

Hypertension in children and adolescents

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Received: August 20, 2011 Revised: October 27, 2011
Accepted: December 16, 2011
Published online: December 23, 2011

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Kollias A. Hypertension in children and adolescents. *World J Hypertens* 2011; 1(1): 15-19 Available from: URL: <http://www.wjgnet.com/2220-3168/full/v1/i1/15.htm> DOI: <http://dx.doi.org/10.5494/wjh.v1.i1.15>

Abstract

Pediatric hypertension (HTN) has become the focus of interest recently due to its increasing prevalence. This is mainly related to the increase in childhood obesity, although the current evidence suggests that other lifestyle factors, apart from obesity, contribute to high blood pressure (BP) in childhood. Traditionally, office BP measurements by the physician have been the cornerstone for the assessment of HTN in children. However, since the white coat and masked HTN phenomena are not rare in childhood, out-of-office BP measurements have significantly improved the accurate diagnosis of HTN and decision making. Ambulatory BP monitoring is regarded as indispensable for the evaluation of pediatric HTN, providing details not only for the staging for HTN, but also for the study of other ambulatory BP patterns. It should be pointed out that HTN in children and adolescents is associated with target-organ damage which is significant in terms of cardiovascular risk. The current knowledge, outlined in the present review, is expected to help in early and accurate diagnosis as well as in the management of HTN in children and adolescents.

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Key words: Hypertension; Blood pressure; Diagnosis; Children; Adolescents

Peer reviewer: Prasenjit Guchhait, PhD, Assistant Professor,

INTRODUCTION

In the last two decades, our knowledge about childhood hypertension (HTN) has substantially increased. It is now recognized that pediatric HTN, particularly among adolescents, is not as uncommon as previously believed and in most cases represents early onset of essential rather than secondary HTN^[1-4]. Moreover, HTN in children is related to preclinical target-organ damage such as left ventricular hypertrophy, microalbuminuria and increased carotid vascular thickness, thus conferring an increased cardiovascular risk in adulthood^[5-8]. Out-of-office blood pressure (BP) measurements, especially ambulatory BP monitoring, have significantly helped in accurate diagnosis of HTN in childhood^[9]. Current guidelines on BP assessment in children and adolescents are widely available, especially among pediatricians and primary care providers, helping them in screening, diagnostic and therapeutic interventions in children with high BP^[10,11].

EPIDEMIOLOGY AND RISK FACTORS

Several studies in Europe and US have shown the prevalence of high BP in children and adolescents to be at about 1%-4%^[1-4]. Ethnic differences, as well as differences in protocols and methodology used to assess BP, account for the inconsistency in the findings worldwide. HTN in children aged < 6 years is usually secondary but in higher age categories (especially > 12 years) essential HTN is the rule^[10,11].

Recent studies show increasing trends of average BP

in children and adolescents^[12,13]. In particular, data from the US National Health and Nutrition Examination Surveys showed that after age, race/ethnicity and sex standardization, systolic and diastolic BPs were respectively 1.4 and 3.3 mmHg higher in 1999-2000 compared with 1988-1994^[12].

The reported increase in childhood HTN may have important implications in terms of cardiovascular health. Longitudinal cohort studies have shown that BP tracks from childhood to adulthood, and that high BP in childhood confers a high risk of HTN in adulthood, thus supporting the need for early identification of high-risk individuals^[14].

A consistent finding in most of the aforementioned studies is the strong association between obesity and high BP. In particular, the obesity epidemic appears to be the major contributor of the increasing trends in childhood HTN. However, apart from obesity, other factors such as adverse lifestyle and dietary habits appear to be associated with increased BP levels in children and adolescents^[15,16]. In particular, lack of physical activity and sedentary behavior, as well as dietary salt intake have been associated with increased BP in children independent of body composition^[15,16].

DIAGNOSIS OF HTN IN CHILDREN AND ADOLESCENTS

Diagnosis of HTN depends on accurate BP measurements. However, there is a fundamental difference in the diagnosis of HTN in children compared to adults. Recommendations for adults are derived from observational and interventional large, long-term outcome studies with hard endpoints of morbidity and mortality. Such studies in children and adolescents are largely unfeasible since, not only are the cardiovascular events far in the future (making follow-up very difficult), but also because multiple confounding factors will infiltrate and influence the cardiovascular risk through time, thereby diluting the net effect of treatment-induced BP decline. Therefore, there is a lack of evidence about threshold BP values for intervention and BP goals in children and adolescents. As a result, many of the classifications and recommendations are based on statistical considerations and assumptions or on extrapolation from evidence obtained in adults.

Measurement of BP by a physician in the office using a mercury sphygmomanometer has been the cornerstone for diagnosis of HTN^[10]. In 2004, the US National High BP Education Program Working Group on High BP in Children and Adolescents published normalcy tables for office BP on the basis of a large database of more than 70 000 children and adolescents^[10]. These tables provide the 50th, 90th, 95th and 99th BP percentiles for each year of age and according to height percentiles (based on the growth charts of the Center for Disease Control and Prevention) for boys and girls^[10]. BP measurement is performed with a mercury sphygmomanometer or, if not available, a calibrated aneroid device and the auscultatory

method, with first (K1) and fifth (K5) Korotkoff sounds defining systolic and diastolic BP respectively^[10]. An appropriate size of cuff is very important and the length of the bladder in the cuff should cover 80%-100% of the individual's arm circumference. It is recommended that all children > 3 years old seen in a medical setting should have their BP measured.

The recent European Society of Hypertension (ESH) recommendations for the management of high BP in children and adolescents also adopted the US Task Force normalcy tables, since these were derived from a large dataset^[11]. According to the 2004 US Task Force and the ESH guidelines, the 90th and 95th office BP percentiles for gender, age and height are used to diagnose normotension, pre-HTN and HTN on the basis of average systolic and diastolic BP levels on at least three separate occasions^[10]. Measurements obtained by oscillometric devices that exceed the 90th percentile should be repeated by auscultation. It should be pointed out that oscillometric monitors used in children should be validated specifically in the pediatric population. As in adults, adolescents with BP levels over 120/80 mmHg should be considered as pre-hypertensives even if their BP is below than the 90th percentile. Both the ESH and the US guidelines categorize hypertensives into stage 1 (95th-99th centile + 5 mmHg) and 2 (> 99th centile + 5 mmHg)^[10,11].

WHITE COAT AND MASKED HTN IN CHILDREN

White coat HTN is characterized by office BP higher than the 95th percentile while outside the clinical setting BP is normal. The first report on the white coat phenomenon in children came from a study published in 1991 in 159 children with a positive family history of HTN, 44% of whom were classified as white-coat hypertensives^[17]. Subsequent studies reported a prevalence of white-coat HTN ranging from 10% to 60% according to the methodology used and the population studied (healthy, referred for elevated BP or other)^[18-20]. The relationship of white-coat HTN with the presence of target-organ damage in children and adolescents seems to be somewhat unclear. More specifically, children with white-coat HTN have been reported to have higher values of left ventricular mass index^[21,22]. On the other hand, Stabouli *et al*^[23] reported that white-coat hypertensives tended to have higher left ventricular mass index compared with normotensives, but the difference was not statistically significant.

Masked HTN refers to high BP values outside the office with normal values in the clinical setting. The first study reporting on masked HTN was conducted in Japan, in 136 normotensive (on the basis of office BP) individuals aged 6-25 years old, showing that the prevalence of masked HTN was 11%^[24]. A larger Spanish study by Lurbe *et al*^[25] including 592 children and adolescents aged 6-18 years old, showed that 90.4% of the children were normotensive, 0.8% hypertensive, 1.2% had white-coat

HTN and 7.6% had masked HTN. Interestingly, 8.8% of subjects with masked HTN developed sustained HTN during the study follow-up, and subjects with persistent masked HTN had increased prevalence of left ventricular hypertrophy compared to normotensives^[25]. A more recent study in Greece using ambulatory BP monitoring in 85 children and adolescents referred for elevated BP, reported that the prevalence of HTN was 25%, of white-coat HTN 13% and of masked HTN 9.4%^[23]. Therefore, in children and adolescents referred for elevated BP, masked HTN and white-coat HTN are common phenomena^[26]. The data for target-organ damage in children with masked HTN are in agreement with findings in adults that showed masked HTN to be associated with increased left ventricular mass^[25].

OUT-OF-OFFICE BP MEASUREMENTS AND ASSOCIATION WITH TARGET-ORGAN DAMAGE

The conventional measurement of BP by the physician in the office or clinic for the assessment of HTN has certain disadvantages, such as the aforementioned white coat and masked HTN phenomena, the observer prejudice and bias and the regression to the mean. Out-of-office BP measurements have been increasingly used in children and adolescents for the accurate assessment of HTN.

Ambulatory BP monitoring

Ambulatory BP monitoring in children and adolescents was first adopted in the early 1990s in the context of the research field, but recently it has been increasingly used for clinical purposes^[27]. In recent guidelines, ambulatory BP is regarded as an indispensable method for the evaluation of pediatric HTN^[10,11].

The normalcy tables for ambulatory BP measurements, based on data from 1141 children and adolescents, provide the 90th and 95th percentiles (proposed threshold for normotension and HTN respectively) according to age and height and have been endorsed by both the American and the European guidelines^[10,11,28,29].

Several studies have examined the relationship of ambulatory BP with subclinical target-organ damage in children and adolescents. Among several indices of pre-clinical target-organ damage, left ventricular hypertrophy appears to be the most extensively studied index due to the wide availability of echocardiography. Several studies have reported the prevalence of left ventricular hypertrophy in hypertensive young individuals ranging from 10% to 46% and have shown an independent association of ambulatory BP monitoring parameters with left ventricular mass index^[30-33]. Also, ambulatory BP in children has been associated with other indices of subclinical target-organ damage such as carotid intima media thickness, glomerular filtration rate and carotid-femoral pulse wave velocity^[8,34,35].

According to the published guidelines, the diagnosis

of ambulatory HTN is defined as average 24-h, daytime or nighttime systolic and/or diastolic ambulatory BP \geq 95th percentile for gender and height or age^[11,29]. However, apart from the diagnosis of HTN and the detection of white-coat and masked HTN, ambulatory BP monitoring is useful in the identification of several ambulatory BP patterns in children and adolescents. More specifically, isolated nocturnal HTN and abnormal nocturnal dipping, which are often seen in subjects with secondary HTN or chronic diseases such as diabetes, can be detected only by using 24-h ambulatory BP monitoring^[29]. Furthermore, ambulatory BP monitoring is of paramount importance in the evaluation of antihypertensive treatment effects and particularly in the assessment of refractory HTN, the evaluation of BP control in children with target-organ damage and in the recognition of symptomatic hypotensive episodes^[29]. Lastly, ambulatory BP monitoring can provide information on arterial stiffness (ambulatory arterial stiffness index)^[35].

Home BP monitoring

In children, the available evidence on the usefulness of home BP monitoring is less than for ambulatory monitoring. Studies have shown that home BP monitoring is feasible in the pediatric population in terms of acquiring a decent number of measurements, with or without (in older children and adolescents) the parent's assistance^[36]. As in the case of adults, home BP monitoring in children might be useful in the diagnosis of HTN and allows the detection of the white coat and the masked HTN phenomena^[37]. Only one study, the Arsakeion study in Greece performed in 778 healthy children and adolescents, has attempted to provide normalcy tables which have been endorsed by the recent ESH guidelines^[36]. Interestingly, home BP has been associated with subclinical target-organ damage in hypertensive children as closely as ambulatory BP^[38].

DIAGNOSTIC EVALUATION

The confirmation of HTN should be combined with a thorough history and physical examination^[10,11]. Past medical history should focus on possible definable causes of hypertension. Questions should be asked about prior hospitalizations, trauma, urinary tract infections, snoring and other sleep problems. Many drugs, especially over the counter and illicit drugs, can increase BP. Family history is also very important. Physical examination should include assessment of the child's body mass index and measurement of BP in both arms and a leg. It should also assess signs and symptoms suggesting renal disease (gross hematuria, edema, fatigue, epigastric/flank bruit, palpable kidneys), heart disease (chest pain, exertional dyspnea, palpitations) and diseases of other organ systems (e.g. endocrinological, rheumatological).

Routine laboratory investigation in children with high BP should include full blood count, plasma sodium, potassium, calcium, urea, creatinine, fasting plasma glucose

and lipids, as well as urinalysis. Organ damage evaluation should include heart, great vessels, kidney, central nervous system and retina. As mentioned before, left ventricular hypertrophy is the main target-organ damage evident in children with HTN and echocardiography is necessary in all these cases. More specialized tests for secondary causes should be restricted in children aged < 12 years, as well as in children with symptomatic or stage 2 HTN. It should be pointed out that the diagnostic evaluation for secondary HTN should always follow confirmation with ambulatory BP monitoring.

MANAGEMENT OF HTN IN CHILDREN AND ADOLESCENTS

Non-pharmacological interventions should be the initial step in the management of HTN in children and adolescents^[10,11,39]. Weight loss, aerobic physical activity and dietary modifications have been shown to be associated with a decrease in BP levels^[10,11,39]. Given that obesity is closely associated with HTN, measures aiming at weight reduction and maintenance of ideal body weight are of paramount importance. A recent meta-analysis showed that a modest reduction in salt intake was associated with significant reductions in systolic and diastolic BP^[40]. Although sodium restriction is difficult to achieve in this age range, avoiding processed foods, paying attention to sodium content (on the food labels) and avoiding table salt are useful practices^[39]. Apart from sodium restriction, a diet rich in fruits and vegetables and poor in saturated fat, sweetened beverages and fast foods may be efficient in terms of BP reduction. In fact, dietary approaches, such as DASH (Dietary Approaches to Stop Hypertension), have been shown to effectively decrease BP levels in younger subjects^[41]. In addition, everyday aerobic physical activity of moderate to vigorous intensity, in combination with a reduction in sedentary activities, is a wise recommendation.

Pharmacological therapy should be initiated when patients have symptomatic HTN, hypertensive target organ damage, secondary HTN or diabetes mellitus type 1 or 2 at the time of presentation, as well as in cases of sustained HTN despite the implementation of non-pharmacological measures^[11]. It should be pointed out that non-pharmacological therapy should be continued after starting pharmacological therapy.

Concerning BP targets, in general BP should be below the 90th age-sex and height specific percentile (except in subjects with chronic kidney disease where BP should be below the 75th percentile in children without proteinuria and below the 50th percentile in cases of proteinuria)^[11].

As in the case of adults, five classes of drugs are suitable for BP control in children and adolescents, including angiotensin converting enzyme inhibitors, angiotensin receptor blockers, β -blockers, calcium channel blockers and diuretics^[11]. It should be noted that the indications for the use of these drugs in children are derived from short-term trials and that there are no trials with cardio-

vascular end points or trials comparing different classes. Thus, guidelines about the use of specific drugs in children are not solid and treatment should be individualized, in some cases directed from underlying pathophysiological mechanisms and extrapolation of data from adults^[39,42,43]. Angiotensin converting enzyme inhibitors and angiotensin receptor blockers are preferred in children with diabetes and microalbuminuria or proteinuric renal disease. Treatment should begin with low doses of each agent and titrated on the basis of BP response and potential adverse effects. In children and adolescents, a significant response can be achieved even with the lowest doses of drugs. Subjects who do not respond to their initial drug may be switched to another category or require combination therapy with different classes of drugs. Monitoring should include assessment of BP levels and potential target-organ damage as well as evaluation of compliance.

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S- Editor Wang JL L- Editor Roemmele A E- Editor Zheng XM