Adult height prediction by bone age determination in children with isolated growth hormone deficiency (IGHD): Analysis of KIGS data

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Background:

The precision of adult height prediction by bone age determination in children with idiopathic growth hormone deficiency (IGHD) is unknown.

Method:

The near adult height (NAH) of patients with IGHD in the KIGS database was compared to adult height prediction based on the Bayley Pinneau (BP) in 315 children and based on the Tanner-Whitehouse 2 (TW2) method in 121 children. Multiple linear regression analyses with the dependent variable NAH minus predicted height by bone age including as independent variables age at GH start, mean dose of GH treatment, years of GH treatment, maximum GH peak in GH stimulation test, and gender were calculated (model A). Furthermore, the same analyses were performed also including target height as independent variable in separate models (model B). Additionally, we calculated the mean difference between NAH and predicted adult height at baseline, after 1 year of GH treatment and at last bone age summarizing all bone ages.

Results:

The mean underestimation of adult height based on the GP method was at baseline 4.0 ± 0.5cm in girls and 4.4 ± 0.4cm in boys, at 1 year of GH treatment 2.0 ± 0.3cm in girls and 0.5 ± 0.3cm in boys, while at last bone age determination adult height was overestimated in mean by 0.4 ± 0.4cm in girls and 3.7 ± 0.3cm in boys.

The mean underestimation of adult height based on the TW2 method was at baseline 1.4 ± 1.3cm in girls and 6.6 ± 0.6cm in boys, at 1 year of GH treatment adult height was overestimated in girls 0.9 ± 0.6cm in girls and underestimated 3.8 ± 0.4 cm in boys, while at last bone age determination adult height was overestimated in mean by 1.1 ± 0.9cm in girls and 4.5 ± 0.5cm in boys.

Characteristics of the study cohort

|	BP		TW2		p-value[1] BP vs Tw2	p-value[1] BP vs Tw2
	female	male	female	male	female	male
Number	122	193	22	99		
baseline					NS	NS
Birth weight	3000 (2360, 3700)	3200 (2580, 3800)	3170 (2380, 3880)	3252.5 (2340, 3920)		
Age [years]	10.4 (9.0, 11.9)	11.3 (9.8, 13.1)	10.6 (9.6, 11.5)	10.8 (9.1, 13.0)	NS	NS
Height SDS	-2.8 (-3.6, -1.9)	-2.7 (-3.5, -1.9)	-2.9 (-3.8, -1.8)	-2.5 (-3.6, -1.8)	NS	NS
Bone age [years]	8.5 (7.5, 10.0)	9.4 (8.0, 10.7)	8.6 (7.5, 9.8)	9.0 (7.5, 10.3)	NS	NS
Bone age delay [years]	2.0 (0.7, 3.2)	2.0 (0.7, 3.5)	2.2 (0.5, -2.9)	2.0 (0.5, 3.4)	NS	NS
GH peak on stimulation test [ng/ml]	6.8 (3.0, 9.6)	6.3 (2.3, 9.0)	6.4 (1.9, 8.5)	6.1 (2.8, 9.3)	NS	NS

Difference between NAH and predicted final height based on the BP method

	baseline				1y GH treatment				Last bone age			
	Model A		Model B		Model A		Model B		Model A		Model B	
Bone age [years]	estimate	p-value	estimate	p-value	estimate	p-value	Estimate	p-value	estimate	p-value	estimate	p-value
7.5	-0.6±0.7	NS	-2.0±0.8	0.034	-7.1±0.5	<.001	-8.3±0.6	<.001	-12.81.3	<.0001	-12.1±1.4	<.001
8	1.0±0.6	NS	-0.4±0.6	NS	-5.5±0.4	<.001	-6.7±0.5	<.001	-12.0±1.2	<.0001	-11.4±1.3	<.001
8.5	2.6±0.4	<.001	1.3±0.5	NS	-3.8±0.4	<.001	-5.1±0.4	<.001	-11.3±1.1	<.0001	-10.7±1.2	<.001
9	4.2±0.4	<.001	2.9±0.5	<.001	-2.2±0.3	<.001	-3.5±0.4	<.001	-10.6±1.0	<.0001	-10.0±1.1	<.001
9.5	5.8±0.4	<.001	4.6±0.5	<.001	-0.6±0.3	NS	-1.9±0.4	<.001	-9.8±1.0	<.0001	-9.3±1.0	<.001
10	7.4±0.5	<.001	6.3±0.5	<.001	1.0±0.3	<.001	-0.3±0.4	NS	-9.1±0.9	<.0001	-8.6±0.9	<.001
10.5	9.0±0.6	<.001	7.9±0.6	<.001	2.7±0.3	<.001	1.3±0.4	<.001	-8.4±0.8	<.0001	-7.9±0.8	<.001
11	10.5±0.7	<.001	9.6±0.8	<.001	4.3±0.3	<.001	2.9±0.4	<.001	-7.6±0.7	<.0001	-7.2±0.7	<.001
11.5					5.9±0.4	<.001	4.6±0.5	<.001	-6.9±0.6	<.0001	-6.5±0.6	<.001
12					7.5±0.5	<.001	6.2±0.5	<.001	-6.2±0.5	<.0001	-5.8±0.6	<.001
12.5					9.1±0.6	<.001	7.8±0.6	<.001	-5.4±0.5	<.0001	-5.0±0.5	<.001
13					10.8±0.6	<.001	9.4±0.7	<.001	-4.7±0.4	<.0001	-4.3±0.4	<.001
13.5					12.4±0.7	<.001	11.0±0.8	<.001	-4.0±0.4	<.0001	-3.6±0.4	<.001
14					14.0±0.8	<.001	12.6±0.8	<.001	-3.2±0.3	<.0001	-2.9±0.4	<.001
14.5					15.6±0.9	<.001	14.2±0.9	<.001	-2.5±0.4	<.0001	-2.2±0.4	<.001

Conclusions:

- **Height prediction by bone age determinations at onset and in the first year of GH treatment underestimates (~4 cm) adult height in prepubertal IGHD children.**
- **In contrast, in mean 6 years after onset of GH treatment height prediction based on bone ages overestimated (females: ~1 cm, males: ~4 cm) adult height.**

Difference between NAH and predicted adult height based on the BP method in boys (A) and girls (B) (model A)
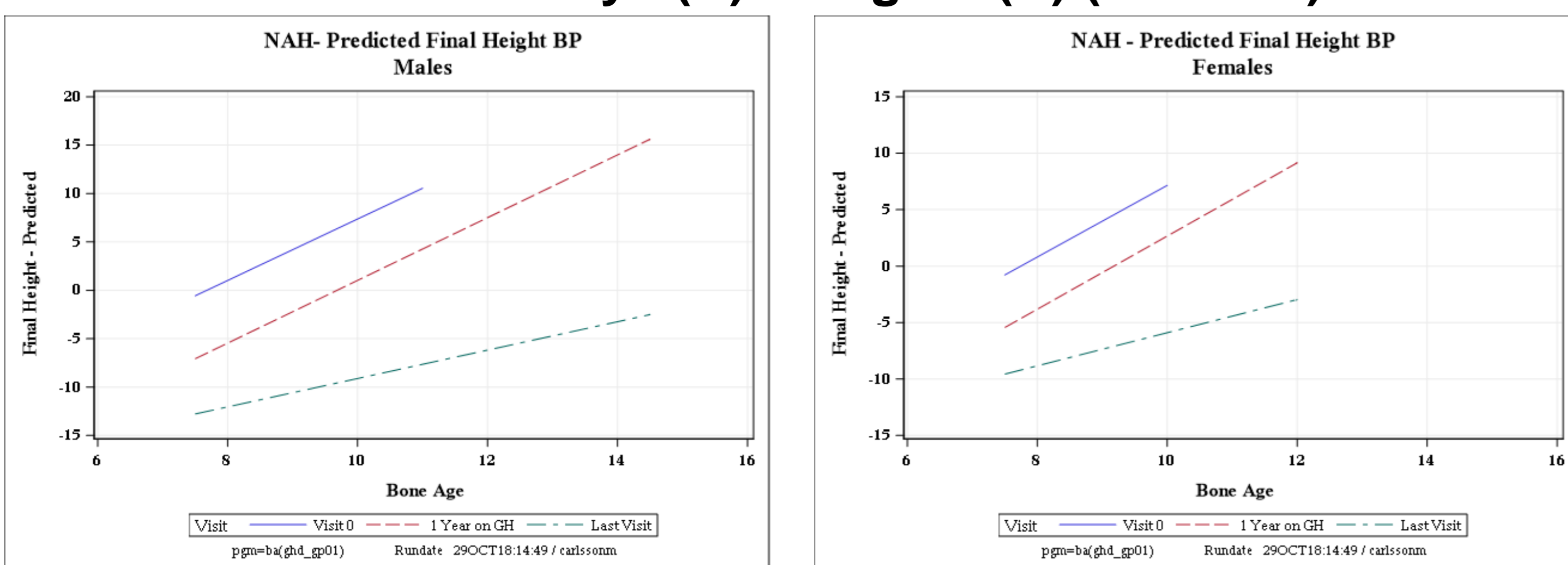
NAH- Predicted Final Height BP Males

NAH - Predicted Final Height BP Females

Difference between NAH and predicted final height based on the TW2 method

	baseline				1y GH treatment				Last bone age			
	Model A		Model B		Model A		Model B		Model A		Model B	
Bone age [years]	estimate	p-value	estimate	p-value	estimate	p-value	estimate	p-value	estimate	p-value	estimate	p-value
7.5	-0.8±0.7	NS	0.8±0.8	NS	-5.4±0.5	<.001	-3.5±0.6	<.001	-9.6±1.2	<.001	-9.7±1.3	<.001
8	0.8±0.6	NS	2.5±0.7	<.001	-3.8±0.5	<.001	-1.9±0.6	<.001	-8.8±1.1	<.001	-9.0±1.2	<.001
8.5	2.4±0.5	<.001	4.1±0.7	<.001	-2.2±0.4	<.001	-0.3±0.5	NS	-8.1±1.1	<.001	-8.3±1.1	<.001
9	4.0±0.5	<.001	5.8±0.7	<.001	-0.6±0.4	NS	1.3±0.5	0.028	-7.4±1.0	<.001	-7.6±1.0	<.001
9.5	5.6±0.5	<.001	7.5±0.7	<.001	1.0±0.3	0.011	2.9±0.5	<.001	-6.6±0.9	<.001	-6.9±0.9	<.001
10	7.2±0.6	<.001	9.1±0.8	<.001	2.7±0.3	<.001	4.5±0.5	<.001	-5.9±0.8	<.001	-6.1±0.9	<.001
10.5					4.3±0.4	<.001	6.1±0.5	<.001	-5.2±0.7	<.001	-5.4±0.8	<.001
11					5.9±0.4	<.001	7.8±0.5	<.001	-4.4±0.6	<.001	-4.7±0.7	<.001
11.5					7.5±0.5	<.001	9.4±0.6	<.001	-3.7±0.5	<.001	-4.0±0.6	<.001
12					9.2±0.5	<.001	11.0±0.6	<.001	-3.0±0.5	<.001	-3.3±0.6	<.001

Discussion:

- The lower accuracy of height prediction in children with IGHD is probably attributed to that fact that the commonly used methods are developed based on data of children with normal height and not short statured children.
- Another well-known factor limiting adult height prediction is the extensive bone age retardation in children with IGHD.
- In contrast to children with constitutional delay of growth and puberty bone age determination leads to an underestimation of adult height in our study at baseline suggesting a positive impact of GH treatment on adult height.
- Adult height prediction at pubertal age in children with IGHD after in mean 6 years GH treatment overestimates adult height in our study fitting well to the observation that adult height in children with IGHD is lower compared to target height in children. An inability of bone age to predict the timing of the pubertal growth spurt has been reported which may explain the overestimation of adult height. Furthermore, the pubertal growth spurt in children with IGHD may be shorter or its degree may be lower compared to healthy children.