Final height of patients with classical congenital adrenal hyperplasia

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The management of children with congenital adrenal hyperplasia (CAH) remains a challenge, especially with regard to their growth potential. We aimed to determine the correlation of the final height of Turkish children with classical CAH to their genetic height potential and to determine the effect of hydrocortisone replacement therapy on the final height.

A total of 24 CAH (16 simple virilizing and 8 salt-wasting form) were included in this retrospective longitudinal study. The final height (FH), final height standard deviation score (FHSDS), target height (TH), target height standard deviation score (THSDS), corrected height for target height (CHSDS), weight, and body mass index (BMI) were calculated for all patients. We evaluated the adult height taking into consideration the correlation with the genetic height potential and the country standards. The average follow-up time was 14.2±3.1 years and the average daily hydrocortisone dose was 19.7±2.9 mg/m^2.

The mean FH and FHSDS were 152.2±7.2 cm and -1.0±1.1 SD, respectively, in females and 163.1±6.6 cm and -1.2±1.0 SD, respectively, in males. The CHSDS was found to be -0.73±0.9 SD. FH was below the TH in 79.1% of our cases. In 20.8% of our patients, FH was less than the third percentile for the standard height for our country. Interestingly, the FH showed no correlation with the dosage of hydrocortisone. Thirteen of our cases (54.2%) reaching FH were obese/overweight. A positive correlation was detected between hydrocortisone treatment and the BMI.

The observations that 79.1% of our classical CAH cases receiving an average daily hydrocortisone dose of 19.7±2.9 mg/m^2 ended up with an adult height below the TH and that 54.2% of the cases were overweight/obese lead us to believe that we should be using the lowest possible dose for treatment.

Key words: congenital adrenal hyperplasia, final height.

It is well known that adult height may be compromised in congenital adrenal hyperplasia (CAH) related to 21-hydroxylase deficiency (21-OHD)[1]. There are two basic reasons why growth can be disturbed. First, if adrenal androgen secretion is not adequately suppressed with glucocorticoid replacement therapy, high levels of androgens will stimulate linear growth and advance skeletal maturation abnormally. This will result in early epiphyseal fusion and adult short stature. The second reason is the suppression of growth, particularly in the first years of life, by excess steroid treatment. In this situation, some catch-up growth may occur with reduction in steroid dose, but full development to normal height is rarely achieved and short stature usually results[2,3].

Achieving normal adult height is one of the most important goals in the treatment of children with 21-OHD as it has been shown in several retrospective studies that their mean final height remains below that of healthy controls[4-8].

In this paper, we report our data on final height, difference between target height and final height, and body mass index (BMI) values in relation to corticosteroid dosage in patients with classical congenital adrenal hyperplasia (CCAH) followed at our center.

Material and Methods

Patients: A retrospective longitudinal study on growth was carried out on patients with CCAH due to 21-OHD treated by pediatric endocrinologists from diagnosis until final height. Twenty-four patients (13 female, 11 male) who reached final height were available for further evaluation. Of the 24 cases, 16 had the simple virilizing (SV) form and 8 the salt-wasting (SW) form. The diagnosis of CAH was based on the clinical signs and detailed endocrinological investigation. Categorization of the patients into the two forms of 21-OHD was based on the phenotype and certain hormonal and biochemical data. The criteria for categorization were as follows:

SW form: Initiation of signs and symptoms in the neonatal period: virilization, failure to thrive, vomiting, hyponatremia, hyperkalemia, high renin values, and 17-OH progesterone (17-OHP) values higher than 90 nmol/L. SV form: Virilization of different degrees, without clinical or biochemical evidence of salt loss and with normal renin values.

The median age at diagnosis of our patients was 18.7 (range: 1-45) days for the SW form and 30.0 (range: 4-98) months for the SV form. The mean bone age was 3.5 years for SV form.

Patients were treated with hydrocortisone, divided into three doses per day. The hydrocortisone dosage ranged from 10.7 to 24.5 mg/m^2/day (mean: 19.7±2.9 mg/m^2/day) during follow-up. Patients with SW form also received mineralocorticoid replacement with fludrocortisone (0.1-0.2 mg/daily). None of the patients with SV form received fludrocortisone treatment because plasma renin was within normal range during the follow-up.

Follow-up appointments were held every three months in infancy and childhood and every six months thereafter. Standard auxiliary assessments were performed at each visit by a specially trained doctor. Bone age was assessed every 6-12 months from an X-ray of the left hand and wrist, using the standards of Greulich and Pyle[9]. Adult height was defined as growth of <1 cm in the previous year and/or a bone age of >15 years in a female or >16 years in a male.

The follow-up period of our cases reaching final height was 14.2±3.1 years (5.3 -19.5 years), and the hydrocortisone dosage was 19.7±2.9 mg/m^2/day.

Method: The height of our patients reaching their final height was measured with a Harpenden stadiometer. The height standard deviation score (HSDS) for chronological age was calculated with the Kabi-Pharmacia Growth Calculator, which is based on the national standards (10). Data on parental height represent actual measurements. Target height (TH) was calculated as (maternal height + paternal height + or – 13 cm for males and females, respectively) / 2. Target height was converted into target height standard deviation score (THSDS) using national standards for adult height. The patients' statures were corrected for their TH according to the formula: Corrected HSDS = HSDS – THSDS. The patients were subdivided into two groups according to their corrected HSDS (CHSDS) as cases with CHSDS ≥0 SD and those with CHSDS <0 SD[11]. A CHSDS value above 0 was accepted as genetically appropriate height and a value less than 0 as a height below the genetic potential.

The body weight of all our patients who had reached final height was measured with a simple scale and the BMI (weight / height^2) calculated. An overweight state was defined as a BMI >85% and obesity as a BMI >95% in childhood using national standards[12].

Data Analysis

Results are expressed as mean (SD) or as median (range) where indicated. For statistical analysis, the Mann-Whitney U test was used as appropriate for between-group comparisons. Spearman correlation coefficient was used to evaluate the correlation of the different study variables with the final height. All statistical procedures were performed with the SPSS software package, release 10.0. Values of $p < 0.05$ were considered significant.

Results

Data on the adult height achieved, mean chronological age, final height, HSDS, THSDS, HSDS corrected for target height (CHSDS), weight, and BMI are depicted for each case in Table I.

Height outcome: The final height of our patients was 152.2±7.2 cm (HSDS: -1.0±1.1 SD) for the females and 163.1±6.6 cm (HSDS: -1.2±1.0 SD) for the males. Mean CHSDS was -0.73±0.9 SD for both sexes. The distribution of the final HSDS (corrected for genetic potential) is shown in Figure 1. The distribution is skewed to the left with four persons (4/24= 16.6%) below the target range (≤-2 SDS). However, 19 patients (79.1%) had a final height below the TH, and only 5 patients (20.9%) had a final height above the TH and a CHSDS value above zero.

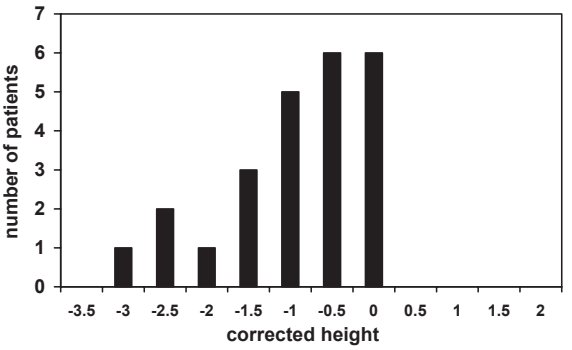

Fig. 1. Distribution of adult height SDS corrected for target height.

Table I. The Clinical and Anthropometric Characteristics of Patients Attaining Their Final Height

At admission				Follow-up	Final Height						
No	Initials	Sex	CAH Type	HC dose (mg/m²/day)	Age (year)	Height (cm)	HSDS	THSDS	CHSDS	Weight (kg)	BMI (%)
1	HS	M	SV	21.75	18.76	176	0.39	0.23	0.16	77.0	24.9 (75)
2	BT	M	SW	21.20	17.70	164.5	-1.42	0.31	-1.73	65.0	24.2 (70)
3	EC	F	SW	21.35	14.10	154	-0.75	-0.84	0.09	64.0	27.0 (95)
4	EB	M	SW	20.00	17.35	153	-1.05	-0.80	-0.20	66.5	28.4 (92)
5	CC	F	SW	10.67	16.90	158.5	-0.25	-0.25	0.00	40.0	16.0 (5)
6	UD	F	SV	22.80	15.67	153.5	-1.02	0.20	-1.22	68.0	29 (>95)
7	ND	F	SV	21.10	14.50	150	-1.51	-1.93	0.42	65.0	28.8 (>95)
8	NK	M	SV	18.00	17.75	168.5	-0.79	-0.15	-0.64	59.5	21.0 (20)
9	AO	F	SV	21.70	15.68	158	-0.26	-0.29	0.03	76.0	30.5 (>95)
10	BK	F	SV	19.99	19.20	154	-1.01	-0.92	-0.09	62.4	26.3 (90)
11	EB	F	SW	14.56	12.98	133	-3.87	-0.67	-3.20	38.5	21.8 (75)
12	HK	M	SW	22.88	14.90	160	-1.02	-0.25	-0.77	68.0	26.5 (92)
13	GA	F	SV	20.50	19.90	153	-1.18	-0.75	-0.43	51.0	21.8 (50)
14	GG	M	SV	19.90	17.00	154	-3.09	-0.55	-2.54	52.0	23.1 (55)
15	YB	M	SV	18.20	14.50	167	0.24	0.61	-0.37	59.9	21.5 (50)
16	DT	F	SV	18.43	17.39	161	0.16	1.34	-1.18	52.0	20.0 (25)
17	LE	M	SV	24.50	16.90	160	-2.14	-0.30	-1.20	67.0	26.2 (87)
18	BD	F	SV	17.47	15.50	159	-0.10	-0.50	-0.40	65.5	25.9 (93)
19	MA	M	SV	21.06	17.00	167	-1.03	-0.20	-0.20	81.0	29.1 (>95)
20	MG	M	SV	19.40	13.50	160	-2.10	-1.50	-0.60	70.0	27.3 (>95)
21	SG	M	SV	17.80	16.50	165	-1.30	-1.10	-0.20	66.0	24.4 (75)
22	EC	F	SV	19.50	15.00	150	-1.40	-0.76	-0.64	49.0	21.7 (60)
23	HK	F	SW	22.80	17.00	149	-1.70	-0.84	-0.86	56.5	25.7 (92)
24	NB	F	SW	19.50	14.50	146	-2.30	0.16	-2.20	62.0	29.5 (>95)
		Female: 13				Female: 152.2±7.2 cm					
Average		Male: 11		19.79	16.25	Male: 163.1±6.6 cm	-1.10	-1.80	-0.73	61.7	25.0
		SD		2.90	1.79		1.0	0.75	0.9	10.5	3.6

CAH: Congenital adrenal hyperplasia. HC: Hydrocortisone. BMI: Body mass index. SV: Simple virilizing form. SW: Salt-wasting form. HSDS: Height standard deviation score. THSDS: Target height standard deviation score. CHSDS: Corrected height standard deviation score.

When we compared the final height of our cases to the Turkish standards, only 5 (20.8%) cases had a HSDS <-2 SDS (<3rd percentile), but 79.2% of the patients reached normal height (>3rd percentile).

When we evaluated the final height of our patients according to the CAH forms, the final height and CHSDS were significantly better in the SV form as compared to the SW form ($p<0.05$). There was no significant difference in the hydrocortisone dosage between the SV and SW forms (Table II).

There was no correlation between the final height and the glucocorticoid dosage in this study (r: -0.01, p: 0.9).

Seven of our cases (29.2%) reaching final height were obese (BMI >95%) but another 6 (25%) were overweight, while 11 cases (45.8%) had normal BMI. There was a positive correlation between the hydrocortisone dosage and the BMI (r: 0.675, $p<0.05$) (Fig. 2).

Discussion

The adult height reached by Turkish children with CCAH was 152.2±7.2 cm (HSDS: -1.0±1.1 SD) for females and 163.1±6.6 cm (HSDS: -1.2±1.0 SD) for males in this study, while the CHSDS was -0.73±0.9 SD. No relationship was found between the glucocorticoid dosage and the final height, but there was a positive correlation between the hydrocortisone dosage and BMI.

Although there are many studies on the final height of CAH patients, our study is the first such study from Turkey. Final height in early- and late-onset CAH patients has been reported as decreased, at 156.4 – 162 cm in females and 167.8 – 173.6 cm in males[3,13,15]. In these studies, a wide variety of dosages and types of glucocorticoids and mineralocorticoids were given. Jääskeläinen[13] reported the adult heights of 92 Finnish 21-OHD patients as -1.0 SDS (159.9 cm) for females and -0.8 SDS (173.6 cm) for males. In another study, the final height and final HSDS of 48 CAH (21-OHD) patients were 170.8±5.6 cm and -0.57±0.8 SD, respectively, for males and 156.7±6.0 cm and -0.61±1.0 SD, respectively, for females with the SW form. These values in those with the SV form were 166.1 cm and -1.0±1.0 SD, respectively, for males, and 151.6±5.4 cm and -1.4±1.0 SD, respectively, for females. There was no difference between the final height and target heights of the SW form patients in this study, but the SV form patients had a final height less than their target height[16]. It has been emphasized in both studies that a high dose of hydrocortisone negatively influences final height. Final height was not related to the cortisol dose at any developmental period, a finding also observed by Cameron et al.[17] and Jääskeläinen et al.[13].

Table II. The Final and Corrected Heights of SV and SW Form CAH Patients

	SW (n=8)	SV (n=16)	Significance
Final height SDS	-1.5±1.1	-1.0±0.9	S
Corrected height SDS	-1.1±1.1	0.54±0.75	S
HC doses (mg/m²/day)	19.1±4.3	20.1±1.9	NS

S=p<0.05.
NS=p>0.05.
SV: Simple virilizing form. SW: Salt-wasting form. CAH: Congenital adrenal hyperplasia. SDS: Standard deviation score. HC: Hydrocortisone.

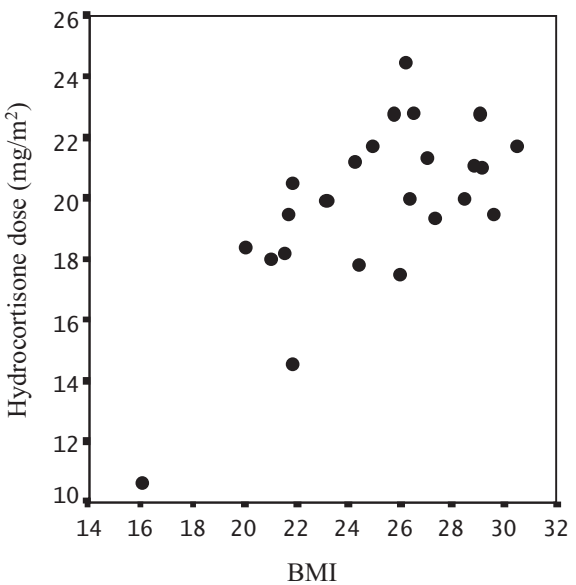

Fig 2. The positive correlation between the hydrocortisone dose and body mass index.

Paganini et al.[18] reported an SD value of -0.41±1.4 for the SW form and -0.01±1.9 for the SV form, with no significant difference between the final heights for the two forms. The average hydrocortisone dose used was similar between the two groups, with 19.1±5.8 mg/m^2/day for the SV form and 19.2±7.8 mg/m^2/day for the SW form, and it was noted that this dosage did not influence the final height[18]. Another study reported the adult heights of 54 CAH cases as 156.4±6.1 cm for females and 165.3±6.4 cm for males. The height SD corrected as to genetic potential was -1.1 SD for both males and females, and most cases were reported to reach their target height[19]. Van der Kamp et al.[20] evaluated 50 CAH patients (26 SV form, 34 SW form) and found a final height corrected for target height of -1.25 SDS for females and -1.27 SDS for males. This study found that the final height of those cases who had received salt supplementation in addition to the treatment in the first year had a final height corrected for target height that was -0.83 SDS better than the other cases. However, the final height was less than the target height in all cases.

In a multi-center study by Hargitai et al.[21], the final height of 598 CAH cases was less than both the target height and the country standards. Although the SW form was diagnosed earlier in this longitudinal study and showed less growth during early childhood due to high-dose steroid usage, there was no significant difference between the final height in patients with SW and SV forms. The final height was 166.47 cm (-1.55 SD) for all CAH males and 156.93 cm (-1.25 SD) for the females. Final height was below the third percentile of the reference in 33.2% of the total population studied. SW and SV boys had a height approximately 9 cm below the target height, while the deviation from target height was 5.97 cm in SW females and 5.36 cm in SV females ($p=0.05$ in SV males, $p<0.001$ in the other group)[21]. We found that the SV form patients had better final heights than the SW form patients despite similar doses of hydrocortisone replacement.

The final height attained in our study was 152.2±7.2 cm (-1.0±1.1 SD) for females and 163.1±6.6 cm (-1.2±1.0 SD) for males. The final height SDS corrected for target height for our cases was -0.73±0.9 SDS and 79.1% had a final height below their target height. However, 79.2% of our patients reached a height above the third percentile for our country's standards. There was no relationship between the dose of hydrocortisone and final heights. Although high-dose hydrocortisone can negatively affect final height in CAH patients, we can not draw a general conclusion because of our low patient number.

The development of an overweight state may be a clinical problem in the long-term management of 21-OHD[5,22]. The increase in BMI from childhood to adulthood as reported in CAH patients is associated with an increase in fat mass as seen in glucocorticoid excess[22]. A correlation between obesity and severe over-treatment (>30mg hydrocortisone equivalent/m^2) has been reported. Patients are now treated with a lower hydrocortisone dosage (15-25 mg/m^2), but there are still reports of obesity in adulthood[5,22,23]. The mean hydrocortisone dose in our population was 19.7±2.9 mg/m^2/day. Seven of our cases (29.2%) were obese and 6 cases (25%) were overweight, while 11 cases (45.8%) had normal BMI. Contrary to Manoli's study[16], we observed a positive correlation between the dose of hydrocortisone used and the BMI. These results led us to postulate that even smaller doses of hydrocortisone used for replacement therapy can lead to a predilection for obesity, despite the results of Knorr et al.[23]. It is of course obvious that the lifestyle accepted by the world population in recent years (sedentary with fast-food diet) will also contribute to the obesity.

In conclusion, the observations that 79.1% of our CCAH cases receiving an average daily hydrocortisone dose of 19.7±2.9 mg/m^2 for 14.2±3.1 years ended up with an adult height below the target height and that 54.2% of the cases were overweight or obese lead us to believe that we should be using the lowest possible dose for treatment.

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