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Evaluation of Blood Pressure and Left Ventricular Parameters in Children with Classical Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency: An Egyptian Experience

Shereen Abdelghaffar, Reem Esmail*, Usama Abdelaziz and Hassan Abuzaid

Department of Pediatrics, Faculty of Medicine, Cairo University, Egypt

Abstract

Background/Aims: Congenital Adrenal Hyperplasia (CAH) patients are at higher risk of systemic hypertension secondary to high steroid dose therapy. Our aim was to look for early cardiovascular changes in young CAH patients, by the analysis of BP levels and echocardiographic parameters. We aimed also to investigate the possible risk factors that may contribute to such effects.

Methods: We evaluated blood pressure measurements (using international percentiles) and echocardiography in 53 CAH pediatric patients. Thirty healthy age and sex matched children were included as controls. Results: It was found that 10(18.9%) patients had elevated BP and 23(43.4%) patients had hypertension. Out of those hypertensive patients, 7 (13.2%) patients had systolic hypertension, 3 (5.6%) patients had diastolic hypertension, and 13 (24.5%) patients had combined systolic and diastolic hypertension. BP levels of CAH cases were positively correlated with Hydrocortisone doses (r=0.14, P value=0.038) and negatively correlated with 17-OH-progesterone levels (r=-0.15, P value=0.023). Our patients had myocardial hypertrophy with increased left ventricular wall thickness, greater mean LVM and LVMI. Age and hypertension were predictors of LV hypertrophy.

Conclusions: The present study showed that a considerable portion of CAH patients had hypertension. Their BP levels were influenced by Glucocorticoids (GCs) doses.

Keywords: Glucocorticoids; Progesterone; Hydrocortisone; Myocardial hypertrophy; Hypertension

Impact of Testosterone on the Skin

The term Congenital Adrenal Hyperplasia (CAH) encompasses a group of autosomal recessive disorders, each of which involves a deficiency of an enzyme involved in the synthesis of cortisol, aldosterone or both [1]. Deficiency of 21-hydroxylase, resulting from mutations of CYP21A, is the most common form of CAH, accounting for more than 90% of cases [2]. It is distinguished by the severity of the enzyme defect, in classical and non-classical form. Approximately 70% individuals with classical CAH are affected by more severe salt-wasting form, characterized by androgen hyper secretion and impaired synthesis of both Glucocorticoids (GCs) and mineralocorticoids (MCs) [3].

The goal of therapy in CAH has always aimed to reduce excessive androgen secretion by replacing the deficient hormones, where proper treatment with GCs and MCs prevents adrenal crisis and virilization, allowing normal growth and development [4,5]. However, clinical management of classic CAH is a difficult balance between hyperandrogenism and hypercortisolism. Under treatment carries the risk of adrenal crisis and allows increased adrenal androgen production, with accelerated bone age and loss of growth potential; overtreatment may suppress growth, increase Blood Pressure (BP), cause iatrogenic Cushing's syndrome or early metabolic syndrome [3,6].

Over treatment with GCs and MCs may affect the BP through stimulation of the MCs receptors, impairment of adreno-medullary function and obesity itself [7-11]. To the best of our knowledge, little is known about early BP and cardiovascular changes in CAH patients and their association with androgen levels as well as GCs, MCs and sodium chloride doses. Pediatric Endocrinologists need such data to modulate and optimize chronic steroid therapy (GCs, MCs) to minimize the risk of hypertension and cardiovascular affection in patients with classical CAH.

The aim of the present study was to look for early cardiovascular changes in young CAH patients, by the analysis of BP levels and echocardiographic parameters. It also aimed to investigate possible risk factors that may contribute to such effects.

Methodology

This cross sectional study was conducted in the outpatient clinic of Diabetes Endocrine Metabolic Pediatric Unit, Cairo University Children Hospital (CUCH), between January 2013 and October 2013. The study was approved by the ethical committee at Cairo University.

We studied 53 children (39 females and 14 males) with classical CAH due to 21- hydroxylase deficiency (all of our patients were salt wasting). They were already diagnosed on clinical and laboratory basis. The diagnosis was confirmed by molecular analysis in all patients. Thirty healthy children, age and sex matched, were included as controls for evaluation of echocardiographic measurements. All cases received treatment in the form of Glucocorticoids (GCs): oral hydrocortisone tablets at a dose range of 10-15 mg/m^2/day, thrice daily with the highest dose at 2 AM and oral fludrocortisone tablets, at a dose range of 0.05-0.2 mg/day, once or twice daily.

Methods

Records of the patients were reviewed for collection of data as

*Corresponding author: Reem Esmail, Department of Pediatrics, Faculty of Medicine, Cairo University, 12 Ahmed Kamel street, Giza, Egypt, Tel: 0201005459071; Fax: 0233939899; E-mail: esmail_reem@yahoo.com

duration of therapy, salt losing manifestations, doses of GCs, MCs and sodium chloride. Anthropometric measurements were retrieved.

Body Mass Index (BMI) was expressed as SDS (normal: ±2SDS, elevated>2SDS, and low<-2SDS).

All CAH patients underwent blood pressure measurement by standardized mercury sphygmomanometer with manually inflated cuff of suitable size and a stethoscope at 3 separate visits with one week interval. The child had been sitting quietly for 5 minutes and seated with his or her back supported, feet on the floor and right arm supported at heart [12]. The BP measurements were done by well-trained observers. BP measurements were assessed using international blood pressure centiles [11,12].We also compared them with the controls, BP measurements.

Hypertension was defined as systolic and/or diastolic BP greater than the 95th centile for age, height and gender on the 3 separate visits. High BP was defined as systolic and/or diastolic BP between the 90th and 95th centile for age, height and gender or if in 2 out of 3 measurements, BP was greater than the 95th centile for age, height and gender.

Normal BP was defined when only one measurement was greater than the 95th centile for age, height and gender or when all measurements were less than 90th centile for age ,height and gender. Echocardiography study was done using a Philips* iE33 Echocardiography System, in order to evaluate heart function and myocardial hypertrophy, according to established methods by the American Society of Echocardiography [13] each measurement was done by 2 observers and Intra-Class Correlation Coefficient (ICC) was calculated.

Two-D guided, M-mode measurements of the left ventricular internal dimensions were made. The following measurements were determined on M-mode tracing, Interventricular Septum Thickness In Diastole (IVSd), Left Ventricular Posterior Wall Thickness in Diastole (LVPWd), Left Ventricular End Systolic Dimension (LVESD) and Left Ventricular End Diastolic Dimension (LVEDD) in millimeters.

Left Ventricular Mass (LVM) was determined by measurement of the Left Ventricle (LV) in grams by using the truncated ellipsoid methods by two-dimensional (2D) echocardiography (recommended from the American Society of Echocardiography [13]. As Left Ventricular Mass (LVM) increases during growth, the normal values must be defined in the context of body size. Height2.7 (in meters) has been validated as an indicator of lean body mass and has been recommended for indexing LVM [14]. Left Ventricular Mass Index (LVMI) (representing LVM corrected for height (=LVM/meters2.7)) was calculated. Left ventricular hypertrophy was defined as LVMI >95th centile for pediatric age [15], that is >38.6 g/m$^{2.7}$.

Statistical Analysis

SPSS statistical package version 14 was used to analyze the data. Descriptive data were described in form of frequencies and percentages, mean ± standard deviation (or median and range if data were not normally distributed). Comparisons of values of BP and echocardiographic assessment between cases and controls were done using Student's t test.

Comparison of frequencies among groups were done using Chi square test. Different correlations between hormone levels, doses of drugs, BP values and LV parameters were performed using Spearman's correlation test. Multivariable linear regression models were fitted in order to evaluate the independent effect of each covariate on BP profile and myocardial hypertrophy parameters. A p value of less than 0.05 was considered significant. Intra-class correlation coefficient was calculated using SPSS package.

Results

The present study included 53 CAH pediatric patients due to 21-OH deficiency with a mean age of 8.01 ± 4.65 years. Fourteen patients were males (26.4%) and 39 were females (73.6%) with a male to female ratio (M:F) of 1:2.8. The mean age of controls was 8.11 ± 3.57, 10 children were males (33.3%) and 20 were females (66.7%) with a male to female ratio (M:F) of 1:3. Anthropometric, clinical and hormonal characteristics of the patient population are listed in Table 1. All patients received treatment in the form of oral hydrocortisone tablets at a mean dose of 14.99 ± 4.65 mg/m²/d and oral fludrocortisone tablets at a mean dose of 0.1 ± 0.06 mg/d.

We compared the measured values of Systolic BP (SBP) and Diastolic BP (DBP) of our patients with the International BP percentiles, according to the Task Force on Blood Pressure Control in Children [11,12]. We found that 23(43.4%) patients had hypertension, 10(18.9%) patients had elevated BP and 20 (37.7%) patients had normal BP levels.

The twenty three hypertensive patients were 7 (13.2%) patients with systolic hypertension, 3(5.6%) patients with diastolic hypertension, and 13 (24.5%) patients with combined systolic and diastolic hypertension.

BP levels of our CAH patients were positively correlated with Hydrocortisone doses (r=0.14, P value=0.038) and negatively correlated with 17-OH-progesterone levels (r=-0.15, P value=0.023).Multivariate logistic regression analysis showed that IVSd (OR 1.4; 95% CI, 1.2-13.6; P=0.02) and Hydrocortisone dose (OR 0.16; 95% CI, 0.99-1.38; P=0.05) were independent predictors of hypertension in patients with CAH.

Cases had a significantly higher BMI compared to controls. The mean systolic and diastolic BP of our patients were significantly higher than controls (120 ± 25 mmHg vs. 103 ± 10.3 mmHg, P 0.001 and 80 ± 10 vs. 63 ± 7.5, P 0.001 respectively).

Echocardiography was done by 2 observers with excellent agreement (ICC>0.75). The patients had significantly thickened IVSd and significantly deceased LVESD in comparison to controls. In addition, they presented left ventricular hypertrophy, as defined by published pediatric criteria (LVMI>38.6 g/m$^{2.7}$) with significantly increased mean LVM and LVMI (Table 2). When we indexed echocardiographic parameters of cases and controls to Body Surface Area (BSA), we still found that the patients had significantly thickened PWd with significantly deceased LVESD and LVEDD in comparison to controls. In addition, the patents had significantly increased mean LVMI (Table 3).

On comparing patients with hypertension and elevated BP in relation to those with normal BP, it was found that IVSd and LVMI were significantly higher in patients with abnormal BP compared to those with normal BP (Table 4).

Multivariable linear regression analysis revealed that IVSd was affected by age(P: 0.007, 95% CI: 2.67 to 14.17, β=8.42), hypertension(P: 0.001, 95% CI: 1.55 to 15.65, β=5.65), and 17-OH-progesterone level (P:

	Mean (±SD)
Age(years)	8.01 ± 4.65
BMI (SDS)	1.21 ± 1.3
17-OH-progesterone(ng/ml)	11.9 ± 10.09
Plasma renin (pg/ml)	56.1 ± 18.4
Hydrocortisone dose (mg/m²/day)	14.99 ± 4.65

BMI: Body Mass Index

Table 1: Anthropometric and hormonal data of the patients.

	CAH cases (n=53) Mean ± SD	Control (n=30) Mean ± SD	P-value
Age	8.01 ± 4.65	8.11 ± 3.57	0.4
BMI (SDS)	1.2 ± 1.3	-1.6 ± 1.07	0.001*
Systolic BP (mmHg)	120 ± 25	103 ± 10.3	0.001*
Diastolic BP (mmHg)	80 ± 10	63 ± 7.5	0.001*
IVSd (mm)	6.96 ± 2.45 (0.95)	5.90 ± 1.43 (0.93)	0.032*
PWd (mm)	6.68 ± 3.23 (0.87)	7.22 ± 6.09 (0.84)	0.60
LVEDD (mm)	37.57 ± 8.05 (0.91)	36.69 ± 7.27 (0.87)	0.623
LVESD (mm)	24.40 ± 5.80 (0.77)	27.40 ± 5.36 (0.83)	0.022*
LVM(gm)	83.08 ± 47.29 (0.85)	47.50 ± 26.39 (0.82)	<0.001*
LVMI(g/m$^{2.7}$)	52.19 ± 24.15 (0.96)	34.08 ± 8.84 (0.91)	<0.001*

*P value ≤0.05 is significant. IVS: Inter-Ventricular Septum; LVPW: Left Ventricular Posterior Wall; LVEDD: Left Ventricular End Diastolic Dimension; LVESD: Left Ventricular End Systolic Dimension; LVM: Left Ventricular Mass; LVMI: Left Ventricular Mass Index; d: Diastole, () intra-class correlation coefficient; if value >0.75=excellent agreement, if value 0.4-0.75=good agreement and if value less than 0.4=poor agreement.
Table 2: Blood pressure and echocardiographic parameters of cases and controls.

P-value	Control (n=30) Mean ± SD	CAH cases (n=53) Mean ± SD	
0.1	7.54 ± 3.25	7.98 ± 3.74	IVSd (mm)
0.05	7.76 ± 5.04	10.94 ± 6.65	PWd (mm)
0.009	52.54 ± 15.65	42.85 ± 11.84	LVEDD (mm)
0.008	30.56 ± 9.89	27.07 ± 8.32	LVESD (mm)
0.9	52.85 ± 35.65	52.92 ± 24.7	LVM (gm)
0.001	37.31 ± 23.45	67.73 ± 31.45	LVMI (g/m$^{2.7}$)

IVS: Inter-Ventricular Septum; PW: Left Ventricular Posterior Wall; LVEDD: Left Ventricular End Diastolic Dimension; LVESD: Left Ventricular End Systolic Dimension; LVM: Left Ventricular Mass; LVMI: Left Ventricular Mass Index; d: Diastole. *P value ≤0.05 is significant.
Table 3: Echocardiographic parameters of cases and controls indexed to Body Surface Area (BSA).

	Abnormal BP cases (n=33)	Normal BP cases (n=20)	P value
Age	7.83 ± 4.03	8.32 ± 5.62	0.7
Height SDS	-0.62 ± 1.49	-0.64 ± 1.71	0.9
BMI SDS	1.20 ± 1.44	1.22 ± 1.22	0.9
Hydrocortisone dose (mg/m²/day)	15.85 ± 4.07	13.58 ± 5.29	0.08
17-OH-progesterone (ng/ml)	10.25 ± 9.38	14.69 ± 10.82	0.12
IVSd (mm)	7.62 ± 2.74	5.87 ± 1.33	0.003*
LVPWd (mm)	6.79 ± 2.66	5.85 ± 1.57	0.16
LVM (g)	91.06 ± 51.07	69.90 ± 37.86	0.12
LVMI (g/m$^{2.7}$)	59.07 ± 28.73	42.75 ± 10.46	0.005*

*P value ≤ 0.05 is significant. BMI: Body Mass Index; IVS: Inter-Ventricular Septum; LVPW: Left Ventricular Posterior Wall; LVM: Left Ventricular Mass; LVMI: Left Ventricular Mass Index; d: Diastole.
Table 4: Comparison between patients with abnormal BP (hypertensive, elevated BP patients) and those with normal BP.

0.007, 95% CI: 0.01 to 0.09, β=0.053).LVM and LVMI were affected by age(P: 0.006, 95% CI: 0.55 to 12.76, β=5.65) and hypertension (P: 0.008, 95% CI: 0.03 to 0.19, β=0.11).LVPW was affected only by hypertension (P: 0.038, 95% CI: 0.40 to 8.76, β=4.58).

Discussion

The present work suggests that significant portion of children with CAH have systemic hypertension 23(43.4%); 7 (13.2%) patients had systolic hypertension, 3(5.6%) patients had diastolic hypertension, and 13 (24.5%) patients had combined systolic and diastolic hypertension.

This is in accordance to other studies that have reported the occurrence of hypertension in 21 OH CAH [16,17]. They examined the prevalence of hypertension among children with classic CAH using 24-hour ambulatory blood pressure (amb BP) monitoring and demonstrated that pre-pubertal and pubertal patients with classic 21-hydroxylase deficiency had elevated 24-hour blood pressure measurements compared to the general population. Roche et al. [16] studied 37 SW CAH children, aged between 6.1 and 18.2 years, and found that 58% of the patients had systolic hypertension and 24%

patients had diastolic hypertension. Similarly, Völkl et al. [17] studied 55 Caucasian classical CAH subjects (45 SW and 10 SV; 32 females and23 males), aged between 5 and 19 years. All of them were treated with GCs, 53 patients received additional MCs. They found that mean diurnal and nocturnal SBP levels were significantly elevated.

This is in contrary to more recent study done by Ubertini et al. [4] who studied 20 young CAH patients (14 females and 6 males) with a mean age of 13.38 ± 4.11 and found that ambBP profile and exercise BP were substantially normal. They reported that mean HC dose (14.16 ± 5.46 mg/ m²/day) which corresponded nearly to a replacement dose and it could not be considered as supra physiologic.

Striking the balance between too much and too little glucocorticoid treatment is especially difficult, because the currently available glucocorticoid formulations cannot replicate the physiological circadian rhythm of cortisol secretion [18-20]. Moreover, in the past recent years, emphasis has moved away from the therapeutic goal of achieving survival towards the longer term effects of either under- or overtreatment with exogenous glucocorticoid [5].

In our study, all patients received MCs in addition to GCs. Adequate mineralocorticoid replacement generally facilitates hydrocortisone dose reduction, with 40 mg hydrocortisone exerting equivalent mineralocorticoid activity to 100 mg fludrocortisone [21].

The hypertension reported in our patients could be explained by the supra-physiological doses of GCs and MCs (14.99 ± 4.65 mg/m²/d and 0.1 + 0.06 mg/d respectively) which are higher than that reported by Ubertini et al. [4]. This is evident by presence of positive correlation between BP values and GCs doses and negative correlation with 17-OHP levels. The multivariate logistic regression analysis showed that Hydrocortisone dose and IVSd was independent predictor of hypertension in our patients. Hypertension due to exogenous glucocorticoid exposure tends to be dose dependent, but administration of cortisol invariably raises Blood Pressure (BP) to some degree [21-23]. Glucocorticoids, the foundation of CAH treatment, is often given in supra-physiological doses to normalize the adrenal androgens, which may lead to unfavorable metabolic consequences: obesity, insulin resistance with type 2 diabetes (T2DM), and hypertension [5].

In this study, obesity may also be a contribution to high BP as 15 (28.8%) patients were obese (BMI higher than 2 SDS). Moreover; cases had significantly higher BMI SDS than controls. This was previously reported by Daniels [24] and Roche et al. [16] who found that BMI SDS was significantly higher and independently related to systolic blood pressure SDS,. Cornean et al. [25] reported significantly increased BMI values in patients with CAH between 5 and 10 years of age. Glucocorticoid exposure, coupled with a reduction in epinephrine and metanephrine stores [8] are the most likely explanations for the higher Body Mass Index (BMI) in CAH patients compared to healthy subjects [25].

Among the subclinical measures, Left Ventricular Mass (LVM) assessed by 2D, M-mode echocardiography has been recognized as an important and powerful predictor of cardiovascular morbidity and mortality, independent of other traditional risk factors [26]. Myocardial hypertrophy with increased left ventricular wall thickness and greater LVMI had been repeatedly described in subjects with high GCs levels due to Cushing's syndrome [27,28].

In our study, we found an evidence of myocardial hypertrophy with significantly increased left ventricular wall thickness in comparison to controls, greater mean LVM and LVMI. On normalizing the echocardiographic parameters to BSA, we still found that the patients had significantly hypertrophied PWd and LVMI, this is in contrast to Ciccone et al. who reported that the echocardiographic parameters showed no significant difference between the two groups when normalized to BSA [29].

Multivariable linear regression showed that age and hypertension are predictors of LV hypertrophy. The relation to age could be explained by the effect of long duration of exposure to supra-phyisological GCs dose with fair hormonal balance.

This is supported by what was previously documented in Cushing's syndrome that exposure to high cortisol leads to development of left ventricular concentric remodeling with high relative wall thickness not related to blood pressure levels [30-32].

Hypertension associated with obesity increases the work of the heart and stimulates cardiac growth. Obesity-related oxidative stress, inflammation, and activation of the renin-angiotensin system can induce cardiac remodeling with increased cardiac myocyte and connective tissue matrix accumulation [33-35].

Our results goes with a large case control analysis (50,656 cases) done by Whitworth et al. who found a significant association between any oral glucocorticoid use and cardiovascular events [36].

The main limitations of this study are an unavailability of an ambBP device for analysis of diurnal and nocturnal systolic and diastolic BP. Also, there was no treadmill for routine evaluation of BP levels at maximal heart rate in our clinic. Two-D and M-mode echocardiography used in this study may neglect proper assessment of basal septum which could be more thickened than the other parts of the septum.

Conclusions

The present study found that a considerable portion of CAH patients had hypertension. BP levels were influenced by GCs doses and this might be explained by the supra physiological doses received by our patients. Our patients had also myocardial hypertrophy with increased left ventricular wall thickness, greater mean LVM and LVMI. Age and hypertension were predictors of LV hypertrophy. We recommend measuring BP regularly with comprehensive assessment for cardiovascular risk factors (lipid profile, fasting glucose and BMI) and echocardiographic study for any CAH patient with hypertension.

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