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Original Article

Congenital Adrenal Hyperplasia in Children: The Relationship between Plasma Renin Activity and Hypertension

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Abstract

Background: Children with Congenital Adrenal Hyperplasia (CAH) have a higher chance of hypertension. The likelihood of hypertension is higher in CAH children who get fludrocortisone medication and have an over-suppression. Plasma renin activity (PRA) is a sensitive indicator when the fludrocortisone dose is insufficient. The objective of this study is to assess the relationship between plasma renin activity with hypertension in 21-hydroxylase-deficient (21-OHD) CAH children.

Methods: This cross-sectional observational analytical study was conducted in 2019 at the Pediatric Endocrinology Outpatient Clinic in Dr. Cipto Mangunkusumo Hospital (RSCM), Jakarta, Indonesia. The subjects were 21-OHD CAH children, aged >6 months to 18 years who had already taken hydrocortisone with or without fludrocortisone for at least 6 months, and were divided into hypertension and non-hypertension groups. The subjects were selected by a consecutive sampling method. Data was analyzed using SPSS software (version 23.0) with unpaired *t* test analysis and multiple logistic regression test. Statistical significance was achieved if $P<0.05$.

Results: Forty 21-OHD CAH patients were included, and 20 subjects (50%) had hypertension. A higher incidence of hypertension was found in salt-wasting CAH than in simple virilizing types (59.3% vs 30.8%). There was a significant mean difference in PRA levels between hypertension and non-hypertension groups in salt-wasting patients ($P=0.016$). A significant difference between the last dose of hydrocortisone with the number of hypertension patients in salt-wasting patients ($P=0.032$) was found, and low PRA levels showed a 1.09 times higher risk of hypertension.

Conclusion: Children with salt-wasting CAH with low PRA levels had a higher risk of getting hypertension.

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Keywords ● Adrenal hyperplasia, congenital ● Hypertension ● Hydrocortisone

What's Known

- Hypertension could be found in children with 21-hydroxylase congenital adrenal hyperplasia (CAH) especially because of corticosteroid treatment.
- Plasma renin activity test indicates water loss. It is helpful to make sure the right amount of corticosteroid treatment is administered in 21-OHD (21-hydroxylase-deficient) CAH patients.

What's New

- Hypertension is higher in Salt Wasting CAH patients than in Simple Virilizing CAH patients.
- Salt-wasting congenital adrenal hyperplasia patients with low plasma renin activity levels have a higher risk of hypertension.

Introduction

Most congenital adrenal hyperplasia (CAH) cases occur because of a defect in the *CYP21A2* gene. This defect causes a deficiency of enzyme 21-hydroxylase (21-OH), leading to a cortisol deficiency in the body. This condition is an autosomal recessive genetic disorder that affects the adrenal cortex.[1, 2] In CAH, an

increase in adrenocorticotrophic hormone (ACTH) is found, which drives adrenocortical hyperplasia and uninhibited synthesis of adrenal androgens. ACTH is not directly influenced by the renin-angiotensin-aldosterone system, which regulates blood pressure (BP) and fluid-electrolyte balance. However, aldosterone insufficiency in CAH causes an increase in circulating levels of angiotensin II, which stimulates vasopressin secretion and augments ACTH release.[3] Therefore, the therapeutic goal for patients with 21-hydroxylase-deficient (21-OHD) CAH is to replace the glucocorticoids and mineralocorticoids to normalize adrenal androgens level and reduce the ACTH concentration.[4, 5] Inadequate mineralocorticoid administration can lead to dehydration through hyponatremia, hyperkalemia, and kidney salt loss. Even though a fludrocortisone overdose can cause hypertension, it is frequently asymptomatic in young patients.[4,6] Consequently, the doctor should routinely check the patient's BP at follow-up appointments.

Children with CAH are reported to have a higher chance of developing hypertension than children in the general population. The likelihood of hypertension was higher in CAH children who got fludrocortisone medication and had an over-suppression.[7] Glucocorticoid and mineralocorticoid overtreatment, an increase in glucocorticoid levels affecting mineralocorticoid receptors, disruption of adrenomedullary function with a negative impact on the regulation of the sympathetic BP, and obesity are a few factors known to interfere with the control of physiologic BP in 21-OHD CAH patients.[6]

Even when the level of electrolytes is normal in the body, plasma renin activity (PRA) is a sensitive indicator of water loss, and PRA level rises when the fludrocortisone dose is insufficient. To guarantee that patients are given the right amount of mineralocorticoids, PRA in CAH patients should be assessed on a regular basis.[7, 8] This study is essential to evaluate the connection between PRA and hypertension in children with 21-OHD CAH.

Materials and Methods

This study is a cross-sectional observational analytic study. The data were collected at the Pediatric Endocrinology Outpatient Clinic in Dr. Cipto Mangunkusumo Hospital (RSCM), Jakarta, Indonesia from September to November 2019. Boys and girls aged >6 months to 18 years with a diagnosis of 21-OHD CAH who had previously taken hydrocortisone with or without fludrocortisone for at least 6 months are the inclusion criteria for this study. Meanwhile, children with 21-OHD CAH who also had kidney disease, heart disease, or diabetes were excluded. The sample size was calculated based on a previous study using a proportion formula with a power of 90%. The proportion formula consists of r as the ratio, as power, as the level of significance with the formula:[9, 10]

$$\frac{(r+1(p))(1-p)(Z_{\beta}+Z_{\alpha/2})^2}{r(p^1-p^2)^2}$$

The minimum sample size for this study was 40 subjects. Following the approval and signing of informed consent, patient data such as sex, age, BP examination, physical examination, anthropometry, 17-hydroxyprogesterone (17-OHP) level, age at CAH diagnosis, and type of CAH (salt-wasting=SW; simple virilizing=SV) were collected. Due to limited laboratory facilities in our country, the type of CAH was diagnosed based on the clinical manifestation of the patients and the level of 17-OHP. Patient with adrenal crisis manifestations was categorized as SW CAH.

This study was approved by the Faculty of Medicine, Universitas Indonesia Ethics Committee, and the number for this study is KET-996/UN2.F1/ETIK/PPM.00.02/2019. Before the study, informed consent was obtained from the participants and their parents. Patients were assigned to one of the two groups including group 21-OHD CAH with hypertension and group 21-OHD CAH without hypertension.

Hypertension

Before taking BP measurements, the child sat comfortably for at least 10 min. The BP measurement was carried out on the child in a sitting position, and then the BP was measured using a digital BP gauge Omron series 6121 on the child's right wrist, ensuring that the cuff was snugly attached. Systolic or diastolic BP measurements more than the 95th percentile for age, sex, and height were used to identify high BP; which is determined based on the children's BP table from the American Academy of Pediatrics (AAP) 2017 to determine whether or not the patient had hypertension.[11] High BP on at least three clinic visits was used to diagnose hypertension. For the analysis in this study, the mean of three BP readings was used.

Body Mass Index (BMI)

In our study, body mass index (BMI) was expressed in Kg/m^2. To calculate the BMI standard deviation (SD) score or BMI score, relative weight measurements adjusted for age and sex were used. The Pediatric-Score

Calculator was used to determine a child's BMI score based on age, sex, BMI, and the appropriate reference standard. The tool is accessible through the Children's Hospital of Philadelphia Research Institute.[12] The patient was classified as obese if his/her BMI score was more than +2.0 SD. Likewise, a BMI score of +2.0 to +1.0 SD was considered overweight, -1.0 to -2.0 SD showed a weight deficiency, and less than -2.0 SD indicated a substantial weight deficiency.[13] In this study, the results were presented as mean±SD.

Plasma Renin Activity Examination

The PRA levels were assessed at Prodia Clinical Laboratory in Jakarta, Indonesia, using the ELISA method and a PRA reagent (IBL International, USA). The inside of the elbow or back of the hand was punctured to take blood from the vein. Blood was drawn in 2 mL increments drawn then placed inside an EDTA tube. The PRA levels were then assessed with a reference value of 0.06-4.69 ng/mL/h.

Statistical Analysis

To examine the relationship between hypertension with PRA levels, fludrocortisone dose, and hydrocortisone dose, an unpaired *t* test was used in this study. Multiple logistic regression was used to perform a multivariate analysis of hypertension association with the confounding factors. The Statistical Package for Social Sciences software (version 23.0) was used for the analysis. In this study, statistical significance was achieved if P<0.05.

Results

Forty 21-OHD CAH patients were recruited in this study, and 20 (50%) had hypertension. The characteristics of the subject data are described in table 1. Hypertension was present in 16 (59.3%) of the 27 subjects with SW CAH and 4 (30.8%) of the 13 SV CAH patients (P=0.18). The last visit hydrocortisone dose was significantly different between the groups with and without hypertension, according to the Mann-Whitney test (P=0.01). Meanwhile, no significant difference in PRA values was found between the groups with and without hypertension (P=0.08).

Subjects with hypertension in SW CAH had lower mean PRA levels (4.84±13.85 ng/mL/h)

Table 1: The characteristics of 21-hydroxylase congenital adrenal hyperplasia with hypertension and with non-hypertension

Characteristics		Hypertension (n=20)	Non-Hypertension (n=20)	P value†
Age (year)		8.71±4.89	6.09±4.28	0.08
BMI (z-scores)		0.6±1.04	0.29±0.89	0.07
Blood Pressure (mmHg; mean±SD)	Systolic	127.45±11.85	94.75±7.94	0.01
	Diastolic	86.85±15.09	58.02±6.34	0.01
Age at diagnosis of CAH (months)		1.55±0.83	1.80±0.95	0.41
Duration of CAH treatment (years; mean±SD)		8.41±4.97	5.62±4.32	0.05
Hypertension diagnosis age (years), n (%)	<5	4 (20)	-	
	5-10	11 (55)	-	
	>10	5 (25)	-	
Sex, n (%)	Male	7 (35)	3 (15)	0.27
	Female	13 (65)	17 (85)	
Type of CAH, n (%)	Salt wasting	16 (80)	11 (55)	0.18
	Simple virilizing	4 (20)	9 (45)	
Family history of CAH, n (%)	Yes	5 (25)	8 (40)	0.31
	No	15 (75)	12 (60)	
Family history of hypertension, n (%)	Yes	13 (65)	10 (50)	0.34
	No	7 (35)	10 (50)	
17-OHP levels (ng/mL; mean±SD)	Diagnosis of CAH	150.35±89.15	104.58±52.01	0.05
	End	19.81±41.69	12.21±27.64	0.90
Fludrocortisone dose at diagnosis (mg/day)	Time of diagnosis	0.09±0.05	0.06±0.06	0.12
	Last visit	0.075±0.05	0.1±0.22	0.18
Hydrocortisone dose (mg/m^2/day)	Time of diagnosis	14.83±1.97	15.10±3.21	0.48
	Last visit	19.48±2.56	16.44±3.73	0.01
PRA (ng/mL/h; mean±SD)		6.72±16.34	12.87±17.62	0.08
Sodium (mEq/L; mean±SD)		138.80±2.61	137.75±2.09	0.17
Potassium (mEq/L; mean±SD)		3.89±0.58	4.11±0.24	0.12
Chloride (mEq/L; mean±SD)		98.79±19.07	102.84±3.51	0.46

†Mann Whitney test. P<0.05 is considered significant. Reference value: 17-OHP (<1.15 ng/mL); PRA (0.06-4.69 ng/mL/h.); Sodium (132-145 mmol/L); Potassium (3.1-5.1 mmol/L); Chloride (96-111 mmol/L); CAH: Congenital adrenal hyperplasia; 17-OHP: 17-Hydroxyprogesterone; PRA: Plasma renin activity; SD: Standard deviation

Table 2: Plasma renin activity levels and hypertension association in salt-wasting congenital adrenal hyperplasia and simple virilization congenital adrenal hyperplasia

Parameter	Salt Wasting (n=27)		P value†	Simple Virilizing (n=13)		P value†
	Hypertension (n=16)	No Hypertension (n=11)		Hypertension (n=4)	No Hypertension (n=9)	
PRA (ng/mL/h)	4.84±13.85	20.97±20.30	0.016	14.23±25.27	2.96±4.59	0.643

†Unpaired *t* test of PRA levels between patients with hypertension and no hypertension in salt-wasting CAH and simple virilizing CAH. P<0.05 is considered significant. PRA: Plasma renin activity

Table 3: Multivariate analysis of confounding factors on hypertension in salt-wasting and simple virilization congenital adrenal hyperplasia

Variable	COR	P value†	AOR	95% CI AOR	P value†
PRA levels	1.21	0.180	1.09	(1.01-1.18)	0.029
Sex	1969.35	0.243	5.85	(0.26-129.35)	0.264
Initial 17-OHP levels	1.06	0.259	1.01	(0.99-1.03)	0.606
Fludrocortisone dose (last visit)	3.088	0.622	2.60	(0.03-230.26)	0.675
Hydrocortisone dose (last visit)	0.16	0.159	0.62	(0.40-0.96)	0.032

†Multiple logistic regression <0.05 is considered significant. AOR: Adjusted odds ratio; CI: Confidence interval; COR: Crude odds ratio; PRA: Plasma renin activity; 17-OHP: 17-Hydroxyprogesterone

than non-hypertension subjects (20.97±20.30 ng/mL/h). In SW CAH, the unpaired *t* test found significant differences in the mean PRA levels between subjects with and without hypertension (P=0.016). Table 2 demonstrates no significant differences in the mean PRA levels in SV CAH (P=0.643).

Logistic regression was performed for the multivariable analysis. The method for multivariable analysis was enter elimination, which is removing the variable with the highest P value one by one to see the percentage change in the OR value of the main variable (PRA level). Table 3 shows that in the association between PRA levels and the occurrence of hypertension in patients with SW CAH, all variables that were considered to be covariate variables were included as independent variables. The independent variables included sex, BMI, family history of hypertension, duration of therapy, fludrocortisone and hydrocortisone doses at diagnosis and last visit, PRA levels, and baseline and late (end) 17-OHP levels.

Initial 17-OHP level, sex, and fludrocortisone dose at the last visit were found to be confounding factors of PRA levels and hypertension incidence in SW-CAH children. After adjusting confounding factors, the risk of hypertension in SW CAH children with low PRA levels was 1.09 times. Additionally, it was found that in patients with SW CAH, the hydrocortisone dose at the last visit was significantly related to the prevalence of hypertension.

Discussion

This study showed that 50% of 21-OHD patients were diagnosed with hypertension. SW CAH children with hypertension had lower mean PRA levels than non-hypertension subjects, and there was a significant difference between the hypertension and non-hypertension groups. It was found that the risk of hypertension in SW CAH children with low PRA levels was 1.09 times higher.

Hypertension is not one of the clinical symptoms and signs in patients with 21-OHD CAH. As a result, information on the prevalence of hypertension in 21-OHD CAH patients is still limited. The incidence of hypertension in individuals with 21-OHD CAH has been recorded in several cross-sectional studies with varying results. The incidence of hypertension with 21-OHD CAH was 47%, according to Maccabee-Ryaboy and others.[14] The prevalence of hypertension among 21-OHD CAH children in this study was similar to the previous study, which was 50%.

Though the patient's age at CAH diagnosis was lower in the hypertension group, there was no significant difference in the mean age between the two groups. Bonfig and others found that high BP was more common in younger children.[9] Our study identified no significant difference in the relation of sex with hypertension, which was in line with the longitudinal study by Bonfig and colleagues that reported no difference in mean BP between girls and boys.[14] BP was highest. Prevalence of systolic hypertension was up to 57·6% at 18 months of age. After 24 months BP levels were lower and at 48 months prevalence of hypertension decreased to 15·2%. Systolic and diastolic BP correlated significantly with the administered fludrocortisone dose (r=0.3, P=0.005). A recent longitudinal study found that only 50% of cases of hypertension in SW females occurred before age of 5 years, while it was 91% in males. It was hypothesized that

estrogen has a protective effect on BP, even in CAH patients.[14]

Even though the proportion of CAH patients with hypertension was higher in SW CAH patients (80%), there was no significant difference between SW CAH and SV CAH regarding the prevalence of hypertension. This finding was consistent with previous studies.[14, 15]

Children with classic CAH had considerably greater BP than those who did not have CAH when given fludrocortisone. Maccabee-Ryaboy and others found a higher hypertension rate in children with classic CAH who received fludrocortisone (55%) than those who did not (31%).[14] According to the hydrocortisone dosage, Kuhn and others discovered no significant difference between systolic and diastolic BP in children with CAH.[16] Similar to those studies, we also did not discover a significant mean difference between the doses of fludrocortisone and hydrocortisone at the time of the initial diagnosis of hypertension, but a significant mean difference was found regarding the last visit hydrocortisone dose between hypertension and non-hypertension groups. Moreover, because the number of patients in this study was limited, there may still be a difference in the length of CAH treatment between the groups with and without hypertension.

From the initial diagnosis in infancy through childhood, the dose of fludrocortisone in SW CAH patients tends to remain quantitatively constant. However, the dose per body surface area decreases as age and weight increase.[16] One hundred µg of fludrocortisone is equal to 1.2 mg hydrocortisone. Therefore, particularly in young patients, it should be considered when determining the total daily dose of glucocorticoids.[17] This is especially crucial in patients with 21-OHD CAH to prevent iatrogenic hypertension.

Dehkordi and others found a statistically significant relationship between 17-OHP and diastolic BP in young-age CAH patients.[18] Conversely, our findings showed that there was no significant difference in 17-OHP levels in hypertension and non-hypertension groups.

The primary marker used to assess mineralocorticoid levels in CAH patients is PRA. In 716 children, Bonfig and others found lower BP in children with routinely measured PRA levels than in children without PRA documentation.[9] Unfortunately, PRA exams are not conducted frequently in Indonesia. This examination is still limited since not all laboratories can perform it, and it is also expensive and not covered by health insurance. Therefore, BP is recommended to be monitored regularly in 21-OHD CAH patients.

According to Bonfig and Schwarz, patients with hypertension had low to suppressed PRA levels. The mean PRA levels were high in the first 3 months, then declined at 18 months, and the lowest level was reached at 24 months.[19] In contrast to Bonfig and Schwarz's work that compared the PRA levels of patients after multiple tests based on their patients' age, this is the first PRA examination performed on our subjects. Hence, we were unable to make such a comparison.

To the best of our knowledge, the relationship between PRA levels and the prevalence of hypertension in 21-OHD CAH children in Indonesia is being evaluated for the first time in this study. The strength of our study lies in our ability to demonstrate PRA levels after adjusting for confounding factors.

The study limitations were that since there were more hypertensive patients in SW CAH than SV CAH patients, we could only evaluate the confounding variables for the SW group. In addition, the literature on hypertension in children with 21-OHD CAH is still limited, and the information exhibits various results. Thus, it is important to look into the risk factors.

Conclusion

SW CAH children have a higher incidence of hypertension than simple-virilizing CAH children. There was a significant difference between PRA levels in hypertension and non-hypertension SW CAH patients. The risk of hypertension in SW patients with low PRA levels was 1.09 times after being controlled for sex, 17 OHP levels, and the last dose of fludrocortisone.

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Authors' Contribution

SM.L: Study design, data acquisition, analysis, and interpretation, drafting and revising; F.S: Study design, data acquisition, analysis, and interpretation, drafting and revising; EAH: Study design, data acquisition, analysis, and

interpretation, drafting and revising; BT.AAP: Study design, data analysis, and interpretation, and reviewing the manuscript; All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest: None declared.

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