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REVIEW ARTICLE

Treatment of Hypertension Induced Target Organ Damage in Children and Adolescents

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Abstract: High blood pressure in children and adolescents may have an adverse impact on the heart, the vessels, the kidney, and the central nervous system causing early functional or structural changes. The most prevalent subclinical hypertensive target organ damage in children and adolescents is left ventricular hypertrophy, and echocardiographic assessment of left ventricular mass is suggested in all hypertensive children. There is evolving evidence that antihypertensive treatment in children and adolescents could lead to regression of target organ damage, emphasizing also the importance of adequate blood pressure control. Assessment of subclinical organ damage could guide clinical decisions from diagnosis with regard to intensity non-pharmacological treatment, time to wait for initiation of pharmacological treatment, and choice of drug. Longitudinal studies are needed to relate the effectiveness of antihypertensive treatment and blood pressure targets in childhood with future cardiovascular or renal events. This review summarizes evidence on the associations of hypertension with target organ damage in children and adolescents and the role of antihypertensive therapy on the regression of target organ damage in the pediatric age group.

Keywords: Hypertension, children, left ventricular hypertrophy, carotid intima-media thickness, executive function, antihypertensive treatment.

1. INTRODUCTION

Epidemiologic data on the prevalence of high blood pressure (BP) in children derived from the National Health and Nutrition Examination Surveys (NHANES) in the United States are available since 1988 [1]. An increase in the prevalence of childhood high BP based on a single occasion BP measurement has been documented. However, after repeated measurements, the prevalence of hypertension is reported lower (~3.5%), because of BP variability and the tendency of regression to mean [2, 3]. High BP may have an adverse impact on the heart, the vessels, the kidney, and the central nervous system causing early functional or structural changes. In the absence of hard outcomes in childhood and adolescence, it has been generally accepted that intermediate markers, left ventricular hypertrophy (LVH), arterial stiffness, carotid intima-media thickness (cIMT), and albuminuria or proteinuria, may be used to estimate the presence of subclinical cardiovascular or renal damage attributed to hypertension [2, 4]. Thus, accurate evaluation of BP levels in children and adolescents is important for the prevention not only of future cardiovascular and renal disease but also of early subclinical target organ damage. Ambulatory blood pressure monitoring (ABPM) is an important tool for accurate diagnosis, revealing the phenotypes of hypertension (white-coat, masked hypertension, and non-dipping status), and evaluating the efficacy of the treatment [4]. Furthermore, many pediatric studies demonstrated closer relationships between ambulatory BP and target organ damage than office BP measurement, and have reported that ABPM may better identify patients at the highest risk for target organ damage.

2. HYPERTENSIVE TARGET ORGAN DAMAGE IN CHILDREN AND ADOLESCENTS

2.1. Cardiac and Vascular Damage

Left ventricular hypertrophy is a significant predictor of cardiovascular morbidity and mortality in adults and the most frequently reported target organ damage in children with primary hypertension. Left ventricular mass has been shown to correlate with lean body mass, fat mass, sex, and systolic BP [5]. Hypertension induced LVH usually presents with increased relative wall thickness without an increase in cavity size resulting in concentric hypertrophy. The prevalence of LVH in hypertensive children is not precisely known, because different definitions for LVH have been used in pediatric populations [6]. Severe LVH, defined by the adult threshold as left ventricular mass index (LVMI) greater than 51 $g/m^{2.7}$, has been reported to present a prevalence of 10-15% in hypertensive children and adolescents [6-8]. Using the pediatric definition, LVMI equal to or greater than the 95th age and sex percentile, the prevalence may be found higher up to 30-40% [6, 9]. Obesity is often present in children with primary hypertension and may additionally confer to increased LVMI levels [10]. LVMI levels present a linear increase with 24h systolic BP values [11]. Stabouli *et al*. evaluated 124 children and adolescents referred for ABPM and demonstrated that LVMI values gradually increase from normotensive to high normal and hypertensive BP levels, independent of age, sex and body mass index [11]. In the same study, the prevalence of LVH was higher in children and adolescents having high normal BP and hypertension, compared to those with normotension based on ambulatory BP levels. In pediatric patients with secondary causes of hypertension, LVH also presents a close association with BP levels. Kupferman *et al*. analyzed prospective data from the Chronic Kidney Disease in Children cohort (CKiD), and showed that LVH was strongly associated with hypertension in children with mild to moderate chronic kidney disease over a 4-year follow-up period [12]. Predictors of LVH in the population were female sex, anemia, systolic BP, and use of antihypertensive medications other than angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). Data on diastolic dysfunction in hypertensive children and adolescents are scarce. Two recently published studies highlighted the potential value of assessing diastolic function via E'/A' ratio in children with hypertension and chronic kidney disease. Despite similar rates of LVH, hypertensive children with chronic kidney disease appeared to more severe diastolic dysfunction compared to children with primary hypertension [13]. The levels of Cystatin C level also predicted diastolic function

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decline via E'/A' ratio in children with chronic kidney disease even after adjusting for GFR [14].

Autopsy studies in adolescents and young adults have demonstrated significant relationships between the level of BP elevation and the presence of atherosclerotic lesions in the aorta and the coronary arteries [15, 16]. Several observational studies in pediatric patients have found associations between BP and carotid intima-media thickness (cIMT) or pulse wave velocity (PWV) [9, 17-19]. Lurbe *et al*. showed that carotid-femoral PWV linearly increases across office systolic and central BP values. Childhood systolic BP has also been shown to be an independent predictor of PWV in adulthood [20]. The combined results of four longitudinal cohort studies demonstrated that the effect of elevated BP in childhood on carotid atherosclerosis at young adulthood is markedly reduced if these individuals become normotensive adults [21].

2.2. Renal Damage

Hypertension is one of the major causes of chronic kidney disease (CKD) in adults, but usually, this is not the case with children. Limited studies have shown a relationship between microalbuminuria and primary hypertension in the pediatric population [22, 23]. Obesity has been shown as a risk factor for future CKD, and coexistence with hypertension in childhood and adolescence may enhance the course of disease [24]. Obesity causes renal vasodilation and glomerular hyperfiltration to compensate for the obesity increased sodium sensitivity, which along with increased BP and metabolic abnormalities may lead to glomerular injury and a vicious cycle between hypertension and renal injury. Assadi *et al*., in a study of 55 adolescents, 11-19 years old, with essential hypertension, found that microalbuminuria was correlated not only with the severity of hypertension but also with the presence of LVH [22]. Furthermore, Wu *et al*. found that albumin to creatinine ratio in healthy Chinese children correlated with systolic, but not diastolic BP [25]. The most robust evidence on the detrimental impact of BP levels on the kidney is provided by the ESCAPE trial, which offers unique randomized longitudinal prospective data on the beneficial effect of low BP levels on kidney survival in children with CKD [26].

2.3. Cognitive Impairment

Longitudinal studies have demonstrated that hypertension from mid-life predicts development of cognitive decline in late life and dementia in the elderly [27]. However, there is evidence that hypertensive target organ damage in the brain may start from childhood. The association between high BP and cognitive function was firstly examined in a cross-sectional analysis of 5,077 children and adolescents, 6-16 years old, in the NHANES III [28]. Children with systolic BP greater than the 90th percentile for age, sex, and height, had lower performance in cognitive tests for digit span, block design and mathematics compared with normotensive ones. Lande *et al*., assessed neurocognitive test performance in 75 untreated hypertensive children and 75 matched normotensive controls. Hypertension was associated with lower performance on measures of learning memory, attention, and executive function [29]. In another study, Adams *et al*., demonstrated that hypertensive children were more likely to be diagnosed with a learning disability, suggesting that these children are at high risk for academic difficulties [30]. Ditto *et al*., further examined the neurocognitive test performance in normotensive children, and found that children with parental history of hypertension and systolic BP in the high normal range had significantly lower performance on verbal learning test, whereas patients without parental history, but systolic BP in the high normal range, had significantly lower performance on spatial learning and memory tests [31]. Noteworthy, Wong *et al*., showed that untreated hypertensive children may present significantly lower hypercapnic reactivity compared to normotensive children [32].

3. TREATMENT OF HYPERTENSION WITH TARGET ORGAN DAMAGE

3.1. Indications and Choice of Treatment

Non-pharmacological treatment remains the cornerstone for the initial management of hypertension in children with primary hypertension, targeting in comorbid risk factors [2, 33]. Current guidelines recommend gradual weight loss to reduce body mass index below to the 85th percentile for age, and sex [2]. Behavioral therapy and adoption of a healthy diet, including Dash diet and reduction of salt consumption, are also advised. Physical exercise of at least 60 min of moderate to vigorous intensity physical activity daily and less than 2 hours of sedentary activity are strongly recommended. All lifestyle changes should be age-appropriate, culturally sensitive, family-centered lifestyle modifications.

The decision to initiate pharmacological treatment is based on the individual child's or adolescent's cardiovascular risk, which in the pediatric population, could not be based on outcome studies, but in intermediate endpoints, target organ damage or presence of factors or diseases that carry an increased risk for cardiovascular or renal events in adulthood. Assessment of subclinical cardiovascular damage may guide clinical decisions from diagnosis regarding the intensity of non-pharmacological treatment, time to wait for initiation of pharmacological treatment, and choice of drug.

The European Society Hypertension (ESH) 2016 guidelines for the management of high BP in children and adolescents recommend to initiate pharmacological treatment in children with primary hypertension, if lifestyle modification for more than 12 months fails to lower BP levels, or if target organ damage is present [2]. Evaluation for LVH and microalbuminuria is recommended at the time of diagnosis to guide treatment decisions (Table **1**). In the new American Academy Pediatrics (AAP) 2017 clinical practice guideline, evaluation for LVH is delayed until consideration of pharmacological treatment, arguing the subjective nature of the echocardiography and high cost of the test [33]. The American guidelines suggest targeting clinical decisions on BP levels, rather than treating an increased left ventricular mass [33]. However, in the BP targets section, it is reported that LVH may appear at BP levels between the 90th and 95th pc and that BP reduction below the 90th pc can reverse LVH. Further keeping a controversy into the same guideline repeated echocardiography is recommended after treatment initiation at regular intervals, including those without LVH at initial echocardiographic assessment if having stage 2, secondary, or resistant hypertension. The frequency of repeated echocardiography during treatment in patients with LVH is recommended every 6-12 months, similar to that recommended by the ESH 2016 guidelines. Of note, the American guidelines endorse the adult criterion of LVMI >51 g/m$^{2.7}$ for children older than 8 years. This is considerably higher than the LVMI 95th pc for age and sex recommended by the European guidelines (difference 10 g/m$^{2.7}$, and 15 g/m$^{2.7}$ for 8-year-old boys and girls, respectively) [34, 35]. Both the ESH 2016 and the AAP 2017 guidelines had do not currently recommend further assessment for diastolic dysfunction in hypertensive children. The clinical utility of routine testing for albuminuria in all patients has been recognized by the European, but not by the American guidelines. Evaluation for proteinuria in the CKD patients with hypertension is recommended by both guidelines for clinical decision-making. With regard to arterial damage, there is an agreement among guidelines concerning the recommendation for non-routine assessment of arterial damage due to insufficient pediatric evidence.

In adults, large interventional studies have established the goals of antihypertensive treatment. The lack of validated BP thresholds in children and adolescents against outcomes has emerged the need of using statistically defined normative data, as well as a

Table 1. Summary of recommendations for the assessment of hypertensive target organ damage in children and adolescents based on ESH 2016 guidelines [2].

Assessment of Target Organ Damage in Children and Adolescents	
Who	• All hypertensive children
When	• At diagnosis
Which marker of TOD	• Left ventricular hypertrophy by echocardiography • Albuminuria or proteinuria
Definitions of TOD	• Left ventricular mass index or relative wall thickness ≥ 95th percentile by age and gender
	• Albuminuria: albumin/creatinine ratio>30mg/g; Proteinuria: albumin/creatinine ratio >300mg/g or 24h urinary protein excretion >200 mg/m²/day
When to initiate pharmacological treatment	• At diagnosis if TOD is present
Follow up	• Echocardiography every 6 months if LVH is present at baseline
	• Assessment for de novo TOD every 12-24 months if no TOD at baseline

Abbreviations: ESH: European Society Hypertension; TOD: target organ damage

dependency on extrapolations from the adult thresholds. The European guidelines recommend the 95th percentile (according to the individual's age, sex, and height) as the upper limit for children younger than 16 years old, below which BP levels should be targeted. However, it is suggested to aim at BP levels lower than the 90th percentile [2]. Similar is the recommended BP target by the American guidelines for children younger than 13 years old, as BP levels between the 90th and 95th percentile are not considered normal, and there is evidence of target organ damage in children with high-normal BP levels [11, 36]. In children with diabetes mellitus or chronic kidney disease, the target BP is below the 75th percentile, if there is no proteinuria, and below the 50th percentile, in the case of existing proteinuria [2]. The American guidelines recommend BP target based on ABPM below the 50th percentile for all children with CKD irrespective of the presence or not of proteinuria, introducing the results of the ESCAPE trial into clinical practice [33]. Finally, the European guidelines recommend the adult BP target for adolescents older than 16 years, and the American ones for adolescents older than 13 years old.

The clinical trials on the efficacy of antihypertensive drugs in the pediatric age range are relative few, and many recommendations have been extrapolated from adult guidelines. In a systematic review of 27 articles on antihypertensive drugs in childhood including both prospective and retrospective studies, systolic and diastolic BP reduction was reported similar with ACE inhibitors (10.7/8.1 mmHg), ARBs (10.5/6.9 mmHg) and calcium-channel blockers (9.3/7.2 mmHg) [37]. Furthermore, in patients with overt proteinuria, ACE inhibitors and ARBs significantly reduced urinary protein excretion by 49% and 59%, respectively, but there were no reports for other drug classes. A Cochrane systematic review including 21 trials, evaluated antihypertensive medications in 3,454 children with follow-up periods ranging from 3 to 24 weeks [38]. Only five studies compared the effects of antihypertensive agents with placebo, whereas other compared escalating doses of the same drug class. ARBs had modest lowering effects and calcium channel blockers had minimal lowering effects. There was no evidence about the superiority of one agent, while all drugs appear safe, at least in the short term. Noteworthy, the investigators did not identify any clinical trials that evaluated the effectiveness of antihypertensive medications on target end-organ damage.

Antihypertensive drugs blocking the renin-angiotensin system and calcium-channel blockers are currently the most frequently prescribed drugs for childhood hypertension both in Europe and United States [39-41]. Most of the antihypertensive agents are approved by the FDA or EMA for use in children older than 6 years of age, because of limited clinical trials in the younger age groups. The antihypertensive treatment should start with a single drug at the lowest dose, with the ability of the titration of the dose [2]. When the maximum recommended or tolerated dose fail to achieve the BP target, a combination of therapy could be used. Drug choice should target the underlying pathophysiology and presence of comorbidities. For pediatric patients with diabetes mellitus and microalbuminuria, or with CKD and proteinuria, an ACE inhibitor or an ARB is the most appropriate first-line agent, because of their antiproteinuric effect [2, 33]. ACE inhibitors or ARBs could also be the first line agents for obese pediatric patients with LVH based on adult studies and some preliminary pediatric observational data [42]. Beta-blockers or calcium channel blockers are preferred in children with hypertension after the surgical repair of aorta coarctation. On the contrary, there are contraindications about specific antihypertensive drugs, such as beta-blockers in asthmatic or diabetic children, or ACE inhibitors and ARBs in females adolescents at high risk of pregnancy. Moreover, in high-performance athletes, beta-blockers or diuretics may be avoided, because they reduce cardiac output and intravascular volume [33]. Finally, the potential negative (or positive) consequences of pharmacotherapy starting at a young age with regard to metabolic side effects, such as weight gain and insulin resistance with beta-blockade have not been studied in the pediatric population, and suggestions for the choice of drugs in children with metabolic abnormalities are mainly based on extrapolation from adult studies [2, 43].

3.2. Pediatric Studies Showing Regression of Hypertensive Target Organ Damage

There is evolving evidence, mainly for observational studies, on the beneficial effect of BP lowering treatment on target organ damage in hypertensive pediatric patients (Table **2**). The cross-mark study remains the ESCAPE trial, the only prospective randomized control study in pediatric hypertension, that enrolled 468 patients with stage 2-4 CKD (glomerular filtration rate of 15 to 80 ml/min/1.73 m^2 of body surface), assigned to the intensified BP control (189 patients with BP below the 50th percentile by ABPM), or the conventional BP control group (196 patients with BP 50th-95th percentile by ABPM) [26]. The primary end was the decline of

Table 2. Studies showing regression of target organ damage in hypertensive children and adolescents.

Author	Country	Study Design	Population	Measure of Target Organ Damage	Treatment	Follow-up	Outcome
Assadi 2006 [22]	United States	Observational prospective cohort study	56 children (age range 11-19 years) with primary HTN	Albumin to creatinine ratio >30 μg/mg LVMI> 38.6 g/m$^{2.7}$	Hydrochlorothiazide +Enalapril ± ARB	12 months	↓45% in microalbuminuria ↓32% in LVMI ↓prevalence of LVH from 38% to 12%
Seeman *et al*., 2007 [47]	Czech Republic	Observational prospective cohort study	19 (median age 15 years) with renal and primary HTN	LVMI >38.6 g/m$^{2.7}$ (95th pediatric percentile), or as LVMI >51 g/m$^{2.7}$	Ramipril	6 months	↓LVMI from 36.8 g/m$^{2.7}$ to 32.6 g/m$^{2.7}$ ↓prevalence of LVH from 42% to 11% by the pediatric percentile definition
Wuhl *et al*., 2009 [26]	Europe	Randomized control study	385 children, age range3 to 18, with stage 2–4 CKD (GFR 15 to 80ml/min 1.73 m^2)	50% decline in GFR or progression to end-stage renal disease	Ramipril ±CCB, β-blockers, or α-adrenergic blockers, diuretics, and centrally active agents	5 years	29.9% in intensified BP control reached the primary end point, vs. 41.7% in the conventional BP control
Kupferman *et al*., 2010 [46]	United States	Retrospective cohort study	21 age range 8-17 years Secondary and primary HTN	LVMI ≥ 95th pc for age and sex	Enalapril± Amlodipine	6 months	↓LVMI from 56.2±12.5 to 43.7±8.38 g/m$^{2.7}$ in children 15 with LVH LVMI normalized in 5/15 cases
Litwin *et al*., 2010 [42]	Poland	Observational prospective cohort study	86 children (14.1 ± 2.4 years) with primary HTN	LVMI >38.6 g/m$^{2.7}$, and LVMI ≥ 51 g/m$^{2.7}$ for severe LVH	Lifestyle changes + Enalapril or losartan or amlodipine	12 months	↓LVMI from 38.5 ± 10.7 to 35.2±7.5 g/m$^{2.7}$ ↓ prevalence of LVH from 46.5% to 31.4% ↓cIMT from 0.44±0.05 to 0.42±0.04 mm ↓WCSA from 7.5±1.3 to 6.9± 1.2 mm^2
Matteucci *et al*., 2013 [45]	Europe	Randomized control study	84 children 3–18 years with stage 2–4 CKD	LVMI >38.6 g/m$^{2.7}$ and LVMI ≥ 95th pc for age and sex	Ramipril ±CCB, βblockers, or α-adrenergic blockers, diuretics, and centrally active agents	2 years	↓LVH from 38% to 25% Improvement in myocardial function, which was associated with reduction in BP
Kupferman *et al*., 2014 [12]	United States	Prospective, multicenter, cohort study (CKiD study)	435 (median age 12 years) with mild to moderate CKD	LVMI ≥ 95th pc for age and sex	ACE/ARB or CCB or other	4 years	LVMI had an average decrease of 40% over 4 years ↓LVH from 5.3% to 12.6% in a systolic BP model and from 15.1% to 12.6% in a diastolic BP model

(Table 2) Contd....

Author	Country	Study design	Population	Measure of target organ damage	Treatment	Follow-up	Outcome
Lande *et al*., 2010 [49]	United States	Prospective, cohort study	22 children with primary HTN and 25 controls, age range 10-18 years	Executive function by parent BRIEF Internalizing and externalizing behaviors by CBCL	Lisinopril	12 months	Parent ratings of executive function improved in hypertensives (BRIEF Global Executive Composite T- score, $\Delta = -5.9$,) but not in the normotensive controls
Lande *et al*., 2018 [50]	United States	Prospective, case-control, multicenter study	55 children with primary HTN and 66 controls, age range 10-18 years	Neurocognitive tests including AVLT, Cog-State GMLT WASI, Grooved Pegboard Test, DKEFS Tower Test, WISC-IV, Cog-State Set Shifting, CPT-II, Parent BRIEF	Lisinopril ±diuretic/ CCB or amlodipine	12 months	Improved scores in subtests of the AVLT, Grooved Pegboard, and DKEFS Tower Test in the hypertensive group, but similar improvements in the control group Lower performance in uncontrolled hypertension

Abbreviations: HTN: hypertension; BP: blood pressure; ACE: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blockers; CCB: calcium cannel blocker; CKD: chronic kidney disease; CKiD: Chronic Kidney Disease in Children cohort; LVMI: left ventricular mass index; LVH: left ventricular hypertrophy; cIMT: carotid intima media thickness; WCSA: wall cross sectional area; BRIEF: Behavior Rating Inventory of Executive Function; CBCL: Achenbach Child Behavior Checklist; AVLT: Rey Auditory Verbal Learning Test; CPT-II: Conners' Continuous Performance Test-II; GMLT: Groton Maze Learning Task; WASI: Wechsler Abbreviated Scales of Intelligence; DKEFS Tower Test: Delis-Kaplan Executive Function System Tower Test; WISC-IV: Wechsler Intelligence Scale for Children - Fourth edition

50% in the glomerular filtration rate or progression to end-stage kidney disease. The long-term renoprotective effect of intensified BP control compared to conventional BP levels was documented among children who were receiving ramipril, either monotherapy or in addition to other drugs not targeting the angiotensin-renin system, over a 5-year follow up. In the intensified BP control 29.9% of children reached the primary end, in comparison to 41.7% in the convectional BP group. The benefit to the kidney function was emphasized, whereas proteinuria gradually rebounded after an initial 50% decrease. Recently, Van den Belt *et al*., analyzed data from ESCAPE study, highlighting the importance of proteinuria lowering in the management of pediatric CKD, as the early antiproteinuric effect of ACE inhibition was associated with long-term preservation of kidney function [44]. A sub-study in the frame of ESCAPE study, included 84 patients with mild to moderate CKD who were followed up with echocardiograms at baseline and at 1- or 2-years follow up [45]. BP lowering resulted in LVMI regression in those with LVH at baseline, and an improvement in myocardial systolic function after 12-24 months of treatment. Intensified BP control led to marginally better myocardial function, but changes in LVMI were independent of BP levels.

Several observational studies have also demonstrated that antihypertensive treatment could induce regression of LVH [12, 22, 42, 46, 47]. In a retrospective study of Seeman *et al*., reported that treated pediatric patients with uncontrolled hypertension had a three times higher prevalence of LVH than children with controlled hypertension [48]. Litwin *et al*., demonstrated that one year of antihypertensive treatment including lifestyle changes and/or blockade of the renin-angiotensin system is effective for target organ regression in children with primary hypertension and metabolic abnormalities; about 90% of the study population were overweight or obese, and 15% presenting with metabolic syndrome [42]. However, the main determinants of LVMI regression in the study population were the decreases in abdominal obesity and the increase in lean body mass, rather than the BP lowering effect. Kupferman *et al*. showed in a 4-year of a follow-up study from the CKiD cohort data a decline in the adjusted prevalence of LVH from 15.3% to 12.6% in relation to systolic BP decreases and from 15.1% to 12.6% in relation to diastolic BP decreases over time [12]. In the same study, the use of ACE inhibitors and ARBs seemed to be protective for the development of LVH. This finding could be explained by the known direct effect of ACE inhibitors and ARBs on myocardial fibrosis, or by the better BP control by these medications compared to other drug classes in the study.

Finally, Lande *et al*., reported an improvement in executive function performance based on parent ratings of Behavior Rating Inventory of Executive Function (BRIEF) test after 12 months of treatment, therapeutic lifestyle modification counseling, and if needed angiotensin-converting enzyme inhibition. [49]. Hypertensive children with baseline LVH or SBP load greater than 50% were more likely to show improvement in executive function, implying that these patients were at high risk for neurocognitive impairment at baseline. This small, single-center study provided evidence about the reversibility of early neurocognitive deficit by hypertension. In a more recent multicenter study by the same investigators, the efficacy of antihypertensive treatment was associated with improvements in neurocognitive performance in the group with BP control compared to children with persistent ambulatory hypertension [50]. However, these findings need to be confirmed by larger studies and possibly with a more comprehensive evaluation of central nervous system function.

CONCLUSION

In the absence of hard endpoints in childhood and adolescence, subclinical hypertensive target organ damage is a useful marker of cardiovascular risk. There is evidence that antihypertensive treat-

ment in children and adolescents could lead to regression of target organ damage highlighting the importance of adequate BP control. Current BP targets based on the statistical distribution of BP levels in healthy children need to be validated against the presence of target organ damage in large studies both in primary and secondary causes of hypertension. Furthermore, future longitudinal studies may relate the effectiveness of BP lowering treatment and BP targets in childhood on future cardiovascular or renal events.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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