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Overestimation of final height prediction in patients with classical congenital adrenal hyperplasia using the Bayley and Pinneau method

Abstract

Background: A typical growth pattern with decreased pubertal growth spurt has been identified in patients with classical congenital adrenal hyperplasia (CAH).
Objective: To evaluate the accuracy of final height predictions in patients with CAH using the Bayley and Pinneau (B&P) method.
Patients and Methods: Using growth and final height data of 92 patients (57 F/35 M) with CAH due to 21-hydroxylase deficiency (38 SV/54 SW), final height predictions with the B&P method were compared to actual final heights.
Results: In females, mean final height was 159.9±5.3 cm (–1.0±0.7 SDS) compared to predicted mean final height of 167.9±10.7 cm (+0.5±1.7 SDS), p<0.001, overestimation 7.3±9.5 cm. In males, mean final height was 170.1±6 cm (–1.2±0.8 SDS) compared to predicted mean final height of 185.6±13.4 cm (+1.2±1.9 SDS), p<0.001, overestimation 13.9±10.8 cm.
Conclusion: In classical CAH, final height prediction using the B&P method results in significant overestimation of final height.

Keywords: bone age; congenital adrenal hyperplasia; growth; growth prediction.

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Introduction

Congenital adrenal hyperplasia (CAH) comprises a group of autosomal recessive disorders caused by a deficiency of one of five enzymes required for the synthesis of cortisol (1, 2). The most common form is 21-hydroxylase deficiency (21OHD), which accounts for more than 90% of the cases (3). The classical form of 21OHD results in genital masculinization in girls, early virilization with acceleration of growth and pubertal development or in salt-wasting crises. Worldwide incidence of CAH calculated from neonatal screening programs has been estimated at 1:14,000.

Overproduction of androgens causes virilization, accelerated growth, advanced skeletal maturation and early epiphyseal fusion. Whereas the various forms of CAH differ in their degree of enzymatic deficiency, they all represent a therapeutic challenge to pediatric endocrinologists attempting to optimize growth.

Traditional treatment consists of the suppression of adrenocorticotropic hormone (ACTH) through glucocorticoid replacement in an attempt to reduce excessive androgen production and its consequences. Parsimonious treatment with glucocorticoids may result in androgen excess with advancement of bone age and a reduced final height. In over treatment, growth is suppressed by growth inhibiting effects of glucocorticoids. Alternate approaches to the treatment of CAH have been investigated recently, including the use of antiandrogens, aromatase inhibitors and adrenalectomy (4). However, the mainstay of therapy remains judicious glucocorticoid treatment along with careful monitoring of growth velocity and skeletal maturation, as well as urine, serum and salivary steroid hormone levels (5).

Reports on long-term follow-up and final height outcomes in patients with CAH are heterogeneous. Previously, we and other authors have shown that total pubertal growth is significantly reduced in CAH patients who have received traditional steroid treatment with hydrocortisone (6–8).

According to an Endocrine Society consensus statement, growth promoting therapy can be offered to CAH patients with a predicted final height below –2.25 SD in the context of clinical studies (9). Therefore, final height predictions should be as accurate as possible. Recently, final height data of CAH patients treated with growth hormone were published (10). In that study, final height was compared to both a control group and to predicted final height using the B&P method (10).

As patients with CAH have a decreased pubertal growth spurt, it is questionable whether final height prediction is appropriate when the B&P tables for healthy children are used.

Basically, final height prediction is reserved for healthy children when the B&P tables are used (11).

In the present study, we evaluated the accuracy of final height prediction using the B&P method in patients with classical CAH and established new tables for final height prediction in these patients considering the characteristics of their growth pattern.

Patients and methods

We followed 92 patients (57 females, 35 males) with 21-hydroxylase deficiency continuously from infancy until final height in our clinic. All patients were exclusively treated with hydrocortisone. We extracted the data retrospectively from all patients born between 1969 and 1987. The diagnosis of CAH was based on both clinical symptoms and signs and hormonal analysis and was confirmed by subsequent comprehensive genotyping (12). At the time of diagnosis, newborn-screening for CAH was not yet available.

Fifty-four patients (32 females) had salt-wasting CAH (elevated plasmarenin activity and sodium <130 mmol/L at diagnosis), whereas 38 patients had the simple virilizing form (25 females, 13 males). Patients with non-classical forms of CAH were not included in this study. All patients were continuously cared for in our clinic, with follow-up appointments every 3 months during the first 2 years of life, and at least every 6 months in childhood and adolescence. All 92 patients had received hydrocortisone (three times daily) for glucocorticoid replacement, and patients with salt-wasting CAH also received fludrocortisone (treatment goal: plasma renin activity <18 ng/mL/h until 6 months of age, <5.5 ng/mL/h above the age of 6 months). Adjustment of the glucocorticoid dose was made using auxological data (linear growth), skeletal maturity (treatment goal: bone age within 1 year of chronological age) and hormonal data (treatment goal: morning serum 17-hydroxyprogesterone <18 nmol/L). None of the patients received GnRH analog or aromatase inhibitor treatment to delay onset of puberty. None of the patients were treated with growth hormone. As patients were followed at a single center, these data represent a homogeneously treated cohort of patients with CAH. Patients older than 18 years of age were considered to have reached final height. In addition, fused epiphyses on X-ray were documented at final height. Total pubertal growth was defined as growth from onset of puberty (B2 in girls and testes volume of >3 mL in boys) until final height. Target height was calculated using the formula: [maternal height+paternal height –13 cm for girls and +13 cm for boys]/2. Data on height and weight, and glucocorticoid dosage were analyzed at 2 years of age, at the onset of puberty (defined as breast Tanner stage two in girls, and testicular volume of ≥3 mL in boys) and at final height. Height standard deviation scores (H-SDS) were calculated with a growth calculator using reference data from Prader et al. (13), which is used in the Alpine region (Switzerland, Austria, Southern Germany). Bone age was assessed yearly by X-ray of the left hand using the Greulich and Pyle method (11). Bone age was read by both an experienced pediatric endocrinologist and a radiologist. Final height prediction was assessed at onset of puberty (as defined above) by the B&P method using the tables for average girls and boys, when bone age was within 1 year of chronological age. When bone age was delayed more than 1 year, the tables for retarded boys and girls were used, and in patients with acceleration of bone age of more than 1 year, tables for accelerated boys and girls were used. The final height prediction was then compared to the real final height.

Corrected FH was defined as the difference between achieved adult height and target height (FH-SDS–TH-SDS) and was calculated individually for each patient. Parental heights were asked and available on all patients.

Statistical analyses were performed with the non-parametric Mann-Whitney U-test for comparison of real and predicted final heights and for between-group comparisons. Statistical analyses were done with the SPSS 10.0 software (SPSS Inc., Chicago, Illinois, 2002). A $p<0.05$ was considered statistically significant.

Results

Data from 92 patients (57 females and 35 males) with classical CAH are presented in this analysis. All patients were exclusively treated with hydrocortisone as glucocorticoid. Patients with salt-wasting CAH (n=54, 32 females, 22 males) were diagnosed early at a mean age of 0.2 years [range 0–2.7 years, median 0 years], whereas patients with the simple virilizing form (n=38, 25 females, 13 males) were diagnosed at a mean age of 2.2 years [range 0–6.0 years, median 2.0 years]. During puberty, the mean daily hydrocortisone dose in the whole group was 16.7±4.1 mg/m^2 body surface area. In females, the mean daily hydrocortisone dose was 16.4±4.1 mg/m^2 (simple virilizing CAH females 17.5±4.1 mg/m^2 and salt-wasting CAH females 15.6±4.1 mg/m^2), and in males the mean daily hydrocortisone dose was 17.5±4.3 mg/m^2 (simple virilizing CAH males 17.7±5.2 mg/m^2 and salt-wasting CAH males 16.6±3.5 mg/m^2). None of the patients had suffered from adrenal crisis once SW-CAH was diagnosed.

Auxological data

Mean final height was 159.9±5.3 cm (−0.8±0.6 SDS) in females (n=57): females with salt-wasting CAH were as tall (160.4±4.9 cm, −0.7±0.8 SDS) as female patients with the simple virilizing form (159.3±5.8 cm, −0.9±1.0 SDS), $p>0.05$.

In males (n=35), mean final height was 170.2±6.1 cm (–1.1±0.9 SDS): male patients with salt-wasting CAH reached a mean final height of 171.1±5.5 cm (−0.9±0.8 SDS), and males with simple virilizing CAH reached a final height of 168.8±6.8 cm (–1.3±1.0 SDS). There was no significant height difference between salt-wasting and

simple virilizing CAH males (p>0.05), although metabolic control was worst in SV CAH males, indicated by the most advanced bone age at onset of puberty (Table 1).

Target height was −0.4±0.8 SDS in females, and −0.2±0.7 in males. This means that parents of the patients with CAH were slightly shorter on average than adults in the normal population. Therefore, corrected FH (FH-SDS–TH-SDS) was −0.6±0.9 in females with SW CAH, and −0.3±0.9 in females with SV CAH, p>0.05.

In males with SW CAH, corrected FH was −0.8±0.8 and –1.0±1.0 SDS in SV CAH male patients, p>0.05.

Mean height SDS at the start of puberty was 0.4±1.4 SDS (in females 0.3±1.3 SDS and in males 0.5±1.5 SDS) and decreased significantly to −0.4±1.1 SDS at the end of puberty (in females −0.5±1.1 SDS and in males −0.3±1.1 SDS), p<0.01, which indicates an insufficient pubertal growth spurt. Total pubertal growth in females was 13.5±6.9 cm and 17.2±6.3 cm in males, which is significantly less than in the reference population of Prader et al. (13–15), with a mean pubertal growth in females 20.3±6.8 cm and 28.2±8.2 cm in males, p<0.01 (Table 1).

Final height prediction

In females, mean final height was 159.9±5.3 cm (–1.0±0.7 SDS) compared to mean predicted final height of 167.9±10.7 cm (+0.5±1.7 SDS), p<0.001, overestimation 7.3±9.5 cm. Bone age was accelerated in 14 females, appropriate for chronological age in 38 females and retarded in 5 females (Table 2).

In males, mean final height was 170.1±6 cm (–1.2±0.8 SDS) compared to mean predicted final height of 185.6±13.4 cm (+1.2±1.9 SDS), p<0.001, overestimation 13.9±10.8 cm. Bone age was accelerated in 15 males, appropriate for chronological age in 18 males and retarded in 2 males. Tables 3 and 4 show the CAH final height prediction model derived by our data.

Discussion

To our knowledge, this is the first study to assess the accuracy of final height prediction using the B&P method in patients with classical CAH. Of course, the G&P and B&P methods are intended to be used for healthy children, but in many studies these methods are used to evaluate the effect of growth-promoting therapies in patients with CAH (10, 4, 16–18). We found that using the B&P tables results in significant overestimation of final height prediction, which can be explained by a significant decrease of total pubertal growth in our cohort of CAH patients. Metabolic control was very good in our cohort, as bone age at the start of puberty was within 1 year of chronologic age in more than two-thirds of the patients. Decreased total pubertal growth has also been observed in other growth studies of CAH patients: In a multinational study of growth patterns in patients with CAH, Frisch et al. found a reduced maximum growth velocity during puberty (19). In their analysis of 41 CAH patients, Manoli et al. confirmed that the height gain during puberty is one of the most potent predictors of final height, in addition to the type of

Type of CAH	Sex	n	FH, cm	FH-SDS	Corr FH-SDS ΔFH-TH – SDS	TPG, cm	Normal TPG, cm (Ref. 13)	ΔBA-CA at start of puberty
SV	F	25	159.3±5.8	−0.9±1.0	−0.3±0.9	13.1±6.2	20.3±6.8 cm	0.9±1.9[a]
	M	13	168.8±6.8	−1.3±1.0	−1.0±1.0	16.2±5.7	28.2±8.2 cm	2.7±2.4[a]
SW	F	32	160.4±4.9	−0.7±0.8	−0.6±0.9	13.8±7.4	20.3±6.8 cm	0.0±1.2[a]
	M	22	171.1±5.5	−0.9±0.8	−0.8±0.8	17.7±6.7	28.2±8.2 cm	0.4±1.3[a]

Table 1 Auxologic data on 92 patients with CAH (mean±SD).
[a]p<0.05 (same sex comparison between SV and SW forms of CAH SV, FH, final height; corr FH, corrected final height (FH-SDS-TH-SDS); TPG, total pubertal growth; SV, simple virilizing; SW, salt-wasting; TH, target height; BA, bone age; CA, chronological age.

	Mean real final height, scm	Predicted final height B&P, cm	Overestimation of final height with the B&P method
Females n=57	159.9±5.3 cm	167.9±10.7 cm	7.3±9.5 cm
Males n=35	170.1±6.0 cm	185.6±13.4 cm	13.9±10.8 cm

Table 2 Final height prediction at onset of puberty with the Greulich and Pyle & Bayley & Pinneau methods compared to real final height in n=92 patients with CAH.

		Females (n=52)	
Bone age	Bone age, years	Percentage of mature height	Percentage of mature height B&P
Accelerated (n=14)	10	89.5	82.8
	11	89.9	88.3
	12	91.7	90.1
	13	96.1	94.5
Normal (n=38)	8	84.2	79.0
	9	89.0	82.7
	10	91.1	86.2
	11	91.5	90.6
	12	94.1	92.2
	13	96.6	95.8

Table 3 New table for final height prediction for female patients with classical adrenal hyperpasia compared to B&P tables.

		Males (n=33)	
Bone age	Bone age, years	Percentage of mature height	Percentage of mature height B&P
Accelerated (n=15)	10	84.2	74.7
	12	88.4	80.9
	13	89.2	85.0
	14	92.8	90.5
	15	96.0	95.8
Normal (n=18)	9	85.3	75.2
	10	88.0	78.4
	11	89.0	80.4
	12	92.0	83.4
	13	93.8	87.6

Table 4 New table for final height prediction for male patients with classical adrenal hyperpasia compared to B&P tables.

CAH, mean hydrocortisone dose in the first 2 years and the mean BMI-SDS in early childhood and after puberty (20). Attenuated growth during puberty was also reported in a multicenter study of 54 patients with CAH in by Muirhead et al. in 2002 (21), as well as in two subsequent studies (22, 23). These data suggest that pubertal growth is significantly attenuated in both forms of classical CAH, irrespective of gender. This decrease in pubertal growth could be explained by excess glucocorticoid administration at the onset of puberty, as supraphysiologic doses of glucocorticoids have been shown to increase hypothalamic somatostatin tone (24) and result in decreased growth hormone secretion, which normally peaks during puberty. Alternatively decreased pubertal height gain may be explained by inappropriate acceleration of bone maturation in patients with poor metabolic control.

According to the latest Endocrine Society clinical practice guideline, growth-promoting therapy could be offered to CAH patients with a predicted final height below –2.25 SD in the context of clinical studies (9). Therefore, final height prediction should be as accurate as possible. We have developed new tables for final height prediction in CAH patients considering the characteristics of the growth pattern in these patients. These new tables now should be evaluated in patients with early CAH diagnosis by newborn-screening and treated with relatively low doses of hydrocortisone from early infancy (25). As glucocorticoid doses have been slightly lowered to 10–15 mg hydrocortisone/m^2/day in the past decade, it will be interesting to see, if these patients exhibit the same growth pattern with decreased pubertal growth spurt.

In summary, patients with CAH exhibit a typical growth pattern with decreased pubertal growth spurt under adequate conventional glucocorticoid therapy. Therefore, final height prediction results in significant overestimation of final height when the B&P tables are used. This is an important finding because in studies using growth-promoting therapies, the achieved final height is frequently compared to the predicted final height. New final height prediction tables were derived from a large group of homogeneously treated patients receiving traditional glucocorticoid and mineralocorticoid treatment, which now need to be evaluated in the future.

Conflict of interest statement

The authors have no conflict of interest to disclose.
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