Non communicable diseases

Final Heights in Patients with Congenital Adrenal Hyperplasia: a Retrospective Cohort Study

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Keywords

Final heights • Congenital Adrenal Hyperplasia • Salt wasting • Simple-virilizing

Summary

Introduction. *Congenital adrenal hyperplasia (CAH) attributed to 21-OHD is one of the most common genetic endocrine disorders that occurs due to the disruption and defects in the steroidogenic enzymes involved in the production of cortisol. The current study aims to assess the final height of patients with classic CAH forms in Iran.*
Methods. *The retrospective cohort study was conducted on 30 patients (determined using the previous studies by the sample size formula to compare two means) studies with classic type CAH who were followed up and treated in the endocrinology clinic of Ali Asghar Hospital during the 2000-2022 years. The history of the patients at the time of diagnosis was extracted from the patient's files and recorded in the checklist. All data was analyzed using IBM SPSS Statistics version 22 software.*
Results. *In the simple virilizing (SV) group, the target and final height for females was 162 and 159.2 cm, and for males were 173 and 171 cm. In the salt-wasting (SW) group, the target and final height for females was 164 and 163.2 cm, and for males were 171.7 and 173.1 cm. There was a significant and reverse correlation between the mean age at the time of diagnosis and the Final Height percentile among all cases (r: -0.55, p: 0.02) and the SW group (r: -0.75, p: 0.002). A positive and significant correlation was seen between the bone age advanced and final height percentile in the SV group (r: 0.04, p: 0.03). The final height percentile increased significantly with an increase in the Duration of treatment regardless of CAH type (r: -0.67, p: 0.009). Also, there was a positive and significant correlation between hydrocortisone dose and final height percentile in the SV group (r: 0.24, p: 0.04).*
Conclusion. *The results of the present study showed that early diagnosis of the disease at a young age, lower bone age of patients, preventing the increase of obesity in children with CAH, and receiving appropriate drugs with standard doses can play an effective role in increasing the final height of CAH patients.*

Introduction

Controlling the production of enzymes in the body is the responsibility of genes, and each person has a pair of genes to create the enzyme that produces cortisol. People with congenital adrenal hyperplasia (CAH) have a pair of defective genes, which do not function properly, resulting in a deficiency of the 21-hydroxylase enzyme [1]. CAH represents an important public health concern as the most common autosomal recessive disorder, with significant impacts on growth, development and quality of life [2, 3]. Early diagnosis and proper management not only prevent acute complications like adrenal crises but also substantially improve quality of life through optimized growth and sexual development [4].
The treatment of patients with CAH is the use of steroid drugs throughout life. Although current treatments cannot restore the body's cortisol levels to normal, studies are underway to develop new formulations of hydrocortisone. A decrease in cortisol causes an increase in adrenocorticotropic hormone (ACTH) and adrenal gland hyperplasia, and the precursors of enzymes increase [5]. The most common enzyme defect that causes this disease is 21-hydroxylase enzyme deficiency, which is seen in 90% of patients, followed by 11-beta-hydroxylase deficiency [6, 7]. As a result of the deficiency of the enzymes mentioned above, the increase of cortisol precursors and its conversion to androgens in female fetuses causes virilizing and various degrees of genital ambiguity. Also, it manifests as false precocious puberty in boys [8]. Virilizing varies from a slight enlargement of the clitoris to a completely masculine appearance of the genitals. On the other hand, aldosterone deficiency causes salt excretion from types of 21-hydroxylase deficiency [2, 9]. Depending on the type of enzyme deficiency, different manifestations and symptoms of the disease and laboratory symptoms occur, the most common manifestations of which are salt wasting, simple masculinization, and false precocious puberty [10]. The problem of these patients is mainly due to late diagnosis and difficulties during treatment. If diagnosed late, many patients with adrenal crises die [10]. Classic CAH disease, if not treated, can cause a salt imbalance in the body and result in dehydration, blood pressure drop, vomiting, shock, and even death. Also, this disease can cause problems in the child's growth and development [3]. One of

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the treatment methods used in patients with CAH is the use of steroids. However, its use causes excessive production of androgens in sufferers and as a result, disrupts the growth of organs [11-13]. If the disease is not well controlled, the height growth rate will increase in the early years of life, but eventually, with the premature closure of the growth plates, the final height will remain short. If the steroid prescribed to the patient is high, height growth will be low at first, and weight growth will increase [14]. According to recent studies, there are conflicting reports of the final height of CAH patients indicating short stature or normal height. Patients with CAH are in a state of hyperandrogenism due to the disease itself, and due to the treatment of the disease, they are in a state of hypercortisolism for the rest of their lives, which can cause short stature. On the other hand, the age of onset of puberty and advanced bone age lead to premature puberty, which can affect the final height. Considering the subject's importance, the current study aims to assess the final height of patients with classic congenital adrenal hyperplasia that includes the salt-wasting (SW) and the non-salt wasting/simple virilizing (SV) forms. Our study provides crucial information on final height outcomes in Iranian CAH patients, addressing a gap in developing country populations where newborn screening is not universal. These findings will help optimize treatment protocols and counseling for families affected by this chronic condition.

Materials and methods

The retrospective cohort study was conducted on 30 patients with classic type CAH who were followed up and treated in the endocrinology clinic of Ali Asghar Hospital during the 2000-2022 years.

Eligibility criteria

Patients with bone age more than 14 years in girls and more than 16 years in boys and classic CAH with 21-hydroxylase deficiency who have been monitored in the endocrinology clinic center since the diagnosis of the disease until reaching the final height, also patients treated with hydrocortisone alone were included. Patients who suffer from other types of CAH, treated with Growth Hormone, GnRh, aromatase inhibitors, or other drugs, taking other drugs that affect growth, such as immunosuppressants were excluded.

Data collection

The history of the patients at the time of diagnosis and the required demographic information (including gender, age at the time of diagnosis, weight, and height at the time of diagnosis) were extracted from the patient's files and recorded in the checklist. Finally, the effect of different factors such as hydroxyprogesterone level, hydrocortisone, and duration of treatment on the final height of the patients was assessed.

Sample size

Using previous studies [15] and comparing the average height of children with their parents, taking into account the average height of children with CAH equal to 159 ± 2 and the average height of parents equal to 154.6 ± 4 and a 95% confidence interval and using the following formula and taking into account the possibility of attrition the sample size of 30 people was calculated.

$$n = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 (\delta_1^2 + \delta_2^2)}{(\mu_1 - \mu_2)^2}$$

In the mentioned formula $Z_{1-a/2}$ and Z_{1-B} were considered 1.96 and 0.84 respectively.

Data analysis

The Shapiro-Wilk test has been performed to evaluate the sample distribution before the mean and standard deviation can be used. Quantitative and Qualitative data were reported as mean ± SD (Due to normal distribution of data) and numbers and percentages respectively. The association between quantitative variables such as height and age with the type of CAH was assessed using the t-test. Also, the correlation between quantitative variables was assessed using the Pearson or Spearman correlation test (In normal and normal and non-normal data). The p-value less than 0.05 was considered a significant level. The data was analyzed using IBM SPSS Statistics version 22 software.

Results

Patient's characteristics at the time of diagnosis

In the current study, 14 patients with SW and 14 with SV were studied (two cases excluded due to incomplete data and this attrition was considered in calculated sample size). The average age of patients in SW and SV at this time was 1.88 and 101 months respectively ($p = 0.04$). Regarding the BMI, the average in SW and SV were 18.85 ± 4.53 and 19.02 (3.74) respectively ($p = 0.77$). In comparing the mean of height, this mean in SW and SV was 52.2 cm ± 40.00 and 126.46 cm ± 22.30 respectively ($p = 0.60$). Considering the mean of weight, this mean in SW and SV was 3.62 kg ± 18.71 and 37.86 kg ± 9.98 respectively ($p = 0.60$). More details about the patient's features at the time of diagnosis were shown in Table I.

Characteristics of CAH patients at the time of study

The average age of patients in SW and SV at this time was 18.5 ± 3.61 and 16.79 ± 1.81 respectively ($p = 0.35$). The average BMI in SW and SV were 23.01 ± 1.98 and 23.96 ± 2.50 respectively ($p = 0.67$). In comparing the mean of Hydrocortisone dose (mg|m^2), this mean in SW and SV were 12.32 ± 4.10 and 11.96 ± 5.11 respectively

Tab. I. Characteristics of CAH patients at the time of diagnosis.

Variables	Males			Females			Total		
	Salt wasting	Simple virilizing	*p*	Salt wasting	Simple virilizing	*p*	Salt wasting	Simple virilizing	*p*
	N = 6	N = 1		N = 8	N = 13		N = 14	N = 14	
Average age of first visit (Month)	2	132	-	1.8	99	0.05	1.88	101	0.04
BMI mean at diagnosis (percentile)	67.3 ± 40.94	68.9	-	63.22 ± 32.51	72.55 ± 23.02	0.55	65.00 ± 34.91	72.2 ± 22.94	0.73
BMI mean at diagnose (kg/m2)	20.50 ± 4.93	23.46	-	17.61 ± 4.08	18.67 ± 3.66	0.41	18.85 ± 4.53	19.02 ± 3.74	0.77
Height mean at diagnosis (percentile)	84.50 ± 17.80	85.77	-	78.79 ± 26.48	76.95 ± 19.42	0.8	81.24 ± 22.54	77.58 ± 18.80	0.05
Weight mean at diagnosis (kg)	30.58 ± 21.87	46	-	3.65 ± 16.37	37.21 ± 9.54	0.16	3.62 ± 18.71	37.86 ± 9.98	0.60
Weight mean at diagnosis (Percentile)	54.67 ± 36.59	87.07	-	55.18 ± 28.70	69.06 ± 26.07	0.55	54.82 ± 31.09	70.35 ± 25.51	0.58
Height means at diagnosis (cm)	52.2 ± 43.95	140	-	52 ± 39.75	125.42 ± 22.85	0.55	52.2 ± 40.00	126.46 ± 22.30	0.60
Bone Age mean at diagnosis (Z.score)	-	1.2	-	-	1.40 ± 0.81	0.27	-	1.39 ± 0.78	_
Predicted mean Adult Height at diagnosis (cm)	_	166.4	-	-	152.9	_	-	152.91 ± 6.02	_
Bone age advanced*	0	4	-	0	3.8	0.65	0	3.81	0.03

* Difference between chronological age and bone age.

($p = 0.73$). The mean of 17 OH Progesterone levels (nmol/dl) in SW and SV were 12.40 ± 16.13 and 18.04 ± 16.35 respectively ($p = 0.08$). In comparing the mean of the duration of treatment (Year), this mean in SW and SV were 18.34 ± 5.17 and 8.37 ± 3.56 respectively ($p = 0.87$). More details are shown in Table II.

Comparison of target, predicted, and final height of CAH patients.

As shown in Table III, the mean of the final height means percentile in SW and SV were 33.7 and 25.3 respectively ($p = 0.21$). Also, after receiving the treatment in both studied groups, the final height was close to the target height. In the SV group, the target and final height for females was 162 and 159.2 cm, and for males were 173 and 171 cm. In the SW group, the target and final height for females was 164 and 163.2 cm, and for males were 171.7 and 173.1 cm. More information is shown in Figure 1 and 2.

The correlation between different variables with the final height of patients

There was a significant and reverse correlation between the mean age at the time of diagnosis and the Final Height percentile (r: -0.55, $p = 0.02$). Also, a similar correlation was seen between the mentioned variables in the SW group (r: -0.75, $p = 0.002$). There was a significant and reverse correlation between the mean BMI at the time of diagnosis and the final height percentile in the SW group (r: -0.55, $p = 0.02$). Regarding the correlation between bone age mean at the time of diagnosis year and with final height percentile, there was a significant and reverse correlation between the mentioned variables in the SV group (r: -0.33, $p = 0.04$). A positive and significant correlation was seen between the bone age advanced and final height percentile in the SV group (r: 0.04, $p = 0.03$). There was a reverse and significant correlation between the mean BMI percentile at the time of study and the final height percentile in the SV group (r: -0.67, $p = 0.009$). The final height percentile increased significantly with an increase in the Duration of treatment regardless of CAH type (r: -0.67, $p = 0.009$). Also, there was a positive and significant correlation between hydrocortisone dose and final height percentile in the SV group (r: 0.24, $p = 0.04$). It means with an increase in hydrocortisone dose the final height percentile will be increased (Tab. IV).

Tab. II. Characteristics of CAH patients at the time of study

Variables	Males			Females			Total		
	Salt wasting N = 6	Simple virilizing N = 1	*p*	Salt wasting N = 8	Simple virilizing N = 13	*p*	Salt wasting N = 14	Simple virilizing N = 14	*p*
Current average age (years)	18 ± 2.97	17	-	18.88 ± 4.19	16.77 ± 1.88	0.41	18.5 ± 3.61	16.79 ± 1.81	0.35
The average duration of treatment (Year)	6.06 ± 18	6	-	18.68 ± 4.60	8.52 ± 3.57	0.55	18.34 ± 5.17	8.37 ± 3.56	0.87
The average age of menarche	-	-	-	10.88 ± 0.79	10.85 ± 1.16	0.86	-	-	-
BMI mean at study (kg/m^2)	23.70 ± 1.97	24.50	-	22.49 ± 1.95	23.92 ± 2.60	0.60	23.01 ± 1.98	23.96 ± 2.50	0.67
BMI mean at study (kg/m^2)_ (Percentile)	69.83 ± 21.66	82.40	-	65.54 ± 23.64	75.35 ± 13.40	0.47	67.38 ± 22.05	75.85 ± 13.01	0.38
Bone Age mean at diagnosis advanced (year)	_	2	-	_	2.08 ± 1.19	_	_	2.07 ± 1.14	_
Hydrocortisone dose mean (mg/ m^2)	11.25 ± 3.79	15	-	13.13 ± 4.38	11.73 ± 5.24	0.46	12.32 ± 4.10	11.96 ± 5.11	0.73
Hydrocortisone dose mean (mg/ m^2)	11.25 ± 3.79	15	-	13.13 ± 4.38	11.73 ± 5.24	0.46	12.32 ± 4.10	11.96 ± 5.11	0.73
17 OH Progesterone level mean (nmol/ dl)	21.67 ± 22.20	7.80	-	5.45 ± 1.50	17.01 ± 18.60	0.003	12.40 ± 16.13	18.04 ± 16.35	0.08

Tab. III. Comparison of target, predicted, and final height of patients.

Variable	Male			Female			Total		
	Salt wasting N = 6	Simple virilizing N = 1	*p*	Salt wasting N = 8	Simple virilizing N = 13	*p*	Salt wating N = 14	Simple virilizing N = 14	*p*
Final height mean (cm)	173.1	171	_	163.2	159.2	0.02	_	_	_
Final height mean (percentile)	40	30	_	29	25	0.01	33.7	25.3	0.21
Predict adult height at diagnosis	_	166.4	_	_	152.9	0.03	_	_	_
Predict adult height at diagnosis (percentile)	_	8	_	_	10	_	_	9.8	_
Target height mean (cm)	171.7	173	_	164	162	0.04	-	-	_
Target height mean (percentile)	40	43	_	53	51	0.04	47	50	_
Advance height	_	4.6	_	6.3	_	_	_	_	_

Discussion

Congenital adrenal hyperplasia (CAH) attributed to 21-OHD is one of the most common genetic endocrine disorders that occurs due to the disruption and defects in the steroidogenic enzymes involved in the production of cortisol. This disorder is diagnosed with the reduction of cortisol feedback and the increase in the secretion of adrenocorticotropic hormone (ACTH) from the pituitary gland and subsequent Adrenal hyperplasia. The most common treatment in all forms of CAH is corticosteroid replacement therapy [16, 17]. Implementation of CAH newborn screening enabled early diagnosis of patients with 21-OHD and consequently prevented Stunting as well as early puberty in children [18, 19]. the current study aims to assess the final height of patients with classic congenital adrenal hyperplasia that includes SW and SV forms in Iran.

The current study was conducted on 30 patients with CAH, and the two main groups were SV (14 people)

Tab. IV. Correlation between different variables with the final height of patients.

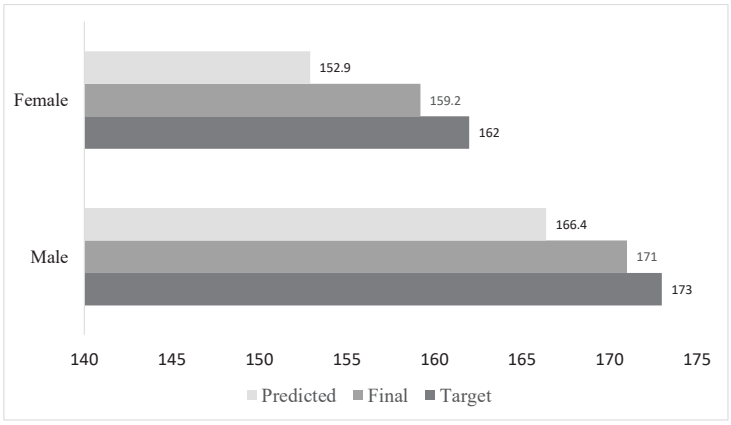
Variables	Group	r (Final Height)	*p*	r (Final Height Percentile)	*p*
Age at diagnosis (months)	Total	-0.059	0.05	-0.558**	0.02
	Salt wasting	-0.089	0.04	-0.759**	0.002
	Simple virilizing	-0.061	0.837	-0.113	0.700
BMI at diagnosis (kg/m²), Percentile	Total	-0.079	0.690	-0.339	0.078
	Salt wasting	-0.319	0.266	-0.647*	0.012
	Simple virilizing	0.153	0.601	0.143	0.625
BMI at study (kg/m²), Percentile	Total	0.107	0.588	-0.275	0.157
	Salt wasting	-0.216	0.459	-0.768**	0.001
	Simple virilizing	0.272	0.346	0.285	0.323
Bone age at diagnosis (years)	Total	–	–	–	–
	Salt wasting	0.369	0.043	-0.336	0.045
Bone age Z-score at diagnosis	Total	–	–	–	–
	Salt wasting	0.04	0.275	0.04	0.244
Bone age advanced	Salt wasting	0.049*	0.038	0.043	0.037
Predicted adult height at diagnosis (cm)	Total	0.271	0.164	-0.216	0.270
	Salt wasting	–	–	–	–
	Simple virilizing	0.017	0.955	0.024	0.934
Height at diagnosis (cm), Percentile	Total	0.118	0.549	0.040	0.842
	Salt wasting	-0.161	0.835	0.232	0.910
	Simple virilizing	0.056	0.045	0.042	0.056
BMI at study, Percentile	Total	-0.29	0.12	-0.458*	0.014
	Salt wasting	-0.046	0.875	-0.183	0.532
	Simple virilizing	-0.639*	0.014	-0.670**	0.009
Target height Z-score	Total	0.059	0.767	0.244	0.210
	Salt wasting	0.172	0.556	0.488	0.076
	Simple virilizing	-0.073	0.805	0.015	0.958
Duration of treatment (years)	Total	-0.050	0.801	0.457*	0.015
	Salt wasting	0.089	0.762	0.759**	0.002
	Simple virilizing	-0.115	0.695	-0.061	0.836
Hydrocortisone dose (mg/m²)	Total	0.022	0.011	0.010	0.059
	Salt wasting	0.055	0.051	0.244	0.020
	Simple virilizing	0.183	0.032	0.244	0.040
17-OH Progesterone (nmol/dl)	Total	-0.277	0.054	-0.697**	0.040
	Salt wasting	0.219	0.451	-0.775**	0.001
	Simple virilizing	-0.496	0.061	-0.519	0.057

* Refer to p<0.05 and ** $p < 0.01$.

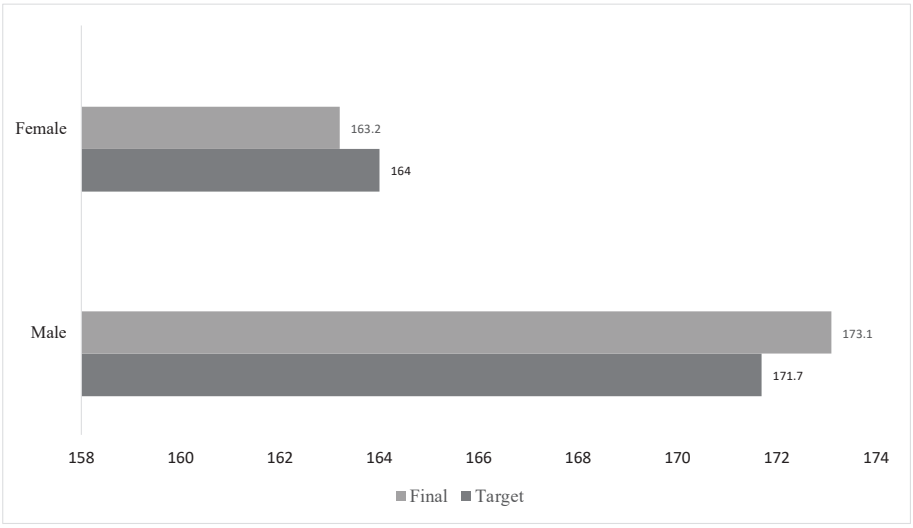
and SW (14 people). The results of the present study showed that the target and final height in both types of disorders are very close in both women and men, which indicates the effectiveness of treatment in preventing Stunting in these people. Some studies have suggested general screening to diagnose CAH, especially the SW type, during infancy. Due to the length of the various stages of the test, the diagnosis may be delayed and lead to severe clinical symptoms in the patient [15]. It must be considered, that despite recent advances in treating CAH, several important questions about patient growth and final height remain unknown. Most of the studies conducted in this field [18, 20, 21], and of them have indicated that the final height is shorter than the target height. The results of a meta-analysis indicated that the average final height was higher than the reported values. However, these values were still lower than the average height of the entire population [22]. The results of another study showed that the final height of CAH patients is lower than the average value of the population and also lower than expected [23, 24].

Regarding the effectiveness of treatment methods, the results of the current study indicate a significant and reverse correlation between the mean age at the time of diagnosis and the final height percentile. Also, a similar correlation was seen between the mentioned variables in salt wasting group. These findings mean that the delay in the diagnosis of CAH can lead to a worsening of the prognosis of the disease. Studies have shown that early diagnosis of CA and good treatment compliance have a positive effect on the final height of patients [22, 23, 25]. Hargitai et al showed that short stature, especially in infancy, is usually associated with poor steroid treatment [26]. Another study in this field showed that timely treatment with GnRH can play an important role in improving the final height of patients and reducing

Fig. 1. Comparison of final, target, and predicted height of cases in Simple virilizing(a) and salt-wasting group (b).



(a)



(b)

the difference from the target height [27]. Alternative treatments such as the use of growth hormone associated with puberty inhibitors, in addition to the anti-estrogen effect, have been effective in improving the prognosis of height in these patients [28-31]. The observed inverse relationship between the final height and the age of the patients indicates that it is possible to reach the desired height in younger patients, and with better treatment of childhood CAH, normal growth can be expected [32]. The results of the present study showed that the final height of cases in the SV group was lower than in Salt-wasting individuals. These results are consistent with the results of a similar study [33, 34].

Our results showed a significant and reverse correlation between the mean BMI at the time of diagnosis and the final height percentile in the SW and SV groups. The BMI status in congenital adrenal hyperplasia cases was assessed in previous studies [35]. The results of these studies have shown that children with CAH are prone to obesity, which can affect their growth.

According to our results, bone age mean at the time of diagnosis showed a significant and reverse correlation with final height in the SV group. The bone age advanced and final height had a positive and significant correlation in the SV group. These findings mean that an increase in bone age advance can lead to an increase in final height. Using the above findings, it can be concluded that the lower bone age at the time of disease diagnosis, can be led to more effective treatment methods and the improved final height.

The current study results showed that the final height percentile increased significantly with an increase in the duration of treatment regardless of CAH type. Our finding indicates a positive and significant correlation between hydrocortisone dose and final height percentile in the SV group. It means with an increase in hydrocortisone dose the final height percentile will be increased. Contrary to our results, Wisniewski et al showed that treatment with hydrocortisone did not have a significant association with height outcomes among children without classic CAH [36]. In the treatment process of CAH, providing conditions for the natural secretion of ACTH in the treatment of CAH to, control the excessive secretion of adrenal androgens, and replace steroids that the adrenal

gland is unable to synthesize has an important role that must be considered(20). In general, prescribing excessive doses of drugs in these patients should be avoided. Treatment with insufficient doses of hydrocortisone leads to an increase in androgens and the aggravation of bone age progression and loss of growth potential. On the other hand, too much glucocorticoid reduces the environmental effects of growth hormone, with a direct impact on bones, it directly causes a reduction in bone growth [37, 38]. Therefore, the dose of corticosteroid used can suppress adrenal androgens and minimize the negative effects of long-term steroid treatment. Therefore, if the patient receives unacceptable doses, for example, more or less than the required level, it may lead to a shortening of the final height [6]. The results of this study have significant applications for healthcare systems, particularly in developing countries where universal newborn screening for CAH is not yet implemented. Our findings demonstrate that early diagnosis and proper treatment initiation can substantially prevent growth and developmental complications in affected individuals. These outcomes may encourage health policymakers to expand nationwide newborn screening programs for early CAH detection. Furthermore, the positive impact of optimized treatment on patients' height outcomes underscores the need for standardized treatment protocol training for physicians and healthcare providers.

The significant correlation between treatment duration and improved growth outcomes highlights the crucial importance of regular long-term follow-up care for CAH patients. These findings can inform the development of more comprehensive care programs for CAH patients, ultimately leading to improved quality of life and reduced economic burden on healthcare systems. The study particularly emphasizes the need for specialized endocrine clinics and multidisciplinary care teams in resource-limited settings to achieve optimal patient outcomes. The current study had some limitations: a relatively small sample size (N = 28), though adequately powered for primary outcomes; a single-center design that may limit generalizability of the results; a lack of data on socioeconomic factors that could influence treatment adherence, and, finally, a retrospective design dependent on the quality of records.

Conclusion

The results of the present study showed that early diagnosis of the disease at a young age, lower bone age of patients, preventing the increase of obesity in children with CAH, and receiving appropriate drugs with standard doses can play an effective role in increasing the final height of CAH patients. Therefore, developing screening programs for the timely detection of these disorders can play a very important role in the height growth of these children and improving their quality of life in both classic types. First, implementing newborn screening programs is crucial for the early detection of CAH. Second, regular growth monitoring and bone age assessments should become standard components of care. Third, glucocorticoid dosing requires careful balancing between androgen suppression and growth preservation. These measures can significantly improve height outcomes and quality of life for CAH patients, particularly in resource-limited settings.

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Data availability

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

Conflicts of interest statement

We declare no conflict of interest.

Authors' contributions

ER and FR: Concept, Methodology, Data collection, writing. EB, ZM, ND: Proof Reading, Formatting, Data collection, and writing.

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