Original Article

Clinical Patterns and Linear Growth in Children with Congenital Adrenal Hyperplasia, an 11-Year Experience

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Abstract

Objective: An important goal in treating children with congenital adrenal hyperplasia (CAH) is to achieve a normal final adult height (FH). The aim of this study was to describe the clinical presentations and evaluate linear growth and possible factors affecting it in children with CAH. **Methods:** This is a retrospective study of 56 patients with CAH followed up in a tertiary center for 11 years. Patient's data including demographics, clinical, anthropometric, and laboratory information at presentation and during follow-up period were collected from medical records. **Results:** Fifty-six children (31 females) with CAH were seen at KAMC-Jeddah over 11-year period and 91% were 21-hydroxylase deficient. Of these, 46.4% had hyponatremia and 28.6% had hyperkalemia (21.4% had hyponatremia and hyperkalemia) at presentation. Positive family history was documented in 53.6%. Ambiguous genitalia were present in 72% of females and the majority required corrective surgery. Males had significantly decreased HtSDS versus females and females had significantly higher body mass index. The HtSDS of children who had had higher 17OHP or salt-losing crisis during treatment was significantly lower than those who had normal 17OHP and those who did not have salt-losing crisis, respectively. **Conclusion:** The final height outcome in our patients with CAH treated with glucocorticoids is lower than the population norm. Proper control of the disease clinically and biochemically through strict compliance to medical therapy as well as close clinical and laboratory monitoring is an important key to achieve normal final adult height in these patients. Side effects, including overweight, obesity, and hypertension are true risk associations and need timely diagnosis and early management.

Keywords: Congenital adrenal hyperplasia, presentation, growth, height SDS, BMI, hydrocortisone dose, 17-hydroxy progesterone

Introduction

Congenital adrenal hyperplasia (CAH) occurs due to an autosomal recessive mutation in one of the five enzymatic steps necessary in the conversion of cholesterol to cortisol. Incidence differs significantly among different populations. It ranges from 1 in 600 live births in Yupik Eskimos of Alaska, to 1 in 5,000 live births in Saudi Arabia, to 1 in 23,000 live births in New Zealand.[1] The classical phenotype is predicted when a patient carries two severe mutations. The nonclassical phenotype is caused by a mild/mild or severe/mild genotype.

The active CYP21A2 and inactive CYP21P genes lie against each other. This allows transfer of genetic material between them, or loss on one chromosome and duplication on the other of the genetic material in the loop. The resulting mutations involving the CYP21A2 gene are associated with variable degrees of impairment in 21-hydroxylase (21-OH) activity, ranging from complete inactivation to partially functioning enzymes, translating into a diverse range of disease severity and phenotypes.

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However, the prediction of phenotype in relation to genotype is not always accurate. A concordance rate also differs among different studies ranging from 50% to 90.5%. One study verified a genotype–phenotype concordance in 90.5% of patients with salt-wasting CAH, 85.1% in simple-virilizing CAH, and 97.8% in nonclassical CAH.[2-5] When considered as a continuum, 21-OH deficiency can manifest in various clinical scenarios from the newborn period through to childhood and adulthood.[6,7]

In the "classical" form of CAH, due to CYP21A2 deficiency, females usually have different grades of genital ambiguity, ~67% of infants present with "salt-wasting" (SW), whereas 33% are classified as "nonsalt-losing" or "simple-virilizing," reflecting the degree of aldosterone deficiency.[8,9] In one study, salt wasting accounted for 57.6% of classical CAH patients.[10]

Replacement glucocorticoid therapy remains the customary treatment for patients with CAH. The growth-suppressing effects of glucocorticoids, however, combined with early epiphyseal fusion from the high androgens in CAH, limit the height potential of patients affected with CAH. Although quite often tall as children, many patients with CAH complete growth prematurely and are ultimately short as adults. Many other factors may contribute in the production of this short final adult height. These include the severity of the phenotype at presentation, the degree of control of hyperandrogenemia, the dose of corticosteroids and mineralocorticoids given and compliance with this medication.[11,12]

An important outcome in treating children with CAH is to attain a normal final adult height (FH). Many factors could affect FH in these patients including, the age at diagnosis, severity of the disease, long-term glucocorticoid intake and their doses, degree of suppression of androgens, and compliance with medications and onset and progression of puberty.

Current information about the clinical presentation and linear growth of patients with CAH in Saudi Arabia is limited. The aim of this study was to describe clinical presentations and evaluate linear growth and possible factors affecting it in all children with CAH followed in King Abdulaziz Medical City – Jeddah (KAMC-J) for 11 years.

Methods

The study was conducted in King Abdulaziz Medical City – Jeddah. All infants and children who were diagnosed with CAH and followed in the pediatric endocrine clinic in KAMC-J were the subjects of this study.

The data of 56 patients were studied. The diagnosis was based on clinical features, endocrine data, and molecular genetic analysis. The children were treated with replacement doses of hydrocortisone and fludrocortisone as required.

The study protocol has been approved by the IRB committee from King Abdullah International Medical research Center (KAIMRC) to do this research, KAIMRC Research Number: RJ15/045/J. Data were collected retrospectively in this study and no signed consent forms were obtained from parents as personal information was anonymous and data were kept confidential.

Patients' data including demographics, clinical presentations, laboratory data, management, and clinical progress during their follow-up, were collected from medical records. These included anthropometric data (age, weight, and height), clinical data including the state of virilization in females and slat-losing manifestations, and laboratory data at diagnosis and follow-up including testosterone and 17-hydroxy progesterone (17-OHP). The anthropometric data at the last visit were recorded. The HtSDS, body mass index (BMI) were calculated. The WHO growth standard references were used. Doses of hydrocortisone per square meter and fludrocortisone were recorded.

Blood samples used for hormonal analysis were obtained between 0800 and 1000 h and ~2 h after morning medications. Serum 17-OHP and testosterone concentrations were measured by standard radioimmunoassay method. Control of adrenal hormone secretion was considered optimal when 17-OHP concentrations were within the range of 6–30 nmol/L. All our classic CAH patients were treated with fludrocortisone at the time of diagnosis in the newborn period and treatment is lifelong; but the requirement decreases with growing age. Mineralocorticoid replacement is monitored by plasma renin activity and electrolytes as well as by blood pressure (BP) readings at clinic visits. The bone age (BA) analysis was based on the left hand and wrist plain *x*-ray films, using the method of Greulich and Pyle.[13]

Statistical analysis

Data of patients are recorded as mean ± SD. Student *t*-test was used to compare variables among the selected groups. $P < 0.05$ is considered significant. Wilcoxon test was used to compare variables when the data were not normally distributed. Linear regression equation was used to investigate possible correlation between variables. For all statistical tests, a P value of <0.05 was accepted as significant. We used the Statistical Package for Social Sciences (SPSS) version 19 for data analysis.

Results

The clinical features at diagnosis showed that, 23/31 females (74.1%) had ambiguous genitalia, 36 cases (64.3%) were diagnosed before the first month of age, and 91.1% had 21-OH deficiency [Table 1].

Initial Lab data at diagnosis showed that males had higher 17OHP and testosterone levels compared with females. Serum Na was significantly lower in females. At the last visit, the levels of 17 OHP, testosterone, and renin did not differ between males and females [Table 2].

Comparison of anthropometric data between males and females showed that female group was significantly older than males in our cohort. Females with CAH had HtSDS and BMI

significantly higher than males. Neither hydrocortisone nor fludrocortisone doses differed among the two groups [Table 3].

Comparison between patients who presented before versus after 1 month of age did not show significant difference in the electrolytes' levels or hormone concentrations among the two groups.

Treatment progress at the last visit showed that 77.4% of females required surgical correction for ambiguous genitalia. Short stature (HtSDS <−2) was detected in 28% of males and 16% of females. Obesity (BMI >30 kg/m^2) was detected in 29% of females and 12% of males. Physicians reported compliance in 71.4% of patients (80% of males and 64% of females).

The relation between different clinical and laboratory parameters to HtSDS and BMI showed the followings [Table 4]: males had significantly decreased HtSDS versus females and females had significantly higher BMI versus males. HtSDS did not differ between those who required versus those who did not require surgical correction. Patients aged >15 years had HTSDS significantly lower than those younger patients. Patients who had salt-losing manifestations at presentation had HtSDS lower than those who did not have salt losing at diagnosis. HtSDS did not differ between those taking daily hydrocortisone dose >10 mg/m^2 compared with those on hydrocortisone dose <10 mg/m^2/day. The HtSDS of children who had salt-losing crisis during treatment was significantly lower than those who did not have salt-losing crisis during treatment. HtSDS of children who had higher 17OHP during treatment was significantly lower than those who did not have high levels during treatment. Patients with advanced BA had lower HtSDS compared with those with less advanced BA.

Table 1: Demographic and clinical characteristics of study populatio

Characteristic	*n* (%)
Gender	
Male	25 (44.6)
Female	31 (55.4)
Clinical feature at diagnosis	
Ambiguous genitalia	23 (74.1)
Positive family history	15 (27.3)
Electrolyte abnormality	12 (21.8)
Age at diagnosis	
<1 month	36 (64.3)
>1 month	20 (35.7)
Current age (mean±SD)	13.7±7.2
Type of CAH	
21-Hydroxylase deficiency	51 (91.1)
Others	5 (8.9)

Discussion

In Saudi Arabia, a calculated incidence of CAH had been postulated to be 1 in 5,000 live births, from the number of patients diagnosed with the disease among the deliveries at King Khalid University Hospital (KKUH) Riyadh Saudi Arabia. Recently introduced universal screening for CAH reported an incidence of 1 in 6,400 live births.[14-25]

Fifty-six children (25 males and 31 females) with CAH were seen at KAMC-Jeddah over 11-year period. Fifty-one (91.2%) were 21-OH deficient. Of these, 27.5% presented with salt-losing manifestations. Positive family history was documented in 53.6%. Ambiguous genitalia were present in 72% of females and the majority required corrective surgery. These results were comparable with other results obtained at different Saudi studies [Table 5] and indicated that salt-losing manifestations became less frequent due to early diagnosis of these patients and stressed the importance of physicians' awareness and the need for a neonatal screening program for early detection and appropriate.[15,26-28]

The pediatric endocrinologist has the tough task of judiciously adjusting medications in actively growing children with CAH so as to avoid overtreatment as well as under treatment. Glucocorticoid excess may result in poor linear growth, weight gain, hypertension, and other side effects. Under treatment may results in excess androgen production and advanced skeletal maturation.[29] An important outcome in treating children with CAH is to achieve a normal final height.

Patients with CAH due to 21-hydroxylase deficiency (21-OHD) often reach a final height significantly below their parentally determined target height. In a meta-analysis, studies between 1977 and 1998 detected a short final height outcome in patients with CAH. It was generally perceived that children with CAH would eventually be short adults and consistently below their genetic potential.[12] The influence of factors including gender, time of diagnosis, and disease control had been analyzed. Overall, mean weighted final height SD scores (FH SDS) for all studies included in the meta-analysis

Table 2: Laboratory findings of the study population by gender

Characteristic	Normal range	Initial examination		*P*	Last examination		*P*
		Males	Females		Males	Females	
Sodium (Na) (mmol/L)	135-145	131.6±7.6*	129.0±11	0.002	137.3±2.3	137.6±2.4	0.655
Potassium (K) (mmol/L)	3.6-5.8	6.9±2.2	7.0±1.9	0.916	4.4±0.40	4.2±0.44	0.311
Renin (pmol/L)	0.21-2.3	364.5±588*	70.9±82.7	0.156	117.4±144	142.5±259	0.725
17 OH Progesterone (nmol/L)	Infants <180 Children <15	1801.5±1,358	424.8±522*	0.049	127.5±214	94.1±225	0.598
Testosterone (ng/dL)	differs with age and sex)	37.1±19.5*	27.9±17.8	0.043	12.9±8.0	9.5.5±6.5	0.193

Table 3: Age, HtSDS, BMI, and hydrocortisone dose by gender

Gender	Age	Height SDS	BMI	Hydrocortisone (mg/m²/day)	Florinef (mg/day)
Males					
Mean	9.86	−1.32	20.47	12.63	0.11
(SD)	7.47	1.39	7.31	9.42	0.04
Females					
Mean	15.36*	-0.80	25.97*	13.3	0.12
(SD)	6.45	1.31	8.16	3.9	0.05

The doses refer to an average dose calculated for these patients during their follow-up

was − 1.37, with mean FH SDS was −1.57 for males and −1.24 for females. For our whole cohort, the HtSDS for females −0.8 was higher than the HtSDS for males −1.39. Thirty patients had final adult height (Age 21.5 ± 4.1 years). Their HtSDS = −1.5 ± 0.8. The other 26 patients did not reach adult height (age = 9.5 ± 3.7 years) with Ht SDS = −0.54 ± 0.4. This confirmed that the height SDS was significantly decreased in adults compared with the childhood period. This effect on stature can be explained by excess androgens not suppressed well during therapy. Subsequently, these children develop fast linear growth during childhood associated with early epiphyseal fusion leading to short adult height. This conforms with other studies reporting decreased FH with males tending to have a slightly inferior outcome than females. Since excess of adrenal androgens can lead to rapid skeletal maturation and acceleration of growth and pubertal development, our patients with advanced BA (>2 years) had lower HtSDS compared with those with less advanced BA (<2 years).[12,30-37]

In a longitudinal study by Eugster *et al.*,[12] there was a great variation in the age at the start of individual spurts and in the time of peak height velocity. Peak height velocity (PHV) in both boys and girls showed a normal magnitude when compared with the timely PHV of the standards; however, the peaks in both sexes occurred ~ 2 years earlier. The early (loss of prepubertal growth) and relatively low PHV might have important implications for further growth and final height in these children.

In addition, the growth of salt-wasting patients with CAH was impaired in infancy and early childhood (0–3 years of age),[12] with normal patterns in childhood until puberty suggesting a great loss of stature occurring early in life.[38-41] Therefore, early diagnosis and proper management appeared to provide better final height prognosis. In previous studies, when time at diagnosis was analyzed, mean FH was −1.11 SDS for patients identified early (less than 1-year old) as compared with −1.61 for patients identified late (after 1-year old). However, all our patients were diagnosed during early infancy (0–6 months of age) that did not allow studying this effect.

Although clinical parameters such as growth velocity and BA remain the gold standard for monitoring the adequacy of therapy in CAH, the proper measuring of serum 17-OHP level can offer a good tool in monitoring their control. There is now substantial evidence that with appropriate clinical management, most children with CAH can obtain a final height that is within their genetic potential. A final adult height nearly equal to target height can be attained following strict compliance and regular clinic visits every three months has also been reported.[42-45] In support of these data, the HtSDS of our children who had higher 17-OHP during treatment was significantly lower (−1.4) compared with those who did not have high levels during treatment (−1). Furthermore, patients who had salt losing manifestation more than once during their course of treatment had lower HtSDS (HtSDS − 1.57 vs. −0.90, respectively). Additionally, our patients with advanced BA >2 SD (presumably due to hyperandrogenemia secondary to poor compliance) had significantly lower HtSDS compared with those with normal BA (−1.28 vs. −0.8, respectively). This documented that the degree of control played an important role in stature growth.[44,46-48] On the other hand, some studies proposed that the degree of short stature does not necessarily correlate with the hormonal control.[30,37,49,50]

Severity of disease may also have some deleterious effect on the final adult height in these patients. In our study, 91% of cases were due to mutations in cytochrome P450, family 21, subfamily A, polypeptide 2 (CYP21A2), the gene coding for the 21-OH enzyme. Depending on the severity of the mutation, 21-OHD ultimately leads to variable degrees of glucocorticoid and mineralocorticoid deficiency due to the inability to produce cortisol and aldosterone. In our cohort, the HtSDS of children who had salt losing crisis at presentation and during treatment (suggesting a severe form of disease) was significantly lower than those who did not have salt losing crisis during treatment. However, the HtSDS of those with high 17-OHP and testosterone levels at presentation was not different than those with relatively lower levels. In addition, the HtSDS of females with ambiguous genitalia who required surgical correction (more severe form of virilization) did not differ than those with less genital ambiguity. A comparison between patients with salt wasting (SW) versus those without salt losing (SV) showed no significant differences in height between the SW and SV groups.[30,37,44-52]

Besides the importance of excess adrenal androgen, other factors can negatively affect the attainment of optimal adult height in these patients. Central precocious puberty may develop in patients with CAH due to androgen activation of the hypothalamic-pituitary-gonadal axis, thus exacerbating premature epiphyseal fusion. In this cohort, two boys had central precocious puberty (testicular growth before 9 years of

Table 4: Height Z-score and BMI in relation to different clinical and lab variables in children with CAH

Variables			Age (years)	HtSDS	BMI	Hydrocortisone (mg/m²/day)	Florinef (mg)	Compliance (%)
Sex								
Males		Mean	9.86	−1.32	20.47	12.63	0.16	71%
		SD	7.47	1.39	7.31	9.42	0.10	
Females		Mean	15.36	−0.80	25.97	8.91	0.11	69%
		SD	6.45	1.31	8.16	5.89	0.04	
Family Hx								
Positive for CAH	Yes	Mean	11.50	−1.26	22.30	13.06	0.15	64%
		SD	7.00	1.40	7.30	3.04	0.10	
Negative	No	Mean	14.80	−0.95	25.50	13.13	13.13	80%
		SD	7.14	1.18	7.70	3.47	3.47	
Age								
>15 years	Yes	Mean	20.00	−1.75	28.30	13.60	0.12	78%
		SD	4.40	1.08	7.00	4.10	0.05	
<15 years	No	Mean	8.10	−0.55	20.40	12.66	0.12	70%
		SD	3.40	1.20	6.10	2.50	0.04	
Ambiguous genitalia (females)								
Required surgical correction	Yes	Mean	9.70	−1.00	21.20	13.50	0.11	67%
		SD	7.00	1.48	7.60	7.86	0.05	
Not required	No	Mean	17.10	−1.14	27.30	8.30	0.15	74%
		SD	5.50	1.10	6.50	2.55	1.00	
Salt losing at presentation								
	Yes	Mean	12.00	−1.30	23.80	12.80	0.13	73%
		SD	8.80	1.50	8.60	8.00	0.06	
	No	Mean	14.40	−0.90	23.70	9.60	0.12	68%
		SD	6.10	1.10	6.90	4.20	0.06	
17OHP at presentation								
>390 nmol/L	Yes	Mean	13.19	−0.96	24.30	13.40	0.13	55%
		SD	6.80	1.24	7.30	3.50	0.05	
<390 nmol/L	No	Mean	13.40	−1.52	23.20	12.06	0.13	91%
		SD	8.70	1.40	7.67	2.50	0.08	
Testosterone at presentation								
High T	Yes	Mean	13.30	−0.60	26.60	10.78	0.13	66%
		SD	8.40	1.20	5.30	6.78	0.07	
Not high	No	Mean	17.20	−1.90	23.80	7.90	0.11	80%
		SD	6.80	1.40	8.10	2.80	0.02	
Hydrocortisone dose								
<10 mg/m²/day	Yes	Mean	17.70	−1.05	28.40	7.40	0.11	66%
		SD	6.50	1.43	6.70	1.60	0.03	
>10 mg/m²/day	No	Mean	9.20	−1.14	19.20	16.40	0.15	68%
		SD	5.30	1.15	5.40	6.80	0.10	
Salt losing crisis during treatment								
	Yes	Mean	11.80	−1.57	22.50	14.10	0.12	69%
		SD	8.80	1.30	8.60	2.80	0.03	
	No	Mean	13.70	−0.90	24.60	12.60	0.13	72%
		SD	6.50	1.23	7.20	3.50	0.08	
17OHP during treatment								
17OHP>x3 normal value	Yes	Mean	13.25	−1.40	23.60	12.20	0.12	52%
		SD	5.90	1.30	7.10	6.40	0.05	
17OHP<x3 normal value	No	Mean	13.10	−1.00	23.60	10.90	0.13	87%
		SD	7.40	1.30	7.60	8.20	0.08	
Bone Age during treatment								

Contd...

Table 4: Contd...

Variables			Age (years)	HtSDS	BMI	Hydrocortisone (mg/m²/day)	Florinef (mg)	Compliance (%)
Advanced >2 SD	Yes	Mean	13.20	−1.28	22.20	10.40	0.11	62%
		SD	7.90	1.30	9.20	3.60	0.06	
Not advanced >2SD	No	Mean	15.30	−0.80	27.70	8.20	0.12	74%
		SD	8.50	1.50	8.30	3.20	0.06	

The compliance in the last column was based on the assessment of the clinician following the patient interview (subjective)

Table 5: Various studies on clinical and growth data of patients with CAH in Saudi Arabia

	Al Jurayyan 1995	Milyani 2018	Alzanbagi 2018	Nasir 2015	Our study 2018
Male/female ratio	30/52	-	32.2/67.8	34/42	25/31
21OHP defect	72%	-		80%	91.1%
Salt losing manifestation	68.4%	33%	47.8%	93%	56.6%
Family history of CAH	71.2%				53.6%
Ambiguous genitalia	52%	50.7%		90%	74%
HtSDS <−2	-	-	25.7%	-	28% males 16% females
BMI >30	-	-	17.6%	-	12% males 29% females
High blood pressure >2 SD	-	-	-	-	10.7%

age), with final adult height was −1.9 and −2.9. This supported the view that precocious puberty may compromise the final adult height. The use of LHRH analogue with or without growth hormone proved to improve final adult height in cases with precocious and/or early puberty.[53-55]

Chronic glucocorticoid therapy, even at replacement doses, has been linked with a higher risk for poor growth. It has been shown that long-term glucocorticoid treatment during childhood, particularly during the pubertal growth spurt, can adversely affect final height. In this study, the HtSDS of patients on doses of hydrocortisone >10 mg/m²/day) was not different than those taking lower doses (<10 mg/m²/day).[56-60] Contrary to our results, a multivariable analysis in one study showed that target-adjusted FH SDS was adversely affected by hydrocortisone dose ($P < 0.001$) and positively related to mineralocorticoid therapy ($P = 0.001$) and ACTH levels ($P = 0.02$). In our study, no correlation was found between HtSDS and either hydrocortisone dose ($r = −0.05$) or fludrocortisone dose ($r = −1.26$).[61]

In addition to the judicious use of standard glucocorticoid, other therapies may help patients to achieve normal adult height. These height-enhancing drugs are to be considered for individuals whose heights are, or are expected to be, significantly shorter than those of peers, defined as a height of at least − 2.25 SDS. A four-drug regimen that combined the androgen antagonist flutamide and the aromatase inhibitor testolactone with a reduced dosage of hydrocortisone (8 mg/m²/day) and fludrocortisone has been suggested. In a 2-year randomized parallel study of 28 children, patients receiving the experimental four-drug regimen had normal growth and bone maturation, despite elevated adrenal steroids. LHRH analogue with GH therapy is another option to promote growth for short children with CAH.[54,62-64]

Children with CAH are at an increased risk of developing obesity. In our study, 11/56 (19.6%) patients were obese (BMI SDS >2) and 4/56 (7%) were overweight (BMI SDS > 1.5 < 2). Patients on higher doses of hydrocortisone (>10 mg/m²/day) had significantly higher BMI compared with those taking lower doses. Females had higher BMI versus males. Older patients >15 years and those with advanced BA had significantly higher BMI compared with younger patients and those who did not have advanced BA. These data were in accordance with a cross-sectional study in children with CAH ($n = 89$) in Germany, which showed that higher glucocorticoid dosage, chronological age, and advanced skeletal maturation were associated with an elevated BMI and obesity. It is generally believed that excess glucocorticoid treatment in children with CAH results in weight gain. In another study, ~50% of the children had at least one BMI measurement ≥95 percentile and about 70% had at least one ≥85 percentile.[65-68]

Hypertension is an additional risk factor associated with CAH.[68-73] Significant hypertension, defined as BP measurements persistently between the 95th and 99th percentile for age and sex, was diagnosed in six of our patients (10.7%). Their dose of hydrocortisone (10.2 ± 3.1 mg/m²/day) and fludrocortisone doses (0.11 ± 0.01 mg/day) did not differ compared with the normotensive group. Their BMI (25 ± 6.9) was not different than the BMI of the normotensive group (24.0 ± 7). Their BMI was not correlated with systolic or diastolic blood pressures ($r = −0.21$ and − 0.17, respectively). Our findings support the study of Nebesio *et al.*,[71] who reported hypertension in 6.6% of their cohort ($n = 91$ patients) and did not find any difference

in their fludrocortisone or hydrocortisone doses compared with normotensive patients. An elevated BMI was not a determining factor in the development of hypertension in their patients. The average BMI was not statistically different between those without hypertension (23.9 ± 9.1) as compared with those with essential hypertension (22.9 ± 2.9).[65-68] However, in a report of 55 subjects with CAH in Germany, abnormal 24-h blood pressure profiles and systolic hypertension correlated with the degree of overweight and obesity. Increased insulin and leptin levels correlated well with BMI and age, but the laboratory markers of CAH control, glucocorticoid dose, and fludrocortisone dose did not correlate with blood pressure.[68] Higher incidence of hypertension as high as 58% was reported in one study in salt-wasting CAH. In their patient's hypertension first occurred before age 5 years in 91% of SW males and 50% of cases in SW females. Children on fludrocortisone who had three or more readings of 17-OHP <400 ng/dL (12.12 nmol/L) had a significantly higher rate of hypertension than those who did not, and hydrocortisone dose was not associated with hypertension. Another study reported an overall prevalence of hypertension was 12.5% in a large cohort of patients ($n = 716$) with CAH. Prevalence of hypertension was higher in younger children than in adolescents (18.5% vs. 4.9%). Until 8 years of age, fludrocortisone dose/m^2/day correlated significantly with BP in regression analysis ($P < 0.0001$). However, the exact mechanism to explain why some individuals with CAH due to 21-OHD develop hypertension is unclear, and further investigation is warranted.[12,66,69-73]

In conclusion, the final height outcome in our patients with CAH treated with glucocorticoids is lower than the population norm. It appears that early diagnosis and proper control of the disease clinically and biochemically through strict compliance to medical therapy as well as close clinical and laboratory monitoring is the key to achieve normal final adult height in children with CAH. Side effects, including overweight, obesity, and hypertension, may or may not be related to glucocorticoid and mineralocorticoid replacement.

Study Limitations

The limitations of this study include the retrospective nature of the data and relatively small number of patients may pose some limitation on the results of this study.

IRP approval this research

We received IRP approval from King Abdullah International Medical research Center (KAIMRC) to do this research. KAIMRC Research Number: RJ15/045/J.

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Conflicts of interest

There are no conflicts of interest.

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