ABSTRACT • Hypertension in the young is increasingly being recognized as an emerging critical healthcare problem, not only because of its increasing prevalence in recent years but also of its significant impact on the health and well-being of children and adolescents and tracking into adult life. A wealth of epidemiological studies has allowed the formulation of guidelines and recommendations on the diagnosis and classification of hypertension in the pediatric group based on normative data. Significant advances in the field of medicine and genetics have paved the way for the identification and demonstration of recent trends in hypertension research in children and adults. This article highlights both established and emerging concepts in order to provide a quick yet panoramic view of the current understanding on pediatric hypertension.

INTRODUCTION

Hypertension (HT) and its sequelae remain as one of the most pressing healthcare problems globally, affecting developed and developing countries alike. It afflicts close to a billion people worldwide and the cost of health services, notwithstanding the economic burden borne from preventing complications and managing disabilities, runs in billions of dollars annually. Hypertension is the most common primary diagnosis in the United States, accounting for more than 37 million clinic visits [1]. It poses a major risk for cardiovascular, renal and neurological diseases, including stroke, for millions of people around the globe. The relationship between an individual’s average blood pressure (BP) and the development of cardiovascular disease is linear, continuous, consistent and independent of other risk factors such as smoking, obesity, hypercholesterolemia, and diabetes mellitus [2]. Cardiovascular disease risk, which begins at approximately 115/75 mmHg, doubles for each 20/10 mmHg increase. In spite of rigorous patient education and concerted efforts to prevent and control the disease and its various complications, there is evidence that the problem is only getting worse. There are 43 million people with HT in the United States alone, which comprises 29% of the middle-aged population. Globally, the number of adults with HT in 2025 is predicted to increase by about 60% to a total of 1.56 billion [3].

Essential HT has been long recognized as an insidious adult-onset disorder. It was not until the last three decades that the disease has been reported to occur in the young and that early predictors of HT have been identified among young children. It is estimated that up to 2% of term and preterm neonates receiving care in modern neonatal intensive care units have HT. Among older children, the prevalence of essential HT ranges between 1-2% and appears to have steadily increased over the years, primarily attributable to the increase in the prevalence of obesity. We discuss here the issues that constitute recent trends in pediatric HT research.

CLASSIFICATION OF PEDIATRIC HYPERTENSION

In the adult population, the relationship between systemic BP and morbidity is quantitative rather than qualitative, thus a classification system for individuals 18 years and older was established for making judicious decisions on
the aggressiveness of treatment and other therapeutic interventions. Pursuant to the guidelines in “The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure”, or JNC VII [2], the diagnosis of HT is made when the average of multiple seated diastolic BP measurements on at least two subsequent clinical visits is 90 mmHg or higher, and/or when the average of multiple seated systolic BP measurements is consistently 140 mmHg or more. A new category, prehypertension, has been added to emphasize the risk of an individual having BP measurements previously considered normal to develop frank HT; prehypertensives are at twice the risk to develop HT than those with lower values. Increased education and awareness is needed to prevent the onset of HT in the general population.

Due to the paucity of available risk information, the current definition of HT in children is based on normative data culled from previous epidemiologic database and the recent 1999-2000 National Health and Nutrition Examination Survey (NHANES). The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents (WGR4) by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents (NHBPEP) provides an updated normative data for BP classification of children aged 1 to 17 according to age, gender, and height for the 50th, 90th, 95th, and 99th percentiles. Blood pressure values are based on auscultatory measurements, pursuant to recommended protocols. The dependence on statistical data to define HT in the young has disadvantages including the difference in BP indices for various populations, variability of BP determinants in a given population over time, and the inclusion of single BP measurements in the database.

Normal BP in the pediatric age group is defined as systolic and diastolic BP that are below the 90th percentile, while HT is defined as the average systolic or diastolic BP that is ≥ 95th percentile on more than two occasions [4]. Analogous to JNC VII, a new category, prehypertension, has been included and is defined as an average systolic or diastolic BP between the 90th and 95th percentiles, or if the BP exceeds 120/80 mmHg regardless of the normative score [4], and is an indication for lifestyle modifications. Moreover, Stage 1 HT is defined as persistent systolic or diastolic BP that is between the 95th and 99th percentiles, while Stage 2 HT is when the average systolic or diastolic BP exceeds the 99th percentile [4]. These stages of HT are intended to facilitate the appropriate and timely management of the affected child.

Despite the detailed instructions on proper BP measurement and guidelines on appropriate diagnostic and therapeutic interventions, recent data showed that these recommended strategies are not adhered to in clinical practice [5]. A recent cohort study revealed that HT and pre-HT are under-diagnosed among children and adolescents [6]. Of the subjects that had HT, only 26% were appropriately diagnosed, while only 11% of prehypertensive subjects were correctly diagnosed. Although the exact reasons for these findings are still unclear, it is possible that unfamiliarity of the diagnostic cut-off scores for HT in the young and the clustering of HT and obesity and lack of confidence on the BP readings obtained in the clinics may contribute to the problem [5].

TARGET-ORGAN DAMAGE

The clinical significance of HT among children and adolescents is difficult to evaluate because of the considerable time interval between the diagnosis of HT and the manifestation of a clinical crisis. However, numerous reports have shown that HT in the young is invariably accompanied by findings of early target organ damage [5, 7]. Left ventricular hypertrophy (LVH), an important predictor of cardiovascular morbidity and mortality in adults, is the most commonly identified measurable cardiac abnormality, occurring in more than a third of children with HT [8-9]. The correlation of BP elevation with the occurrence of LVH has been reported by several groups [8-9], but not by others [10]. The exact mechanism underlying the development of LVH remains to be defined, although abnormalities in diastolic function and cardiac ischemia due to increased oxygen consumption have been postulated [7].

Another consequence of sustained HT is vascular damage, such as increased carotid intima-media thickness (cIMT), a marker of atherosclerosis and a strong predictor of cardiovascular morbidity and mortality in adults. Studies have shown that there is increased incidence of cIMT in several childhood diseases that increase cardiovascular risk like diabetes, hypercholesterolemia and end-stage renal disease [11]. The usefulness in using cIMT as a marker of hypertensive vascular damage has been demonstrated in a recent matched controlled study that showed increased cIMT in hypertensive children independent of obesity – another risk factor for increased cIMT – and that higher cIMT correlated with more severe HT [12]. Lower levels of high density cholesterol are also associated with cIMT in children [13]. The occurrence of hypertensive retinopathy, another marker of hypertensive vascular damage in adults, has also been reported in 50% of affected infants studied, although the retinal abnormalities resolved with the normalization of the BP [14].

Other clinical sequelae of HT in the young include impaired cognitive function [15] and renal damage. More recently, French-Canadian boys with elevated systolic BP were found to have lower scores on a spatial learning and memory factor score relative to boys with lower BP that could not be related to differences in socioeconomic status [16]. Although it is frequently seen in children with chronic kidney disease and undoubtedly contributes to the progression of disease, HT is rarely the cause of the disease in children [17]. Microalbuminuria accompanies more than half of hypertensive adolescents, occurring more in those with Stage 2 HT compared to Stage 1 [18]; however, microalbuminuria correlates more with LVH than with renal damage [18-19].
AMBULATORY BLOOD PRESSURE MONITORING

Measurable target organ damage has been documented to occur even in children with unconventional forms of HT such as white-coat and masked HT.

White-coat HT is defined as a condition in which a patient has an average BP reading ≥ 95th percentile when measured in a clinical setting but falls below the 90th percentile elsewhere. This form of HT is more prevalent among obese subjects [20], appears to be relatively common in children with Stage 1 compared to those with Stage 2 HT [5], and is accompanied by left ventricular mass indices that are intermediate between those of normotensive and hypertensive subjects [5] and characterized by decreased performance on exercise testing [21].

Masked, or isolated ambulatory HT, on the other hand, is defined as a condition in which patients have normal BP in the clinic but are hypertensive in their regular environment [4]. This condition is more prevalent in non-obese subjects [20] and is associated with greater-than-normal prevalence of organ damage, such as increased prevalence of metabolic risk factors, left ventricular mass index, cIMT, and impaired large artery distensibility [22], all important indices of cardiovascular disease. In children and adolescents, increased BMI is a predictor of masked HT [23].

Thus, ambulatory BP monitoring, a well established technique that involves the recording of BP at 20-minute intervals throughout a 24-hour duration, has been endorsed by WGR4 primarily for the identification of unconventional forms of HT and for the prediction of target-organ damage [5, 23]. Since the BP of an individual is dynamic and oscillates with his Circadian pattern, physical activity and level of stress – BP is higher during the day and falls by 10% during sleep – ambulatory BP monitoring provides not only a better reflection of the variability of the subject’s actual BP and an objective BP in his normal environment but also allows a better prognostication for end-organ damage compared to regular BP measurement [7]. Several studies have been performed to establish normal values for ambulatory BP monitoring in children and young adults and to compare and contrast these values with those obtained by regular BP measurements. These studies revealed that the diastolic ambulatory BP is independent of height and that the subjects have higher daytime diastolic and systolic ambulatory BP values, especially in the shorter groups. The reasons for these disparities are still not fully understood. Furthermore, ambulatory BP monitoring can be used to distinguish between primary and secondary forms of HT; secondary HT is characterized by daytime diastolic BP and nocturnal systolic BP elevations [24].

Indications for the use of ambulatory BP monitoring include Stage 1 HT, obesity not accompanied by HT, a strong family history of HT, or an early cardiovascular event. It can also prove useful for the assessment of refractory HT or drug-induced hypotension [22].

BLOOD PRESSURE TRACKING IN CHILDREN

Several studies have shown that precursors of adult cardiovascular diseases such as obesity and dyslipidemias begin early during childhood, although abnormal levels of risk factors by adult criteria are not evident in children and only appear in young adults. For instance, data gleaned from autopsy reports demonstrate the presence of fatty streaks and plaque formation in children and young adults with cardiovascular disease risk factors years before the development of frank disease.

Blood pressure tracking, or the predictability of adult BP based on BP measurements early in an individual’s life, has been demonstrated by several large longitudinal studies [25]. Hypertension during childhood has been shown to more likely follow patients into adulthood [26]. Adult BP correlates with childhood BP and BMI. Blood pressure tracking has important clinical implications as it is tied to the development of atherosclerosis and the progression of metabolic syndrome in the young adults [27]. Moreover, data on BP tracking provide insights into the efficacy of various therapeutic approaches to manage HT in the young and could help determine the extent of influence of genetics vs. environment on BP control [5]. An inadequate compensatory increase in urinary sodium excretion in response to a stress-induced BP increase could lead to the premature development of essential HT and has recently been suggested as a new intermediate phenotype to study the etiology of HT [28]. Moreover, cardiovascular reactivity to stress may be a predictor of BP.

FETAL PROGRAMMING OF HYPERTENSION

Fetal programming or imprinting refers to the cogent association between adverse prenatal environmental events and altered fetal growth and development with persistent, abnormal pathophysiology and frank disease later in life. Based on observations that factors found in utero may be involved in the development of cardiovascular disease, Barker and colleagues hypothesized that fetal influences that retard fetal growth could program and permanently result in alterations of the body’s structure and physiology and thus set the stage for the development of cardiovascular disease in adults [29]. Numerous epidemiological studies support the inverse relationship between low birth weight and HT. Fetal growth and development are governed by several determinants including the fetal genetic endowment, maternal health and placental capacity to supply oxygen and nutrients to the fetus [30]. Suboptimal fetal conditions and other insults during crucial windows of growth and development, which may coincide with periods of rapid cell proliferation, may result in adaptive changes in the structure and function of vulnerable tissues, which conceivably are antecedents of HT. Alterations to genetic pattern during fetal development may be influenced by the nature, timing, duration and severity of the insult.

Studies on humans reveal two distinct mechanisms
that link low birth weight with HT. First, birth weight has been shown to be a strong predictor of nephron number and mean glomerular volume [31]. In fact, retarded intrauterine growth often results in significant reduction in nephron number, which translates to reduced filtration surface area. This consequently leads to progressive renal insufficiency and systemic adult HT. Fetal programming regulates nephrogenesis up to 34-36 weeks of gestational age, hence intrauterine growth retardation or prenatal or postnatal insults in preterm infants may result in reduced nephron number [32]. Second, low birth weight individuals exhibit impaired endothelial function, probably due to perturbation of angiogenesis and vascular function during fetal development [33]. The altered vascular physiology related to low birth weight is invariably irreversible. Smaller birth weight is also associated with chronic low-grade inflammation in children and adolescents [34], further supporting the observation that low birth weight is related to increased risk of coronary heart disease in adults and to the pathogenesis of atherosclerosis in later life.

Glucocorticoids are potent regulators of fetal growth, development and morphogenesis. The placenta is highly enriched with the enzyme 11beta-hydroxysteroid dehydrogenase that inactivates maternally derived glucocorticoids, and thus keeps the circulating levels of fetal glucocorticoids low under normal conditions [30]. Numerous studies, in both humans and animals, have shown that antenatal exposure to exogenous or increased endogenous glucocorticoids results in low birth weight, HT, impaired sugar metabolism, and alterations in behavior and neuroendocrine responses throughout the lifespan, possibly through various mechanisms that include changes in the "set point" of the hypothalamic-pituitary-adrenal axis and tissue glucocorticoid receptor expression [35]. Preterm babies who received a single course of maternal betamethasone do not have long-term metabolic risks other than decreased GFR, indicating impaired nephrogenesis [36].

Utero-placental insufficiency may also lead to HT, as shown in several animal models [37]. Uterine artery ligation during the early phase of gestation results in growth retardation and elevations in BP [38]. Interestingly, the initiating event in pregnancy-induced HT has been postulated to involve reduced utero-placental perfusion, which leads to impaired maternal vascular endothelial function [39].

ASSOCIATION WITH THE METABOLIC SYNDROME

Hypertension is frequently associated with other anthropometric and metabolic abnormalities such as visceral obesity, dyslipidemia, glucose intolerance, insulin resistance, and hyperuricemia, which are collectively called the metabolic syndrome [42]. The metabolic syndrome is more prevalent among patients with HT than in the general population and is more prevalent in women than in men. The prevalence of obesity now approaches 20% in children 4-11 years of age [5], and is highest in American Indian/Native Alaskan, Hispanic and non-Hispanic blacks and lowest in non-Hispanic whites and Asians [43]. In children, as in adults, the prevalence of HT is increased with obesity, and may be as high as 10% in overweight adolescents [44]. The incidence of prehypertension in adolescents, which is about 12%, and 60% in adults, is greater in the obese than in the non-obese [4].

OBESITY, INFLAMMATION AND REACTIVE OXYGEN SPECIES (ROS)

A common link to the abnormalities in metabolic syndrome is subclinical inflammation which, along with insulin resistance and adiposity, is implicated in the development of type 2 diabetes and cardiovascular disease [45]. Elevated markers of subclinical systemic inflammation (e.g., C-reactive protein, coagulopathy) are present in cardiovascular disease, including atherosclerosis and HT in adults and children [46]. Reactive oxygen species (ROS) is important in the pathogenesis of HT [47]. As stated above, children born small for gestational age have increased incidence of HT and increased oxidative stress. Obesity is associated with increased secretion of proinflammatory cytokines, and decreased secretion of anti-inflammatory cytokines by adipocytes [48]. Inflammation contributes to increased insulin resistance [49]. Weight loss secondary to diet, exercise, and/or surgery results in a decrease in circulating inflammatory cytokines [50] and increase in insulin sensitivity [51].

LIFESTYLE MODIFICATION AND PREVENTION OF HYPERTENSION

Dietary modification is recommended as a first-line approach for pediatric patients with elevated BP. Promising research in adults supports the use of a diet high in fruits, vegetables, and low-fat dairy foods, the so-called DASH diet, to normalize BP among hypertensive individuals. Modest reduction of dietary salt for a short duration has a significant effect on BP control in both individuals with normal and elevated BP, however, dietary sodium restriction may not be beneficial to all, and some have suggested that chloride rather than sodium should be restricted. Salt depletion may promote insulin resistance, one of the criteria used to define the metabolic syndrome. A low salt diet may also have a paradoxical effect on BP. Preterm infants (33 weeks gestation or less) who are not

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GENETICS OF BLOOD PRESSURE AND HYPERTENSION

Hypertension is a multifactorial, polygenic complex trait. It was estimated through twin and family studies that about 30% of BP variations is due to variations in genes. Recent genome-wide association studies have shown genetic loci that account for about 2% of genetic factors that influence BP level [40]. The kidney was shown to be the major organ where the inherited tendency of HT predominantly resides in through transplantation studies [41]. Genetics of HT is the topic of a separate paper in this issue of the LMJ.
provided with a diet containing 4-5 mmol NaCl/day may be predisposed to poor neurodevelopmental outcome in the second decade of life. Indeed, salt restriction can decrease cognitive function in adult salt-sensitive rats. Underlying genetic models of salt-sensitive, low-renin, and possibly other subclasses of hypertension are variable [47].

In children, waist circumference has been associated with systolic HT while high total fat intake was related to diastolic HT. The amount of dietary omega-3 polyunsaturated fatty acid intake is inversely associated with cardiovascular disease mortality and morbidity in several populations. The protective effect may arise from their ability to promote vasodilatory and anti-inflammatory eicosanoid generation, reduce angiotensin-converting enzyme activity, enhance endothelial nitric oxide production, and activate the parasympathetic activity. Preliminary clinical trials showed that omega-3 polyunsaturated fatty acids are able to slightly improve arterial HT [52].

Sedentary lifestyle has been shown to markedly increase the risk for cardiovascular disease [53]. Sedentary behavior, such as TV viewing and screen time, but not computer use, were positively associated with both systolic and diastolic BP as well as obesity in children [54]. A TV in the child’s bedroom is an even stronger marker of increased risk of being overweight [55]. This topic has been discussed in detail elsewhere in this issue of the LMJ.

SUMMARY

Essential HT is increasingly recognized in children. Hypertension in the young may already be associated with target-organ damage. Blood pressure levels and HT during childhood track into adulthood. There is fetal programming of BP; low birth weight is associated with HT later in life. High BP may also be caused by genetic factors. A healthy diet, maintenance of normal body weight and waist circumference, and active lifestyle are important in the treatment and prevention of HT. Whether or not these beneficial effects carry throughout adult life remain to be determined by long-term longitudinal studies.

REFERENCES


21. Kavey RE, Kveselis DA, Atallah N, Smith FC. White...
41. Crowley SD, Coffman TM. In hypertension, the kidney breaks your heart. Curr Cardiol Rep 2008; 10: 470-6.