Original Paper

HORMONE RESEARCH IN PÆDIATRICS

Horm Res Paediatr 2016;86:161–168
DOI: 10.1159/000448553

Received: June 16, 2016
Accepted: July 19, 2016
Published online: September 6, 2016

Validation of Prediction Models for Near Adult Height in Children with Idiopathic Growth Hormone Deficiency Treated with Growth Hormone: A Belgian Registry Study

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Key Words
Growth hormone deficiency · Growth hormone therapy · Prediction model · Validation · Adult height

Abstract
Background/Aim: To validate prediction models for near final adult height (nFAH) by Ranke et al. [Horm Res Paediatr 2013;79:51–67]. ***Methods:*** Height data of 127 (82 male) idiopathic growth hormone (GH)-deficient children, treated with GH until nFAH, were retrieved from the database of the Belgian Society for Pediatric Endocrinology and Diabetology (BESPEED). nFAH was predicted after first-year GH treatment, applying prediction models by Ranke et al. Bland-Altman plots and Clarke error grid analyses were performed to assess clinical significance of the differences between observed and predicted nFAH. ***Results:*** In males, the predicted nFAH was higher than the observed nFAH (difference: 0.2 ± 0.7 SD; $p < 0.01$). In females, there was no significant difference. Bland-Altman analyses showed that the means of the differences between observed and predicted nFAH were close but not equal to zero, with overprediction for smaller heights and underprediction for taller heights. Clarke error grid analysis: in males, 59–61% of the predicted nFAH were within 0.5 SDS and 88% within 1.0 SDS from the observed nFAH; in females, 40–44% of the predicted nFAH were within 0.5 SDS and 76–78% within 1.0 SDS from the observed nFAH. ***Conclusion:*** Ranke's models accurately predicted nFAH in females and overpredicted nFAH in males by about 1.5 cm. In most individuals, the predicted nFAH was within 1 SDS of observed nFAH. These models can be of help in giving realistic expectations of adult height.

Introduction

Children with a short stature and their parents have in general great expectations about the effect of growth hormone (GH) therapy on final height. In a Belgian study, 76% of parents of short small for gestational age children expected a gain in adult height of ≥10 cm when starting GH treatment [1]. A long-term negative impact on psychosocial functioning has been described in children when these high expectations are not met [2].

An accurate prediction of the treatment effect on final height at onset or within the first years of GH treatment may help clinicians to give parents and children more realistic expectations. A model that can predict the effect of GH treatment at the onset of therapy would be ideal in

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clinical practice. However, adult height outcome is strongly influenced by the first-year response to GH [3]. Therefore, adult height prediction becomes more accurate if this first-year response is included in the model. Furthermore, a clinically relevant prediction model should be preferentially based on readily available and standardized variables. It should not only explain a large fraction of the variability in treatment response, but must also be easy to use in clinical practice [3]. Lastly, the prediction model must have been validated in the cohort of interest [4, 5].

Ranke et al. [6] developed 2 prediction models for near final adult height (nFAH) in GH-deficient (GHD) patients after 1 year of GH treatment, based on the KIGS data, including, among other variables, the prediction of first-year growth (index of responsiveness).

We here describe the validation of Ranke et al.'s [6] final height prediction models with an independent cohort from the Belgian Registry.

Patients and Methods

Patients

The auxological data and GH treatment characteristics of children diagnosed with idiopathic GHD (iGHD) between 1987 and 2005, and who had attained nFAH, were retrieved from the Belgian Registry of GH-treated patients, which is administrated by the Belgian Society for Pediatric Endocrinology and Diabetology (BESPEED), formerly known as the Belgian Study Group for Pediatric Endocrinology (BSGPE). The Registry stores only coded data, and informed consent was secured prior to entry of data in the registry.

nFAH was considered as the height obtained after uninterrupted GH treatment when height velocity (HV) was <2 cm/year, calculated over a period of minimum 9 months, with a chronological age >17 years in boys and >15 years in girls or skeletal age >16 years in boys and >14 years in girls. The diagnosis of iGHD was made by the treating physician according to national guidelines and the KIGS Aetiology Classification System [7], including a HV below the 25th percentile, a low to low-normal IGF-I concentration, a delayed bone age, and a peak GH concentration <20 mU/l in 2 GH provocation tests (glucagon and insulin test). GHD was defined as isolated if no other pituitary hormone deficiencies were present at the start or during GH therapy. A peak GH response <10 mU/l in both GH provocation tests was considered severe GHD. Both patients with and without developmental anatomical anomalies of the pituitary were included. Inclusion criteria were chosen to reflect the criteria used for the Ranke prediction model: (1) treatment with recombinant human GH on a daily, or 6 days a week, regimen for at least 4 consecutive years, and (2) a prepubertal status during the first year of treatment. Exclusion criteria were: (1) any medication or medical condition other than GHD that could interfere with the growth response to GH. In total, 127 patients (82 males and 45 females) with iGHD (90 with isolated GHD and 37 with multiple pituitary hormone deficiency, MPHD) met all the inclusion and exclusion criteria.

Methods

Variables retrieved from the register were (a) status at birth: gender, birth weight, and length; (b) midparental height (MPH); (c) patient variables at the start of the treatment period: chronological age, height, weight, body mass index (BMI), the highest peak GH concentration of two provocation tests, the presence of other pituitary hormone deficiencies; (d) treatment modality: average GH dose (μg/kg/day) during the first year of GH treatment, and (e) outcome parameters: the nFAH, in centimeters and expressed as height SDS (Ht SDS), the total ΔHt SDS, calculated as the nFAH SDS minus Ht SDS at the start of GH therapy, and the final height relative to MPH as an index of achieving genetic height potential, calculated as nFAH SDS minus MPH SDS.

Birth weight for gestational age was transformed into SDS, based on the standards of Niklasson et al. [8]. Height, weight, BMI, and HV were converted to SDS using the Belgian reference data by Roelants et al. [9]. The MPH (SDS) was calculated as follows: (father's Ht SDS + mother's Ht SDS)/1.61 [10, 11]. For the validation of the prediction models, height at the start of GH treatment, father's height, and mother's height were converted to SDS using reference data by Prader [12].

Observed first-year HV (cm/year) was calculated as the increment in height between the start of treatment and a measurement made after minimum 9 months and maximum 15 months of GH therapy, subsequently scaled to 12 months. Predicted first-year HV (cm/year) was calculated using the tool that can be found at www.growthpredictions.org, which uses the KIGS first-year prediction models [13]. Studentized residuals (SR) were calculated as follows: SR with GH peak: [observed HV (cm/year) – predicted HV (cm/year)]/1.46, and SR without GH peak: [observed HV (cm/year) – predicted HV (cm/year)]/1.72.

Predicted nFAH was calculated according to the Ranke model derived from the KIGS database [6]. There are 2 prediction formulas, as follows: the first one includes the maximum GH level during a GH provocation test and uses the following equation: nFAH SDS = 2.34 + [0.34 × MPH, SDS (Prader)] + [0.18 × birth weight, SDS] + [0.59 × height at the start of GH treatment, SDS (Prader)] + [0.29 × first-year SR with maximum GH] + [1.28 × mean GH dose, mg/kg/week] + [–0.37 × ln maximum GH level to provocation test, ln μg/l] + [–0.10 × age at the start of GH treatment, years]). The second prediction equation does not take the results of the GH provocation test into account: nFAH SDS = 1.76 + [0.40 × MPH, SDS (Prader)] + [0.21 × birth weight, SDS] + [0.53 × height at the start of GH treatment, SDS (Prader)] + [0.37 × first-year SR without maximum GH] + [1.15 × mean GH dose, mg/kg/week] + [–0.11 × age at the start of GH treatment, years].

Statistical Analysis

The variables are reported as the median (10th–90th percentile) and mean (±SD). A one-sample Kolmogorov-Smirnov test was used to test for normal distribution. Differences between groups were tested with a t test when the distribution of data was normal, and with a Mann-Whitney U test otherwise.

Bland-Altman plots were constructed to assess agreement between the observed and predicted nFAH and to look for proportional bias [14, 15].

Clarke error grid analysis was performed to assess the clinical significance of the differences found between the observed and predicted nFAH. Zone A (= no fault) was arbitrarily defined as a difference between observed and predicted nFAH SDS of <0.5 SD,

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Table 1. Background and baseline characteristics of the study population

	Total						MPHD						Isolated GHD					
	n	median	p10	p90	mean	SD	n	median	p10	p90	mean	SD	n	median	p10	p90	mean	SD
Background																		
Birth weight, SDS	127	−0.55	−2.08	0.95	−0.66	1.21	37	−0.52	−1.96	0.58	−0.58	1.14	90	−0.60	−2.35	1.07	−0.69	1.24
Birth length, SDS	112	−0.88	−2.38	1.04	−0.75	1.27	33	−0.83	−2.35	0.73	−0.69	1.15	79	−0.95	−2.52	1.05	−0.78	1.33
Father height, SDS	127	−1.20	−2.55	−0.11	−1.23	1.13	37	−1.05[c]	−2.16	0.63	−0.84[d]	1.06	90	−1.32	−2.68	−0.22	−1.40	1.12
Mother height, SDS	127	−1.11	−2.66	0.24	−1.13	1.21	37	−0.78	−3.34	0.88	−0.92	1.56	90	−1.11	−2.61	0.23	−1.22	1.02
MPH, SDS	127	−1.52	−3.02	−0.07	−1.47	1.16	37	−1.07[d]	−3.06	0.72	−1.09[d]	1.41	90	−1.66	−2.77	−0.31	−1.62	1.00
Maximum GH peak, µg/l	127	4.6	1.2	8.6	4.8	2.7	37	2.9[b]	1.1	6.1	3.2[b]	1.9	90	5.6	1.8	8.8	5.4	2.7
At the start of GH treatment																		
Age, years	127	7.0	2.3	11.0	7.1	3.1	37	5.9[c]	1.7	9.6	5.9[c]	2.6	90	7.7	2.7	11.2	7.5	3.2
Height, SDS	127	−3.42	−5.11	−2.48	−3.58	1.00	37	−3.75[d]	−5.75	−2.36	−3.97[d]	1.34	90	−3.30	−4.55	−2.61	−3.42	0.78
Ht SDS minus MPH SDS	127	−2.36	−4.09	−0.93	−2.39	1.27	37	−2.93[b]	−5.25	−1.13	−3.08[b]	1.61	90	−2.22	−3.13	−0.78	−3.08	1.61
Weight, SDS	127	−2.71	−5.09	−1.38	−3.02	1.51	37	−2.91	−6.33	−1.05	−3.32	1.90	90	−2.64	−4.88	−1.44	−2.89	1.31
BMI, SDS	119	−0.28	−1.99	0.87	−0.43	1.09	33	0.07	−1.76	1.25	−0.16	1.15	86	−0.36	−2.00	0.64	−0.53	1.06
GH dose, µg/kg/day	127	27.6	23.6	35.5	28.7	4.8	37	27.9	22.6	38.2	29.4	5.7	90	27.4	23.7	34.9	28.4	4.4
At nFAH																		
Age, years	127	17.5	15.0	19.2	17.4	1.5	37	17.9[d]	15.9	19.2	17.8[d]	1.3	90	17.2	14.8	19.3	17.2	1.6
nFAH all, SDS	127	−1.63	−3.05	−0.16	−1.63	1.06	37	−1.39[d]	−2.97	0.26	−1.35[d]	1.22	90	−1.77	−3.08	−0.26	−1.74	0.98
nFAH males, cm	82	169.7	160	178.4	169.5	6.7	27	171.7	161.8	181.7	171.9	7.6	55	169.1	160	175.0	168.3	6.0
nFAH males, SDS	82	−1.63	−3.13	−0.35	−1.70	1.01	27	−1.39	−2.87	0.10	−1.36	1.15	55	−1.77	−3.12	−0.91	−1.87	0.90
nFAH females, cm	45	157	149.4	167	157.8	6.8	10	157.2	152.4	167.7	158.7	8.7	35	157.0	149.6	166.3	157.5	6.3
nFAH females, SDS	45	−1.62	−2.91	0.07	−1.49	1.15	10	−1.58	−2.40	0.19	−1.34	1.46	35	−1.62	−2.86	−0.03	−1.53	1.07
Total ΔHt SDS[a]	127	1.79	0.83	3.45	1.96	1.24	37	2.26[b]	1.13	4.73	2.62[b]	1.41	90	1.59	0.59	2.92	1.69	1.06
nFAH SDS minus MPH SDS	127	−0.37	−1.70	0.69	−0.43	0.97	37	−0.42	−1.89	1.06	−0.46	1.08	90	−0.35	−1.53	0.68	−0.42	0.93
BMI, SDS	119	−0.09	−1.89	1.32	−0.23	1.27	37	−0.06	−1.67	1.42	−0.13	1.31	82	−0.10	−1.94	1.27	−0.27	1.25
Duration of GH therapy, years	127	9.6	5.3	13.7	9.6	3.1	37	10.9[c]	7.3	15.4	10.9[c]	2.8	90	8.8	5.0	13.6	9.0	3.1
Duration of GH therapy before puberty, years	125	5.2	1.9	9.4	5.4	2.9	37	6.7[c]	2.7	10.9	6.6[c]	2.8	88	4.4	1.5	8.6	4.8	2.8

MPHD = Multiple pituitary hormone deficiency; GHD = growth hormone deficiency; MPH = midparental height; GH = growth hormone; BMI = body mass index; nFAH = near-final adult height. The reference by Roelants et al. [9] was used for the SDS calculations except for birth weight and birth length SDS for which Niklasson et al. [8] was used. [a] Gain in Ht SDS from the start of GH treatment until nFAH. [b] $p < 0.001$; [c] $p < 0.01$; [d] $p < 0.05$ for comparison between MPHD and isolated GHD.

zone B (= acceptable fault) was defined as a difference between observed and predicted nFAH SDS between 0.5 and 1 SD, and zone C (= unacceptable fault) was defined as a difference between observed and predicted nFAH SDS of >1 SD. The height SD for adults was taken from the Prader curve of 20-year olds: for adult men, 1 SD is 6.9 cm, and for adult females, 1 SD is 5.9 cm.

Significance was considered at the 5% level ($p < 0.05$). The IBM SPSS Statistics 21® software was used for all statistical analyses.

Results

Background and Baseline Characteristics

The background and baseline auxological characteristics are listed in table 1, with data of isolated GHD (n = 90) and MPHD (n = 37) given separately. Children with MPHD started GH therapy at a younger age ($p < 0.05$), were shorter ($p < 0.05$), and had taller parents ($p < 0.05$) than children with isolated GHD.

Final Height Outcome Data

The near adult height data are listed in table 1. The mean duration of GH therapy was 9.6 years, with a mean duration before pubertal onset of 5.4 years. Children with MPHD had a significantly longer mean duration of GH therapy than those with isolated GHD (10.9 vs. 9.0 years; $p < 0.01$) due to a younger mean age at the start of GH therapy (5.9 vs. 7.5 years; $p < 0.05$). Girls reached nFAH earlier than boys (16.5 vs. 17.8 years; $p < 0.001$). The mean nFAH for boys was 169.5 ± 6.7 cm (–1.70 ± 1.01 SDS), and the mean nFAH for girls was 157.8 ± 6.8 cm (–1.49 ± 1.15 SDS). The median total increase in Ht SDS was 1.79, and the mean nFAH SDS minus MPH SDS was –0.43. On average, children with MPHD had a greater median total ΔHt SDS and a greater mean nFAH than children with isolated GHD, but there was no difference in nFAH corrected for MPH.

Validation of the Ranke Prediction Models for nFAH

The Ranke nFAH predictions with both formulas (with and without maximum GH) were not significantly different from the observed nFAH in females. In contrast, the predicted nFAH was significantly higher than the observed nFAH in males (model with GH peak: difference: 0.20 ± 0.67; 95% CI 0.06–0.35; $p < 0.01$; model without GH peak: difference: 0.22 ± 0.66; 95% CI 0.07–0.36; $p < 0.01$).

The Bland-Altman analyses show that the means of the differences between the observed and predicted nFAH are close but not equal to zero; on average, the predicted nFAH is higher than the observed nFAH in males and lower in females (fig. 1). For both formulas, the Bland-Altman analyses also show a proportional bias in both genders, with an overprediction for the smaller adult heights and an underprediction for the taller individuals. This proportional bias falls within the CI for the mean difference for observed nFAH values between –4.0 and +1.5 SDS (fig. 1).

The Clarke error grid analyses are shown in figure 2. In males, 59% of the predicted nFAH values (model with GH peak) and 61% (model without GH peak) are in zone A (<0.5 SD difference from observed nFAH), 29% (model with GH peak) and 27% (model without GH peak) of the predictions are in zone B (0.5–1 SD difference from observed nFAH), and 12% (model with and without GH peak) of the values are in zone C (>1 SD difference from observed nFAH). In females, 40% (model with GH peak) and 44% (model without GH peak) of the predicted nFAH are in zone A, 38% (model with GH peak) and 31% (model without GH peak) are in zone B, and 22% (model with GH peak) and 24% (model without GH peak) are in zone C.

Discussion

We found that in Belgium, children with iGHD, either isolated or part of a MPHD, when treated with a mean GH dose of 28.7 μg/kg/day and at least 1 year before pubertal onset gained around 1.8 SDS in height. Although these children were treated before pubertal onset, they remained short compared to their peers (nFAH SDS: –1.6 on Belgian references), but they almost reached their MPH (nFAH minus MPH SDS: –0.4). The final adult height outcome of the studied cohort was higher in MPHD than in isolated iGHD. Although we used quite strict criteria for near final height, some patients may have gained some height afterwards and their ultimate final height outcome may be better.

In the last decades, several prediction models for nFAH in GHD patients treated with GH have been developed [6, 16–21]. Thomas et al. [16] developed a model based on a rather small cohort (n = 61) of Belgian GHD children. Carel et al. [17] developed a model based on a cohort (n = 1,885) of the French National database that contains 10 parameters. De Ridder et al. [18] analyzed the data of the Dutch growth database and described models for prepubertal and pubertal children at the start and after the first year of GH treatment. Carrascosa et al. [19] retrieved data from 184 Spanish children from different medical centers and described a model at the end of the

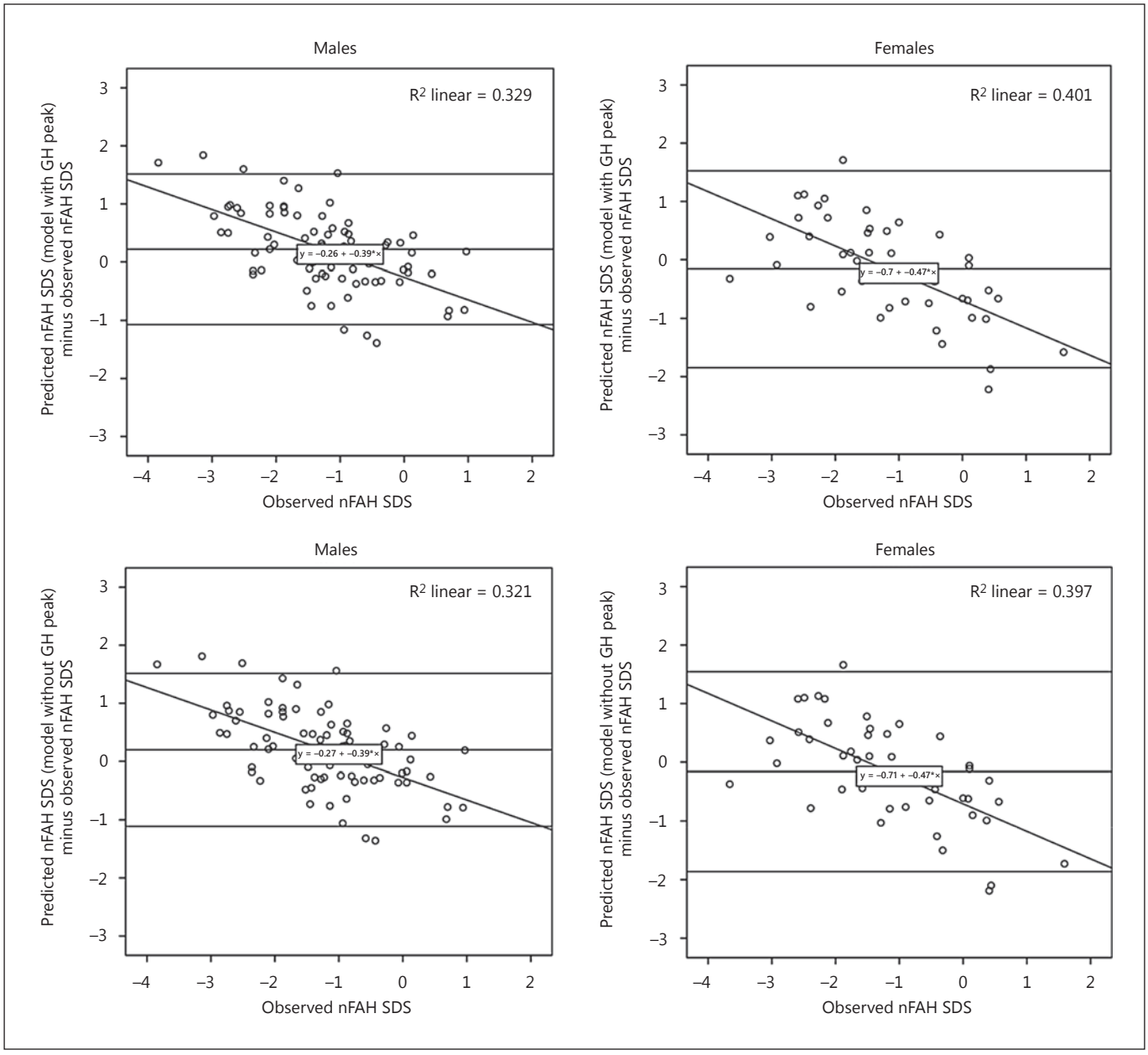

Fig. 1. Bland-Altman plots. The horizontal lines show the mean differences and the 95% confidence intervals. Upper panels: prediction models including the GH peak; lower panels: prediction models without GH peak. All SDS calculations are based on Prader et al. [12].

second treatment year as well as a model at the onset of the pubertal growth spurt, predicting the Ht SDS gain to be achieved at adult height age. Blethen et al. [20] described a model derived from the Genentech study (n = 121). Cutfield et al. [21] developed models for children with isolated GHD (n = 1,091) and MPHD (n = 604) based on the KIGS database. These models could not be validated in our Belgian cohort because they did not include the first-year response [12, 17–21], they used several parameters that were not always available in the Belgian Registry (e.g. bone age within 3 months of GH start [18], BMI, and height at the onset of the pubertal growth spurt [19]), and/or because they included patients treated with only 3 doses of GH per week [17, 20], and/or because

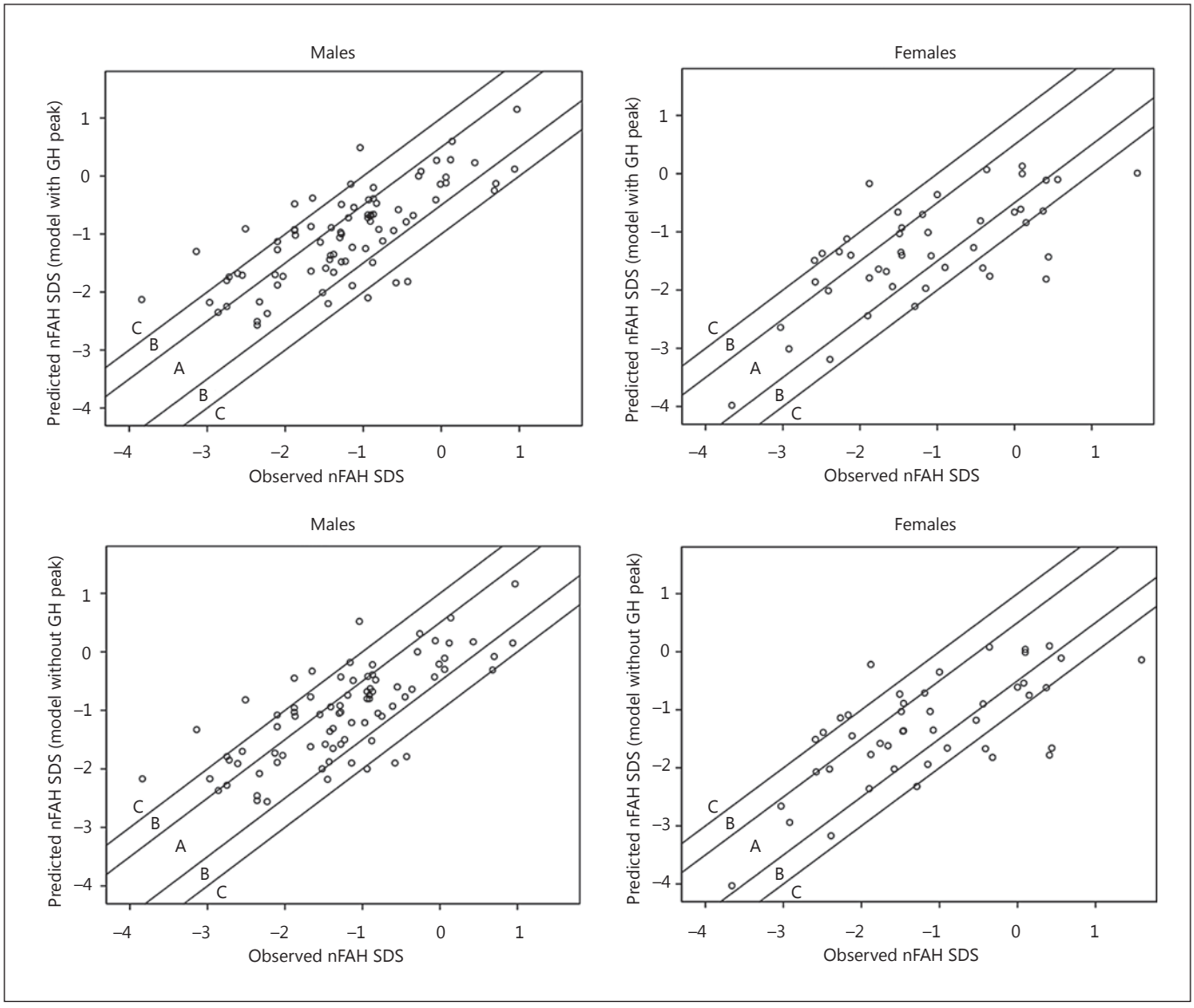

Fig. 2. Clarke error grid analyses. Upper panels: prediction models including the GH peak; lower panels: prediction models without GH peak. Zone A: difference between predicted and actual nFAH SDS <0.5. Zone B: difference between predicted and actual nFAH SDS 0.5–1.0. Zone C: difference between predicted and actual nFAH SDS >1.0. All SDS calculations are based on Prader et al. [12].

they contain parameters not usable to predict adult height at 1 year of GH treatment, such as the total duration of GH treatment [20, 21] and the 2-year growth response to GH [19].

We validated both clinically and statistically the Ranke prediction model for adult height in this Belgian cohort. A clinically validated model is likely to be more useful than a statistically validated one [5]. Statistical analysis of our outcome data showed no significant difference between observed and predicted nFAH for females. For males, the predicted nFAH is 0.20–0.22 SD (1.4–1.5 cm) higher than the observed nFAH. This difference is statistically significant, but the absolute error does not make the method invalid for clinical practice. Alternatively, one may choose to subtract 0.2 SD from the height predictions in males. However, this does not reduce the number of unacceptable (zone C) predictions in the Clarke error grid analysis, since it creates more underpredictions (data not shown).

The Bland-Altman analysis shows a proportional bias for both genders and both formulas (with and without GH peak in the stimulation test). This bias is rather mild and falls within the confidence limits for the mean difference between the predicted and the observed nFAH, at least for the range of final height data that are mostly encountered in clinical practice (i.e. –4.0 to +1.5 SDS). Therefore, it is not necessary to correct for this bias [15].

For the Clarke error grid analysis, we arbitrarily determined the zone A as a difference between predicted and observed nFAH <0.5 SDS. Prediction errors of <1 SD are still acceptable if compared to other methods for final height prediction, such as the Tanner and Whitehouse and the Greulich-Pyle Bayley-Pinneau prediction models [22, 23].

The Clarke error grid analyses show that 59–61% of males and 40–44% of females have a predicted nFAH which deviates from the initially predicted nFAH by <0.5 SD (about 3–3.5 cm). In males, 88% of the predictions fall within 1 SD of the observed nFAH (error grid zones A and B). The prediction error is larger for females than for males; 76–78% of the predictions fall within 1.0 SD of the observed nFAH in females. In our opinion, Ranke's prediction models for both genders are clinically valid, since only 12% of males and 22–24% of females in the Belgian Registry cohort have an observed nFAH which deviates >1 SD (6.9 cm for males and 5.9 cm for females) from the predicted nFAH.

In conclusion, children with iGHD, when treated at least for 4 years with GH and 1 year before pubertal onset, had a significant median total height gain of 1.8 SD. Their final height was still relatively short compared to their peers (mean nFAH –1.6 SD) but only slightly below their MPH. The Ranke prediction model for nFAH after the first year of GH therapy accurately predicted nFAH in females and overpredicted nFAH in males by 0.2 SDS (about 1.5 cm). In most individuals, the nFAH prediction after GH therapy was within 1 SDS of the observed nFAH. Therefore, the Ranke prediction models are useful in clinical practice for predicting nFAH after 1 year of GH treatment.

Acknowledgements

We would like to thank Christine Derycke for her help in data collection. In addition to the authors, the following investigators are members of BESPEED and contributed to the Belgian Registry for the Study of Growth and Puberty Problems: A. France, H. Dotremont, M. Den Brinker (University Hospital Antwerp), M. Cools, K. De Waele, M. Craen, S. Van Aken, S. van der Straaten (University Hospital Ghent), I. Gies, J. Vanbesien (University Hospital Brussels), J.P. Bourguignon, M.C. Lebrethon, A.S. Parent (University Hospital Liège), C. Heinrichs, S. Tenoutasse, C. Brachet, E. Boros (University Children's Hospital HUDE, Brussels), M. Maes, V. Beauloye, P Lysy (University Hospital Saint-Luc, Brussels), G. Massa, R. Zeevaert (Jessa Hospital, Hasselt), F. de Zegher, I. Francois, D. Beckers, M. Van Helvoirt, K. Casteels (University Hospital Leuven), D. Beckers, T. Mouraux (CHU UCL Mont Godinne), K. Logghe (Delta Hospital Roeselare), G. Thiry-Counson (Clinique Saint-Joseph Liège), O. Chivu (CHC Espérance, Montegnée), S. Depoorter (AZ St. Jan Brugge).

This study was supported by a research grant from the Belgian Society for Pediatric Endocrinology and Diabetology (BESPEED).

Disclosure Statement

The authors have no conflict of interest to disclose.

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