.5 ± 1.2	6.3 - 9.2	7	5.7 ± 0.7	4.9 - 6.8	5	4.5 ± 1.9	1.3 - 6.1	64	6.3±2.9	1.3 - 26.3
	Δ Height SD*	38	1.81 ± 0.88	0.75 - 4.76	7	1.70 ± 0.84	0.53 - 2.80	7	2.39 ± 1.24	1.29 - 5.01	7	1.11 ± 0.42	0.50 - 1.83	5	0.59 ± 1.07	-0.08 to 1.71	64	1.69±0.97	-0.77 to 5.01
6	GV (cm/y)	31	6.3 ± 1.5	2.9 - 11.1	6	5.6 ± 1.0	4.4 - 7.0	6	6.2 ± 0.8	5.3 - 7.2	6	4.8 ± 0.5	4.4 - 5.4	5	4.5 ± 3.4	0.5 - 8.0	54	5.9±1.7	0.5 - 11.1
	Δ Height SD*	31	1.97 ± 1.00	0.66 - 4.84	6	1.47 ± 0.72	0.51 - 2.63	6	2.68 ± 1.30	1.38 - 5.17	6	1.02 ± 0.46	0.34 - 1.78	5	0.68 ± 0.93	-0.42 to 1.93	54	1.77±1.08	-0.42 to 5.17
7	GV (cm/y)	20	6.7 ± 1.8	4.2 - 11.6	5	6.1 ± 1.3	5.0 - 8.2	4	5.0 ± 1.5	3.4 - 6.7	6	5.3 ± 1.1	3.8 - 6.6	5	3.3 ± 3.5	0.3 - 8.5	40	5.8±2.2	0.3 - 11.6
	Δ Height SD*	20	2.10 ± 1.23	0.70 - 5.36	5	1.60 ± 0.80	0.32 - 2.53	4	2.23 ± 0.65	1.47 - 2.95	6	0.95 ± 0.55	0.27 - 1.85	5	0.70 ± 077	-0.04 to 1.85	40	1.7±1.12	-0.04 to 5.36
8	GV (cm/y)	13	6.4 ± 2.1	3.5 - 10.4	3	4.3 ± 1.6	2.6 - 5.7	4	4.2 ± 2.3	0.8 - 5.5	5	5.7 ± 0.9	4.9 - 6.8	3	3.0 ± 2.0	0.6 - 4.2	28	5.4±2.2	0.6 - 10.4
	Δ Height SD*	13	2.44 ± 1.30	0.64 - 5.26	3	1.36 ± 1.16	0.06 - 2.28	4	2.16 ± 0.68	1.53 - 2.92	5	1.06 ± 0.56	0.35 - 1.87	3	0.80 ± 1.01	-0.19 to 1.83	28	1.86±1.21	-0.19 to
9	GV (cm/y)	7	7.4 ± 1.6	5.7 - 10.4				3	5.1 ± 3.1	1.6 - 7.5	4	5.6 ± 2.3	3.9 - 9.0				14	6.2±2.2	1.6 - 10.4
	Δ Height SD*	7	3.20 ± 1.44	1.50 - 5.48				3	2.54 ± 0.58	1.94 - 3.09	4	1.06 ± 0.95	0.11 - 2.37				14	2.27±1.55	0.15 to 5.48
10	GV (cm/y)	3	7.3 ± 2.1	5.1 - 9.2				2	3.1 ± 2.9	1.0 - 5.1	2	4.3 ± 0.5	3.9 - 4.7				7	5.2±2.4	1.0 - 9.2
	Δ Height SD*	3	2.88 ± 1.48	2.02 - 4.58				2	2.77 ± 0.61	2.34 - 3.20	2	0.40 ± 0.23	0.24 - 0.56				7	1.9±1.53	0.23 -4.58

Abbreviations: GV, growth velocity; SD, standard deviation. *Δ Height SD represents the difference of annualized height SD to height SD at rhGH start with reference to the MPH. ** MPH missing

Table 3: Efficacy of GH treatment.

SD Height-increase from baseline to most recent visit (ΔHSD)			
Predictor	Estimate	95%CI	p
(Intercept)	-1.96	-4.16 – 0.24	0. 080
Adherence of GH therapy (per 10%)	0.36	0.04 – 0.67	0.026
Sex (male)	0.39	-0.01– 0. 67	0.05
Duration of treatment (years)	0.16	0.08 – 0.23	<0.001
Observations	102		

Abbreviations: 95%CI, 95 % confidence interval; p, p-value; The measure of ΔHSD is in reference to individual midparental height expectancy.

Table 4: Regression model coefficients to predict height increase (SD) since start of GH therapy.

Discussion

In this single-center, retrospective cohort study of children and adolescents on rhGH treatment, adherence to rhGH therapy was positively associated with height gain over a mean duration of 5.4 years (SD 2.9). Besides adherence, duration of treatment and male sex was positively associated with height gain. Poor adherence to rhGH treatment is associated with impaired growth [4-6,21,22] and consequently, with unnecessary costs due to possible poorer final height outcomes [11]. The largest study on adherence investigated the connected easypod electronic drug delivery device with automated transmission of adherence data over 48 months. In a total of 13,553 children, a majority of 71% maintained an adherence rate ≥85% during the study period [23]. Using the same device in the French Easypod Connect Observational Study in 220 children (122 with growth hormone deficiency, 79 born SGA and 19 with TS), a mean daily dose <30 µg/kg per day given on at least 3 days a week was associated with a 20% higher mean yearly height gain compared to when less than 3 injections per week were received [22]. Van Dommelen et.al. Recently showed that missing one injection per week (adherence rate of 86%) was associated with 0.11 SD decrease in height gain per treatment year [24]. Several previous studies have reported a positive association between medication adherence and treatment efficacy, when followed-up between 1 and 3.2 years [4,22,25,26]. Adherence rate declines with treatment duration as previously reported [27], and recently confirmed by Koledova E et al. [28], using the connected easypod electronic drug delivery device in 1190 pediatric patients (75% with growth hormone deficiency): adherence rate dropped from 87.2% after 3 years to 75.5% after 4 years and 70.2% after 5 years of rhGH treatment. In the same study, Koledova E et al. [28] also showed that the adherence rate after one year of treatment was not associated with the rhGH treatment indication (i.e, irrespective of whether the indication was growth hormone deficiency, SGA, Turner syndrome). Similarly, Cutfield et. al. [6] did not find an association between treatment indication and rhGH adherence in a complete national cohort of New Zealand children and adolescents. Our study was not sufficiently powered to test for effects of treatment indication on adherence. Sex has been investigated as a covariate for adherence/compliance, revealing inconsistent results. In our study, we found a trend for male sex towards better ΔHSD (β-coefficient of 0.39, 95%CI -0,01 to 0.78, p-value 0.053). Most of the recent literature on adherence to rhGH stems from investigations using electronic drug delivery devices, their main aim being improvement in medication adherence [29]. Whereas these devices allow an objective assessment of adherence, not all patients are willing to use such a device, and usage of an electronic device per se does not improve adherence. Besides factores related to patient attributes and the health care system, interaction and communication skills of the care giver (such as to enhance patient motiviation, to provide emotional support or to build a partnership with a family) are key determinants of adherence and subsequent patient health outcomes [30]. Our simple and quick clinical method of assessing adherence offers an improved calculation of supplies remaining at home, and an opportunity to assess and directly address poor adherence when height gain is below expectations. Concerning treatment efficacy, our results are concordant with the literature. Maximum growth velocity and catch-up growth was seen during the first two years of treatment as shown in Figures 1 and 2. Patients treated for isolated growth hormone deficiency (group 1a) responded best to rhGH therapy. Patients born small for gestational age (SGA) nearly reached their target height SDS after 8 years of rhGH therapy as shown in Figure 2 [31-33]. There was a male preponderance in our study cohort of 61%, which may be a consequence of factors previously identified to contribute to sex disparity in rhGH treatment such as: screening bias by primary care physician, referal bias to pediatric endocrionologists for evaluation, bias of acceptable height cut-offs and interpretation of GH testing results, as well as bias related to prescribing and starting GH treatment [34]. Strengths of this study include duration, completeness and comprehensiveness of individual follow-up data. Limitations include the inability to identify modifiable determinants for adherence (such as lack of knowledge about consequences of missing injections; discomfort with injections; dissatisfaction with treatment results [9,35]. Accordingly, further studies to generate more appropriate measures are needed [36]. Our approach to assess adherence is based on a strictly centre-based distribution of rhGH. Insufficient data prevented a subanalysis of adherence based on our patient categorization.

Conclusion

Our approach to estimate adherence provides an easy and assessable method to identify patients who need further support to optimize treatment outcome. Any measure of adherence would be improved by methods that identify determinants for poor adherence.

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form from the corresponding author on reasonable request.

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