Research Article

Pamukkale Medical Journal
doi:https://dx.doi.org/10.31362/patd.1366476

Evaluation of final heights in patients with congenital adrenal hyperplasia

Konjenital adrenal hiperplazili hastalarda final boyun değerlendirilmesi

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Posted date:27.09.2023 Acceptance date:23.01.2024

Abstract

Purpose: Congenital adrenal hyperplasia (CAH) is an autosomal recessive disease that occurs as a result of a deficiency of any of the enzymes required for the synthesis of glucocorticoids, mineralocorticoids and sex steroids from cholesterol in the adrenal cortex. In this study, we have aimed both to evaluate the final heights in patients with CAH secondary to 21-hydroxylase and 11β- hydroxylase deficiency and also to investigate the factors affecting the final heights.

Material and methods: The anthropometric, clinical, and laboratory findings of patients diagnosed with CAH in the Pediatric Endocrinology Clinic were evaluated retrospectively. Among patients who reached their final heights and adhered to their regular control visits, a total of 39 CAH patients without precocious puberty, and any additional disease diagnosed during their follow-up were included in the study.

Results: Among cases with 21- hydroxylase deficiency, mean final heights of female, and male patients with classic simple virilizing CAH were 158.2±5.46 cm, and 168.8±11.67 cm, while in salt-wasting CAH the corresponding final heights were 152.2±5.94 cm, and 156.5±6.2 cm, respectively. In the group with non-classic CAH, mean final heights of female, and male patients were 155.9±7.59 cm, and 157 cm, respectively. The final height SD of all classic CAH cases was - 1.41±1.45, and it was calculated as -0.81±1.12 (-2.30-0.80) in cases with simple virilizing type classic CAH and -1.79±1.53 (-3.70-0.70) in cases with salt-wasting type classic CAH. In non-classic CAH cases, the final height SD was calculated as -1.65±1.69. When patients with salt-wasting CAH and simple virilizing CAH were compared in terms of final height SDs and genetically adjusted height SDs, the final heights of patients with simple virilizing CAH were significantly higher (p<0.05), and the final heights of cases with 11 β- hydroxylase deficiency were significantly shorter than all groups (p<0.05). In CAH, both hyperandrogenism resulting from inadequate treatment and high-dose glucocorticoid treatment may result in a comparatively shorter final height. For this reason, patients should be evaluated at regular intervals in terms of early recognition of CAH through CAH screening programs, administration of glucocorticoid therapy in appropriate doses (10-15 mg/m²/day), and metabolic control monitoring.

Conclusion: In our study, the best average final height was found in the group using hydrocortisone dose of 10-15 mg/m²/day. We have revealed that when daily doses ranging between 5-10 mg/m² were used, androgens were not suppressed sufficiently and the epiphyses closed prematurely, and in cases where daily doses exceeding 15 mg/m² were administered, the final heights were relatively shorter due to the use of excess doses of glucocorticoids.

Keywords: Congenital adrenal hyperplasia, 21-OH deficiency, final height, corticosteroid treatment.

Kurtipek FB, Bayramoglu E, Keskin M, Aycan Z. Evaluation of final heights in patients with congenital adrenal hyperplasia. Pam Med J 2024;17:265-276.

Öz

Amaç: Konjenital adrenal hiperplazi (KAH), adrenal kortekste kolesterolden glukokortikoid, mineralokortikoid ve seks steroidinin sentezi için gerekli olan enzimlerden herhangi birinin eksikliği sonucu ortaya çıkan otozomal resesif bir hastalıktır. Bu çalışmada 21-hidroksilaz ve 11 Beta hidroksilaz eksikliğine bağlı KAH hastalarında son boy uzunluğunun değerlendirilmesi ve bunu etkileyen faktörlerin araştırılması amaçlandı.

Gereç ve yöntem: Çocuk Endokrinoloji Kliniğinde KAH tanısı konulan hastaların antropometrik, klinik ve laboratuvar bulguları retrospektif olarak değerlendirildi. Çalışmaya düzenli kontrolleri olan, takiplerinde erken puberte geçirmeyen, takiplerinde ek hastalığı olmayan ve son boya ulaşan 39 KAH hastası dahil edildi.

Bulgular: 21 hidroksilaz eksikliğine bağlı klasik basit virilizan KAH'lı kadın olgularda final boy 158,2±5,46 cm, erkek olgularda final boy 168,8±11,67 cm, tuz kaybettiren tip kadın olgularda final boy 152,2±5,94 cm, tuz kaybettiren erkek olgularda final boy ise 156,5±6,2 cm idi. Non-Klasik kadın olgularda final boy 155,9±7,59 cm, 1 erkek olguda ise final boy 157 cm olarak tespit edildi. Klasik tip KAH olgularının tamamının final boy SD-1,41±1,45 SD olup, basit virilize tip klasik KAH olgularında -0,81±1,12 (-2,30-0,80), tuz tüketen tip klasik

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KAH vakalarında -1,79±1,53 (-3,70-0,70) olarak hesaplandı. Klasik olmayan KAH vakalarında son boy SD'si -1,65±1,69 SD olarak hesaplandı. Tuz kaybettiren KAH ve basit virilize KAH'lı hastalar final boy SD'si ve genetiğe göre düzeltilmiş boy SD'si açısından karşılaştırıldığında, basit virilize KAH'lı hastaların final boyları anlamlı derecede yüksek (p<0,05) ve 11 Beta hidroksilaz eksikliği olan hastaların final boyları ise vakaları tüm gruplara göre anlamlı olarak daha kısaydı (p<0,05).
KAH'ta hem yetersiz tedaviden kaynaklanan hiperandrojenizm, hem de yüksek doz glukokortikoid tedavisi boy kısalığına neden olabilir. Bu nedenle KAH tarama programları ile KAH'ın erken tanınması, uygun dozlarda (10-15 mg/m²/gün) glukokortikoid tedavisinin uygulanması ve metabolik kontrol takibi açısından hastaların düzenli aralıklarla değerlendirilmesi gerekmektedir.
Sonuç: Çalışmamızda en iyi ortalama final boy uzunluğu 10-15 mg/m²/gün hidrokortizon dozu kullanan grupta bulundu. 5-10 mg/m²/gün kullanıldığında androjenlerin yeterince baskılanmadığını ve epifizlerin erken kapandığını, >15 mg/m²/gün kullanıldığında ise glukokortikoid fazlalığına bağlı olarak son boyun kısaldığını saptadık.

Anahtar kelimeler: Konjenital adrenal hiperplazi, final boy, 21-OH eksikliği, kortikosteroid tedavisi.

Kurtipek FB, Bayramoğlu E, Keskin M, Aycan Z. Konjenital adrenal hiperplazili hastalarda final boyun değerlendirilmesi. Pam Tıp Derg 2024;17:265-276.

Introduction

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disease that occurs as a result of deficiency of any of the enzymes required for the synthesis of glucocorticoids, mineralocorticoids, and sex steroids from cholesterol in the adrenal cortex [1-7]. While CAH due to 21-hydroxylase enzyme deficiency constitutes 90-95% of all cases, 11 β - hydroxylase deficiency is the second common cause of CAH. Clinical findings vary depending on the type and degree of enzyme deficiency. In our treatment, we have aimed to replace the unsynthesized cortisol, as well as to prevent the increase in androgen secretion by suppressing the adrenocorticothyropic hormone (ACTH) secretion. The gap between the doses used in undertreatment and overtreatment is extremely narrow, and the risk of complications increases if the doses used are not individualized. In cases where inadequate doses used for the treatment of CAH, excessive androgen exposure causes bone age progression and precocious puberty, increasing the adult final heights. On the other hand, treatment with higher doses of glucocorticoid also suppresses linear growth by adversely affecting the growth hormone-IGF-1 axis. As a result, final heights may remain short in those receiving low or high doses of glucocorticoids. The glucocorticoid dose that is used for treatment should be high enough to suppress the excessive production of sex steroids and low enough to minimize the side effects that may develop due to hypercortisolism [8, 9].

The dose of glucocorticoids required to normalize ACTH levels in patients with CAH may be much higher than used in other forms of adrenal insufficiency. Therefore, when planning treatment in classic CAH, a balance should be maintained between avoiding overtreatment, which may cause many negative side effects on growth rate, metabolic, cardiovascular status and bone health, or undertreatment, which carries the risk of life-threatening adrenal crisis and virilization [10].

In this study, we have aimed to evaluate the final heights in patients with CAH due to 21-hydroxylase or 11 β-hydroxylase deficiency and to investigate the factors affecting the final heights.

Materials and method

The anthropometric, clinical and laboratory findings of patients diagnosed with CAH in the Pediatric Endocrinology Clinic of our university hospital were evaluated retrospectively. Among patients who reached their final heights and adhered to their regular control visits, a total of 39 CAH patients without precocious puberty, and any additional disease diagnosed during their follow-up were included in the study. Based on patients' complaints on admission (suspicious genitalia, signs of salt wasting CAH, pubic hair growth, accelerated somatic development, early puberty), genotypic sex determination by karyotype analysis, levels of basal or ACTH-stimulated serum 17-OHP, adrenal androgens (DHEAS, androstenedione), serum testosterone and ACTH, results of

genetic tests performed to diagnose CAH due to 21-hydroxylase deficiency, patients were grouped as follows: Classic CAH due to 21-hydroxylase deficiency (13 salt-wasting and 7 simple virilizing CAH patients), non-classical CAH (n:13) and 11 β-hydroxylase-deficient group (n:6). The diagnosis of congenital adrenal hyperplasia due to 11 β-hydroxylase deficiency is based on raised serum 11-deoxycortisol and 11- deoxycorticosterone levels together with increase in the levels of adrenal androgens.

All patients received hydrocortisone treatment. The treatment doses received by the patients and their stages of puberty were recorded.

Anthropometric evaluations (height, body weight, BMI, waist circumference, growth rate) of the patients were made at each control visit. Body mass indices were calculated according to the formula: BMI=weight(kg)/height(m)}^{2}. The SD value of the relevant anthropometric value for each case was calculated by taking into account the standards of our country. Final height was defined as bone age ≥15 years in girls, and ≥16 years in boys, or growth rate of <1cm/year.

For metabolic monitoring, serum basal 17-OHP, ACTH, testosterone, androstenedione, and in salt-wasting CAH patients' plasma renin activity levels were measured. During the follow-up, serum 17-OHP and ACTH measurements were made at least 3 times a year to check whether the desired levels were achieved. The desired level was accepted as <10 nmol/lt (3.3 ng/ml) for 17-OHP and <70 pg/ml for ACTH. In all control visits, the patients who achieved the desired metabolic control values of 70% or higher for ACTH and 17-OHP levels were interpreted as having good metabolic control, while the others were interpreted as having poor metabolic control. In salt wasting CAH patients, serum Na and K and plasma renin levels were measured at each follow-up visit, and subtle signs of salt wasting were investigated. In addition, care was taken to ensure that testosterone and androstenedione levels remained within normal ranges in patients with good metabolic control. In routine controls, blood samples were taken from the patients between 08:00 and 09:00 AM, following an 8-hour fasting period. Glucose, cortisol, 17-OHP, ACTH, aldosterone, PRA, DHEAS, androstenedione and testosterone levels were studied from the blood samples taken. Glucose levels were examined using an Architect c16000 autoanalyzer. Total testosterone and DHEAS levels were measured by a chemiluminescent immunoassay method (Advia Centaur® XP). ACTH measurement was also performed with the chemiluminescence method (Immulite® 2000XPI). Serum androstenedione, 17-OHP, and plasma renin levels were examined by radioimmunoassay method.

The mean daily hydrocortisone (HC) or HC-equivalent glucocorticoid doses (mg/m^2) used during the whole follow-up period were also calculated. Bone age assessment was done annually according to the Greulich Pyle radiographic atlas of skeletal development of the hand and wrist.

Target heights (THs) of the study participants were calculated by the sum of the average heights of the parents as follows: Boys: Sum of mother's and father's heights+13 cm)/2, Girls: (Sum of mother's and father's heights - 13 cm)/2. TH SDs were calculated as follows: For girls (target height-163 cm)/5.93, and for boys (target height-176 cm)/6.3 was used. Adjusted height SD ≥0 was interpreted as appropriate height according to genetic height potential, and <0 as height below genetic height potential. The height of the patients who reached the final height was also evaluated considering that their target height was within ±5 cm of their final heights. Based on our assessments, patients whose final heights were at least 6 cm shorter than their target heights did not reach their target heights Approval for the study was received from the Educational Planning Board of Dr. Sami Ulus Gynecology, Child Health and Diseases Training and Research Hospital.

Statistical analyses

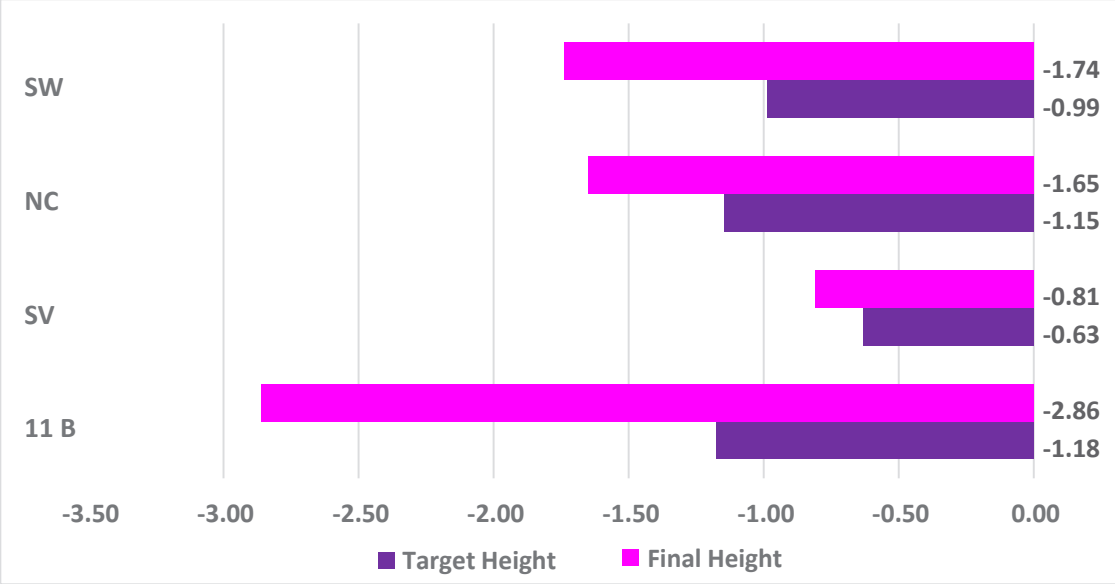
All statistical analyses were performed using the IBM SPSS for Windows Version 22.0 package program. Numerical variables were summarized as mean ± standard deviation, and median [minimum-maximum] values. Categorical variables were shown in numbers and percentages. Differences between both groups in terms of numerical variables (if any) was investigated with the Mann-Whitney U

test. Spearman correlation coefficient was used to examine the correlation between different variables. According to Pearson correlation analysis, correlation coefficients (r) of 0.25, 0.26-0.50, 0.26-0.50, and 0.76-1 indicated the presence of weak, moderate, strong, and very strong correlations between different variables The level of statistical significance level was accepted as $p<0.05$.

Results

Our study population consisted of 30 (76.9%) female, and 9 (23.1%) male patients. The average age at diagnosis of all cases was 3.0±5.46 years (0-17 years) and 13 of them were diagnosed in the neonatal period. Mean ages at diagnosis of cases with classic type 21-hydroxylase deficiency (1.7±2.7 years), non-classic type 21-hydroxylase deficiency (11.3±3.8 years,) and 11 β-hydroxylase deficiency (2.4±1.4 years) were as indicated cases diagnosed with CAH had 21-hydroxylase deficiency (n:33; 84.6%), 11 β- hydroxylase deficiency (n:6; 15.4%), while patients with 21-hydroxylase deficiency had salt-wasting classic CAH (n:13; 33.3%), simple virilizing classic CAH (n:7; 17.9%), and non-classic CAH (n:13; 33.3%).

The mean final heights were 158.2±5.46 cm in female and 168.8±11.67 cm in male cases with classic simple virilizing CAH due to 21-hydroxylase deficiency. Female, and male cases with salt-wasting classic CAH had mean final heights of 152.2±5.94 cm and 156.5±6.2 cm, respectively. In female cases cases with non-classic CAH mean final height was 155.9±7.59 cm. and 157 cm in 1 non-classic male case. The final height of all classic type CAH cases was - 1.41±1.45 SD, and they were -0.81±1.12 (-2.30-0.80) in cases with simple virilizing type classic CAH and -1.79±1.53 (-3.70-0.70) in cases with salt-wasting type classic CAH. In non-classic CAH cases, final height SD was calculated as -1.65±1.69. When patients with salt-wasting CAH and simple virilizing CAH were compared in terms of final height SD scores and genetically adjusted height SD scores, the final heights of patients with simple virilizing CAH were significantly higher ($p<0.05$), and the final heights of 11 β-hydroxylase deficiency cases were significantly shorter than all groups ($p<0.05$). Graph 1 shows the final height SDS and target height SDS by CAH types.



Graph 1. Final height SDs and target height SDs by CAH types

SW: Salt wasting, NC: Non-classic, SV: Simple Virilizating

The average daily hydrocortisone doses used were 13.14±5.06 mg/m² in all cases. While average daily hydrocortisone doses used were 15.06±3.78 mg/m², 14.42±3.49 mg/m², in the simple virilizing CAH, 15.40±4.02 mg/m² in the salt-wasting type CAH, 7.90±2.74 mg/m² in o non-classic CAH and 18.08±2.59 mg/m²/g in 11 β-hydroxylase deficiency groups. The average daily HC doses were 5-10 mg/m² in 11 (28.2%), 10-15 mg/m² in 12 (30.8%), and ≥15 mg/m² in 16 (41%) patients. Among all groups the highest dose of hydrocortisone was used for patients with 11 β-hydroxylase deficiency (p<0.05).

Table 1 shows the distribution of patients' characteristics at diagnosis and clinical follow-up.

Indicated numbers of cases reached their target heights in groups of classic salt-wasting type CAH (n:10; 76.8%) simple virilizing classic type CAH (n:7; 100%), non-classic CAH (n:10; 76.8%), and 11 β-hydroxylase deficiency (n:3; 50%). Table 2 shows the clinical and demographic characteristics of the patients who could not achieve their target heights.

When final height SDs of the cases were evaluated in consideration of average hydrocortisone doses used, we have noticed that respective mean final height SDs, and genetically adjusted height SDs of the cases who used average daily hydrocortisone doses of 5-10 mg/m² (n:11) (-1.72±1.58, and -0.55±1.3) or 10-15 mg/ m² (n:12) (0.75±0.98, and -0.22±1.0) or ≥15 mg/m² (n:16) (-2.18±1.29, and 1.17±0.8) were as indicated in parentheses (Graph 2). Final height SD was found to be significantly lower in those using daily hydrocortisone doses of ≥15 mg/m². The final height of the patients whose daily HC doses were in the range of 10-15 mg/m²/day reached a statistically significantly higher average final height compared to the other patients (p<0.05). In addition, the patients using daily hydrocortisone doses of 10-15 mg/m² had a statistically significantly higher genetically adjusted mean height than the patients using daily hydrocortisone doses of 15 mg/m² (p<0.05).

Nineteen (48.7%) of our cases had achieved good and 20 (51.3%) cases had poor metabolic control. The mean final height, and genetically adjusted height SD SDs of the patients with good metabolic control were -1.15 SD and -0.34 SD, respectively, while the corresponding SDs for patients with classic CAH with poor metabolic control were -2.25 SD and -1.08 SD, respectively (Graph 3). The final height SD and genetically adjusted height SD of patients with CAH with good metabolic control were significantly higher when compared to those with classic CAH with poor metabolic control (p<0.05).

Table 1. Diagnosis and follow-up data of patients

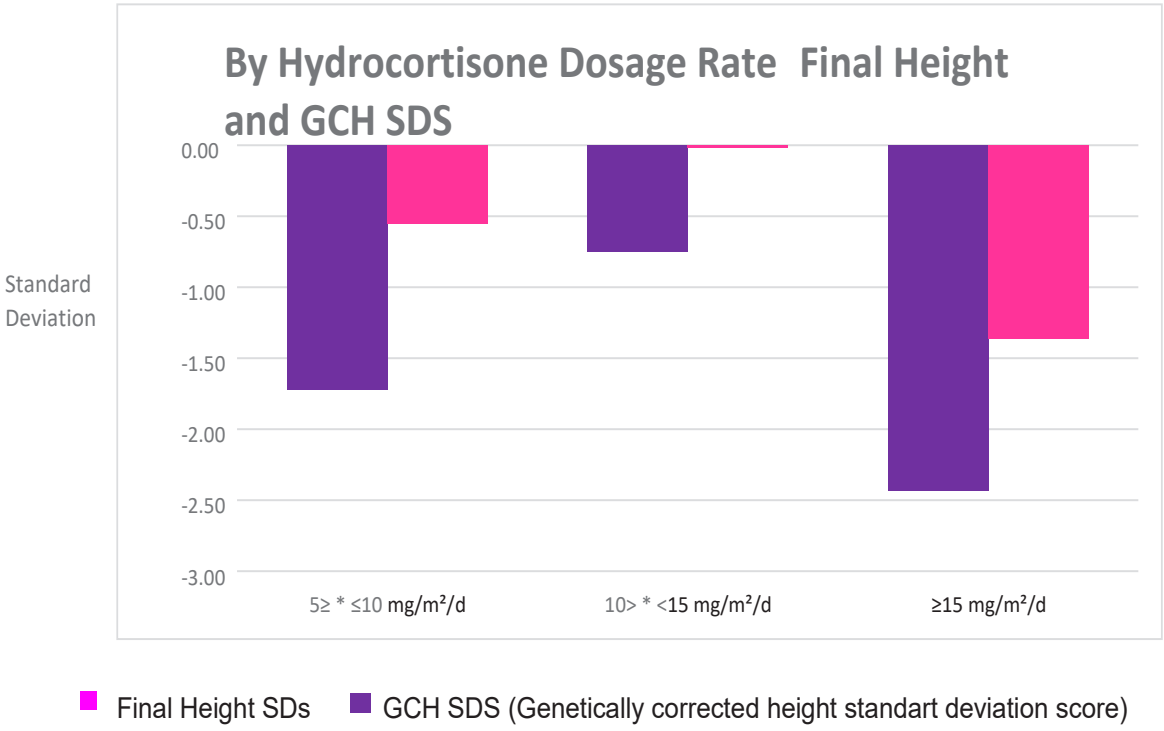
Gender	
Famele	30 (76.9%)
Male	9 (23.1%)
Age at diagnosis	3.0±5.46 years (yd-17 years)
Newborn	13 (33.3%)
>1 month	26 (66.7%)
CAH type	
21 OH	33 (84.6)
Salt-wasting	13(33.3%)
Simple virilizing	7 (17.9%)
Non-classic	13 (33.3%)
11B	6 (15.4)
Average HC dose (mg/m²/day)	
All cases	13.14±5.06 (5.1-27.0)
21 OH (n:33)	12.25±4.89 (5.1-27.0)
Classic CAH (n:20)	15.06±3.78 (10.1-27.0)
Simple-virilizing (n:7)	14.42±3.49 (10.1-18.3)
Salt-wasting (n:13)	15.40±4.02 (10.3-27.0)
Non-Classic CAH (n:13)	7.90±2.74 (5.1-15.3)
11B (n:6)	18.08±2.59 (15.2-22.0)
HC dose (mg/m²/day)	
5-10	11 (28.2%)
10-15	12 (30.8%)
≥15	16 (41.0%)
Metabolic control	
Good	19 (48.7%)
Poor	20 (51.3%)
Final Height SDS (by diagnosis)	
All cases	-1.41±1.45 (-3.70-0.80)
21 OH (n:33)	-1.51±1.53 (-4.60-0.86)
Classic CAH (n:20)	-1.41±1.45 (-3.70-0.80)
Simple-virilizing (n:7)	-0.81±1.12 (-2.30-0.80)
Salt-wasting (n:13)	-1.79±1.53 (-3.70-0.70)
Non-Classic CAH (n:13)	-1.65±1.69 (-4.60-0.86)
11 β (n:6)	-2.86±1.53 (-5.40 - -1.30)
Final Height (by gender)	
Genotypic female (46, XX)	155.60±7.79 cm (139.7-168.0)
Genotypic male (46, XY)	160.36±7.52 cm (150.6-177.1)

CAH: Congenital adrenal hyperplasia, HC: Hydrocortisone, 21 OH: 21 Hydroxylase deficiency, 11 β: 11 Beta-hydroxylase deficiency
SDS: Standard Deviation Score

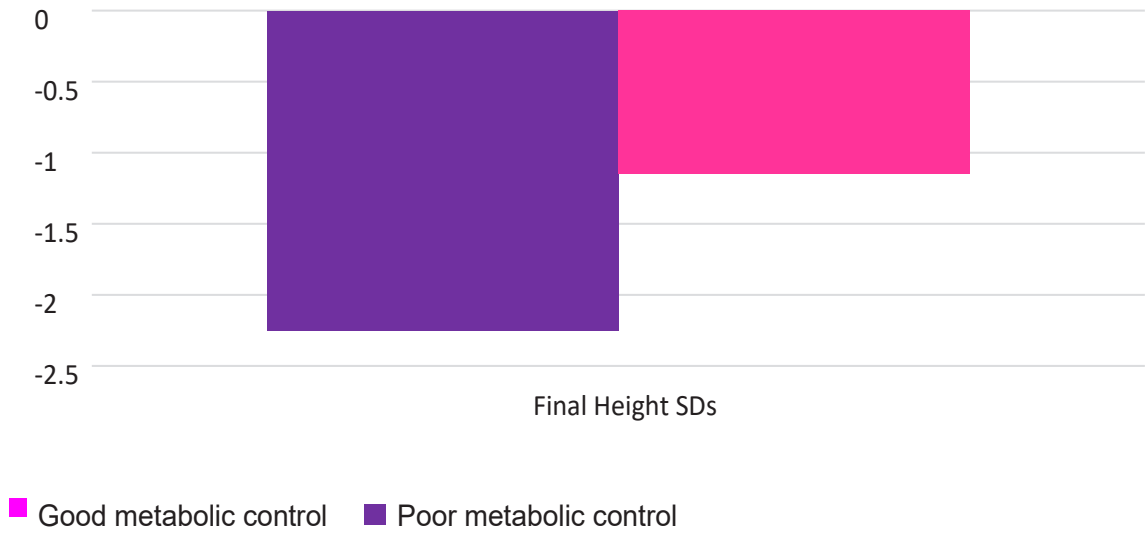
Table 2. Clinical and demographic characteristics of patients who could not achieve their target heights

Case	CAH type	Gender	Age at diagnosis (years)	Age at final height (years)	Calendar Age (years)	HC Dose (mg/m^2/ day)	Final Height (cm)	Target Height (cm)	Final Height SD	Target Height SD	GGDB SD	Body weight (kg)	BMI (kg/m^2)	BMI SD	Metabolic/ Control
1 ÖB	SW	46XX	NB	11	18	15.3	148.0	154.2	-3.40	-1.50	-1.90	57.30	24.00	0.920	Poor
2 HU	SW	46XY	5	12	16	18.3	150.6	168.0	-3.70	-1.30	-2.40	63.00	27.60	1.500	Poor
3 TH	SW	46XY	0	16	20	12.2	155.9	165.0	-3.00	-1.78	-1.22	80.40	33.30	2.450	Poor
4 DY	NC	46XX	7	13.5	15	15.3	148.1	154.0	-3.40	-1.53	-1.87	43.05	19.60	-0.450	Good
5 FA	NC	46XY	10	15	20	5.1	157.0	166.5	-2.85	-1.54	-1.31	60.00	22.20	0.660	Good
6 FT	NC	46XX	15	15	19	7.5	144.7	158.5	-4.60	-0.78	-3.82	50.65	24.10	0.800	Poor
7 MS	11 β	46XX	3	14	18	19.0	140.6	156.2	-3.71	-1.20	-2.51	44.00	22.13	0.250	Good
8 HO	11 β	46XY	3	13.1	25	22.0	155.3	169.3	-3.00	-0.99	-2.01	65.00	26.60	-0.990	Good
9 MS	11 β	46XX	4	14	16	15.6	139.7	166.5	-5.40	-1.54	-3.86	45.10	23.30	0.330	Poor

CAH: Congenital adrenal hyperplasia, HC: Hydrocortisone, SD: Standard Deviation, GGDB: Genetically adjusted height, BMI: Body mass index, NB: Newborn, SW: Salt wasting, NC: Non-Classic; 11 β:11 beta-hydroxylase deficiency



Graph 2. Final height SDs and GCH SDs by hydrocortisone doses



Graph 3. Metabolic control-final height SDs

Discussion

In our study, the final heights of 39 patients followed up with the diagnosis of congenital adrenal hyperplasia and the factors affecting their final heights were evaluated, and 60% of the cases achieved their target heights. Although the best final height average was achieved in patients with simple virilizing CAH, and in 11 β-hydroxylase deficiency, the final height average of the former group was lower when compared with 21-hydroxylase deficiency cases. The age at diagnosis, hydrocortisone dose, and metabolic control were important factors affecting the achievement of final and target heights.

Congenital adrenal hyperplasia is an autosomal recessive disease that occurs as a result of the deficiency of any of the enzymes required for the synthesis of glucocorticoids and mineralocorticoids from cholesterol in the adrenal cortex, causing glucocorticoid and mineralocorticoid deficiency. However, the selection of metabolic criteria to be used as a parameter in monitoring the patients with good and poor metabolic control, and the determination of the ideal treatment dose are still controversial issues [8]. Recent studies have emphasized that metabolic status evaluated by serum 17-OHP levels lead to the use of higher doses of steroids, and attention is drawn to the use of serum testosterone and androstenedione levels as metabolic control measures. Despite all these suggestions, there is no consensus on the gold standard monitoring parameter to be used for the adjustment of the treatment dose in CAH.

In different studies, along with heart rate monitoring, anthropometric measurements, and bone age assessments, serum 17-OHP and/or ACTH levels were measured [11]. Serum 17-OHP, ACTH and testosterone levels were evaluated in prepubertal patients [8], and serum 17-OHP and pregnanetriol and 17-ketosteroid were measured in 24-hour urine samples [12]. Although it is recommended to measure serum 17-OHP levels at 08:00 AM, considering the diurnal variations, it is emphasized that it is more appropriate to evaluate serum 17-OHP levels using the 17-OHP profile determined based on measurementa at different time points (08:00 AM, 12:00 AM, 05:00 PM, and 10:00 PM) [13]. The most important points to be emphasized in the treatment of CAH are to normalize ACTH secretion, inhibit the excessive secretion of adrenal androgens, and replace steroids that are not synthesized in the adrenal gland [1-4, 8]. Therefore, the dose of corticosteroid used should be kept in the dose range that will suppress adrenal androgens and at the same time minimize the negative effects of the long-term steroid treatment. If the patient has received excessive or insufficient treatment doses, relatively shorter final height may be achieved, and maintained due to the failure to control early pubertal findings, the acceleration in somatic development and the resulting epiphyseal closure [6]. Due to all these disadvantages encountered in the management of the disease and the complications that may develop, it is extremely important to follow up CAH patients conscientiously. In our study, we evaluated serum ACTH, 17-OHP, testosterone and androstenedione levels, as well as anthropometric parameters, to evaluate metabolic control in CAH patients. If our patients' growth rate decreased and they became overweight during follow-up period, we reduced the steroid dose. On the other hand, rapid progression in growth rate and bone age was taken as an evidence of insufficient maintenance doses of steroids used, and increase in androgen levels urged us to increase the steroid dose. We meticulously adjusted and individualized the steroid doses of our patients during their follow-up, taking into account both anthropometric and hormonal changes. In our study population we used serum ACTH and 17-OHP levels as metabolic control measures. Therefore, during the follow-up of these patients, serum 17-OHP levels between 1-10 ng/ml and ACTH levels below 71 pg/ml were used as criteria for good metabolic control. Patients who achieved 70% of the desired values in all measurements were included in the good metabolic control group.

Accordingly, 52% of the cases were evaluated as having good metabolic control. Although the final height deviations of the cases in the good control group - though not statistically significantly-were better than those in the poor control group. When the metabolic controls and average heights of our cases were examined, it was seen that patients with good metabolic control reached a better final height than those with poor metabolic control.

The final height SDs of patients with good, and poor metabolic control were 0.15±0.51 SD, and -2.25±0.89 SD, respectively ($p<0.05$).

Wasniewska et al. [14] reported that hydrocortisone treatment did not significantly affect height outcomes in children without classic CAH. However, they commented that wide differences in the number of patients included in their study groups could affect the reliability of the results. In our study, we found that hydrocortisone treatment used in appropriate doses favorably affected final heights of the patients.

Although the required physiological daily doses of hydrocortisone range between 6-7

mg/m², in cases with CAH, hydrocortisone treatment should be given at daily doses of 10-15 mg/m² tid to suppress androgen production from the adrenal cortex [4, 7, 8]. In the literature, widely different average daily HC doses used in studies conducted in children and adolescent patient groups were reported by Cordeiro et al. [15]; (13.7 mg/m²), Volkl et al. [16]; (14.8±4.76 mg/m²), Ambroziak et al. [17] (18.55±4.8 mg/m²), and Aycan et al. [18] (19.7±2.9 mg/m²). As expected in our study, the mean HC dose used was lower in the non-classic CAH group than in the classic CAH group. In the CAH group due to 11 β-hydroxylase deficiency, the mean HC dose was higher than in all other groups. The mean HC doses calculated in our study were consistent with the literature.

In the treatment of congenital adrenal hyperplasia, uncontrolled use of glucocorticoids exceeding the physiological doses is known to disrupt the growth process with its negative effects on both the growth hormone/IGF-1 axis and the bone cartilage [19-22]. Sarafoglou et al. [23] found that daily HC doses of 104 patients had negatively affected estimated adult height, with a 0.37cm decrease from the final height for each mg/m² increase in daily doses. In their retrospective study with 92 patients, Hargitai et al. [24] emphasized that the daily hydrocortisone doses should not exceed 17 mg/m² during puberty in order to optimize the final height of patients with classic adrenal hyperplasia. In a study performed with 31 cases with 21-hydroxylase deficiency Cordeiro et al. [15] used average daily HC dose of 13.7 mg/m² (dose range: 10.9-40 mg/m²/day) and the final height SD of these patients achieved was -2.13±1.11 SD, without any significant difference between the final height, gender, clinical form of CAH and hormone control of the treated groups. However, they found a significant negative correlation between final height and hydrocortisone dose

The common conclusion of all these studies is that the most important factor affecting the increases in the heights of the patients in CAH is the high doses of steroid therapy. Girgis et al. [25] reported that 32 patients with CAH did not develop short stature after at least 4 years of treatment with hydrocortisone at daily doses of 10-15 mg/m². In our study, the effect of the hydrocortisone dose and target height on the final height was examined by linear regression analysis, and it was seen that the target height variable had a positive, while the HC dose had a negative effect on the final height, and optimal final height was achieved with daily HC doses ranging between 10-15 mg/m².

In a study on 124 patients with CAH, Hargitai et al. [24] found the height SD -1.55 in male and 1.25 SD in female patients. In our previous research we conducted in 2006, the average daily hydrocortisone dose was 17.64±3.60 mg/m², and the average height SD was -1.77 SD [26]. In the study we conducted in 2009, final height and final height SD were 152.2±7.2 cm and -1.0±1.1 SD in girls; and 163.1±6.6 cm and -1.2±1.0 SD in boys, while the average daily hydrocortisone dose received by the patients was 19.7±2.9 mg/m² [18]. In this study, we reported that 79.1% of the cases could not achieve their target height, and obesity developed in 54% of the cases. In these studies, we attributed higher rates of inability to achieve final target heights and the development of obesity in these cases to the use of excessive doses of hydrocortisone used, and strongly suggested use of lower doses of hydrocortisone in these patients, as we applied in our clinical practice. As a matter of fact, our most recent study included the results of treatment with lower doses of hydrocortisone in which we observed better final height results relative to our previous studies. While only 20% of the cases with classic CAH in the previous study achieved the genetic height potential, in our current study 60% of the cases achieved their genetic height potential. Smaller number of our cases diagnosed with 11β hydroxylase deficiency, who had to receive HC treatment at higher doses achieved their mean final and target heights compared to the cases with classic type 21-hydroxylase deficiency which demonstrated unfavorable effects of hydrocortisone overdose

In a multicenter study by Hargitai et al. [24], 341 of 598 CAH cases were followed longitudinally from birth to the time they reached their final heights. According to the data obtained from this study, it was determined that the final heights of all cases were shorter than both country references and target heights. In the longitudinal follow-up, it was emphasized that patients with simple virilizing CAH were taller in early childhood when compared to their gender- and age-matched groups, while

those with salt-wasting CAH were shorter than their peers at 0-3 years of age. In this study, they attributed relative tallness of the patients with simple virilizing CAH in early childhood to delayed diagnosis and advanced bone age and suggested that earlier diagnosis and use of high doses of steroids in the salt-wasting CAH may negatively affect growth rate. In case of delayed treatment, advanced bone age should be taken into consideration as another factor that negatively affects height rate. Advanced bone age in cases of delayed diagnosis and steroid overload together with poor monitoring have the same negative effect. Hargitai et al. [24] suggested that short stature diagnosed especially in infancy is commonly related to poorly monitored steroid therapy. Similarly, in our study, the average final height and percentage of achieving the target height in cases with simple virilizing type CAH were higher than those with salt-wasting type CAH which may be due to the fact that patients with salt-wasting type CAH were exposed to high-dose HC treatment in early infancy. Although the enzyme activity in patients with non-classic CAH is higher than the enzyme activity in simple virilizing patients, the shorter mean final height is associated with a longer exposure to hyperandrogenemia due to the delayed diagnosis. There is little data on the final height of patients with 11 β-hydroxylase deficiency. In our study, the mean final height SDS of 6 cases diagnosed with 11 β-hydroxylase deficiency who achieved their final heights was lower than the cases diagnosed with 21-hydroxylase deficiency (-5.40±1.30 vs -2.86±1.53) which was attributed to the delayed diagnosis of cases with 11 β-hydroxylase deficiency and the fact that these patients received higher doses of hydrocortisone.

In conclusion, in patients with CAH, both inadequate and high-dose glucocorticoid treatment may result in relatively shorter final height. For this reason, early recognition of CAH through CAH screening programs, application of glucocorticoid therapy in appropriate doses (10-15 mg/m²/day) and regular evaluation of patients for metabolic control monitoring can ensure achievement of adequate final height. In our study, the best average final target height was found in the group using daily hydrocortisone doses of 10-15 mg/m². Indeed, when daily doses of 5-10 mg/m² were used, androgens were not suppressed sufficiently and the epiphyses closed prematurely, and in cases where daily doses of >15 mg/m² were used, the age-adjusted targeted final height was not achieved due to the excess glucocorticoid dose.

Conflict of interest: No conflict of interest was declared by the authors.

References

1. New MI, Dupont B, Pang S, Pollack M, Levine LS. An update of congenital adrenal hyperplasia. Recent Prog Horm Res 1981;37:105-181. https://doi.org/10.1016/b978-0-12-571137-1.50008-6
2. Charmandari E, Chrousos GP. Metabolic syndrome manifestations in classic congenital adrenal hyperplasia: do they predispose atherosclerotic cardiovascular disease and secondary polycystic ovary syndrome? Ann N Y Acad Sci 2006;1083:37-53. https://doi.org/10.1196/annals.1367.005
3. Speiser PW, Azziz R, Baskin LS, et al. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2010;95:4133-4160. https://doi.org/10.1210/jc.2009-2631
4. Riepe FG, Sippell WG. Recent advances in diagnosis, treatment, and outcome of congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Rev Endocr Metab Disord 2007;8:349-363. https://doi.org/10.1007/s11154-007-9053-1
5. Levine LS. Congenital adrenal hyperplasia. Pediatr Rev 2000;21:159-70; quiz 171. https://doi.org/10.1542/pir.21-5-159
6. White PC, Speiser PW. Congenital adrenal hyperplasia due to 21- hydroxylase deficiency. Endocr Rev 2000;21:245-291. https://doi.org/10.1210/edrv.21.3.0398
7. Merke DP, Bornstein SR. Congenital adrenal hyperplasia. Lancet 2005,365:2125-2136. https://doi.org/10.1016/S0140-6736(05)66736-0
8. Joint LWPES/ESPE CAH Working Group. Consensus statement on 21-hydroxylase deficiency from the Lawson Wilkins Pediatric Endocrine Society and the European Society for Paediatric Endocrinology. J Clin Endocrinol Metab 2002;87:4048-4053. https://doi.org/10.1210/jc.2002-020611
9. Merke D, Kabbani M. Congenital adrenal hyperplasia: epidemiology, management and practical drug treatment. Paediatr Drugs 2001;3:599-611. https://doi.org/10.2165/00128072-200103080-00005
10. Claahsen-van der Grinten HL, Speiser PW, Ahmed SF, et al. Congenital adrenal hyperplasia-current insights in pathophysiology, diagnostics, and management. Endocr Rev 2022;43:91-159. https://doi.org/10.1210/endrev/bnab016

11. Bode HH, Rivkees SA, Cowley DM, Pardy K, Johnson S. Home monitoring of 17 hydroxyprogesterone levels in congenitx127drenal hyperplasia with filter paper blood samples. J Pediatr 1999;134:185-189. https://doi.org/10.1016/s0022-3476(99)70413-0
12. Ercan O, Hatemi S, Kutlu E, Turan N. Effect of treatment on growth in congenital adrenal hyperplasia. Indian J Pediatr 2000;67:783-789. https://doi.org/10.1007/BF02726219
13. Erhardt E, Solyom J, Homoki J, Juricskay S, Soltesz G. Correlation of blood-spot 17-hydroxyprogesterone daily profiles and urinary steroid profiles in congenital adrenal hyperplasia. J Pediatr Endocrinol Metab 2000;13:205-210. https://doi.org/10.1515/jpem.2000.13.2.205
14. Wasniewska MG, Morabito LA, Baronio F, et al. Adrenal Diseases Working Group of the Italian society for pediatric endocrinology and diabetology. Growth trajectory and adult height in children with nonclassical congenital adrenal hyperplasia. Horm Res Paediatr 2020;93:173-181. https://doi.org/10.1159/000509548
15. Cordeiro GV, Silva IV, Goulart EMA, das Chagas AJ, Kater CE. Final height in congenital adrenal hyperplasia: the dilemma of hypercortisolism versus hyperandrogenism. Arq Bras Endocrinol Metabol 2013;57:126-131. https://doi.org/10.1590/s0004-27302013000200005
16. Volkl TMK, Simm D, Beier C, Dörr HG. Obesity among children and adolescents with classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Pediatrics 2006;117:98-105. https://doi.org/10.1542/peds.2005-1005
17. Ambroziak U, Bednarczuk T, Ginalska Malinowska M, et al. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency—management in adults. Endokrynol Pol 2010;61:142-145.
18. Aycan Z, Akbuğa S, Cetinkaya E, et al. Final height of patients with classical congenital adrenal hyperplasia. Turk J Pediatr 2009;51:539-544.
19. Van den Brande J. Postnatal growth and its endocrine regulation. Pediatric Endocrinology 1993;2:154-174.
20. Mehls O, Tönshoff B, Kovacs G, Mayer C, Schurek J, Oh J. Interaction between glucocorticoids and growth hormone. Acta Paediatr Suppl 1993;388:77-82. https://doi.org/10.1111/j.1651-2227.1993.tb12850.x
21. Stewart PM, Toogood AA, Tomlinson JW. Growth hormone, insulin-like growth factor-I and the cortisol-cortisone shuttle. Horm Res 2001;56:1-6. https://doi.org/10.1159/000048126
22. Mauras N. Growth hormone therapy in the glucocorticosteroid-dependent child: metabolic and linear growth effects. Horm Res 2001;56:13-18. https://doi.org/10.1159/000048128
23. Sarafoglou, K, Addo OY, Turcotte L, et al. Impact of hydrocortisone on adult height in congenital adrenal hyperplasia-the Minnesota cohort. J Pediatr 2014;164:1141-1146. https://doi.org/10.1016/j.jpeds.2014.01.011
24. Hargitai G, Solyom J, Battelino T, et al. Growth patterns and final height in congenital adrenal hyperplasia due to classical 21-hydroxylase deficiency. Results of a multicenter study. Horm Res 2001;55:161-171. https://doi.org/10.1159/000049990
25. Girgis R, WinterJS. The effects of glucocorticoid replacement therapy on growth, bone mineral density, and bone turnover markers in children with congenital adrenal hyperplasia. J Clin Endocrinol Metab 1997;82:3926-3929. https://doi.org/10.1210/jcem.82.12.4320
26. Aycan Z, Ocal G, Berberoglu M, Cetinkaya E, Adiyaman P, Evliyaoglu O. Experience with long-term glucocorticoid treatment in congenital adrenal hyperplasia: growth pattern compared with genetic height potential. J Pediatr Endocrinol Metab 2006;19:245-251. https://doi.org/10.1515/jpem.2006.19.3.245

Ethics committee statement: Ethics committee approval was not received, because this is a thesis study performed before the year 2017.

Authors' contributions to the article

Z.A. and F.B.K. have constructed the main idea and hypothesis of the study. They developed the theory and arranged/edited the material and method section. E.B. and M.K. have evaluated the data in the Results section. Discussion section of the article was written by F.B.K.

Z.A. reviewed, corrected and approved the final version of the manuscript. In addition, all authors critically reviewed the entire study and approved the final version of the manuscript.