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THE ROLE OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM IN THE DEVELOPMENT OF NEPHROGENIC ARTERIAL HYPERTENSION IN CHILDREN

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Abstract
This study investigates the functional activity of the renin-angiotensin-aldosterone system (RAAS) in secondary (nephrogenic) hypertension in children. Symptomatic hypertension refers to arterial hypertension (AH) that arises as a consequence of various pathological processes, where elevated blood pressure (BP) is one of the manifestations of an underlying disease. Symptomatic hypertension, which is involved in the regulation of BP, accounts for 3–25% of all hypertension cases. This paper examines the role of RAAS in the development of renoparenchymal and renovascular arterial hypertension (RVH).

Keywords: Blood pressure, symptomatic arterial hypertension, renoparenchymal arterial hypertension, renovascular arterial hypertension, renin-angiotensin-aldosterone system, plasma renin activity, chronic glomerulonephritis, renal artery stenosis.

Introduction

Renal-origin hypertension, mainly caused by parenchymal kidney diseases (41.96% of cases) and congenital anomalies of the urinary system (33.6% of cases), occupies a leading position among the causes of symptomatic arterial hypertension (AH) in children [9, 13, 15]. It is well known that disturbances in the body's water-electrolyte homeostasis play a significant role in the mechanisms of elevated blood pressure (BP), and one of the main regulators of this balance is the renin-angiotensin-aldosterone system (RAAS) [1, 6, 10]. However, data characterizing the functional state of RAAS in secondary (including nephrogenic) hypertension in children are limited and most often relate to changes in plasma renin activity (PRA) [14, 15, 16]. This study investigates the functional activity of RAAS in children with secondary (renovascular) hypertension and chronic pyelonephritis.

Materials and Methods

A total of 52 children aged 7 to 16 years with nephrogenic hypertension were examined. The control group consisted of 30 healthy children of the same age. The diagnosis of nephrogenic arterial hypertension (AH) was established after a thorough clinical and laboratory examination in an inpatient setting, which in some cases included abdominal aortography. All participants were

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divided into two groups: the first group included 29 patients with renovascular hypertension (RVH), and the second group comprised 23 patients with hypertension associated with chronic pyelonephritis. The state of the renin-angiotensin-aldosterone system (RAAS) was assessed by the following parameters: plasma renin activity (PRA) of peripheral blood, plasma aldosterone concentration, and urinary excretion of aldosterone and electrolytes. Aldosterone concentrations in blood and urine, as well as PRA, were measured by radioimmunoassay using reagent kits from Sea-Ire-Sorin (France). Electrolyte concentrations in urine were determined by flame photometry using the FLM-2 device (Radiometer, Denmark).

Results and Discussion

Adolescents with renovascular hypertension (RVH) had significantly higher blood pressure compared to healthy controls. The main etiological factors were fibromuscular dysplasia of the renal artery (35%), congenital stenosis of the renal arteries and/or the descending abdominal aorta (35%), anomalies in the number of renal arteries (20%), aortoarteritis, and renal artery aneurysms (10%). Patients with RVH showed a significant increase in plasma renin activity (PRA), consistent with other studies [15] suggesting that excessive renin secretion plays a key role in the pathogenesis of this form of hypertension. A positive correlation was found between PRA and both systolic ($r = 0.31$, $p < 0.05$) and mean arterial pressure ($r = 0.30$, $p < 0.05$), supporting this hypothesis. However, individual analysis revealed elevated PRA in only 39% of RVH patients, while the rest had normal or slightly decreased PRA despite high blood pressure. The highest PRA (7.35 ± 2.76 ng/mL/h) was observed in patients with hypertension duration of less than one year, while in those with a history of hypertension of 3 years or more, PRA decreased approximately twofold (to 3.08 ± 0.94 ng/mL/h). Children in group I showed significantly increased blood aldosterone levels and urinary aldosterone excretion, indicating activation of the adrenal mineralocorticoid function. Renal excretory function remained intact in all patients. The highest aldosterone levels (207.2 ± 32.1 pg/mL) were observed in children with a hypertension history of more than 3 years—i.e., in the chronic stage of RVH. Normal PRA in these patients may be partially explained by a negative feedback mechanism of elevated aldosterone on the juxtaglomerular apparatus. Given aldosterone's major role in regulating water-salt homeostasis, a reduced urinary Na^+/K^+ ratio in children and adolescents with RVH compared to healthy peers supports the presence of hyperaldosteronism and suggests its important contribution to blood pressure elevation in this form of hypertension. This is further supported by a positive correlation between plasma aldosterone concentration and diastolic blood pressure ($r = 0.53$; $p < 0.05$). Thus, in children with RVH, both components of the RAAS were activated: the vasoconstrictive renin-angiotensin system and the aldosterone system regulating electrolyte balance. To assess the pathogenetic features of RVH in relation to the degree of vascular involvement, the RVH group was divided into two subgroups: Subgroup A included 18 patients with unilateral renal artery lesions, and Subgroup B included 11 patients with bilateral lesions. PRA in Subgroup A was significantly higher than in healthy controls (+149%) and also higher than in Subgroup B (+66%). This subgroup also showed the highest blood pressure values (178 ± 7.42 / 104 ± 5.39 mmHg). The parallel increase in BP and PRA suggests that elevated renin directly contributes to vascular tone, and the correlation between these indicators ($r = 0.66$; $p < 0.05$) confirms the renin-dependent

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nature of hypertension in unilateral renal artery stenosis. While RAAS activation in Subgroup A led to increased plasma aldosterone, it did not cause sodium and water retention due to the presence of a functioning contralateral kidney. This is supported by the urinary Na^+/K^+ ratio, which remained similar to that in the control group. In Subgroup B, PRA was also elevated but less markedly (+49%) than in Subgroup A. The absence of a correlation between BP and PRA in this subgroup suggests that the renin-angiotensin system is not the primary factor in hypertension pathogenesis in these patients. However, plasma aldosterone concentrations were extremely high (+236%), indicating that hypertension may be driven more by aldosterone. This mismatch between PRA and aldosterone levels may stem from increased adrenal sensitivity to angiotensin II or the development of secondary, partially autonomous adrenal hyperplasia. Despite increased excretion of aldosterone metabolites (18-glucuronide and its free fraction), hyperaldosteronism persisted. This is confirmed by a reduced urinary Na^+/K^+ ratio compared to healthy children and Subgroup A. A positive correlation between BP and plasma aldosterone levels ($r = 0.38$; $p < 0.05$) underscores the hormone's important role in Subgroup B. In summary, RAAS activation is a key pathogenic factor in RVH among children and adolescents. In unilateral renal artery lesions, hypertension appears primarily renin-dependent, while in bilateral vascular compromise, it is more strongly associated with sodium and water retention due to hyperaldosteronism. Among children and adolescents with hypertension caused by chronic pyelonephritis, PRA was higher than in the control group, likely due to renal ischemia resulting from parenchymal destruction and intrarenal vascular changes such as endarteritis and hyperplastic arteriosclerosis, leading to impaired renal hemodynamics and RAAS activation [12]. These findings are consistent with previously published data [1, 10, 11]. Plasma aldosterone levels were also elevated in this group, accompanied by sodium retention, as indicated by a reduced urinary Na^+/K^+ ratio. However, despite full RAAS activation, no clear correlation between BP, PRA, and aldosterone levels was found. Particularly noteworthy was a subgroup of 7 children with pyelonephritis complicated by vesicoureteral reflux. These patients showed significantly higher PRA compared to both healthy controls and pyelonephritis patients without urinary tract obstruction, likely due to more severe renal ischemia caused by increased intrarenal pressure and vascular compression. Plasma aldosterone concentrations were also highest in this subgroup. The pronounced hyperaldosteronism was likely due not only to increased adrenal production stimulated by elevated PRA but also to impaired renal excretion and metabolism of aldosterone. Excretion of the 18-glucuronide aldosterone metabolite and the free hormone fraction was lower than in patients with normal urine flow. This may be explained by degenerative changes in renal tissue. RAAS activation in children with urinary tract obstruction contributed to sodium and water retention, as reflected by a sharp decrease in the urinary Na^+/K^+ ratio. Consequently, their blood pressure was significantly higher than in children with uncomplicated pyelonephritis (144.3 ± 4.2 / 105.3 ± 3.2 mmHg vs. 133.4 ± 4.72 / 88.8 ± 4.06 mmHg; $p < 0.05$). A direct correlation between BP and both PRA ($r = 0.48$; $p < 0.05$) and plasma aldosterone levels ($r = 0.53$; $p < 0.05$) in this subgroup—absent in children with uncomplicated pyelonephritis—suggests a greater role of RAAS in the pathogenesis of hypertension in cases with impaired urinary outflow.

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Conclusions

1.In children with renovascular hypertension, the degree of activation of the renin-angiotensin-aldosterone system (RAAS) depends on the duration of the disease.

2. A direct correlation between blood pressure levels and both plasma renin activity and plasma aldosterone concentration confirm the involvement of RAAS in the pathogenesis of renovascular hypertension.

3. Elevated blood pressure in unilateral renal artery lesions is predominantly renin-dependent, whereas in bilateral renal vascular impairment, hypertension manifests as a mixed renin- and volume-dependent form.

4. In nephrogenic hypertension associated with pyelonephritis, RAAS activity is also increased; however, its contribution to blood pressure elevation is significantly more pronounced in children with impaired urinary flow due to vesicoureteral reflux.

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