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Investigation of the factors influencing primary hypertension in childhood

Çocukluk çağı primer hipertansiyonuna etki eden faktörlerin araştırılması

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Abstract

Aim: Primary hypertension is the most important risk factor for chronic kidney disease in adulthood. The genesis of essential hypertension is likely to be multifactorial. The aim of this study is to investigate the causing factors of primary hypertension detected by ambulatory blood pressure monitoring in children.

Materials and Methods: Fifty-six patients who had blood pressure higher than 90 percentile during the healthy children follow-up and 27 healthy children with the normal blood pressure were included in the study. Twenty-four hour blood pressure measurements with the blood pressure monitor were recorded as the day-night mean blood pressure, the blood pressure loads and the dipper-non-dipper characteristics. Plasma renin levels, serum aldosterone, nitric oxide and endothelin levels and amounts of sodium and potassium excretion in the 24 hour urine and were investigated in all patients and the control group.

Results: Laboratory evaluations of the patients showed that the patient group has higher mean levels of plasma renin, lower mean levels of blood endothelin and mean levels of urinary sodium excretion than the control group.

Conclusion: In the pathogenesis of childhood primary hypertension and white coat hypertension, which were seen in the half of the children diagnosed as primary hypertension, plasma renin and urinary sodium excretion had important roles.

Keywords: Primary hypertension, endothelin, renin.

Öz

Amaç: *Primer hipertansiyon erişkin çağındaki kronik böbrek yetmezliği için başlıca risk faktörlerinden biridir. Esansiyel hipertansiyon sebepleri multifaktoriyeldir. Amacımız ambulatuar kan basıncı monitorizasyonu yapılmış primer hipertansiyon saptanan çocuklarda etyolojik faktörleri araştırmaktır.*

Gereç ve Yöntem: *Çalışmaya rutin sağlıklı çocuk kontrollerinde kan basınçları 90 persentilin üzerinde saptanan 56 çocuk ve kan basıncı 90 persentilin altında olan 27 sağlıklı çocuk alındı. Yirmi dört saatlik yaşam içi kan basıncı monitorizasyonu yapılarak gece gündüz kan basıncı ortalamaları, kan basıncı yükleri, dipper-non dipper özellikleri kaydedildi. Plazma renin aktivitesi, serum aldosteron, nitrik oksit, endotelin seviyeleri 24 saatlik idrarda sodyum ve potasyum atılımları karşılaştırıldı.*

Bulgular: *Laboratuvar değerlendirmelerinde hasta grupta kontrol gruba göre plazma renin aktivitesi yüksek, endotelin seviyesi düşük ve idrar sodyum atılımı yüksek saptandı.*

Sonuç: *Çocukluk çağı primer hipertansiyonu ve beyaz önlük hipertansiyonunda plazma renin düzeyinin ve idrar sodyum atılımının önemli rol oynadığı sonucuna varılmıştır.*

Anahtar Sözcükler: *Primer hipertansiyon, endotelin, renin.*

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Introduction

In recent years, the prevalence of primary hypertension in children has increased (1,2). It is thought that many different combinations of factors play role in the etiology and pathophysiology of primary hypertension. Obesity, insulin resistance, activation of sympathetic nervous system, sodium homeostasis, renin-angiotensin system, vascular smooth muscle structure and reactivity, serum uric acid levels, genetic factors and fetal programming have been implicated in primary hypertension (1-4)**.**

Hypertension is fundamentally a hemodynamic disorder indicating a disturbance in cardiac output and/or systemic vascular resistance (1)**.** Salt retention is a major contributor to increased intravascular fluid and may result from either excessive intake, or increased renal tubular resorption of sodium, as is seen with activation of the renin–angiotensin–aldosterone system and hyperinsulinemia (3). The renin–angiotensin system (RAS) is the major hormonal system affecting blood pressure (BP). Angiotensin II (ANG II) is a potent vasoconstrictor and thus increases blood pressure. It also stimulates the release of aldosterone from the zona glomerulosa of the adrenal gland, which results in a further rise in blood pressure from aldosterone-mediated sodium and water retention (1). Dietary sodium intake early in life may affect BP in later life. Potassium supplementation is associated with a decrease in BP in adults (1). In children the relationship between blood pressure and urinary excretion of electrolytes has been rarely studied.

Changes in peripheral vascular resistance result from either functional or structural abnormalities. Increased angiotensin II, elevated sympathetic activity, increased endothelins decreased endothelial relaxation factors as nitric oxide, and genetic abnormalities in vascular cell receptors are all associated with increased vascular smooth muscle contractility, and thus raise peripheral vascular resistance. Endothelin-1 (ET-1) is an endothelial-derived, potent vasoconstrictive peptide containing 21 amino acids (5,6). In addition to its potent renal vasoconstriction action, ET-1 has a direct stimulating effect on sodium reabsorption in renal proximal convoluted tubules, resulting in an increased blood volume (6). Genetic variation in ET-1 expression may be involved in the pathogenesis of essential hypertension. Endothelial ET-1 synthesis is inhibited by nitric oxide. Nitric oxide (NO) is an endothelium-derived gas, synthesized from the amino acid L-arginine by the endothelial isoform of nitric oxide synthase (NOS). Nitric oxide is a vasodilator, and the balance between nitric oxide and various endothelium-derived vasoconstrictors and the sympathetic nervous system maintains physiologic blood vessel tone (1). Inhibition NO synthesis increases renal vascular tone, reducing glomerular filtration rate. Similar effects reproduced in other vascular beds result in systemic hypertension (1,3,7).

The aim of this study was to investigate the role of plasma renin, serum aldosterone, nitric oxide, endothelin levels and urine sodium (Na) and potassium (K) excretion on childhood primary hypertension detected also by ambulatory blood pressure monitoring.

Materials and Methods

Subjects

Patients who had blood pressure higher than 90 percentile during the healthy children follow up and healthy with the normal blood pressure (without diabetes mellitus, vasculitis, congenital heart disease, non-metabolic disorders such as hypercholesterolemia) were included to the study. All patients underwent the same workup for secondary causes of hypertension, which included determination of body mass index (BMI), serum thyroid hormone, glucose, cholesterol, urea and creatinine levels, heart echocardiography, renal ultrasound with Doppler, and urinalysis. Patients with secondary forms of hypertension were subsequently excluded from the analysis. Patients with no identifiable causes of hypertension were labelled as essential hypertension. None of the patients included in this study was using antihypertensive drugs as angiotensin-converting enzyme (ACE) inhibitors. A total of 56 children (29 boys, 27 girls) with hypertension based on repeated office blood pressure measurements and 27 normotensive controls (15 boys, 12 girls) were included to the study. The mean age of the patients was 10.4±3.8 (5-17) years and the control group was 10.9±2.6 (7-16) years. According to BMI, 32% of the children were obese in study group.

In all hypertensive children and controls three measurements of blood pressures were performed using a cuff appropriate to the size of the upper arm. Fourth Report on the Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents was used as the reference values for the casual clinic blood pressure (8). On the basis of these measurements the group with stage 1 and 2 hypertension and the group with prehypertension were selected.

Ambulatory blood pressure monitoring

Ambulatory blood pressure monitoring was performed using the oscillometric Welch Allyn-24 hour ABP Monitor, ver. 12. The monitors were programmed to measure the blood pressure every 20 minute during day time and every 30 minute during night-time. Standard deviation scores according to gender and height were calculated as systolic and diastolic arterial blood

pressure during the daytime and night-time and as 24-h mean blood pressure values using the method of Soergel et al. (9), and the results were evaluated according to the reference values reported by Wühl et al. (10). The nocturnal blood pressure decrease (dipping) was calculated as the day-night BP difference expressed as a percentage of the daytime BP mean. The nondipping phenomenon was diagnosed as dipping of the systolic or diastolic BP of <10%. Blood pressure systolic and diastolic loads during the daytime and at night-time were derived for each child from 24-h recording. These were calculated as the percentage of readings exceeding the child's 90th percentile by sex, age and height.

Normal blood pressure was defined as <95 percentile by casual blood pressure, <95 percentile by ABPM and <25 systolic blood pressure load. White coat hypertension was as casual BP > 95th percentile in medical pressure setting, ABPM <95th percentile and <25% systolic blood pressure load. Masked hypertension was as casual BP <95th percentile in medical pressure setting, ABPM > 95th percentile and >25% systolic blood pressure load. Prehypertension was defined as casual BP >95th percentile in medical pressure setting, ABPM < 95th percentile and 25-50% systolic blood pressure load. Ambulatory hypertension was casual BP >95th percentile in medical pressure setting, ABPM > 95th percentile and 25-50% systolic blood pressure load. Severe ambulatory hypertension was defined as casual BP >95th percentile in medical pressure setting, ABPM >95th percentile, and >50% systolic blood pressure load (11).

Biochemical analysis

Blood samples for renin was taken in the supine position in the morning and the blood samples for renin, aldosterone, nitric oxide and endothelin were frozen at -20ºC until analysis.

Plasma renin levels were determined by using commercial DRG human ELISA kit (EIA-5125) (DRG International, Inc., USA). The test results were calculated by bioelisa reader Elx800 using standard curve at 450 nm. Results were given as pg/mL. Serum aldosterone levels were determined by using commercial DRG human ELISA kit (EIA-4410) (DRG International, Inc., USA). The test results were calculated by bioelisa reader Elx800 by using standard curve at 450 nm. Results were given as pg/mL. Serum ET-1 levels were determined by using commercial Biomedica human ELISA kit (BI-20052) (Biomedica Medizinprodukte GmbH & Co KG, A-1210 Wien, Divischgasse 4, GERMANY). The test results were calculated by bioelisa reader Elx800 using standard curve at 450 nm. Results were given as fmol/mL. NO (nitrite + nitrate) was assayed by a modification of cadmium-reduction method as mentioned by Navarro-Gonzalves. The samples were analysed spectrophotometrically using a microplate reader and quantified automatically against $NaNO_2$ standard curve and the results were expressed as μM/L.

After 24 h urine collection, a specimen of about 15 mL was frozen at -20ºC until analysis. Before the analysis the specimen was thawed at room temperature. The urinary Na and K levels were measured by a method with ion selective electrode.

Ethics

Informed consent was obtained for each child from both parents, and the study protocol conformed to the ethical guidelines. The study was approved by the ethics committee in our institution.

Statistical analysis

The data were analysed using the SPSS ver. 19 software package. The Kolmogorov-Smirnov test was used to assess the normality of numeric variables. Data were expressed as the mean (SD) or median (range). Differences between the two groups were determined by the Student's t test or Mann-Whitney U test. The proportions between certain subgroups were compared using the chi-square test. Correlation between blood pressure SDS values and plasma renin levels, serum aldosterone, ET-1, NO levels, urine Na and K values were tested by the Spearman correlation coefficient. Values with p<0,05 were considered to be statistically significant.

Results

Clinical characteristics of the patient and control group were shown in Table-1.

Table-1. Clinical Characteristics of the Patients and Control Group.

	Study N=56	**Control N=27**	**p**
Gender (Girl / Boy)	27 / 29	12 / 15	0.930
Age (years)	10.5±3.9	10.9±2.7	0.535
Weight (kg)	46.1±19.5	39.8±12.9	0.085
Height (cm)	142.8±21.6	149.1±15.8	0.139
BMI (kg/m^2)	20.8±4.7	17.5±2.7	<0.001
The presence of hypertension in the family	46	11	0.104

By casual blood pressure measurement, 9% of children were diagnosed to have prehypertension, 19% of children stage 1 hypertension, 72% of children stage 2 hypertension. All children in the control group had normal blood pressure values. After performing the ambulatory blood pressure monitoring, white coat hypertension was found as 52%, prehypertension was found as 25%, ambulatory hypertension was found as 23%. No masked hypertension was found in the control

group. 40% of the children with normal mean blood pressure levels had elevated blood pressure loads.

The results of the plasma renin, serum aldosterone, nitric oxide, endothelin levels and urinary Na and K excretions were given in the Table-2. The mean plasma renin levels were found to be significantly higher in children with primary hypertension than the control group (Table-2, Figure-1). No significant correlation was found between plasma renin levels and systolic-diastolic blood pressure, blood pressure load and dipping. No significant correlation was found between plasma renin levels and serum aldosterone, NO levels, ET-1 levels, urinary Na and K excretions.

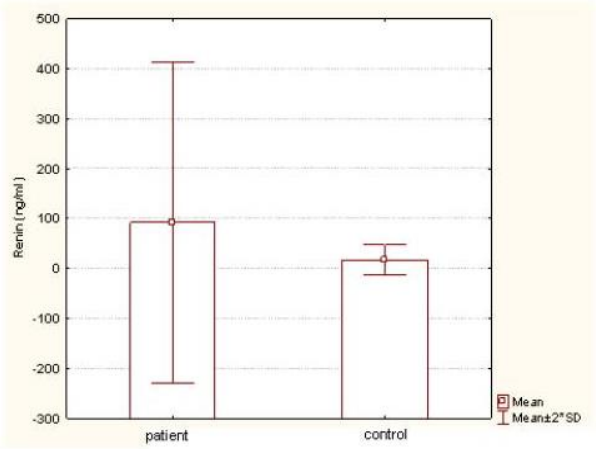

Figure-1. Plasma renin levels in patients with primary hypertension and control groups.

Table-2. Serum Renin, Aldosterone, NO, ET-1, Urinary Na and K Results in Patients with Primary Hypertension and Control Groups.

	Patient	Control	p
Renin (ng/mL)	92.50±160.80	17.80±14.50	0.002*
Aldosterone (pg/mL)	349.30±297.50	506.70±628.10	0.82
NO (µmol/L)	27.60±1.50	23.60±1.02	0.18
ET-1 (fmol/mL)	0.76±0.91	0.88±0.44	0.030*
Urinary Na (mEq/L)	106.00±16.80	138.00±13.20	0.006*
Urinary K (mEq/L)	37.00±2.30	41.40±3.60	0.500

* Statistically significant.

The mean serum aldosterone levels in children with primary hypertension were not significantly different than the control group (Table-2). No significant correlation was found between serum aldosterone levels and systolic-diastolic blood pressure, blood pressure load and dipping. No significant correlation was found between serum aldosterone levels and plasma renin levels, NO levels, urinary Na and K excretions. Insignificant positive correlation was found between serum aldosterone and ET-1 levels.

The mean serum ET-1 levels were found to be significantly decreased in children with primary hypertension compared to the control group (p=0.03) (Table-2, Figure-2). Insignificant positive correlation was found between serum ET-1 and aldosterone levels (r=0.28 p=0.011). No significant correlation was found between serum ET-1 levels and systolic-diastolic blood pressure, blood pressure load and dipping. No significant correlation was found between serum ET-1 levels and plasma renin levels, NO levels, urinary Na and K excretion.

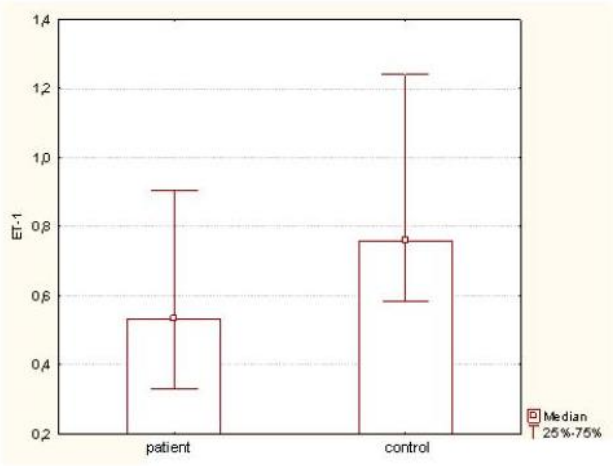

Figure-2. Serum ET-1 levels in patients with hypertension and control groups.

The mean serum NO levels in children with hypertension were not significantly different than the control group. No significant correlation was found between serum NO levels and ET-1 levels, plasma renin levels, serum aldosterone levels, urinary Na and K excretion.

Urinary Na excretion was found to be significantly decreased in children with primary hypertension compared to the control group (p=0.006) (Table-2, Figure-3). No significant correlation was found between urinary Na excretion and plasma renin levels, serum aldosterone, ET-1, NO levels. Urinary K excretion in children with hypertension was not significantly different than the control group. Insignificant positive correlation was found between urine Na and K excretion.

The mean plasma renin levels were found to be significantly higher in children with white coat hypertension (43.70±6.00 ng/mL) than the control group (17.80±14.50 ng/mL) (Table-3). However, serum aldosterone, NO and ET-1 levels were similar in two groups. Urinary Na excretion was found to be significantly decreased in children with white coat hypertension (109.60±157.50 mEq/L) compared to the

control group (138.30±66.30 mEq/L) (Table-3). However, there was no significant difference in urinary K between two groups.

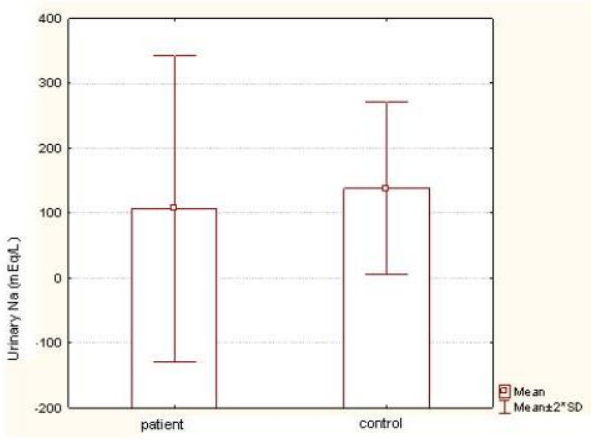

Figure-3. Urinary Na excretion in patients with hypertension and control groups.

Table-3. Serum Renin Levels and Urinary Na Excretion in Patients With White Coat Hypertension (WCH) and the Control Group.

	WCH (29)	Control (27)	p
Renin (ng/mL)	43.70±6.00	17.80±14.50	0.036*
Urinary Na (mEq/L)	109.60±157.50	138.30±66.30	0.007*

* Statistically significant.

Discussion

Although it was known that renin and aldosterone played role in the pathogenesis of primary hypertension, many conflicting results were reported. In a study comparing the patients with family history of hypertension, no major difference in RAS activity was shown, although they had differences in blood pressure levels (12). A recent cross-sectional study performed in healthy normotensive children with hypertensive and normotensive parents replicated similar findings. Although the two groups of children were normotensive, the group of children with hypertensive parents had a higher systolic blood pressure (SBP) index than those with normotensive parents. In spite of this difference, there were no significant differences in serum aldosterone, plasma renin activity or aldosterone/renin ratio (13). Silva et al. (14) suggested PRA, angiotensin I, angiotensin II, angiotensin 1-7 levels were significantly higher in renovascular hypertensive patients than in normotensive children. In contrast with renovascular disease, only angiotensin 1-7 levels were significantly increased in essential hypertensive patients compared with normotensive. These results showed different RAS profiles in childhood hypertension and suggest a blood pressure-independent change of angiotensin 1-7 in essential hypertension. Baracco et al. (15) compared the proportions of abnormal laboratory and imaging tests between primary and secondary hypertension groups. There was no significant difference in PRA between primary and secondary HTN groups. In our study levels of blood renin was found to be significantly higher in children with primary hypertension than the control group. However, serum aldosterone levels in children with hypertension were not significantly different than the control group. It is thought that renin might have a role in the pathogenesis of primary hypertension in children.

Endothelin-1 inhibits release of renin from isolated rat glomeruli but stimulates release of aldosterone from isolated cortical zona glomerulosa cells. Akter et al. (16) suggest that the ET-1 levels were significantly higher in the hypertensive than in the non-hypertensive subjects. Gu X et al. (17) found plasma ET-1 levels were higher in hypertensives than controls. Schneider et al. (18) showed that increased circulating immunoreactive ET might have a role in the development of high blood pressure. Schiffrin's (19) data supported the hypothesis of a role of endothelin-1 in blood pressure elevation in this hypertensive model with malignant hypertension. Another study of Schiffrin (20) supported endothelin-1 gene expression is normal or reduced in spontaneously hypertensive rats (SHR). Severe vascular hypertrophy is present in DOCA-salt hypertensive rats but not in SHR. Nar et al. (21) study reported that ET-1 levels were similar between hypertensive and normotensive individuals. In our study serum ET-1 levels was found to be significantly decreased in children with primary hypertension compared to the control group. Insignificant positive correlation was found between serum ET-1 and aldosterone levels. No significant correlation was found between serum ET-1 levels and systolic-diastolic blood pressure, blood pressure load and dipping. No significant correlation was found serum ET-1 levels and plasma renin levels, NO levels, urinary Na and K excretion. It is thought that ET-1 levels might be high in salt sensitive hypertension and extreme hypertension also the results could be variable in essential hypertension. No significant increase in serum endothelin levels were thought to be due to the degree of hypertension of our patients. It also thought ET-1 levels in circulation could not reflect ET-1 levels in local vascular structures.

Nitric oxide is a vasodilator, and the balance between nitric oxide and various endothelium-derived vasoconstrictors and the sympathetic nervous system maintains physiologic blood vessel tone. It has been reported that NO production was reduced in patients

with essential hypertension compared with normotensive (22,23). In our study serum NO levels in children with hypertension was not significantly different than the control group. No significant correlation was found serum NO levels and ET-1 levels, plasma renin levels, serum aldosterone levels, urinary Na and K excretion. It made us think that these results may be related to the patient group consist of mostly white coats and prehypertensive groups also not to begin the changes endothelin levels in early stages. We thought that NO was not affected in the early stage of primary hypertension.

Dietary sodium intake early in life may affect BP in later life (1). Hofman et al. (24) compared infants receiving a low or normal sodium-containing infant formula for the first 6 months of life. At 25 weeks, systolic pressure was 2.1 mm Hg lower in the low-sodium group than in the normal-sodium group. Normally, sodium excretion was found to increase when there is an acute increase in blood pressure. Genetic alterations in the expression or regulation of vasoactive mediators or transport molecules involved in sodium excretion may also contribute to the development of hypertension (25). Soltysiak et al. (26) suggested that in children with type 1 diabetes mellitus (DM1), increased levels of urinary angiotensinogen excretion might reflect early renal involvement, before the onset of microalbuminuria. Decreased sodium excretion seems to be involved in the development of HTN and early renal injury. In our study urinary Na excretion was found to be significantly decreased in children with hypertension compared to the control group. No significant correlation was found between urinary Na excretion and plasma renin levels, serum aldosterone levels. It was also thought that urinary sodium excretion had an important role in the pathogenesis of childhood primary hypertension.

Potassium supplementation is associated with a decrease in BP in adults[1]. Longer-term supplementation trials with potassium in hypertensive children induced lower age-related BP increases in SBP and DBP, compared with nonsupplemented children (27). However, Berry et al. (28) showed no evidence of benefit of dietary advice to increase K intake above usual intakes in the subjects with early stages of hypertension. According to our study, Urinary K excretion in children with hypertension was not significantly different than the control group. Insignificant positive correlation was found between urine Na and K excretion.

In our study, the ratio of white coat hypertension was found as 52%. The respectable high ratio of white coat hypertension denoted the importance of ABPM. Plasma renin levels was found to be significantly increased and urinary Na excretion was found to be significantly in children with white coat hypertension than the control group.

Conclusion

Blood renin and urinary sodium excretion had important roles in the pathogenesis of childhood moderate primary hypertension and white coat hypertension.

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Conflict of interest

The authors declare that no conflict of interest between them.

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