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Management of blood pressure in children

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Abstract

Purpose of review—This review summarizes recent insights into the epidemiology of primary hypertension in children, with emphasis on the most important risk factors for the development of hypertension, and also updates current options for treating primary hypertension in children.

Recent findings—There is growing evidence that the prevalence of hypertension has increased over the past decade and that the epidemic of obesity has played a key role in the increase of blood pressure (BP) in the USA and abroad. Recent studies have shown that in addition to obesity, environmental factors such as second-hand smoking and sedentary lifestyle are important in development of hypertension even in preschool age children. Studies also have confirmed the effect of vegetables and fruits on lowering BP. Recent clinical trials of valsartan and olmesartan have provided efficacy and safety information for use in children.

Summary—The increased prevalence of hypertension in children in recent years emphasizes the need for a more aggressive approach to screen and diagnose elevated BP even in early childhood. Early initiation of treatment is important to decrease the risk of cardiovascular morbidity in adulthood.

Keywords

children; hypertension; management

INTRODUCTION

Elevated blood pressure (BP) has been recognized as an important health issue in the pediatric population over the past three decades. The majority of data indicate that average BP levels and prevalence of hypertension have risen substantially among children in the Western world. Obesity and other lifestyle factors such as physical inactivity and high calorie, high salt intake and fast food are thought to be responsible. Hypertension in children is viewed now as a significant risk factor for the development of adult cardiovascular disease in adulthood.

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Conflicts of interest

There are no conflicts of interest.

PREVALENCE OF HYPERTENSION

The majority of studies published last year showed that the prevalence of elevated BP in children and adolescents has been increasing. This tendency is evident not only in the United States but also in Asia (9.4–24%) [1,2], Europe (12.8%) [3], and Latin America (4.8–15%) [4]. Significant variability in the rate of hypertension among referenced studies is likely due to different methodologies applied to measure BP including differences in equipment use (office manual and electronic, 24-h ambulatory BP monitoring) and number of BP measurements (single versus multiple) to diagnose hypertension.

In contrast to the above studies, a relatively low prevalence of hypertension was found in two recent studies in which recommended and accepted screening procedures were applied. For example, the study from Iceland evaluated BP in 1071 children aged 9–10 years [5]. The prevalence of elevated BP was 13.1, 6, and 3.1% after the first, second, and third screens, respectively. Another study of 6193 Hong Kong Chinese adolescents determined that the prevalence of hypertension on the first, second, and third screens was 9.54, 2.77, and 1.44%, respectively [6]. Regardless of lower or higher prevalence of hypertension, elevated BP was independently associated with increased rate of obesity and sedentary lifestyle in these studies [1–6].

Furthermore, data from the Korean National Health and Nutrition Examination Survey from 1998 to 2008, which included a total of 5909 children 10–19 years of age, demonstrated a remarkable decrease in BP among all age and socioeconomic groups [7[■]]. In this study, childhood hypertension and prehypertension prevalence decreased by 52 and 86%, respectively. In contrast to other studies, these results were not explained by changes in childhood obesity (BMI and waist circumferences), health behaviors (cigarette smoking and physical activity), nutritional factors (sodium, potassium, total energy, protein, and fat intake), psychological factors (perceived stress and sleep duration), and sociodemographic factors (annual household income and family size).

The incidence of elevated triage BP in pediatric emergency patients was determined in a study by Ricke *et al.* [8[■]]. This retrospective review randomly selected patients ($n = 907$) seen in a large academic pediatric emergency department for 13 months. Elevated triage BP was rarely recognized by practitioners: 55% had elevated BP (90th percentile) with only 1% ($n = 7$) recognized; 20% of children had severely elevated BP (stage 2) with only 0.7% ($n = 5$) of cases being recognized.

RISK FACTORS

The most comprehensive analysis of potential anthropometric, prenatal, environmental, and familial risk factors for high BP was performed by Simmonetti *et al.* [9[■]] as part of a screening project in 4236 preschool children in Germany. As expected, a strong linear correlation between BP and BMI was observed. Obese children displayed significantly higher systolic and diastolic BP than lean children. Among prenatal risk factors, children born preterm or with low birth weight showed significantly higher systolic BP than children born at term or children with birth weight above 2500 g. Children exposed to maternal smoking during pregnancy displayed significantly higher systolic BP than unexposed

children, and children of mothers with pregnancy-related hypertension showed significantly higher systolic and diastolic BP.

This study also evaluated parental and environmental risk factors for elevated BP [9^{***}]. Children of hypertensive parents showed higher BP than children of normotensive parents. Similarly, BP was higher in children of obese parents than in children of nonobese parents. A lower parental educational level was significantly associated with higher systolic BP of the offspring. Children exposed to parental smoking at home had higher systolic and diastolic BP than unexposed children. The amount of maternal cigarette consumption correlated linearly with systolic BP.

Full adjustment for potential confounders by multivariable regression analysis in this study identified gender, height, BMI, birth weight, gestational hypertension, parental smoking, and parental hypertension as significant risk factors for systolic hypertension. Importantly, systolic and diastolic BP increased progressively in children with the cumulative number of parent-related risk factors (parental obesity, hypertension, and smoking).

Brady *et al.* [10] analyzed racial differences among 184 children aged 3–20 years with an established diagnosis of primary hypertension. Overall, children categorized as African–Americans had a higher prevalence of overweight/obesity and left ventricular hypertrophy (LVH) than children who were categorized as non-African–Americans. African–American children who were aged 13 years or older had higher BPs for both casual and ambulatory measurements. The authors concluded that African–American children with hypertension may be at greater cardiovascular risk because of their increased prevalence of obesity, LVH, and more pronounced BP elevations.

Tu *et al.* [11^{***}] investigated the relationship between BP and the full range of adiposity in a cohort of 1111 children. The effect of relative adiposity on BP was minimal until the BMI percentile reached 85, at which point the effect of adiposity on BP increased four-fold. Importantly, this relationship between BMI and BP was observed in all age categories (10, 11–14 years, and 15 years). The serum leptin level together with heart rate (HR) paralleled the rise in BP and BMI in these children, thus implicating a possible mediating role for leptin in development of hypertension acting through the sympathetic nervous system.

Pacifico *et al.* [12] determined associations of serum 25-hydroxyvitamin D(3) [25(OH)D(3)] concentrations with components of metabolic syndrome, including hypertension. In multiple regression analysis, the adjusted odds ratio (OR) (95% confidence interval) for those in the lowest (<17 ng/ml) compared with the highest tertile (>27 ng/ml) of 25(OH)D(3) for hypertension was 1.72 (1.02–2.92), and for metabolic syndrome, it was 2.30 (1.20–4.40). A similar pattern of association between 25(OH)D(3), high BP, and metabolic syndrome was observed when models were adjusted for waist circumference.

Frequency of familial hyperaldosteronism type 1, an autosomal-dominant disorder of the chimeric *CYP11B1/CYP11B2* gene, was evaluated in 130 consecutive untreated hypertensive children (4–16 years of age) in the study by Aglony *et al.* [13^{*}]. The authors found four (3.08%) children with chimeric gene who belonged to four unrelated families. In addition, four children and five adults were identified who were affected among 21 first-

degree relatives. Of the eight affected children, six presented with severe hypertension, one presented with prehypertension, and one presented with normal BP. The authors concluded that the prevalence of familial hyperaldosteronism type 1 in a pediatric hypertensive pediatric population was surprisingly high. They also commented on a high variability in the clinical and biochemical characteristics of the affected patients, which suggests that familial hyperaldosteronism type 1 is a heterogeneous disease with a wide spectrum of presentations even within the same family.

An association of hypertension with prematurity has been confirmed in the study by Duncan *et al.* [14], who showed that neonates born preterm and with very low birth weight (<1500 g) are at risk of hypertension as early as 1 year of age that persists after 3 years of age. Another study evaluated the incidence and risk factors for hypertension in the neonatal ICU (NICU) [15]. A total of 123 847 NICU encounters were identified in the database. After exclusion of the 44 861 neonates with congenital cardiac disorders, 764 (1%) were coded with the diagnosis of hypertension. In multivariate analysis, the risk for hypertension was greatest in those neonates with a high All Patient Refined Diagnosis Related Groups severity of illness assessment (OR = 35.8), previous extracorporeal membrane oxygenation (OR = 3.8), a coexisting renal disorder (OR = 4.7), and renal failure (OR = 2.4).

LIFESTYLE MODIFICATION

Damasceno *et al.* [16] examined the associations of BP with fruits, vegetables, and fruit juice consumption among a random sample of 794 adolescents from 12 private schools in northeast Brazil. Regular consumption of fruits (more than twice per day) was associated with lower systolic and diastolic BP, whereas consumption of vegetables was associated with a significant decrease in systolic BP only.

The relationships between childhood lifestyle risk factors and adulthood pulse wave velocity (PWV) have been evaluated in 1622 individuals of the Cardiovascular Risk in Young Finns Study followed up for 27 years since baseline [17^{***}]. Decreased vegetable consumption was an independent predictor of high PWV in adulthood when adjusted for lifestyle or traditional risk. The number of lifestyle risk factors (the lowest quintile for vegetable consumption, fruit consumption, physical activity, and smoking) in childhood was directly associated with PWV in adulthood ($P = 0.001$). These findings suggest that lifetime lifestyle risk factors, with low consumption of fruits and vegetables in particular, are related to arterial stiffness in young adulthood.

The Greek adolescents study analyzed data from 496 students aged 12–17 years who submitted information on the frequency and duration of physical activity and the amount of time spent in sedentary activities [18]. As expected, HRs were significantly lower as the level of activity rose. However, intense physical activity was associated with higher systolic BP and pulse pressure, with positive correlations of $r = 0.139$ ($P = 0.003$) and $r = 0.22$ ($P = 0.0001$), respectively. The authors concluded that physical activity should be practiced at a moderate intensity level in everyday life.

Maggio *et al.* [19] performed a follow-up study of 20 young adolescents who participated in the randomized controlled trial of the effect of physical activity on cardiovascular risk

factors. The authors showed that even 2 years after stopping the trial, the reduction in BP was maintained. In addition, arterial intima-media thickness, BMI z-score, and body fat remained stable 2 years after stopping the physical activity program. These results were more prominent in the patients that decreased their BMI during the exercise program.

PHARMACOLOGICAL TREATMENT

The efficacy and safety of olmesartan in children with hypertension was established in a recent clinical trial [20[¶]]. In this trial, the active treatment phase was conducted in two periods, with two cohorts in each period (cohort A, 62% ($n = 118$) white; cohort B, 100% ($n = 112$) black). In period one (dose dependent), statistically significant reductions in systolic and diastolic BP for both cohorts were evident, with BP reductions numerically smaller in cohort B than in cohort A. In period two (olmesartan versus placebo), BP control worsened in those patients switching to placebo, whereas patients continuing to receive olmesartan maintained consistent BP reduction. Adverse events were generally mild and unrelated to study medication. The trial concluded that olmesartan was well tolerated and efficacious in children with hypertension.

A clinical trial of valsartan also showed a significant reduction of BP in children between 6 and 16 years [21[¶]]. The maximal BP reduction was dose dependent. The dose varied between 0.1 mg/kg and 4.6 mg/kg. The main side effect was headache, which was observed in less than 5% of patients. Only 0.4% developed hyperkalemia at a dose of 80 mg, and 0.4% experienced gastroenteritis on 40 mg of valsartan. In nonobese patients, the most pronounced BP reduction was seen in the high-dose group (3.2 mg/kg) [22] with no further reduction in BP at higher doses. In obese patients, mean reduction in BP plateaued at the medium dose, a mean weight-adjusted dose of 1.1 mg/kg. Schaefer *et al.* [22] compared efficacy and safety of valsartan with enalapril in a 12-week, randomized, double-blind, parallel-group, active-controlled study of hypertensive children aged 6–17 years. Both valsartan and enalapril provided comparable BP reductions and effective BP control and were well tolerated in children.

A retrospective analysis of 391 doses of isradipine, a second-generation dihydropyridine calcium channel blocker, administered to 282 hospitalized children with acute hypertension was performed by Miyashita *et al.* [23]. The decrease in systolic BP was $16.3 \pm 11.6\%$ and diastolic BP was $24.2 \pm 17.2\%$. BP was significantly lower in all age groups and in all diagnosis categories following isradipine administration. The decrease in BP was the highest in children younger than 2 years of age. The authors concluded that isradipine effectively reduces BP in a wide variety of hospitalized children with acute hypertension. A lower initial dose of 0.05 mg/kg may be appropriate in children younger than 2 years.

To determine the efficacy and safety of labetalol for hypertensive crisis in children 24 months of age or less, Thomas *et al.* [24] conducted a retrospective chart review of 27 patients treated with 37 intravenous infusions of labetalol, nicardipine, or nitroprusside. Continuous infusion of labetalol reduced mean systolic BP by at least 20% in less than 8 h. This effect was similar to nicardipine and nitroprusside infusions. The authors noted that

patients receiving labetalol and presenting with ischemic or traumatic brain injury were likely to develop hypotension requiring infusion discontinuation.

Use of antihypertensive medications in the NICU was evaluated in study by Blowey *et al.* [15]. The medications most used in the NICU were vasodilators in 64.2% (hydralazine was the most common vasodilator), angiotensin converting enzyme inhibitor (ACEI) in 50.8%, calcium channel blockers in 24%, and α and β blockers in 18.4%. Of the neonates exposed to antihypertensive medications (diuretics excluded), 55% were exposed to one antihypertensive drug and 45% to two or more antihypertensive drugs. Similarly, 59.1% of exposures to antihypertensive drugs were limited to a single drug class, 27% to two drug classes, 9% to three drug classes, and 4% to all four drug classes.

Litwin *et al.* [25] evaluated the effect of 12 months standard pharmacological and nonpharmacological therapy on reduction of target-organ damage in 86 pediatric patients with primary hypertension. Nonpharmacological therapy included advice on lifestyle changes (increase exercise, salt and sugar restriction). Pharmacological therapy included ACEI, angiotensin receptor blockers, and amlodipine. Thirty-seven patients required only lifestyle modification and 49 children needed antihypertensive medications to achieve adequate BP control. A significant decrease in the prevalence of LVH (46.5 vs. 31.4%) and in carotid artery intima-media thickness (0.44 ± 0.05 vs. 0.42 ± 0.04 mm, both $P < 0.001$) were observed. The authors concluded that standard antihypertensive treatment lowered BP and led to significant regression of target-organ damage in hypertensive children. Lean body mass increase and decrease in abdominal obesity correlated with target-organ damage regression.

CONCLUSION

Hypertension in children is often underdiagnosed. The alterations in end-organ structure and function noted in adult hypertensive patients begin in childhood. As treatment of hypertension has been shown to improve cardiovascular outcomes and to reduce the risk for development of these complications in the adult population, prompt recognition of elevated BP, specific risk factors for hypertension and its complications in children and adolescents may prevent future morbidity and mortality in these patients.

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KEY POINTS

- Primary hypertension can develop in children of preschool age.
- Hypertension is frequently unrecognized in children.
- Obesity epidemic and physical inactivity are the major causes of elevated blood pressure (BP).
- Currently available nonpharmacological therapy, if implemented, is effective in BP control in children.
- Combination of lifestyle modification and pharmacological treatment can decrease end-organ damage associated with elevated BP in children.