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Observation of Hypertension in Children with 21-Hydroxylase Deficiency

A Preliminary Report

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The most common cause of congenital adrenal hyperplasia is 21-hydroxylase deficiency (21OHD). The prevalence of hypertension (HTN) in children with 21OHD is unknown, and HTN has not been reported to be a component of this disorder. As children with 21OHD are at risk of developing obesity, we hypothesized that an elevated body mass index (BMI) would be a predictive factor in the development of HTN. A retrospective chart review of children with 21OHD seen in our pediatric endocrine clinics for the past 21 yr was performed. Ninety-one children with 21OHD were identified (54% female). Of these children, six (6.6%) had HTN, and five (5.6%) had essential HTN, which was defined as HTN of unknown etiology. Elevated body mass index was not a determining factor in the development of HTN. Children with 21OHD do appear to have a higher prevalence of HTN when compared to historical reports of pediatric populations. The coexistence of HTN with a salt-wasting state and mineralocorticoid deficiency in some children with 21OHD is paradoxical and of unclear etiology.

Key Words: Congenital adrenal hyperplasia; 21-hydroxylase deficiency; obesity; body mass index; hypertension; essential hypertension.

Introduction

Children with 21-hydroxylase deficiency (21OHD) are at risk of developing obesity *(1,2)*, which is a well-known correlate of blood pressure percentiles in the pediatric population *(3)*. Although the prevalence of hypertension (HTN) in children with congenital adrenal hyperplasia (CAH) due to 21OHD is unknown, we have occasionally observed this constellation in the clinical setting. We hypothesized that an elevated body mass index (BMI) would be a predictive factor in the development of HTN among children with 21OHD. Therefore, the aim of our study was to investigate the prevalence and relationship to BMI of HTN in a cohort of children and adolescents with 21OHD.

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Results

Ninety-three patients with CAH were identified. Two patients had CAH due to 11-hydroxylase deficiency and were not included in the analysis. Therefore, ninety-one patients (54% female) with CAH due to 21OHD were identified. 21OHD was diagnosed on the basis of typical clinical and laboratory findings *(4)*. Six (6.6%) children were identified with 21OHD and HTN. One child had HTN due to a history of rhabdomyolysis and acute renal failure secondary to an adrenal crisis and shock. Five (5.5%) of ninety-one children with 21OHD were identified as having essential HTN. Clinical characteristics and treatment course for each child with essential HTN are presented in Table 1. Family history for HTN was negative in all subjects who had essential HTN. Two children with HTN had a positive family history of CAH, one in an older sister and another in a first cousin.

Three (60%) of the children with essential HTN had salt-wasting CAH. At the time of diagnosis of essential HTN, the average hydrocortisone dose was 16.4 ± 1.6 mg/m^2/d, and the average fludrocortisone dose was 0.09 ± 0.05 mg/d. None of the patients had a suppressed plasma renin or elevated sodium level. Furthermore, where available, the average 17-hydroxyprogesterone (17OHP) level at diagnosis of essential HTN was 493 ± 475 ng/dL (86–1178). The average age at diagnosis of essential HTN was 4.9 ± 5.9 yr (4.2 ± 3.2 mo for salt-wasters; 9.5 ± 4.4 yr for simple-virilizers). Only one child (patient #1) was able to discontinue antihypertensive medications (AHM). Another child (patient #3) presented in a hypertensive emergency. Peak blood pressure was 300/150, and she required IV diazoxide and admission to the intensive care unit for blood pressure stabilization.

Table 1
Clinical Characteristics and Treatment Course of Children with CAH Due to 21OHD and Essential HTN

	Patient #1	Patient #2	Patient #3	Patient #4	Patient #5
Gender	Female	Female	Female	Male	Female
Race	White	White	Black	White	White
Type of CAH	SW	SV	SW	SV	SW
Diagnosis of CAH					
Age	1 d	2.1 yr	4 d	4.6 yr	19 d
Exam	Ambiguous genitalia	Ambiguous genitalia	Ambiguous genitalia	Tanner III pubic hair	Ambiguous genitalia
Diagnosis of HTN					
Age	6.5 mo	6.4 yr	58 d	12.6 yr	N/A
Peak recorded SBP	115	146	300	146	N/A
BMI (kg/m^2)	18.8	19.2	16.5	22.2	N/A
HC dose (mg/m^2/d)	16.7	16.9	17.9	14.1	N/A
Fludrocortisone dose (mg/d)	0.15	0.1	0.05	0.05	N/A
HTN evaluation (*all studies were normal)	Electrolytes, PRA, thyroid studies, urinalysis, complete blood cell count, echocardiogram	Electrolytes, aldosterone, PRA, urinalysis, thyroid studies, complete blood cell count, renal ultrasound, echocardiogram	Electrolytes, PRA, EKG, echocardiogram, thyroid studies, renal scan, renal ultrasound	Electrolytes, PRA, chest radiograph, echocardiogram	Electrolytes, PRA, urinalysis, 24-hour urine studies, thyroid studies, echocardiogram, renal ultrasound
AHM	Hydralazine	CCB	ACEI and hydralazine. Restarted on ACEI and later changed to CCB.	ACEI	ACEI and HCTZ
Length of AHM treatment	7.1 yr	1.7 yr	4.3 yr , then off for 1.5 yr, and then on for 12.1 yr	9 mo	N/A
Age at last clinic visit	10.3 yr	8.1 yr	18.1 yr	13.3 yr	15.3 yr

SW = salt-wasting; SV = simple-virilizing; N/A = not available; SBP = systolic blood pressure; BMI = body mass index; HC = hydrocortisone; PRA = plasma renin activity; AHM = antihypertensive medication; ACEI = ACE inhibitor; CCB = calcium channel blocker; HCTZ = hydrochlorothiazide.

BMI for girls and boys with and without essential HTN are shown in Fig. 1. Only one child (patient #2) with essential HTN had a BMI ≥ 95th percentile. At the time of last clinic visit, the average BMI of children with essential HTN was 22.9 ± 2.9 (20.2–27.3) with 40% at risk for overweight (BMI between 85 and 95th percentile) and 20% being overweight (BMI ≥ 95th percentile). Of those without essential HTN, the average BMI was 23.9 ± 9.1 (14.8–55.3) with 16% at risk for overweight and 48% being overweight. There were no statistically significant differences between the groups.

Discussion

HTN has not been considered to be a component of CAH due to 21OHD. In contrast, other rarer forms of CAH, including 11-beta-hydroxylase and 17-alpha-hydroxylase deficiencies, are associated with HTN due to elevated adrenal hormone metabolites with mineralocorticoid activity. In 21OHD, adrenal metabolites in the mineralocorticoid pathway are low, leading to variable degrees of overt salt-wasting *(4)*. Thus, HTN in the setting of a condition typified by mineralocorticoid deficiency is unexpected and seems paradoxical.

Minimal data are available regarding blood pressures in children with 21OHD. In one small study, blood pressure values did not correlate with the duration of glucocorticoid treatment *(5)*. In another study, 84% of children with salt-wasting 21OHD had absence of the physiologic nocturnal dip in systolic blood pressure. Blood pressure measurements were not correlated with any markers of biochemical control of CAH, such as plasma renin activity (PRA), andro-

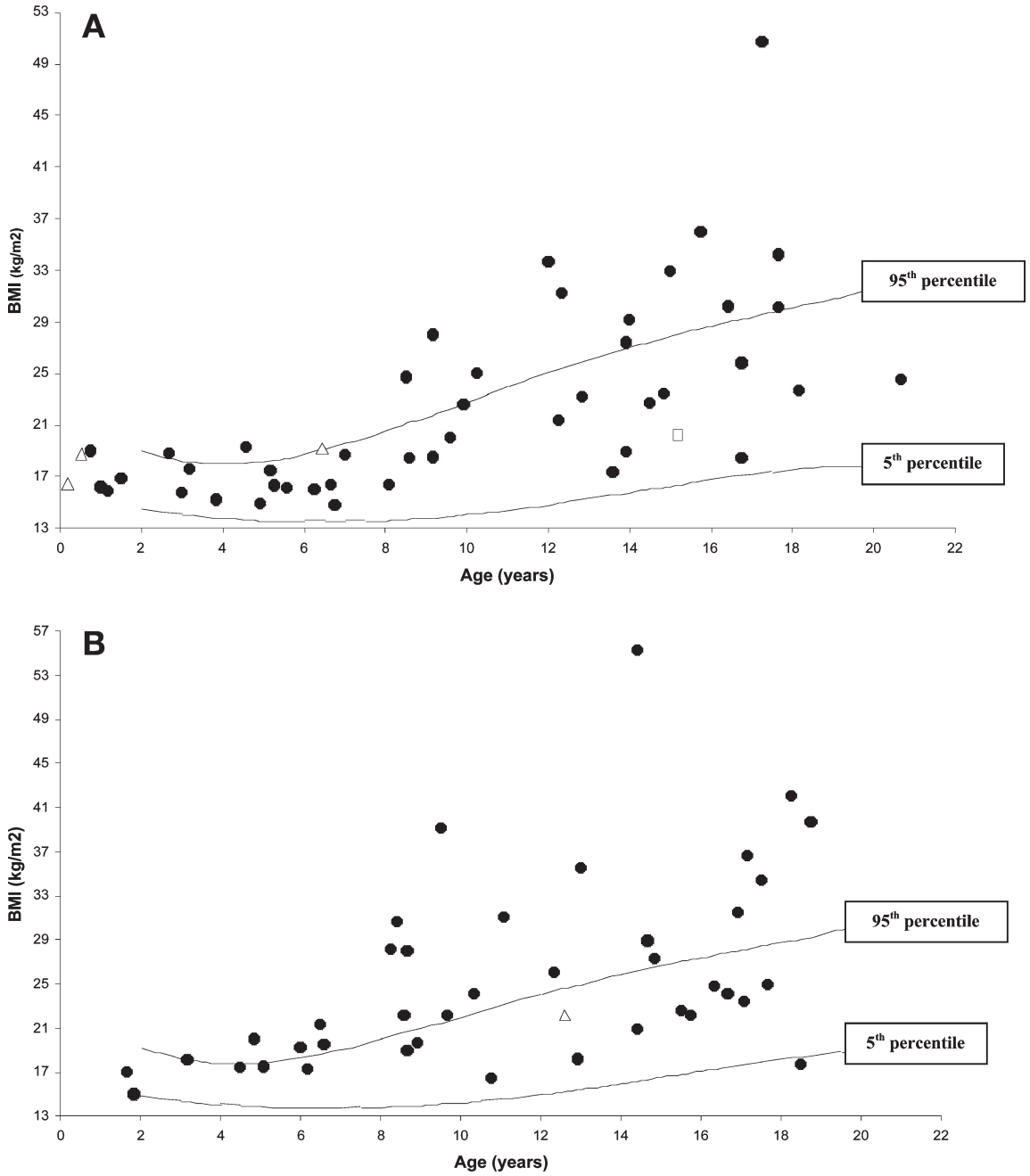

Fig. 1. BMI of girls (**A**) and boys (**B**) with CAH due to 21OHD. Solid circles indicate the BMI at last clinic visit in children without HTN. Open triangles indicate the BMI in children with HTN at time of diagnosis of essential HTN. The open square indicates the BMI of patient #5 at her last clinic visit.

stenedione, or 17OHP. However, an elevated blood pressure was strongly associated with obesity in this group of children with 21OHD, particularly in females *(6)*.

In our cohort of children with 21OHD, the prevalence of HTN is greater than the historically reported 1% prevalence of HTN in children *(7,8)* and also greater than the 4.5% prevalence of HTN noted in an overweight pediatric population *(9)*. Although not statistically significant, more nonhypertensive children were either at risk for overweight or were overweight than those with essential HTN. The average dose of hydrocortisone at the time of diagnosis of essential HTN in our sample was 16.4 ± 1.6 mg/m^2/d, which is within the preferred hydrocortisone replacement guidelines of 10–20 mg/m^2/d for infants and children with CAH *(4)*. Although some reports note that 10–15 mg/m^2/d is a typical hydrocortisone dose for children with CAH *(10)*, two of our patients with HTN were infants, who often require up to 25 mg/m^2/d of hydrocortisone replacement *(4,10)*. Furthermore, this dose of hydrocortisone is not high enough to cause HTN by cross-reacting with the mineralocorticoid

receptor, which occurs at higher, stress doses of hydrocortisone. Only one child had a 17OHP level at diagnosis of essential HTN below the recommended target range for 21OHD replacement *(4)*, suggesting that the majority of patients were not being overtreated with glucocorticoids. Physiologic replacement of fludrocortisone was given to all children in order to normalize mineralocorticoid levels, which is part of the standard treatment in children with 21OHD *(4,10)*. None of the children with HTN had suppressed PRA levels, suggesting that mineralocorticoid replacement was not excessive and thus likely not the cause of HTN. In addition, the average dose of fludrocortisone was typical for maintenance replacement *(4,10)*. As this is a retrospective study and includes only referred subjects, the true prevalence of HTN in children with CAH is likely underestimated because we used strict criteria for classifying a child as hypertensive, which included both a blood pressure > 95th percentile for age *(11)* and referral to a pediatric nephrologist or cardiologist. Limitations of this study include the retrospective nature, as well as minimal available data for subject #5.

ACE inhibitors were the most commonly prescribed medication for the treatment of HTN in our patients, followed by calcium channel blockers, hydralazine, and hydrochlorothiazide. As part of the treatment regimen for children with 21OHD, renin or PRA levels are closely monitored. ACE inhibitors often lead to a reactive rise in renin *(12)*. Therefore, if a child with 21OHD is started on an ACE inhibitor, the renin or PRA level may be elevated and could lead to inappropriate increases in fludrocortisone, which may theoretically worsen HTN. An AHM that does not interfere with the renin–angiotensin system, such as calcium channel blockers, may be a better first-line option in the treatment of HTN in children with 21OHD.

In summary, this study is the first to demonstrate essential HTN requiring pharmacologic therapy independent of BMI in children with 21OHD. The etiology of essential HTN in children with 21OHD is unknown, but it is likely due to an intrinsic dysregulation related to CAH. Studies in animals and humans have suggested that abnormalities in glucocorticoid metabolism or variations in the glucocorticoid receptor gene may contribute to some forms of essential hypertension *(13,14)*. Prospective studies and targeted investigations of the physiologic parameters that contribute to blood pressure control will likely yield valuable insights into this interesting phenomenon. Awareness of the potential development of HTN in children with 21OHD provides important information that will contribute to anticipatory guidance in this patient population.

Methods

After institutional review board approval, medical records of children with 21OHD seen in our pediatric endocrine clinics from 1984 through 2005 were reviewed. Patient charts were identified by searching for ICD-9 code 255.2 (adrenogenital syndrome or CAH) in our clinical database. Children were classified as having essential HTN if they had a negative evaluation for underlying causes of HTN and were started on AHM by a pediatric nephrologist or cardiologist. HTN was determined based on published reference values (blood pressure > 95th percentile) for age and gender *(11)*. None of the children with essential HTN were ill at the time of diagnosis of HTN. Blood pressures were obtained in outpatient subspecialty clinics, which has been shown to be an accurate method of detecting tendencies of blood pressure elevations in children with 21OHD *(15)*.

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